

1 **Fevipirant, a prostaglandin D<sub>2</sub> receptor 2 antagonist, in patients with persistent**  
2 **eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-**  
3 **controlled trial**

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25

26 **Abstract**

27 **Background**

28 Eosinophilic airway inflammation is often present in asthma and interventions that reduce it  
29 result in improved clinical outcomes. Antagonism of the prostaglandin D<sub>2</sub> receptor 2 (DP<sub>2</sub>)  
30 may reduce eosinophilic airway inflammation.

31

32 **Methods**

33 We performed a single-centre, 12-week, randomised, double-blind, placebo-controlled,  
34 parallel-group clinical trial of the DP<sub>2</sub> receptor antagonist fevipiprant (QAW039) 225mg  
35 twice per day orally in 61 subjects with persistent moderate-to-severe asthma and an elevated  
36 sputum eosinophil count. The primary outcome was the change in sputum eosinophil  
37 percentage from baseline to post-treatment. Secondary and exploratory outcomes included  
38 changes in Asthma Control Questionnaire score (ACQ-7), standardised Asthma Quality of  
39 Life Score (AQLQ(S)), forced expiratory volume in one second (FEV<sub>1</sub>), and bronchial  
40 submucosal inflammation. This trial is registered with ClinicalTrials.gov (NCT01545726).

41

42 **Findings**

43 Sputum eosinophil percentage fell from a geometric mean of 5·4% at baseline to 1·1% post-  
44 treatment in the fevipiprant group and from 4·7% at baseline to 3·9% post-treatment in the  
45 placebo group (between group difference 3·5-fold; 95% confidence interval 1·7 to 7·0; p =  
46 0·0014). Bronchial submucosal eosinophils were reduced 2·5-fold in the fevipiprant group  
47 compared to placebo (p = 0·040). ACQ-7 score fell by 0·32 points in the fevipiprant group  
48 compared to placebo (p = 0·17) and by 0·56 points in the subgroup with poor control ( $\geq 1·5$   
49 points) at baseline (p = 0·046). In the fevipiprant group compared to placebo AQLQ(S)

50 improved by 0.59 points ( $p = 0.0080$ ) and post-bronchodilator FEV<sub>1</sub> improved by 0.16 L ( $p =$   
51 0.021). Feviprant displayed a favourable safety profile, with no serious adverse events  
52 reported.

53

#### 54 **Interpretation**

55 Feviprant reduces eosinophilic airway inflammation in patients with persistent asthma and  
56 raised sputum eosinophil counts despite inhaled corticosteroid treatment. This is associated  
57 with improved lung function and asthma-related quality of life, and a favourable safety  
58 profile.

59

#### 60 **Funding**

61 Novartis Pharmaceuticals, AirPROM project, National Institute for Health Research

62 **Research in context**

63 **Evidence before this study**

64 We searched PubMed for reports published in English before February 1 2016, on the use of  
65 DP<sub>2</sub>/CRTH<sub>2</sub> receptor antagonists in asthma with the terms “DP<sub>2</sub>”, “CRTH<sub>2</sub>”, “prostaglandin  
66 D<sub>2</sub>”, and “asthma”. We also searched the reference lists of identified reports. The most  
67 relevant reports identified were of two randomised controlled trials of the compound  
68 OC000459, which was found to improve forced expiratory volume in one second and asthma  
69 quality of life in steroid-naïve patients. The compound BI671800 was evaluated in two  
70 separate randomised controlled trials, one in steroid-naïve adults with asthma, and one in  
71 patients receiving inhaled fluticasone. In both cases, six weeks of treatment resulted in  
72 modest but statistically significant improvements in forced expiratory volume in one second  
73 compared to placebo.

74

75 **Added value of this study**

76 This is the first study to evaluate a DP<sub>2</sub> receptor antagonist in a group of patients with  
77 moderate-to-severe asthma. We showed that fevipiprant reduces eosinophilic airway  
78 inflammation in this group of patients and is associated with improved lung function and  
79 asthma-related quality of life. Control of eosinophilic airway inflammation is an important  
80 goal of asthma treatment since it has been previously shown to reduce asthma exacerbation  
81 rates.

82

83 **Implications of all the available evidence**

84 Fevipiprant is potentially an important advance because it is a well-tolerated orally acting  
85 agent which achieves significant reductions in eosinophilic airway inflammation in patients

86 with moderate-to-severe asthma who are already receiving high-dose inhaled or oral  
87 corticosteroids.

88

89 **Introduction**

90 Asthma is a chronic inflammatory airway disease that is characterised by heterogeneity with  
91 respect to clinical phenotype and response to therapy<sup>1</sup>. Eosinophilic airway inflammation,  
92 mediated by type 2 immunity, is a common feature of asthma<sup>1</sup>. Treatment strategies that  
93 specifically target eosinophilic airway inflammation substantially reduce exacerbations of  
94 asthma in those patients with uncontrolled eosinophilic airway inflammation, and to a lesser  
95 extent improve lung function and asthma control<sup>2-7</sup>.

96

97 There is increasing evidence that prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), acting upon the DP<sub>2</sub> receptor,  
98 also known as receptor homologous molecule expressed on T-helper 2 cells (CRTH2), may  
99 play an important role in mediating eosinophilic airway inflammation in asthma. The DP<sub>2</sub>  
100 receptor mediates the migration of T-helper 2 (T<sub>H2</sub>) cells, delays their apoptosis and  
101 stimulates them to produce the cytokines IL-4, IL-5 and IL-13<sup>8-10</sup>. DP<sub>2</sub> also influences the  
102 migration of and cytokine release from type 2 innate lymphoid cells<sup>11</sup>, and importantly the  
103 receptor is expressed by eosinophils, and directly mediates their chemotaxis and  
104 degranulation<sup>12,13</sup>. The number of DP<sub>2</sub><sup>+</sup> cells in the bronchial submucosa increases with  
105 increasing severity of asthma<sup>14</sup>. DP<sub>2</sub> is also expressed on airway epithelial cells and directly  
106 promotes their migration and differentiation<sup>14</sup>. DP<sub>2</sub> is therefore a highly promising novel drug  
107 target in the treatment of asthma. Fevipiprant (QAW039) is an orally administered highly  
108 selective and potent antagonist of the DP<sub>2</sub> receptor, but not to the more general homeostatic  
109 PGD<sub>2</sub> receptor DP<sub>1</sub>.

110

111 We tested the hypothesis that, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent,  
112 moderate-to-severe asthma, 12-weeks' treatment with fevipiprant at a dose of 225mg twice  
113 per day, on top of conventional treatment, reduces the levels of eosinophils in induced

114 sputum compared to placebo. Secondary objectives were to determine the effects of  
115 fevipiprant on asthma symptoms, as measured by the seven-point Asthma Control  
116 Questionnaire (ACQ-7)<sup>15</sup>, and to assess safety and tolerability of fevipiprant. Exploratory  
117 objectives included assessment of the effect of fevipiprant on the forced expiratory volume in  
118 one second (FEV<sub>1</sub>), lung volumes using body plethysmography, health-related quality of life  
119 as measured by the standardised Asthma Quality of Life Questionnaire (AQLQ(S))<sup>16</sup>, airway  
120 inflammation and remodelling in bronchial biopsies and airway morphometry and lung  
121 density assessed by quantitative computed tomography (CT).

122

## 123 **Methods**

### 124 **Subjects**

125 Participants were older than 18 years of age and had a clinical diagnosis of asthma that was  
126 supported by one or more objective criteria, as described in the appendix. Participants were  
127 recruited from a regional refractory asthma clinic providing tertiary care for a population of 4  
128 million people. Suitable participants were also identified from secondary care asthma and  
129 general respiratory clinics in the region, and through screening of local primary care  
130 databases. Inclusion criteria were current treatment with inhaled corticosteroids (ICS), a  
131 sputum eosinophil count of  $\geq 2\%$  at screening, and either an ACQ-7 score  $\geq 1.5$  at  
132 randomization or  $\geq 1$  severe exacerbations in the past 12 months requiring an increase in  
133 systemic corticosteroid therapy for three days or more. Exclusion criteria included serious  
134 coexisting illness and pregnancy or lactation, and are listed in full in the appendix. All  
135 subjects provided written informed consent. The study protocol was approved by the National  
136 Research Ethics Committee (Leicestershire, Northamptonshire and Rutland, approval no.  
137 11/EM/0402) and the United Kingdom Medicines and Healthcare Products Regulatory

138 Agency. The trial was registered with ClinicalTrials.gov (NCT01545726) and EudraCT  
139 (2011-004966-13).

140

#### 141 **Design of the study**

142 The study was a single-centre, randomised, double-blind, placebo-controlled, parallel-group  
143 clinical trial conducted from February 2012 through June 2013. The funding organisation  
144 (Novartis Pharmaceuticals) supplied the study drug and placebo.

145

146 The study design is illustrated in Figure 1a. Participants were given the option of undergoing  
147 bronchoscopy at the baseline and post-treatment visits as part of the study. Patients attended a  
148 screening visit (Visit 1, Day -21), at which inclusion and exclusion criteria were reviewed.  
149 Regular treatment was kept constant from this time point until the end of the study. One week  
150 later, a two-week single-blind placebo run-in period was commenced (Visit 2, Day -14).  
151 Following this, patients attended a baseline visit (Visit 3, Day 0), at which the inclusion and  
152 exclusion criteria were again assessed, taking into account the ACQ-7 score. If patients  
153 fulfilled the criteria, they proceeded to undertake the remainder of the study visit tests, and  
154 were then randomized in a 1:1 ratio to receive either fevipiprant at a dose of 225 mg twice per  
155 day, or an identical placebo. Patients attended a mid-treatment visit (Visit 4, Day 42), and a  
156 post-treatment visit (Visit 5, Day 84). At the post-treatment visit, patients began a six-week  
157 single-blind placebo washout period, and then attended an end-of-study visit (Visit 6, Day  
158 126). Details of measurements and safety assessments performed at each study visit are  
159 shown in the appendix. Criteria for withdrawal from the study were defined *a priori*, and  
160 included withdrawal of informed consent, asthma exacerbation, pregnancy, and adverse  
161 events for which continued exposure to the study drug would be detrimental.

162



163 **Randomisation and masking**

164 Randomisation was performed by the trial pharmacist using previously generated treatment  
165 allocation cards, and was stratified by whether or not participants were receiving treatment  
166 with regular oral corticosteroids, and whether they were undergoing bronchoscopy. All other  
167 site staff, patients and sponsor personnel remained blinded to treatment allocation until the  
168 study had been completed and the trial database locked. Results of sputum and blood  
169 eosinophil counts subsequent to the baseline visit were not disclosed to the investigators  
170 during the study because of the expected anti-eosinophilic effects of fevipiprant.

171

172 **Statistical analysis**

173 The primary outcome of the study was the change in sputum eosinophil percentage between  
174 the baseline visit and the post-treatment visit. As sputum eosinophil percentage is known to  
175 follow a log-normal distribution, the analysis was based on a  $\log_{10}$ -transformed scale with  
176 results back-transformed to obtain the within-group ratios of geometric means at the end of  
177 treatment compared to baseline. We report the reciprocal of these ratios as fold-reductions  
178 from baseline within each group, and the ratio of these ratios as a measure of how many times  
179 greater the reduction in the fevipiprant group was compared to the reduction in the placebo  
180 group. The secondary outcome was the change from baseline to post-treatment with respect  
181 to ACQ-7 score. Exploratory outcomes included the change from baseline to post-treatment  
182 with respect to ACQ-7 score in the subgroup with baseline score  $\geq 1.5$ , AQLQ(S) score,  
183 FEV<sub>1</sub> and submucosal eosinophil count on bronchial biopsy. Statistical analyses were  
184 performed using SAS/STAT software, versions 9.3 and 9.4 of the SAS System for AIX (SAS  
185 Institute Inc., Cary, NC, USA) and Prism 6 (GraphPad, La Jolla, CA, USA). Changes in  
186 efficacy outcomes from the baseline to post-treatment visits were analysed using an analysis  
187 of covariance (ANCOVA) model, with treatment as the fixed effect. Randomisation strata

188 and baseline values of efficacy variables were entered as factors in the ANCOVA model for  
189 analysis of the primary outcome, secondary outcome and exploratory outcomes detailed in  
190 the statistical analysis plan (see Supplementary Appendix). Exploratory endpoints not  
191 explicitly detailed in the statistical analysis plan were analysed without correction for  
192 randomisation stratum or baseline values. Efficacy outcomes were analysed by intention to  
193 treat and safety outcomes were analysed by treatment received. One patient was assigned to  
194 fevipiprant but incorrectly dispensed placebo at the mid-treatment visit. One patient was  
195 assigned to fevipiprant but incorrectly dispensed placebo throughout the course of the study.  
196 They were included in the fevipiprant group for efficacy analyses, but the latter patient was  
197 included in the placebo group for safety analyses. The planned sample size of 60 randomised  
198 patients was calculated so that at least 24 patients per arm would complete the post-treatment  
199 assessment in order to ensure 80% power at the two-sided 5% significance, assuming a 50%  
200 reduction in sputum eosinophil percentage with fevipiprant<sup>17</sup>.

201

## 202 **Role of the funding source**

203 The sponsor contributed to the study design, data interpretation and writing of the report, and  
204 coordinated data collection and analysis. The authors had full access to the data and vouch for  
205 the accuracy of the findings. The corresponding author had final responsibility for the  
206 decision to submit for publication.

207

## 208 **Results**

209 Participants were recruited between Feb 10, 2012 and Jan 30, 2013. A total of 117 patients  
210 attended a screening visit, of which 61 fulfilled the inclusion and exclusion criteria and were  
211 randomised (Figure 1b). Thirty-one patients were assigned to receive placebo and 30 to  
212 receive fevipiprant. Four patients withdrew in the placebo group and three patients in the

213 fevipirant group, in each case due to an exacerbation of asthma. The randomised groups  
214 were well-matched for baseline characteristics, as shown in Table 1. Efficacy outcomes are  
215 shown in Figures 2-4, and in Tables S1-S3 in the appendix.

216

217 The geometric mean sputum eosinophil percentage fell from 5·4% at baseline to 1·1% post-  
218 treatment in the fevipirant group, and from 4·7% at baseline to 3·9% post-treatment in the  
219 placebo group. The ratio of geometric means post-treatment to baseline for the sputum  
220 eosinophil percentage was 0·78 (1·3-fold reduction) in the placebo group and 0·22 (4·5-fold  
221 reduction) in the fevipirant group, with a 3·5-fold (95% confidence interval [CI] 1·7 to 7·0-  
222 fold) greater reduction in the fevipirant group compared to placebo ( $p = 0\cdot0014$ ).

223

224 The mean ACQ-7 score fell by 0·32 points from baseline to post-treatment in the fevipirant  
225 group compared to the change seen with placebo, but this improvement did not reach  
226 statistical significance (95% CI -0·78, 0·14;  $p = 0\cdot17$ ). However, among the subset of patients  
227 ( $n = 40$ ) uncontrolled at baseline (ACQ-7 score  $\geq 1\cdot5$ ), the mean ACQ-7 score fell by 0·56  
228 points compared to placebo, which was both clinically and statistically significant (95% CI -  
229 1·12, -0·01;  $p = 0\cdot046$ ). The mean AQLQ(S) score improved by 0·59 points in the fevipirant  
230 group compared to placebo, which was statistically significant (95% CI 0·16, 1·03;  $p =$   
231  $0\cdot0080$ ). The mean post-bronchodilator FEV<sub>1</sub> increased by 0·16L from baseline to post-  
232 treatment in the fevipirant group compared to placebo, with a statistically significant  
233 difference between the groups (95% CI 0·03, 0·30;  $p = 0\cdot021$ ). There were no significant  
234 differences between the groups with respect to changes in pre-bronchodilator FEV<sub>1</sub>. There  
235 were no significant changes in peripheral blood eosinophil count or exhaled nitric oxide in  
236 either group.

237

238 Paired bronchial biopsies (baseline and post-treatment) were obtained in 14 patients in the  
239 fevipiprant group and 12 patients in the placebo group. We observed a 2·5-fold greater  
240 reduction in bronchial submucosal eosinophil numbers from baseline to post-treatment in the  
241 fevipiprant group compared to the placebo group ( $p = 0\cdot040$ ). There was a 1·4-fold reduction  
242 in bronchial epithelial eosinophil numbers from baseline in favour of fevipiprant, but the  
243 treatment difference did not reach statistical significance. Subjects treated with fevipiprant  
244 demonstrated a 27·8 percentage point increase in the proportion of intact epithelium (95% CI  
245 2·9, 52·7;  $p = 0\cdot030$ ), and a 26·6 percentage point reduction in the proportion of denuded  
246 epithelium (95% CI -44·9, -8·3;  $p = 0\cdot0062$ ), compared to the change seen with placebo.  
247 Changes in epithelial integrity were not significantly correlated with changes in sputum or  
248 bronchial mucosal eosinophilic inflammation, as shown in Figure S1 in the appendix.

249

250 Functional residual capacity (FRC) fell by 0·31 L in the fevipiprant group compared to the  
251 change seen with placebo (95% CI -0·62, -0·001;  $p = 0\cdot049$ ) and expiratory CT lung volume  
252 fell by 216 cm<sup>3</sup> in the fevipiprant group compared to the placebo group (95% CI -391, -40;  $p$   
253 = 0·017), but no significant treatment differences were observed with respect to other  
254 quantitative CT parameters. Significant positive correlations were observed between changes  
255 in plethysmographic and CT-derived measures of expiratory air trapping, as shown in Figure  
256 S2 in the appendix.

257

258 Outcomes measured following the 6 week washout period returned to baseline without any  
259 significant differences between baseline and post-washout for any outcome. Fevipiprant had  
260 an acceptable side-effect profile throughout the study period. Total adverse events and  
261 adverse events within each organ class were balanced between the two treatment groups.

262 There were no deaths or serious adverse events reported, and no patient withdrawals  
263 suspected by the investigator to be related to the study drug, as shown in Table 2.

264

## 265 **Discussion**

266 We found that fevipiprant significantly reduced eosinophilic inflammation in the sputum and  
267 bronchial submucosa compared to placebo in patients with persistent, moderate-to-severe  
268 asthma and sputum eosinophilia. Fevipiprant significantly improved AQLQ(S) scores, post-  
269 bronchodilator FEV<sub>1</sub> and functional residual capacity compared to placebo in all patients, and  
270 ACQ-7 scores in the sub-group of patients who had poor asthma control at baseline (ACQ-7  
271  $\geq 1.5$  points). Exploratory analyses of bronchial biopsies suggested that fevipiprant led to  
272 improvements in epithelial integrity, but did not affect epithelial goblet cell number or  
273 MUC5A expression.

274

275 The magnitude of reduction in eosinophilic inflammation reported here was comparable to  
276 that observed with mepolizumab<sup>3,4</sup>. Unlike mepolizumab<sup>3,4</sup>, and other anti-IL5(R) targeted  
277 biologics reslizumab and benralizumab, fevipiprant did not have any significant effect on the  
278 blood eosinophil count. This suggests that DP<sub>2</sub> receptor blockade attenuates the migration of  
279 eosinophils into the airway tissues, but is unlikely to have a substantial effect upon release  
280 from the bone marrow although it might exert a small indirect effect through a reduction in  
281 circulating IL-5<sup>10,11</sup>. Previous interventional studies have shown that anti-eosinophilic  
282 treatments or strategies exert their major therapeutic effect through the reduction in asthma  
283 exacerbations<sup>2-5,7</sup>, although effects on FEV<sub>1</sub> have also been observed, particularly in patients  
284 with blood eosinophilia<sup>6,7</sup>. The treatment period in this study was not long enough to observe  
285 a significant effect on exacerbations. Whether fevipiprant reduces the frequency of  
286 exacerbations in patients with eosinophilic asthma is an important question for future studies.

287

288 We noted a prompt return to baseline values following a six-week placebo wash-out period in  
289 the fevipirant group with respect to sputum eosinophil percentage, ACQ-7 and AQLQ(S)  
290 scores, and post-bronchodilator FEV<sub>1</sub>. There were no statistically significant differences  
291 between baseline values and those recorded following the placebo wash-out. This suggests  
292 that the short-term improvements in asthma quality of life and post-bronchodilator FEV<sub>1</sub> seen  
293 with fevipirant were driven by reversible processes rather than underlying disease  
294 modification. However, we observed significant improvements in epithelial integrity  
295 following 12 weeks of treatment with fevipirant compared to placebo. Whether this effect  
296 was a consequence of reduced eosinophilic inflammation which is known to cause epithelial  
297 damage or a direct effect upon epithelial repair and differentiation as observed *in vitro*<sup>14</sup>  
298 remains uncertain, although the lack of an association between changes in sputum eosinophil  
299 counts and epithelial integrity in response to fevipirant favours a direct mechanistic effect  
300 upon the epithelium.

301

302 Previous clinical trials of DP<sub>2</sub> receptor antagonists in asthma have yielded mixed results. The  
303 compound OC000459 was found to improve pre-bronchodilator FEV<sub>1</sub> and asthma quality of  
304 life in steroid-free patients<sup>19</sup>, with a subsequent study finding that the beneficial effect was  
305 confined to patients with a baseline peripheral blood eosinophil count >250/ $\mu$ l<sup>20</sup>. However,  
306 this compound has not yet been tested in patients with moderate-to-severe asthma. AMG853,  
307 a dual DP<sub>1</sub> and DP<sub>2</sub> antagonist, was not effective in improving asthma symptoms or either  
308 pre- or post-bronchodilator FEV<sub>1</sub> in patients with moderate-to-severe asthma<sup>21</sup>, but there is  
309 evidence that DP<sub>1</sub> and DP<sub>2</sub> stimulation may have opposing effects on a number of  
310 inflammatory mechanisms<sup>22</sup>. The efficacy of BI671800 was evaluated in two separate  
311 randomised controlled trials, one in steroid-naïve adults with asthma, and one in patients

312 receiving inhaled fluticasone<sup>23</sup>. In both cases, six weeks of treatment resulted in modest but  
313 statistically significant improvements in pre-bronchodilator FEV<sub>1</sub> compared to placebo. In  
314 these previous studies patient selection was not based upon evidence of eosinophilic airway  
315 inflammation. Previous experience has shown that targeting anti-eosinophilic therapies to  
316 patients with evidence of uncontrolled type 2 inflammation is associated with more clear  
317 evidence of efficacy<sup>3-7</sup>, and the positive results obtained in our study should therefore not be  
318 extrapolated to an unselected group of patients with moderate-to-severe asthma.

319

320 One limitation of our study is the relatively small sample size undertaken in a single centre.  
321 However, the effect size in our primary outcome the sputum eosinophil count was large and  
322 other positive clinical outcomes showed both statistically and clinically important differences  
323 between the fevipirant and placebo groups. Furthermore, our study design allowed a  
324 significant loss of efficacy to be demonstrated when fevipirant was stopped. In contrast to  
325 many clinical trials the clinical outcomes in the group that received placebo were typically  
326 worse following intervention compared to their baseline, suggesting deterioration in this  
327 group. The lack of a positive placebo effect in this study may be explained by the fact that  
328 many of the participants were drawn from a tertiary refractory asthma clinic, and their  
329 treatment had previously been fully optimised. We also included a two-week single-blind  
330 placebo run-in period prior to the baseline visit specifically in order to minimise the placebo  
331 effect. Finally, our inclusion and exclusion criteria mandated a six-week period of clinical  
332 stability before patients could participate in the study, thus minimising the potential for  
333 changes to occur as a result of regression to the mean. Baseline characteristics of the groups  
334 were in general well-matched, although the median inhaled corticosteroid dose was  
335 numerically higher in the fevipirant group than the placebo group. However, since  
336 background treatment remained stable throughout the study it is unlikely that this would have

337 caused a systematic bias in the efficacy outcome measures. During the study two dispensing  
338 errors occurred, with one patient randomised to fevipiprant and receiving placebo throughout,  
339 and a second randomised to fevipiprant and receiving placebo in the second half of the  
340 treatment period. Since efficacy outcomes were analysed by intention to treat, this could have  
341 increased the chance of a type II error. However, when efficacy outcomes were analysed by  
342 treatment received there were no significant changes in the results obtained (data not shown).

343

344 We conclude that the DP<sub>2</sub> receptor antagonist fevipiprant is effective at attenuating  
345 eosinophilic airway inflammation in patients with persistent eosinophilic asthma, and appears  
346 to have a favourable safety profile over a 12-week treatment period. There is evidence that  
347 fevipiprant improves lung function and asthma-related quality of life, as well as expiratory air  
348 trapping and epithelial integrity. Longer-term multi-centre studies are required to confirm  
349 these findings and to investigate the effect of fevipiprant on asthma exacerbations.

350



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358

359 **Author contributions**

360 SG contributed to study design, participant recruitment, data collection, data interpretation,  
361 literature search and manuscript writing; RB performed bronchoscopies, analysed bronchial  
362 biopsies, and contributed to participant recruitment, data collection and manuscript writing;  
363 AS and MB contributed to participant recruitment and data collection; RH analysed CT  
364 scans; MFML and GB contributed to study design and management; BH performed statistical  
365 analysis; VM analysed sputum samples; IDP contributed to participant recruitment, data  
366 interpretation and manuscript writing; AHM and AJW contributed to participant recruitment;  
367 SHS performed bronchoscopies and contributed to participant recruitment; RAK contributed  
368 to study design, data interpretation, literature search, manuscript writing, and produced the  
369 figures. CEB was the Principal Investigator of the study and contributed to study design,  
370 participant recruitment, bronchoscopies, data collection, data interpretation, literature search  
371 and manuscript writing. All authors reviewed and commented on the manuscript.

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**Table 1. Baseline Characteristics of Randomised Population**

Characteristic	Fevipirant (n = 30)	Placebo (n = 31)
Sex (no. of subjects)		
Male	18	13
Female	12	18
Age (yr)		
Mean	50	50
Range	20 – 80	19 – 68
Duration of asthma (yr)	32 ± 16	29 ± 15
Body-mass index (kg/m <sup>2</sup> )	31.0 ± 5.9	29.6 ± 6.0
Positive atopic status (% of subjects)‡	87	84
Number of exacerbations in previous year	1.8 ± 1.7	2.2 ± 2.8
Number of patients (%) with rhinosinusitis	12/30 (40.0)	11/31 (35.5)
Number of patients (%) with nasal polyps	5/30 (16.7)	3/31 (9.7)
Total IgE (U/ml)		
Median	414	388
Interquartile range	216 – 863	181 – 1121
FEV <sub>1</sub> before bronchodilator use (% of predicted value)	72.5 ± 23.8	75.1 ± 27.3
FEV <sub>1</sub> /FVC before bronchodilator use (%)		
Median	68.0	69.2
Interquartile range	46.7 – 73.6	52.1 – 73.5
Improvement in FEV <sub>1</sub> after bronchodilator use (%)		
Median	9.3	12.0
Interquartile range	5.5 – 12.6	6.1 – 29.9
Eosinophil count in sputum (%) ¶	5.31 (2.77)	4.24 (4.03)

Eosinophil count in blood ( $\times 10^9/L$ ) ¶¶	0.28 (1.31)	0.28 (0.79)
FENO <sub>50</sub> (ppb)	30 ± 24	48 ± 43
Score on Asthma Control Questionnaire	1.9 ± 0.8	2.2 ± 0.9
Score on Asthma Quality of Life Questionnaire	5.4 ± 1.1	5.0 ± 1.0
Inhaled corticosteroid dose (beclomethasone dipropionate equivalent [ $\mu$ g])		
Median	1600	1000
Interquartile range	800 – 1600	800 – 1600
Number of patients (%) using long-acting beta-agonists	27/30 (90)	26/31 (84)
Number of patients (%) using regular oral prednisolone	7/30 (23)	7/31 (23)
Global Initiative for Asthma treatment step (number of patients)*		
Step 2	1	1
Step 3	1	4
Step 4	21	19
Step 5	7	7

FEV<sub>1</sub> denotes forced expiratory volume in one second, FVC forced vital capacity, and FENO<sub>50</sub> fraction of exhaled nitric oxide in exhaled air at a flow rate of 50 ml/s.

Plus-minus values are means ± standard deviation (SD) unless otherwise stated.

‡ Positive atopic status was defined as a positive skin test for any of a panel of specified aeroallergens (grass pollen, tree pollen [alder, silver birch, hazel], moulds [*Aspergillus fumigatus*, *Alternaria tenius*, *Cladosporium*, *Penicillium notatum*], cat fur, dog dander, and house dust mite [*Dermatophagoides pteronyssimus*])

¶ Expressed as geometric mean (coefficient of variation)

\* Global Initiative for Asthma treatment steps<sup>18</sup>.

**Table 2. Summary of Adverse Events**

Group	Period between baseline and post-treatment visits		Period between baseline and end-of-study visits	
	Fevipirant (N=29) n (%)	Placebo (N=32) n (%)	Fevipirant (N=29) n (%)	Placebo (N=32) n (%)
<b>Patients with at least 1 AE</b>	<b>21 (72·4)</b>	<b>25 (78·1)</b>	<b>24 (82·8)</b>	<b>26 (81·3)</b>
<b>Primary system organ class</b>				
Infections and infestations	8 (27·6)	8 (25·0)	11 (37·9)	10 (31·3)
Respiratory, thoracic and mediastinal disorders	6 (20·7)	9 (28·1)	12 (41·4)	15 (46·9)
Gastrointestinal disorders	3 (10·3)	6 (18·8)	5 (17·2)	8 (25·0)
Nervous system disorders	3 (10·3)	6 (18·8)	3 (10·3)	8 (25·0)
Injury, poisoning and procedural complications	5 (17·2)	1 (3·1)	5 (17·2)	2 (6·3)
Musculoskeletal and connective tissue disorders	1 (3·4)	3 (9·4)	3 (10·3)	3 (9·4)
General disorders and administration site conditions	3 (10·3)	1 (3·1)	3 (10·3)	2 (6·3)
Blood and lymphatic system disorders	2 (6·9)	0	2 (6·9)	0
Eye disorders	0	2 (6·3)	0	2 (6·3)
Investigations	1 (3·4)	1 (3·1)	2 (6·9)	2 (6·3)
Metabolism and nutrition disorders	2 (6·9)	0	2 (6·9)	0
Cardiac disorders	0	1 (3·1)	0	1 (3·1)
Renal and urinary disorders	1 (3·4)	0	2 (6·9)	0
Reproductive system and breast disorders	0	1 (3·1)	0	1 (3·1)
Skin and subcutaneous tissue disorders	0	1 (3·1)	1 (3·4)	1 (3·1)
Immune system disorders	0	0	0	1 (3·1)
Surgical and medical procedures	0	0	0	1 (3·1)
Vascular disorders	0	0	0	1 (3·1)



## **Figure Legends**

### **Figure 1: Summary of study protocol and participant flow**

Panel A shows the timings of study visits and treatment allocations. Panel B shows the number of patients who attended screening, were randomised, and completed each of the study visits.

### **Figure 2: Comparison of eosinophilic inflammation outcomes between the study groups**

Panels A and B show fold-reductions in sputum and blood eosinophil counts respectively at each study visit compared to the baseline visit, in the placebo (blue square) and fevipirant (orange circle) groups. P values refer to differences between the study groups with respect to change from the baseline visit. Panels C and D show lamina propria and epithelial eosinophil numbers respectively at the baseline and post-treatment visits, in the placebo (blue square) and fevipirant (orange circle) groups. Box and whisker plots show the median, 25<sup>th</sup> and 75<sup>th</sup> percentiles as a box, and the 10<sup>th</sup> and 90<sup>th</sup> percentiles as whiskers. P values refer to differences between the study groups with respect to change from the baseline visit to the post-treatment visit.

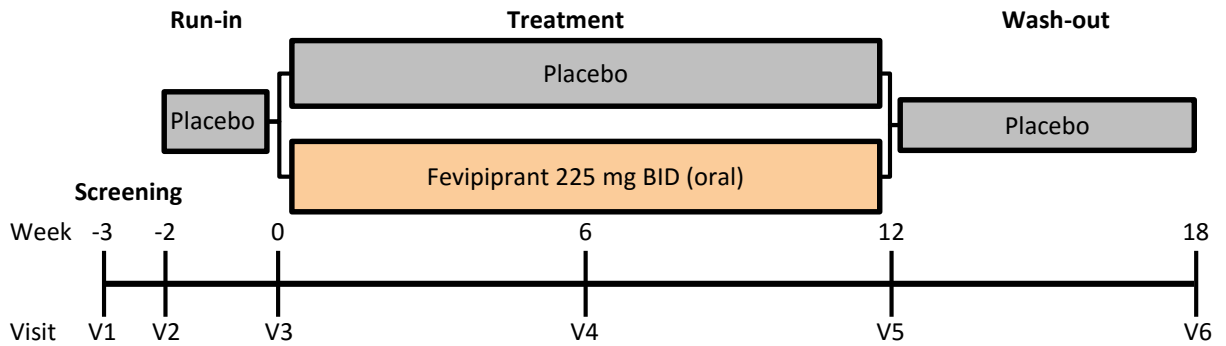
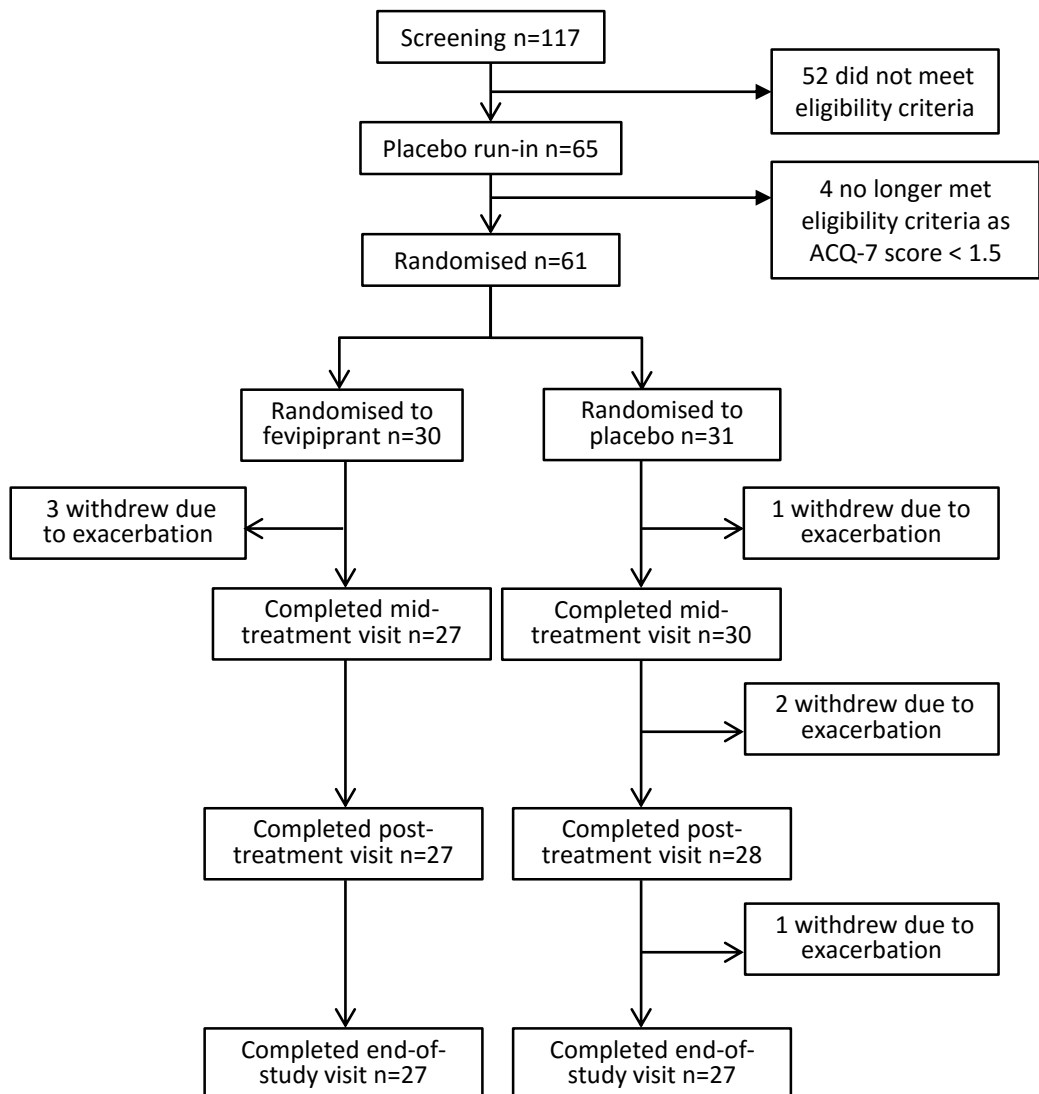
### **Figure 3: Comparison of patient-reported and lung function outcome measures between the study groups**

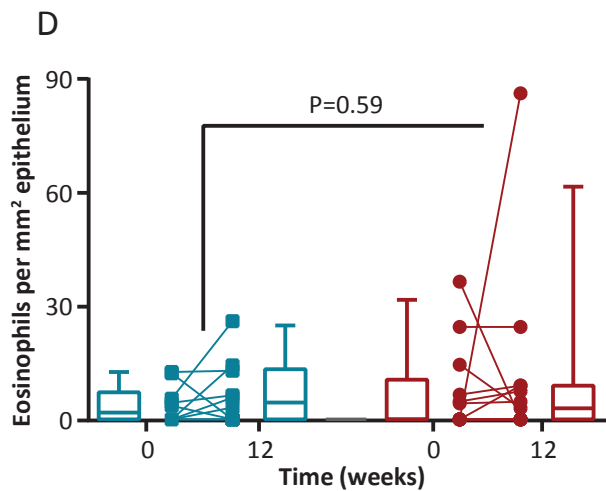
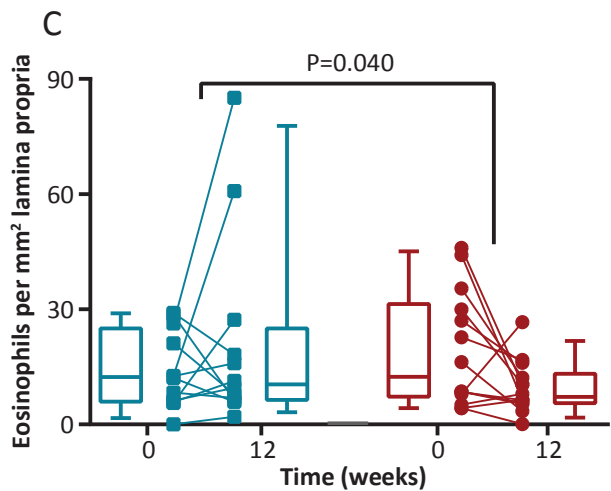
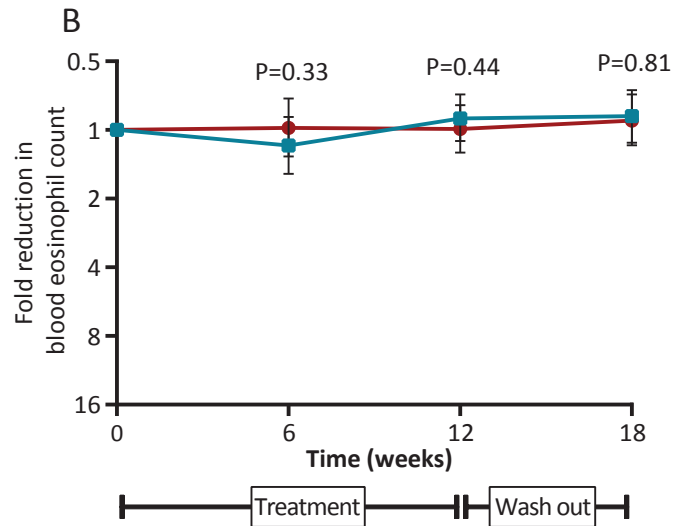
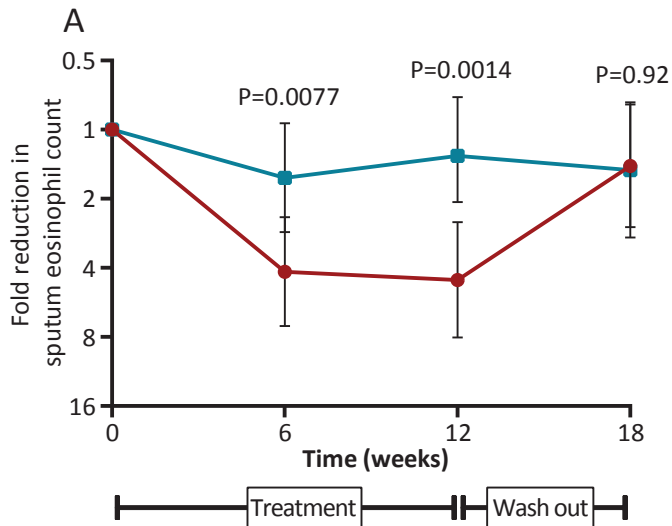
Changes compared to the baseline visit are shown in the placebo (blue square) and fevipirant (orange circle) groups with respect to Asthma Control Questionnaire score (ACQ7) in the Full Analysis Set (FAS, Panel A), ACQ7 in the subgroup with a baseline value  $\geq 1.5$  (Panel B), standardised Asthma Quality of Life Questionnaire score (AQLQ(S), Panel C), forced expiratory volume in one second (FEV<sub>1</sub>) performed before the administration of a

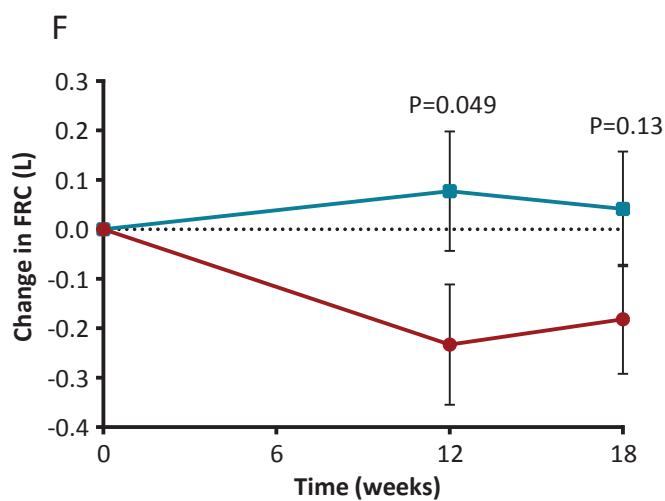
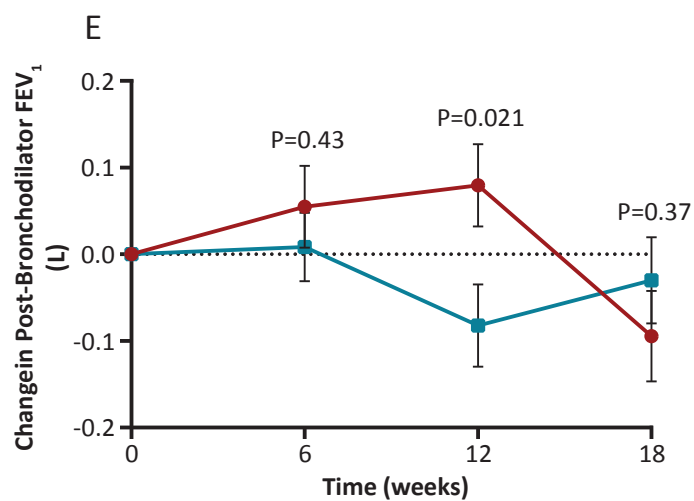
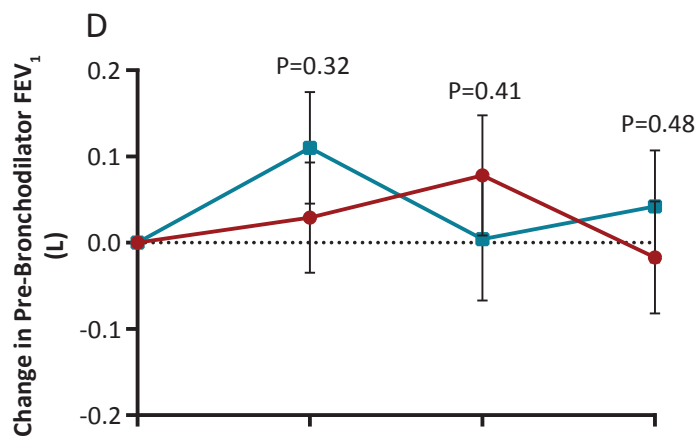
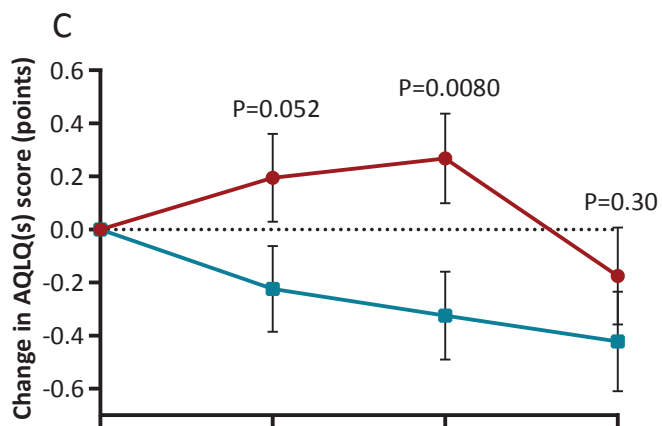
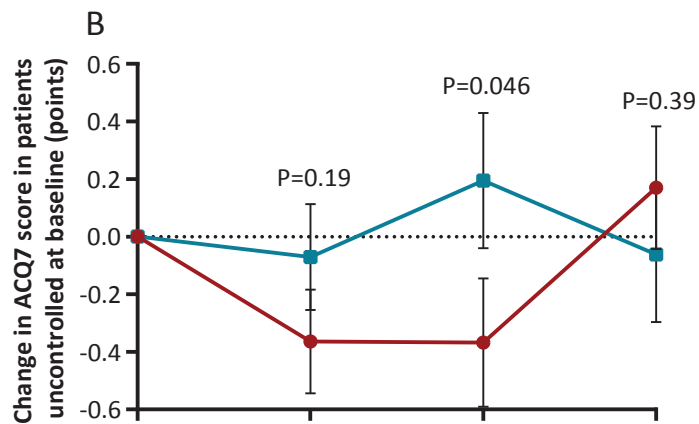
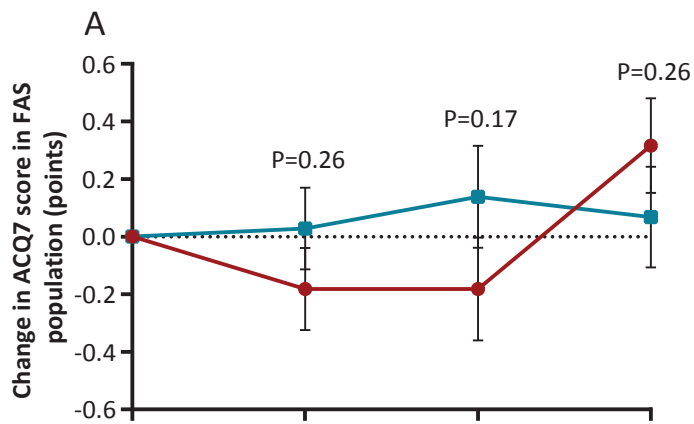
bronchodilator (Panel D), FEV<sub>1</sub> performed after the administration of a bronchodilator (Panel E), and functional residual capacity (FRC, Panel F). P values refer to differences between the study groups with respect to change from the baseline visit.

**Figure 4: Comparison of epithelial damage outcome measures between the study groups**

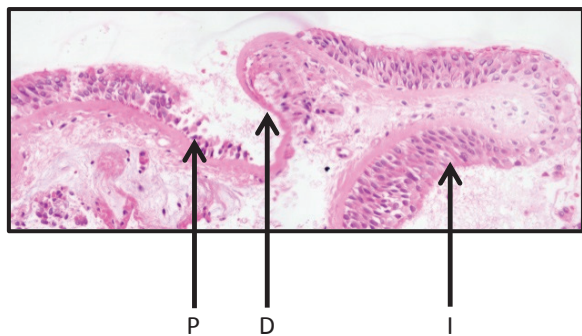
Panel A shows a photomicrograph of a bronchial biopsy specimen demonstrating the appearance of intact epithelium (I), partially denuded epithelium (P) and denuded epithelium (D). Panels B-D show percentage of epithelium that is intact, percentage of epithelium that is denuded and thickness of intact epithelium respectively at the baseline and post-treatment visits, in the placebo (blue square) and fevipiprant (orange circle) groups. Error bars indicate the mean plus or minus the standard error of the mean. P values refer to differences between the study groups with respect to change from the baseline visit to the post-treatment visit.

**A****B**

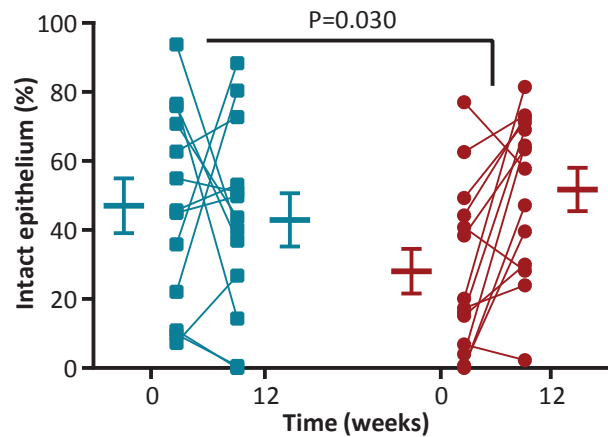




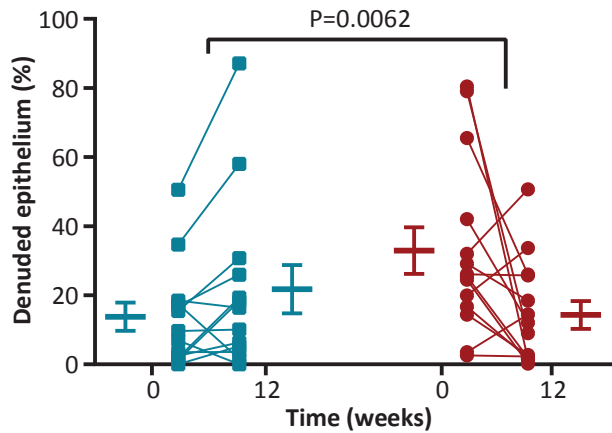
A



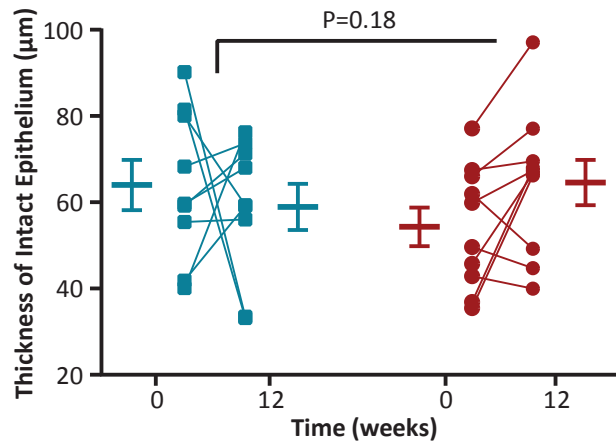
B



C



D



1 Supplementary Appendix

2 **Fevipirant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent**  
3 **eosinophilic asthma: a single centre, randomised, double-blind, parallel-group, placebo-**  
4 **controlled trial**

5

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10

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26

27 **Methods**

28

29 **Subjects**

30 Participants were older than 18 years of age and had a clinical diagnosis of asthma that was  
31 supported by one or more of the following criteria: an increase in forced expiratory volume  
32 (FEV<sub>1</sub>) of  $\geq 12\%$  and  $\geq 200\text{ml}$  from its pre-bronchodilator value following the inhalation of  
33  $400\mu\text{g}$  salbutamol, a provoked fall in FEV<sub>1</sub> of 20% by methacholine at  $\leq 16\text{mg/ml}$  while on  
34 inhaled corticosteroids (ICS), or a change in FEV<sub>1</sub> of  $> 12\%$  over two non-exacerbation-  
35 related measurements during the previous year. Inclusion criteria were current treatment with  
36 ICS, a sputum eosinophil count of  $\geq 2\%$  at screening, and either an Asthma Control  
37 Questionnaire (ACQ-7) score  $\geq 1.5$  at randomization or  $\geq 1$  exacerbations (requiring higher  
38 than the patient's normal dose of systemic corticosteroids for  $\geq 3$  days) in the past 12 months.  
39 Exclusion criteria included serious coexisting illness, pregnancy or lactation, the possibility  
40 of conception, a history of malignancy within the previous five years, recent (within 6 weeks  
41 of screening) lower respiratory tract infection or exacerbation of asthma requiring oral  
42 prednisolone, the use of omalizumab within 6 months before randomization into the study,  
43 and the use of immunosuppressive medication (except low-dose [ $\leq 10\text{mg}$  prednisolone per  
44 day] oral corticosteroids) within 30 days before randomization.

45

46 **Study visit protocol**

47 At a screening visit (Visit 1, Day -21), demographic and clinical details were collected, and  
48 inclusion and exclusion criteria were reviewed. An induced sputum sample was collected and  
49 cell count was performed, in order to assess eligibility based upon a sputum eosinophil count  
50 of  $\geq 2\%$ . Regular treatment was kept constant from this time point until the end of the study.



51 One week later, a two-week single-blind placebo run-in period was commenced (Visit 2, Day  
52 -14). Following this, patients attended a baseline visit (Visit 3, Day 0), at which they  
53 completed the ACQ-7 questionnaire, and eligibility based upon the inclusion and exclusion  
54 criteria was again assessed, taking into account the ACQ-7 score. If patients fulfilled the  
55 criteria, they proceeded to undertake the remainder of the study visit tests, and were then  
56 randomized in a 1:1 ratio to receive either fevipiprant at a dose of 225 mg twice per day, or  
57 an identical placebo.

58

59 All tests performed at the baseline and post-treatment visits were carried out on the same day,  
60 with the exception of bronchoscopy, which was performed on a separate day not more than  
61 seven days following the other tests, but not on the day immediately following them, due to  
62 the possibility of interaction between the sputum induction procedure and bronchial biopsies.  
63 The time interval between the two testing days was kept constant for each patient between the  
64 baseline and post-treatment visits. On the first testing day, patients completed the ACQ-7 and  
65 Standardized Asthma Quality of Life Questionnaire (AQLQ(S)). The fractional exhaled nitric  
66 oxide at 50ml/s (FeNO<sub>50</sub>) was measured using a NIOX MINO device (Aerocrine AB, Solna,  
67 Sweden). Patients undertook body plethysmography, measurement of carbon monoxide  
68 diffusing capacity and pre-bronchodilator spirometry. An induced sputum sample was then  
69 collected and cell count performed. Salbutamol (400 µg via a metered-dose inhaler and  
70 spacer) was administered, followed by the measurement of post-bronchodilator spirometry. A  
71 blood sample was drawn for the measurement of blood eosinophil count. Inspiratory and  
72 expiratory computed tomography (CT) was then performed. On the second testing day,  
73 bronchoscopy was performed.

74

75 Six weeks following randomization, patients attended a mid-treatment visit (Visit 4, Day 42),  
76 at which they completed the ACQ-7 and AQLQ(S) questionnaires, pre- and post-  
77 bronchodilator spirometry was performed, an induced sputum sample was obtained, and a  
78 blood sample was drawn for the measurement of blood eosinophil count. Twelve weeks  
79 following randomization, patients attended a post-treatment visit (Visit 5, Day 84), which  
80 incorporated the same assessment schedule as the baseline visit. Patients then began a six-  
81 week single-blind placebo washout period. Following this, patients attended an end-of-study  
82 visit (Visit 6, Day 126) and undertook the same assessments as at the baseline and post-  
83 treatment visits, except that bronchoscopy and CT scans were not performed.

84

85 Safety was assessed at each study visit on the basis of patient-reported adverse events,  
86 physical examination, vital signs, haematology, blood chemistry, urinalysis and an  
87 electrocardiogram.

88

### 89 **Pulmonary function tests and sputum induction**

90 Spirometry was performed using a rolling seal spirometer (Vitalograph, UK) according to  
91 American Thoracic Society / European Respiratory Society (ATS / ERS) guidelines<sup>1</sup>, and  
92 repeated twenty minutes after inhalation of 400µg salbutamol. Bronchial provocation testing  
93 to methacholine was performed using the tidal breathing method as previously described<sup>2</sup>.  
94 Methacholine was inhaled to a maximum concentration of 16mg/ml and the PC<sub>20</sub> calculated  
95 by linear interpolation of the log-transformed plot. The procedure was only performed in  
96 those in whom no other objective evidence supporting the diagnosis was available. Body  
97 plethysmography and carbon monoxide transfer factor were performed according to ATS /  
98 ERS guidelines (Medisoft, Belgium)<sup>3,4</sup>. The fractional exhaled nitric oxide was measured  
99 using a NIOX MINO device (Aerocrine AB, Solna, Sweden), as previously described<sup>5</sup>.

100 Sputum induction and processing was performed as previously described<sup>6</sup>. Differential cell  
101 counts were recorded by a blinded individual and expressed as percentage values of a sample  
102 containing at least 400 non-squamous cells.

103

#### 104 **Skin tests for allergy**

105 Skin prick tests for allergy were performed at Visit 2 to assess atopic status unless historical  
106 positive results were available. Patients were tested against a panel of aeroallergens  
107 comprising grass pollen, tree pollen [alder, silver birch, hazel], moulds [*Aspergillus*  
108 *fumigatus*, *Alternaria tenius*, *Cladosporium*, *Penicillium notatum*], cat fur, dog dander, and  
109 house dust mite [*Dermatophagoides pteronyssimus*. Small droplets of purified allergen  
110 extracts were placed on the subject's forearm, as well as a positive control (histamine) and  
111 negative control (saline). A sterile lancet was passed through each droplet so as to break the  
112 epidermis of the skin underneath the droplet without drawing blood. A new lancet was used  
113 for each droplet, which was then immediately discarded. Surplus fluid was then blotted from  
114 the skin. After 15 minutes the diameter of the wheal produced by each allergen was  
115 measured. A wheal diameter of 3mm or more greater than that of the negative control was  
116 considered to be a positive result.

117

#### 118 **Bronchial biopsy analysis**

119 All bronchoscopies were performed by blinded senior clinicians, in accordance with  
120 published guidelines<sup>7</sup>. During bronchoscopy, subjects had up to six endobronchial biopsies.  
121 Biopsy specimens were processed as previously described and embedded in glycol  
122 methacrylate<sup>8</sup>.

123

124 Two micrometre sections were cut and stained with Haematoxylin & Eosin (H&E) and  
125 Periodic acid–Schiff (PAS). Furthermore, immunohistochemical staining was done with the  
126 following mAbs: anti–mast cell tryptase clone AA1 (Dako UK, Ely, United Kingdom), anti-  
127 human smooth muscle actin (SMA) clone 1A4 (Dako UK, Ely, United Kingdom), anti-  
128 eosinophil major basic protein clone BMK-13 (Monosan, Uden, The Netherlands), anti-  
129 neutrophil elastase clone NP57 (Dako UK, Ely, United Kingdom), anti-CD3 polyclonal  
130 antibody (Becton Dickinson, San Jose, California, USA), anti-endothelium clone EN4  
131 (Monosan, Uden, The Netherlands) and anti-mucin 5AC (MUC5AC) clone 45M1 (Abcam,  
132 Cambridge, UK). Appropriate isotype controls were used.

133

134 For image analysis and morphometry ZEN 2012 image analysis software for light  
135 microscopy (Carl Zeiss AG, Jena, Germany) was used. Tissue section areas were measured in  
136 H&E and SMA stained sections. Total area, airway smooth muscle area and epithelial area  
137 were measured directly, while lamina propria area was calculated by subtracting the all the  
138 other areas and the area occupied by vessels and lymphatics from the total section area. All  
139 areas were expressed in mm<sup>2</sup> and also as percentages of the total area. All morphometry  
140 measurements and cellular counts were performed by one blinded observer on two non-  
141 contiguous tissue sections at least 20µm apart from the same biopsy block.

142

143 Reticular basement membrane (RBM) thickness was measured at x200 magnification by  
144 measuring 50 points 20µm apart according to the method validated by Sullivan *et al*<sup>9</sup>.  
145 Epithelial thickness was measured using the method described by Cohen *et al*<sup>10</sup>. Briefly, areas  
146 of intact and tangentially orientated epithelium were identified and measured. Subsequently,  
147 to calculate the epithelial thickness, this area was divided by the lengths of the corresponding  
148 RBM. Both RBM and epithelial thickness were expressed in µm. Vascularity was measured

149 using the Chalkley count, a surrogate of both vessel density and vascular area. As described  
150 previously, a Chalkley eyepiece graticule (NG52 Chalkley Point Array, Pyser-SGI Ltd,  
151 Edenbridge, UK) was used at x200 to measure Chalkley counts in four non-overlapping  
152 vascular hotspots (1-2/section)<sup>11</sup>. The mean Chalkley count (MCC) was calculated as the  
153 mean of the four measurements. Epithelial integrity was assessed by measuring the lengths of  
154 intact epithelial denuded epithelium. These were expressed as percentage of all the RBM  
155 length present in the section. For inflammatory cell counts, submucosal nucleated stained  
156 inflammatory cells (eosinophils, mast cells and neutrophils) were counted on the  
157 corresponding stained sections and expressed at cells/mm<sup>2</sup> of lamina propria.

158

### 159 **Computed Tomography**

160 Volumetric whole lung scans were obtained using a Siemens Sensation 16 scanner (16 x 0.75  
161 mm collimation, 1.5 mm pitch, 120 kVp, 40 mAs, 0.5 seconds rotation time and scanning  
162 field of view of 500 mm). The scans were obtained at full inspiration (near total lung  
163 capacity) and at the end of expiration (near functional residual capacity). All subjects were  
164 coached in the breath holding techniques, and practised breath holding, immediately prior to  
165 scanning. All subjects were scanned within 60 minutes of receiving 400 micrograms of  
166 salbutamol via a spacer. Images were reconstructed with a slice thickness of 0.75 mm at a 0.5  
167 mm interval using B35f kernel. Post processing was performed on semi-automated software,  
168 Apollo (VIDA Diagnostics, Iowa).

169

170 QCT parameters obtained included; morphometry, measured in mm<sup>2</sup>, Lumen Area (LA),  
171 Total Area (TA), Wall Area (WA) ( $TA - LA$ ) and percentage Wall Area (%WA)  
172  $\left(100 \times \left(\frac{TA-LA}{TA}\right)\right)$ . Air-trapping measures were Mean Lung Density Expiratory to Inspiratory

173 ratio ( $MLD_{E/I}$ ) measured in Hounsfield Units (HU). Density at 15<sup>th</sup> percentile point (Perc15)  
174 was measured in HU. All morphometry measures were corrected for Body Surface Area

175  $mm^2/m^2$  (BSA)  $\left( \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}} \right)$ .

176

### 177 **Supplementary results**

178 We observed a significant negative correlation between the change in expiratory CT lung  
179 volume and the change in post-bronchodilator FEV<sub>1</sub>, taking the fevipiprant and placebo  
180 groups together ( $R = -0.317$ ,  $p = 0.041$ ), and this correlation was more pronounced with CT-  
181 derived lower lobe lung volume ( $R = -0.523$ ,  $p = 0.0004$ ) (Figure S2). Positive correlations  
182 were also observed between changes in expiratory CT lung volume and changes in both  
183 residual volume (RV) and the ratio of RV to total lung capacity (TLC) measured using body  
184 plethysmography, but these correlations only reached statistical significance with CT-derived  
185 lower lobe lung volumes ( $R = 0.374$ ,  $p = 0.014$  for RV;  $R = 0.361$ ,  $p = 0.017$  for RV/TLC).

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**Table S1 (part a). Outcome Measures at Baseline and Post-Treatment in the Full Analysis Set Population**

Outcome	Baseline values		Post-treatment values		Change from baseline to post-treatment			
	Fevipirant	Placebo	Fevipirant	Placebo	Fevipirant (N = 27)	Placebo (N = 30)	Treatment difference (Fevipirant vs placebo)	P value
Eosinophil count in sputum (%) ‡	5.42 (287.65)	4.65 (391.44)	1.12 (0.65, 1.93)	3.88 (2.26, 6.67)	0.22 (0.13, 0.39)	0.78 (0.45, 1.33)	0.29 (0.14, 0.58)	0.0014
Eosinophil count in blood ( $\times 10^9/L$ ) ‡	0.29 (95.03)	0.28 (80.63)	0.29 (0.23, 0.36)	0.32 (0.25, 0.41)	1.01 (0.79, 1.28)	1.13 (0.89, 1.43)	0.89 (0.66, 1.20)	0.44
FENO <sub>50</sub> (ppb)	37.72 (4.75)	43.67 (6.97)	34.88 (3.97)	38.48 (4.32)	-5.82 (-13.79, 2.16)	-2.21 (-10.90, 6.48)	-3.60 (-13.93, 6.72)	0.49
ACQ-7 score	1.91 (0.15)	2.22 (0.16)	1.89 (0.18)	2.21 (0.18)	-0.18 (-0.54, 0.18)	0.14 (-0.22, 0.49)	-0.32 (-0.78, 0.14)	0.17
ACQ-7 score in subjects with baseline $\geq 1.5$ †	2.37 (0.11)	2.57 (0.15)	1.69 (0.22)	2.25 (0.23)	-0.37 (-0.82, 0.08)	0.20 (-0.28, 0.67)	-0.56 (-1.12, -0.01)	0.046
ACQ-6 score	1.71 (0.18)	2.11 (0.17)	1.66 (0.19)	2.11 (0.19)	-0.26 (-0.65, 0.13)	0.19 (-0.20, 0.59)	-0.45 (-0.96, 0.05)	0.077
AQLQ score Total	5.43 (0.20)	5.02 (0.18)	5.48 (0.17)	4.89 (0.17)	0.27 (-0.07, 0.61)	-0.33 (-0.66, 0.01)	0.59 (0.16, 1.03)	0.0080

<b>Table S1 (part b). Outcome Measures at Baseline and Post-Treatment in the Full Analysis Set Population</b>								
Outcome	Baseline values		Post-treatment values		Change from baseline to post-treatment			
	Fevipirant	Placebo	Fevipirant	Placebo	Fevipirant (N = 27)	Placebo (N = 30)	Treatment difference (Fevipirant vs placebo)	P value
AQLQ score Symptoms	5.22 (0.21)	4.73 (0.20)	5.25 (0.22)	4.62 (0.21)	0.28 (-0.15, 0.72)	-0.34 (-0.77, 0.09)	0.63 (0.07, 1.18)	0.028
AQLQ score Activities	5.58 (0.20)	5.28 (0.20)	5.70 (0.15)	5.16 (0.15)	0.28 (-0.03, 0.59)	-0.26 (-0.57, 0.05)	0.54 (0.14, 0.93)	0.0087
AQLQ score Emotions	5.48 (0.26)	4.90 (0.21)	5.50 (0.22)	4.65 (0.21)	0.33 (-0.10, 0.76)	-0.53 (-0.95, -0.11)	0.86 (0.31, 1.40)	0.0027
AQLQ score Environmental	5.62 (0.27)	5.28 (0.23)	5.74 (0.19)	5.19 (0.18)	0.30 (-0.08, 0.67)	-0.25 (-0.62, 0.12)	0.55 (0.07, 1.02)	0.025
Pre-bronchodilator FEV <sub>1</sub> (L)	2.27 (0.17)	2.27 (0.18)	2.35 (0.07)	2.28 (0.07)	0.08 (-0.06, 0.22)	0.004 (-0.14, 0.15)	0.07 (-0.10, 0.25)	0.41
Pre-bronchodilator FEV <sub>1</sub> /FVC (%)	63.67 (2.85)	64.23 (2.17)	65.49 (0.88)	63.61 (0.88)	1.54 (-0.22, 3.29)	-0.34 (-2.12, 1.43)	1.88 (-0.38, 4.14)	0.10
Post-bronchodilator FEV <sub>1</sub> (L)	2.49 (0.17)	2.71 (0.19)	2.66 (0.05)	2.50 (0.05)	0.06 (-0.05, 0.17)	-0.10 (-0.21, 0.01)	0.16 (0.03, 0.30)	0.021
Post-bronchodilator FEV <sub>1</sub> /FVC (%)	66.90 (2.82)	69.72 (2.14)	70.42 (1.02)	67.31 (1.03)	2.10 (0.05, 4.15)	-1.00 (-3.07, 1.06)	3.11 (0.46, 5.75)	0.023

<b>Table S1 (part c). Outcome Measures at Baseline and Post-Treatment in the Full Analysis Set Population</b>								
<b>Outcome</b>	<b>Baseline values</b>		<b>Post-treatment values</b>		<b>Change from baseline to post-treatment</b>			
	<b>Fevipirant</b>	<b>Placebo</b>	<b>Fevipirant</b>	<b>Placebo</b>	<b>Fevipirant (N = 27)</b>	<b>Placebo (N = 30)</b>	<b>Treatment difference (Fevipirant vs placebo)</b>	<b>P value</b>
RV (L)	2.78 (0.22)	2.87 (0.23)	2.66 (0.13)	2.79 (0.12)	-0.17 (-0.42, 0.09)	-0.03 (-0.29, 0.22)	-0.14 (-0.46, 0.19)	0.40
TLC (L)	6.49 (0.29)	6.41 (0.29)	6.40 (0.13)	6.37 (0.13)	-0.04 (-0.30, 0.21)	-0.08 (-0.33, 0.18)	0.04 (-0.29, 0.36)	0.83
RV/TLC (%)	42.28 (2.30)	44.29 (2.49)	40.70 (1.30)	43.08 (1.32)	-2.64 (-5.24, -0.04)	-0.260 (-2.92, 2.40)	-2.38 (-5.69, 0.93)	0.15
FRC (L)	3.90 (0.26)	3.73 (0.24)	3.58 (0.12)	3.88 (0.12)	-0.23 (-0.48, 0.01)	0.08 (-0.17, 0.32)	-0.31 (-0.62,-0.001)	0.049
KCO (% predicted)	108.93 (4.39)	104.87 (3.28)	106.47 (1.72)	109.01 (1.70)	-0.32 (-3.78, 3.14)	2.22 (-1.20, 5.63)	-2.54 (-6.90, 1.83)	0.25

FENO<sub>50</sub> denotes the fraction of exhaled nitric oxide in exhaled air at a flow rate of 50 ml/s, ACQ-7 seven-point Asthma Control Questionnaire score, ACQ-6 six-point Asthma Control Questionnaire score (not including spirometry contribution), AQLQ Asthma Quality of Life Questionnaire score, FEV<sub>1</sub> forced expiratory volume in one second, FVC forced vital capacity, RV residual volume, TLC total lung capacity, FRC functional residual capacity, and KCO carbon monoxide transfer coefficient.

Baseline and post-treatment values are mean (standard error), change from baseline to post-treatment is mean change (lower limit, upper limit of 95% confidence interval), and treatment difference is mean change in fevipirant group minus mean change in placebo group (lower limit, upper limit of 95% confidence interval), unless otherwise stated. Post-treatment and changes from baseline to post-treatment are covariate-adjusted (least square mean) values.

‡ Baseline values are geometric mean (% coefficient of variation), post-treatment values are geometric mean (lower limit, upper limit of 95% confidence interval), change from baseline to post-treatment is geometric mean fold-change (lower limit, upper limit of 95% confidence interval), and treatment difference is ratio of geometric mean fold-change in fevipirant group to geometric mean fold-change in placebo group (lower limit, upper limit of 95% confidence interval).

†N = 18 in fevipirant group and N = 22 in placebo group.

<b>Table S2 (part a). Bronchial biopsy outcome measures</b>								
<b>Outcome</b>	<b>Baseline values</b>		<b>Post-treatment values</b>		<b>Change from baseline to post-treatment</b>			
	<b>Fevipirant</b>	<b>Placebo</b>	<b>Fevipirant</b>	<b>Placebo</b>	<b>Fevipirant (N = 14)</b>	<b>Placebo (N = 12)</b>	<b>Treatment difference (Fevipirant vs placebo)</b>	<b>P value</b>
Eosinophils/mm <sup>2</sup> lamina propria*	13.9 (23.5)	9.1 (39.4)	6.7 (28.8)	15.8 (33.3)	0.6 (0.3, 1.0)	1.4 (0.7, 2.7)	0.4 (0.2, 1.0)	0.040
CD3+ cells/mm <sup>2</sup> lamina propria*	9.0 (37.7)	11.1 (31.2)	14.4 (29.8)	14.6 (31.0)	1.6 (0.7, 3.9)	1.3 (0.5, 3.3)	1.2 (0.3, 4.3)	0.75
Mast cells/mm <sup>2</sup> lamina propria*	5.5 (36.7)	8.9 (26.5)	4.7 (27.4)	11.9 (28.5)	0.9 (0.5, 1.5)	1.3 (0.8, 2.3)	0.6 (0.3, 1.4)	0.25
Neutrophils/mm <sup>2</sup> lamina propria*	1.3 (38.5)	3.1 (36.5)	1.3 (31.8)	3.5 (33.1)	1.0 (0.4, 2.4)	1.1 (0.4, 2.8)	0.9 (0.2, 3.2)	0.84
Eosinophils/mm <sup>2</sup> epithelium*	2.5 (45.9)	2.2 (42.8)	2.4 (50.5)	3.5 (67.3)	1.0 (0.4, 2.8)	1.5 (0.4, 5.4)	0.7 (0.2, 2.9)	0.59
CD3+ cells/mm <sup>2</sup> epithelium*	2.0 (38.8)	3.9 (53.8)	4.1 (47.0)	3.2 (56.8)	1.7 (0.5, 5.4)	0.8 (0.2, 3.2)	2.0 (0.3, 12.0)	0.42
Mast cells/mm <sup>2</sup> epithelium*	0.8 (21.2)	1.0 (22.7)	1.7 (32.8)	1.8 (39.2)	1.9 (1.0, 3.4)	1.8 (0.9, 3.6)	1.0 (0.4, 2.6)	0.93
Neutrophils/mm <sup>2</sup> epithelium*	0.7 (8.6)	2.1 (53.2)	0.8 (18.7)	0.8 (22.2)	1.1 (0.6, 2.3)	0.4 (0.2, 0.8)	3.1 (1.0, 9.1)	0.044

<b>Table S2 (part b). Bronchial biopsy outcome measures</b>								
Outcome	Baseline values		Post-treatment values		Change from baseline to post-treatment			
	Fevipirant	Placebo	Fevipirant	Placebo	Fevipirant (N = 14)	Placebo (N = 12)	Treatment difference (Fevipirant vs placebo)	P value
Mast cells/mm <sup>2</sup> airway smooth muscle*	3.4 (43.4)	4.3 (51.1)	2.9 (53.8)	4.8 (56.6)	0.7 (0.2, 1.9)	1.1 (0.4, 3.0)	0.6 (0.1, 2.6)	0.48
MUC5AC cells/mm intact epithelial length†	38.3 (6.7)	24.6 (7.9)	55.6 (7.6)	37.1 (7.9)	12.8 (-7.3, 32.9)	10.2 (-7.6, 27.9)	2.7 (-24.1, 29.5)	0.84
MUC5AC cells/mm <sup>2</sup> intact epithelial area†	738.2 (134.8)	461.6 (128.2)	836.6 (140.7)	666.6 (146.9)	37.0 (-349.0, 423.4)	192.9 (-148, 533.7)	-156 (-671, 359.3)	0.53
Percentage of intact epithelial area positive for MUC5AC†	5.4 (2.6)	4.7 (1.7)	10.6 (2.6)	4.5 (2.7)	4.7 (-1.1, 10.5)	-0.2 (-5.3, 4.9)	4.9 (-2.8, 12.6)	0.20
Goblet cells/mm intact epithelial length†	13.7 (4.2)	11.6 (3.3)	22.3 (4.2)	23.2 (4.8)	7.9 (-0.6, 16.5)	11.6 (3.6, 19.7)	-3.7 (-15.5, 8.0)	0.51
Goblet cells/mm <sup>2</sup> intact epithelial area†	287.8 (83.6)	209.7 (48.5)	366.9 (90.7)	457.0 (103.4)	58.9 (-147, 265.2)	247.4 (51.7, 443.0)	-188 (-473, 95.9)	0.18
Vessel score (mean Chalkley count)†	5.8 (0.3)	6.6 (0.5)	5.9 (0.4)	5.8 (0.4)	0.1 (-0.8, 1.0)	-0.8 (-1.8, 0.1)	0.9 (-0.4, 2.2)	0.17

<b>Table S2 (part c). Bronchial biopsy outcome measures</b>								
<b>Outcome</b>	<b>Baseline values</b>		<b>Post-treatment values</b>		<b>Change from baseline to post-treatment</b>			
	<b>Fevipirant</b>	<b>Placebo</b>	<b>Fevipirant</b>	<b>Placebo</b>	<b>Fevipirant (N = 14)</b>	<b>Placebo (N = 12)</b>	<b>Treatment difference (Fevipirant vs placebo)</b>	<b>P value</b>
Intact epithelium (% of total length)†	28.0 (6.5)	47.0 (7.9)	51.7 (6.9)	42.9 (7.1)	23.7 (6.4, 41.0)	-4.1 (-22.0, 13.8)	27.8 (2.9, 52.7)	0.030
Partially intact epithelium (% of total length)†	39.0 (4.3)	39.2 (6.4)	34.0 (4.8)	35.3 (5.0)	-5.0 (-19.6, 9.5)	-3.9 (-18.9, 11.2)	-1.2 (-22.1, 19.7)	0.91
Denuded epithelium (% of total length)†	33.0 (6.7)	13.8 (4.1)	14.3 (5.5)	21.7 (5.7)	-18.6 (-31.4, -5.9)	8.0 (-5.2, 21.2)	-26.6 (-44.9, -8.3)	0.0062
Epithelial thickness (µm)†	54.3 (4.5)	64.0 (5.8)	67.3 (4.3)	58.4 (4.9)	10.3 (-5.6, 26.2)	-5.1 (-21.9, 11.7)	15.4 (-7.7, 38.5)	0.18
RBM thickness (µm)†	14.9 (1.2)	10.4 (1.0)	11.3 (1.1)	13.4 (1.2)	-1.5 (-3.8, 0.7)	0.6 (-1.9, 3.0)	-2.1 (-5.4, 1.2)	0.20

\*Baseline and post-treatment values are geometric mean (% coefficient of variation), change from baseline to post-treatment is geometric mean fold-change (lower limit, upper limit of 95% confidence interval), and treatment difference is ratio of geometric mean fold-change in fevipirant group to geometric mean fold-change in placebo group (lower limit, upper limit of 95% confidence interval).

†Baseline and post-treatment values are mean (standard error), change from baseline to post-treatment is mean change (lower limit, upper limit of 95% confidence interval), and treatment difference is mean change in fevipirant group minus mean change in placebo group (lower limit, upper limit of 95% confidence interval).



**Table S3 (part a). Quantitative computed tomography and densitometry**

Outcome	Baseline values		Post-treatment values		Change from baseline to post-treatment			
	Fevipirant	Placebo	Fevipirant	Placebo	Fevipirant (N = 23)	Placebo (N = 26)	Treatment difference (Fevipirant vs placebo)	P value
RB1 wall area / BSA (mm <sup>2</sup> /m <sup>2</sup> )	19.74 (1.09)	19.59 (0.94)	20.89 (1.50)	18.37 (1.41)	1.15 (-0.89, 3.18)	-1.23 (-3.14, 0.68)	2.38 (-0.41, 5.17)	0.093
RB1 luminal area / BSA (mm <sup>2</sup> /m <sup>2</sup> )	12.54 (1.45)	11.11 (0.79)	14.22 (2.05)	11.02 (1.92)	1.68 (-1.55, 4.90)	-0.09 (-3.12, 2.93)	1.77 (-2.65, 6.19)	0.42
RB1 percentage wall area (%)	62.7 (1.3)	64.5 (0.8)	63.2 (1.1)	63.1 (1.1)	0.4 (-1.3, 2.2)	-1.4 (-3.0, 0.3)	1.8 (-0.6, 4.2)	0.14
Average wall area / BSA (mm <sup>2</sup> /m <sup>2</sup> )	17.3 (0.5)	17.7 (0.6)	17.6 (0.6)	17.8 (0.6)	0.3 (-0.5, 1.1)	0.1 (-0.7, 0.9)	0.2 (-0.9, 1.3)	0.75
Average lumen area / BSA (mm <sup>2</sup> /m <sup>2</sup> )	10.6 (0.5)	10.9 (0.6)	10.7 (0.6)	11.5 (0.6)	0.2 (-0.6, 1.0)	0.6 (-0.2, 1.3)	-0.4 (-1.5, 0.7)	0.45
Average percentage wall area (%)	63.2 (0.5)	62.8 (0.4)	62.9 (0.3)	62.3 (0.3)	-0.3 (-1.0, 0.4)	-0.5 (-1.1, 0.1)	0.2 (-0.7, 1.1)	0.67
Inspiratory MLD (HU)	-829.1 (7.7)	-837.2 (6.9)	-839.7 (5.4)	-846.5 (5.1)	-10.6 (-20.7, -0.6)	-9.3 (-18.7, 0.2)	-1.4 (-15.2, 12.4)	0.84
Expiratory MLD (HU)	-704.8 (15.0)	-719.1 (10.6)	-706.6 (12.7)	-732.7 (11.7)	-1.0 (-11.5, 9.6)	-13.0 (-22.8, -3.2)	12.0 (-2.4, 26.4)	0.099

**Table S3 (part b). Quantitative computed tomography and densitometry**

Outcome	Baseline values		Post-treatment values		Change from baseline to post-treatment			
	Fevipirant	Placebo	Fevipirant	Placebo	Fevipirant (N = 23)	Placebo (N = 26)	Treatment difference (Fevipirant vs placebo)	P value
MLD E/l	0.851 (0.016)	0.861 (0.013)	0.841 (0.014)	0.865 (0.013)	-0.010 (-0.026, 0.005)	0.003 (-0.012, 0.017)	-0.013 (-0.034, 0.008)	0.22
Inspiratory VI <-950 HU (cm <sup>3</sup> )	13.7 (1.4)	14.3 (1.2)	15.2 (1.2)	14.9 (1.2)	1.5 (0.0, 3.1)	0.7 (-0.8, 2.1)	0.8 (-1.2, 2.9)	0.42
Expiratory VI <-856 HU (cm <sup>3</sup> )	21.4 (3.7)	22.0 (2.8)	21.8 (3.4)	24.1 (3.1)	0.4 (-2.0, 2.8)	2.2 (-0.1, 4.4)	-1.8 (-5.1, 1.5)	0.27
CTLV expiratory (cm <sup>3</sup> )	3040 (199)	3209 (188)	3004 (225)	3420 (206)	-10 (-138, 118)	205 (86, 325)	-216 (-391, -40)	0.017
CTLV inspiratory (cm <sup>3</sup> )	5221 (252)	5588 (297)	5419 (266)	5809 (251)	198 (-58, 454)	222 (-19, 462)	-24 (-375, 328)	0.89
CT lung volume E/l	0.588 (0.026)	0.583 (0.030)	0.557 (0.026)	0.582 (0.024)	-0.030 (-0.066, 0.006)	-0.006 (-0.040, 0.027)	-0.024 (-0.073, 0.026)	0.34
P <sub>15</sub> (HU)	-939.7 (5.3)	-942.4 (4.0)	-946.5 (3.6)	-947.2 (3.4)	-6.9 (-13.2, -0.5)	-4.8 (-10.7, 1.2)	-2.1 (-10.8, 6.6)	0.63
Pi10 (mm <sup>2</sup> )	15.6 (0.4)	14.8 (0.2)	16.0 (0.4)	15.0 (0.4)	0.3 (-0.2, 0.9)	0.2 (-0.3, 0.8)	0.1 (-0.7, 0.9)	0.76
Po20 (%)	56.5 (0.3)	56.5 (0.4)	57.8 (0.7)	56.8 (0.7)	1.3 (0.0, 2.6)	0.4 (-0.9, 1.6)	0.9 (-0.9, 2.7)	0.32

MLD denotes mean lung density, HU Hounsfield unit, E/I expiratory/inspiratory, RB1 right upper lobe apical segmental bronchus, BSA body surface area, VI voxel index, CTLV computed tomography lung volume,  $P_{15}$  Hounsfield unit value below which 15% of voxel attenuation values fall,  $P_{i10}$  wall area of a theoretical airway with an internal perimeter of 10mm, and  $P_{o20}$  percentage wall area of a theoretical airway with an external perimeter of 20mm.

Baseline and post-treatment values are mean (standard error), change from baseline to post-treatment is mean change (lower limit, upper limit of 95% confidence interval), and treatment difference is mean change in fevipirant group minus mean change in placebo group (lower limit, upper limit of 95% confidence interval).

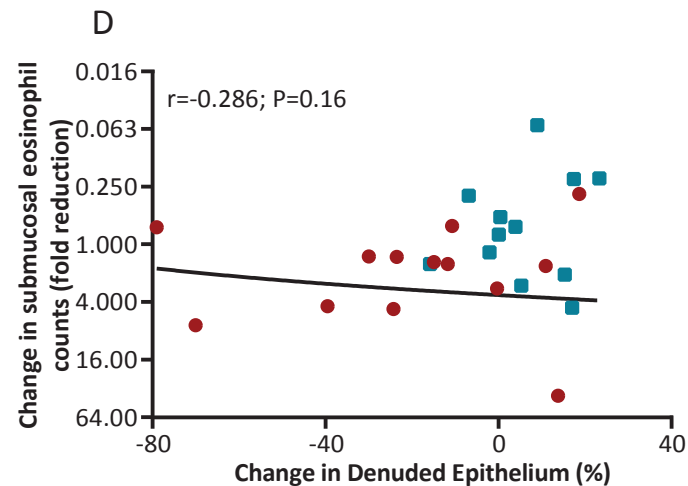
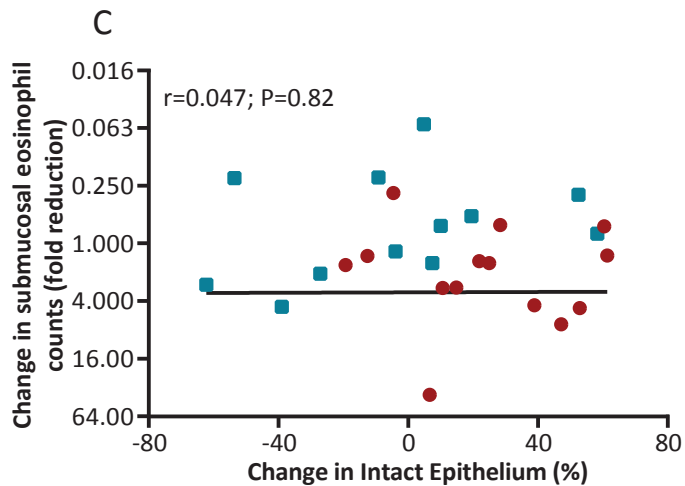
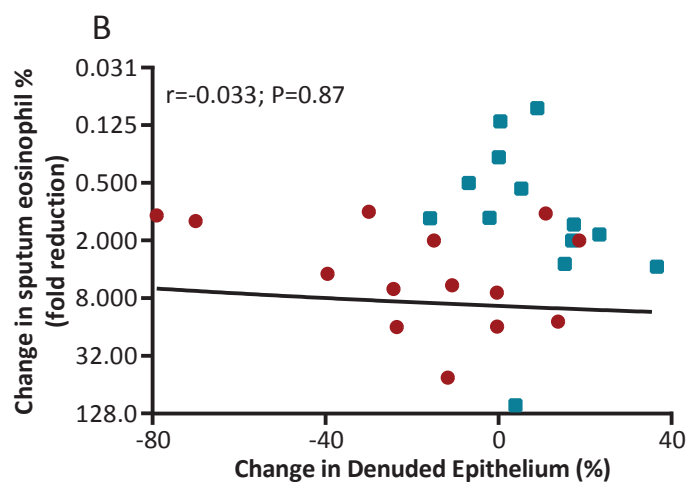
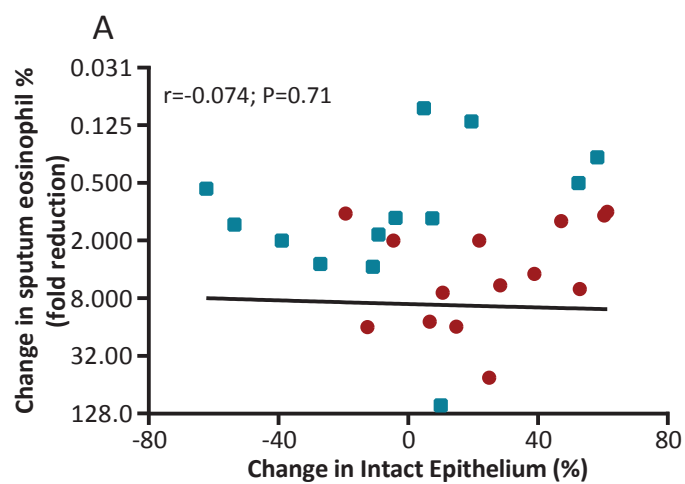
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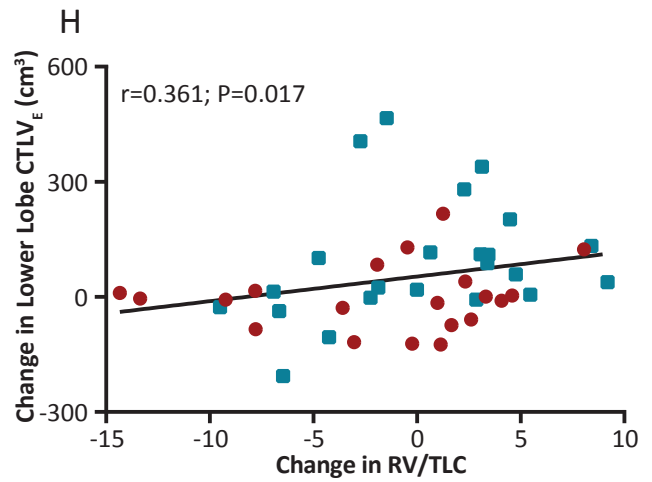
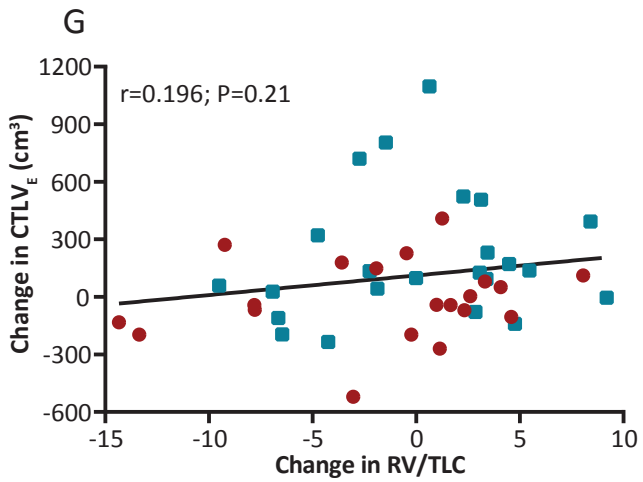
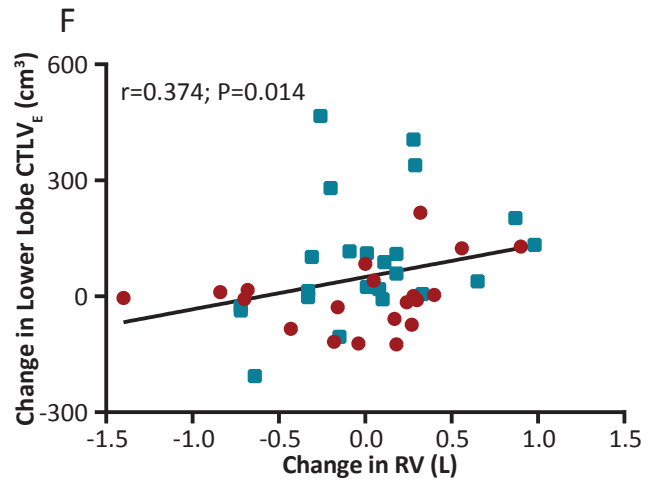
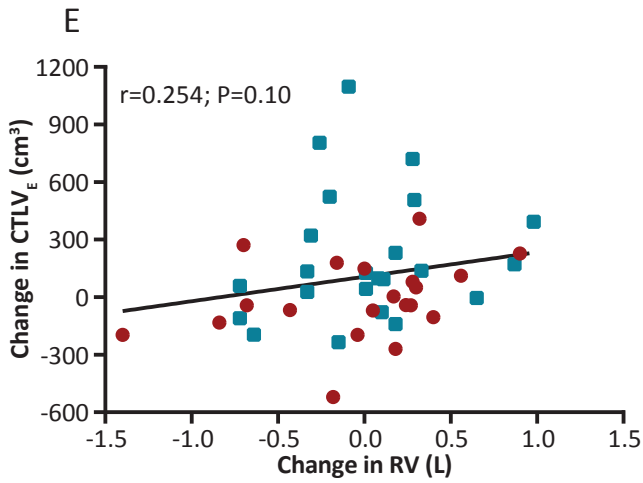
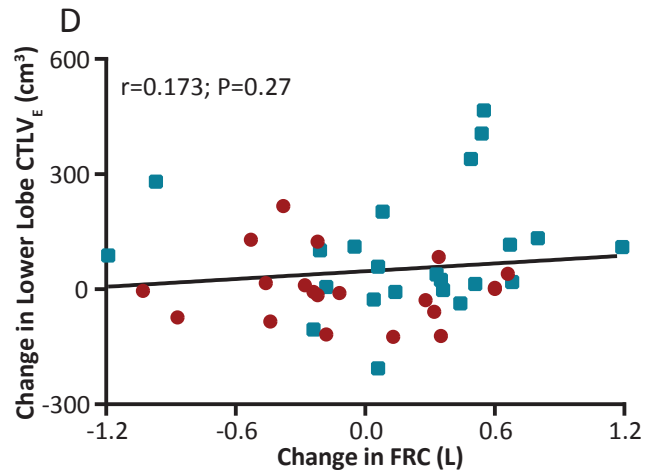
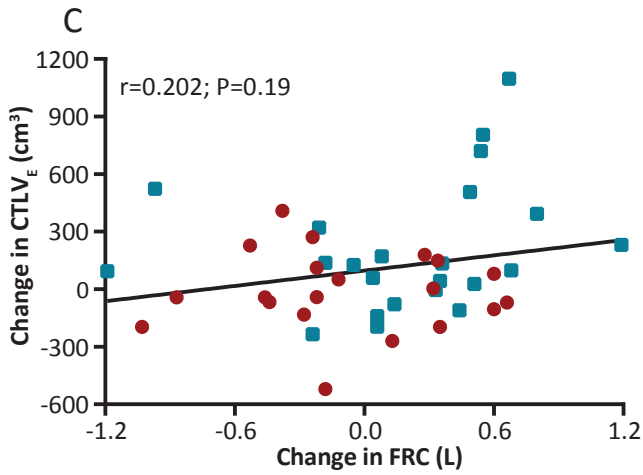
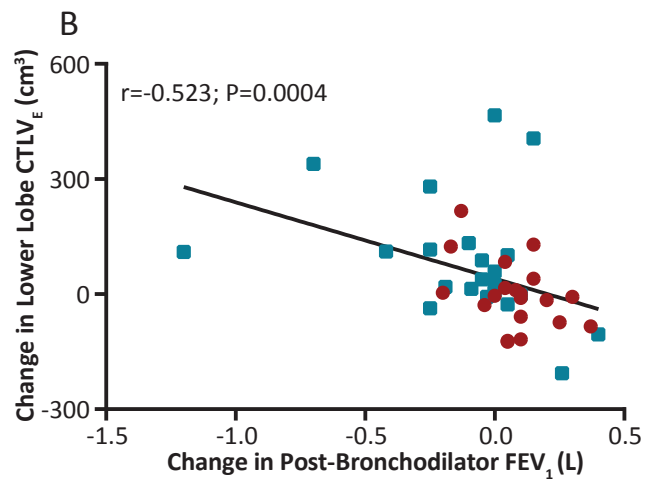
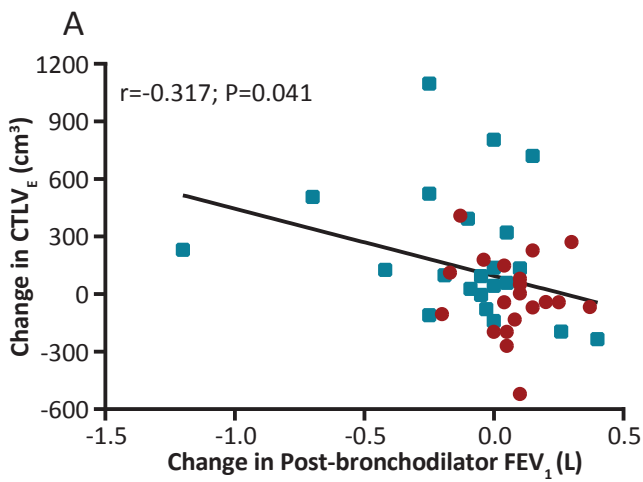
### **Figure S1: Correlations between changes in eosinophilic airway inflammation and changes in epithelial damage between the baseline and post-treatment visits**

Panels A and B show correlations between fold-change in sputum eosinophil count and change in intact or denuded epithelial percentage respectively. Panels C and D show correlations between fold-change in submucosal eosinophil count and change in intact or denuded epithelial percentage respectively. Participants in the placebo and fevipirant groups are represented by blue squares and orange circles respectively, and best-fit linear regression lines are shown for the combined group. Spearman correlation coefficients ( $r$ ) and associated P values are shown.

### **Figure S2: Correlations between changes in computed tomography-derived lung volumes and changes in lung function outcomes between the baseline and post-treatment visits**

Correlations are shown between changes in expiratory computed tomography-derived lung volumes ( $CTLV_E$ ) in the whole lung or specifically the lower lobes, and changes in post-bronchodilator forced expiratory volume in one second ( $FEV_1$ , Panels A and B), functional residual capacity (FRC, Panels C and D), residual volume (RV, Panels E and F), and the ratio of residual volume to total lung capacity (RV/TLC, Panels G and H). Participants in the placebo and fevipirant groups are represented by blue squares and orange circles respectively, and best-fit linear regression lines are shown for the combined group. Spearman correlation coefficients ( $r$ ) and associated P values are shown.





This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

Clinical Development

QAW039

CQAW039A2208

**A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma**

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## List of abbreviations

ACD	Asthma Control Diary
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AHR	Airways Hyperreactivity
ALT	alanine aminotransferase
AQLQs	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Curve
AUCtau	Area Under the Curve from time zero to the end of the dosing interval tau
BAL	Bronchoalveolar Lavage
b.i.d.	Twice a day
BMI	Body Mass Index
CD4	Cluster of Differentiation Antigen 4
CK	Creatinine Phosphokinase
CK-MB	MB isoform of Creatinine Phosphokinase
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper)
CRO	Contract Research Organization
CRTH2	Chemoattractant Receptor-Homologous molecule expressed on TH2
DDI	Drug-Drug Interaction
DP2	Alternative nomenclature for CRTH2 receptor
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
ERS	European Respiratory Society
FDA	Food and Drug Administration
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
eGFR	Estimated Glomerular Filtration Rate

GINA	Global Initiative for Asthma
Gd-DTPA	Gadolinium-diethylenetriaminepentaacetic acid
He-3 MRI	Hyperpolarized Helium Magnetic Resonance Imaging
hCG	Human Chorionic Gonadotropin
HGC	Hard Gelatin Capsules
HRCT	High Resolution Computed Tomography
IC50	Inhibitory Concentration 50% (half maximal)
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IOM	Impulse Oscillometry
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
IV	Intravenous
LABA	Long Acting $\beta$ 2 Agonist
MBW	Multiple Breath Washout
MDRD	Modification of Diet in Renal Disease
MDI	Metered Dose Inhaler
MID	Minimally Important Difference
NOAEL	No-Observable Adverse Event Level
OATP1B1	Organic Anion Transporter Protein family member 1B1
PEFR	Peak Expiratory Flow Rate
PG	Prostaglandin
PGD2	Prostaglandin D2
PGt	Pharmacogenetic
PGx	Pharmacogenomic
PK	Pharmacokinetic
p.o.	Taken by mouth
MBW	Multiple Breath Washout
q.d.	Quaque die/once a day

RAST	Radioallergosorbent test
SABA	Short Acting $\beta$ 2 Agonist
SAE	Serious Adverse Event
ULN	Upper Limit of Normal
WOCBP	Women of Child Bearing Potential

## Glossary of Terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	The investigational drug whose properties are being tested in the study as well as their associated placebo and active treatment controls. This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination.
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug/treatment	Any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints



## Protocol synopsis

**Title of study:** A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma

**Purpose and rationale:** The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

**Objectives:** The primary objective of this study is to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

The secondary objectives include:

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.
- To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

**Population:** The study population will include male and female symptomatic patients with sputum eosinophilia and moderate-to-severe asthma (GINA 2-5) who are incompletely controlled on their current therapy. They will be chosen to investigate the efficacy of QAW039 as an add-on to their current therapy. Patients aged over 18 years will be selected for the trial. A total of 60 patients (30 per treatment arm) will be randomized from a single center in the UK.

### Inclusion/Exclusion criteria:

Inclusion criteria:

- Written informed consent must be obtained before any assessment is performed.
- Males and females of any race who are over the age of 18 years at the time informed consent is obtained.
- Physician diagnosis of asthma, as per GINA guidelines GINA guidelines and currently prescribed ICS or ICS-LABA therapy.
- Patients who are demonstrated to have reversible airway obstruction, significant FEV1 variability or airway hyperresponsiveness (AHR), or who have shown such responses in previous test(s) within the last five years.

- An ACQ score  $\geq 1.5$  at randomisation or  $\geq 1$  exacerbations (requiring higher than the patient's normal dose of OCS or IV corticosteroids for  $\geq 3$  days) in the past 12 months. The definition of exacerbations includes episodes during which the patient self-administered higher doses of OCS as part of a documented self-management plan initiated by the patient's general practitioner or respiratory physician.
- Patients currently on GINA step 2 to step 5 asthma therapies.
- Sputum eosinophil count  $\geq 2\%$  at screening.

Exclusion criteria:

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (CRTH2 antagonists).
- History of long QT syndrome or whose QTc interval (Fridericia's) is prolonged  $> 450$  msec for males and  $>470$  msec for females at screening or baseline.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test ( $> 5$  mIU/mL).
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study treatment and for 5 days (5 half-lives) after treatment.
- Acute illness other than asthma which, in the investigator's opinion, may compromise the well-being of the patient or study endpoint assessments at the start of the study
- Patients who are considered unsuitable for inclusion by the assessing physician due to serious co-morbidities such as cancer, emphysema or significant bronchiectasis.
- Recent (within 6 weeks of screening) or current lower respiratory tract infection.
- Patients who have been hospitalized or required high-dose ( $>10$ mg prednisolone/day) oral corticosteroid (OCS) therapy within 6 weeks of the screening visit.
- Patients with clinically significant laboratory abnormalities (not associated with the study indication) at screening.
- Patients who have a clinically significant abnormality on a 12-lead ECG recorded within one month prior to or at screening.
- Patients with a body mass index (BMI)  $< 17$  or  $> 40$  kg/m<sup>2</sup>.

- Patients on maintenance immunotherapy who either began their immunotherapy regimen or had a clinically relevant change to their immunotherapy within 1 month prior to granting informed consent.
- Use of immunosuppressive medication (except inhaled and topical corticosteroids and low dose ( $\leq 10$ mg prednisolone/day) oral corticosteroids) within 30 days before randomization into the study.
- Use of Xolair (omalizumab) within 6 months before randomization into the study.
- History of alcohol or other substance abuse.
- A positive hepatitis B surface antigen or hepatitis C virus antibody, as determined by medical history and/or subject's verbal report.
- A positive human immunodeficiency virus test or is taking anti-retroviral medications, as determined by medical history and/or subject's verbal report.
- Patients on high-dose statin therapy.
- Patients on statin therapy with a CK level  $>2$  X ULN at screening.

Additional exclusion criteria for patients who have agreed to take part in the in the MR Imaging part of the study

- Patients with a contra-indication to MRI scanning: i.e. patients who are non MRI compatible (ferro-magnetic metallic implants, pacemakers) as per the MRI questionnaire.
- Patients with potential adverse reactions to Gd-DTPA intravascular MRI contrast agent.

**Investigational and reference therapy:** QAW039 (and matching placebo) will be provided as hard gelatin capsules in blister packs of 2 dose strengths (25mg and 150mg) to deliver 225 mg b.i.d..

**Study design:** This study uses a 2-treatment arm (Placebo or QAW039), parallel-group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients will undergo a 2-week placebo run-in period during which their clinical stability and suitability for randomisation will be assessed. Asthma patients who are already receiving ICS or ICS-LABA therapy are the target population for this study. All patients will be allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients will receive placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study will be single-blind because physicians will know that patients are on placebo, however the 12-week treatment period will be double-blind.

Visits to assess safety and efficacy are scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives will be performed at the end of the treatment period (week 12).

**Efficacy assessments:**

- Sputum cell analysis
- Spirometry
- Impulse oscillometry
- High resolution computed tomography
- Multiple breath washout
- Hyperpolarized Helium-3 MRI imaging
- Bronchial biopsies and brushings
- Asthma Control Questionnaire
- Asthma Quality of Life Questionnaire - standardized
- Volatile organic compounds
- Fraction of Exhaled Nitric Oxide

**Other assessments:**

- Adverse events, laboratory values, vital signs and ECG
- Pharmacokinetics
- Biomarkers in blood and sputum

**Data analysis:** The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

The primary variable of the study is the change from baseline in sputum eosinophil percentage at week 12. As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log<sub>10</sub>-transformed scale. The baseline measurement is defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing (on log<sub>10</sub>-transformed scale)

## 1 Introduction

### 1.1 Background

Many patients with asthma fail to achieve adequate control of symptoms and exacerbations when treated with inhaled corticosteroids (ICS) or combinations of ICS and long-acting beta-agonists (LABA). Failure to respond to topical therapy may be due to multiple factors, including poor adherence, inadequate inhaler technique or corticosteroid resistance. Furthermore, there is evidence that some patients with asthma have prominent small airway disease that cannot be reached by standard inhalers. Such patients may require systemic (oral) therapy to control their airway inflammation. Current treatment options include the addition of a leukotriene modifier such as montelukast, but not all patients respond to this, and a significant proportion require step-up to long-term oral corticosteroids to achieve control, an unattractive option given the well-known side-effects of osteoporosis, muscle wasting and bruising. There is thus a need for effective oral anti-inflammatory therapies for asthma with greater efficacy than montelukast.

QAW039 is a highly selective and potent antagonist of prostaglandin D2 (PGD2) that binds to the CRTH2 (DP2) receptor, but not to the more general homeostatic PGD2 receptor, DP1. QAW039 is expected to work by binding CRTH2 receptors on eosinophils and CRTH2+ T lymphocytes in the blood, thus inhibiting the migration of eosinophils and CRTH2+ CD4+ lymphocytes into the airway tissues. Since these are major effector cells that drive the airway inflammation in asthma, the symptoms of the disease should be improved.

The study has been focussed on sputum eosinophilia, as a primary endpoint, for a number of reasons. Firstly, the reduction of sputum eosinophilia will be further confirmation of the mechanism of action of this target in man and will provide comparative data against earlier studies with competitor compounds ([Singh et al, 2009](#); [Barnes et al, 2011](#)). Secondly, the control of sputum eosinophilia has been shown to be an important measure in predicting the efficacy of anti-inflammatory treatments in asthma. Adults who had treatment adjusted to sputum eosinophils had a significantly reduced number of exacerbations compared with controls who did not. The comparative risk for exacerbations of standard care versus tailored care was 726 per 1000 versus 488 per 1000 (OR 0.36 [90% CI: 0.2 to 0.64]) ([Petsky et al, 2010](#); [Petsky et al 2007](#); [Chlumsky et al, 2006](#); [Jayaram et al, 2006](#); [Green et al, 2002](#)). Finally, therapeutic reduction of sputum eosinophilia has been shown to significantly decrease hospitalisations due to asthma exacerbation and to have beneficial impact on the geometry of the respiratory tract ([Haldar et al, 2009](#)).

Further information regarding QAW039 can be obtained from the Investigators' Brochure.

### 1.2 Purpose

The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to

establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

## 2 Study objectives

### 2.1 Primary objective

The primary objective of this study is to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

### 2.2 Secondary objectives

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.
- To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

### 2.3 Exploratory objectives

- To demonstrate that QAW039 provides significant improvement in standard physiological markers such as FEV<sub>1</sub>, as well as specific small airway markers measured with multiple breath washout (MBW) and impulse oscillometry, namely S<sub>acin</sub>, R5-R20 and AX, compared to placebo.
- To explore whether the efficacious effect of QAW039 therapy persists following the cessation of therapy.
- To explore whether quantitative computed tomography (CT) biomarkers at baseline predict response to therapy with QAW039.
- To explore changes in air trapping, as evaluated by quantitative computed tomography (CT), after 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in health-related quality of life as measured by the standardised Asthma Quality of Life Questionnaire (AQLQs) after 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in blood proteomic and transcriptomic profile following 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in exhaled volatile organic compounds (VOCs) following 12 weeks of treatment with QAW039 versus placebo.
- To explore the effect of QAW039 on ventilation heterogeneity, as measured by hyperpolarised helium-3 MRI (He-3 MRI), compared to placebo.
- To explore whether QAW039 attenuates eosinophilic airway inflammation as measured by bronchial brushings and bronchial biopsies, compared to placebo.
- To explore whether QAW039 attenuates features of remodelling in bronchial biopsies (including but not limited to the assessment of histological features of inflammatory and

goblet cell number, reticular basement membrane thickness and assessment of collagen deposition) compared to placebo.

- To assess the pharmacokinetics of QAW039 in this population of asthma patients.

### 3 Investigational plan

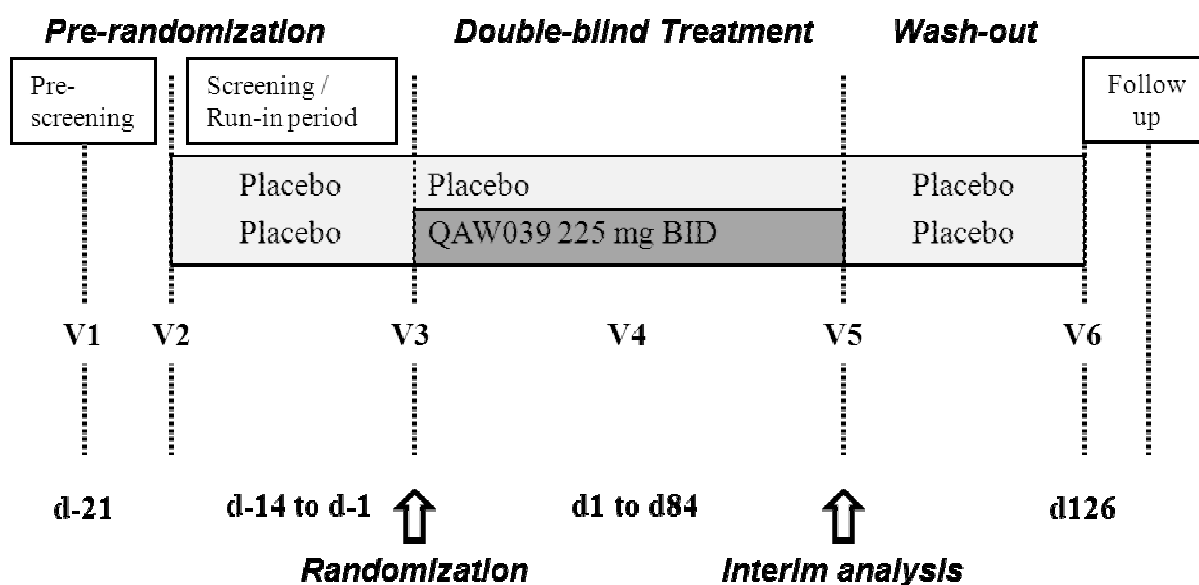
#### 3.1 Study design

This study uses a 2-treatment arm (Placebo or QAW039), parallel-group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients will undergo a 2-week placebo run-in period during which their clinical stability and suitability for randomisation will be assessed. Asthma patients who are already receiving ICS or ICS-LABA therapy are the target population for this study. All patients will be allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients will receive placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study will be single-blind because physicians will know that patients are on placebo, however the 12-week treatment period will be double-blind.

Visits to assess safety and efficacy are scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives will be performed at the end of the treatment period (week 12). An interim analysis will occur at Visit 5 in order to consider the need for possible re-sizing of the study and to allow early delivery of efficacy data to facilitate forward planning of the program.

**Figure 3-1 CQAW039A2208 study design**



### 3.2 Rationale of study design

The study is designed to explore the anti-inflammatory and disease-modifying potential of QAW039 in asthmatics in vivo. It will examine the effect of QAW039 on top of conventional background therapy in a group of persistent, uncontrolled, moderate-to-severe asthmatics with sputum eosinophilia. In order to preserve trial integrity, this will be a parallel design study in which treatment is allocated in a randomized, double-blind and placebo-controlled manner. Placebo will be used in both active and placebo treatment groups during the run-in period in order to minimize the impact of “placebo-effect” on baseline fluctuations in patient reported outcomes prior to randomization. All patients will be allocated to placebo at visit 5 so that the knowledge that treatment has been withdrawn does not influence their assessment of their disease status.

The rationale for studying this group of patients is supported by the findings from an interim analysis of our on-going study, CQAW039A2201, in mild-to-moderate asthmatics. In this analysis, we found that patients who either have the most pronounced baseline reduction in predicted FEV<sub>1</sub> (<70%) and/or those who have pre-treatment, circulating eosinophilia (>300 eosinophils per  $\mu$ L blood) appeared to benefit to the greatest extent from 4 weeks treatment with the CRTH2 antagonist, QAW039, either in terms of change in ACQ score or % change in pre-bronchodilator FEV<sub>1</sub> or both.

By enriching further still for these two characteristics – sputum eosinophilia and circulating eosinophilia both correlate with disease severity and aspect of lung function in asthma ([Snell & Newbold, 2008](#)) – and allowing further time for the therapeutic response to develop ([section 3.3](#) below), we believe we will enhance the chance of measuring an enhanced therapeutic response and the possibility of observing fundamental changes in the underlying structure/function relationship in the asthmatic lung.

### 3.3 Rationale of dose/regimen, duration of treatment

Data from a one month study with a CRTH2 antagonist showed a continuous increase in FEV<sub>1</sub> over 4 weeks ([Barnes et al, 2011](#)). This observation is consistent with the mechanism of action, since CRTH2 antagonists, such as QAW039, should block inflammatory cells from entering the lung. The duration of 12 weeks was chosen because it is not clear when maximal efficacy will be observed from this type of treatment and this is the longest time covered by current toxicology studies for QAW039. Furthermore, as observations are being made with regards to changes in lung histology and geometry, we wished to give the maximal time to allow the best signal of efficacy to develop.

In CQAW039A2201, patients were dosed once daily for 4 weeks with 500 mg. At interim analysis when the first 63 patients had completed the study, no SAEs or deaths had occurred and the AEs observed did not significantly differ in their nature or severity between the active- and placebo-treated cohorts of patients.

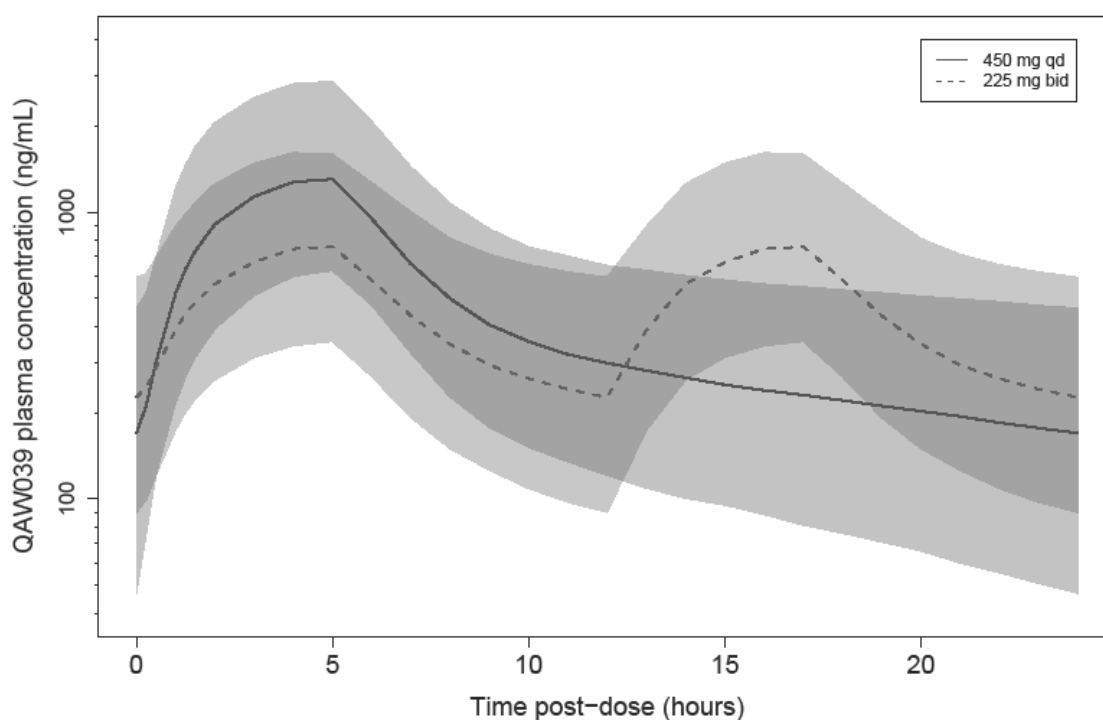
A twice daily dose of 225 mg (totaling 450 mg per day) will be included in this study and will be dummied with matching placebo in order to prevent bias. Using a population based PK model constructed using data from earlier studies (CQAW039A2101 and CQAW039A2102) the anticipated plasma AUC<sub>tau</sub> of 11.6  $\mu$ g.h/mL [90% CI: 5.39-24.5] overlaps considerably



with the AUCtau modeled from a 500 mg daily dose (AUCtau 12.9  $\mu\text{g}\cdot\text{h}/\text{mL}$  [90% CI: 6.00 – 27.1]).

At steady state, the fluctuation index determined following 7 days of dosing in CQAW039A2102 was 315 % and 349 % following 100 mg q.d. and 300 mg q.d. dosing, is reduced to 135 % following 250 mg b.i.d. dosing reflecting the large peak to trough ratio following a q.d. regimen. The 450 mg will therefore be given in 2 equal doses (225 mg b.i.d., total of 8 capsules per day) to minimize the peak to trough ratio observed following q.d. dosing. In this way, we will maintain a higher minimum drug concentration compared to a once-daily regimen. The simulated concentration time profiles following 450 mg q.d. and 225 mg b.i.d. are illustrated below.

**Figure 3-2 Illustration of simulated repeat dose blood concentration time profiles at steady-state along with the blood  $\text{IC}_{90}$  ranges\***



\*Dashed and solid lines represent the median model derived concentration time profiles (i.e. for the typical individual) and the shaded areas around represents the 5<sup>th</sup> and 95<sup>th</sup> quartiles of the simulated profile (i.e. they predict where we would expect 90% of the PK profiles to be in). Overlapping areas are represented by darker shades

### 3.4 Rationale for choice of comparator

Placebo will be used to preserve trial integrity.

As both placebo and QAW039 will be given in addition to the patients' conventional (pre-study) treatment there is no appropriate positive control that can be used in this situation given the range of disease severities to be included.

### 3.5 Purpose and timing of interim analyses/design adaptations

There will be an interim analysis of the data collected at Visit 5, once all patients have gone through this milestone.

The purpose of this interim analysis is to consider the need for possible re-sizing of the study and to allow early delivery of efficacy data to facilitate forward planning of the program.

### 3.6 Risks and benefits

The most significant preclinical findings have been an increase in heart rate in dogs and liver findings in mice (see exposure margins in investigator brochure). Neither of these events has been observed in other species. Both of these findings are readily monitored and have not been identified in the three healthy volunteer studies so far completed. Indeed, every indication from these studies suggests that QAW039 is safe and well tolerated. Our interim analysis of the first 63 mild-to-moderate, persistent asthmatic patients in the CQAW039A2201 study also showed no fatalities or serious adverse events and demonstrated no significant differences in the frequencies of adverse events between placebo and actively treated subjects.

A potential risk we have identified of relevance to this study, given the likely frequency of statin co-medication in this group of patients (estimated to be around 25%), is the interaction of QAW039 with the drug transporter molecule, OATP1B1. QAW039 is capable of inhibiting the OATP drug transporters (OATP1B1: IC<sub>50</sub> 1.8 µM, OATP1B3: IC<sub>50</sub> 14 µM and OATP2B1: IC<sub>50</sub> 145 µM, respectively). Of the three, it is the interaction with OATP1B1 which is of the highest potential importance because it has the lowest margin between the IC<sub>50</sub> of transporter inhibition and the maximum unbound exposure. The predicted maximal unbound concentration at steady-state following 450 mg q.d. dosing is 0.363 µM (90 %CI 0.174, 0.786) based on a population based pharmacokinetic model using data from CQAW0392201, and a protein binding of 88.2 % (DMPK R0800735). The maximal unbound steady state concentration relative to the IC<sub>50</sub> of OATP1B1 of 1.8 µM ranges from 2 to 10 fold, with a median of 5 fold. This exceeds the 10-fold recommended margin which suggests the need for a DDI study ([The International transporter Consortium, 2010](#)). The potential risk will be mitigated by moving to a 225 mg b.i.d. dosing regimen when the margin to the IC<sub>50</sub> will increase in the range from 4 to 20 fold (median of 10 fold) where the need for a DDI study becomes a borderline requirement.

As an additional precaution, only patients on low-to-medium statin doses (see [section 5.1.2](#)) will be allowed to take part in this study. Furthermore, exclusion of patients on statins with high baseline CK levels will take place and patients on statin medication who are included in the study will have regular monitoring for relevant symptoms and be subject to stopping criteria based on persistent myalgia and blood CK levels ([Jacobson, 2008](#)).

Investigative bronchoscopy is considered to be safe in asthmatic subjects ([Hattotuwa et al, 2002](#)) It is well tolerated even in those with severe asthma. Asthma exacerbations are rare and reduction in pulmonary function after the procedure is similar to that in subjects with less severe asthma ([Moore et al, 2011](#)). Professor Brightling's group has undertaken in excess of 300 research bronchoscopies at the Glenfield Hospital in Leicester in the last 8 years. Sore throat, small amounts of hemoptysis for 24-48h is commonly observed. One of his patients

was admitted over night following bronchoalveolar lavage (BAL) for observation but no treatment was required. BAL will not be performed in CQAW039A2208. None of his subjects have had a pneumothorax and they have had no deaths. The use of sedation and local anesthetics will be closely controlled and patients will be pre-medicated with bronchodilator and will be continuously monitored throughout the procedure. The procedure is therefore considered low risk.

The HRCT scan will expose the patients to a higher dose of radiation than they would normally be exposed to, and this may cause a very small increase in the risk of developing cancer. Careful radiation logs will be maintained to allow for margins to the 5 mSv over 3 years exposure limits. Although both inspiratory and expiratory scans are planned, the actual numbers of scans performed (with expiratory scans taking priority) will be determined in order to maintain an acceptable margin.

Low radiation dose HRCT scans will be performed for the purpose of this study. Each HRCT scan will be equivalent to approximately eight months' natural radiation exposure in the UK. We will closely monitor the radiation dose due to HRCT scans during the course of the study and the upper limit of radiation exposure will be equivalent to two years' natural radiation exposure in the UK.

The natural risk of fatal cancer in the UK population is about 1 in 4. We estimate that the amount of additional radiation exposure in this study will increase this risk slightly to 1 in 3.994 ([Health Protection Agency, 2011](#)).

Given that there is (a) preliminary data for QAW039 and published evidence from a competitor compound suggesting that CRTh2 antagonism is efficacious in asthmatic subjects ([Barnes et al, 2011](#)), (b) that patients with pre-existing heart and/or liver disease will be excluded (c) that cardiac and hepatic function will be monitored and (d) that the potential risk of statin co-administration is being managed by both CK-based exclusion criteria, lowering the QAW039 Cmax levels through b.i.d. dosing, and restrictions on the statin medication dose levels in recruited patients and relevant stopping criteria, Novartis consider both that the risks to these patients are modest and the benefit-risk ratio for the patients participating in this study is acceptable.

## 4 Population

The study population will include male and female symptomatic patients with sputum eosinophilia and moderate-to-severe asthma (GINA 2-5) who are incompletely controlled on their current therapy. They will be chosen to investigate the efficacy of QAW039 as an add-on to their current therapy. Patients aged over 18 years will be selected for the trial. A total of 60 patients (30 per treatment arm) will be randomized from a single center in the UK.

### 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Males and females of any race who are over the age of 18 years at the time informed consent is obtained.

3. Physician diagnosis of asthma, as per GINA guidelines and currently prescribed ICS or ICS-LABA therapy.
4. Patients who are demonstrated to have reversible airway obstruction, significant airflow variability or airway hyperresponsiveness (AHR), or who have shown such responses in previous test(s) within the last five years.
  - Reversible airway obstruction is defined as an increase of  $\geq 12\%$  and  $\geq 200$  ml in FEV<sub>1</sub> over the patient's pre-bronchodilator value in liters within 10-15 minutes after inhaling a total of 360  $\mu\text{g}$  of albuterol or 400  $\mu\text{g}$  salbutamol via MDI (reversibility test). The administration of albuterol or salbutamol for the reversibility test is to be within 30 minutes after pre-bronchodilator spirometry.
  - A positive airways hyper-reactivity (AHR) test result is defined as a provoked fall in FEV<sub>1</sub> of 20% (PC20) by methacholine at  $\leq 8$  mg/ml when not on ICS or  $\leq 16$ mg/ml on ICS therapy.
  - A change in FEV<sub>1</sub> of  $> 12\%$  over two measurements over the previous year ([Huang et al, 2011](#)).
5. An ACQ score  $\geq 1.5$  at randomisation or  $\geq 1$  exacerbations (requiring higher dose than the patient's normal dose of OCS or IV corticosteroids for  $\geq 3$  days) in the past 12 months. The definition of exacerbations includes episodes during which the patient self-administered higher doses of OCS as part of a documented self-management plan initiated by the patient's general practitioner or respiratory physician.
6. Patients currently on GINA step 2 to step 5 asthma therapies.
7. Sputum eosinophil count  $\geq 2\%$  at screening.

## 4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives to the time of enrollment, whichever is longer.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (CRTH2 antagonists).
3. History of long QT syndrome or whose QTc interval (Fridericia's) is prolonged  $> 450$  msec for males and  $> 470$  msec for females at screening or baseline.
4. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test ( $> 5$  mIU/mL).
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during

dosing of study treatment and for 5 days (5 half-lives) after treatment. **Effective contraception methods include:**

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential

7. Acute illness other than asthma which, in the investigator's opinion, may compromise the well-being of the patient or study endpoint assessments at the start of the study.
8. Patients who are considered unsuitable for inclusion by the assessing physician due to serious co-morbidities such as cancer, emphysema or significant bronchiectasis.
9. Recent (within 6 weeks of screening) or current lower respiratory tract infection.
10. Patients who have been hospitalized or required high-dose (>10mg prednisolone/day) oral corticosteroid (OCS) therapy within 6 weeks of the screening visit.
11. Patients with clinically significant laboratory abnormalities (not associated with the study indication) at screening including (but not limited to):
  - Total white blood cell count <2500 cells/ $\mu$ L at screening.
  - AST or ALT >2.0 X ULN or total bilirubin >1.3 X ULN at screening
  - Estimated Glomerular Filtration Rate (eGFR) by the MDRD equation <55 mL/minute/1.73 m<sup>2</sup> at screening.
12. Patients who have a clinically significant abnormality on a 12-lead ECG recorded within one month prior to or at screening.
13. Patients with a body mass index (BMI) < 17 or > 40 kg/m<sup>2</sup>.

14. Patients on maintenance immunotherapy who either began their immunotherapy regimen or had a clinically relevant change to their immunotherapy within 1 month prior to granting informed consent.
15. Use of immunosuppressive medication (except inhaled and topical corticosteroids and low dose ( $\leq 10$ mg prednisolone/day) oral corticosteroids) within 30 days before randomization into the study.
16. Use of Xolair (omalizumab) within 6 months before randomization into the study.
17. History of alcohol or other substance abuse.
18. A positive hepatitis B surface antigen or hepatitis C virus antibody, as determined by medical history and/or subject's verbal report.
19. A positive human immunodeficiency virus test or is taking anti-retroviral medications, as determined by medical history and/or subject's verbal report.
20. Patients on high-dose statin therapy, defined as:  
  
Only patients on 40 mg or less of fluvastatin, 20 mg or less of simvastatin and atorvastatin or 20 mg or less of pravastatin or rosuvastatin (10 mg or less if Asian) will be recruited into the study. No increase in statin doses in excess of those listed above will be permitted during the study
21. Patients on statin therapy with a CK level  $>2$  X ULN at screening.

**Additional exclusion criteria for patients who have agreed to take part in the in the MR Imaging part of the study**

22. Patients with a contra-indication to MRI scanning: i.e. patients who are non MRI compatible (ferro-magnetic metallic implants, pacemakers) as per the MRI questionnaire.
23. Patients with potential adverse reactions to Gd-DTPA intravascular MRI contrast agent.

## **5 Treatment**

### **5.1 Protocol requested treatment**

#### **5.1.1 Investigational treatment**

- Name: QAW039
- Formulation: hard gelatin capsule
- Appearance: size - 0, color - pink opaque
- Unit dose: 2 strengths – 25 and 150 mg
- Packaging: Blister packs

QAW039 will be supplied in blister packs of two strengths: 25 mg (3 capsules to be taken morning and night) and 150 mg (1 capsule to be taken morning and night). The patients will therefore take 225 mg twice daily for the period of the study.

The placebo is of identical appearance and will be identically packaged.

### 5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

### 5.1.3 Treatment arms

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1.

- Arm 1: QAW039 225mg (1 capsule of QAW039 150 mg and 3 capsules of QAW039 25mg)
- Arm 2: Placebo (1 capsule of Placebo for QAW039 150mg and 3 capsules of Placebo for QAW039 25mg)

Patients will be stratified into two cohorts based on use/not use of Oral Corticosteroids.

### 5.1.4 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible patients in accordance with entry into the study. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Treatment Allocation Cards will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

### 5.1.5 Treatment blinding

This is a double-blind study in which medication will be supplied in a single blind fashion utilizing an un-blinded pharmacist. Patients and Investigator will remain blinded to the treatment allocation during double blind treatment period. During run-in and washout period only patients will remain blinded. The active drug (QAW039) will be supplied in blister packs of two strengths 25mg and 150mg. The Placebo capsules are of identical appearance and will be identically packed.

## 5.2 Treating the patient

### 5.2.1 Patient numbering

#### Randomization number

Patients will be assigned randomization numbers using Treatment Allocation Cards based on stratification into use/not use of oral corticosteroids. See [Table 5-1](#).

**Table 5-1 Treatment Assignment Numbering**

Cohort	Cohort description	Randomization numbers
Cohort 1	Use of Oral corticosteroids	5101 – 5130
Cohort 2	Not use of Oral corticosteroids	5131 – 5160

Patients who are prematurely withdrawn from the study will not be replaced.

## 5.2.2 Dispensing the study treatment

Study site will be supplied by Novartis with study drug organized in blinded medication kits. Study medication kits comprise cartons containing blisters of Hard Gelatin Capsules (HGCs) of QAW039 25mg, QAW039 150mg and Placebo to QAW039. Each patient will receive one kit at each dispensing visit. At Visits 2 and 5, all kits dispensed will contain placebo. **In order to maintain the blind from the patient's point of view, investigators should not divulge information regarding the fact that all individuals will be assigned to placebo during the run-in and wash-out phase of the study.**

Study medication kits dispensed to all subjects at Visit 2 will contain the following medication:

1. 1 folding carton containing 5 blisters of 7 HGCs of Placebo for QAW039 150mg (Blue label)
2. 1 folding carton containing 13 blisters of 7 HGCs of Placebo for QAW039 25mg (White label)

Study medication kits dispensed to subjects randomized to get Active treatment at Visit 3 and 4 will contain the following medication:

1. 3 folding cartons each containing 5 blisters of 7 HGCs of QAW039 150mg (Blue label)
2. 3 folding cartons each containing 13 blisters of 7 HGCs of QAW039 25mg (White label)

Study medication kits dispensed to subjects randomized to get Placebo treatment at Visit 3 and 4 will contain the following medication:

1. 3 folding cartons each containing 5 blisters of 7 HGCs of Placebo for QAW039 150mg (Blue label)
2. 3 folding cartons each containing 13 blisters of 7 HGCs of Placebo for QAW039 25mg (White label)

Study medication kits dispensed to all subjects at Visit 5 will contain the following medication:

1. 3 folding cartons each containing 5 blisters of 7 HGCs of Placebo for QAW039 150mg (Blue label)
2. 3 folding cartons each containing 13 blisters of 7 HGCs of Placebo for QAW039 25mg (White label)

All the carton and blister labels will be double-blinded. All the kits have a 2-part single-blinded label. Immediately before dispensing a kit, the un-blinded investigator staff (un-blinded pharmacist) will detach the tear-off part of the label from the packaging and affix it to the source document for that patient's unique patient number.

The un-blinded pharmacist will have to write patient # / randomization # and visit # on kit label, box labels as well as blister labels before dispensing the medication kit.

**Capsules should only be removed from the blister immediately before dosing.**

**All blister packs and outer kit cartons must be returned to the site** at each of the following Visits 3, 4, 5 and 6 (or the final visit for patients who withdraw from the study prematurely).



### **5.2.3 Supply, storage and tracking of study treatment**

Study treatment must be received by a designated person (un-blinded pharmacist) at the study site, handled and stored safely and properly, and kept in a secured location to which only the designated persons have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in English language and comply with the UK legal requirements. They will include storage conditions for the drug, but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by an unblinded monitor during site visits and at the completion of the trial. Patients will be asked to return all remaining unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or designee or to the Novartis address provided in the investigator folder at the site.

No study medication should be destroyed until completion of the final clinical study report and notification is received from the Clinical Trial Head.

### **5.2.4 Instructions for prescribing and taking study treatment**

QAW039 and matching placebo will be provided as oral capsules, equally matched in size, shape and color.

Medication labels will comply with the UK legal requirements and be printed in English language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

Patients will be instructed to come to the clinic in time to complete pre-dosing assessments and to allow QAW039/placebo study medication to be taken in the morning between 08:00 and 11:00 am. Patients must be instructed to withhold the use of short acting  $\beta$ 2-agonists (rescue medication) for at least 6 hours prior to all clinic visits, unless the use is absolutely necessary.

On non-visit days, patients will be instructed to take all four capsules in the morning between 08:00 and 11:00 from their QAW039/placebo medication kits.

On all days, patients should take their four evening capsules of QAW039/placebo approximately 12 hours after their AM dose +/- 30 minutes.

The investigator should instruct the patient to take the study drug exactly as prescribed and by stating that adherence is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

All used and unused blister kits must be returned by the patient at Visits 3, 4, 5 and 6 (or their final visit for patients who withdraw from the study prematurely).

The date and time of dose administration at each clinic visit (Visits 2-6) will be recorded on the Dosage Administration Record CRF.

### 5.2.5 Permitted dose adjustments and interruptions of study treatment

No adjustments to the study drug dosage or schedule is permitted throughout the trial.

### 5.2.6 Rescue medication

Patients should be instructed to abstain from taking rescue medication (e.g. such as salbutamol or albuterol) within 6 hours of the start of each visit unless absolutely necessary.

If rescue medication is taken within 6 hours prior to spirometry or prior to administering study medication at Visit 3 onward (if needed), the visit should be rescheduled to the next possible day. The investigator must use their judgment when deciding how many times a visit for an individual patient should be rescheduled.

In the event that a patient uses a dose of rescue medication after taking study medication at that visit or during any other visits then the visit should continue as planned but the number of puffs of rescue medication and the approximate time taken will be captured in the patient's CRF.

### 5.2.7 Background therapy

All patients should keep their background therapy doses unchanged during the course of the study. If their background medication needs to be altered, patients should be discontinued from the study. Patients may vary the dose of their rescue medication as necessary.

### 5.2.8 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts study must be listed on the Concomitant medications/Significant non-drug therapies of study CRF.

### 5.2.9 Prohibited treatment

The medications in [Table 5-2](#) are only permitted under the circumstances given. Each concomitant drug must be individually assessed against all exclusion criteria and the table below to see if it is allowed. If in doubt the investigator should contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started.

**Table 5-2 Medications allowed under certain conditions**

Class of medication	Condition
Inactivated vaccine	Not administered within 48 h prior to a study visit
Short acting $\beta$ 2-agonist	Rescue medication to be taken as needed
*This table is to be used as a guide only. Each medication that a patient takes must be assessed	

for adherence to this table and also all other inclusion/exclusion criteria.

### **5.3 Discontinuation of study treatment and premature patient withdrawal**

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

Study treatment must be discontinued and the patient withdrawn from the trial under the following circumstances:

- Withdrawal of informed consent
- Asthma exacerbation
- Adverse events for which continued exposure to the study drug would be detrimental
- Heart rate of >100 b.p.m. measured on 2 occasions, approximately 10 minutes apart, with the patient at rest
- Abnormal laboratory results violate liver function rules:
  - a. ALT or AST  $\geq$  5xULN or
  - b. ALT or AST  $\geq$  2.5xULN and total bilirubin  $\geq$  1.5xULN
- Pregnancy
- If the patient has had excessive use of rescue medication the investigator should assess whether it is safe for the patient to continue in the study: specifically, an increase in  $\beta$ 2-agonist rescue medication use on at least 2 of any 3 consecutive days exceeding the equivalent of 8 puffs/day salbutamol/albuterol MDI.
- If patients on statin therapy complain of persistent muscle pain without any obvious cause for greater than 3 days accompanied by increase in CK levels > 10 X ULN or persistent intolerable muscle pain regardless of the accompanying CK level.
- Unblinding of the study treatment for any reason

Protocol deviations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

If premature withdrawal occurs for any reason, the patient should return to the clinic as soon as possible for a Premature Subject Withdrawal (PSW) visit. The investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment CRF.

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should

show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

#### **5.4 Asthma exacerbations**

An asthma exacerbation is defined as a worsening of asthma as judged clinically significant by the physician, requiring treatment with rescue oral or IV corticosteroids for 3 days or more.

The initiation of or the increase in systemic corticosteroid marks the start of an asthma exacerbation episode and cessation of the increase in systemic corticosteroids regimen will mark the end of an exacerbation episode.

Patients who are deemed to have had an exacerbation should either not be enrolled into this study (if the exacerbation is in the run-up to randomization) or should be withdrawn from this study if the exacerbation occurs during the treatment or washout periods of the study.

Patients who have had an exacerbation during the run-in period may be screened for study entry again at a later stage once a minimum of 6 weeks following recovery has elapsed.

#### **5.5 Emergency unblinding of treatment assignment**

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Two sets of emergency code cards are provided to the Novartis Pharma Organization. One set is to be retained by the country Pharma Organization and one set is to be distributed to the investigators. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secured place but must be accessible in case of an emergency. The investigator will receive a masked code break card for each patient, with details of the drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason except other than an emergency. When the investigator removes a scratch-off cover he/she must note the date, time and reason for removing it and retain this information with the patient case report form documentation. The unmasking treatment code should not be recorded in the patient's CRF. The investigator must also immediately inform the Novartis local monitor or designee that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case emergency unmasking is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unmasking. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken or for any non-emergency reason.

## 5.6 Study completion and post-study treatment

Study completion for a patient will occur after he/she has completed 20 weeks of treatment (through to Visit 6) or they have prematurely withdrawn. Completion of the study will be when all randomized patients have completed 20 weeks of treatment.

Patients completing the treatment period will not be given further access to study drug because the risk/benefit ratio will not yet have been substantiated and there are already other marketed therapeutic alternatives available to treat these patients. At the time of study completion or early termination, all patients will be placed on the appropriate asthma treatment as prescribed by the investigator.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

## 5.7 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the ECs of the early termination of the trial.

## 6 Visit schedule and assessments

Table 6-1 lists all of the assessments to be performed in the study and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day or as close to it as possible.

Patients who discontinue study treatment should also return for the visit indicated by the asterisk (\*).

**Table 6-1 Assessment schedule**

Visit	1	2 <sup>c</sup>	3 <sup>d</sup>	4 <sup>d</sup>	5 <sup>c</sup> and STC	6 <sup>d</sup> and TD and/or PSW*
Day	-21	-14	1	42	84	126
Evaluations						
Obtain informed consent	x					
Inclusion/Exclusion criteria	x	x	x			
Demographic information	x					
Medical and Asthma history	x					
BD reversibility / PC20 <sup>1</sup>		x				
Skin prick test		x <sup>10</sup>				
PK <sup>6</sup>				x	x	
Leicester asthma diary <sup>8</sup>	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x

Visit	1	2 <sup>c</sup>	3 <sup>d</sup>	4 <sup>d</sup>	5 <sup>c</sup> and STC	6 <sup>d</sup> and TD and/or PSW*
Day	-21	-14	1	42	84	126
Evaluations						
Height	x					
Weight	x					x
Vital signs	x					x
ECG	x		x	x	x	x
Urinalysis	x	x	x	x	x	x
Pregnancy test <sup>7</sup>	x					x
Safety biomarkers						
Haematology	x		x	x	x	x
Serum Chemistry	x		x	x	x	x
Assessment of AEs		x	x	x	x	x
Autoantibodies <sup>5</sup>			x			
Pulmonary function tests						
Spirometry <sup>a</sup>			x	x	x	x
Impulse oscillometry			x		x	x
Multiple breath washout			x		x	x
Efficacy biomarkers						
Sputum analysis	x <sup>9</sup>		x	x	x	x
HRCT(Quantitative) <sup>a,b</sup>			x <sup>2</sup>		x <sup>3</sup>	
He-3 MRI imaging <sup>a</sup>			x		x	
Bronchoscopy & Bronchial biopsy <sup>a</sup>			x		x	
Volatile organic compounds			x		x	x
Fraction exhaled nitric oxide (FeNO <sub>50</sub> )			x		x	x
Blood biomarkers			x	x	x	x
mRNA analysis <sup>4</sup>			x		x	x
DNA analysis <sup>4</sup>			x			
Patient reported outcomes						
ACQ		x	x	x	x	x
AQLQs		x	x	x	x	x
Study processes						
Study randomization			x			
Dispense Study Medication		x	x	x	x	
Study Completion form						x

## Notes

STC = Study treatment completion

TD = Treatment discontinuation

PSW = Premature Subject Withdrawal

X = assessment to be recorded on clinical data base

S = assessment to be recorded on source documentation only and will not be entered into the CRF

1 = If tests have not been previously performed.

2 = Performed on both inspiration and expiration

3 = Performed on expiration only

4 = Separate informed consent will be obtained before any RNA/DNA collection. Refusal to consent to collection of RNA/DNA material will not exclude the patient from participation in the study.

5 = Autoantibody sample will be taken and stored and only analyzed if pre-existing autoimmune disease has to be excluded

6 = Blood for PK assessments will be drawn prior to taking the morning study medication on day 42 and BOTH prior to and 3 hours after study medication has been taken on the morning of day 84

7 = A serum pregnancy test will be performed on female patients at visit 2, while a urinary pregnancy test will be performed at visit 6 and TD or PSW

8 = "Leicester" diary is local diary used by site to monitor patients' condition data from this will not be entered into our databases

9 = Patients' sputum will only be tested for % sputum eosinophil count at this visit. Patients, who do not have a sputum eosinophil count  $\geq 2\%$  at visit 1, may return approximately 1 week later for re-testing. If at re-testing the sputum inclusion criterion is met, visit 2 should be scheduled to occur 1 week later

10 = Patients with historical positive skin prick tests need not repeat them at this visit

a = These assessments will take an average of three separate clinic days to perform. The tests are grouped into study days A, B and C (see below). Therefore, they will be spread over a period of at most one week that includes the nominal visit date above. The bronchoscopy needs to be performed last as there maybe carryover effects for a couple of days on airway inflammation, in particular. Due to potential interference between assessments, induced sputum analysis and bronchoscopy cannot be performed on consecutive days, but the (A) and (B) study day groupings can be interchanged providing there is still a day between sputum and bronchoscopy.

Study day A: Breath tests, sputum, HRCT (to be performed in this order whenever possible)

Study day B: He-MRI

Study day C: Bronchoscopy and biopsy

b = Subject's individual levels of radiation exposure will be monitored during the course of the study. The maximum allowed radiation dose from research studies will be 5mSv over the course of this and all other previous research studies in the previous three years. Patients who are likely to exceed this dose will not have further CT scans. If some but not all scans can be performed due to radiation dose constraints in a particular patient, priority will be given to expiratory CT scans.

c = assessments to occur  $\pm 4$  days of this date.

d = visits to occur  $\pm 3$  days of this date

**A follow-up telephone call will take place approximately 1 week after study completion or discontinuation of therapy for any reason.**

## **6.1 Information to be collected on screening failures**

Patients discontinuing prior to randomization are considered screening failures.

If a patient discontinues before starting the study medication (at visit 2), only the demographic information, any adverse events or asthma exacerbations plus the related concomitant medication and Screening Log entry with the primary reason for screening failure should be

completed in the CRF. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.

The following information/demographics will be collected and recorded in the CRF:

- Subject number
- Subject's initials
- Date of birth
- Gender
- Race and ethnicity
- Primary reason for not continuing
- Adverse events or asthma exacerbations that have occurred since signing Informed

Consent

- Related concomitant medication for any AEs or asthma exacerbations.

## **6.2 Patient demographics/other baseline characteristics**

The following demographics / baseline characteristics will be collected and recorded in the CRF:

- Date of birth
- Gender
- Race and ethnicity
- Height
- Weight
- Date of diagnosis of asthma
- Smoking history
- Relevant medical history, including any documented asthma exacerbation that occurred during the previous year
- Prior concomitant medications (asthma related and non-asthma related)
- Baseline physical examination (not data based other than in context of relevant medical history)
- Vital signs
- ECG findings
- Hematology and clinical chemistry
- Urinalysis
- Historical evidence of reversibility or airways hyper-reactivity and allergy or atopy (specify test or tests), if available and relevant timings should be included.
- Baseline spirometry (FEV1 and FVC), and reversibility (if no historical data)



### **6.3 Treatment exposure and compliance**

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording capsule counts from the previously dispensed blister strips.

The total number of doses of study drug administered since the last dispensing visit will be recorded in the CRFs at Visits 3, 4, 5 and 6 for each patient on the CRF. For patients who discontinued during the study this will be recorded at the discontinuation visit.

All doses of study drug taken at the clinic visits should be from the newly assigned medication packs. Returned study drug should not be used for dosing.

### **6.4 Efficacy**

As this is a single center study, central reading centers will not be required.

#### **6.4.1 Sputum cell analysis**

Sputum will be induced and assessed for differential cellular content (absolute numbers and percentages) as previously described ([Pavord et al, 1997](#)). Sputum induction will be performed through the inhalation of hypertonic saline. All subjects will have a baseline FEV1 measured and the procedure stopped if:

- a. The subject's FEV1 drops by greater than 20% of the post-salbutamol FEV1 baseline value
- b. The subjects feels any discomfort and does not want to continue with the saline inhalation procedure
- c. The investigator feels it is unsafe to continue with the saline inhalation

#### **6.4.2 Spirometry**

All clinic visits for spirometry will occur in the morning.

Equipment for spirometry assessments will be provided locally and all measurements will be reviewed by trained spirometry technicians or appropriate physicians. Refer to [Appendix 3 Spirometry Guidance](#), for further details on spirometry testing.

#### **6.4.3 Impulse Oscillometry**

Impulse oscillometry (IOS) is performed using a commercially-available system, Jaeger MasterScreen Impulse Oscillometry System, according to standard guidelines. This is calibrated daily using a 3-litre syringe and a standard 0.2 kPaL-1s-1 calibration mesh. Participants wear a nose clip and audible pulses of sound containing a range of frequencies from 5-20 Hz are delivered to their airways by means of a mouthpiece while they breathe normally. Patients are asked to support their cheeks during the test in order to avoid dissipation of the impulses in the mouth. Measures of the frequency-dependence of resistance and reactance, designated R5-R20 (resistance at 5 Hz minus resistance at 20 Hz) and AX (reactance area) respectively, are calculated by the IOS software.

#### **6.4.4 High Resolution Computed Tomography (HRCT)**

All images will be acquired with spirometric gating. Before CT scanning, supine spirometry will be performed to obtain supine lung volume measurements (slow vital capacity [SVC], inspiratory capacity and expiratory reserve volume). Inspiratory and expiratory CT scans at pre-determined SVC (e.g. 80% and 20% SVC) will be obtained. Expiratory scans allow quantitative analysis of air trapping and emphysema, while inspiratory scans allow the quantification of bronchial wall thickening

#### **6.4.5 Multiple Breath Washout (MBW)**

MBW is performed using a modified Innocor gas analyser. Participants wear a nose clip and breathe a known concentration (0.2%) of an inert and non-absorbed gas, sulphur hexafluoride (SF<sub>6</sub>), via a mouthpiece connected to the Innocor device, until the concentration in their exhaled breath reaches a steady state (the wash-in phase). Participants are then switched to breathing room air and encouraged to maintain a steady respiratory frequency of 12 breaths per minute and a tidal volume of approximately 1 litre, making use of a real-time display of these parameters. The concentration of SF<sub>6</sub> in exhaled breath is recorded during this 'wash-out' phase until it reaches 1/40 of the original concentration (0.005%). A number of parameters are derived from the raw MBW data using custom software, including Scond and Sacin. Scond is thought to represent ventilation inhomogeneity arising from conductive airway disease, while Sacin represents ventilation inhomogeneity arising from acinar airspace disease.

#### **6.4.6 Hyperpolarized Helium-3 MRI Imaging (He-3 MRI)**

##### **6.4.6.1 <sup>3</sup>He Hyperpolarization**

<sup>3</sup>He will be hyperpolarized on site in Sheffield with regulatory approved (UK-MAIMP-29724) equipment and administered through a Tedlar bag. <sup>3</sup>He will be delivered in 300-400 ml doses according to total lung capacity made up to one liter with 600-700 ml nitrogen.

##### **6.4.6.1.1 <sup>3</sup>He MRI**

Patients will be placed inside a custom <sup>3</sup>He body coil inside the 1.5T magnet and the following <sup>3</sup>He MRI pulse sequences will be acquired with sensitivity to: (i) static breathold ventilation heterogeneity, (ii) Apparent Diffusion Coefficient mapping and (iii) dynamic gas flow and washout.

- a. A low flip angle 3D gradient echo sequence will be used to image ventilation distribution. Images will be acquired during a 13 second breath hold following inhalation of the gas from FRC. This exam will be performed twice in the first session as a means of assessment of baseline repeatability of ventilated volume.
- b. ADC images will be acquired with simultaneous ventilation images for spatial registration to the ventilation images described above. ADC images will be processed and the results will also be presented as spatial ADC maps for comparison with HRCT and in histogram format.
- c. 3D dynamic images of gas inflow and washout will be acquired with a time resolved sequence and the washout time constants will be derived for comparison with MBW.

#### 6.4.6.1.2 1H lung MRI

1H lung MRI (anatomy and contrast enhanced Gd-DTPA perfusion scans) will also be performed.

A dedicated Research Radiographer will be present at all times to perform the scans alongside the Research MRI physicist.

#### 6.4.7 Bronchial Biopsies and Brushings

Patients are placed into the supine or semi-recumbent position and venous access is inserted. The patient receives premedication (e.g. midazolam 0.07 mg/kg). Oxygen levels are monitored and oxygen supplementation is provided. The throat and larynx area is anaesthetized with a local anesthetic spray (lidocaine, max dose 20 puffs = 3mg/kg) and a flexible endoscope is introduced. After initial orientation and documentation of appearance of the airways, brushings and endobronchial biopsies will be taken from the right main bronchus and segmental and sub-segmental bronchi. The brushes are cut off and transferred into a 15 ml V-tube (polypropylene) containing 2 ml RNA protect reagent or culture medium. The bronchial biopsies will be placed in normal saline, PFA (paraformaldehyde) or PMSF (phenylmethanesulphonylfluoride) as appropriate. After the procedure patients will remain under medical supervision for 2 hours.

#### 6.4.8 Asthma Control Questionnaire (ACQ)

In this study, the ACQ will be used to assess improvements in asthma symptom control. The ACQ was originally validated in patients with asthma aged 17 to 90 years ([Juniper 1999, 2005](#)), and is one of several asthma control measures recommended by GINA Guidelines. The ACQ consists of 7 items: 5 items on symptom assessment, 1 item on rescue bronchodilator use, and 1 item on airway caliber (FEV1 % predicted). The ACQ has been fully validated, including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5). The ACQ will be self-administered at the clinic (questions 1-6 only) and it only takes a few minutes to complete. Patients are asked how they have been feeling during the past week and to score each item on a 7-point response scale, where 0 indicates 'totally controlled' and 6 indicates 'severely uncontrolled.' Study staff score question 7 based on % predicted FEV1 (ideally pre-bronchodilator). The total score is calculated as the mean of all questions. The questionnaire should always be completed before any other assessments.

A **SAMPLE** of the Asthma Control Questionnaire is included in [Appendix 4](#).

#### 6.4.9 Asthma Quality of Life Questionnaire – Standardized (AQLQs)

In this study, the disease-specific, standardized version of the asthma quality of life questionnaire (AQLQs) will be used to measure health-related quality of life in trial patients.

The measure was originally validated for use in patients with asthma aged 17 to 70 years ([Juniper et al, 1999](#)). The AQLQs is a 32-item questionnaire designed to measure functional impairments that are most important to patients with asthma. It consists of 4 domains: symptoms, emotional function, environmental stimuli and activity limitation. Full validation has been demonstrated, including a minimal important difference (MID) or smallest change

that can be considered clinically important (0.5). The AQLQs will be self-administered at the clinic and takes about 4 to 5 minutes to complete. Given that the AQLQs will be administered along with the ACQ, which has a 1-week recall, patients completing the AQLQs will also be asked to recall their experiences during the past week, and to score each item on a 7- point scale (7 = not at all impaired to 1 = severely impaired). The AQLQs yields domain-specific scores and a total score, which is the mean response to all 32 questions. The questionnaire should always be completed before any other non-PRO assessments.

A **SAMPLE** of the Asthma Quality of Life Questionnaire is included in [Appendix 5](#).

#### **6.4.10 Volatile Organic Compounds**

Testing is performed using bespoke equipment loaned from Loughborough University. Subjects are asked to refrain from applying cosmetics on the day of the test. Subjects wear a tight-fitting mask supplied with air and with a sample tube attached, and breathe normally until 2.5 L of exhaled breath are collected through the sample tube. Sample tubes are sent to Loughborough University for analysis ([Ibrahim et al, 2011](#)).

#### **6.4.11 Fraction of Exhaled Nitric Oxide (FeNO<sub>50</sub>)**

Exhaled Nitric Oxide is widely accepted as a non-invasive marker for airway inflammation. Fractional exhaled nitric oxide will be measured following the recently published guidelines on standardized techniques including calibration of equipment as appropriate for measuring exhaled Nitric Oxide by ATS and ERS ([ATS/ERS guidelines 2005](#)).

To ensure consistency in the measurement of FeNO, all sites will be provided with a NIOX MINO FeNO machine.

#### **Recommendations for FeNO Measurements**

FeNO measurements should be performed PRIOR to spirometry assessments, as spirometric manoeuvres have been shown to transiently reduce exhaled NO levels.

FeNO measurements have to be performed at the same time of day (preferably within 4 hours of rising).

Repeated, reproducible exhalations should be performed to obtain two measurements within 10% of each other. Exhaled NO is the mean of these two values. The duration of exhalation must be sufficient (up to 10 seconds) to achieve a stable NO plateau.

Allow subjects at least 30 seconds of relaxed tidal breathing to rest between repeated exhalations in order not to exhaust the patient.

The patient should be seated comfortably with the equipment at the proper height and position.

Patients should refrain from eating and drinking at least 2 hours before measurements.

Patients should avoid strenuous exercise for 1 hour before measurements.

The time of last bronchodilator should be noted, as FeNO levels may vary with the degree of airway obstruction or after bronchodilation.

Respiratory tract infections may lead to increased levels of exhaled NO in asthma, therefore the infection should be recorded in the patient's medical file (and as an AE in the CRF).

Breath-hold results in NO accumulation which causes NO peaks in the exhalations profiles of NO versus time and should therefore be discouraged.

#### **6.4.12 Appropriateness of efficacy assessments**

The spirometry, patient reported outcome measures, sputum assessments and exhaled NO measurements are typical of a study of this type. The other, more exploratory measures, of lung histology, pulmonary function and imaging as well as systemic protein and mRNA measurements are part of attempt to gain a holistic understanding of how the immunology, genetics and pathology impact upon lung function and, ultimately, on patient symptomatology and disease progression in asthma.

We are collaborating with the AIRPROM initiative, through Professors Brightling & Wild, which is attempting to build an in silico model of asthma to better predict how insults and therapies might impact the course of patients' disease.

### **6.5 Safety**

The following safety assessments will be performed:

- History and physical examination
- Vital signs
- Hematology
- Blood chemistry including but not limited to Liver function tests: ALT (SGOT), AST (SGPT), total bilirubin, Metabolic panel: glucose, creatinine, urea (BUN), Na, K, Ca, Cl, Mg, triglycerides, lipase, cholesterol, albumin, total protein, alkaline phosphatase,  $\gamma$ -GT, uric acid, total bilirubin, CK and Immunoglobulins
- Urinalysis by dipstick. If dipstick is positive, then a microscopic examination should be performed.
- CK-MB, Troponin I (in response to CK results outside of the normal range)
- HbA1c (collected at screening only)
- Pregnancy test (females of childbearing potential)
- ECG
- Adverse events including serious adverse events

ECG will be analyzed locally and laboratory assessments (excluding histology and sputum analysis) will be performed externally.

#### **6.5.1 Physical examination**

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's CRF. Significant findings made after informed consent is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's CRF.

### 6.5.2 Vital Signs

Vital signs include body temperature, respiratory rate, systolic and diastolic blood pressure, and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured. Patient's condition must be monitored to rule out any clinically relevant arrhythmia or tachycardia.

Clinically notable vital signs are defined in [Appendix 1](#).

### 6.5.3 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

### 6.5.4 Laboratory Evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in [Appendix 1](#).

#### 6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

#### 6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), bilirubin, calcium, chloride, cholesterol, CK, creatinine,  $\gamma$ -GT, glucose, LDH, magnesium, phosphate, potassium, sodium, triglycerides, urea (BUN), uric acid and immunoglobulins (IgG and possibly including but not limited to IgG1, IgG2 and IgG4) will be measured.

Patients exhibiting liver function test values of

- ALT or AST  $\geq$  5xULN **or**
- ALT or AST  $\geq$  2.5xULN **and** total bilirubin  $\geq$  1.5xULN

at any visit should be withdrawn from the trial.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal range, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason

other than drug-related adverse experiences is identified, even after the study medication has discontinued.

#### **6.5.4.3 Urinalysis**

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed. If the urine dipstick is abnormal, the sample will be sent to central laboratory for additional testing, including assessment of WBC and RBC sediments.

#### **6.5.5 Electrocardiogram (ECG)**

Standard 12-lead ECGs will be acquired. A paper tracing must be obtained for immediate safety assessment and subsequently archived at the site. ECGs should contain the subject number, randomization number, the date and time of the tracing and the study code "QAW039A2206". The paper tracings must be signed and dated by the investigator or another physician at the clinical site. Interpretation of ECGs will be performed by the investigator or another physician at the clinical site.

ECGs must be acquired only after subjects have been quietly at rest in the sitting position for at least 10 minutes. During ECG acquisition, subjects must be perfectly still and not speak.

When the ECG acquisition time coincides with vital signs and blood draws, the ECG must be acquired first, followed by vital signs and the blood draws.

ECGs should be free of baseline wander and noise. Prior to acquisition, the ECG operator should check the tracing to ensure that it is of high quality

#### **6.5.6 Pregnancy and Assessments of Fertility**

All pre-menopausal women who are not surgically sterile will have a serum (at screening) or urine (all other indicated visits) pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum B-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial.

#### **6.5.7 Skin Prick Test**

Skin prick test to assess allergic status will be performed unless historical positive test results are already available.

#### **6.5.8 Appropriateness of safety measurements**

The safety assessments selected are standard for this indication/patient population.

### **6.6 Other assessments**

#### **6.6.1 Pharmacokinetics**

All subjects will have one blood sample at Visit 4 and two blood samples collected for pharmacokinetic analysis on Visit 5. At Visit 4 a sample will be taken prior to the morning dose. At Visit 5, one sample will be taken before the administration of the morning dose of the study drug and the second sample will be taken 3 hours after the administration of the study drug. Each sample will be processed to produce 2 aliquots of acidified plasma (A and

B). All samples will be given a unique sample number (as listed in the PK blood log in [Appendix 2](#)) and a collection number. The site is to ensure the correct sample number is reflected on the respective tube. Both the date and time of that morning's (either day 42 or day 84) study drug dose administration and the actual PK sample collection date and time will be entered on the PK blood collection page of the CRF. Sampling problems will be commented on in the CRFs.

Both aliquots per timepoint, aliquot A and aliquot B should be shipped to the central laboratory (and then forwarded to the bioanalytical facility for sample analysis on separate occasion).

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters (with the exception of the pre-dose samples).

Analysis of QAW039 will be conducted in the collected acidified plasma samples. Bioanalysis will be performed using a validated LC/MS/MS assay.

Full details on pharmacokinetic sampling, processing, collection and shipment will be provided in the laboratory and procedures manual.

## **6.6.2 Biomarkers**

As part of an effort to determine whether biomarkers that predict clinical efficacy responses can be identified, the following samples will be collected in this trial.

Sample testing and collection procedures for the biomarkers identified in this section are described in greater detail in the central lab manual, which will be provided as part of this study.

### **6.6.2.1 Pharmacogenetic Assessments**

The Study includes an optional pharmacogenetic component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents these options to the subject.

Exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors which may influence the response to QAW039. These genetic factors include those that may (1) be related to asthma, (2) predict response to treatment with QAW039, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects. The hope is to develop a better understanding of how subjects respond to QAW039.

Polymorphisms that may be studied relating to the absorption, distribution, metabolism, and excretion (ADME) of QAW039 may include UGT1A1 and other UGT polymorphisms.

Despite continuing advances in genetics research, not all of the polymorphisms relevant to drug metabolism and drug action may have been identified. Therefore, additional polymorphisms will be added within the restricted scope of these studies as described above.



In addition, recent advances in genotyping technologies have made genome-wide association (GWA) studies possible. GWA studies may also be undertaken within the restricted scope of these studies as described above.

Sample collection: One 10 mL blood sample will be collected at Day 1 (Visit 4) in an EDTA tube. After collection, the sample must be inverted several times to prevent clotting. If the blood draw at Visit 4 is missed, the sample should be taken at the next visit that a blood draw is already scheduled.

The samples should be kept frozen at  $-70^{\circ}\text{C}$  until shipped frozen to the central lab for DNA extraction. The extracted DNA will then be transferred to Novartis for pharmacogenetic analysis and storage.

Any DNA derived from the sample that remains after analysis may be stored for up to 15 years to address scientific questions related to QAW039 or asthma.

In the event that a subject requests to destroy the pharmacogenetic sample, the following process should be followed: (1) the subject should contact the investigator; (2) the investigator will then provide the sponsor with the required study and subject numbers; (3) any remaining samples (e.g. blood or DNA) will be located and destroyed; and (4) the sponsor sends a letter back to the investigator to confirm that the sample was destroyed.

A lab manual will be provided with detailed information on sample collection, handling and shipment. The sample collection date and exact time must be entered on the sample collection CRF page.

### **6.6.2.2 Transcriptomic assessments**

Messenger RNA expression profiling will be carried-out in enrolled asthma patients who are willing to participate in this exploratory biomarker evaluation from both blood and/or biopsy or brushing material. Exploratory pharmacogenomic assessments in this study aim at increasing our understanding of the molecular heterogeneity of asthma, and at identifying predictors of response to treatment.

RNA samples will be profiled using the Illumina Human HT-12 v3 Expression BeadChip or equivalent. Significance Analysis of Microarrays (SAM) will be used to identify differentially expressed genes, and statistical clustering techniques will be used to analyze the dataset. Genotyping will be performed using the Illumina 660W genotyping array that contains 660000 polymorphisms (SNPs and CNVs) evenly spread across the human genome, or an equivalent. This data will contribute towards genome-wide association studies of asthma phenotypes. One serum sample per patient - to be prepared from 10.0 mL whole blood - will be collected pre-dose at Visit 3 and at Visit 5 and Visit 6.

These samples will be stored at the central lab until onward shipment for genomic data generation and analysis. Exploratory biomarker clinical samples remaining after analysis may be stored for up to 15 years to address additional relevant scientific questions.

### **6.6.2.3 Serum and plasma proteins**

Serum proteins will be measured both to see if they might identify populations who are more likely to respond to QAW039 than the total population and to see if changes in concentration

correlate with response: these may include but are not limited to eosinophilic cationic protein (ECP), eotaxin-1, IL-5, IL-13, serum total IgE, hsCRP, TNF- $\alpha$ , MCP-1 and IL-8. Samples will be collected at before the commencement of treatment at Visit 3 and Visits 4, 5 and 6.

A sample will be taken at baseline for potential autoantibody measurement to rule out any pre-existing autoimmune condition (in particular Churg-Strauss Syndrome) should that prove necessary.

#### **6.6.2.4 Fluorescent activated cell sorting (FACS)**

A FACS assay will be used to quantify the following cell populations (at least): CD3; CD4; CD8; CCR3 (gating of eosinophils); CRTh2. These will be measured in all patients at Visits 3, 4, 5 and 6.

#### **6.6.2.5 Prostaglandins and Leukotrienes**

Analytes that will be measured may include but are not limited to PGD2, PGE2, PGJ2, DKPGD2,  $\Delta$ 12-PGD2, 15d-PGD2,  $\Delta$ 12-PGJ2, 9 $\alpha$ ,11 $\beta$ -PGF2, LTB4, LTC4, LTD4 and LTE4.

The prostaglandins will be measured by LC-MS in all patients at Visits 3, 4, 5 and 6.

#### **6.6.2.6 Sputum soluble factor analysis**

Sputum may be assessed (from visit 3 onwards) for soluble factor levels (potentially including but not limited to IgE, Eotaxin-1, IL-5, IL-13, IL-8, ECP, prostaglandins and leukotrienes and TNF- $\alpha$ ).

#### **6.6.3 Resource utilization**

Resource utilization will not be captured as an endpoint in this trial.

## **7 Safety monitoring**

### **7.1 Adverse Events**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the placebo that is given during any phase of the study. Medical conditions/diseases present before starting the study are only considered adverse events if they worsen after starting the study. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade [mild, moderate, severe]
2. its relationship to the study drug(s) (suspected/not suspected)

3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## **7.2 Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to the site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **7.3 Pregnancies**

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## **8 Data Review and database management**

### **8.1 Site Monitoring**

Before study initiation, a Novartis representative will review the protocol and CRFs with the investigators and their staff at a site initiation visit or at an investigator's meeting.

During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

### **8.2 Data Collection**

Designated investigator staff will enter the data required by the protocol into Case Report Forms. The Investigator must certify that the data entered into the Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

### **8.3 Database management and quality control**

Novartis staff or designee review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions.

1. Queries are sent to the investigational site using a data query.
2. Designated investigator site staff is/are required to respond to the query and confirm or correct the data using a paper Data Query Form which will be faxed to the site.
3. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or designee who will make the correction to the database.
4. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples (except cytology for sputum samples and bronchial brushings and biopsies) will be processed centrally and the results will be sent to Novartis (or a designated CRO).

ECG readings will be processed locally, at the study site and the results will be sent to Novartis (or a designated CRO).

Spirometry and FeNO readings will be processed and the results will be sent to Novartis (or a designated CRO).

To maximize confidentiality, all pharmacogenetic samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics is exploratory. Any results from this pharmacogenetic study will not be placed in the patient's medical records and will not be disclosed to patients or the patient's family.

## **9 Data analysis**

### **9.1 Analysis sets.**

The randomized set (RAN), which comprises all randomized patients, regardless of whether or not they actually received study medication, will be used for summaries of patient disposition and analysis populations.

The full analysis set (FAS) will include all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. FAS will be used for all efficacy variables, unless otherwise stated.

The per-protocol set (PP) will include all patients in the FAS without any major protocol deviations. Major protocol deviations will be defined in the validation analysis plan prior to database lock and the un-blinding of the study. Patients will be analyzed according to the treatment they were assigned to. PP will be used for the supportive analysis of the primary variable.

The safety set (SAF) will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also the FAS assigns randomized treatment and the safety set assigns received treatment.

## 9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized using the safety set including age, gender, race, ethnicity, height, weight, body mass index (BMI), duration of asthma, smoking history, screening spirometry (% predicted FEV<sub>1</sub>, reversibility, etc.), vital signs (systolic and diastolic blood pressure, pulse rate), concomitant medications, ECG, hematology, blood chemistry, urinalysis, autoantibodies, and relevant medical histories.

## 9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

The number of patients and the length of time (in days) exposed to each study drug will be summarized by treatment for the safety set.

Prior and concomitant medications will be summarized by treatment for the safety set separated for asthma related and non-asthma related medications. Asthma related concomitant medications will be summarized by pre-specified categories, route of administration and preferred term. Non-asthma related concomitant medications will be summarized by the preferred term.

Treatment compliance will be summarized by treatment for the safety set.

## 9.4 Analysis of the primary and key secondary variable(s)

The FAS (Full Analysis Set) will be used for analysis of the primary and secondary variables, unless otherwise specified.

### 9.4.1 Variable(s)

#### 9.4.1.1 Primary Variable

The primary variable of the study is the change from baseline in sputum eosinophil percentage at week 12. As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log<sub>10</sub>-transformed scale. The baseline measurement is defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing (on log<sub>10</sub>-transformed scale).

#### 9.4.1.2 Secondary variable

The secondary variables include the change from baseline to week 12 in ACQ. The baseline is defined as the assessment measured at Visit 3 (Day 1) prior to the first dosing.

### *ACQ*

The ACQ measures asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV<sub>1</sub> % predicted). All 7 questions of the ACQ are equally weighted. Items 1-6 are scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. The 7<sup>th</sup> item on % predicted FEV<sub>1</sub> (pre-bronchodilator) is scored by clinic staff on a 7-point scale (0 – > 95%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%). The average score of the 7 questions at each visit will be calculated as the sum of scores divided by the number of

questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and the missing item is neither question 1 nor question 7.

#### **9.4.2 Statistical model, hypothesis, and method of analysis**

The primary variable and the secondary variables will be summarized by treatment and analyzed using an ANCOVA model with treatment as the fixed effect and the respective baseline value as the covariate.

Least square mean for each respective treatment group and for the treatment difference will be presented along with associated 95% confidence interval and p-value (2-sided) for within and between group comparisons.

#### **9.4.3 Handling of missing values/censoring/discontinuations**

Missing data will be imputed for the primary variable using last observation carried forward (LOCF). Only post-baseline observation will be used for this purpose.

Only 1 missing item is allowed for scoring the ACQ and, preferably, this should not be question 1 or question 7. The single missing value may be interpolated by utilizing prior or subsequent completions of the questionnaire. The averaged ACQ score will not be imputed.

#### **9.4.4 Supportive analyses**

##### **9.4.4.1 Primary Variable**

For the primary variable, the analysis will be repeated for the patients in FAS without LOCF.

Longitudinal data analysis will be performed as sensitivity analysis on the primary variable in the FAS, as an alternative to LOCF. Treatment effects, together with 95% confidence interval for difference in treatments at each visit will be presented.

The normality assumption will be checked with a Q-Q plot of residuals for each treatment group. In addition, within-treatment difference between baseline and week 12 will be analyzed using Wilcoxon paired sample signed-rank test; between-treatment comparison on the change from baseline to week 12 will be analyzed using Wilcoxon/Mann-Whitney rank-sum test.

##### **9.4.4.2 Secondary Variable**

For the secondary variable, additional analyses will be conducted as follows:

- An ACQ change of 0.5 has been validated as the minimally important clinical difference ([Juniper et al, 2005](#)). The proportion of patients with a decrease in ACQ of > 0.5 will be summarized by treatment and analyzed using a logistic regression. The model includes terms for treatment as the fixed effect and the baseline ACQ score as a covariate. The odds ratio of QAX576/Placebo will be computed, along with associated 95% confidence intervals.
- A sensitivity analysis using different imputation algorithms for missing data at week 12 will be performed in the FAS.



- Longitudinal data analysis will be also performed in the FAS to account for the dependency among the visits within patient. Treatment effects, together with 95% confidence interval for difference in treatments at each visit will be presented.

## **9.5 Analysis of other variables**

### **9.5.1 Efficacy variables**

#### **9.5.1.1 Sputum cell analysis**

The change from baseline at week 6 and at week 18 will be also summarized by treatment and analyzed using an ANCOVA model with treatment as the fixed effect and the baseline sputum eosinophil percentage as the covariate. The normality assumption will be checked with a Q-Q plot of residuals for each treatment group and if this is not adequately met a non-parametric test will be used instead (refer to Section 9.4.4.1).

To explore the persistency of efficacious effect following the cessation of therapy, data will be also analyzed similarly based on change from week 12 to week 18.

#### **9.5.1.2 Asthma control questionnaire (ACQ)**

The change from baseline at week 6 and at week 18 and the change from week 12 and week 18 will be summarized and analyzed similarly with baseline ACQ as the covariate. Refer to Section 9.5.1.1.

#### **9.5.1.3 Pulmonary function tests**

##### **9.5.1.3.1 Spirometry**

% predicted FEV<sub>1</sub> (pre-bronchodilator) is calculated as:

$$\frac{100 \times \text{FEV}_1 (\text{pre } \beta_2\text{-agonists at V2})}{\text{Predicted FEV}_1}$$

The change from baseline to week 6, week 12, and week 18 in % predicted FEV<sub>1</sub> will be summarized and analyzed in a similar way as described in Section 9.5.1.1 with baseline % predicted FEV<sub>1</sub> as the covariate. To explore the persistency of efficacious effect following the cessation of therapy, data will be also analyzed similarly based on change from week 12 to week 18.

##### **9.5.1.3.2 Impulse Oscillometry**

R5-R20 (kPaL<sup>-1</sup>s<sup>-1</sup>) and AX (kPaL<sup>-1</sup>) are measured with impulse oscillometry. The change from baseline at week 12 and at week 18 and the change from week 12 and week 18 will be summarized and analyzed similarly with the respective baseline value as the covariate. Refer to Section 9.5.1.1.

### 9.5.1.3.3 Multiple Breath Washout (MBW)

$S_{acin}$  ( $L^{-1}$ ) is measured with multiple breath washout. The change from baseline at week 12 and at week 18 and the change from week 12 and week 18 will be summarized and analyzed similarly with the respective baseline value as the covariate. Refer to Section 9.5.1.1.

## 9.5.2 Safety variables

All safety endpoints (i.e. adverse events, laboratory data, vital signs, and ECG) will be summarized by treatment for all patients of the safety population. All data will be included in the analysis regardless of rescue medication use.

### 9.5.2.1 Adverse events

All adverse events which start after the first dose of study medication will be considered as a treatment emergent adverse event. Adverse events that start during the study but before the time of the first dose of study drug (e.g. screening period) will be classified as a prior adverse event and will be included in adverse events listings, but will not be summarized.

Treatment emergent adverse events with the number and percentage of patients having any adverse event overall, by system organ class and preferred term will be provided for:

- all adverse events
- adverse events by maximum severity
- adverse events suspected by the investigator as study drug-related
- serious adverse events
- adverse events leading to permanent discontinuation of study drug

### 9.5.2.2 Laboratory data

A central laboratory will be used to analyze and report blood chemistry/hematology/urinalysis

The following analyses will be performed, where appropriate, for central measurements of hematology and blood chemistry tests:

- standard descriptive statistics for values measured at baseline and post-baseline visits including changes from baseline
- shift tables relative to the normal ranges between baseline and post-baseline visits
- number (and percentage) of patients with clinically notable changes for selected tests

### 9.5.2.3 Vital signs

Vital signs (i.e. blood pressure and pulse rate) will be summarized with standard descriptive statistics of raw data and changes from baseline for each visit separately. The numbers of patients with vital signs meeting the definition of notably abnormal will be presented by parameter.

#### **9.5.2.4 Electrocardiogram**

The ECGs will be centrally read by an ECG vendor, including quantitative assessments (RR, PR, QRS and QT intervals, and heart rate) and qualitative diagnoses. The QTc will be calculated by the ECG vendor from the QT interval and RR (in seconds) by two methods:

(1) Using Bazett's formula:  $QTc = QT/\sqrt{RR}$

(2) Using Fridericia's formula:  $QTc = QT / \sqrt[3]{RR}$ , where  $\sqrt[3]{}$  denotes the cube root

The quantitative assessments will be based on the mean of the measurements at each scheduled time point for each visit separately. The analysis, such as change from baseline and clinical notables, will be summarized by treatment based on the averaged values. The baseline measurement will be the mean of measurement at Visit 4 pre-dose (-35 min).

Changes from baseline will be summarized by treatment for the mean heart rate and ECG intervals including QTc for each scheduled time point at each visit and for the maximum post-baseline value.

Notable QTc values will be summarized. A notable value is defined as a QTc interval of greater than 450 msec for males and greater than 470 msec females. Patients meeting a more extreme notable criterion of >500 msec will be also summarized for males and females. The notable change in QTc will be also summarized. The categories used for the change in QTc are less than 30 msec, 30 to 60 msec and greater than 60 msec.

The qualitative assessment includes overall ECG interpretation and Morphological and rhythm abnormalities. Shift tables will be provided in order to compare a patient's baseline overall ECG interpretation to the interpretation at each time point at each post-baseline visit. Using the morphologic determinations, the number and percentage of patients with qualitative ECG abnormality will be summarized for each visit and each timepoint. The abnormality will be summarized by baseline condition (NO/YES) for each type of abnormality (i.e. newly occurring cases, or persistent/recurrent cases). The qualitative ECG abnormality will be determined by abnormality of Rhythm, Arrhythmia, Conduction, Morphology, Myocardial infarction, ST segment, T wave abnormalities, abnormal U wave.

#### **9.5.3 Resource utilization**

Healthcare resource utilization will not be collected in this study.

#### **9.5.4 Health-related Quality of Life**

##### **9.5.4.1 Asthma control questionnaire (AQLQs)**

See section 9.4.

##### **9.5.4.2 Asthma quality of life (AQLQs)**

The 32 items in the AQLQ(s) are divided into four domain-specific scores and a total score as follows:

Activity limitations = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)

Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)

Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)

Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)

Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL. There is a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means no more than 3 missing responses for the overall score and no more than 1 missing response per domain. For the symptoms and activity domain scores, one missing value per domain is allowed. For the emotional function and environmental stimuli domain scores, no missing values are allowed.

The minimal important difference (MID), defined as "the smallest difference in score which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patients management," has been established as 0.5 points per item (Juniper et al, 2006).

Between treatments analyses of change from baseline scores by visit will be performed using the same model as specified in section 9.4.2 with baseline AQLQ score as the covariate. Least squares means and associated 95% confidence intervals will be presented for treatments and treatment differences.

### **9.5.5 Pharmacokinetics**

All subjects with evaluable pharmacokinetic (PK) parameter data will be included in the pharmacokinetic data analysis.

#### **Pharmacokinetic variables**

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters (with the exception of the pre-dose samples).

PK samples are being collected to assess patient compliance with the dosage regimen therefore due to the sparse nature of the sample collection scheme pharmacokinetic parameters will not be determined using non-compartmental method(s). Descriptive statistics of plasma concentrations data will include mean, SD, and CV, min and max.

### **9.5.6 Pharmacogenetics/pharmacogenomics**

#### **9.5.6.1 Pharmacogenetic data analyses**

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible

associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

### **9.5.6.2 Pharmacogenomic data analyses**

The analysis of pharmacogenomic data will be performed at the Fundacio Privada Parc, Cientfic DE, Barcelona, Spain. Quality control of all individual samples and molecular data will be conducted. The analysis of genomic data per se may be assisted by the use of “in house’ and commercial expert applications and databases. A range of statistics-based approaches - both supervised and unsupervised - will be applied to the data.

### **9.5.7 Biomarkers**

#### **9.5.7.1 Fractional exhaled Nitric Oxide (FeNO)**

Exhaled Nitric Oxide is a non-invasive marker for airway inflammation. It will be measured following the recently published guidelines on standardized techniques.

The change from baseline will be summarized by treatment group. The mean FeNO as calculated from two measurements will be used for analysis. Treatment group comparisons will be performed by the same model as specified in Section 9.5.1.1 with baseline FeNO as the covariate. Least squares means and associated 95% confidence intervals will be presented for treatments and treatment differences.

#### **9.5.7.2 Other efficacy biomarkers**

Other efficacy biomarkers are measured, including

- High Resolution Computed Tomography (HRCT)
- Hyperpolarized Helium-3 MRI Imaging (He-3 MRI)
- Bronchial Biopsies and Brushings
- Volatile Organic Compounds

Data will be summarized and analyzed in a similar way as described in section 9.5.1.1.

### **9.5.8 PK/PD**

Population modeling may be undertaken to evaluate the pharmacokinetics of QAW039 based on the sparse data collected in this study as well as in other clinical studies from the QAW039 program. A search may be performed to identify variables that impact PK. This will include, but is not limited to, an investigation of patient demographics and other baseline characteristics. Results from such population analyses will be reported separately.

PK/PD modeling may also be attempted for exploratory purposes.

## 9.6 Interim analyses

An interim analysis (IA) will be conducted when all the patients complete the treatment phase (i.e. week 12, visit 5). This IA is intended to allow possible re-sizing of the study to be considered and to provide early delivery of efficacy data to facilitate forward planning of the QAW039 program. This IA will include all the applicable primary/secondary/exploratory efficacy endpoints, as well as safety data available at the time of IA.

## 9.7 Sample size calculation

Table 9-1 provides the sample sizes required for each respective outcome measure (the primary and secondary variables) in order to achieve an 80% power to detect the minimally important difference at a two-tailed 5% significance level.

This study is aimed to power for a 50% reduction in sputum eosinophil percentage. This is equivalent to an absolute reduction in  $\log_{10}$  (sputum eosinophil percentage) of  $\log_{10}2 = 0.301$  (Inman et al, 2002, Barnes et al, 2011). The minimally important differences for the primary and key secondary endpoints are listed in Table 9-1.

**Table 9-1 Sample size calculations for primary and secondary endpoints**

Endpoint	Assumption		N per treatment group	
	SD <sup>†</sup>	Minimally important difference	BT <sup>‡</sup> comparison	
			2-group T-test	WMW <sup>§</sup> rank-sum
$\Delta^{\dagger}$ in sputum eosinophil percentage on $\log_{10}$ scale	0.333	0.301 $\yen$	21	23
$\Delta^{\dagger}$ in ACQ	0.385	0.5 $\text{€}$	11	13

<sup>†</sup>  $\Delta$ =change from baseline at week 12

<sup>\*</sup> SD = standard deviation for the endpoint to be analyzed

<sup>‡</sup> BT = between-treatment

<sup>§</sup> WMW = Wilcoxon/Mann-Whitney rank-sum test

$\yen$  (Inman et al, 2002)

$\text{€}$  (Juniper et al, 2005)

With 30 patients per arm to be randomized, it is expected that 24 patients per arm will complete week 12 assessment, assuming the dropout rate during the course of treatment phase (12 weeks) is 20%. With this sample size, the primary and secondary endpoints achieve  $\geq 80\%$  power to detect minimally important difference between QAW039 and placebo, as specified in Table 9-1.

## 10 Ethical considerations

### 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local

regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## **10.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor or designee after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

The study includes some optional components which require a separate signature if the patient agrees to participate. It is required as part of this protocol that the investigator presents these options to the patient. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these assessments will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

## **10.3 Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all

of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## **10.4 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as [clinicaltrials.gov](http://clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

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## 13 Appendices

### Appendix 1 Clinically notable laboratory values and vital signs

Patients with an ALT or AST  $\geq 5$  x ULN, **or** with ALT or AST  $\geq 2.5$  x ULN **and** total bilirubin  $\geq 1.5$ xULN, at any visit should be withdrawn from trial. An alert should be sent to the investigator and sponsor if patients experience these abnormal liver function test results.

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant in the CRF.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows: heart rate of  $<40$  and  $>90$  bpm; systolic blood pressure of  $<90$  and  $>140$  mmHg; diastolic blood pressure of  $<50$  and  $>90$  mmHg.

For ECGs a notable QTc value is defined as a QTc (Fridericia's) interval of greater than 450 msec for males and 470 msec for females – all such ECGs will be flagged by the cardiologist and require assessment for clinical relevance by the Investigator.

Patients with a heart rate of  $>100$  bpm measured on 2 occasions, approximately 10 minutes apart, whilst resting, should be withdrawn from the trial.

## Appendix 2: Blood, Sputum & PK Logs

### Sputum and Blood Log

Study Phase	Safety	Pregnancy test	Pharmacogenomic	Biomarker Sample 1 (serum and plasma proteins)	Sputum	Pharmacogenetic	Biomarker Sample 2 (prostaglandins and leukotrienes)	Autoantibody	Fluorescent activated cell sorting (FACS)	Total IgE/ hsCRP	PK											
Matrix	Whole blood	Serum	Serum	Serum; Plasma	Sputum	Whole blood	Plasma	Serum	Whole blood	Serum	Plasma											
Assay type	ELISA/Multiplex			ELISA/Multiplex	LC-MS; ELISA/Multiplex; Cellular count	PCR/DNA sequencing	LC-MS		FACS analysis	ELISA/Multiplex	LC-MS-MS											
Name and type of analyte	Standard hematology and chemistry assessments, plus immunoglobulins	Serum B-hCG	mRNA expression profiling	ECP, IL-5, IL-13, TNF-alpha; Eotaxin-1, MCP-1, IL-8	Leukotrienes: Eotaxin-1, ECP, IL 5, IL-8, IL-13, IgE, TNF-alpha, MCP-1; Eosinophils	UGT1A1 and other UGT polymorphism, GWA	PGD2, PGE2, PGJ2, DK-PGD2, Δ12-PGD2, 15d-PGD2, Δ12-PGJ2, 9α,11β-PGF2, LTB4, LTC4, LTD4 and LTE4		CD3; CD4; CD8; CCR3 (gating of eosinophils); CRTh2	IgE, hsCRP	QAW039 levels											
Day	(ml)	Serum B-hCG	Sample No	(ml)	Sample No	(ml)	Sample No	(mg)	Sample No	(ml)	Sample No	(ml)	Sample No	(ml)	Sample No	(ml)	Sample No	(ml)				
Screening (Visit 1) Day-21	15	5*					401 <sup>S</sup>	200														
Day -14 (Visit 2)																						
Baseline (Visit 3)	15		201	5	301	10	402	200	501	10	601	10	701	10	801	10	901	10				
Day 42 (Visit 4)	15				302	10	403	200			602	10			802	10	902	10	101	10		
Day 84 (Visit 5) pre-AM dose	15		202	5	303	10	404	200			603	10			803	10	903	10	102	10		
Day 84 (Visit 5) 3 hr post-AM dose																			103	10		
Day 126 (Visit 6)	15		203	5	304	10	405	200			604	10			804	10	904	10				
Total blood (mL)	75	5	15		40				10		40	10			40		40				30	
Study total (excluding PK)	305																					
* In women of child bearing potential only																						
§ cellular counts and % eosinophil analysis only to be performed																						
# Sample 502 not to be taken or analysed if sample 501 allows patient to meet inclusion criteria																						
Safety sample volumes include blood obtained for hematology and chemistry assessments																						

### PK Blood Log

Study Phase	Time	Continuous time post dose	PK blood samples		
			PK Col No	Sample No	(ml)
Day					
Day 42 (Visit 4)	<i>Pre-dose</i>	<i>984 hours</i>	1	101	2x5
Day 84 (Visit 5)	<i>Pre-dose</i>	<i>1992 hours</i>	2	102	2x5
	<i>3h</i>	<i>1995 hours</i>	2	103	2x5
For PK assessments at time-points up to and including 3 hours, a window of $\pm 5$ mins is allowed					
For PK assessments at time-points over 3 hours, a window of $\pm 30$ mins is allowed					

## **Appendix 3: Spirometry Guidance**

### **Spirometry**

#### **Equipment**

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry<sup>1</sup>. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

#### **Calibration**

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration reports should be printed and stored as source data at the site.

#### **Preparing the test subject**

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 1 hour of testing
- Exposure to environmental smoke, dust or areas with strong odors

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended to reduce risks related to dizziness or syncope. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

#### **Performing Spirometry**

The subject's age, height and gender will be entered into the spirometer. It is important that the height is measured accurately at the study site. Spirometry, an effort-dependent test, requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

#### **Number of trials**

A minimum of 3 acceptable forced vital capacity (FVC) maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing may be discontinued.

### **Acceptability**

An acceptable maneuver has the following characteristics:

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

### **Repeatability**

The 2 largest FVC and FEV<sub>1</sub> values from 3 acceptable maneuvers should not vary by more than 0.150 L.

### **Recording of data**

The highest FEV<sub>1</sub> and FVC from any of the acceptable curves are recorded. (The highest FEV<sub>1</sub> and FVC may not necessarily result from the same acceptable curve).

### **Predicted normal**

For subjects greater than 18 years of age, this study will utilize the spirometric predication equation standards for the European Community for Coal and Steel 2 or Nhanes3. For children ages less than 18 years of age the reference ranges published by Polgar 4 will be used.

### **Reversibility**

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing<sup>1</sup>. A baseline spirometry assessment should be performed after a washout period of at least:

- 6 h for short-acting  $\beta$ 2-agonists
- 8 h short-acting anticholinergics
- 48 h for long-acting  $\beta$ 2-agonist
- 7 days long-acting anticholinergic
- 7 days indacaterol

Administer 400 $\mu$ g of salbutamol/360 $\mu$ g of albuterol following the completion of the baseline assessment. A second spirometry assessment is then performed within 10 to 15 minutes after administration of the salbutamol/albuterol.

Reversibility is calculated as:

$$\frac{100 \times \text{FEV}_1 (\text{post } \beta 2\text{-agonists}) - \text{FEV}_1 (\text{baseline})}{\text{FEV}_1 (\text{baseline})}$$

Subjects will be considered reversible if an increase of at least 12% (and 200 ml) is demonstrated after administration of the bronchodilator.

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## Appendix 4: Asthma Control Questionnaire

A **SAMPLE** of Asthma Control Questionnaire is included below. The format of the administered test may vary.

Please answer questions 1 - 6.

**Circle** the number of the response that best describes how you have been during the past week.

- |   |   |
|---|---|
| 1. On average, during the past week, how often were you <b>woken by your asthma</b> during the night?               | 0 Never<br>1 Hardly ever<br>2 A few times<br>3 Several times<br>4 Many times<br>5 A great many times<br>6 Unable to sleep because of asthma                 |
| 2. On average, during the past week, how <b>bad were your asthma symptoms when you woke up</b> in the morning?      | 0 No symptoms<br>1 Very mild symptoms<br>2 Mild symptoms<br>3 Moderate symptoms<br>4 Quite severe symptoms<br>5 Severe symptoms<br>6 Very severe symptoms   |
| 3. In general, during the past week, how <b>limited were you in your activities</b> because of your asthma?         | 0 Not limited at all<br>1 Very slightly limited<br>2 Slightly limited<br>3 Moderately limited<br>4 Very limited<br>5 Extremely limited<br>6 Totally limited |
| 4. In general, during the past week, how much <b>shortness of breath</b> did you experience because of your asthma? | 0 None<br>1 A very little<br>2 A little<br>3 A moderate amount<br>4 Quite a lot<br>5 A great deal<br>6 A very great deal                                    |

5. In general, during the past week, how much time did you **wheeze**?  
0 Never  
1 Hardly any of the time  
2 A little of the time  
3 A moderate amount of the time  
4 A lot of the time  
5 Most of the time  
6 All the time
6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day?  
*(If you are not sure how to answer this question, please ask for help)*  
0 None  
1 1 - 2 puffs/inhalations most days  
2 3 - 4 puffs/inhalations most days  
3 5 - 8 puffs/inhalations most days  
4 9 - 12 puffs/inhalations most days  
5 13 - 16 puffs/inhalations most days  
6 More than 16 puffs/inhalations most days

**To be completed by a member of the clinic staff**

7. FEV<sub>1</sub>pre-bronchodilator: ..... 0 > 95% predicted  
1 95 - 90%  
FEV<sub>1</sub>predicted:..... 2 89 - 80%  
3 79 - 70%  
FEV<sub>1</sub>%predicted:..... 4 69 - 60%  
(Record actual values on the dotted 5 59 - 50%  
lines and score the FEV<sub>1</sub> % predicted 6 < 50% predicted  
in the next column)

## Appendix 5: Asthma Quality of Life Questionnaire – standardized

A **SAMPLE** of the Asthma Quality of Life Questionnaire is included below. The format of the administered test may vary.

### Asthma Quality of Life (AQLQ) Questionnaire

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma**.

HOW LIMITED HAVE YOU BEEN **DURING THE LAST 2 WEEKS** IN THESE ACTIVITIES AS A RESULT OF YOUR ASTHMA?

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7
*If you are not employed or self-employed, these should be tasks you have to do most days.							
5. SLEEPING	1	2	3	4	5	6	7

HOW MUCH **DISCOMFORT OR DISTRESS** HAVE YOU FELT **DURING THE LAST 2 WEEKS**?

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7

Clinical Development

QAW039

CQAW039A2208

**A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma**

Author(s): Kay Richard, Huilin Hu, Goldsmith Paul, El Baghdady Yasser, Erpenbeck Veit, Gupta Sachin, Laurencin Marie, Brightling Chris, Gonem Sherif, Siddiqui Salman, Wild James

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## List of abbreviations

ACD	Asthma Control Diary
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AHR	Airways Hyperreactivity
ALT	alanine aminotransferase
AQLQs	Asthma Quality of Life Questionnaire
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Curve
AUCtau	Area Under the Curve from time zero to the end of the dosing interval tau
BAL	Bronchoalveolar Lavage
b.i.d.	Twice a day
BMI	Body Mass Index
CD4	Cluster of Differentiation Antigen 4
CK	Creatinine Phosphokinase
CK-MB	MB isoform of Creatinine Phosphokinase
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper)
CRO	Contract Research Organization
CRTH2	Chemoattractant Receptor-Homologous molecule expressed on TH2
DDI	Drug-Drug Interaction
DP2	Alternative nomenclature for CRTH2 receptor
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
ERS	European Respiratory Society
FDA	Food and Drug Administration
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
eGFR	Estimated Glomerular Filtration Rate

GINA	Global Initiative for Asthma
Gd-DTPA	Gadolinium-diethylenetriaminepentaacetic acid
He-3 MRI	Hyperpolarized Helium Magnetic Resonance Imaging
hCG	Human Chorionic Gonadotropin
HGC	Hard Gelatin Capsules
HRCT	High Resolution Computed Tomography
IC50	Inhibitory Concentration 50% (half maximal)
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IOM	Impulse Oscillometry
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUD	Intra-Uterine Device
IUS	Intra-Uterine System
IV	Intravenous
LABA	Long Acting $\beta$ 2 Agonist
MBW	Multiple Breath Washout
MDRD	Modification of Diet in Renal Disease
MDI	Metered Dose Inhaler
MID	Minimally Important Difference
NOAEL	No-Observable Adverse Event Level
OATP1B1	Organic Anion Transporter Protein family member 1B1
OCS	Oral Corticosteroids
PEFR	Peak Expiratory Flow Rate
PG	Prostaglandin
PGD2	Prostaglandin D2
PGt	Pharmacogenetic
PGx	Pharmacogenomic
PK	Pharmacokinetic
p.o.	Taken by mouth
MBW	Multiple Breath Washout

q.d.	Quaque die/once a day
RAST	Radioallergosorbent test
SABA	Short Acting $\beta$ 2 Agonist
SAE	Serious Adverse Event
ULN	Upper Limit of Normal
WOCBP	Women of Child Bearing Potential

## Glossary of Terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	The investigational drug whose properties are being tested in the study as well as their associated placebo and active treatment controls. This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination.
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug/treatment	Any drug or combination of drugs in any study arm administered to the patient as part of the required study procedures, including placebo and active drug run-ins
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

## Amendment rationale

This protocol has been amended mainly to provide clarification about the interim analysis to be performed in the study.

At time of writing nine patients had been enrolled into the study. The amendment is not expected to impact the study results and the changes do not impact on the safety of patients participating in the study.

## Changes to the protocol

More information regarding type and timing of the interim analysis to be performed in the study has been provided making clear that a futility analysis will be performed when approximately 30 patients have completed their Visit 5. Main protocol sections modified due to this change are sections 3.1, 3.5 and 9.6.

The upper limit for the range of admissible Body Mass Index (BMI) has been increased from 40 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup>. This change has been made in order to allow the inclusion of more patients with severe asthma as it is now apparent that many of the more severely asthmatic patients in our study population have higher BMIs. Main protocol sections modified due to this change are Section 4.2 and the Protocol Synopsis section.

The time points for performing body plethysmography and carbon monoxide transfer have been indicated in the assessment schedule (Table 6-1).

Further, clarification has been provided that the burden of tests assessment with regards to testing for volatile organic compounds applies to all patients and not only those undergoing MRI. This clarification is reflected in Section 6.4.10 and footnote 9c in the assessment schedule (Table 6-1).

Also incorporated, are other smaller editorial changes that include correction of typographical errors and rewording to ensure consistency between protocol sections.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

## Protocol synopsis

**Title of study:** A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma

**Purpose and rationale:** The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

**Objectives:** The primary objective of this study is to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

The secondary objectives include:

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.
- To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

**Population:** The study population will include male and female symptomatic patients with sputum eosinophilia and moderate-to-severe asthma (GINA 2-5) who are incompletely controlled on their current therapy. They will be chosen to investigate the efficacy of QAW039 as an add-on to their current therapy. Patients aged over 18 years will be selected for the trial. A total of 60 patients (30 per treatment arm) will be randomized from a single center in the UK.

### Inclusion/Exclusion criteria:

Inclusion criteria:

- Written informed consent must be obtained before any assessment is performed.
- Males and females of any race who are over the age of 18 years at the time informed consent is obtained.
- Physician diagnosis of asthma, as per GINA guidelines GINA guidelines and currently prescribed ICS or ICS-LABA therapy.
- Patients who are demonstrated to have reversible airway obstruction, significant FEV1 variability or airway hyperresponsiveness (AHR), or who have shown such responses in previous test(s) within the last five years.

- An ACQ score  $\geq 1.5$  at randomisation or  $\geq 1$  exacerbations (requiring higher than the patient's normal dose of OCS (oral corticosteroids) or IV corticosteroids for  $\geq 3$  days) in the past 12 months. The definition of exacerbations includes episodes during which the patient self-administered higher doses of OCS as part of a documented self-management plan initiated by the patient's general practitioner or respiratory physician.
- Patients currently on GINA step 2 to step 5 asthma therapies.
- Sputum eosinophil count  $\geq 2\%$  at screening.

Exclusion criteria:

- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (CRTH2 antagonists).
- History of long QT syndrome or whose QTc interval (Fridericia's) is prolonged  $> 450$  msec for males and  $>470$  msec for females at screening or baseline.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test ( $> 5$  mIU/mL).
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the study treatment and for 5 days (5 half-lives) after treatment.
- Acute illness other than asthma which, in the investigator's opinion, may compromise the well-being of the patient or study endpoint assessments at the start of the study
- Patients who are considered unsuitable for inclusion by the assessing physician due to serious co-morbidities such as cancer, emphysema or significant bronchiectasis.
- Recent (within 6 weeks of screening) or current lower respiratory tract infection.
- Patients who have been hospitalized or required high-dose ( $>10$ mg prednisolone/day) oral corticosteroid (OCS) therapy within 6 weeks of the screening visit.
- Patients with clinically significant laboratory abnormalities (not associated with the study indication) at screening.
- Patients who have a clinically significant abnormality on a 12-lead ECG recorded within one month prior to or at screening.
- Patients with a body mass index (BMI)  $< 17$  or  $> 45$  kg/m<sup>2</sup>.

- Patients on maintenance immunotherapy who either began their immunotherapy regimen or had a clinically relevant change to their immunotherapy within 1 month prior to granting informed consent.
- Use of immunosuppressive medication (except inhaled and topical corticosteroids and low dose ( $\leq 10$ mg prednisolone/day) oral corticosteroids) within 30 days before randomization into the study.
- Use of Xolair (omalizumab) within 6 months before randomization into the study.
- History of alcohol or other substance abuse.
- A positive hepatitis B surface antigen or hepatitis C virus antibody, as determined by medical history and/or subject's verbal report.
- A positive human immunodeficiency virus test or is taking anti-retroviral medications, as determined by medical history and/or subject's verbal report.
- Patients on high-dose statin therapy.
- Patients on statin therapy with a CK level  $>2$  X ULN at screening.

Additional exclusion criteria for patients who have agreed to take part in the in the MR Imaging part of the study

- Patients with a contra-indication to MRI scanning: i.e. patients who are non MRI compatible (ferro-magnetic metallic implants, pacemakers) as per the MRI questionnaire.
- Patients with potential adverse reactions to Gd-DTPA intravascular MRI contrast agent.

**Investigational and reference therapy:** QAW039 (and matching placebo) will be provided as hard gelatin capsules in blister packs of 2 dose strengths (25mg and 150mg) to deliver 225 mg b.i.d..

**Study design:** This study uses a 2-treatment arm (Placebo or QAW039), parallel-group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients will undergo a 2-week placebo run-in period during which their clinical stability and suitability for randomisation will be assessed. Asthma patients who are already receiving ICS or ICS-LABA therapy are the target population for this study. All patients will be allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients will receive placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study will be single-blind because physicians will know that patients are on placebo, however the 12-week treatment period will be double-blind.

Visits to assess safety and efficacy are scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives will be performed at the end of the treatment period (week 12).

**Efficacy assessments:**



- Sputum cell analysis
- Spirometry
- Body plethysmography
- Carbon monoxide transfer factor
- Impulse and forced oscillometry
- High resolution computed tomography
- Multiple breath washout
- Hyperpolarized Helium-3 MRI imaging
- Bronchial biopsies and brushings
- Asthma Control Questionnaire
- Asthma Quality of Life Questionnaire - standardized
- Volatile organic compounds
- Fraction of Exhaled Nitric Oxide

**Other assessments:**

- Adverse events, laboratory values, vital signs and ECG
- Pharmacokinetics
- Biomarkers in blood and sputum

**Data analysis:** The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

The primary variable of the study is the change from baseline in sputum eosinophil percentage at week 12. As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log<sub>10</sub>-transformed scale. The baseline measurement is defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing (on log<sub>10</sub>-transformed scale)

## 1 Introduction

### 1.1 Background

Many patients with asthma fail to achieve adequate control of symptoms and exacerbations when treated with inhaled corticosteroids (ICS) or combinations of ICS and long-acting beta-agonists (LABA). Failure to respond to topical therapy may be due to multiple factors, including poor adherence, inadequate inhaler technique or corticosteroid resistance. Furthermore, there is evidence that some patients with asthma have prominent small airway disease that cannot be reached by standard inhalers. Such patients may require systemic (oral) therapy to control their airway inflammation. Current treatment options include the addition of a leukotriene modifier such as montelukast, but not all patients respond to this, and a significant proportion require step-up to long-term oral corticosteroids to achieve control, an unattractive option given the well-known side-effects of osteoporosis, muscle wasting and bruising. There is thus a need for effective oral anti-inflammatory therapies for asthma with greater efficacy than montelukast.

QAW039 is a highly selective and potent antagonist of prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) that binds to the CRTH2 (DP<sub>2</sub>) receptor, but not to the more general homeostatic PGD<sub>2</sub> receptor, DP<sub>1</sub>. QAW039 is expected to work by binding CRTH2 receptors on eosinophils and CRTH2<sup>+</sup> T lymphocytes in the blood, thus inhibiting the migration of eosinophils and CRTH2<sup>+</sup> CD4<sup>+</sup> lymphocytes into the airway tissues. Since these are major effector cells that drive the airway inflammation in asthma, the symptoms of the disease should be improved.

The study has been focussed on sputum eosinophilia, as a primary endpoint, for a number of reasons. Firstly, the reduction of sputum eosinophilia will be further confirmation of the mechanism of action of this target in man and will provide comparative data against earlier studies with competitor compounds ([Singh et al, 2009](#); [Barnes et al, 2011](#)). Secondly, the control of sputum eosinophilia has been shown to be an important measure in predicting the efficacy of anti-inflammatory treatments in asthma. Adults who had treatment adjusted to sputum eosinophils had a significantly reduced number of exacerbations compared with controls who did not. The comparative risk for exacerbations of standard care versus tailored care was 726 per 1000 versus 488 per 1000 (OR 0.36 [90% CI: 0.2 to 0.64]) ([Petsky et al, 2010](#); [Petsky et al 2007](#); [Chlumsky et al, 2006](#); [Jayaram et al, 2006](#); [Green et al, 2002](#)). Finally, therapeutic reduction of sputum eosinophilia has been shown to significantly decrease hospitalisations due to asthma exacerbation and to have beneficial impact on the geometry of the respiratory tract ([Haldar et al, 2009](#)).

Further information regarding QAW039 can be obtained from the Investigators' Brochure.

### 1.2 Purpose

The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to

establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

## 2 Study objectives

### 2.1 Primary objective

The primary objective of this study is to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

### 2.2 Secondary objectives

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.
- To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

### 2.3 Exploratory objectives

- To demonstrate that QAW039 provides significant improvement in standard physiological markers such as FEV<sub>1</sub>, as well as specific small airway markers measured with multiple breath washout (MBW) and impulse oscillometry, namely S<sub>acin</sub>, R5-R20 and AX, compared to placebo.
- To explore whether the efficacious effect of QAW039 therapy persists following the cessation of therapy.
- To explore whether quantitative computed tomography (CT) biomarkers at baseline predict response to therapy with QAW039.
- To explore changes in air trapping, as evaluated by quantitative computed tomography (CT), after 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in health-related quality of life as measured by the standardised Asthma Quality of Life Questionnaire (AQLQs) after 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in blood proteomic and transcriptomic profile following 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in exhaled volatile organic compounds (VOCs) following 12 weeks of treatment with QAW039 versus placebo.
- To explore the effect of QAW039 on ventilation heterogeneity, as measured by hyperpolarised helium-3 MRI (He-3 MRI), compared to placebo.
- To explore whether QAW039 attenuates eosinophilic airway inflammation as measured by bronchial brushings and bronchial biopsies, compared to placebo.
- To explore whether QAW039 attenuates features of remodelling in bronchial biopsies (including but not limited to the assessment of histological features of inflammatory and goblet cell number, reticular basement membrane thickness and assessment of collagen deposition) compared to placebo.

- To assess the pharmacokinetics of QAW039 in this population of asthma patients.

### 3 Investigational plan

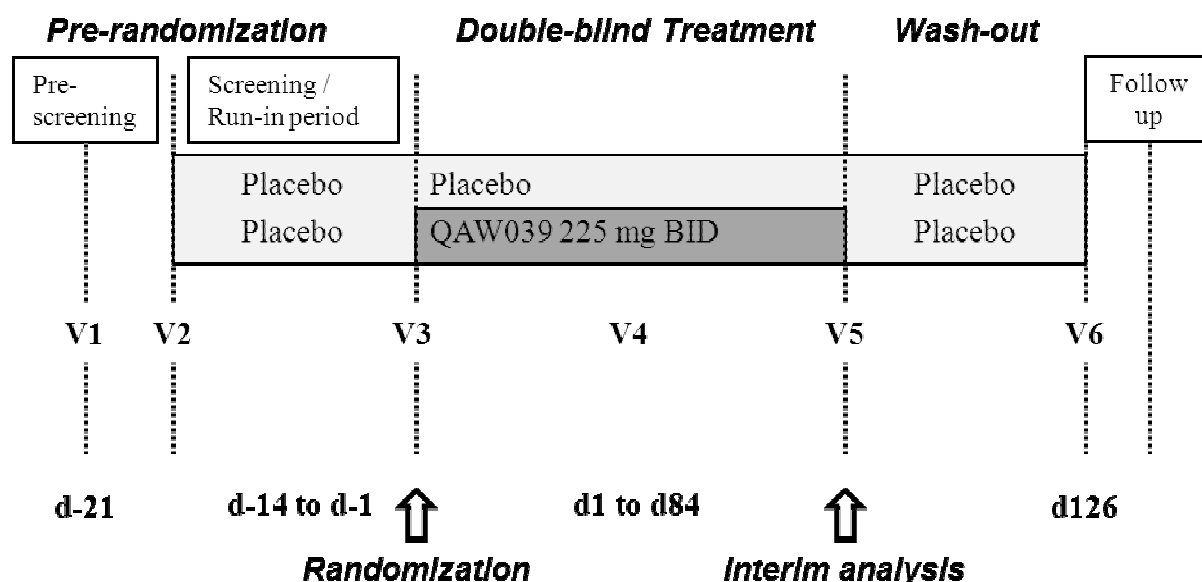
#### 3.1 Study design

This study uses a 2-treatment arm (Placebo or QAW039), parallel-group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients will undergo a 2-week placebo run-in period during which their clinical stability and suitability for randomisation will be assessed. Asthma patients who are already receiving ICS or ICS-LABA therapy are the target population for this study. All patients will be allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients will receive placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study will be single-blind because physicians will know that patients are on placebo, however the 12-week treatment period will be double-blind.

Visits to assess safety and efficacy are scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives will be performed at the end of the treatment period (week 12). An interim analysis for futility will be conducted when approximately 50% of the patients have completed their Visit 5. This interim analysis is intended to provide early delivery of key data points to facilitate forward planning of the program.

**Figure 3-1 CQAW039A2208 study design**



### 3.2 Rationale of study design

The study is designed to explore the anti-inflammatory and disease-modifying potential of QAW039 in asthmatics in vivo. It will examine the effect of QAW039 on top of conventional background therapy in a group of persistent, uncontrolled, moderate-to-severe asthmatics with sputum eosinophilia. In order to preserve trial integrity, this will be a parallel design study in which treatment is allocated in a randomized, double-blind and placebo-controlled manner. Placebo will be used in both active and placebo treatment groups during the run-in period in order to minimize the impact of “placebo-effect” on baseline fluctuations in patient reported outcomes prior to randomization. All patients will be allocated to placebo at visit 5 so that the knowledge that treatment has been withdrawn does not influence their assessment of their disease status.

The rationale for studying this group of patients is supported by the findings from an interim analysis of our clinical study, CQAW039A2201, in mild-to-moderate asthmatics. In this analysis, we found that patients who either have the most pronounced baseline reduction in predicted FEV<sub>1</sub> (<70%) and/or those who have pre-treatment, circulating eosinophilia (>300 eosinophils per  $\mu$ L blood) appeared to benefit to the greatest extent from 4 weeks treatment with the CRTH2 antagonist, QAW039, either in terms of change in ACQ score or % change in pre-bronchodilator FEV<sub>1</sub> or both.

By enriching further still for these two characteristics – sputum eosinophilia and circulating eosinophilia both correlate with disease severity and aspect of lung function in asthma ([Snell & Newbold, 2008](#)) – and allowing further time for the therapeutic response to develop ([section 3.3](#) below), we believe we will enhance the chance of measuring an enhanced therapeutic response and the possibility of observing fundamental changes in the underlying structure/function relationship in the asthmatic lung.

### 3.3 Rationale of dose/regimen, duration of treatment

Data from a one month study with a CRTH2 antagonist showed a continuous increase in FEV<sub>1</sub> over 4 weeks ([Barnes et al, 2011](#)). This observation is consistent with the mechanism of action, since CRTH2 antagonists, such as QAW039, should block inflammatory cells from entering the lung. The duration of 12 weeks was chosen because it is not clear when maximal efficacy will be observed from this type of treatment and this is the longest time covered by current toxicology studies for QAW039. Furthermore, as observations are being made with regards to changes in lung histology and geometry, we wished to give the maximal time to allow the best signal of efficacy to develop.

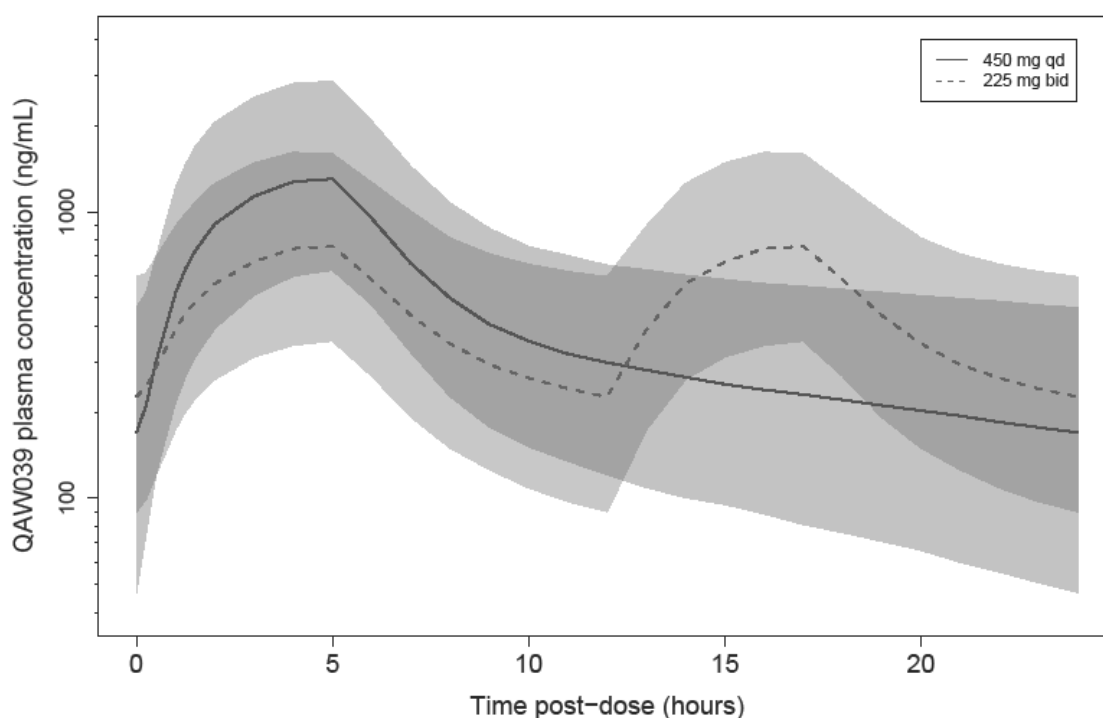
In CQAW039A2201, patients were dosed once daily for 4 weeks with 500 mg. At interim analysis when the first 63 patients had completed the study, no SAEs or deaths had occurred and the AEs observed did not significantly differ in their nature or severity between the active- and placebo-treated cohorts of patients.

A twice daily dose of 225 mg (totaling 450 mg per day) will be included in this study and will be dummied with matching placebo in order to prevent bias. Using a population based PK model constructed using data from earlier studies (CQAW039A2101 and CQAW039A2102) the anticipated plasma AUC<sub>tau</sub> of 11.6  $\mu$ g.h/mL [90% CI: 5.39-24.5] overlaps considerably

with the AUC<sub>tau</sub> modeled from a 500 mg daily dose (AUC<sub>tau</sub> 12.9 µg.h/mL [90% CI: 6.00 – 27.1]).

At steady state, the fluctuation index determined following 7 days of dosing in CQAW039A2102 was 315 % and 349 % following 100 mg q.d. and 300 mg q.d. dosing, is reduced to 135 % following 250 mg b.i.d. dosing reflecting the large peak to trough ratio following a q.d. regimen. The 450 mg will therefore be given in 2 equal doses (225 mg b.i.d., total of 8 capsules per day) to minimize the peak to trough ratio observed following q.d. dosing. In this way, we will maintain a higher minimum drug concentration compared to a once-daily regimen. The simulated concentration time profiles following 450 mg q.d. and 225 b.i.d. are illustrated below.

**Figure 3-2 Illustration of simulated repeat dose blood concentration time profiles at steady-state along with the blood IC<sub>90</sub> ranges\***



\*Dashed and solid lines represent the median model derived concentration time profiles (i.e. for the typical individual) and the shaded areas around represents the 5<sup>th</sup> and 95<sup>th</sup> quartiles of the simulated profile (i.e. they predict where we would expect 90% of the PK profiles to be in). Overlapping areas are represented by darker shades

### 3.4 Rationale for choice of comparator

Placebo will be used to preserve trial integrity.

As both placebo and QAW039 will be given in addition to the patients' conventional (pre-study) treatment there is no appropriate positive control that can be used in this situation given the range of disease severities to be included.

### 3.5 Purpose and timing of interim analyses/design adaptations

There will be an interim analysis for futility when data has been collected for approximately 50% of the patients following their Visit 5.

The purpose of this interim analysis is to provide early delivery of key data points to facilitate forward planning of the program.

### 3.6 Risks and benefits

The most significant preclinical findings have been an increase in heart rate in dogs and liver findings in mice (see exposure margins in investigator brochure). Neither of these events has been observed in other species. Both of these findings are readily monitored and have not been identified in the three healthy volunteer studies so far completed. Indeed, every indication from these studies suggests that QAW039 is safe and well tolerated. Our interim analysis of the first 63 mild-to-moderate, persistent asthmatic patients in the CQAW039A2201 study also showed no fatalities or serious adverse events and demonstrated no significant differences in the frequencies of adverse events between placebo and actively treated subjects.

A potential risk we have identified of relevance to this study, given the likely frequency of statin co-medication in this group of patients (estimated to be around 25%), is the interaction of QAW039 with the drug transporter molecule, OATP1B1. QAW039 is capable of inhibiting the OATP drug transporters (OATP1B1: IC<sub>50</sub> 1.8 µM, OATP1B3: IC<sub>50</sub> 14 µM and OATP2B1: IC<sub>50</sub> 145 µM, respectively). Of the three, it is the interaction with OATP1B1 which is of the highest potential importance because it has the lowest margin between the IC<sub>50</sub> of transporter inhibition and the maximum unbound exposure. The predicted maximal unbound concentration at steady-state following 450 mg q.d. dosing is 0.363 µM (90 %CI 0.174, 0.786) based on a population based pharmacokinetic model using data from CQAW0392201, and a protein binding of 88.2 % (DMPK R0800735). The maximal unbound steady state concentration relative to the IC<sub>50</sub> of OATP1B1 of 1.8 µM ranges from 2 to 10 fold, with a median of 5 fold. This exceeds the 10-fold recommended margin which suggests the need for a DDI study ([The International transporter Consortium, 2010](#)). The potential risk will be mitigated by moving to a 225 mg b.i.d. dosing regimen when the margin to the IC<sub>50</sub> will increase in the range from 4 to 20 fold (median of 10 fold) where the need for a DDI study becomes a borderline requirement.

As an additional precaution, only patients on low-to-medium statin doses (see [section 5.1.2](#)) will be allowed to take part in this study. Furthermore, exclusion of patients on statins with high baseline CK levels will take place and patients on statin medication who are included in the study will have regular monitoring for relevant symptoms and be subject to stopping criteria based on persistent myalgia and blood CK levels ([Jacobson, 2008](#)).

Investigative bronchoscopy is considered to be safe in asthmatic subjects ([Hattotuwa et al, 2002](#)) It is well tolerated even in those with severe asthma. Asthma exacerbations are rare and reduction in pulmonary function after the procedure is similar to that in subjects with less severe asthma ([Moore et al, 2011](#)). Professor Brightling's group has undertaken in excess of 300 research bronchoscopies at the Glenfield Hospital in Leicester in the last 8 years. Sore throat, small amounts of hemoptysis for 24-48h is commonly observed. One of his patients

was admitted over night following bronchoalveolar lavage (BAL) for observation but no treatment was required. BAL will not be performed in CQAW039A2208. None of his subjects have had a pneumothorax and they have had no deaths. The use of sedation and local anesthetics will be closely controlled and patients will be pre-medicated with bronchodilator and will be continuously monitored throughout the procedure. The procedure is therefore considered low risk.

The HRCT scan will expose the patients to a higher dose of radiation than they would normally be exposed to, and this may cause a very small increase in the risk of developing cancer. Careful radiation logs will be maintained to allow for margins to 10 mSv over 3 years exposure limits. Although both inspiratory and expiratory scans are planned, the actual numbers of scans performed will be determined in order to maintain an acceptable margin.

Low radiation dose HRCT scans will be performed for the purpose of this study. Each HRCT scan will be equivalent to approximately eight months' natural radiation exposure in the UK. We will closely monitor the radiation dose due to HRCT scans during the course of the study and the upper limit of radiation exposure will be equivalent to four years' natural radiation exposure in the UK.

The natural risk of fatal cancer in the UK population is about 1 in 4. We estimate that the amount of additional radiation exposure in this study will increase this risk slightly to 1 in 3.994 ([Health Protection Agency, 2011](#)).

Given that there is (a) preliminary data for QAW039 and published evidence from a competitor compound suggesting that CRTh2 antagonism is efficacious in asthmatic subjects ([Barnes et al, 2011](#)), (b) that patients with pre-existing heart and/or liver disease will be excluded (c) that cardiac and hepatic function will be monitored and (d) that the potential risk of statin co-administration is being managed by both CK-based exclusion criteria, lowering the QAW039 Cmax levels through b.i.d. dosing, and restrictions on the statin medication dose levels in recruited patients and relevant stopping criteria, Novartis consider both that the risks to these patients are modest and the benefit-risk ratio for the patients participating in this study is acceptable.

## 4 Population

The study population will include male and female symptomatic patients with sputum eosinophilia and moderate-to-severe asthma (GINA 2-5) who are incompletely controlled on their current therapy. They will be chosen to investigate the efficacy of QAW039 as an add-on to their current therapy. Patients aged over 18 years will be selected for the trial. A total of 60 patients (30 per treatment arm) will be randomized from a single center in the UK.

### 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed
2. Males and females of any race who are over the age of 18 years at the time informed consent is obtained.



3. Physician diagnosis of asthma, as per GINA guidelines and currently prescribed ICS or ICS-LABA therapy.
4. Patients who are demonstrated to have reversible airway obstruction, significant airflow variability or airway hyperresponsiveness (AHR), or who have shown such responses in previous test(s) within the last five years.
  - Reversible airway obstruction is defined as an increase of  $\geq 12\%$  and  $\geq 200$  ml in FEV<sub>1</sub> over the patient's pre-bronchodilator value in liters within 10-15 minutes after inhaling a total of 360  $\mu$ g of albuterol or 400  $\mu$ g salbutamol via MDI (reversibility test). The administration of albuterol or salbutamol for the reversibility test is to be within 30 minutes after pre-bronchodilator spirometry.
  - A positive airways hyper-reactivity (AHR) test result is defined as a provoked fall in FEV<sub>1</sub> of 20% (PC20) by methacholine at  $\leq 8$  mg/ml when not on ICS or  $\leq 16$ mg/ml on ICS therapy.
  - A change in FEV<sub>1</sub> of  $> 12\%$  over two measurements over the previous year ([Huang et al, 2011](#)).
5. An ACQ score  $\geq 1.5$  at randomisation or  $\geq 1$  exacerbations (requiring higher dose than the patient's normal dose of OCS or IV corticosteroids for  $\geq 3$  days) in the past 12 months. The definition of exacerbations includes episodes during which the patient self-administered higher doses of OCS as part of a documented self-management plan initiated by the patient's general practitioner or respiratory physician.
6. Patients currently on GINA step 2 to step 5 asthma therapies.
7. Sputum eosinophil count  $\geq 2\%$  at screening.

## 4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives to the time of enrollment, whichever is longer.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (CRTH2 antagonists).
3. History of long QT syndrome or whose QTc interval (Fridericia's) is prolonged  $> 450$  msec for males and  $> 470$  msec for females at screening or baseline.
4. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test ( $> 5$  mIU/mL).
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and for 5 days (5 half-lives) after treatment. **Effective contraception methods include:**

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential

7. Acute illness other than asthma which, in the investigator's opinion, may compromise the well-being of the patient or study endpoint assessments at the start of the study.
8. Patients who are considered unsuitable for inclusion by the assessing physician due to serious co-morbidities such as cancer, emphysema or significant bronchiectasis.
9. Recent (within 6 weeks of screening) or current lower respiratory tract infection.
10. Patients who have been hospitalized or required high-dose (>10mg prednisolone/day) oral corticosteroid (OCS) therapy within 6 weeks of the screening visit.
11. Patients with clinically significant laboratory abnormalities (not associated with the study indication) at screening including (but not limited to):
  - Total white blood cell count <2500 cells/ $\mu$ L at screening.
  - AST or ALT>2.0 X ULN or total bilirubin >1.3 X ULN at screening
  - Estimated Glomerular Filtration Rate (eGFR) by the MDRD equation <55 mL/minute/1.73 m<sup>2</sup> at screening.
12. Patients who have a clinically significant abnormality on a 12-lead ECG recorded within one month prior to or at screening.
13. Patients with a body mass index (BMI) < 17 or > 45 kg/m<sup>2</sup>.
14. Patients on maintenance immunotherapy who either began their immunotherapy regimen or had a clinically relevant change to their immunotherapy within 1 month prior to granting informed consent.

15. Use of immunosuppressive medication (except inhaled and topical corticosteroids and low dose ( $\leq 10$ mg prednisolone/day) oral corticosteroids) within 30 days before randomization into the study.
16. Use of Xolair (omalizumab) within 6 months before randomization into the study.
17. History of alcohol or other substance abuse.
18. A positive hepatitis B surface antigen or hepatitis C virus antibody, as determined by medical history and/or subject's verbal report.
19. A positive human immunodeficiency virus test or is taking anti-retroviral medications, as determined by medical history and/or subject's verbal report.
20. Patients on high-dose statin therapy, defined as:  
  
Only patients on 40 mg or less of fluvastatin, 20 mg or less of simvastatin and atorvastatin or 20 mg or less of pravastatin or rosuvastatin (10 mg or less if Asian) will be recruited into the study. No increase in statin doses in excess of those listed above will be permitted during the study
21. Patients on statin therapy with a CK level  $>2 \times$  ULN at screening.

**Additional exclusion criteria for patients who have agreed to take part in the in the MR Imaging part of the study**

22. Patients with a contra-indication to MRI scanning: i.e. patients who are non MRI compatible (ferro-magnetic metallic implants, pacemakers).
23. Patients with potential adverse reactions to Gd-DTPA intravascular MRI contrast agent.

## **5 Treatment**

### **5.1 Protocol requested treatment**

#### **5.1.1 Investigational treatment**

- Name: QAW039
- Formulation: hard gelatin capsule
- Appearance: size - 0, color - pink opaque
- Unit dose: 2 strengths – 25 and 150 mg
- Packaging: Blister packs

QAW039 will be supplied in blister packs of two strengths: 25 mg (3 capsules to be taken morning and night) and 150 mg (1 capsule to be taken morning and night). The patients will therefore take 225 mg twice daily for the period of the study.

The placebo is of identical appearance and will be identically packaged.

#### **5.1.2 Additional study treatment**

No additional treatment beyond investigational treatment is requested for this trial.

### 5.1.3 Treatment arms

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1.

- Arm 1: QAW039 225mg (1 capsule of QAW039 150 mg and 3 capsules of QAW039 25mg)
- Arm 2: Placebo (1 capsule of Placebo for QAW039 150mg and 3 capsules of Placebo for QAW039 25mg)

### 5.1.4 Treatment assignment

Randomization numbers will be assigned in ascending, sequential order to eligible patients in accordance with entry into the study. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. Treatment Allocation Cards will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

### 5.1.5 Treatment blinding

This is a double-blind study in which medication will be supplied in a single blind fashion utilizing an un-blinded pharmacist. Patients and Investigator will remain blinded to the treatment allocation during double blind treatment period. During run-in and washout period only patients will remain blinded. The active drug (QAW039) will be supplied in blister packs of two strengths 25mg and 150mg. The Placebo capsules are of identical appearance and will be identically packed. **In order to maintain the blind from the patient's point of view, investigators should not divulge information regarding the fact that all individuals will be assigned to placebo during the run-in and wash-out phase of the study.**

## 5.2 Treating the patient

### 5.2.1 Patient numbering

#### Randomization number

Patients will be assigned randomization numbers using Treatment Allocation Cards based on stratification into use/not use of oral corticosteroids and bronchoscopy/no bronchoscopy. See [Table 5-1](#).

**Table 5-1 Randomization Strata**

Strata	Strata description
Stratum 1	Use of OC and bronchoscopy
Stratum 2	Use of OC and no bronchoscopy
Stratum 3	Not use of OC and bronchoscopy
Stratum 4	Not use of OC and no bronchoscopy

Patients who are prematurely withdrawn from the study will not be replaced.

### 5.2.2 Dispensing the study treatment

Study site will be supplied with study drug by Novartis organized in single blinded medication kits. Study medication kits comprise cartons containing blisters of Hard Gelatin Capsules (HGCs) of QAW039 25mg, QAW039 150mg and Placebo to QAW039.

All the kits have a 2-part single-blinded label on the outside. Immediately before dispensing a kit, the un-blinded investigator staff (un-blinded pharmacist) will detach the tear-off part of this label from the packaging and affix it to the source document for that patient's unique patient number.

**Capsules should only be removed from the blister immediately before dosing.**

**All blister packs and outer kit cartons must be returned to the site** at each of the following Visits 3, 4, 5 and 6 (or the final visit for patients who withdraw from the study prematurely).

### 5.2.3 Supply, storage and tracking of study treatment

Study treatment must be received by a designated person (un-blinded pharmacist) at the study site, handled and stored safely and properly, and kept in a secured location to which only the designated persons have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in English language and comply with the UK legal requirements. They will include storage conditions for the drug, but no information about the patient except for the subject number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by an unblinded monitor during site visits and at the completion of the trial. Patients will be asked to return all remaining unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or designee or to the Novartis address provided in the investigator folder at the site.

No study medication should be destroyed until completion of the final clinical study report and notification is received from the Clinical Trial Head.

### 5.2.4 Instructions for prescribing and taking study treatment

QAW039 and matching placebo will be provided as oral capsules, equally matched in size, shape and color.

Patients will be instructed to come to the clinic in time to complete pre-dosing assessments and to allow QAW039/placebo study medication to be taken as soon as possible thereafter.

On non-visit days, patients will be instructed to take all four capsules in the morning between 08:00 and 11:00 from their QAW039/placebo medication kits.

On all days, patients should take their four evening capsules of QAW039/placebo approximately 12 hours after their AM dose +/- 30 minutes.

The investigator should instruct the patient to take the study drug exactly as prescribed and by stating that adherence is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

All used and unused blister kits must be returned by the patient at Visits 3, 4, 5 and 6 (or their final visit for patients who withdraw from the study prematurely).

The date and time of dose administration at each clinic visit (Visits 2-6) will be recorded on the Dosage Administration Record CRF.

### 5.2.5 Permitted dose adjustments and interruptions of study treatment

No adjustments to the study drug dosage or schedule is permitted throughout the trial.

### 5.2.6 Medication restrictions

Medication	Withdrawal time
Short-acting bronchodilator	6 hrs
Long-acting bronchodilator	12 hrs
Xanthines (Theophyllines)	12 hrs
Short-acting anticholinergics	8 hrs
Long-acting anticholinergic	24 hrs
Leukotrine antagonist (LTRA)	12 hrs
Inactivated vaccine	No administration within 48 hrs prior to a study visit

Patients will be instructed to abstain from taking any restricted medication prior to each spirometry visit unless absolutely necessary.

If any restricted medication is taken in less than the permissible withdrawal time indicated in table 5.2.6 prior to spirometry testing, patients will be given another opportunity within the next 2 days to undergo spirometry testing with the requirement to withhold from taking any restricted medication for the required time periods indicated in table 5.2.6. If patients are unable to comply on the second attempt then this will be recorded in the patients' notes. Thereafter, at all subsequent spirometry testing points, patients will be required to withhold restricted medication prior to testing in accordance with table 5.2.6.

All other scheduled visit assessments should continue as planned but the dose and the approximate time of taking restricted medication will be captured in the patient's CRF

### **5.2.7 Background therapy**

All patients should keep their background therapy doses unchanged during the course of the study. If their background medication needs to be altered, patients should be discontinued from the study. Patients may vary the dose of their rescue medication as necessary.

### **5.2.8 Concomitant treatment**

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts study must be listed on the Concomitant medications/Significant non-drug therapies of study CRF.

### **5.2.9 Prohibited treatment**

Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt the investigator should contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started.

## **5.3 Discontinuation of study treatment and premature patient withdrawal**

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

Study treatment must be discontinued and the patient withdrawn from the trial under the following circumstances:

- Withdrawal of informed consent
- Asthma exacerbation
- Adverse events for which continued exposure to the study drug would be detrimental
- Heart rate of >100 b.p.m. measured on 2 occasions, approximately 10 minutes apart, with the patient at rest
- Abnormal laboratory results violate liver function rules:
  - a. ALT or AST  $\geq$  5xULN or
  - b. ALT or AST  $\geq$  2.5xULN and total bilirubin  $\geq$  1.5xULN
- Pregnancy
- If the patient has had excessive use of rescue medication the investigator should assess whether it is safe for the patient to continue in the study
- If patients on statin therapy complain of persistent muscle pain without any obvious cause for greater than 3 days accompanied by increase in CK levels > 10 X ULN or persistent intolerable muscle pain regardless of the accompanying CK level.

- Unblinding of the study treatment for any reason

Protocol deviations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

If premature withdrawal occurs for any reason, the patient should return to the clinic as soon as possible for a Premature Subject Withdrawal (PSW) visit. The investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the End of Treatment CRF.

In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

#### 5.4 Asthma exacerbations

Criteria for asthma worsening are based on diary data, clinic visit spirometry, and investigators clinical judgment. All the worsening of asthma symptoms considered by the investigators to be asthma exacerbation will be captured on the asthma exacerbation episode CRF.

A **severe asthma** exacerbation is defined as treatment with rescue or increase in maintenance systemic corticosteroids for at least 3 days (or equivalent) and hospitalization or emergency department visit (greater than 24 hours) or death due to asthma. A **moderate asthma** exacerbation is treatment with rescue or increase in maintenance systemic corticosteroids either as an outpatient or in emergency department visits (less than or equal to 24 hours).

Patients who are deemed to have had an exacerbation should either not be enrolled into this study (if the exacerbation is in the run-up to randomization) or should be withdrawn from this study if the exacerbation occurs during the treatment or washout periods of the study.

Patients who have had an exacerbation during the run-in period may be screened for study entry again at a later stage once a minimum of 6 weeks following recovery has elapsed.

#### 5.5 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Two sets of emergency code cards are provided to the Novartis Pharma Organization. One set is to be retained by the country Pharma Organization (or any entity to which this responsibility has been delegated) and one set is to be distributed to the investigators. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secured place but must be accessible in case of an



emergency. The investigator will receive a masked code break card for each patient, with details of the drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason except other than an emergency. When the investigator removes a scratch-off cover he/she must note the date, time and reason for removing it and retain this information with the patient case report form documentation. The unmasking treatment code should not be recorded in the patient's CRF. The investigator must also immediately inform the Novartis local monitor or designee that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable.

Study drug must be discontinued after emergency unmasking. Study drug must also be discontinued for any patient whose treatment code has been inadvertently broken or for any non-emergency reason.

## **5.6 Study completion and post-study treatment**

Study completion for a patient will occur after he/she has completed 20 weeks of treatment (through to Visit 6) or they have prematurely withdrawn. Completion of the study will be when all randomized patients have completed 20 weeks of treatment.

Patients completing the treatment period will not be given further access to study drug because the risk/benefit ratio will not yet have been substantiated and there are already other marketed therapeutic alternatives available to treat these patients. At the time of study completion or early termination, all patients will be placed on the appropriate asthma treatment as prescribed by the investigator.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

## **5.7 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the relevant ethics committees of the early termination of the trial.

## **6 Visit schedule and assessments**

Table 6-1 lists all of the assessments to be performed in the study and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day or as close to it as possible.

Patients who discontinue study treatment should also return for the visit indicated by the asterisk (\*).

**Table 6-1 Assessment schedule**

Visit	1	2	3	4	5 and STC	6 and TD and/or PSW*
Visit window		+/- 3days	+/- 3days	+/- 3days	+/- 3days	+/- 3days
Day	-21	-14	1	42	84	126
<b>Evaluations</b>						
Obtain informed consent	x					
Inclusion/Exclusion criteria	x	x	x			
Demographic information	x					
Medical and Asthma history	x					
BD reversibility / PC20 <sup>1</sup>		x				
Skin prick test		x <sup>10</sup>				
PK <sup>6</sup>				x	x	
Leicester asthma diary <sup>8</sup>	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x
Height	x					
Weight	x					x
Vital signs	x					x
ECG	x		x	x	x	x
Urinalysis	x	x	x	x	x	x
Pregnancy test <sup>7</sup>	x					x
<b>Safety biomarkers</b>						
Haematology	x		x	x	x	x
Serum Chemistry	x		x	x	x	x
Assessment of AEs		x	x	x	x	x
Autoantibodies <sup>5</sup>			x			
<b>Pulmonary function tests</b>						
Spirometry <sup>a</sup>			x	x	x	x
Body plethysmography			x		x	x
CO transfer factor			x		x	x
Forced and Impulse oscillation technique			x		x	x
Multiple breath washout			x		x	x
<b>Efficacy biomarkers</b>						
Sputum analysis	x <sup>9</sup>		x	x	x	x
HRCT(Quantitative) <sup>a,b</sup>			x <sup>2</sup>		x <sup>3</sup>	
He-3 MRI imaging <sup>a</sup>			x		x	
Bronchoscopy & Bronchial biopsy <sup>a</sup>			x		x	
Volatile organic compounds			x		x	x
Fraction exhaled nitric oxide (FeNO <sub>50</sub> )			x		x	x

Visit	1	2	3	4	5 and STC	6 and TD and/or PSW*
Visit window		+/- 3days	+/- 3days	+/- 3days	+/- 3days	+/- 3days
Day	-21	-14	1	42	84	126
Evaluations						
Blood biomarkers			x	x	x	x
mRNA analysis <sup>4</sup>			x		x	x
DNA analysis <sup>4</sup>			x			
Patient reported outcomes						
ACQ		x	x	x	x	x
AQLQs		x	x	x	x	x
Study processes						
Study randomization			x			
Dispense Study Medication		x	x	x	x	
Study Completion form						x

## Notes

STC = Study treatment completion

TD = Treatment discontinuation

PSW = Premature Subject Withdrawal

X = assessment to be recorded on clinical data base

S = assessment to be recorded on source documentation only and will not be entered into the CRF

1 = If tests have not been previously performed.

2 = Performed on both inspiration and expiration

3 = Performed on expiration only

4 = Separate informed consent will be obtained before any RNA/DNA collection. Refusal to consent to collection of RNA/DNA material will not exclude the patient from participation in the study.

5 = Autoantibody sample will be taken and stored and only analyzed if pre-existing autoimmune disease has to be excluded

6 = Blood for PK assessments will be drawn prior to taking the morning study medication on day 42 and BOTH prior to and 3 hours after study medication has been taken on the morning of day 84

7 = A serum pregnancy test will be performed on female patients at visit 1, while a urinary pregnancy test will be performed at visit 6 and TD or PSW

8 = "Leicester" diary is local diary used by site to monitor patients' condition data from this will not be entered into our databases

9 = Patients' sputum will only be tested for % sputum eosinophil count at this visit. Patients, who do not have a sputum eosinophil count  $\geq 2\%$  at visit 1, may return approximately 1 week later for re-testing. If at re-testing the sputum inclusion criterion is met, visit 2 should be scheduled to occur 1 week later

10 = Patients with historical positive skin prick tests need not repeat them at this visit

a = These assessments will take an average of three separate clinic days to perform. The tests are grouped into study days A, B and C (see below). Therefore, they will be spread over a period of at most one week that includes the nominal visit date above. The bronchoscopy needs to be performed last as there may be carryover effects for a couple of days on airway inflammation, in particular. Due to potential interference between assessments, induced sputum analysis and bronchoscopy cannot be performed on consecutive days, but the (A) and (B) study day groupings can be interchanged providing there is still a day between sputum and bronchoscopy.

Study day A: Breath tests, sputum, HRCT (to be performed in this order whenever possible)

Study day B: He-MRI

Study day C: Bronchoscopy and biopsy

b = Subject's individual levels of radiation exposure will be monitored during the course of the study. The maximum allowed radiation dose from research studies will be 10mSv over the course of this and all other previous research studies in the previous three years. Patients who are likely to exceed this dose will not have further CT scans. These scans will not be performed for female patients who are under the age of 30 years

c = May not be performed on subjects depending on investigator's assessment of burden of tests

**A follow-up telephone call will take place approximately 1 month after study completion or discontinuation of therapy for any reason.**

## **6.1 Information to be collected on screening failures**

Patients discontinuing prior to randomization are considered screening failures.

If a patient discontinues before starting the study medication (at visit 2), only the demographic information, any adverse events or asthma exacerbations plus the related concomitant medication and Screening Log entry with the primary reason for screening failure should be completed in the CRF. It is not necessary to complete all the required evaluations at the time of discontinuation unless medically indicated.

The following information/demographics will be collected and recorded in the CRF:

- Subject number
- Subject's initials
- Date of birth
- Gender
- Race and ethnicity
- Primary reason for not continuing
- Adverse events or asthma exacerbations that have occurred since signing Informed

Consent

- Related concomitant medication for any AEs or asthma exacerbations.

## **6.2 Patient demographics/other baseline characteristics**

The following demographics / baseline characteristics will be collected and recorded in the CRF:

- Date of birth

- Gender
- Race and ethnicity
- Height
- Weight
- Date of diagnosis of asthma
- Smoking history
- Relevant medical history
- Prior concomitant medications (asthma related and non-asthma related)
- Baseline physical examination (not data based other than in context of relevant medical history)
- Vital signs
- ECG findings
- Hematology and clinical chemistry
- Urinalysis
- Historical evidence of reversibility or airways hyper-reactivity and allergy or atopy (specify test or tests), if available and relevant timings should be included.
- Baseline spirometry (FEV1 and FVC), and reversibility (if no historical data)

### **6.3 Treatment exposure and compliance**

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits by recording capsule counts from the previously dispensed blister strips.

The total number of doses of study drug administered since the last dispensing visit will be recorded in the CRFs at Visits 3, 4, 5 and 6 for each patient on the CRF. For patients who discontinued during the study this will be recorded at the discontinuation visit.

All doses of study drug taken at the clinic visits should be from the newly assigned medication packs. Returned study drug should not be used for dosing.

### **6.4 Efficacy**

As this is a single center study, central reading centers will not be required.

#### **6.4.1 Sputum cell analysis**

Sputum will be induced and assessed for differential cellular content (absolute numbers and percentages) as previously described ([Pavord et al, 1997](#)). Sputum induction will be performed through the inhalation of hypertonic saline. All subjects will have a baseline FEV1 measured and the procedure stopped if:

- a. The subject's FEV1 drops by greater than 20% of the post-salbutamol FEV1 baseline value
- b. The subjects feels any discomfort and does not want to continue with the saline inhalation procedure
- c. The investigator feels it is unsafe to continue with the saline inhalation

#### **6.4.2 Spirometry**

All clinic visits for spirometry, body plethysmography and carbon monoxide transfer factor will occur in the morning.

Equipment for spirometry assessments will be provided locally and all measurements will be reviewed by trained spirometry technicians or appropriate physicians. Refer to [Appendix 3 Spirometry Guidance](#), for further details on spirometry testing. Body plethysmography and carbon monoxide transfer factor will be performed according to standard ATS / ERS guidelines.

#### **6.4.3 Oscillometry**

The forced oscillation technique (FOT) will be performed using a commercially available impulse oscillometry device, namely the Jaeger MasterScreen Impulse Oscillometry System, as well as a specially built device from the University of Nottingham. The device from the University of Nottingham will only be used in subjects who undergo MRI.

The forced oscillation device from the University of Nottingham will be calibrated before each test using a standard protocol. Participants will wear a nose clip and oscillations will be delivered to their airways by means of a mouthpiece while they breathe slowly. The minimum resistance at 2 Hz and 8 Hz will be recorded during deep inspirations performed at the instruction of the investigator.

Impulse oscillometry (IOS) is performed using a commercially-available system, according to standard guidelines. This is calibrated daily using a 3-litre syringe and a standard 0.2 kPaL-1s-1 calibration mesh. Participants wear a nose clip and audible pulses of sound containing a range of frequencies from 5-20 Hz are delivered to their airways by means of a mouthpiece while they breathe normally. Patients are asked to support their cheeks during the test in order to avoid dissipation of the impulses in the mouth. Measures of the frequency-dependence of resistance and reactance, designated R5-R20 (resistance at 5 Hz minus resistance at 20 Hz) and AX (reactance area) respectively, are calculated by the IOS software.

#### **6.4.4 High Resolution Computed Tomography (HRCT)**

All images will be acquired with spirometric gating. Before CT scanning, supine spirometry will be performed to obtain supine lung volume measurements (slow vital capacity [SVC], inspiratory capacity and expiratory reserve volume). Inspiratory and expiratory CT scans at pre-determined SVC (e.g. 80% and 20% SVC) will be obtained. Expiratory scans allow quantitative analysis of air trapping and emphysema, while inspiratory scans allow the quantification of bronchial wall thickening

#### **6.4.5 Multiple Breath Washout (MBW)**

MBW is performed using a modified Innocor gas analyser. Participants wear a nose clip and breathe a known concentration (0.2%) of an inert and non-absorbed gas, sulphur hexafluoride (SF<sub>6</sub>), via a mouthpiece connected to the Innocor device, until the concentration in their exhaled breath reaches a steady state (the wash-in phase). Participants are then switched to breathing room air and encouraged to maintain a steady respiratory frequency of 12 breaths per minute and a tidal volume of approximately 1 litre, making use of a real-time display of

these parameters. The concentration of SF<sub>6</sub> in exhaled breath is recorded during this 'wash-out' phase until it reaches 1/40 of the original concentration (0.005%). A number of parameters are derived from the raw MBW data using custom software, including Scnd and Sacin. Scnd is thought to represent ventilation inhomogeneity arising from conductive airway disease, while Sacin represents ventilation inhomogeneity arising from acinar airspace disease.

## **6.4.6 Hyperpolarized Helium-3 MRI Imaging (He-3 MRI)**

### **6.4.6.1 <sup>3</sup>He Hyperpolarization**

<sup>3</sup>He will be hyperpolarized on site in Sheffield with regulatory approved (UK-MAIMP-29724) equipment and administered through a Tedlar bag. <sup>3</sup>He will be delivered in 300-400 ml doses according to total lung capacity made up to one liter with 600-700 ml nitrogen.

#### **6.4.6.1.1 <sup>3</sup>He MRI**

Patients will be placed inside a custom <sup>3</sup>He body coil inside the 1.5T magnet and the following <sup>3</sup>He MRI pulse sequences will be acquired with sensitivity to: (i) static breathold ventilation heterogeneity, (ii) Apparent Diffusion Coefficient mapping and (iii) dynamic gas flow and washout.

- a. A low flip angle 3D gradient echo sequence will be used to image ventilation distribution. Images will be acquired during a 13 second breath hold following inhalation of the gas from FRC. This exam will be performed twice in the first session as a means of assessment of baseline repeatability of ventilated volume.
- b. ADC images will be acquired with simultaneous ventilation images for spatial registration to the ventilation images described above. ADC images will be processed and the results will also be presented as spatial ADC maps for comparison with HRCT and in histogram format.
- c. 3D dynamic images of gas inflow and washout will be acquired with a time resolved sequence and the washout time constants will be derived for comparison with MBW.

#### **6.4.6.1.2 <sup>1</sup>H lung MRI**

<sup>1</sup>H lung MRI (anatomy and contrast enhanced Gd-DTPA perfusion scans) will also be performed.

## **6.4.7 Bronchial Biopsies and Brushings**

Patients are placed into the supine or semi-recumbent position and venous access is inserted. The patient receives premedication (e.g. midazolam 0.07 mg/kg). Oxygen levels are monitored and oxygen supplementation is provided. The throat and larynx area is anaesthetized with a local anesthetic spray (lidocaine, max dose 20 puffs = 3mg/kg) and a flexible endoscope is introduced. After initial orientation and documentation of appearance of the airways, brushings and endobronchial biopsies will be taken from the right main bronchus and segmental and sub-segmental bronchi. The brushes are cut off and transferred into a 15 ml V-tube (polypropylene) containing 2 ml RNA protect reagent or culture medium. The

bronchial biopsies will be placed in normal saline, PFA (paraformaldehyde) or PMSF (phenylmethanesulphonylfluoride) as appropriate. After the procedure patients will remain under medical supervision for 2 hours.

#### **6.4.8 Asthma Control Questionnaire (ACQ)**

In this study, the ACQ will be used to assess improvements in asthma symptom control. The ACQ was originally validated in patients with asthma aged 17 to 90 years (Juniper 1999, 2005), and is one of several asthma control measures recommended by GINA Guidelines. The ACQ consists of 7 items: 5 items on symptom assessment, 1 item on rescue bronchodilator use, and 1 item on airway caliber (FEV1 % predicted). The ACQ has been fully validated, including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5). The ACQ will be self-administered at the clinic (questions 1-6 only) and it only takes a few minutes to complete. Patients are asked how they have been feeling during the past week and to score each item on a 7-point response scale, where 0 indicates 'totally controlled' and 6 indicates 'severely uncontrolled.' Study staff score question 7 based on % predicted FEV1 (ideally pre-bronchodilator). The total score is calculated as the mean of all questions. The questionnaire should always be completed before any other assessments.

A **SAMPLE** of the Asthma Control Questionnaire is included in [Appendix 4](#).

#### **6.4.9 Asthma Quality of Life Questionnaire – Standardized (AQLQs)**

In this study, the disease-specific, standardized version of the asthma quality of life questionnaire (AQLQs) will be used to measure health-related quality of life in trial patients.

The measure was originally validated for use in patients with asthma aged 17 to 70 years (Juniper et al, 1999). The AQLQs is a 32-item questionnaire designed to measure functional impairments that are most important to patients with asthma. It consists of 4 domains: symptoms, emotional function, environmental stimuli and activity limitation. Full validation has been demonstrated, including a minimal important difference (MID) or smallest change that can be considered clinically important (0.5). The AQLQs will be self-administered at the clinic and takes about 4 to 5 minutes to complete. Given that the AQLQs will be administered along with the ACQ, which has a 1-week recall, patients completing the AQLQs will also be asked to recall their experiences during the past week, and to score each item on a 7- point scale (7 = not at all impaired to 1 = severely impaired). The AQLQs yields domain-specific scores and a total score, which is the mean response to all 32 questions. The questionnaire should always be completed before any other non-PRO assessments.

A **SAMPLE** of the Asthma Quality of Life Questionnaire is included in [Appendix 5](#).

#### **6.4.10 Volatile Organic Compounds**

Testing is performed using bespoke equipment loaned from Loughborough University. Subjects are asked to refrain from applying cosmetics on the day of the test. Subjects wear a tight-fitting mask supplied with air and with a sample tube attached, and breathe normally until 2.5 L of exhaled breath are collected through the sample tube. Sample tubes are sent to Loughborough University for analysis (Ibrahim et al, 2011). This procedure may not be



performed for some patients if it becomes necessary to reduce the burden of tests on these patients.

#### **6.4.11 Fraction of Exhaled Nitric Oxide (FeNO<sub>50</sub>)**

Exhaled Nitric Oxide is widely accepted as a non-invasive marker for airway inflammation. Fractional exhaled nitric oxide will be measured following the recently published guidelines on standardized techniques including calibration of equipment as appropriate for measuring exhaled Nitric Oxide by ATS and ERS ([ATS/ERS guidelines 2005](#)).

To ensure consistency in the measurement of FeNO, all sites will be provided with a NIOX MINO FeNO machine.

#### **Recommendations for FeNO Measurements**

FeNO measurements should be performed PRIOR to spirometry assessments, as spirometric manoeuvres have been shown to transiently reduce exhaled NO levels.

FeNO measurements have to be performed at the same time of day (preferably within 4 hours of rising).

Repeated, reproducible exhalations should be performed to obtain two measurements within 10% of each other. Exhaled NO is the mean of these two values. The duration of exhalation must be sufficient (up to 10 seconds) to achieve a stable NO plateau.

Allow subjects at least 30 seconds of relaxed tidal breathing to rest between repeated exhalations in order not to exhaust the patient.

The patient should be seated comfortably with the equipment at the proper height and position.

Patients should refrain from eating and drinking at least 2 hours before measurements.

Patients should avoid strenuous exercise for 1 hour before measurements.

The time of last bronchodilator should be noted, as FeNO levels may vary with the degree of airway obstruction or after bronchodilation.

Respiratory tract infections may lead to increased levels of exhaled NO in asthma, therefore the infection should be recorded in the patient's medical file (and as an AE in the CRF).

Breath-hold results in NO accumulation which causes NO peaks in the exhalations profiles of NO versus time and should therefore be discouraged.

#### **6.4.12 Appropriateness of efficacy assessments**

The spirometry, patient reported outcome measures, sputum assessments and exhaled NO measurements are typical of a study of this type. The other, more exploratory measures, of lung histology, pulmonary function and imaging as well as systemic protein and mRNA measurements are part of attempt to gain a holistic understanding of how the immunology, genetics and pathology impact upon lung function and, ultimately, on patient symptomatology and disease progression in asthma.

We are collaborating with the AIRPROM initiative, through Professors Brightling & Wild, which is attempting to build an in silico model of asthma to better predict how insults and therapies might impact the course of patients' disease.

## 6.5 Safety

The following safety assessments will be performed:

- History and physical examination
- Vital signs
- Hematology
- Blood chemistry including but not limited to Liver function tests: ALT (SGOT), AST (SGPT), total bilirubin, Metabolic panel: glucose, creatinine, urea (BUN), Na, K, Ca, Cl, Mg, triglycerides, lipase, cholesterol, albumin, total protein, alkaline phosphatase,  $\gamma$ -GT, uric acid, total bilirubin, CK and Immunoglobulins
- Urinalysis by dipstick. If dipstick is positive, then a microscopic examination should be performed.
- CK-MB, Troponin I (in response to CK results outside of the normal range)
- HbA1c (collected at screening only)
- Pregnancy test (females of childbearing potential)
- ECG
- Adverse events including serious adverse events

ECG will be analyzed locally and laboratory assessments (excluding histology and sputum analysis) will be performed externally.

### 6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's CRF. Significant findings made after informed consent is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's CRF.

### 6.5.2 Vital Signs

Vital signs include body temperature, respiratory rate, systolic and diastolic blood pressure, and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured. Patient's condition must be monitored to rule out any clinically relevant arrhythmia or tachycardia.

Clinically notable vital signs are defined in [Appendix 1](#).

### 6.5.3 Height and Weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

### 6.5.4 Laboratory Evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in [Appendix 1](#).

#### 6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured.

#### 6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, AST (SGOT), ALT (SGPT), bilirubin, calcium, chloride, cholesterol, CK, creatinine,  $\gamma$ -GT, glucose, LDH, magnesium, phosphate, potassium, sodium, triglycerides, urea (BUN), uric acid and immunoglobulins (IgG and possibly including but not limited to IgG1, IgG2 and IgG4) will be measured.

Patients exhibiting liver function test values of

- ALT or AST  $\geq$  5xULN **or**
- ALT or AST  $\geq$  2.5xULN **and** total bilirubin  $\geq$  1.5xULN

at any visit should be withdrawn from the trial.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal range, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. All patients with laboratory tests containing clinically significant abnormalities should be followed regularly until the values return to within the normal ranges or until a valid reason other than drug-related adverse experiences is identified, even after the study medication has discontinued.

#### 6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, pH, protein, glucose and blood will be performed. If the urine dipstick is abnormal, the sample will be sent to central laboratory for additional testing, including assessment of WBC and RBC sediments.

### 6.5.5 Electrocardiogram (ECG)

Standard 12-lead ECGs will be acquired. A paper tracing must be obtained for immediate safety assessment and subsequently archived at the site. ECGs should contain the subject number, the date and time of the tracing and the study code "QAW039A2208". The paper tracings must be signed and dated by the investigator or another physician at the clinical site. Interpretation of ECGs will be performed by the investigator or another physician at the clinical site.

ECGs must be acquired only after subjects have been quietly at rest in the sitting position for at least 10 minutes. During ECG acquisition, subjects must be perfectly still and not speak.

When the ECG acquisition time coincides with vital signs and blood draws, the ECG must be acquired first, followed by vital signs and the blood draws.

ECGs should be free of baseline wander and noise. Prior to acquisition, the ECG operator should check the tracing to ensure that it is of high quality

### **6.5.6 Pregnancy and Assessments of Fertility**

All pre-menopausal women who are not surgically sterile will have a serum (at screening) or urine (all other indicated visits) pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum B-hCG is performed and found to be negative. If positive, the patient must be discontinued from the trial.

### **6.5.7 Skin Prick Test**

Skin prick test to assess allergic status will be performed unless historical positive test results are already available.

### **6.5.8 Appropriateness of safety measurements**

The safety assessments selected are standard for this indication/patient population.

## **6.6 Other assessments**

### **6.6.1 Pharmacokinetics**

All subjects will have one blood sample at Visit 4 and two blood samples collected for pharmacokinetic analysis on Visit 5. At Visit 4 a sample will be taken prior to the morning dose. At Visit 5, one sample will be taken before the administration of the morning dose of the study drug and the second sample will be taken 3 hours after the administration of the study drug. Each sample will be processed to produce 2 aliquots of acidified plasma (A and B). All samples will be given a unique sample number (as listed in the PK blood log in [Appendix 2](#)) and a collection number. The site is to ensure the correct sample number is reflected on the respective tube. Both the date and time of that morning's (either day 42 or day 84) study drug dose administration and the actual PK sample collection date and time will be entered on the PK blood collection page of the CRF. Sampling problems will be commented on in the CRFs.

Both aliquots per timepoint, aliquot A and aliquot B should be shipped to the central laboratory (and then forwarded to the bioanalytical facility for sample analysis on separate occasion).

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters (with the exception of the pre-dose samples).

Analysis of QAW039 will be conducted in the collected acidified plasma samples. Bioanalysis will be performed using a validated LC/MS/MS assay.

Full details on pharmacokinetic sampling, processing, collection and shipment will be provided in the laboratory and procedures manual.

## **6.6.2 Biomarkers**

As part of an effort to determine whether biomarkers that predict clinical efficacy responses can be identified, the following samples will be collected in this trial.

Sample testing and collection procedures for the biomarkers identified in this section are described in greater detail in the central lab manual, which will be provided as part of this study.

### **6.6.2.1 Pharmacogenetic Assessments**

The Study includes an optional pharmacogenetic component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents these options to the subject.

Exploratory pharmacogenetics research studies are planned as a part of this study with the objectives of identifying inherited genetic factors which may influence the response to QAW039. These genetic factors include those that may (1) be related to asthma, (2) predict response to treatment with QAW039, (3) predict relative susceptibility to drug-drug interactions, or (4) predict genetic predisposition to side effects. The hope is to develop a better understanding of how subjects respond to QAW039.

Polymorphisms that may be studied relating to the absorption, distribution, metabolism, and excretion (ADME) of QAW039 may include UGT1A1 and other UGT polymorphisms.

Despite continuing advances in genetics research, not all of the polymorphisms relevant to drug metabolism and drug action may have been identified. Therefore, additional polymorphisms will be added within the restricted scope of these studies as described above.

In addition, recent advances in genotyping technologies have made genome-wide association (GWA) studies possible. GWA studies may also be undertaken within the restricted scope of these studies as described above.

Sample collection: One 10 mL blood sample will be collected at Day 1 (Visit 3) in an EDTA tube. After collection, the sample must be inverted several times to prevent clotting. If the blood draw at Visit 3 is missed, the sample should be taken at the next visit that a blood draw is already scheduled.

The samples should be kept frozen at -70°C until shipped frozen to the central lab for DNA extraction. The extracted DNA will then be transferred to Novartis for pharmacogenetic analysis and storage.

Any DNA derived from the sample that remains after analysis may be stored for up to 15 years to address scientific questions related to QAW039 or asthma.

In the event that a subject requests to destroy the pharmacogenetic sample, the following process should be followed: (1) the subject should contact the investigator; (2) the investigator

will then provide the sponsor with the required study and subject numbers; (3) any remaining samples (e.g. blood or DNA) will be located and destroyed; and (4) the sponsor sends a letter back to the investigator to confirm that the sample was destroyed.

A lab manual will be provided with detailed information on sample collection, handling and shipment. The sample collection date and exact time must be entered on the sample collection CRF page.

### **6.6.2.2 Transcriptomic assessments**

Messenger RNA expression profiling will be carried-out in enrolled asthma patients who are willing to participate in this exploratory biomarker evaluation from both blood and/or biopsy or brushing material. Exploratory pharmacogenomic assessments in this study aim at increasing our understanding of the molecular heterogeneity of asthma, and at identifying predictors of response to treatment.

RNA samples will be profiled using the Illumina Human HT-12 v3 Expression BeadChip or equivalent. Significance Analysis of Microarrays (SAM) will be used to identify differentially expressed genes, and statistical clustering techniques will be used to analyze the dataset. Genotyping will be performed using the Illumina 660W genotyping array that contains 660000 polymorphisms (SNPs and CNVs) evenly spread across the human genome, or an equivalent. This data will contribute towards genome-wide association studies of asthma phenotypes. One serum sample per patient - to be prepared from 10.0 mL whole blood - will be collected pre-dose at Visit 3 and at Visit 5 and Visit 6.

These samples will be stored at the central lab until onward shipment for genomic data generation and analysis. Exploratory biomarker clinical samples remaining after analysis may be stored for up to 15 years to address additional relevant scientific questions.

### **6.6.2.3 Serum and plasma proteins**

Serum proteins will be measured both to see if they might identify populations who are more likely to respond to QAW039 than the total population and to see if changes in concentration correlate with response: these may include but are not limited to eosinophilic cationic protein (ECP), eotaxin-1, IL-5, IL-13, serum total IgE, hsCRP, TNF- $\alpha$ , MCP-1 and IL-8. Samples will be collected at before the commencement of treatment at Visit 3 and Visits 4, 5 and 6.

A sample will be taken at baseline for potential autoantibody measurement to rule out any pre-existing autoimmune condition (in particular Churg-Strauss Syndrome) should that prove necessary.

### **6.6.2.4 Fluorescence activated cell sorting (FACS)**

A FACS assay will be used to quantify the following cell populations (at least): CD3; CD4; CD8; CCR3 (gating of eosinophils); CRTh2. These will be measured in all patients at Visits 3, 4, 5 and 6.

### **6.6.2.5 Prostaglandins and Leukotrienes**

Analytes that will be measured may include but are not limited to PGD2, PGE2, PGJ2, DKPGD2,  $\Delta$ 12-PGD2, 15d-PGD2,  $\Delta$ 12-PGJ2, 9 $\alpha$ ,11 $\beta$ -PGF2, LTB4, LTC4, LTD4 and LTE4.

The prostaglandins will be measured by LC-MS in all patients at Visits 3, 4, 5 and 6.

#### **6.6.2.6 Sputum soluble factor analysis**

Sputum may be assessed (from visit 3 onwards) for soluble factor levels (potentially including but not limited to IgE, Eotaxin-1, IL-5, IL-13, IL-8, ECP, prostaglandins and leukotrienes and TNF- $\alpha$ ).

#### **6.6.3 Resource utilization**

Resource utilization will not be captured as an endpoint in this trial.

## **7 Safety monitoring**

### **7.1 Adverse Events**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the placebo that is given during any phase of the study. Medical conditions/diseases present before starting the study are only considered adverse events if they worsen after starting the study. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade [mild, moderate, severe]
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## **7.2 Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to the site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.



Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **7.3 Pregnancies**

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## **8 Data Review and database management**

### **8.1 Site Monitoring**

Before study initiation, a Novartis representative will review the protocol and CRFs with the investigators and their staff at a site initiation visit or at an investigator's meeting.

During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

## 8.2 Data Collection

Designated investigator staff will enter the data required by the protocol into Case Report Forms. The Investigator must certify that the data entered into the Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

## 8.3 Database management and quality control

Novartis staff or designee review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions.

1. Queries are sent to the investigational site using a data query.
2. Designated investigator site staff is/are required to respond to the query and confirm or correct the data using a paper Data Query Form which will be faxed to the site.
3. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or designee who will make the correction to the database.
4. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples (except cytology for sputum samples and bronchial brushings and biopsies) will be processed centrally and the results will be sent to Novartis (or a designated CRO).

ECG readings will be processed locally, at the study site and the results will be sent to Novartis (or a designated CRO).

Spirometry and FeNO readings will be processed and the results will be sent to Novartis (or a designated CRO).

To maximize confidentiality, all pharmacogenetic samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

The use of pharmacogenetics is exploratory. Any results from this pharmacogenetic study will not be placed in the patient's medical records and will not be disclosed to patients or the patient's family.

## **9 Data analysis**

### **9.1 Analysis sets.**

The randomized set (RAN), which comprises all randomized patients, regardless of whether or not they actually received study medication, will be used for summaries of patient disposition and analysis populations.

The full analysis set (FAS) will include all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. FAS will be used for all efficacy variables, unless otherwise stated.

The per-protocol set (PP) will include all patients in the FAS without any major protocol deviations. Major protocol deviations will be defined in the validation analysis plan prior to database lock and the un-blinding of the study. Patients will be analyzed according to the treatment they were assigned to. PP will be used for the supportive analysis of the primary variable.

The safety set (SAF) will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also the FAS assigns randomized treatment and the safety set assigns received treatment.

### **9.2 Patient demographics and other baseline characteristics**

Demographics and baseline characteristics will be summarized using the safety set including age, gender, race, ethnicity, height, weight, body mass index (BMI), duration of asthma, smoking history, screening spirometry (% predicted FEV<sub>1</sub>, reversibility, etc.), vital signs (systolic and diastolic blood pressure, pulse rate), concomitant medications, ECG, hematology, blood chemistry, urinalysis, autoantibodies, and relevant medical histories.

### **9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

The number of patients and the length of time (in days) exposed to each study drug will be summarized by treatment for the safety set.

Prior and concomitant medications will be summarized by treatment for the safety set separated for asthma related and non-asthma related medications. Asthma related concomitant medications will be summarized by pre-specified categories, route of administration and preferred term. Non-asthma related concomitant medications will be summarized by the preferred term.

Treatment compliance will be summarized by treatment for the safety set.

## **9.4 Analysis of the primary and key secondary variable(s)**

The FAS (Full Analysis Set) will be used for analysis of the primary and secondary variables, unless otherwise specified.

### **9.4.1 Variable(s)**

#### **9.4.1.1 Primary Variable**

The primary variable of the study is the change from baseline in sputum eosinophil percentage at week 12. As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log<sub>10</sub>-transformed scale. The baseline measurement is defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing (on log<sub>10</sub>-transformed scale).

#### **9.4.1.2 Secondary variable**

The secondary variables include the change from baseline to week 12 in ACQ. The baseline is defined as the assessment measured at Visit 3 (Day 1) prior to the first dosing.

#### ***ACQ***

The ACQ measures asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV<sub>1</sub> % predicted). All 7 questions of the ACQ are equally weighted. Items 1-6 are scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. The 7<sup>th</sup> item on % predicted FEV<sub>1</sub> (pre-bronchodilator) is scored by clinic staff on a 7-point scale (0 – > 95%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%). The average score of the 7 questions at each visit will be calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and the missing item is neither question 1 nor question 7.

### **9.4.2 Statistical model, hypothesis, and method of analysis**

The primary variable and the secondary variables will be summarized by treatment and analyzed using an ANCOVA model with treatment as the fixed effect and the respective baseline value as the covariate.

Least square mean for each respective treatment group and for the treatment difference will be presented along with associated 95% confidence interval and p-value (2-sided) for within and between group comparisons.

### **9.4.3 Handling of missing values/censoring/discontinuations**

Missing data will be imputed for the primary variable using last observation carried forward (LOCF). Only post-baseline observation will be used for this purpose.

Only 1 missing item is allowed for scoring the ACQ and, preferably, this should not be question 1 or question 7. The single missing value may be interpolated by utilizing prior or subsequent completions of the questionnaire. The averaged ACQ score will not be imputed.

## 9.4.4 Supportive analyses

### 9.4.4.1 Primary Variable

For the primary variable, the analysis will be repeated for the patients in FAS without LOCF.

Longitudinal data analysis will be performed as sensitivity analysis on the primary variable in the FAS, as an alternative to LOCF. Treatment effects, together with 95% confidence interval for difference in treatments at each visit will be presented.

The normality assumption will be checked with a Q-Q plot of residuals for each treatment group. In addition, within-treatment difference between baseline and week 12 will be analyzed using Wilcoxon paired sample signed-rank test; between-treatment comparison on the change from baseline to week 12 will be analyzed using Wilcoxon/Mann-Whitney rank-sum test.

### 9.4.4.2 Secondary Variable

For the secondary variable, additional analyses will be conducted as follows:

- An ACQ change of 0.5 has been validated as the minimally important clinical difference (Juniper et al, 2005). The proportion of patients with a decrease in ACQ of > 0.5 will be summarized by treatment and analyzed using a logistic regression. The model includes terms for treatment as the fixed effect and the baseline ACQ score as a covariate. The odds ratio of QAX576/Placebo will be computed, along with associated 95% confidence intervals.
- A sensitivity analysis using different imputation algorithms for missing data at week 12 will be performed in the FAS.
- Longitudinal data analysis will be also performed in the FAS to account for the dependency among the visits within patient. Treatment effects, together with 95% confidence interval for difference in treatments at each visit will be presented.

## 9.5 Analysis of other variables

### 9.5.1 Efficacy variables

#### 9.5.1.1 Sputum cell analysis

The change from baseline at week 6 and at week 18 will be also summarized by treatment and analyzed using an ANCOVA model with treatment as the fixed effect and the baseline sputum eosinophil percentage as the covariate. The normality assumption will be checked with a Q-Q plot of residuals for each treatment group and if this is not adequately met a non-parametric test will be used instead (refer to Section 9.4.4.1).

To explore the persistency of efficacious effect following the cessation of therapy, data will be also analyzed similarly based on change from week 12 to week 18.

### 9.5.1.2 Asthma control questionnaire (ACQ)

The change from baseline at week 6 and at week 18 and the change from week 12 and week 18 will be summarized and analyzed similarly with baseline ACQ as the covariate. Refer to Section 9.5.1.1.

### 9.5.1.3 Pulmonary function tests

#### 9.5.1.3.1 Spirometry

% predicted FEV<sub>1</sub> (pre-bronchodilator) is calculated as:

$$\frac{100 \times \text{FEV}_1(\text{pre } \beta_2\text{-agonists at V2})}{\text{Predicted FEV}_1}$$

The change from baseline to week 6, week 12, and week 18 in % predicted FEV<sub>1</sub> will be summarized and analyzed in a similar way as described in Section 9.5.1.1 with baseline % predicted FEV<sub>1</sub> as the covariate. To explore the persistency of efficacious effect following the cessation of therapy, data will be also analyzed similarly based on change from week 12 to week 18.

#### 9.5.1.3.2 Impulse Oscillometry

R5-R20 (kPaL<sup>-1</sup>s<sup>-1</sup>) and AX (kPaL<sup>-1</sup>) are measured with impulse oscillometry. The change from baseline at week 12 and at week 18 and the change from week 12 and week 18 will be summarized and analyzed similarly with the respective baseline value as the covariate. Refer to Section 9.5.1.1.

#### 9.5.1.3.3 Multiple Breath Washout (MBW)

S<sub>acin</sub> (L<sup>-1</sup>) is measured with multiple breath washout. The change from baseline at week 12 and at week 18 and the change from week 12 and week 18 will be summarized and analyzed similarly with the respective baseline value as the covariate. Refer to Section 9.5.1.1.

## 9.5.2 Safety variables

All safety endpoints (i.e. adverse events, laboratory data, vital signs, and ECG) will be summarized by treatment for all patients of the safety population. All data will be included in the analysis regardless of rescue medication use.

### 9.5.2.1 Adverse events

All adverse events which start after the first dose of study medication will be considered as a treatment emergent adverse event. Adverse events that start during the study but before the time of the first dose of study drug (e.g. screening period) will be classified as a prior adverse event and will be included in adverse events listings, but will not be summarized.

Treatment emergent adverse events with the number and percentage of patients having any adverse event overall, by system organ class and preferred term will be provided for:

- all adverse events
- adverse events by maximum severity

- adverse events suspected by the investigator as study drug-related
- serious adverse events
- adverse events leading to permanent discontinuation of study drug

#### 9.5.2.2 Laboratory data

A central laboratory will be used to analyze and report blood chemistry/hematology/urinalysis

The following analyses will be performed, where appropriate, for central measurements of hematology and blood chemistry tests:

- standard descriptive statistics for values measured at baseline and post-baseline visits including changes from baseline
- shift tables relative to the normal ranges between baseline and post-baseline visits
- number (and percentage) of patients with clinically notable changes for selected tests

#### 9.5.2.3 Vital signs

Vital signs (i.e. blood pressure and pulse rate) will be summarized with standard descriptive statistics of raw data and changes from baseline for each visit separately. The numbers of patients with vital signs meeting the definition of notably abnormal will be presented by parameter.

#### 9.5.2.4 Electrocardiogram

The ECGs will be read for quantitative assessments including (RR, PR, QRS and QT intervals, and heart rate) and qualitative diagnoses. The QTc will be calculated from the QT interval and RR (in seconds) by two methods:

(1) Using Bazett's formula:  $QTc = QT / \sqrt{RR}$

(2) Using Fridericia's formula:  $QTc = QT / \sqrt[3]{RR}$ , where  $\sqrt[3]{}$  denotes the cube root

The quantitative assessments will be based on the mean of the measurements at each scheduled time point for each visit separately. The analysis, such as change from baseline and clinical notables, will be summarized by treatment based on the averaged values. The baseline measurement will be the mean of measurement at Visit 4 pre-dose (-35 min).

Changes from baseline will be summarized by treatment for the mean heart rate and ECG intervals including QTc for each scheduled time point at each visit and for the maximum post-baseline value.

Notable QTc values will be summarized. A notable value is defined as a QTc interval of greater than 450 msec for males and greater than 470 msec females. Patients meeting a more extreme notable criterion of >500 msec will be also summarized for males and females. The notable change in QTc will be also summarized. The categories used for the change in QTc are less than 30 msec, 30 to 60 msec and greater than 60 msec.

The qualitative assessment includes overall ECG interpretation and Morphological and rhythm abnormalities. Shift tables will be provided in order to compare a patient's baseline overall ECG interpretation to the interpretation at each time point at each post-baseline visit.

Using the morphologic determinations, the number and percentage of patients with qualitative ECG abnormality will be summarized for each visit and each timepoint. The abnormality will be summarized by baseline condition (NO/YES) for each type of abnormality (i.e. newly occurring cases, or persistent/recurrent cases). The qualitative ECG abnormality will be determined by abnormality of Rhythm, Arrhythmia, Conduction, Morphology, Myocardial infarction, ST segment, T wave abnormalities, abnormal U wave.

### **9.5.3 Resource utilization**

Healthcare resource utilization will not be collected in this study.

### **9.5.4 Health-related Quality of Life**

#### **9.5.4.1 Asthma control questionnaire (AQLQs)**

See section 9.4.

#### **9.5.4.2 Asthma quality of life (AQLQs)**

The 32 items in the AQLQ(s) are divided into four domain-specific scores and a total score as follows:

Activity limitations = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)

Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)

Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)

Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)

Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL. There is a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means no more than 3 missing responses for the overall score and no more than 1 missing response per domain. For the symptoms and activity domain scores, one missing value per domain is allowed. For the emotional function and environmental stimuli domain scores, no missing values are allowed.

The minimal important difference (MID), defined as "the smallest difference in score which patients perceive as beneficial and would mandate, in the absence of troublesome side effects and excessive cost, a change in the patients management," has been established as 0.5 points per item ([Juniper et al, 2006](#)).

Between treatments analyses of change from baseline scores by visit will be performed using the same model as specified in [section 9.4.2](#) with baseline AQLQ score as the covariate. Least squares means and associated 95% confidence intervals will be presented for treatments and treatment differences.



### **9.5.5 Pharmacokinetics**

All subjects with evaluable pharmacokinetic (PK) parameter data will be included in the pharmacokinetic data analysis.

#### **Pharmacokinetic variables**

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters (with the exception of the pre-dose samples).

PK samples are being collected to assess patient compliance with the dosage regimen therefore due to the sparse nature of the sample collection scheme pharmacokinetic parameters will not be determined using non-compartmental method(s). Descriptive statistics of plasma concentrations data will include mean, SD, and CV, min and max.

### **9.5.6 Pharmacogenetics/pharmacogenomics**

#### **9.5.6.1 Pharmacogenetic data analyses**

The exploratory pharmacogenetic studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests (chi-square tests, ANCOVAs, linear and logistic regression) are used for the analyses. Additional data, from subsequent clinical trials, are often needed to confirm associations. Alternatively, if the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data may be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

#### **9.5.6.2 Pharmacogenomic data analyses**

The analysis of pharmacogenomic data will be performed at the Fundacio Privada Parc, Cientfic DE, Barcelona, Spain. Quality control of all individual samples and molecular data will be conducted. The analysis of genomic data per se may be assisted by the use of “in house’ and commercial expert applications and databases. A range of statistics-based approaches - both supervised and unsupervised - will be applied to the data.

### **9.5.7 Biomarkers**

#### **9.5.7.1 Fractional exhaled Nitric Oxide (FeNO)**

Exhaled Nitric Oxide is a non-invasive marker for airway inflammation. It will be measured following the recently published guidelines on standardized techniques.

The change from baseline will be summarized by treatment group. The mean FeNO as calculated from two measurements will be used for analysis. Treatment group comparisons will be performed by the same model as specified in Section 9.5.1.1 with baseline FeNO as

the covariate. Least squares means and associated 95% confidence intervals will be presented for treatments and treatment differences.

#### **9.5.7.2 Other efficacy biomarkers**

Other efficacy biomarkers are measured, including

- High Resolution Computed Tomography (HRCT)
- Hyperpolarized Helium-3 MRI Imaging (He-3 MRI)
- Bronchial Biopsies and Brushings
- Volatile Organic Compounds

Data will be summarized and analyzed in a similar way as described in section 9.5.1.1.

#### **9.5.8 PK/PD**

Population modeling may be undertaken to evaluate the pharmacokinetics of QAW039 based on the sparse data collected in this study as well as in other clinical studies from the QAW039 program. A search may be performed to identify variables that impact PK. This will include, but is not limited to, an investigation of patient demographics and other baseline characteristics. Results from such population analyses will be reported separately.

PK/PD modeling may also be attempted for exploratory purposes.

### **9.6 Interim analyses**

An interim analysis (IA) will be conducted when approximately 50% of the patients have completed their treatment phase (i.e. week 12, Visit 5). This IA is intended to provide early delivery of key data to facilitate forward planning of the QAW039 program. The key data points to be analyzed in the IA may include, but is not limited to, some of the exploratory endpoints as well as the following:

- sputum eosinophil percentage at week 12
- ACQ at week 12
- AQLQ at week 12
- FEV<sub>1</sub> at week 12

Since the trial will not be stopped for overwhelming efficacy, no adjustment of the alpha level is planned for the final analysis. The details of the interim analysis results will be kept blinded to the trial personnel, participating investigators, and patients during the course of the study. The analysis will be performed by the independent statistician and independent programmer who will be fully unblinded to the patient-level information. Only the comparative results between treatment groups will be released and reviewed by an authorized group for future planning of the QAW039 program. The authorized group, external to the clinical trial team, will receive the results under a confidentiality agreement that the results must by no means be disclosed to anybody outside authorized group.

The predictive power will be used as the basis for futility decision when there is little evidence of a beneficial treatment effect. The predictive power is the probability that the final

study result will be statistically significant given the data observed thus far weighted averaging over a range of future treatment effect. The weights are based on the posterior distribution of treatment effect given the observed data at interim with non-informative prior. If the predictive probability is below a pre-specified level for futility (0.05 for instance), stopping the trial before it is finished may be considered. The decision rule to be used at the interim analysis stage and the operating characteristics will be described and evaluated in a separate document.

## 9.7 Sample size calculation

Table 9-1 provides the sample sizes required for each respective outcome measure (the primary and secondary variables) in order to achieve an 80% power to detect the minimally important difference at a two-tailed 5% significance level.

This study is aimed to power for a 50% reduction in sputum eosinophil percentage. This is equivalent to an absolute reduction in  $\log_{10}$  (sputum eosinophil percentage) of  $\log_{10}2 = 0.301$  (Inman et al, 2002, Barnes et al, 2011). The minimally important differences for the primary and key secondary endpoints are listed in Table 9-1.

**Table 9-1 Sample size calculations for primary and secondary endpoints**

Endpoint	Assumption		N per treatment group	
	SD <sup>*</sup>	Minimally important difference	BT <sup>†</sup> comparison	
			2-group T-test	WMW <sup>§</sup> rank-sum
$\Delta^{\dagger}$ in sputum eosinophil percentage on $\log_{10}$ scale	0.333	0.301 $\yen$	21	23
$\Delta^{\dagger}$ in ACQ	0.385	0.5 $\text{€}$	11	13

<sup>†</sup>  $\Delta$ =change from baseline at week 12

<sup>\*</sup> SD = standard deviation for the endpoint to be analyzed

<sup>‡</sup> BT = between-treatment

<sup>§</sup> WMW = Wilcoxon/Mann-Whitney rank-sum test

$\yen$  (Inman et al, 2002)

$\text{€}$  (Juniper et al, 2005)

With 30 patients per arm to be randomized, it is expected that 24 patients per arm will complete week 12 assessment, assuming the dropout rate during the course of treatment phase (12 weeks) is 20%. With this sample size, the primary and secondary endpoints achieve  $\geq 80\%$  power to detect minimally important difference between QAW039 and placebo, as specified in Table 9-1.

## 10 Ethical considerations

### 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local

regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

## **10.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor or designee after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

The study includes some optional components which require a separate signature if the patient agrees to participate. It is required as part of this protocol that the investigator presents these options to the patient. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these assessments will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or ethics committee approval will be obtained.

## **10.3 Responsibilities of the investigator and IRB/IEC**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all

of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## **10.4 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as [clinicaltrials.gov](http://clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **11 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **11.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed in accordance with local guidelines.

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## 13 Appendices

### Appendix 1 Clinically notable laboratory values and vital signs

Patients with an ALT or AST  $\geq 5 \times$  ULN, **or** with ALT or AST  $\geq 2.5 \times$  ULN **and** total bilirubin  $\geq 1.5 \times$ ULN, at any visit should be withdrawn from trial. An alert should be sent to the investigator and sponsor if patients experience these abnormal liver function test results.

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant in the CRF.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows: heart rate of  $<40$  and  $>90$  bpm; systolic blood pressure of  $<90$  and  $>140$  mmHg; diastolic blood pressure of  $<50$  and  $>90$  mmHg.

For ECGs a notable QTc value is defined as a QTc (Fridericia's) interval of greater than 450 msec for males and 470 msec for females – all such ECGs will be flagged by the cardiologist and require assessment for clinical relevance by the Investigator.

Patients with a heart rate of  $>100$  bpm measured on 2 occasions, approximately 10 minutes apart, whilst resting, should be withdrawn from the trial.



## Appendix 2: Blood, Sputum & PK Logs

### Sputum and Blood Log

Study Phase	Safety	Pregnancy test	Pharmacogenomic	Biomarker Sample 1 (serum and plasma proteins)	Sputum	Pharmacogenetic	Biomarker Sample 2 (prostaglandins and leukotrienes)	Autoantibody	Fluorescent activated cell sorting (FACS)	Total IgE/ hsCRP	PK							
Matrix	Whole blood	Serum	Whole blood (PAX)	Serum; Plasma	Sputum	Whole blood	Plasma	Serum	Whole blood	Serum	Plasma							
Assay type	ELISA/Multiplex			ELISA/Multiplex	LC-MS; ELISA/Multiplex; Cellular count	PCR/DNA sequencing	LC-MS		FACS analysis	ELISA/Multiplex	LC-MS-MS							
Name and type of analyte	Standard hematology and chemistry assessments, plus immunoglobulins	Serum B-hCG	mRNA expression profiling	ECP, IL-5, IL-13, TNF-alpha; Eotaxin-1, MCP-1, IL-8	Leukotrienes; Eotaxin-1, ECP, IL-5, IL-8, IL-13, IgE, TNF-alpha, MCP-1; Eosinophils	UGT1A1 and other UGT polymorphism, GWA	PGD2, PGE2, PGJ2, DK-PGD2, Δ12-PGD2, 15d-PGD2, Δ12-PGJ2, 9α,11β-PGF2, LTB4, LTC4, LTD4 and LTE4		CD3; CD4; CD8; CCR3 (gating of eosinophils); CRTh2	IgE, hsCRP	QAW039 levels							
Day	(ml)	Serum B-hCG	Sample No (ml)	Sample No (ml)	Sample No (mg)	Sample No (ml)	Sample No (ml)	Sample No (ml)	Sample No (ml)	Sample No (ml)	Sample No (ml)	Sample No (ml)						
Screening (Visit 1) Day-21	15	5*			501 <sup>\$</sup>	200												
Day -14 (Visit 2)					502 <sup>##</sup>	200												
Baseline (Visit 3)	15		301	5	401	10	503	200	601	10	701	10	801	10	901	10	952	10
Day 42 (Visit 4)	15				402	10	504	200			702	10			902	10	953	10
Day 84 (Visit 5)	15		302	5	403	10	505	200			703	10			903	10	954	10
Day 126 (Visit 6) pre-AM dose	15		303	5	404	10	506	200			704	10			904	10	955	10
Day 126 (Visit 6) 3h post-AM dose																		
Total blood (mL)	75	5	15		40				10		40		10		40		40	
Study total (excluding PK)	295																	
* In women of child bearing potential only																		
\$ cellular counts and % eosinophil analysis only to be performed																		
# Sample 502 not to be taken or analysed if sample 501 allows patient to meet inclusion criteria																		
Safety sample volumes include blood obtained for hematology and chemistry assessments																		

## PK Blood Log

Study Phase	Time	Continuous time post dose	PK blood samples		
			PK Col No	Sample No	(ml)
Day					
Day 42 (Visit 4)	<i>Pre-dose</i>	<i>984 hours</i>	1	101	2x5
Day 84 (Visit 5)	<i>Pre-dose</i>	<i>1992 hours</i>	2	102	2x5
	<i>3h</i>	<i>1995 hours</i>	2	103	2x5
For PK assessments at time-points up to and including 3 hours, a window of $\pm 5$ mins is allowed					
For PK assessments at time-points over 3 hours, a window of $\pm 30$ mins is allowed					

## Appendix 3: Spirometry Guidance

### Spirometry

#### Equipment

Spirometers must meet the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry<sup>1</sup>. Spirometers must have the capacity to print FVC tracings. All spirometry values should be reported at BTPS by the method established by the manufacturer.

#### Calibration

The spirometer should be calibrated every morning before any spirometric measurements for the study are performed. Calibration values will be recorded and stored as source data at the site.

#### Preparing the test subject

On study days when spirometry will be performed, patients should refrain from the following:

- Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods and ice cold beverages for 4 hours prior to spirometry
- Alcohol for 4 hours prior to spirometry
- Strenuous activity for 12 hours prior to spirometry
- Smoking within at least 2 hour of testing
- Medication within the following timelines:

Medication	Withdrawal time
Short-acting bronchodilator	6 hrs
Long-acting bronchodilator	12 hrs
Xanthines (Theophyllines)	12 hrs
Short-acting anticholinergics	8 hrs
Long-acting anticholinergic	24 hrs
Leukotrine antagonist (LTRA)	12 hrs
Inactivated vaccine	No administration within 48 h prior to a study visit

Every effort should be made to assure consistent testing conditions throughout the study. A seated position with nose clips is recommended. When possible, spirometry should be conducted by the same technician using the same spirometer. To minimize the effects of diurnal variation on lung function, spirometry visits should start at approximately the same time of day at each visit.

#### Performing Spirometry

As spirometry is an effort-dependent test, it requires careful instruction and cooperation of the subject. The technician should ensure a good seal around the mouthpiece, and confirm that the subject's posture is correct. The subject should be instructed to perform a maximal inspiration, followed by maximum forced expiration until no more air can be exhaled or for at least 6 seconds. Expiration must be rapid with exertion of maximal effort. The results of spirometry should meet the ATS/ERS criteria for acceptability and repeatability. Acceptability criteria should be applied before repeatability is determined.

### **Number of trials**

A minimum of 3 acceptable forced vital capacity (FVC) maneuvers should be performed. If a subject is unable to perform a single acceptable maneuver after 8 attempts, testing may be discontinued.

### **Acceptability**

An acceptable maneuver has the following characteristics:

- No hesitation or false start;
- A rapid start;
- No cough, especially during the first second of the maneuver;
- No glottic closure or obstruction by tongue or dentures
- No early termination of exhalation (minimum exhalation time of 6 seconds is recommended, or no volume change for at least 1 second) or the subject cannot continue to exhale further

### **Repeatability**

The 2 largest FVC and FEV1 values from 3 acceptable maneuvers should not vary by more than 0.150 L.

### **Recording of data**

The highest FEV1 and FVC from any of the acceptable curves are recorded. (The highest FEV1 and FVC may not necessarily result from the same acceptable curve).

### **Predicted normal**

For subjects greater than 18 years of age, this study will utilize the spirometric predication equation standards for the European Community for Coal and Steel 2

### **Reversibility**

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing. A baseline spirometry assessment should be performed after a medication washout period. (please see spirometry guidelines provided above)

Administer 400µg of salbutamol/360µg of albuterol following the completion of the baseline assessment. A second spirometry assessment is then performed within 10 to 15 minutes after administration of the salbutamol/albuterol.

Reversibility is calculated as:

100 x FEV<sub>1</sub> (post β<sub>2</sub>-agonists) – FEV<sub>1</sub> (baseline)

FEV<sub>1</sub> (baseline)

Subjects will be considered reversible if an increase of at least 12% (and 200 ml) is demonstrated after administration of the bronchodilator.

### References

1. Miller MR et al, Standardization of Lung Function Testing. Eur Resp J 2005;26:153-161.
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3. Hankinson JL, Odencrantz JR, Fedan KB (1999) Spirometric reference values from a sample of the general US population. Am J Respir Crit Care Med 159:179–187.
4. Polgar, G. & Promadhat, V. (1971) Pulmonary function testing in children: Techniques and Standards. W.B. Saunders, Philadelphia.

## Appendix 4: Asthma Control Questionnaire

A **SAMPLE** of Asthma Control Questionnaire is included below. The format of the administered test may vary.

Please answer questions 1 - 6.

**Circle** the number of the response that best describes how you have been during the past week.

- |   |   |
|---|---|
| 1. On average, during the past week, how often were you <b>woken by your asthma</b> during the night?               | 0 Never<br>1 Hardly ever<br>2 A few times<br>3 Several times<br>4 Many times<br>5 A great many times<br>6 Unable to sleep because of asthma                 |
| 2. On average, during the past week, how <b>bad were your asthma symptoms when you woke up</b> in the morning?      | 0 No symptoms<br>1 Very mild symptoms<br>2 Mild symptoms<br>3 Moderate symptoms<br>4 Quite severe symptoms<br>5 Severe symptoms<br>6 Very severe symptoms   |
| 3. In general, during the past week, how <b>limited were you in your activities</b> because of your asthma?         | 0 Not limited at all<br>1 Very slightly limited<br>2 Slightly limited<br>3 Moderately limited<br>4 Very limited<br>5 Extremely limited<br>6 Totally limited |
| 4. In general, during the past week, how much <b>shortness of breath</b> did you experience because of your asthma? | 0 None<br>1 A very little<br>2 A little<br>3 A moderate amount<br>4 Quite a lot<br>5 A great deal<br>6 A very great deal                                    |

5. In general, during the past week, how much time did you **wheeze**?  
0 Never  
1 Hardly any of the time  
2 A little of the time  
3 A moderate amount of the time  
4 A lot of the time  
5 Most of the time  
6 All the time
6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day?  
*(If you are not sure how to answer this question, please ask for help)*  
0 None  
1 1 - 2 puffs/inhalations most days  
2 3 - 4 puffs/inhalations most days  
3 5 - 8 puffs/inhalations most days  
4 9 - 12 puffs/inhalations most days  
5 13 - 16 puffs/inhalations most days  
6 More than 16 puffs/inhalations most days

**To be completed by a member of the clinic staff**

7. FEV<sub>1</sub>pre-bronchodilator: ..... 0 > 95% predicted  
1 95 - 90%  
FEV<sub>1</sub>predicted:..... 2 89 - 80%  
3 79 - 70%  
FEV<sub>1</sub>%predicted:..... 4 69 - 60%  
5 59 - 50%  
(Record actual values on the dotted lines and score the FEV<sub>1</sub> % predicted in the next column) 6 < 50% predicted

## Appendix 5: Asthma Quality of Life Questionnaire – standardized

A **SAMPLE** of the Asthma Quality of Life Questionnaire is included below. The format of the administered test may vary.

### Asthma Quality of Life (AQLQ) Questionnaire

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma**.

**HOW LIMITED HAVE YOU BEEN DURING THE LAST 2 WEEKS IN THESE ACTIVITIES AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
1. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
2. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
3. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
4. WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

\*If you are not employed or self-employed, these should be tasks you have to do most days.

5. SLEEPING	1	2	3	4	5	6	7
-------------	---	---	---	---	---	---	---

**HOW MUCH DISCOMFORT OR DISTRESS HAVE YOU FELT DURING THE LAST 2 WEEKS?**

	A Very Great Deal	A Great Deal	A Good Deal	Moderate Amount	Some	Very Little	None
6. How much discomfort or distress have you felt over the last 2 weeks as a result of CHEST TIGHTNESS?	1	2	3	4	5	6	7



## **Summary of Changes**

### **Amendment 1 (29 Feb 2012)**

#### **Amendment rationale**

This protocol has been amended mainly to provide more information about the pulmonary function tests being performed in the study so as to promote clarity on the types of tests included. The other main reason for the amendment was to add another stratification factor of patients undergoing bronchoscopy versus those not undergoing bronchoscopy to the randomization scheme in an effort to minimize major imbalances between patients receiving placebo and those receiving active study medication.

At time of writing one patient had been enrolled into the study. The amendment is not expected to impact the study results and the changes do not impact on the safety of patients participating in the study.

#### **Changes to the protocol**

The types of pulmonary function tests being performed in the study to assess patients' lung function have been clarified to make more explicit that these tests include body plethysmography, carbon monoxide transfer factor, impulse and forced oscillometry. Main protocol sections modified due to this change are sections 6.4.2 and 6.4.3.

Another stratification factor has been added to minimize the chances of having unequal allocation of treatment for patients opting to undergo bronchoscopy versus those not wishing to. This change warranted a new randomization scheme and a revised randomization strata table (table 5-1) has been included. Main protocol sections modified due to this change are sections 5.1.3 and 5.2.1.

Further, information regarding treatment blinding and dispensing was clarified and made succinct. The emboldened section reminding investigators to not reveal information to patients regarding the assignment to placebo for the run-in and washout phase of the study was moved from Section 5.2.2 and added to Section 5.1.5. Section 5.2.2 was made more succinct in order to increase the usefulness of the information provided.

In Section 5.2.5, information regarding the use of restricted medication was refined to provide more clarity on withdrawal timelines. The assessment schedule table (table 6-1) was revised to make consistent with the information provided in the body of the protocol.

Also incorporated, are other smaller changes based on recommendations, as well as some editorial changes that include correction of typographical errors and some clarifications and rewording to ensure consistency between protocol sections.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. A copy of this amended protocol

will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

## **Amendment 2 (26 Jun 2012)**

This protocol has been amended mainly to provide clarification about the interim analysis to be performed in the study.

At time of writing nine patients had been enrolled into the study. The amendment is not expected to impact the study results and the changes do not impact on the safety of patients participating in the study.

### **Changes to the protocol**

More information regarding type and timing of the interim analysis to be performed in the study has been provided making clear that a futility analysis will be performed when approximately 30 patients have completed their Visit 5. Main protocol sections modified due to this change are sections 3.1, 3.5 and 9.6.

The upper limit for the range of admissible Body Mass Index (BMI) has been increased from 40 kg/m<sup>2</sup> to 45 kg/m<sup>2</sup>. This change has been made in order to allow the inclusion of more patients with severe asthma as it is now apparent that many of the more severely asthmatic patients in our study population have higher BMIs. Main protocol sections modified due to this change are Section 4.2 and the Protocol Synopsis section.

The time points for performing body plethysmography and carbon monoxide transfer have been indicated in the assessment schedule (Table 6-1).

Further, clarification has been provided that the burden of tests assessment with regards to testing for volatile organic compounds applies to all patients and not only those undergoing MRI. This clarification is reflected in Section 6.4.10 and footnote 9c in the assessment schedule (Table 6-1).

Also incorporated, are other smaller editorial changes that include correction of typographical errors and rewording to ensure consistency between protocol sections.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed

Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

# Statistical Plans

Please note that the primary, secondary and exploratory endpoints detailed in the Novartis-Statistical plan were analyzed in accordance with that plan. Exploratory endpoints not explicitly detailed in the Novartis statistical analysis plan were analyzed according to the AirPROM-Statistical analysis plan.

Clinical Development

QAW039

QAW039A2208

A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma

## **RAP Module 3 – Detailed Statistical Methodology**

Author: Dey, Debarshi,; Lu, Cindy  
Document type: RAP Documentation  
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**Document History – Changes compared to previous version of RAP module 3.**

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Version	Date	Changes
		Not applicable. Initial RAP M3

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## **1 Introduction**

This document contains details of the statistical methods which will be used in the phase II clinical trial CQAW039A2208. The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

Data will be analyzed according to the data analysis section 9 of the study protocol (unless otherwise stated below) which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

### **1.1 Study Design**

This study uses a 2-treatment arm (Placebo or QAW039), parallel group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients will undergo a 2-week placebo run-in period during which their clinical stability and suitability for randomization will be assessed. Asthma patients who are already receiving ICS or ICS-LABA therapy are the target population for this study. All patients will be allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients will receive placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study will be single-blind because physicians will know that patients are on placebo, however the 12-week treatment period will be double-blind.

Visits to assess safety and efficacy are scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives will be performed at the end of the treatment period (week 12).

### **1.2 Study Objectives**

#### **1.2.1 Primary objective**

The primary objective of this study is to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

### **1.2.2 Secondary Objectives**

To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.

To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

### **1.2.3 Exploratory Objectives**

To demonstrate that QAW039 provides significant improvement in standard physiological markers such as FEV<sub>1</sub>, as well as specific small airway markers measured with multiple breath washout (MBW) and impulse oscillometry, namely S<sub>acin</sub>, R5-R20 and AX, compared to placebo.

To explore whether the efficacious effect of QAW039 therapy persists following the cessation of therapy.

To explore whether quantitative computed tomography (CT) biomarkers at baseline predict response to therapy with QAW039.

. To explore changes in air trapping, as evaluated by quantitative computed tomography (CT), after 12 weeks of treatment with QAW039 versus placebo.

. To explore changes in health-related quality of life as measured by the standardised Asthma Quality of Life Questionnaire (AQLQs) after 12 weeks of treatment with QAW039 versus placebo.

. To explore changes in blood proteomic and transcriptomic profile following 12 weeks of treatment with QAW039 versus placebo.

. To explore changes in exhaled volatile organic compounds (VOCs) following 12 weeks of treatment with QAW039 versus placebo.

. To explore the effect of QAW039 on ventilation heterogeneity, as measured by Hyper-polarised helium-3 MRI (He-3 MRI), compared to placebo.

. To explore whether QAW039 attenuates eosinophilic airway inflammation as measured by bronchial brushings and bronchial biopsies, compared to placebo.

. To explore whether QAW039 attenuates features of remodelling in bronchial biopsies (including but not limited to the assessment of histological features of inflammatory and goblet cell number, reticular basement membrane thickness and assessment of collagen deposition) compared to placebo.



To assess the pharmacokinetics of QAW039 in this population of asthma patients.

To explore the changes in body plethysmography measurements following 12 weeks of treatment with QAW039 versus placebo.

## 2 Project standards

### 2.1 Analysis sets

**Table 2-1 Subject classification based on protocol deviations and non-PD criteria**

Analysis set	PD severity codes that cause a subject to be excluded	Non-PD criteria that cause a subject to be excluded
RAN (Randomized set)	8	
FAS (Full Analysis Set following ITT principle)	0,8	NA
Safety	5, 8	NA
Per Protocol	0, 1, 8	e.g. <i>Discontinued the study early per CRF completion panel</i>

- **The Randomized Set (RAN)**, which comprises all randomized patients, regardless of whether or not they actually received study medication, will be used for summaries of patient disposition and analysis sets, and listings of major protocol deviations and premature discontinuations, etc. Patients in RAN will be analyzed according to the treatment they were randomized to. This analysis set is not necessary unless the Full analysis set is different from the randomized set.
- **The Full Analysis Set (FAS)** will include all randomized patients who received at least one dose of study drug. FAS will be used to analyze all efficacy endpoints, unless otherwise stated. Following the intention-to-treat principle, patients in the FAS will be analyzed according to the treatment they were randomized to. The potential biases arising from excluding the randomized patients who took no study medication are negligible since the decision of whether or not to begin treatment could not be influenced by knowledge of whether being assigned study drug or placebo. Although some Phase III trials may include an active control arm, the primary comparisons in all trials will be between investigational study drug and placebo.
- **The per-protocol (PP) set** will include all patients in the FAS without any major protocol deviations that could confound the interpretation of analyses conducted on the FAS. Major protocol deviations will be defined prior to database lock and without knowing the

treatment of individual cases. Patients will be analyzed according to the treatment group as randomized. PP will be used for supportive analysis to assess robustness of the primary analysis. Patients with compliance less than 80% and more than 120% during double-blind treatment period will be excluded from the PP set.

- **The Safety set (SAF)** will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they received. If patients switch treatment during the study, they will be analyzed, *for example, according to the treatment they were randomized to or as the highest dose of Novartis compound*. The safety set will be used in the analysis of all safety endpoints and in the listings of certain notable safety data.
- **The pharmacokinetic set (PK)** will include all randomized patients who receive at least one dose of study medication and have evaluable plasma concentration data. The PK set will be used in PK analysis. Patients will be analyzed according to the treatment they received.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also the FAS set assigns randomized treatment and the safety set assigns received treatment.

The analyses of the primary objective and other efficacy variables will be performed on the FAS. The PPS will be used for the supportive analysis of the primary variable. The safety set will be used in the analysis of all safety variables.

Protocol deviations severity/Analysis Classification codes defined in VAP Module 3 leading to patient classification into the analysis sets are as follows:

<b>Code</b>	<b>Action</b>
0	Exclude from all efficacy analysis (including ITT)
1	Exclude from Per-Protocol analysis
2	Exclude from data analysis from this date
3	Exclude from data analysis from this date for a specified number of days
4	Exclude from data analysis on this date
5	Exclude from all safety analyses
6	Exclude from Main Analysis Set
7	Exclude from 2 <sup>nd</sup> Per-Protocol analysis
8	Exclude from all analysis
9	Include in all efficacy analysis
10	Exclude patient from 3 <sup>rd</sup> Per-Protocol analysis
11	Exclude from 2 <sup>nd</sup> ITT population
12	Exclude from 3 <sup>rd</sup> ITT population
13	Exclude from 3 <sup>rd</sup> ITT population
14	Exclude from 3 <sup>rd</sup> Safety population
15	Exclude patient from 4 <sup>th</sup> Per-Protocol analysis
16	Exclude from 4 <sup>th</sup> ITT population
17	Exclude from 4 <sup>th</sup> Safety population
18	Exclude from dose-finding population
20	Exclude patient from PK population
49	Report relevant protocol deviation – include in all analyses

## **2.2 Sample stratification**

There will be stratification of patients based on use/not use of oral corticosteroids and bronchoscopy/no bronchoscopy.

## **2.3 Assessment windows, baseline and post baseline definitions, missing data handling**

Data from unplanned or unscheduled visits or the early discontinuation visits will be listed.

### **2.3.1 Study Day**

Study day is defined as the number of days since the date of first dose of study medication. The date of first dose of study medication was defined as Day 1 and the day before the first dose of study medication was defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study medication,

Study day = Assessment date – Date of first dose of study medication + 1;

- for dates prior to the first date of study medication,

Study day = Assessment date – Date of first dose of study medication

### 2.3.2 Assessment windows

Patients should be seen for all visits on the designated day or as close to it as possible.

Patients should be seen for all visits on the designated day, with an allowed visit window of ±3 days. The visit window for the screening period is +7 days.

Patients who discontinue study drug before completing the study, or prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time the assessments performed for the final visit will be assessed. The visit number of such a final assessment with visit numbers such as 777 (or 777.1, 777.2 etc) will be remapped as follows: if the visit is greater or equal to half of the visit interval from the preceding scheduled visit then the visit number will be assigned to the next scheduled visit; if the visit is less than half of the visit interval then the final visit will be remapped accordingly as a repeat visit.

Only the final visit will be remapped as above, no remapping will be undertaken for any other visits. For example an unscheduled visit like visit 5.1 will not be remapped. Only end of study visit (visit 777) and corresponding unscheduled visits (777.1, 777.2 etc.) will be remapped.

For patients who complete the study, the study completion visit will be remapped to Week 18 (visit 6). For patients who do not complete the study, the premature discontinuation visit will not be remapped to week 18 (visit 6).

### 2.3.3 Imputation of partial dates

Unless otherwise stated in RAP M8, the partial dates (missing in day or month) will be imputed as per the following table:

	Assessment month < treatment start Month	Assessment month = treatment start Month	Assessment month > treatment start Month	Assessment month is missing
Assessment year < treatment start year	01MMMYYYY	01MMMYYYY	01MMMYYYY	01JULYYYY
Assessment year = treatment start	01MMMYYYY	Treatment start date + 1	01MMMYYYY	Treatment start date + 1

year				
Assessment year > treatment start year	01MMMYYYY	01MMMYYYY	01MMMYYYY	01JANYYYY
Assessment Year is missing	NA	NA	NA	NA

### 2.3.4 Baseline definitions

In general, baseline is defined as the last measurement prior to the first dose of study treatment unless otherwise stated.

1. Baseline Sputum eosinophil measure. Patients' sputum will be tested for % sputum eosinophil count at Visit 3. This will be the baseline value of the sputum eosinophil count. For patients, who do not have a sputum eosinophil count  $\geq 2\%$  at visit 3, their % sputum eosinophil at Visit 1 will be considered to be the baseline.

2. Baseline ACQ score. ACQ score is calculated as the mean of the 7 questions, calculated as the sum of scores divided by the number of questions that were answered by the patient. For ACQ questionnaires the baseline is defined as the values recorded by the patient at visit 3. If any one of the seven item is missing at Visit 3, it will be imputed from Visit 2. For imputation logic see Section 2.8.2. If after imputation from Visit 2, question 1 and 7 is non-missing and not more than one question from 2 to 6 is missing, then baseline ACQ score will be the average value of the six non-missing values. If after imputation from Visit 2, question 1 or 7 or more than two questions from 2 to 6 is missing, then that ACQ value will be set as missing. If ACQ values for Visit 3 is missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

3. Baseline AQLQ score. AQLQ score is calculated by taking the average of the total scores obtained from a questionnaire of 32 items. The 32 items are divided into 4 domains- activity, symptom, emotional and environmental and considering them all together we get the total score. Baseline AQLQ score (domain wise and total) is defined as the value obtained at visit 3. If any of the 32 items is missing it will be imputed from Visit 2. For imputation logic see 2.10.1. If even after imputation we have more than 10% items missing, that is more than 3 items missing, then the total score will be set as missing. Further, for the activity and symptom domains, the

recommendation is no more than 1 missing value per domain, and for the emotional function and environmental stimuli domains, no missing responses at all. These conditions will be checked after imputation from Visit 2. If these conditions are not met, then the baseline value at Visit 3 is put as missing. If AQLQ values for Visit 3 is missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values. This will be followed for the total score as well as the domain score.

4. Baseline Spirometry end-points. Baseline FEV1 is defined as the FEV1 measurement taken prior to the first dose of study drug (Visit 3). If this assessment is missing (or is not confirmed to be pre-dose), then the Visit 2 assessment will be considered as baseline. If the FEV1 measurements are missing both on Day 1 and at the screening visit, the respective baseline values will be set to missing and the mean of the baseline values of the non-missing patients will be imputed as baseline values. The baseline FVC is defined similar to FEV1 baseline.

5. Baseline FENO. For FeNO, baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 is missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

6. Baseline Body Plethysmography end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

7. Baseline CO Transfer factor end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

8. Baseline Oscillometry end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

9. Baseline High Resolution Computed Tomography (HRCT) end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

10. Baseline Multiple Breath Washout end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

11. Baseline Hyperpolarized Helium-3 MRI Imaging (He-3 MRI) end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

12. Baseline Bronchial Biopsy end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

13. Baseline Laboratory end-points. Laboratory data include hematology, biochemistry and urinalysis. Baseline hematology, biochemistry and urinalysis are defined as the last scheduled assessment taken prior to first dose of study drug on Day 1. Checks will be performed to ensure baseline hematology, biochemistry and urinalysis laboratory values were indeed assessed pre-dose. If the pre-dose measurement on Day 1 is missing (or was not confirmed to be pre-dose), then the last available assessment prior to day 1 will be used. Otherwise, the baseline laboratory data will be set to missing.

14. Vital signs include pulse rate and systolic and diastolic blood pressures. Baseline vital signs are defined as the last scheduled assessment taken pre-dose on Day 1. Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study drug on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last available value taken prior to day 1 will be used for baseline.

15. Baseline height and weight are defined as the measurements taken at the screening visit. Missing baseline will not be imputed.

16. Baseline ECG is defined as mean of 2 consecutive ECG measurements taken at 35 minutes prior to dosing on day 1 (Visit 3). Checks will be performed to ensure the ECG was indeed assessed prior to the first dose of study drug. If one of the two values is missing (or not confirmed to be pre-dose) then the non-missing values will be taken as the baseline. If all values are missing (or not confirmed to be pre-dose) then the last assessment taken prior to day 1 will be used. Otherwise, the ECG baseline will be set to missing without imputation. For baseline ECG interpretation there will only be one assessment at each time-point, and hence this will be used as the baseline ECG interpretation (pre-dose Day 1 value if present and confirmed to be pre-dose, otherwise last available visit prior to day 1).

17. Baseline smoking status will be the smoking status at the screening visit (visit 1).

### **2.3.5 Post baseline definitions**

Post baseline measurements are defined as those assessments on or after the start of study treatment.

For safety data, post baseline measurements include measurements recorded up to +7 days for AEs and +30 days for SAEs after the last dose of study drug or last visit whichever is later.

When change from baseline and percent change from baseline are of interest the following formula will be used where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value

Percent change from baseline = Change from baseline/baseline value x 100%.

Safety measurements may include ECG, vital signs, laboratory analysis and adverse events. When deriving the ECG and vital signs, values which have complete date and time values are assigned to pre or post-dose assessment based on the actual date/time. However, values with missing date/time are assigned to their respective scheduled visit date and time.

### **2.3.6 Missing data handling**

Missing dates will be imputed as appropriate using standard Novartis data imputation rules (see M8 for further details) with the exception of duration of Asthma defined in section 2.5.3. The handling of other missing data will be dealt with where appropriate in the specific analysis sections below.



## **2.4 General output guidelines**

Unless otherwise stated, tables, and figures will be based on all subjects included in the analysis set under consideration.

### **2.4.1 Summary tables**

The data will be summarized in the summary tables as follows:

- Categorical data will be presented as proportions (frequencies and percentages) or as intensity (adjusted for treatment exposure).
- Continuous data will be presented in terms of mean, standard deviation, minimum, Q1 (25<sup>th</sup> percentile), median, Q3 (75<sup>th</sup> percentile) and maximum.

### **2.4.2 Decimal places**

Decimal places for demographic, background characteristics and duration of exposure variables will be as follows:

- 2 decimal places for standard errors and standard deviations.
- 1 decimal place for means and medians.
- 1 decimal place for minimums, maximums and quartiles
- 1 decimal place for percentages.
- if percentage = 100, no decimal is required and no percentage will be displayed if the frequency count is zero.
- The respective numbers in each column will be decimally aligned.

Decimal places for efficacy and other safety summary tables will be as follows:

- standard errors and standard deviations: data precision + 2 decimal places.
- means and medians: data precision + 1 decimal place.
- minimums, maximums and quartiles: same as data precision.
- percentages: 1 decimal place.
- All p-values will be presented to 4 decimal places.
- Event intensity (events per week) will be presented to 2 decimal places.
- if percentage = 100, no decimal is required and no percentage will be displayed if the frequency count is zero.
- The respective numbers in each column will be decimally aligned.

### **2.4.3 Visit labeling**

In tables and figures (as applicable), visits will be labeled using Days.

## **2.5 Patient disposition, demographic and baseline characteristics**

All summary tables in this section used the Safety analysis set (SAF). Certain tables, where stated, will be repeated for the Full analysis set (FAS).

### **2.5.1 Patient disposition**

Randomized set (RAN) will be used for the summary and listing of patient disposition.

The number of patients screened, randomized, completed and discontinued from the study will be summarized with reasons for discontinuation.

Patient randomization number and whether they completed or discontinued from the study will be listed, with date of last dose and primary reason for discontinuation, including unblinding date if applicable, and any other details specified.

Time to premature discontinuation will be displayed graphically for each treatment group using a Kaplan-Meier curve for the safety analysis set. The date of premature discontinuation is defined as the maximum of the last known visit date and the date of last dose of study medication. Patients who did not discontinue early will be censored at the final visit.

The time to premature discontinuation will be analyzed for the safety population using the Cox regression model. Covariates will be treatment, baseline oral corticosteroids use and baseline bronchoscopy.

The number of subjects with protocol deviations will be tabulated by category and deviation (see Section 2.1).

Protocol deviations will be listed with date and study day of occurrence, deviation code and severity.

The number of subjects included in each analysis set will be tabulated. Reasons for exclusion from analysis populations will be tabulated for all patients.

Patient exclusion from analysis populations will be listed for all patients with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

### **2.5.2 Demographics**

Safety analysis set (SAF) will be used for the summary of patient demographics. Following variables will be included in the demographics summary.

- Gender
- Race and ethnicity
- Age (derived – numeric)
- Baseline height
- Baseline weight
- Baseline body mass index (BMI)

BMI will be calculated as follows:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)} * \text{Height (m)}]$$

- Baseline BMI category ( $\leq 30\text{kg/m}^2$ ,  $>30\text{kg/m}^2$ )

Continuous variables will be summarized using descriptive statistics (mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles, minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

### **2.5.3 Baseline characteristics**

Following variables will be included in the summary of baseline disease characteristics. The summary will be presented for Safety analysis set.

- The duration period of Asthma (years)

The duration will be calculated as follows:

$$\text{Duration of asthma} = (\text{Date of screening visit (Visit 1)} - \text{Date first diagnosed}) / 365.25$$

Duration of asthma is calculated from the date of asthma first diagnosed recorded on the CRF until Visit 1. If the date is missing in day and/or month, it will be imputed as described in section 2.4.3.

- Smoking history (ex-, never, current)
- Smoking history (pack years)

Estimated number of pack years is calculated by the total years of smoking multiplied by cigarette packs smoked per day. This will be summarized as recorded on the CRF. Smoking history in package years was calculated as the total years of smoking multiplied by cigarette packs smoked per day. For example, 1 pack year = 20 cigarettes (1 pack) per day for 1 year, or 10 cigarettes (0.5 pack) per day for 2 years, or 40 cigarettes (2 packs) per day for half a year.

- Smoking history (time since stopped - years)

The time since stopped will be calculated as follows:

$$\text{Time since smoking stopped} = (\text{Date of screening visit (Visit 1)} - \text{Date of stopping smoking}) / 365.25$$

For this calculation, partial dates will be imputed as described in section 2.3.3.

- History of asthma exacerbation (Yes/No)
- Baseline ICS or ICS+LABA
- Baseline use/not use of oral corticosteroids
- Baseline bronchoscopy/no bronchoscopy
- Baseline ACQ score will be summarized as continuous variables and as categorical data as defined in section 2.3.

The ACQ measures asthma symptom control and consists of 7 items. All 7 questions of the ACQ are equally weighted. The ACQ score is the mean of the responses to the 7

questions. The resultant score will be between 0 and 6. Please refer to section 2.3.4 for baseline calculation and section 2.8.2 for the missing data handling.

- IgE, FeNO, eosinophil, and CRTh<sub>2</sub> will be summarized as continuous variables as defined in section 2.
- Reversibility and hyper-reactivity

Continuous variables will be summarized using descriptive statistics (mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles, minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

#### **2.5.4 Spirometry at screening**

FEV<sub>1</sub> before and after Salbutamol / Albuterol inhalation, FEV<sub>1</sub> reversibility, predicted FEV<sub>1</sub> and % predicted FEV<sub>1</sub> will be summarized and listed for the FAS and safety analysis sets. FVC will be summarized and listed for the Full analysis set only.

- % of (pre-bronchodilator) predicted FEV<sub>1</sub> (%) is obtained as a percentage of FEV<sub>1</sub> relative to the predicted normal value. The value at screening and at randomization as well as the ratio (randomization vs screening) of % (pre-bronchodilator) predicted FEV<sub>1</sub> will be summarized as continuous variables.

The following Quanjer equations will be used by third party vendors to give predicted FEV<sub>1</sub> (L):

Male: (4.30 x Height in meters) – (0.029 x Age in years) – 2.49

Female: (3.95 x Height in meters) – (0.025 x Age in years) – 2.60

If Race = Black or Ethnicity = Indian then the predicted normal given by the formulae above was multiplied by 0.9.

- FEV<sub>1</sub> reversibility (mL) is calculated as an increase of FEV<sub>1</sub> values after inhalation of SABA relative to FEV<sub>1</sub> values prior to the inhalation. The % FEV<sub>1</sub> reversibility (%) is defined as a percentage of FEV<sub>1</sub> reversibility relative to FEV<sub>1</sub> values prior to the inhalation (see calculation below). The data will be summarized as continuous variables using descriptive statistics.

$$100 \times \frac{\text{FEV}_1(\text{post-inhalation}) - \text{FEV}_1(\text{pre-inhalation})}{\text{FEV}_1(\text{pre-inhalation})}$$

- Baseline FEV<sub>1</sub> will be summarized as continuous variables.

No imputation will be done for missing values.

#### **2.5.5 Relevant medical history**

Medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the safety analysis set, by primary

system organ class and preferred term, and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was active at the time of first study drug dose.

### **2.5.6 Prior medications**

Prior medications are defined as those medications which were taken prior to screening and stopped prior to the first dose of study drug.

Medications will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

Prior medications will be summarized separately for asthma related and non-asthma related treatments.

#### **2.5.6.1 Asthma related prior medications**

For asthma related medications, incomplete end dates will be imputed as detailed in RAP Module 8. Prior asthma related medications will be defined as those medications with an imputed end date before the date of first dose of study drug. These will be summarized by category.

Asthma related medications will be listed with all recorded details: verbatim name, dose, unit, frequency, route, reason, category, start and end dates and study days and whether continuing at final visit.

#### **2.5.6.2 Non-asthma related prior medications**

Prior medications not related to asthma (those marked as Prior on the CRF) will be summarized by ATC class. More than one ATC class per medication is possible and each medication will be reported under all classes.

Non-asthma related medications will be listed with reason for taking

## **2.6 Treatments (study drug and concomitant medication)**

### **2.6.1 Study drug administration**

The number of patients and the length of time (in days) exposed to each study drug will be summarized by treatment for the safety set.

Duration of exposure will be calculated as the number of days between the 1<sup>st</sup> dose date and the last visit date in treatment phase. To be calculated as:

Duration of exposure (days) = (Last visit date in treatment phase – Date of first dose of study drug + 1)

For patients who completed the treatment phase the visit date of week 12 will be used. For patients being prematurely withdrawn during the treatment phase the last visit date in the treatment phase will be used to calculate the duration of exposure.

This will be summarized by treatment for safety analysis set as a continuous variable with the standard descriptive statistics. In addition, the duration of exposure can also be summarized as a categorical variable classified into

<= 7 days, 8 days – <= 14 days, 15 days - <= 28 days, 29 days – <= 56 days, 57 days - <= 84 days, >84 days.

Dose administration data will be listed for patients in the safety analysis set.

Patients in the randomized set who received any wrong study medications will be listed. These patients will be identified using the information recorded on the DAR page of the CRF. If there is a record with reason = dispensing error, then the pack number will be used to identify whether or not the patient received the wrong study drug. Any patients who did will be included in the listing.

## **2.6.2 Compliance**

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits according to the procedures defined in a study protocol. The total number of capsules administered since the last dispensing visit will be recorded in the CRFs.

For each patient whether completing the study or not, the percentage of study drugs being used less than 80% or greater than 120% of the total number of drugs between the first dispensing visit to the last visit can be captured as a protocol deviation.

The overall compliance during the course of study will be calculated as the percentage of the number of capsules taken by patients relative to the total number of capsules prescribed between the first dispensing visit up to the last visit in the study, using the total number of capsules taken captured on the CRF.

That is, Overall compliance =  $100 \times \text{number of capsules taken by patient} / \text{total number of capsules prescribed between Day 1 and the last known scheduled visit}$ .

The compliance per dispensing interval is calculated as the percentage of capsules taken relative to the number of capsules prescribed between the dispensing visits.

In addition, the overall compliance during double-blinded treatment period will be calculated as the percentage of number of capsules taken relative to the total number of capsules prescribed from day 1 to the last known visit of double-blinded treatment period.

Compliance can be categorized by: <80%, 80% ~ <100%, 100% ~ <120%, and >=120% and summarized by treatment and visit for the safety analysis set.

## **2.7 Concomitant medications**

Medications will be coded using the ATC classification system.

All summary tables will use the safety analysis set.

Concomitant medications will be summarized separately for asthma related and non-asthma related treatments. For asthma related medications, incomplete end dates will be imputed as detailed in RAP Module 8. Concomitant asthma related medications are defined as those

medications with an imputed end date on or after the date of first study drug dose. These will be summarized by category.

Concomitant medications not related to asthma (those marked as Concomitant or Prior/Concomitant on the CRF) will be summarized by ATC class. More than one ATC class per medication is possible and each medication will be reported under all classes.

Asthma related medications will be listed with all recorded details: verbatim name, dose, unit, frequency, route, reason, category, start and end dates and study days and whether continuing at final visit. Non-asthma related medications will be listed with reason for taking.

Concomitant medications will be checked for protocol deviations by the clinical team. Patients who took prohibited concomitant medications will be included in the protocol deviations data provided by data management.

SABA (short acting  $\beta$ 2-agonist) usage during the screening period will be summarized.

The dose of LABA (long acting  $\beta$ 2-agonist) or fixed dose combinations of inhaled corticosteroid (ICS)/LABA must be stable for at least four weeks prior to Visit 2 and unless clinically indicated should not be adjusted during the study. Usage of LABA and ICS will be summarized at Visit 2 including the number of patients taking LABA/ICS medication and the type of medication taken (as recorded on the CRF). Usage of oral corticosteroids (OCS) will also be summarized. The doses of ICS and OCS will also be summarized, using conversion factors described in appendix 16.1.9 of the CSR.

## **2.8 Efficacy evaluation**

The purpose of this study is to determine whether, in patients with some sputum eosinophilia and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum.

### **Subgroups**

Primary variable and some other variables will be analyzed using subgroups. The sub-groups considered are:

- i. ACQ: Patients with ACQ score  $<1.5$  at baseline and Patients with ACQ score  $\geq 1.5$  at baseline,
- ii. % Predicted FEV1: Patients with % predicted FEV1  $<70\%$  at baseline and patients with % predicted FEV1  $\geq 70\%$  at baseline
- iii. FENO: Patients  $<50$  ppb at baseline and patients  $\geq 50$  ppb at baseline.
- iv. OCS use: Patients with OCS use at baseline: Yes or No.

### **Scope of CSR and CSR Addendum**

The scope of CSR and CSR Addendum will be defined in the table below for all endpoints mentioned in this section. The endpoints presented in the FIR are:

- $\Delta \log$  sputum eosinophil percentage
- % change of FEV1
- eosinophil counts (per unit area lamina propria)
- $\Delta$ ACQ score (with/without LOCF)
- $\Delta$ AQLQ score

TYPE OF ANALYSIS	ANALYTES (Endpoints)	Scope
Sputum cell analysis	1. $\Delta \log$ sputum eosinophil percentage	CSR
Spirometry	1. Change of FEV1 (L) 2. % change of FEV1 3. Change of FEV1(% predicted) 4. Change of FVC (L) 5. % change of FVC 6. Change of FEV1 (L) as a proportion of reversibility at baseline	CSR; Points #3, 4 and 5 for the CSR Addendum
Body plethysmography	1. Change of RV (L) 2. Change of RV (% predicted) 3. Change of TLC (L) 4. Change of TLC (% predicted) 5. Change of RV/TLC (%) 6. Change of RV/TLC (% predicted) 7. Change of VC (L) 8. Change of VC (% predicted) 9. Change of FRC (L) 10. Change of FRC (% predicted)	CSR Addendum
CO transfer factor	1. Change of CO transfer factor (% predicted) 2. Change of Alveolar volume (% predicted) 3. Change of CO transfer co-efficient (% predicted)	CSR Addendum
Oscillometry	1. Change of AX ( $\text{kPa L}^{-1} \text{s}^{-1}$ ) 2. Change of R5-R20 ( $\text{kPa L}^{-1} \text{s}^{-1}$ )	CSR



	<ol style="list-style-type: none"> <li>3. Change of R5 (<math>\text{kPa L}^{-1} \text{s}^{-1}</math>)</li> <li>4. Change of R20 (<math>\text{kPa L}^{-1} \text{s}^{-1}</math>)</li> </ol>	
HRCT	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>RB1 wall area corrected for body SA (<math>\text{mm}^2</math>)</li> <li>2. <math>\Delta</math>RB1 wall area percentage (%)</li> <li>3. <math>\Delta</math>RB1 luminal area</li> <li>4. <math>\Delta</math>RB10 wall area cor for body SA</li> <li>5. <math>\Delta</math>RB10 wall area percentage (%)</li> <li>6. <math>\Delta</math>RB10 luminal area</li> <li>7. <math>\Delta</math> Expiratory mean lung density</li> <li>8. <math>\Delta</math> Inspiratory mean lung density</li> <li>9. <math>\Delta</math> Expiratory /Inspiratory mean lung density (derived not in CRF)</li> </ol>	CSR
Multiple breath washout (mean values)	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>FRC (L)</li> <li>2. <math>\Delta</math>LCI</li> <li>3. <math>\Delta</math>Scond (L-1)</li> <li>4. <math>\Delta</math>S acin (L-1)</li> </ol>	CSR
He-3 MRI (pre BD and post PD)	<ol style="list-style-type: none"> <li>1. <math>\Delta</math> Mean ADC</li> <li>2. <math>\Delta</math> ADC SD</li> <li>3. <math>\Delta</math> Mean fractional ventilation ratio</li> <li>4. <math>\Delta</math> Mean signal to noise ratio</li> <li>5. <math>\Delta</math> fractional ventilation of voxels (peripheral 1/3<sup>rd</sup> and proximal 2/3<sup>rd</sup>)</li> <li>6. <math>\Delta</math> ventilation voxels percentage (peripheral 1/3<sup>rd</sup> and proximal 2/3<sup>rd</sup>)</li> <li>7. <math>\Delta</math> number of ventilation defects (peripheral 1/3<sup>rd</sup> and proximal 2/3<sup>rd</sup>)</li> </ol>	<p>CSR #1-7, by pre BD and post BD</p> <p>CSR Addendum will include change between pre and post BD for #1-7</p>
Bronchial biopsy	<ol style="list-style-type: none"> <li>1. RBM thickness</li> <li>2. eosinophil counts (per unit area lamina propria)</li> <li>3. MUC5a cells (per unit area epithelium)</li> <li>4. total inflammatory cells count (eosinophils, Neutrophils, T-cells and mast cells in the lamina propria per unit)</li> </ol>	CSR
ACQ	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>ACQ score (with/without LOCF)</li> <li>2. proportion of patients with an improvement in ACQ of <math>\geq 0.5</math></li> <li>3. proportion of patients with an worsening of ACQ of <math>\geq 0.5</math></li> <li>4. proportion of patients with ACQ between -0.5 and +0.5</li> <li>5. proportion of patients with <math>\text{ACQ} &lt; 1.5</math></li> </ol>	<p>CSR</p> <p>Points #2-4 in the CSR addendum</p>

AQLQ	1.ΔAQLQ score 2. proportion of patients with an improvement in AQLQ of >=0.5	CSR
NO	1.Average eNO	CSR

### 2.8.1 Primary Variable

The primary variable of the study is the change from baseline in sputum eosinophil percentage at week 12 (Visit 5). As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log10-transformed scale. The baseline measurement is defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing.

Missing data will be imputed for the primary variable using last observation carried forward (LOCF). Only post-baseline observation will be used for this purpose.

All the analyses associated with the primary variable sputum eosinophil percentage will be reported in CSR.

#### 2.8.1.1 Model, and method of analysis of primary variable - Primary Analysis of Primary Variable

##### 2.8.1.1.1 Analysis of Covariance with LOCF

Here we will consider patients in FAS with LOCF.

The primary variable will be summarized by treatment and analyzed using an ANCOVA model with treatment (QAW039 or placebo), maintenance OCS use (Yes/No), Bronchoscopy (yes/no) as fixed effect and the log10 of baseline sputum eosinophil percentage as covariate.

Estimated LS means of treatment effects and estimated difference in treatment effects will be back transformed to original scale to present estimated geometric means for treatment effects and ratio of geometric means of treatment effects along with 95% CI.

The Geometric Means will be plotted by treatment.

The ratio of Geometric means of treatment and Placebo and 95% CI will also be plotted.

The code for analysis is given below –

```
proc mixed data=<dataset name>;
  class treatment OCS bronchoscopy;
  model logchg = treatment ocs bronchoscopy logbase / s;
  estimate "A v/s B" treatment 1 -1 / cl alpha=0.05;
  lsmeans treatment;
  ods output estimates = est;
  ods output lsmeans = lsm;
run;
```

## **2.8.1.2 Supportive Analysis of Primary Variable**

### **2.8.1.2.1 Analysis of Covariance without LOCF**

Here we will repeat the ANCOVA analyses as mentioned in 2.8.1.1.1 for patients in FAS without LOCF.

### **2.8.1.2.2 Analysis of Covariance at Week 6 and Week 18.**

The change from baseline at week 6 , at week 18 and change from week 12 and week 18 will be also summarized by treatment and analyzed using an ANCOVA model as mentioned in 2.8.1.1.1. for patients without LOCF.

The Geometric Means will be plotted by visit and treatment.

The ratio of Geometric means of treatment and Placebo and 95% CI will also be plotted by visit.

### **2.8.1.2.3 Analysis of Covariance with % predicted FEV1 at baseline as covariate**

Similar to 2.8.1.1.1, to examine how the %predicted FEV1 at baseline in a continuous scale impacts the endpoints of interest, the primary endpoint will also be analyzed using an ANCOVA model by including %predicted FEV1 at baseline as an additional covariate. Multicollinearity has to be checked as there is a possibility of correlation between baseline value of the primary endpoint and the baseline value of % predicted FEV1. If the Variance Inflation Factor(VIF) of the model with both the baseline values present is more than 10, then we will drop the baseline value of the primary end-point in the covariate and only include the baseline value of % predicted FEV1 and perform our ANCOVA analyses.

### **2.8.1.2.4 Normality Assumption and Non-parametric methods**

In all the above cases the normality assumption will be checked with a Q-Q plot of residuals for each treatment group.

Only if evidences show the normality assumption does not hold for the data, the following non-parametric analysis will be performed.

i. within-treatment difference between baseline and week 12 (Visit 5), baseline and week 6, baseline and week 18, and week 12 and week 18 will be analyzed using Wilcoxon paired sample signed-rank test;

ii. between-treatment comparison on the change from baseline to week 12 (Visit 5), baseline and week 6, baseline and week 18, and week 12 and week 18 will be analyzed using Wilcoxon/Mann-Whitney rank sum test.

The code for Wilcoxon paired sample signed-rank test:

```
proc univariate data = <dataset name>;  
    by visit;  
    var logchg;  
run;
```

The code for Wilcoxon/Mann-Whitney ranksum test:

```
proc nparlway data=<dataset name> wilcoxon;  
    class treatment;  
    by visit;  
    var logchg;  
run;
```

### **2.8.1.3 Subgroup Analyses of Primary Variable**

We will perform ANCOVA on the primary variable as given in 2.8.1.1.1., 2.8.1.2.1 and 2.8.1.2.2 for the previously mentioned subgroups.

### **2.8.2 Secondary variable**

The secondary variables include the change from baseline to week 12 in ACQ. The baseline is defined as the assessment measured at Visit 3 (Day 1) prior to the first dosing.

The ACQ measures asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV<sub>1</sub> % predicted). All 7 questions of the ACQ are equally weighted. Items 1-6 are scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. Question 7 deals with FEV<sub>1</sub> % predicted pre-bronchodilator. In case the values of FEV<sub>1</sub> % predicted pre-bronchodilator are also available from the central spirometry reading in addition to the ACQ Q7 from CRF, the central reading will be used to derive the ACQ score. The value of ACQ Q7 will be used only if the central reading is not available. This single missing value may be interpolated by utilizing prior completions of the questionnaire as described in Section 2.5.3. The 7th item on % predicted FEV<sub>1</sub> (pre-bronchodilator) is scored by clinic staff on a 7-point scale (0 – > 95- 99%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%).

The average score of the 7 questions at each visit will be calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as

there were at least 6 questions answered and the missing item is neither question 1 nor question 7.

### Data Handling

If a measure of FEV<sub>1</sub> % predicted pre-bronchodilator is missing in the central spirometry data, then we get it from the ACQ Q7 in CRF. The ACQ score will then be calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and preferable not question 1 (night time awakenings) or 7 (FEV<sub>1</sub> % predicted).

For a missing individual item, the recommended method for handling missing data to reduce the risk of bias is to interpolate using either previous or subsequent completions of the questionnaire. For instance,

Item	Visit 1	Visit 2
1	4	6
2	3	5
3	0	0
4	4	4
5	0	0
6	2	missing
7	5	6

Total visit 1 score for items answered on both visits is  $4+3+0+4+0+5=16$  (A)

Total visit 2 score for items answered on both visits is  $6+5+0+4+0+6=21$  (B)

Item 6 score at visit 1=2

Item 6 score at visit 2=  $B/A * 2=21/16*2=2.63$

The ACQ score for visit 1 is  $(4+3+0+4+0+2+5)/7=2.57$

The ACQ score for visit 2 is  $(6+5+0+4+0+2.63+6)/7=3.38$

It should be noted that a post-treatment missing data can only be imputed using a post treatment visit, and a missing value at baseline (visit 3) can only be interpolated using a value from Visit 2. That is, if the missing is at baseline (visit 3), then we can only do backward interpolation using Visit 2 and if we have missing data on Visit 4, we can only do forward interpolation using Visit 5. If Visit 5 has data missing then we can do forward as well as backward interpolation using either Visit 6 or Visit 4.

#### 2.8.2.1 Model, and method of analysis of Secondary variable

Analyses associated with ACQ endpoints 1 and 5 as defined below will be reported in the CSR, and the rest below will be included in CSR Addendum.

1.  $\Delta$ ACQ score (with/without LOCF)
2. proportion of patients with an improvement in ACQ of  $\geq 0.5$
3. proportion of patients with a worsening of ACQ of  $\geq 0.5$
4. proportion of patients with ACQ between -0.5 and +0.5
5. proportion of patients with  $ACQ < 1.5$

#### **2.8.2.1.1 Analysis of Covariance with LOCF**

The secondary variable, change of ACQ7 with LOCF from baseline at week 12 will be summarized by treatments (QAW039 and placebo) and analyzed using an ANCOVA model with treatment (QAW039 or placebo), maintenance OCS use (Yes/No), Bronchoscopy (yes/no) as fixed effect and the baseline ACQ score as covariate.

Estimated LS means of treatment effects and estimated difference in treatment effects along with 95% CI will be presented.

Estimated LS means differences between treatment and Placebo and 95% CI will also be plotted.

#### **2.8.2.2 Supportive Analysis of Primary Variable**

##### **2.8.2.2.1 Analysis of Covariance without LOCF**

For FAS patients, ACQ7 without LOCF, ACQ 6 (average of first 6 ACQ questions) without LOCF, and ACQ 5 (average of first 5 ACQ questions) without LOCF will be analyzed and presented in the same way as mentioned in 2.8.2.1.1.

##### **2.8.2.2.2 Analysis of Covariance at Week 6 and Week 18.**

The method mentioned in 2.8.2.1.1 and 2.8.2.2.1 will be repeated for change from baseline at Visit 4, Visit 6 and change from Visit 5 and Visit 6 for ACQ7 without LOCF, ACQ6 and ACQ5.

##### **2.8.2.2.3 Analysis of Covariance with % predicted FEV1 at baseline as covariate**

Similar to 2.8.2.1.1, to examine how the %predicted FEV1 at baseline in a continuous scale impacts the endpoints of interest, the secondary endpoint will also be analyzed using an ANCOVA model by including %predicted FEV1 at baseline as an additional covariate.

Multicollinearity has to be checked as there is a possibility of correlation between baseline value of the secondary endpoint and the baseline value of % predicted FEV1. If the Variance Inflation Factor(VIF) of the model with both the baseline values present is more than 10, then we will drop the baseline value of the secondary end-point in the covariate and only include the baseline value of % predicted FEV1 and perform our ANCOVA analyses.

#### **2.8.2.2.4 Responder Rate Analyses for change (improvement and worsening) in ACQ of 0.5 or greater**

An ACQ change of 0.5 has been validated as the minimally important clinical difference (Juniper et al, 2005).

The proportion of patients with a decrease in ACQ of  $\geq 0.5$  at week 12 (Visit 5) from baseline will be summarized by treatment and analyzed using a logistic regression. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented. The model includes terms for treatment, OCS use(yes/no) and Bronchoscopy (yes/no) as fixed effects and the baseline ACQ score as a covariate.

The code for above analysis is

```
proc glimmix data= <dataset name>;  
  class treatment OCS;  
  model chgcat = treatment OCS Bronchoscopy base / DIST=binomial link = logit;  
  estimate 'A v/s B' treatment 1 -1 / cl alpha=0.05 oddsratio cl;  
  lsmeans treatment;  
  ods output estimates=est;  
  ods output lsmeans=lsm;  
run;
```

The odds ratio of QAW039/Placebo will be computed, along with associated 95% confidence intervals.

All the analysis defined above for the full ACQ 7 with and without LOCF questions is also to be repeated based on the mean of the first 5 ACQ questions (ACQ5) and mean of the first 6 ACQ questions (ACQ6).

The responder rate will be analyzed for proportion of patients with an improvement in ACQ ( $\geq 0.5$ ) at week 18 from baseline.

Similar analysis will also be done for proportion of patients showing a worsening (increase) from baseline in ACQ score of  $\geq 0.5$  at visit 4, visit 5, visit 6. The logistic regression model

will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented.

Similar analysis will also be done for proportion of patients showing an improvement (decrease) from baseline in ACQ score of less than 0.5 and a worsening (increase) from baseline in ACQ score of less than 0.5 at visit 4, visit 5, visit 6. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented.

#### **2.8.2.2.5 Responder rate analyses for proportion of patients with ACQ < 1.5**

The proportion of patients with the mean of the 7 ACQ questions (ACQ7) < 1.5 will be analyzed using a repeated measure logistic regression model. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented. If we do not have sufficient events for ACQ7<1.5 in each group but on the other hand, sufficient events show for ACQ7>=1.5 in each group, responder rate analysis for ACQ7>=1.5 will be provided instead.

The model will contain treatment, ocs use (yes/no), Bronchoscopy (yes/no) , visit and visit by treatment interaction as fixed effects and baseline ACQ score as covariate. Proportion of subjects with ACQ7 score less than 1.5 will be the dependent variable. Visits will be used as repeated measurement. Unstructured covariance matrix will be used for this analysis.

The odds ratio of QAW039/Placebo will be computed and plotted along with associated 95% confidence intervals.

The code for above analysis is

```
proc GENMOD data= <dataset name>;
  class treatment OCS bronchoscopy;
  model chgcat = treatment OCS Bronchoscopy visit*treatment base base*visit /
DIST=binomial link = logit;
  repeated / subject = patient type = UN;
  estimate "A v/s B" treatment 1 -1 / cl alpha=0.05;
  lsmeans treatment;
  ods output estimates = est;
  ods output lsmeans = lsm;
run;
```



run;

The above analysis will also be repeated for ACQ6 and ACQ5.

#### **2.8.2.2.6 Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

#### **2.8.2.3 Subgroup Analyses:**

We will perform ANCOVA on the ACQ7 with LOCF as given in 2.8.2.1.1 for the above mentioned subgroups:

### **2.8.3 Pulmonary Function Tests**

#### **2.8.3.1 Spirometry**

FEV<sub>1</sub> and FVC will be measured at the clinic visits prior to dosing at baseline (visit 3) and at week 6, 12 and 18 (Visit 4, 5 and 6 respectively).

Only spirometry measurements classed as ‘acceptable’ will be analyzed Spirometry measurements taken within 6 hours of a SABA , within 12 hours of a LABA, within 24 hours of long acting anti-cholinergics or within 8 hours of short acting anti-cholinergics will be excluded.

Treatment group comparisons by visit will be performed for the following spirometry variables. Analyses associated with spirometry endpoints i, ii, vii will be reported in the CSR and others will be included in CSR Addendum:

- i. Change of FEV1 (in L) from baseline,
- ii. Percent change of FEV1 from baseline, and
- iii. Change in % predicted FEV1 from baseline, where post-baseline % predicted FEV1 is defined as: 
$$\frac{100 \times FEV1}{\text{predicted } FEV1 \text{ at Visit } 2}$$
- iv. Change of FVC (in L) from baseline,
- v. Percent change of FVC from baseline,
- vii. Change from baseline in FEV1 (L) in proportion to FEV1 reversibility (L) taken at Visit 2, termed as “% Reversibility FEV1” and defined by

$$\frac{100 \times \{FEV1 - FEV1(pre - SABA \text{ Visit } 2)\}}{(Post - SABA - Pre - SABA) FEV1 \text{ in Visit } 2}$$

Change is considered to be change from baseline at week 6, change from baseline at week 12, change from baseline at week 18 and change from week 12 and week 18.

For each post-baseline visit the spirometry variables will be summarized by treatments (QAW039 and placebo).

### **2.8.3.1.1 Analysis of Covariance**

The spirometry variables will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for primary variable.

#### **Subgroup Analyses:**

We will perform ANCOVA on the spirometry parameters FEV1 and FVC as mentioned in 2.8.3.1.1 for the above mentioned subgroups.

### **2.8.3.1.2 Analysis of Covariance with % predicted FEV1 at baseline as covariate**

Similar to 2.8.2.1.1, to examine how the %predicted FEV1 at baseline in a continuous scale impacts the change from baseline of FEV1 and FVC during post-baseline the endpoints of interest, the change from baseline in FEV1 and FVC will also be analyzed using an ANCOVA model by including %predicted FEV1 at baseline as a covariate.

In case of FEV1 we will replace baseline FEV1 covariate with baseline % predicted FEV1 as covariate in the ANCOVA model. In case of FVC, we will include baseline % predicted FEV1 as an additional covariate in the ANCOVA model.

Multicollinearity has to be checked as there is a possibility of correlation between baseline value of FVC and the baseline value of % predicted FEV1. If the Variance Inflation Factor(VIF) of the model with both the baseline values present is more than 10, then we will drop the baseline value of the secondary end-point in the covariate and only include the baseline value of % predicted FEV1 and perform our ANCOVA analyses.

### **2.8.3.1.3 Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

## **2.8.4 Body Plethysmography**

All analyses associated with Body plethysmography defined below will be reported in CSR Addendum.

1. Change in RV
2. Change in RV (% predicted)
3. Change in TLC
4. Change in TLC (% predicted)
5. Change in RV/TLC
6. Change in RV/TLC (% predicted)
7. Change in VC
8. Change in VC (% predicted)
9. Change in FRC
10. Change in FRC (% predicted)

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The Body plethysmography end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary variable.

### **2.8.5 Impulse Oscillometry**

All analyses associated with impulse oscillometry defined below will be reported in CSR.

1. Change in AX ( $\text{kPaL}^{-1}\text{S}^{-1}$ )
2. Change in R5-R20 ( $\text{kPaL}^{-1}\text{S}^{-1}$ )
3. R5 ( $\text{kPaL}^{-1}\text{S}^{-1}$ )
4. R20 ( $\text{kPaL}^{-1}\text{S}^{-1}$ )

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The Impulse Oscillometry parameters will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for primary variables.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.6 Multiple Breath Washout (MBW)**

All analyses associated with multiple breath-washout defined below will be reported in CSR.

1. Change in FRC (L)
2. Change in LCI
3. Change in Scond ( $L^{-1}$ )
4. Change in S acin ( $L^{-1}$ )

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The MBW parameters will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.7 CO Transfer Factor**

All analyses associated with CO Transfer Factor defined below will be reported in CSR Addendum.

1. Change of CO transfer factor (% predicted)
2. Change of Alveolar volume (% predicted)
3. Change of CO transfer co-efficient (% predicted)

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 to week 18.

The CO Transfer factors end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.8 He3-MRI**

The MRI endpoints are observed twice in every visit- Pre-bronchodilator and Post-bronchodilator. Analyses associated with the endpoints defined below for both Pre and Post-bronchodilator change from baseline will be reported in CSR and the analysis for change of Post-bronchodilator from Pre-Brochodilator values in those endpoints will be included in CSR Addendum.

1. Change from baseline in Pre-Brochodilator Mean ADC
2. Change from baseline in Pre-Brochodilator ADC SD
3. Change from baseline in Pre-Brochodilator Mean fractional ventilation ratio
4. Change from baseline in Pre-Brochodilator Mean signal to noise ratio
5. Change from baseline in Pre-Brochodilator Fractional ventilation of voxels (peripheral 1/3rd and proximal 2/3rd)
6. Change from baseline in Pre-Brochodilator Fractional ventilation of voxels (peripheral 1/3rd)
7. Change from baseline in Pre-Brochodilator Fractional ventilation of voxels (proximal 2/3rd)
8. Change from baseline in Pre-Brochodilator Ventilation voxels percentage (peripheral 1/3rd and proximal 2/3rd)
9. Change from baseline in Pre-Brochodilator Ventilation voxels percentage (peripheral 1/3rd)
10. Change from baseline in Pre-Brochodilator Ventilation voxels percentage (proximal 2/3rd)
11. Change from baseline in Pre-Brochodilator Number of ventilation defects (peripheral 1/3rd and proximal 2/3<sup>rd</sup>)
12. Change from baseline in Pre-Brochodilator Number of ventilation defects (peripheral 1/3rd)
13. Change from baseline in Pre-Brochodilator Number of ventilation defects (proximal 2/3rd)
14. Change from baseline in Post-Brochodilator Mean ADC
15. Change from baseline in Post-Brochodilator ADC SD

16. Change from baseline in Post-Brochodilator Mean fractional ventilation ratio
17. Change from baseline in Post-Brochodilator Mean signal to noise ratio
18. Change from baseline in Post-Brochodilator Fractional ventilation of voxels (peripheral 1/3rd and proximal 2/3rd)
19. Change from baseline in Post-Brochodilator Ventilation voxels percentage (peripheral 1/3rd and proximal 2/3rd)
20. Change from baseline in Post-Brochodilator Number of ventilation defects (peripheral 1/3rd and proximal 2/3rd)
21. Change of Post-bronchodilator from Pre-Brochodilator in Mean ADC
22. Change of Post-bronchodilator from Pre-Brochodilator in ADC SD
23. Change of Post-bronchodilator from Pre-Brochodilator in Mean fractional ventilation ratio
24. Change of Post-bronchodilator from Pre-Brochodilator in Mean signal to noise ratio
25. Change of Post-bronchodilator from Pre-Brochodilator in Fractional ventilation of voxels (peripheral 1/3rd and proximal 2/3rd)
26. Change of Post-bronchodilator from Pre-Brochodilator in Ventilation voxels percentage (peripheral 1/3rd and proximal 2/3rd)
27. Change of Post-bronchodilator from Pre-Brochodilator in Number of ventilation defects (peripheral 1/3rd and proximal 2/3rd)

The He3-MRI end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

### **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

#### **2.8.9 HRCT**

All analyses associated with HRCT endpoints defined below will be included in CSR.

1. Change in RB1 wall area corrected for body SA (mm<sup>2</sup>)
2. Change in RB1 wall (area)percentage (%)
3. Change in RB1 luminal area (mm<sup>2</sup>)
4. Change in RB10 wall area cor for body SA (mm<sup>2</sup>)
5. Change in RB10 wall (area) percentage (%)

6. Change in RB10 luminal area (mm<sup>2</sup>)
7. Change in Expiratory mean lung density
8. Change in Inspiratory mean lung density
9. Change in Expiratory /Inspiratory mean lung density (derived not in CRF)

Change is considered to be change from baseline to week 12.

The HRCT end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

Body Surface Area is calculated using the Mosteller formula given by:

$$BSA = \sqrt{\frac{W \times H}{3600}} = 0.016667 \times W^{0.5} \times H^{0.5}$$

where, W=Weight(kg), H=Height(cm) and BSA in m<sup>2</sup>.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.10 Bronchial Biopsy**

All analyses associated with bronchial biopsy defined below will be reported in CSR.

1. Change in RBM thickness (µm)
2. Change in eosinophil counts (per unit area lamina propria) (cells/ mm<sup>2</sup> tissue)
3. Change in MUC5a cells (per unit area epithelium) (cells/ mm<sup>2</sup> tissue)
4. Change in total inflammatory cells count (eosinophils, Neutrophils, T-cells and mast cells in the lamina propria per unit) (cells/ mm<sup>2</sup> tissue)

Change is considered to be change from baseline to week 12.

The Bronchial Biopsy end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.11 FeNO**

The analyses associated with FeNO defined below will be reported in CSR.

1. Change in average eNO (ppm)

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 to week 18.

The FeNO end-point will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.12 Serum and Plasma Biomarker**

The serum and plasma biomarker data will be summarized in a report separate from the CSR/CSR Addendum. Summary statistics will be presented along with graphic presentations if appropriate.

### **2.8.13 FACS Analysis**

The FACS analysis data will be summarized in a report separate from the CSR/CSR Addendum. Summary statistics will be presented along with graphic presentations if appropriate.

### **2.8.14 Sputum soluble factor analysis**

The sputum soluble factor analysis data will be summarized in a report separate from the CSR/CSR Addendum. Summary statistics will be presented along with graphic presentations if appropriate.



## **2.9 Resource utilization**

Healthcare resource utilization will not be collected in this study.

## **2.10 Health-related Quality of Life**

### **2.10.1 Asthma Quality of Life (AQLQs)**

A 32-item disease specific questionnaire, each answered on a 7-point scale (1 = totally limited/problems all the time, 7 = not at all limited/no problems).

The domain scores will be calculated from the sum of individual question responses as follows:

Activity limitations = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)

Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)

Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)

Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)

Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL. There is a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means that for a questionnaire of 32 items, no more than 3 items should be missing. Further, for the activity and symptom domains, the recommendation is no more than 1 missing value per domain, and for the emotional function and environmental stimuli domains, no missing responses at all.

The recommended method for handling missing data to reduce the risk of bias is to interpolate (pro-rate) missing values using either previous or subsequent completed questionnaires per domain, in a similar way as described in the data handling section for the analysis of ACQ.

The analyses associated with AQLQ defined below will be reported in CSR.

1.  $\Delta$ AQLQ score

2. proportion of patients with an improvement in AQLQ of  $\geq 0.5$

#### **2.10.1.1 ANCOVA**

Change is considered to be change from baseline to week 6, change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The AQLQ domains will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for primary variable.

### **Subgroup Analyses:**

We will perform ANCOVA on the AQLQ as mentioned for the primary variable for the above mentioned subgroups.

#### **2.10.1.2 Responder Rate**

It will be done similarly as in the case of the secondary variable but only for improvement from baseline in AQLQ of  $\geq 0.5$  at Visit 4, 5 and 6. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented.

#### **2.10.1.3 Normality assumptions and Nonparametric Methods**

It will be done similarly as in the case of the primary variable.

## **2.11 Analyses of other Secondary Objectives**

### **Asthma exacerbations**

Criteria for asthma exacerbations are based on clinic visit spirometry, and investigators clinical judgment. All asthma exacerbations are recorded on the asthma exacerbation episode CRF.

A **severe asthma** exacerbation is defined as treatment with rescue or increase in maintenance systemic corticosteroids for at least 3 days (or equivalent) and hospitalization or emergency department visit (greater than 24 hours) or death due to asthma.

A **moderate asthma** exacerbation is treatment with rescue or increase in maintenance systemic corticosteroids either as an outpatient or in emergency department visits (less than or equal to 24 hours).

Every event of moderate/severe asthma exacerbation leading to discontinuation will be summarized for the three periods- the run-in period, double blind treatment period, and double blind treatment period and Wash-out period.

The total number of moderate/severe asthma exacerbations will be summarized along with the number of weeks for all the three treatment periods- the run-in period, double blind treatment period, and double blind treatment period and Wash-out period. For the Run-in period we will present it for all patients. For the double-blind treatment period and the combined the double-blind treatment period and wash-out period we will present it separately for the two treatment arms.

The number of days at risk for a time-period is defined as number of days from treatment start date to last date of the corresponding treatment period or discontinuation date for discontinuers.

## **2.11.1 Proportion of Exacerbations**

### **2.11.1.1 Logistic regression**

The proportion of patients with  $\geq 1$  moderate/severe asthma exacerbation (leading to discontinuation) during the 12 week double-blind treatment period, the 6 week washout period, the 30 days follow up period and the combined period(12 week treatment+6 week washout+ 30 days follow-up) will be presented and analyzed using logistic regression, provided there is sufficient events in each group for each analysis. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted.

The model will include parameters for treatment, maintenance OCS use at screening (Yes/No) and Bronchoscopy at screening (yes/no).

An estimate of the odds ratio between treatment groups, together with a 95% confidence interval and p-value, will be presented.

### **2.11.2 Time to first exacerbation**

The time to first asthma exacerbation will be defined as the start date of the exacerbation as recorded on the asthma exacerbation CRF.

Time to first moderate/severe asthma exacerbation during the 12 week double-blind treatment period and the 6 week washout period of QAW039 compared to Placebo with will be analysed in the FAS by fitting a Cox regression model including parameters for treatment, maintenance OCS use at screening (Yes/No), Bronchoscopy at screening (yes/no).

Patients with no moderate/severe asthma exacerbations (or no exacerbation in the all exacerbation analysis) will be censored at last visit during the course of the study (including the follow up period).

The hazard ratio of QAW039 /Placebo will be computed, along with associated 95% confidence intervals.

Kaplan-Meier analysis stratified by treatment group will be also presented and displayed graphically.

Time to first severe/moderate asthma exacerbation was analyzed with a Cox proportional hazards regression model.

The null-hypothesis was

$$H_0: \lambda_Q(t) / \lambda_P(t) = 1$$

versus the alternative

$$H_a: \lambda_Q(t) / \lambda_P(t) \neq 1$$

where  $\lambda(t)$  is the hazard function for the failure time of patients treated with QAW039 (Q) and placebo (P), respectively.

The SAS procedure PHREG was used with the following code:

```
proc phreg data=... ;  
model TIME0T0*CNSR(1) = TRT01P ROCMNT BRO ATHEB /rl ties=exact;  
run;
```

where

TIME0T0 = Censoring or event day

CNSR = Censoring flag

TRT01P = Treatment group (planned)

ROCMNT = maintenance OCS use

BRO= Bronchoscopy at baseline

The model fit of the primary model will be diagnosed by plotting Schoenfeldt residuals against time for the primary model.

All analyses associated with exacerbation described above will be reported in CSR.

## **2.12 Safety evaluation**

The standard frequency tables on treatment-emergent events will be used to quantify the safety topics of interest after the start of study drug administration. They will provide the

number and percentage of subjects experiencing each safety topic of interest. Exposure time-adjusted analyses will also be provided.

The relative risk will be calculated with 95% confidence intervals for QAW with placebo as reference. The incidence rate and 95% confidence interval per treatment group will be presented as appropriate.

In addition, listings will be provided presenting which subjects experienced which risk, together with timing of onset relative to study medication, event duration, age, and gender. Medical history and co-medication will be listed for those patients with risk of interest.

All summary tables in this section used the safety analysis set.

All analysis planned in this section will be reported in the CSR.

## **2.12.1 AE of special interest**

### **2.12.1.1 The risk of liver toxicity (SPP risk, Routine risk)**

#### **(1) Cases defined by lab parameters**

The liver function tests (LFT) under consideration include the following serum blood chemistry lab parameters: ALT, AST, ALP, and TBL. The lab standard tables and figures, such as summary table of change from baseline (including mean, SD, median, IQR, min, and max), shift table with respect to normal reference range, and box plots, will be produced over time.

In addition, to evaluate potential indicators of drug-induced liver injury or dysfunction, patients with newly occurring elevations in LFT at any time post-baseline are summarized and listed based on the following thresholds in lab tests.

- ALT or AST > 3x, 5x, 8x, 10x, 20x ULN
- ALP > 1.5x, 2x, 3x ULN
- TBL > 1.5x, 2x, 3x ULN
- ALP > 3x ULN concurrently with TBL > 2x ULN
- Potential Hy's law cases : (ALT or AST > 3x, 5x, 8x, 10x, 20x ULN) concurrently with TBL > 1.5x, 2x ULN
- Potential Hy's law cases: (ALT or AST > 3x ULN) concurrently with both TBL > 2x ULN & ALP < 2x ULN

This is to identify if there is any evidence of increases in AST or ALT, beyond expected adjustment time and to investigate whether they are accompanied by a similar (delayed) increase over time in Total Bilirubin. For a criterion with combined components, such as lab criteria for Hy's Law which has at least 3 components, each condition has to happen exactly at the same time to meet the criteria. A case is considered as newly occurring if the baseline condition does not meet the clinically notable criterion but clinically notable at post-baseline. For patients with missing value in baseline for at least one component, post-baseline values meeting the notable criterion will be considered as newly occurring.

Matrix graphs of maximum /ULN-normalized liver function test values will be also produced. This is a matrix display of maximum post-baseline /ULN-normalized values in form of scatter plots of all 6 pairs LFTs, i.e. ALT, AST, ALT, and TBIL. These plots allow one to visualize multivariate relationships by a matrix of bivariate distributions and to identify, for example, Hy's law cases.

For all subjects with liver values (AST, ALT, ALP, TBL) matching any of above thresholds single subject profile graphs will be generated showing all AST, ALT, ALP, TBL lab values reported for this study and the time of study treatment.

## **(2) Cases identified through SMQ**

In addition to liver function tests, adverse events of hepatic disorders will be also summarized. The cases will be identified through SMQ search on "Drug related hepatic disorders - comprehensive search (SMQ)", which is a level 2 child SMQ under the level 1 "Hepatic disorders (SMQ)".

The number and percentage of subjects with AEs will be summarized by SMQ level for all the hierarchies (child SMQs) under level 1 "Hepatic disorders (SMQ)" to provide an overview. The data will be then summarized by SMQ and preferred term for only events under level 2 "Drug related hepatic disorders - comprehensive search (SMQ)". This is to identify if there is any evidence of a clinically significant imbalance in the overall Level2 SMQ or any of its child SMQs.

### **2.12.1.2 Other AE of special interest**

The following AE's of special interest will also be summarized in the table with number and percentage of subjects with AEs by SMQ levels:

- 1) Tachyarrhythmia (incl supraventricular and ventricular tachyarrhythmias) broad SMQ (code: 20000054)
- 2) Cardiac Failure SMQ (code: 20000004)
- 3) Increase in platelet counts Using HLT of "Platelet analyses" (coded as 10035523).

Numbers and percentages of patients with change from baseline in heart rate in categories of <-30, -30 to -20, -20 to -10 to -5, -5 to 0, 0 to 5, 5 to 10, 10 to 20, 20 to 30, >30 are also summarized as an analysis of risk of Tachycardia.

## **2.12.2 Other safety evaluation**

### **2.12.2.1 Adverse events**

Adverse events that start during the study but before the time of the first administration of study drug (e.g. screening period) will be classified as a prior adverse event.

An event of asthma exacerbation will be included in the adverse events analysis.

Asthma related adverse events will be identified using SMQ broad search. Asthma exacerbations will be included in all the adverse event related analysis. Use SMQ code 20000025 (Asthma/bronchospasm (SMQ)) for identifying Asthma related AE's.

Frequency tables (number and percentage of patients) of the incidence of adverse events will be produced for the following:

- Overall by system organ class and preferred term
- Overall by system organ class, preferred term and maximum severity
- Suspected drug-related adverse events by system organ class and preferred term
- Serious adverse events by system organ class and preferred term
- Adverse events leading to permanent discontinuation of study-drug by system organ class and preferred term
- Asthma related adverse events by system organ class and preferred term, using SMQ broad search, (SMQ code 20000025 - Asthma/bronchospasm (SMQ)).
- Other significant AE's (project specific- Liver toxicity, cardiac findings and increase in platelet count)
- Prior adverse events, if the number of prior adverse events is low, listings will be used instead of summaries.

Listings will be produced for the following, with preferred term, system organ class, seriousness, severity, relationship to study drug, action taken, start and end dates and times and whether continuing at final visit:

- All adverse events
- Serious adverse events
- Adverse events causing study drug discontinuation
- Adverse events requiring dose adjustment or interruption
- Adverse events requiring significant additional therapy (this is combination of concomitant medications and / or non-drug therapy)
- Adverse events related to asthma

A summary of deaths according to the affected primary system organ class and preferred term for the investigator-reported principal cause of death will be presented by primary system organ class, preferred term, and treatment groups regardless of study drug relationship.

Any deaths within 30 days of last dose will be listed with dates and study days of death and last dose, and principal cause of death with associated coded terms.

#### **2.12.2.2 Laboratory data**

All the laboratory samples were processed through the Central Laboratory. Laboratory data consist of hematology, biochemistry and urinalysis measurements. All data will be listed with abnormal values flagged. The following sub-sections will describe the method of summary.

Baseline for laboratory parameters is the last available measurement prior to first dose of study medication.

#### 2.12.2.2.1 Summary of absolute values

For all continuous laboratory parameters, the absolute laboratory values, including the worst case post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits), will be summarized with standard descriptive statistics by parameter, scheduled visit and time-point, and treatment. An example of the direction of interest for worst case post-baseline for selected hematology and biochemistry parameters is shown in Table 2-6. For continuous urinalysis parameters the direction of interest is always High.

For categorical urinalysis laboratory parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit and time-point, and treatment. Worst-case post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits) will also be included.

Patient profile plots can be produced for hematology and biochemistry continuous laboratory parameters, with a line for each patient plotting the result against time. There will be a separate plot for each parameter and each treatment group.

#### 2.12.2.2.2 Summary of change from baseline

For continuous laboratory parameters, the change from baseline at each scheduled visit and time-point, and the change from baseline to the worst case post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits) will be summarized by laboratory parameter, scheduled visit and time-point, and treatment with standard descriptive statistics.

#### 2.12.2.2.3 Shift tables

Shift tables for laboratory parameter will be provided in order to compare a patient's baseline value to the value at each time point at each study visit, relative to the normal reference range for each lab parameter. For the shift tables, normal reference ranges provided by the central lab will be used to evaluate whether a particular laboratory test value for each time point at each visit is normal, low, high or non-available relative to the baseline value also categorized as normal, low, high, or non-available. These summaries will be presented by laboratory test, visit, time point, and treatment group.

In addition, shift tables relative to the normal reference ranges will be used to summarize the change from baseline to the most extreme post-dose value for each laboratory parameter. For each laboratory test, the patients will be classified into one of the four mutually exclusive groups (low, normal, high, and low+high), defined as follows:

- ◆ Low: at least one post-baseline value below the normal range and none above the normal range
- ◆ High: at least one post-baseline value above the normal range and none below the normal range



- ◆ Normal: all the post-baseline values within the normal range
- ◆ Low+High: at least one post-baseline value below the normal range and at least one above the normal range

Categorical parameters in the urinalysis panel will also be summarized with shift tables showing the shift from one categorical result to another. The shift from baseline to most extreme post-dose value will also be summarized, with the least to most extreme scale assumed to be negative, trace, +, ++, +++, +++++.

#### 2.12.2.2.4 Notable values

For selected laboratory tests, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria will be summarized by laboratory parameter, post-baseline visit, time point and treatment. An additional section will be included for abnormalities occurring at any time-point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Patients with any newly occurring or worsening value meeting the clinically notable criteria will be counted under the applicable criteria.

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value which is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For patients with missing value in baseline, any post-baseline notable value will be considered as newly occurring.

Guidelines for clinically notable criteria for laboratory tests are based on the FDA Guidelines for adults in SI units. For those parameters where ranges are available, the criteria for clinically notable results are presented in Tables 2-1 and 2-2 as an example.

Listings of patients with notable laboratory values will be provided by laboratory parameter, treatment group, and patient number.

**Table 2-1 Direction of interest for worst case value for laboratory parameters**

<b>Laboratory Parameter</b>	<b>Direction of interest for worst case value</b>
<b>A. Hematology</b>	
Basophils	High
Eosinophils	High
Hematocrit	Low and High
Hemoglobin	Low and High
Lymphocytes	low and high
Monocytes	High
Neutrophils	low and high
Platelets	Low and High
RBC	Low and High
WBC total	Low and high
<b>B. Chemistry</b>	
Albumin	Low
Sodium	Low and High
Alk. Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Gamma GT	High
Glucose (random)	Low and high
Potassium	Low and high
Total protein	Low and High

Table 2-2 Clinical notable criteria for selected laboratory tests

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
<b>Hematology</b>		
Hematocrit (v/v)		
Male	0.37	
Female	0.32	
Hemoglobin (g/L)		
Male	115	
Female	95	
Thrombocytes (x10 <sup>9</sup> /L)	75	700
WBC's (x10 <sup>9</sup> /L)	2.8	16.0
<b>Chemistry</b>		
Alkaline Phosphatase (U/L)	-	3xULN
Total Bilirubin (mcmol/L)	-	34.2
Creatinine (mcmol/L)		176.8
Potassium (mmol/L)	3	6
Glucose (mmol/L)	2.78	9.99
SGOT (U/L)	-	3 x ULN
SGPT (U/L)	-	3 x ULN
BUN/Serum Urea (mmol/L)		9.99
Sodium (mmol/L)	125	160
Albumin (g/L)	25	-
Total protein (g/L)	40	95
Gamma GT (U/L)		3 x ULN

v = volume, ULN = upper limit of normal

### 2.12.2.3 Vital signs

#### 2.12.2.3.1 Summary of absolute values

Data from the vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized by treatment at the scheduled visits and time-points. The maximum and minimum systolic blood pressure, diastolic blood pressure, and pulse rate post-baseline (including values from post-baseline unscheduled and premature discontinuation visits) can also be summarized by treatment. Absolute body weight will be summarized by scheduled visit.

Vital signs will also be summarized by categories:

- pulse rate: < 40 bpm, 40 – 90 bpm, and > 90 bpm
- systolic blood pressure: < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
- diastolic blood pressure: < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg.

#### 2.12.2.3.2 Summary of change from baseline

The change from baseline to each scheduled post-baseline visit will be summarized similarly as the laboratory parameters where baseline and post-baseline values are both available. The summary will be presented by vital sign parameter, scheduled visit and time-point, and treatment with standard descriptive statistics.

### 2.12.2.3.3 Notable absolute values and change from baseline

The number and percentage of patients with newly occurring or worsening notable values, including notable change from baseline, will be summarized by vital sign parameter, post-baseline visit and treatment group. An additional section will be included for abnormalities occurring at any time-point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Notable absolute values and notable changes from baseline for each vital sign parameter are defined in Table 2-3 as an example (The notable criteria may be changed depending on the lab used).

For a patient to meet the criterion of a newly clinically notable occurrence, the patient needs to have a baseline value which does not meet the criteria for categorizing a value as notable. For a patient to meet the criterion of a worsening occurrence, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For patients with a missing value at baseline, post-baseline values meeting the notable criterion will be considered as newly occurring.

**Table 2-3 Clinical notable criteria for vital signs**

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
<b>Notable value considering newly occurring or worsening cases</b>		
Systolic blood pressure (mmHg)	< 75	> 200
Diastolic blood pressure (mmHg)	< 40	> 115
Pulse rate (bpm)	< 40	> 130
<b>Notable change from baseline</b>		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15
Weight (kg)	Decrease ≥ 7% from baseline	Increase ≥ 7% from baseline

### 2.12.2.4 Electrocardiogram (ECG)

If more than one ECG is taken at a scheduled time point the ECG values will be averaged for the quantitative ECG assessments and analysis. For qualitative assessments, if multiple ECG values were taken, the worst case will be chosen for all summaries.

#### 2.12.2.4.1 Summary of absolute values

The following quantitative variables will be summarized by treatment at each scheduled post-dose visit and time point: ventricular rate, QT interval, RR interval, PR interval, QRS duration, heart rate, and Fridericia's QTc. The maximum QTc (including values from post-baseline unscheduled and premature discontinuation visits) will also be summarized.

QTc will also be summarized by categories:  $\leq 450$  msec,  $> 450 - 480$  msec,  $> 480 - 500$  msec,  $> 500$  msec.

#### 2.12.2.4.2 Summary of change from baseline

The changes from baseline will be summarized by ECG parameter, schedule visit and time point where baseline and post baseline values are both available.

#### 2.12.2.4.3 Overall ECG interpretation

The Overall ECG interpretation is the qualitative ECG assessment. ECGs will be centrally reviewed by a cardiologist. If the central cardiologist reported that an ECG was abnormal, then the investigator commented in the CRF as to whether the ECG abnormality was "normal", "clinically insignificant abnormality" or "clinically significant abnormality". The overall interpretation is based on the evaluation provided by the investigators and the central readings, respectively.

Shift tables will be provided to compare a patient's overall ECG interpretation at screening to the interpretation at the end of the study.

#### 2.12.2.4.4 ECG abnormalities

Using the morphologic determinations, the number and percentage of patients with qualitative ECG abnormality will be summarized *overall during the study period as well as for each visit/ timepoint*.

The abnormality will be summarized by baseline condition (NO/YES, i.e. newly occurring cases, or persistent/recurrent cases) for each evaluation type and finding. The qualitative ECG abnormality will be determined by abnormality of Rhythm, Arrhythmia, Conduction, Morphology, Myocardial infarction, ST segment, T wave abnormalities, and abnormal U wave for example. A patient with multiple occurrence of an abnormality will be counted only once for that treatment.

#### 2.12.2.4.5 Notable QTc values

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value which is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For patients with a missing value at baseline, post-baseline values meeting the notable criterion will be considered as newly occurring. The number and percentage of patients who have newly occurring or worsening clinically notable values, or notable changes from baseline, will

be presented by post-baseline visit. Notable values will be summarized for Fridericia's QTc. Data from unscheduled visits and from premature discontinuation visits will be included. A listing of all newly occurring or worsening abnormalities will be provided. The clinically notable ranges for selected ECG parameters and notable changes from baseline are show in Table 2-7 as an example.

**Table 2-4 Clinical notable criteria for selected ECG parameters**

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTc (msec)	> 450 for male and >470 for female
QTc (msec)	> 500
Notable change from baseline	
QTc	30 – 60
QTc	> 60

### 2.13 Interim analyses

RAP M3 for Interim Analysis is documented in a separate document.

### 2.14 Determination of Sample Size

Table 2-1 provides the sample sizes required for each respective outcome measure (the primary and secondary variables) in order to achieve an 80% power to detect the minimally important difference at a two-tailed 5% significance level.

This study is aimed to power for a 50% reduction in sputum eosinophil percentage. This is equivalent to an absolute reduction in log<sub>10</sub> (sputum eosinophil percentage) of log<sub>10</sub>2 = 0.301 (Inman et al, 2002, Barnes et al, 2011). The minimally important differences for the primary and key secondary endpoints are listed in Table 9-1.

**Table 2-5 Sample size calculations for primary and secondary endpoints**

Endpoint	Assumption		N per treatment group	
	SD <sup>*</sup>	Minimally important difference	BT <sup>#</sup> comparison	
			2-group T-test	WMW <sup>§</sup> rank-sum
Δ <sup>†</sup> in sputum eosinophil percentage on log <sub>10</sub> scale	0.333	0.301¥	21	23
Δ <sup>†</sup> in ACQ	0.385	0.5€	11	13

Δ<sup>†</sup> = change from baseline at week 12

SD\* = Standard deviation for the endpoint to be analyzed

BT# = between-treatment

WMW<sup>s</sup> = Wilcoxon/Mann-Whitney rank sum test

¥ (Inman et al, 2002)

€ (Juniper et al, 2005)

With 30 patients per arm to be randomized, it is expected that 24 patients per arm will complete week 12 assessment, assuming the dropout rate during the course of treatment phase (12 weeks) is 20%. With this sample size, the primary and secondary endpoints achieve  $\geq 80\%$  power to detect minimally important difference between QAW039 and placebo, as specified in Table 2-1.

Clinical Development

QAW039

QAW039A2208

A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma

### **RAP Module 3 – Detailed Statistical Methodology**

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**Document History – Changes compared to previous version of RAP module 3.**

Version	Date	Changes
Addendum 1	20/1/2014	Removed inappropriate baseline definition for sputum eosinophil
		Removed the contents associated with CSR addendum as all outputs contained in this document will be included in core CSR
		Added imputation rule for sputum eosinophil value 0s
	20/4/2014	Added analysis for per-protocol analysis
		Added description of MMRM for primary and secondary analysis
	20/5/2014	Added PK analysis with summary statistics and listings

## **1 Introduction**

This document contains details of the statistical methods which will be used in the phase II clinical trial CQAW039A2208. The purpose of this study is to determine whether, in patients with sputum eosinophilia ( $\geq 2\%$ ) and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum. As well as providing comparative (against placebo) safety data from this population of patients, measurements made in this study will also be used to establish whether this treatment improves other measures of asthma disease activity, lung function and lung pathology.

Data will be analyzed according to the data analysis section 9 of the study protocol (unless otherwise stated below) which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

### **1.1 Study Design**

This study uses a 2-treatment arm (Placebo or QAW039), parallel group, double-blind, randomized, placebo-controlled design.

After signing informed consent (Visit 1), patients will undergo a 2-week placebo run-in period during which their clinical stability and suitability for randomization will be assessed. Asthma patients who are already receiving ICS or ICS-LABA therapy are the target population for this study. All patients will be allowed to continue on their current therapy. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for a treatment duration of 12 weeks. At the end of the 12-week treatment period (visit 5), all patients will receive placebo until the 6-week post-treatment assessment (visit 6). Both during the run-in and wash-out periods, the study will be single-blind because physicians will know that patients are on placebo, however the 12-week treatment period will be double-blind.

Visits to assess safety and efficacy are scheduled at 6, 12, and 18 weeks post-randomization. The assessment to address the primary objectives will be performed at the end of the treatment period (week 12).

## **1.2 Study Objectives**

### **1.2.1 Primary objective**

The primary objective of this study is to demonstrate a statistically significant reduction in sputum eosinophil levels in inadequately controlled, moderate-to-severe asthmatics (GINA 2-5), with sputum eosinophilia after treatment with QAW039 for 12 weeks compared to placebo.

### **1.2.2 Secondary Objectives**

To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo.

To assess safety and tolerability of QAW039 in this moderate-to-severe asthmatic population as compared to placebo.

### **1.2.3 Exploratory Objectives**

To demonstrate that QAW039 provides significant improvement in standard physiological markers such as FEV<sub>1</sub>, as well as specific small airway markers measured with multiple breath washout (MBW) and impulse oscillometry, namely S<sub>acin</sub>, R5-R20 and AX, compared to placebo.

To explore whether the efficacious effect of QAW039 therapy persists following the cessation of therapy.

To explore whether quantitative computed tomography (CT) biomarkers at baseline predict response to therapy with QAW039.

To explore changes in air trapping, as evaluated by quantitative computed tomography (CT), after 12 weeks of treatment with QAW039 versus placebo.

To explore changes in health-related quality of life as measured by the standardised Asthma Quality of Life Questionnaire (AQLQs) after 12 weeks of treatment with QAW039 versus placebo.

To explore changes in blood proteomic and transcriptomic profile following 12 weeks of treatment with QAW039 versus placebo.

To explore changes in exhaled volatile organic compounds (VOCs) following 12 weeks of treatment with QAW039 versus placebo.

- . To explore the effect of QAW039 on ventilation heterogeneity, as measured by Hyper-polarised helium-3 MRI (He-3 MRI), compared to placebo.
- . To explore whether QAW039 attenuates eosinophilic airway inflammation as measured by bronchial brushings and bronchial biopsies, compared to placebo.
- . To explore whether QAW039 attenuates features of remodelling in bronchial biopsies (including but not limited to the assessment of histological features of inflammatory and goblet cell number, reticular basement membrane thickness and assessment of collagen deposition) compared to placebo.
- . To assess the pharmacokinetics of QAW039 in this population of asthma patients.
- . To explore the changes in body plethysmography measurements following 12 weeks of treatment with QAW039 versus placebo.

## 2 Project standards

### 2.1 Analysis sets

**Table 2-1 Subject classification based on protocol deviations and non-PD criteria**

Analysis set	PD severity codes that cause a subject to be excluded	Non-PD criteria that cause a subject to be excluded
RAN (Randomized set)	8	
FAS (Full Analysis Set following ITT principle)	0,8	NA
Safety	5, 8	NA
Per Protocol	0, 1, 8	<i>e.g. Discontinued the study early per CRF completion panel</i>

- **The Randomized Set (RAN)**, which comprises all randomized patients, regardless of whether or not they actually received study medication, will be used for summaries of patient disposition and analysis sets, and listings of major protocol deviations and premature discontinuations, etc. Patients in RAN will be analyzed according to the treatment they were randomized to. This analysis set is not necessary unless the Full analysis set is different from the randomized set.
- **The Full Analysis Set (FAS)** will include all randomized patients who received at least one dose of study drug. FAS will be used to analyze all efficacy endpoints, unless otherwise stated. Following the intention-to-treat principle, patients in the FAS will be analyzed according to the treatment they were randomized to. The potential biases arising from excluding the randomized patients who took no study medication are negligible since the decision of whether or not to begin treatment could not be influenced by knowledge of whether being assigned study drug or placebo. Although some Phase III trials may include an active control arm, the primary comparisons in all trials will be between investigational study drug and placebo.
- **The per-protocol (PP) set** will include all patients in the FAS without any major protocol deviations that could confound the interpretation of analyses conducted on the FAS. Major protocol deviations will be defined prior to database lock and without knowing the treatment of individual cases. Patients will be analyzed according to the treatment group as randomized. PP will be used for supportive analysis to assess robustness of the primary, secondary analyses and some spirometry endpoints as exploratory analyses. Patients with compliance less than 80% and more than 120% during double-blind treatment period will be excluded from the PP set.
- **The Safety set (SAF)** will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they received. If patients switch treatment during the study, they will be analyzed, *for example, according to the treatment they were randomized to or as the highest dose of Novartis compound*. The safety set will be used in the analysis of all safety endpoints and in the listings of certain notable safety data.
- **The pharmacokinetic set (PK)** will include all randomized patients who receive at least one dose of study medication and have evaluable plasma concentration data. The PK set will be used in PK analysis. Patients will be analyzed according to the treatment they received.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error. Also the FAS set assigns randomized treatment and the safety set assigns received treatment.

The analyses of the primary objective and other efficacy variables will be performed on the FAS. The PPS will be used for the supportive analysis of the primary variable. The safety set will be used in the analysis of all safety variables.

Protocol deviations severity/Analysis Classification codes defined in VAP Module 3 leading to patient classification into the analysis sets are as follows:

<b>Code</b>	<b>Action</b>
0	Exclude from all efficacy analysis (including ITT)
1	Exclude from Per-Protocol analysis
2	Exclude from data analysis from this date
3	Exclude from data analysis from this date for a specified number of days
4	Exclude from data analysis on this date
5	Exclude from all safety analyses
6	Exclude from Main Analysis Set
7	Exclude from 2 <sup>nd</sup> Per-Protocol analysis
8	Exclude from all analysis
9	Include in all efficacy analysis
10	Exclude patient from 3 <sup>rd</sup> Per-Protocol analysis
11	Exclude from 2 <sup>nd</sup> ITT population
12	Exclude from 3 <sup>rd</sup> ITT population
13	Exclude from 3 <sup>rd</sup> ITT population
14	Exclude from 3 <sup>rd</sup> Safety population
15	Exclude patient from 4 <sup>th</sup> Per-Protocol analysis
16	Exclude from 4 <sup>th</sup> ITT population
17	Exclude from 4 <sup>th</sup> Safety population
18	Exclude from dose-finding population
20	Exclude patient from PK population
49	Report relevant protocol deviation – include in all analyses

## **2.2 Sample stratification**

There will be stratification of patients based on use/not use of oral corticosteroids and bronchoscopy/no bronchoscopy.

## **2.3 Assessment windows, baseline and post baseline definitions, missing data handling**

Data from unplanned or unscheduled visits or the early discontinuation visits will be listed.

### **2.3.1 Study Day**

Study day is defined as the number of days since the date of first dose of study medication. The date of first dose of study medication was defined as Day 1 and the day before the first dose of study medication was defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study medication,

Study day = Assessment date – Date of first dose of study medication + 1;

- for dates prior to the first date of study medication,

Study day = Assessment date – Date of first dose of study medication

### **2.3.2 Assessment windows**

Patients should be seen for all visits on the designated day or as close to it as possible.

Patients should be seen for all visits on the designated day, with an allowed visit window of  $\pm 3$  days. The visit window for the screening period is +7 days.

Patients who discontinue study drug before completing the study, or prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time the assessments performed for the final visit will be assessed. The visit number of such a final assessment with visit numbers such as 777 (or 777.1, 777.2 etc) will be remapped as follows: if the visit is greater or equal to half of the visit interval from the preceding scheduled visit then the visit number will be assigned to the next scheduled visit; if the visit is less than half of the visit interval then the final visit will be remapped accordingly as a repeat visit.

Only the final visit will be remapped as above, no remapping will be undertaken for any other visits. For example an unscheduled visit like visit 5.1 will not be remapped. Only end of study visit (visit 777) and corresponding unscheduled visits (777.1, 777.2 etc.) will be remapped.

For patients who complete the study, the study completion visit will be remapped to Week 18 (visit 6). For patients who do not complete the study, the premature discontinuation visit will not be remapped to week 18 (visit 6).

### 2.3.3 Imputation of partial dates

Unless otherwise stated in RAP M8, the partial dates (missing in day or month) will be imputed as per the following table:

	Assessment month < treatment start Month	Assessment month = treatment start Month	Assessment month > treatment start Month	Assessment month is missing
Assessment year < treatment start year	01MMMYYYY	01MMMYYYY	01MMMYYYY	01JULYYYY
Assessment year = treatment start year	01MMMYYYY	Treatment start date + 1	01MMMYYYY	Treatment start date + 1
Assessment year > treatment start year	01MMMYYYY	01MMMYYYY	01MMMYYYY	01JANYYYY
Assessment Year is missing	NA	NA	NA	NA

### 2.3.4 Baseline definitions

In general, baseline is defined as the last measurement prior to the first dose of study treatment unless otherwise stated.

1. Baseline Sputum eosinophil measure. Patients' sputum will be tested for % sputum eosinophil count at Visit 3. This will be the baseline value of the sputum eosinophil count.



2. Baseline ACQ score. ACQ score is calculated as the mean of the 7 questions, calculated as the sum of scores divided by the number of questions that were answered by the patient. For ACQ questionnaires the baseline is defined as the values recorded by the patient at visit 3. If any one of the seven items is missing at Visit 3, it will be imputed from Visit 2. For imputation logic see Section 2.8.2. If after imputation from Visit 2, question 1 and 7 is non-missing and not more than one question from 2 to 6 is missing, then baseline ACQ score will be the average value of the six non-missing values. If after imputation from Visit 2, question 1 or 7 or more than two questions from 2 to 6 is missing, then that ACQ value will be set as missing. If ACQ values for Visit 3 is missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

3. Baseline AQLQ score. AQLQ score is calculated by taking the average of the total scores obtained from a questionnaire of 32 items. The 32 items are divided into 4 domains- activity, symptom, emotional and environmental and considering them all together we get the total score. Baseline AQLQ score (domain wise and total) is defined as the value obtained at visit 3. If any of the 32 items is missing it will be imputed from Visit 2. For imputation logic see 2.10.1. If even after imputation we have more than 10% items missing, that is more than 3 items missing, then the total score will be set as missing. Further, for the activity and symptom domains, the recommendation is no more than 1 missing value per domain, and for the emotional function and environmental stimuli domains, no missing responses at all. These conditions will be checked after imputation from Visit 2. If these conditions are not met, then the baseline value at Visit 3 is put as missing. If AQLQ values for Visit 3 is missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values. This will be followed for the total score as well as the domain score.

4. Baseline Spirometry end-points. Baseline FEV1 is defined as the FEV1 measurement taken prior to the first dose of study drug (Visit 3). If this assessment is missing (or is not confirmed to be pre-dose), then the Visit 2 assessment will be considered as baseline. If the FEV1 measurements are missing both on Day 1 and at the screening visit, the respective baseline values will be set to missing and the mean of the baseline values of the non-missing patients will be imputed as baseline values. The baseline FVC is defined similar to FEV1 baseline.

5. Baseline FENO. For FeNO, baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 is missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

6. Baseline Body Plethysmography end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

7. Baseline CO Transfer factor end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

8. Baseline Oscillometry end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

9. Baseline High Resolution Computed Tomography (HRCT) end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

10. Baseline Multiple Breath Washout end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

11. Baseline Hyperpolarized Helium-3 MRI Imaging (He-3 MRI) end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

12. Baseline Bronchial Biopsy end-points. Baseline will be defined as the values recorded by the patient at visit 3, irrespective of whether values were taken prior to or following first dose. If values for Visit 3 are missing then for those patients with missing values, the mean of the baseline values of the non-missing patients will be imputed as baseline values.

13. Baseline Laboratory end-points. Laboratory data include hematology, biochemistry and urinalysis. Baseline hematology, biochemistry and urinalysis are defined as the last scheduled assessment taken prior to first dose of study drug on Day 1. Checks will be performed to ensure baseline hematology, biochemistry and urinalysis laboratory values were indeed assessed pre-dose. If the pre-dose measurement on Day 1 is missing (or was not confirmed to be pre-dose), then the last available assessment prior to day 1 will be used. Otherwise, the baseline laboratory data will be set to missing.

14. Vital signs include pulse rate and systolic and diastolic blood pressures. Baseline vital signs are defined as the last scheduled assessment taken pre-dose on Day 1. Checks will be performed to ensure the assessments were indeed taken prior to the first dose of study drug on Day 1. If this assessment is missing or not confirmed to be pre-dose, the last available value taken prior to day 1 will be used for baseline.

15. Baseline height and weight are defined as the measurements taken at the screening visit. Missing baseline will not be imputed.

16. Baseline ECG is defined as mean of 2 consecutive ECG measurements taken at 35 minutes prior to dosing on day 1 (Visit 3). Checks will be performed to ensure the ECG was indeed assessed prior to the first dose of study drug. If one of the two values is missing (or not confirmed to be pre-dose) then the non-missing values will be taken as the baseline. If all values are missing (or not confirmed to be pre-dose) then the last assessment taken prior to day 1 will be used. Otherwise, the ECG baseline will be set to missing without imputation. For baseline ECG interpretation there will only be one assessment at each time-point, and hence this will be used as the baseline ECG interpretation (pre-dose Day 1 value if present and confirmed to be pre-dose, otherwise last available visit prior to day 1).

17. Baseline smoking status will be the smoking status at the screening visit (visit 1).

### **2.3.5 Post baseline definitions**

Post baseline measurements are defined as those assessments on or after the start of study treatment.

For safety data, post baseline measurements include measurements recorded up to +7 days for AEs and +30 days for SAEs after the last dose of study drug or last visit whichever is later.

When change from baseline and percent change from baseline are of interest the following formula will be used where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value

Percent change from baseline = Change from baseline/baseline value x 100%.

Safety measurements may include ECG, vital signs, laboratory analysis and adverse events. When deriving the ECG and vital signs, values which have complete date and time values are assigned to pre or post-dose assessment based on the actual date/time. However, values with missing date/time are assigned to their respective scheduled visit date and time.

### **2.3.6 Missing data handling**

Missing dates will be imputed as appropriate using standard Novartis data imputation rules (see M8 for further details) with the exception of duration of Asthma defined in section 2.5.3. The handling of other missing data will be dealt with where appropriate in the specific analysis sections below.

## **2.4 General output guidelines**

Unless otherwise stated, tables, and figures will be based on all subjects included in the analysis set under consideration.

### **2.4.1 Summary tables**

The data will be summarized in the summary tables as follows:

- Categorical data will be presented as proportions (frequencies and percentages) or as intensity (adjusted for treatment exposure).
- Continuous data will be presented in terms of mean, standard deviation, minimum, Q1 (25<sup>th</sup> percentile), median, Q3 (75<sup>th</sup> percentile) and maximum.

### **2.4.2 Decimal places**

Decimal places for demographic, background characteristics and duration of exposure variables will be as follows:

- 2 decimal places for standard errors and standard deviations.
- 1 decimal place for means and medians.
- 1 decimal place for minimums, maximums and quartiles
- 1 decimal place for percentages.
- if percentage = 100, no decimal is required and no percentage will be displayed if the frequency count is zero.
- The respective numbers in each column will be decimally aligned.

Decimal places for efficacy and other safety summary tables will be as follows:

- standard errors and standard deviations: data precision + 2 decimal places.
- means and medians: data precision + 1 decimal place.
- minimums, maximums and quartiles: same as data precision.
- percentages: 1 decimal place.
- All p-values will be presented to 4 decimal places.
- Event intensity (events per week) will be presented to 2 decimal places.
- if percentage = 100, no decimal is required and no percentage will be displayed if the frequency count is zero.
- The respective numbers in each column will be decimally aligned.

### **2.4.3 Visit labeling**

In tables and figures (as applicable), visits will be labeled using Days.

## **2.5 Patient disposition, demographic and baseline characteristics**

All summary tables in this section used the Safety analysis set (SAF). Certain tables, where stated, will be repeated for the Full analysis set (FAS).

### **2.5.1 Patient disposition**

Randomized set (RAN) will be used for the summary and listing of patient disposition.

The number of patients screened, randomized, completed and discontinued from the study will be summarized with reasons for discontinuation.

Patient randomization number and whether they completed or discontinued from the study will be listed, with date of last dose and primary reason for discontinuation, including unblinding date if applicable, and any other details specified.

Time to premature discontinuation will be displayed graphically for each treatment group using a Kaplan-Meier curve for the safety analysis set. The date of premature discontinuation is defined as the maximum of the last known visit date and the date of last dose of study medication. Patients who did not discontinue early will be censored at the final visit.

The time to premature discontinuation will be analyzed for the safety population using the Cox regression model. Covariates will be treatment, baseline oral corticosteroids use and baseline bronchoscopy.

The number of subjects with protocol deviations will be tabulated by category and deviation (see Section 2.1).

Protocol deviations will be listed with date and study day of occurrence, deviation code and severity.

The number of subjects included in each analysis set will be tabulated. Reasons for exclusion from analysis populations will be tabulated for all patients.

Patient exclusion from analysis populations will be listed for all patients with reasons for exclusion (i.e. including both protocol and non-protocol deviations).

### **2.5.2 Demographics**

Safety analysis set (SAF) will be used for the summary of patient demographics. Following variables will be included in the demographics summary.

- Gender
- Race and ethnicity
- Age (derived – numeric)
- Baseline height
- Baseline weight
- Baseline body mass index (BMI)

BMI will be calculated as follows:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (m)} * \text{Height (m)}]$$

- Baseline BMI category ( $\leq 30\text{kg/m}^2$ ,  $>30\text{kg/m}^2$ )

Continuous variables will be summarized using descriptive statistics (mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles, minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

### **2.5.3 Baseline characteristics**

Following variables will be included in the summary of baseline disease characteristics. The summary will be presented for Safety analysis set.

- The duration period of Asthma (years)

The duration will be calculated as follows:

Duration of asthma = (Date of screening visit (Visit 1) – Date first diagnosed) / 365.25

Duration of asthma is calculated from the date of asthma first diagnosed recorded on the CRF until Visit 1. If the date is missing in day and/or month, it will be imputed as described in section 2.4.3.

- Smoking history (ex-, never, current)
- Smoking history (pack years)

Estimated number of pack years is calculated by the total years of smoking multiplied by cigarette packs smoked per day. This will be summarized as recorded on the CRF. Smoking history in package years was calculated as the total years of smoking multiplied by cigarette packs smoked per day. For example, 1 pack year = 20 cigarettes (1 pack) per day for 1 year, or 10 cigarettes (0.5 pack) per day for 2 years, or 40 cigarettes (2 packs) per day for half a year.

- Smoking history (time since stopped - years)

The time since stopped will be calculated as follows:

Time since smoking stopped = (Date of screening visit (Visit 1) – Date of stopping smoking) / 365.25

For this calculation, partial dates will be imputed as described in section 2.3.3.

- History of asthma exacerbation (Yes/No)
- Baseline ICS or ICS+LABA
- Baseline use/not use of oral corticosteroids
- Baseline bronchoscopy/no bronchoscopy
- Baseline ACQ score will be summarized as continuous variables and as categorical data as defined in section 2.3.

The ACQ measures asthma symptom control and consists of 7 items. All 7 questions of the ACQ are equally weighted. The ACQ score is the mean of the responses to the 7 questions. The resultant score will be between 0 and 6. Please refer to section 2.3.4 for baseline calculation and section 2.8.2 for the missing data handling.

- IgE, FeNO, eosinophil, and CRTh<sub>2</sub> will be summarized as continuous variables as defined in section 2.
- Reversibility and hyper-reactivity

Continuous variables will be summarized using descriptive statistics (mean, SD, median, 25<sup>th</sup> and 75<sup>th</sup> percentiles, minimum and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

## 2.5.4 Spirometry at screening

FEV<sub>1</sub> before and after Salbutamol / Albuterol inhalation, FEV<sub>1</sub> reversibility, predicted FEV<sub>1</sub> and % predicted FEV<sub>1</sub> will be summarized and listed for the FAS and safety analysis sets. FVC will be summarized and listed for the Full analysis set only.

- % of (pre-bronchodilator) predicted FEV<sub>1</sub> (%) is obtained as a percentage of FEV<sub>1</sub> relative to the predicted normal value. The value at screening and at randomization as well as the ratio (randomization vs screening) of % (pre-bronchodilator) predicted FEV<sub>1</sub> will be summarized as continuous variables.

The following Quanjer equations will be used by third party vendors to give predicted FEV<sub>1</sub> (L):

Male: (4.30 x Height in meters) – (0.029 x Age in years) – 2.49

Female: (3.95 x Height in meters) – (0.025 x Age in years) – 2.60

If Race = Black or Ethnicity = Indian then the predicted normal given by the formulae above was multiplied by 0.9.

- FEV<sub>1</sub> reversibility (mL) is calculated as an increase of FEV<sub>1</sub> values after inhalation of SABA relative to FEV<sub>1</sub> values prior to the inhalation. The % FEV<sub>1</sub> reversibility (%) is defined as a percentage of FEV<sub>1</sub> reversibility relative to FEV<sub>1</sub> values prior to the inhalation (see calculation below). The data will be summarized as continuous variables using descriptive statistics.

$$100 \times \frac{\text{FEV}_1(\text{post-inhalation}) - \text{FEV}_1(\text{pre-inhalation})}{\text{FEV}_1(\text{pre-inhalation})}$$

- Baseline FEV<sub>1</sub> will be summarized as continuous variables.

No imputation will be done for missing values.

## 2.5.5 Relevant medical history

Medical history was coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the safety analysis set, by primary system organ class and preferred term, and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was active at the time of first study drug dose.

## 2.5.6 Prior medications

Prior medications are defined as those medications which were taken prior to screening and stopped prior to the first dose of study drug.

Medications will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.



Prior medications will be summarized separately for asthma related and non-asthma related treatments.

### **2.5.6.1 Asthma related prior medications**

For asthma related medications, incomplete end dates will be imputed as detailed in RAP Module 8. Prior asthma related medications will be defined as those medications with an imputed end date before the date of first dose of study drug. These will be summarized by category.

Asthma related medications will be listed with all recorded details: verbatim name, dose, unit, frequency, route, reason, category, start and end dates and study days and whether continuing at final visit.

### **2.5.6.2 Non-asthma related prior medications**

Prior medications not related to asthma (those marked as Prior on the CRF) will be summarized by ATC class. More than one ATC class per medication is possible and each medication will be reported under all classes.

Non-asthma related medications will be listed with reason for taking

## **2.6 Treatments (study drug and concomitant medication)**

### **2.6.1 Study drug administration**

The number of patients and the length of time (in days) exposed to each study drug will be summarized by treatment for the safety set.

Duration of exposure will be calculated as the number of days between the 1<sup>st</sup> dose date and the last visit date in treatment phase. To be calculated as:

Duration of exposure (days) = (Last visit date in treatment phase – Date of first dose of study drug + 1)

For patients who completed the treatment phase the visit date of week 12 will be used. For patients being prematurely withdrawn during the treatment phase the last visit date in the treatment phase will be used to calculate the duration of exposure.

This will be summarized by treatment for safety analysis set as a continuous variable with the standard descriptive statistics. In addition, the duration of exposure can also be summarized as a categorical variable classified into

<= 7 days, 8 days – <= 14 days, 15 days - <= 28 days, 29 days – <= 56 days, 57 days - <= 84 days, >84 days.

Dose administration data will be listed for patients in the safety analysis set.

Patients in the randomized set who received any wrong study medications will be listed. These patients will be identified using the information recorded on the DAR page of the CRF. If there is a record with reason = dispensing error, then the pack number will be used to identify whether or not the patient received the wrong study drug. Any patients who did will be included in the listing.

## **2.6.2 Compliance**

Study drug compliance will be assessed by the investigator and/or center personnel at designated visits according to the procedures defined in a study protocol. The total number of capsules administered since the last dispensing visit will be recorded in the CRFs.

For each patient whether completing the study or not, the percentage of study drugs being used less than 80% or greater than 120% of the total number of drugs between the first dispensing visit to the last visit can be captured as a protocol deviation.

The overall compliance during the course of study will be calculated as the percentage of the number of capsules taken by patients relative to the total number of capsules prescribed between the first dispensing visit up to the last visit in the study, using the total number of capsules taken captured on the CRF.

That is, Overall compliance =  $100 \times \text{number of capsules taken by patient} / \text{total number of capsules prescribed between Day 1 and the last known scheduled visit}$ .

The compliance per dispensing interval is calculated as the percentage of capsules taken relative to the number of capsules prescribed between the dispensing visits.

In addition, the overall compliance during double-blinded treatment period will be calculated as the percentage of number of capsules taken relative to the total number of capsules prescribed from day 1 to the last known visit of double-blinded treatment period.

Compliance can be categorized by: <80%, 80% ~ <100%, 100% ~ <120%, and >=120% and summarized by treatment and visit for the safety analysis set.

## **2.7 Concomitant medications**

Medications will be coded using the ATC classification system.

All summary tables will use the safety analysis set.

Concomitant medications will be summarized separately for asthma related and non-asthma related treatments. For asthma related medications, incomplete end dates will be imputed as detailed in RAP Module 8. Concomitant asthma related medications are defined as those medications with an imputed end date on or after the date of first study drug dose. These will be summarized by category.

Concomitant medications not related to asthma (those marked as Concomitant or Prior/Concomitant on the CRF) will be summarized by ATC class. More than one ATC class per medication is possible and each medication will be reported under all classes.

Asthma related medications will be listed with all recorded details: verbatim name, dose, unit, frequency, route, reason, category, start and end dates and study days and whether continuing at final visit. Non-asthma related medications will be listed with reason for taking.

Concomitant medications will be checked for protocol deviations by the clinical team. Patients who took prohibited concomitant medications will be included in the protocol deviations data provided by data management.

SABA (short acting  $\beta$ 2-agonist) usage during the screening period will be summarized.

The dose of LABA (long acting  $\beta$ 2-agonist) or fixed dose combinations of inhaled corticosteroid (ICS)/LABA must be stable for at least four weeks prior to Visit 2 and unless clinically indicated should not be adjusted during the study. Usage of LABA and ICS will be summarized at Visit 2 including the number of patients taking LABA/ICS medication and the type of medication taken (as recorded on the CRF). Usage of oral corticosteroids (OCS) will also be summarized. The doses of ICS and OCS will also be summarized, using conversion factors described in appendix 16.1.9 of the CSR.

## **2.8 Efficacy evaluation**

The purpose of this study is to determine whether, in patients with some sputum eosinophilia and persistent, moderate-to-severe asthma, 12-weeks treatment with QAW039 at a dose of 225 mg b.i.d. (compared to placebo), on top of conventional treatment, reduces the levels of eosinophils in induced sputum.

### **Subgroups**

Primary variable and some other variables will be analyzed using subgroups. The sub-groups considered are:

- i. ACQ: Patients with ACQ score  $<1.5$  at baseline and Patients with ACQ score  $\geq 1.5$  at baseline,
- ii. % Predicted FEV1: Patients with % predicted FEV1  $<70\%$  at baseline and patients with % predicted FEV1  $\geq 70\%$  at baseline
- iii. FENO: Patients  $<50$  ppb at baseline and patients  $\geq 50$  ppb at baseline.
- iv. OCS use: Patients with OCS use at baseline: Yes or No.

### **Scope of CSR**

The scope of CSR will be defined in the table below for all endpoints mentioned in this section. The endpoints presented in the FIR are:

- $\Delta$ log sputum eosinophil percentage

- % change of FEV1
- eosinophil counts (per unit area lamina propria)
- $\Delta$ ACQ score (with/without LOCF)
- $\Delta$ AQLQ score

TYPE OF ANALYSIS	ANALYTES (Endpoints)	
Sputum cell analysis	1. $\Delta$ log sputum eosinophil percentage	
Spirometry	1. Change of FEV1 (L) 2. % change of FEV1 3. Change of FEV1(% predicted) 4. Change of FVC (L) 5. % change of FVC 6. Change of FEV1 (L) as a proportion of reversibility at baseline	
Body plethysmography	1. Change of RV (L) 2. Change of RV (% predicted) 3. Change of TLC (L) 4. Change of TLC (% predicted) 5. Change of RV/TLC (%) 6. Change of RV/TLC (% predicted) 7. Change of VC (L) 8. Change of VC (% predicted) 9. Change of FRC (L) 10. Change of FRC (% predicted)	
CO transfer factor	1. Change of CO transfer factor (% predicted) 2. Change of Alveolar volume (% predicted) 3. Change of CO transfer co-efficient (% predicted)	
Oscillometry	1. Change of AX ( $\text{kPa L}^{-1} \text{s}^{-1}$ ) 2. Change of R5-R20 ( $\text{kPa L}^{-1} \text{s}^{-1}$ )	

	<ol style="list-style-type: none"> <li>3. Change of R5 (<math>\text{kPa L}^{-1} \text{s}^{-1}</math>)</li> <li>4. Change of R20 (<math>\text{kPa L}^{-1} \text{s}^{-1}</math>)</li> <li>5. Rmin at 2 Hz (<math>\text{kPa L}^{-1} \text{s}^{-1}</math>)</li> <li>6. Rmin at 8 Hz (<math>\text{kPa L}^{-1} \text{s}^{-1}</math>)</li> </ol>	
HRCT	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>RB1 wall area corrected for body SA (<math>\text{mm}^2</math>)</li> <li>2. <math>\Delta</math>RB1 wall area percentage (%)</li> <li>3. <math>\Delta</math>RB1 luminal area</li> <li>4. <math>\Delta</math>RB10 wall area cor for body SA</li> <li>5. <math>\Delta</math>RB10 wall area percentage (%)</li> <li>6. <math>\Delta</math>RB10 luminal area</li> <li>7. <math>\Delta</math> Expiratory mean lung density</li> <li>8. <math>\Delta</math> Inspiratory mean lung density</li> <li>9. <math>\Delta</math> Expiratory /Inspiratory mean lung density (derived not in CRF)</li> </ol>	
Multiple breath washout (mean values)	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>FRC (L)</li> <li>2. <math>\Delta</math>LCI</li> <li>3. <math>\Delta</math>Scond (L-1)</li> <li>4. <math>\Delta</math>S acin (L-1)</li> </ol>	
He-3 MRI (pre BD and post PD)	<ol style="list-style-type: none"> <li>1. <math>\Delta</math> Mean ADC</li> <li>2. <math>\Delta</math> ADC SD</li> <li>3. <math>\Delta</math> Mean fractional ventilation ratio</li> <li>4. <math>\Delta</math> Mean signal to noise ratio</li> <li>5. <math>\Delta</math> fractional ventilation of voxels (peripheral 1/3<sup>rd</sup> and proximal 2/3<sup>rd</sup>)</li> <li>6. <math>\Delta</math> ventilation voxels percentage (peripheral 1/3<sup>rd</sup> and proximal 2/3<sup>rd</sup>)</li> <li>7. <math>\Delta</math> number of ventilation defects (peripheral 1/3<sup>rd</sup> and proximal 2/3<sup>rd</sup>)</li> </ol>	
Bronchial biopsy	<ol style="list-style-type: none"> <li>1. RBM thickness</li> <li>2. eosinophil counts (per unit area lamina propria)</li> <li>3. MUC5a cells (per unit area epithelium)</li> <li>4. total inflammatory cells count (eosinophils, Neutrophils, T-cells and mast cells in the lamina propria per unit)</li> </ol>	

ACQ	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>ACQ score (with/without LOCF)</li> <li>2. proportion of patients with an improvement in ACQ of <math>\geq 0.5</math></li> <li>3. proportion of patients with an worsening of ACQ of <math>\geq 0.5</math></li> <li>4. proportion of patients with ACQ between -0.5 and +0.5</li> <li>5. proportion of patients with <math>ACQ &lt; 1.5</math></li> </ol>	
AQLQ	<ol style="list-style-type: none"> <li>1. <math>\Delta</math>AQLQ score</li> <li>2. proportion of patients with an improvement in AQLQ of <math>\geq 0.5</math></li> </ol>	
NO	1. Average eNO	

### 2.8.1 Primary Variable

The primary variable of the study is the change from baseline in sputum eosinophil percentage at week 12 (Visit 5). As sputum eosinophil percentage has been found to follow a log-normal distribution, the analysis will be based on log<sub>10</sub>-transformed scale. The baseline measurement is defined as sputum eosinophil percentage at Visit 3 (Day 1) prior to the first dosing.

Missing data will be imputed for the primary variable using last observation carried forward (LOCF). Only post-baseline observation will be used for this purpose.

All the analyses associated with the primary variable sputum eosinophil percentage will be reported in CSR.

#### 2.8.1.1 Model, and method of analysis of primary variable - Primary Analysis of Primary Variable

##### 2.8.1.1.1 Analysis of Covariance with LOCF

Here we will consider patients in FAS with LOCF.

The primary variable will be summarized by treatment and analyzed using an ANCOVA model with treatment (QAW039 or placebo), maintenance OCS use (Yes/No), Bronchoscopy (yes/no) as fixed effect and the log<sub>10</sub> of baseline sputum eosinophil percentage as covariate.

Estimated LS means of treatment effects and estimated difference in treatment effects will be back transformed to original scale to present estimated geometric means for treatment effects and ratio of geometric means of treatment effects along with 95% CI.

The Geometric Means will be plotted by treatment.

The ratio of Geometric means of treatment and Placebo and 95% CI will also be plotted.  
The code for analysis is given below –

```
proc mixed data=<dataset name>;  
    class treatment OCS bronchoscopy;  
    model logchg = treatment ocs bronchoscopy logbase / s;  
    estimate "A v/s B" treatment 1 -1 / cl alpha=0.05;  
    lsmeans treatment;  
    ods output estimates = est;  
    ods output lsmeans = lsm;  
run;
```

Imputations of LoQ value (0.25%) for sputum eosinophil will be applied to cases with sputum eosinophil values collected in the database as 0.

### **2.8.1.2 Supportive Analysis of Primary Variable**

#### **2.8.1.2.1 Analysis of Covariance without LOCF**

Here we will repeat the ANCOVA analyses as mentioned in 2.8.1.1.1 for patients in FAS without LOCF.

#### **2.8.1.2.2 Mixed Model with Repeated Measurements (MMRM)**

A MMRM model will be applied for primary endpoint at Week 6, 12 and 18 to handle missing data with a missing at random (MAR) assumption. The model will include the treatment, maintenance OCS use (Yes/No), Bronchoscopy (yes/no), visit as a categorical covariate, treatment-by-visit interaction, as well as baseline and baseline-by-visit interaction. An unstructured variance-covariance structure will be used to model the within-patient errors, shared across treatments.

#### **2.8.1.2.3 Analysis of Covariance at Week 6 and Week 18.**

The change from baseline at week 6, at week 18 and change from week 12 and week 18 will be also summarized by treatment and analyzed using an ANCOVA model as mentioned in 2.8.1.1.1. for patients without LOCF.

The Geometric Means will be plotted by visit and treatment.

The ratio of Geometric means of treatment and Placebo and 95% CI will also be plotted by visit.

#### 2.8.1.2.4 Analysis of Covariance with % predicted FEV1 at baseline as covariate

Similar to 2.8.1.1.1, to examine how the %predicted FEV1 at baseline in a continuous scale impacts the endpoints of interest, the primary endpoint will also be analyzed using an ANCOVA model by including %predicted FEV1 at baseline as an additional covariate. Multicollinearity has to be checked as there is a possibility of correlation between baseline value of the primary endpoint and the baseline value of % predicted FEV1. If the Variance Inflation Factor(VIF) of the model with both the baseline values present is more than 10, then we will drop the baseline value of the primary end-point in the covariate and only include the baseline value of % predicted FEV1 and perform our ANCOVA analyses.

#### 2.8.1.2.5 Normality Assumption and Non-parametric methods

In all the above cases the normality assumption will be checked with a Q-Q plot of residuals for each treatment group.

Only if evidences show the normality assumption does not hold for the data, the following non-parametric analysis will be performed.

- i. within-treatment difference between baseline and week 12 (Visit 5), baseline and week 6, baseline and week 18, and week 12 and week 18 will be analyzed using Wilcoxon paired sample signed-rank test;
- ii. between-treatment comparison on the change from baseline to week 12 (Visit 5), baseline and week 6, baseline and week 18, and week 12 and week 18 will be analyzed using Wilcoxon/Mann-Whitney rank sum test.

The code for Wilcoxon paired sample signed-rank test:

```
proc univariate data = <dataset name>;  
    by visit;  
    var logchg;  
run;
```

The code for Wilcoxon/Mann-Whitney ranksum test:

```
proc npar1way data=<dataset name> wilcoxon;  
    class treatment;  
    by visit;  
    var logchg;  
run;
```



### **2.8.1.3 Subgroup Analyses of Primary Variable**

We will perform ANCOVA on the primary variable as given in 2.8.1.1.1., 2.8.1.2.1 and 2.8.1.2.2 for the previously mentioned subgroups.

### **2.8.2 Secondary variable**

The secondary variables include the change from baseline to week 12 in ACQ. The baseline is defined as the assessment measured at Visit 3 (Day 1) prior to the first dosing.

The ACQ measures asthma symptom control and consists of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV<sub>1</sub> % predicted). All 7 questions of the ACQ are equally weighted. Items 1-6 are scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. Question 7 deals with FEV<sub>1</sub> % predicted pre-bronchodilator. In case the values of FEV<sub>1</sub> % predicted pre-bronchodilator are also available from the central spirometry reading in addition to the ACQ Q7 from CRF, the central reading will be used to derive the ACQ score. The value of ACQ Q7 will be used only if the central reading is not available. This single missing value may be interpolated by utilizing prior completions of the questionnaire as described in Section 2.5.3. The 7th item on % predicted FEV<sub>1</sub> (pre-bronchodilator) is scored by clinic staff on a 7-point scale (0 – > 95-99%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%).

The average score of the 7 questions at each visit will be calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and the missing item is neither question 1 nor question 7.

#### **Data Handling**

If a measure of FEV<sub>1</sub> % predicted pre-bronchodilator is missing in the central spirometry data, then we get it from the ACQ Q7 in CRF. The ACQ score will then be calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and preferable not question 1 (night time awakenings) or 7 (FEV<sub>1</sub> % predicted).

For a missing individual item, the recommended method for handling missing data to reduce the risk of bias is to interpolate using either previous or subsequent completions of the questionnaire. For instance,

Item	Visit 1	Visit 2
1	4	6
2	3	5
3	0	0
4	4	4
5	0	0
6	2	missing
7	5	6

Total visit 1 score for items answered on both visits is  $4+3+0+4+0+5=16$  (A)

Total visit 2 score for items answered on both visits is  $6+5+0+4+0+6=21$  (B)

Item 6 score at visit 1=2

Item 6 score at visit 2=  $B/A * 2=21/16*2=2.63$

The ACQ score for visit 1 is  $(4+3+0+4+0+2+5)/7=2.57$

The ACQ score for visit 2 is  $(6+5+0+4+0+2.63+6)/7=3.38$

It should be noted that a post-treatment missing data can only be imputed using a post treatment visit, and a missing value at baseline (visit 3) can only be interpolated using a value from Visit 2. That is, if the missing is at baseline (visit 3), then we can only do backward interpolation using Visit 2 and if we have missing data on Visit 4, we can only do forward interpolation using Visit 5. If Visit 5 has data missing then we can do forward as well as backward interpolation using either Visit 6 or Visit 4.

### **2.8.2.1 Model, and method of analysis of Secondary variable**

Analyses associated with ACQ endpoints 1 and 5 are defined below

1.  $\Delta$ ACQ score (with/without LOCF)
2. proportion of patients with an improvement in ACQ of  $\geq 0.5$
3. proportion of patients with an worsening of ACQ of  $\geq 0.5$
4. proportion of patients with ACQ between -0.5 and +0.5
5. proportion of patients with  $ACQ < 1.5$

#### **2.8.2.1.1 Analysis of Covariance with LOCF**

The secondary variable, change of ACQ7 with LOCF from baseline at week 12 will be summarized by treatments (QAW039 and placebo) and analyzed using an ANCOVA model with treatment (QAW039 or placebo), maintenance OCS use (Yes/No), Bronchoscopy (yes/no) as fixed effect and the baseline ACQ score as covariate.

Estimated LS means of treatment effects and estimated difference in treatment effects along with 95% CI will be presented.

Estimated LS means differences between treatment and Placebo and 95% CI will also be plotted.

## **2.8.2.2 Supportive Analysis of Primary Variable**

### **2.8.2.2.1 Analysis of Covariance without LOCF**

For FAS patients, ACQ7 without LOCF, ACQ 6 (average of first 6 ACQ questions) without LOCF, and ACQ 5 (average of first 5 ACQ questions) without LOCF will be analyzed and presented in the same way as mentioned in 2.8.2.1.1.

### **2.8.2.2.2 Mixed Model with Repeated Measurements (MMRM)**

A similar model as described in 2.8.1.2.2 will be applied for ACQ7 to handle missing data with an assumption of MAR.

### **2.8.2.2.3 Analysis of Covariance at Week 6 and Week 18.**

The method mentioned in 2.8.2.1.1 and 2.8.2.2.1 will be repeated for change from baseline at Visit 4, Visit 6 and change from Visit 5 and Visit 6 for ACQ7 without LOCF, ACQ6 and ACQ5.

### **2.8.2.2.4 Analysis of Covariance with % predicted FEV1 at baseline as covariate**

Similar to 2.8.2.1.1, to examine how the %predicted FEV1 at baseline in a continuous scale impacts the endpoints of interest, the secondary endpoint will also be analyzed using an ANCOVA model by including %predicted FEV1 at baseline as an additional covariate. Multicollinearity has to be checked as there is a possibility of correlation between baseline value of the secondary endpoint and the baseline value of % predicted FEV1. If the Variance Inflation Factor(VIF) of the model with both the baseline values present is more than 10, then we will drop the baseline value of the secondary end-point in the covariate and only include the baseline value of % predicted FEV1 and perform our ANCOVA analyses.

#### **2.8.2.2.5 Responder Rate Analyses for change (improvement and worsening) in ACQ of 0.5 or greater**

An ACQ change of 0.5 has been validated as the minimally important clinical difference (Juniper et al, 2005).

The proportion of patients with a decrease in ACQ of  $\geq 0.5$  at week 12 (Visit 5) from baseline will be summarized by treatment and analyzed using a logistic regression. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented. The model includes terms for treatment, OCS use(yes/no) and Bronchoscopy (yes/no) as fixed effects and the baseline ACQ score as a covariate.

The code for above analysis is

```
proc glimmix data= <dataset name>;  
  class treatment OCS;  
  model chgcat = treatment OCS Bronchoscopy base / DIST=binomial link = logit;  
  estimate 'A v/s B' treatment 1 -1 / cl alpha=0.05 oddsratio cl;  
  lsmeans treatment;  
  ods output estimates=est;  
  ods output lsmeans=lsm;  
run;
```

The odds ratio of QAW039/Placebo will be computed, along with associated 95% confidence intervals.

All the analysis defined above for the full ACQ 7 with and without LOCF questions is also to be repeated based on the mean of the first 5 ACQ questions (ACQ5) and mean of the first 6 ACQ questions (ACQ6).

The responder rate will be analyzed for proportion of patients with an improvement in ACQ ( $\geq 0.5$ ) at week 18 from baseline.

Similar analysis will also be done for proportion of patients showing a worsening (increase) from baseline in ACQ score of  $\geq 0.5$  at visit 4, visit 5, visit 6. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented.

Similar analysis will also be done for proportion of patients showing an improvement (decrease) from baseline in ACQ score of less than 0.5 and a worsening (increase) from baseline in ACQ score of less than 0.5 at visit 4, visit 5, visit 6. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented.

#### **2.8.2.2.6 Responder rate analyses for proportion of patients with ACQ < 1.5**

The proportion of patients with the mean of the 7 ACQ questions (ACQ7) < 1.5 will be analyzed using a repeated measure logistic regression model. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented. If we do not have sufficient events for ACQ7 < 1.5 in each group but on the other hand, sufficient events show for ACQ7  $\geq 1.5$  in each group, responder rate analysis for ACQ7  $\geq 1.5$  will be provided instead.

The model will contain treatment, ocs use (yes/no), Bronchoscopy (yes/no) , visit and visit by treatment interaction as fixed effects and baseline ACQ score as covariate. Proportion of subjects with ACQ7 score less than 1.5 will be the dependent variable. Visits will be used as repeated measurement. Unstructured covariance matrix will be used for this analysis.

The odds ratio of QAW039/Placebo will be computed and plotted along with associated 95% confidence intervals.

The code for above analysis is

```
proc GENMOD data= <dataset name>;  
  class treatment OCS bronchoscopy;
```

```
model chgcat = treatment OCS Bronchoscopy visit*treatment base base*visit /  
DIST=binomial link = logit;  
repeated / subject = patient type = UN;  
estimate "A v/s B" treatment 1 -1 / cl alpha=0.05;  
lsmeans treatment;  
ods output estimates = est;  
ods output lsmeans = lsm;  
run;  
  
run;
```

The above analysis will also be repeated for ACQ6 and ACQ5.

### **2.8.2.2.7 Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.2.3 Subgroup Analyses:**

We will perform ANCOVA on the ACQ7 with LOCF as given in 2.8.2.1.1 for the above mentioned subgroups:

## **2.8.3 Pulmonary Function Tests**

### **2.8.3.1 Spirometry**

FEV<sub>1</sub> and FVC will be measured at the clinic visits prior to dosing at baseline (visit 3) and at week 6, 12 and 18 (Visit 4, 5 and 6 respectively).

Only spirometry measurements classed as 'acceptable' will be analyzed Spirometry measurements taken within 6 hours of a SABA , within 12 hours of a LABA, within 24 hours of long acting anti-cholinergics or within 8 hours of short acting anti-cholinergics will be excluded.

Treatment group comparisons by visit will be performed for the following spirometry variables.

- i. Change of FEV1 (in L) from baseline,

- ii. Percent change of FEV1 from baseline, and
- iii. Change in % predicted FEV1 from baseline, where post-baseline % predicted FEV1 is defined as: 
$$\frac{100 \times FEV1}{\text{predicted FEV1 at Visit 2}}$$
- iv. Change of FVC (in L) from baseline,
- v. Percent change of FVC from baseline,
- vii. Change from baseline in FEV1 (L) in proportion to FEV1 reversibility (L) taken at Visit 2, termed as “% Reversibility FEV1” and defined by

$$\frac{100 \times \{FEV1 - FEV1(\text{pre-SABA Visit2})\}}{(\text{Post-SABA} - \text{Pre-SABA}) FEV1 \text{ in Visit 2}}$$

Change is considered to be change from baseline at week 6, change from baseline at week 12, change from baseline at week 18 and change from week 12 and week 18.

For each post-baseline visit the spirometry variables will be summarized by treatments (QAW039 and placebo) .

### **2.8.3.1.1 Analysis of Covariance**

The spirometry variables will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for primary variable.

#### **Subgroup Analyses:**

We will perform ANCOVA on the spirometry parameters FEV1 and FVC as mentioned in 2.8.3.1.1 for the above mentioned subgroups.

### **2.8.3.1.2 Analysis of Covariance with % predicted FEV1 at baseline as covariate**

Similar to 2.8.2.1.1, to examine how the %predicted FEV1 at baseline in a continuous scale impacts the change from baseline of FEV1 and FVC during post-baseline the endpoints of interest, the change from baseline in FEV1 and FVC will also be analyzed using an ANCOVA model by including %predicted FEV1 at baseline as a covariate.

In case of FEV1 we will replace baseline FEV1 covariate with baseline % predicted FEV1 as covariate in the ANCOVA model. In case of FVC, we will include baseline % predicted FEV1 as an additional covariate in the ANCOVA model.

Multicollinearity has to be checked as there is a possibility of correlation between baseline value of FVC and the baseline value of % predicted FEV1. If the Variance Inflation Factor(VIF) of the model with both the baseline values present is more than 10, then we will drop the baseline value of the secondary end-point in the covariate and only include the baseline value of % predicted FEV1 and perform our ANCOVA analyses.

#### **2.8.3.1.3 Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

#### **2.8.4 Body Plethysmography**

Analyses associated with Body plethysmography are defined below

1. Change in RV
2. Change in RV (% predicted)
3. Change in TLC
4. Change in TLC (% predicted)
5. Change in RV/TLC
6. Change in RV/TLC (% predicted)
7. Change in VC
8. Change in VC (% predicted)
9. Change in FRC
10. Change in FRC (% predicted)

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The Body plethysmography end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary variable.

#### **2.8.5 Impulse Oscillometry**

All analyses associated with impulse oscillometry defined below will be reported in CSR.



1. Change in AX ( $\text{kPa L}^{-1} \text{s}^{-1}$ )
2. Change in R5-R20 ( $\text{kPa L}^{-1} \text{s}^{-1}$ )
3. R5 ( $\text{kPa L}^{-1} \text{s}^{-1}$ )
4. R20 ( $\text{kPa L}^{-1} \text{s}^{-1}$ )
5. Rmin at 2 Hz ( $\text{kPa L}^{-1} \text{s}^{-1}$ )
6. Rmin at 8 Hz ( $\text{kPa L}^{-1} \text{s}^{-1}$ )

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The Impulse Oscillometry parameters will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for primary variables.

### **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

#### **2.8.6 Multiple Breath Washout (MBW)**

All analyses associated with multiple breath-washout defined below will be reported in CSR.

1. Change in FRC (L)
2. Change in LCI
3. Change in Scond ( $\text{L}^{-1}$ )
4. Change in Sacin ( $\text{L}^{-1}$ )

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The MBW parameters will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.7 CO Transfer Factor**

Analyses associated with CO Transfer Factor are defined below

1. Change of CO transfer factor (% predicted)
2. Change of Alveolar volume (% predicted)
3. Change of CO transfer co-efficient (% predicted)

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 to week 18.

The CO Transfer factors end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.8 He3-MRI**

The MRI endpoints are observed twice in every visit- Pre-bronchodilator and Post-bronchodilator. The following endpoints will be reported in CSR for MRI:

1. Change from baseline in Pre-Brochodilator Mean ADC
2. Change from baseline in Pre-Brochodilator ADC SD
3. Change from baseline in Pre-Brochodilator Mean fractional ventilation ratio
4. Change from baseline in Pre-Brochodilator Mean signal to noise ratio
5. Change from baseline in Pre-Brochodilator Fractional ventilation of voxels (peripheral 1/3rd and proximal 2/3rd)

6. Change from baseline in Pre-Brochodilator Fractional ventilation of voxels (peripheral 1/3rd)
7. Change from baseline in Pre-Brochodilator Fractional ventilation of voxels (proximal 2/3rd)
8. Change from baseline in Pre-Brochodilator Ventilation voxels percentage (peripheral 1/3rd and proximal 2/3rd)
9. Change from baseline in Pre-Brochodilator Ventilation voxels percentage (peripheral 1/3rd)
10. Change from baseline in Pre-Brochodilator Ventilation voxels percentage (proximal 2/3rd)
11. Change from baseline in Pre-Brochodilator Number of ventilation defects (peripheral 1/3rd and proximal 2/3<sup>rd</sup>)
12. Change from baseline in Pre-Brochodilator Number of ventilation defects (peripheral 1/3rd)
13. Change from baseline in Pre-Brochodilator Number of ventilation defects (proximal 2/3rd)
14. Change from baseline in Post-Brochodilator Mean ADC
15. Change from baseline in Post-Brochodilator ADC SD
16. Change from baseline in Post-Brochodilator Mean fractional ventilation ratio
17. Change from baseline in Post-Brochodilator Mean signal to noise ratio
18. Change from baseline in Post-Brochodilator Fractional ventilation of voxels (peripheral 1/3rd and proximal 2/3rd)
19. Change from baseline in Post-Brochodilator Ventilation voxels percentage (peripheral 1/3rd and proximal 2/3rd)
20. Change from baseline in Post-Brochodilator Number of ventilation defects (peripheral 1/3rd and proximal 2/3rd)
21. Change of Post-bronchodilator from Pre-Brochodilator in Mean ADC
22. Change of Post-bronchodilator from Pre-Brochodilator in ADC SD
23. Change of Post-bronchodilator from Pre-Brochodilator in Mean fractional ventilation ratio
24. Change of Post-bronchodilator from Pre-Brochodilator in Mean signal to noise ratio
25. Change of Post-bronchodilator from Pre-Brochodilator in Fractional ventilation of voxels (peripheral 1/3rd and proximal 2/3rd)
26. Change of Post-bronchodilator from Pre-Brochodilator in Ventilation voxels percentage (peripheral 1/3rd and proximal 2/3rd)
27. Change of Post-bronchodilator from Pre-Brochodilator in Number of ventilation defects (peripheral 1/3rd and proximal 2/3rd)

The He3-MRI end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.9 HRCT**

All analyses associated with HRCT endpoints defined below will be included in CSR.

1. Change in RB1 wall area corrected for body SA (mm<sup>2</sup>)
2. Change in RB1 wall (area)percentage (%)
3. Change in RB1 luminal area (mm<sup>2</sup>)
4. Change in RB10 wall area cor for body SA (mm<sup>2</sup>)
5. Change in RB10 wall (area) percentage (%)
6. Change in RB10 luminal area (mm<sup>2</sup>)
7. Change in Expiratory mean lung density
8. Change in Inspiratory mean lung density
9. Change in Expiratory /Inspiratory mean lung density (derived not in CRF)

Change is considered to be change from baseline to week 12.

The HRCT end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

Body Surface Area is calculated using the Mosteller formula given by:

$$BSA = \sqrt{\frac{W \times H}{3600}} = 0.016667 \times W^{0.5} \times H^{0.5}$$

where, W=Weight(kg), H=Height(cm) and BSA in m<sup>2</sup>.

## **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.10 Bronchial Biopsy**

All analyses associated with bronchial biopsy defined below will be reported in CSR.

1. Change in RBM thickness ( $\mu\text{m}$ )
2. Change in eosinophil counts (per unit area lamina propria) ( $\text{cells}/\text{mm}^2$  tissue)
3. Change in MUC5a cells (per unit area epithelium) ( $\text{cells}/\text{mm}^2$  tissue)
4. Change in total inflammatory cells count (eosinophils, Neutrophils, T-cells and mast cells in the lamina propria per unit) ( $\text{cells}/\text{mm}^2$  tissue)

Change is considered to be change from baseline to week 12.

The Bronchial Biopsy end-points will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis, without covariate bronchoscopy(yes/no).

### **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

### **2.8.11 FeNO**

The analyses associated with FeNO defined below will be reported in CSR.

1. Change in average eNO (ppm)

Change is considered to be change from baseline to week 12, change from baseline to week 18 and change from week 12 to week 18.

The FeNO end-point will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for the primary analysis.

### **Normality Assumption and Non-parametric methods**

Similar process and principal will be hold as in the case of the primary variable.

## **2.8.12 Serum and Plasma Biomarker**

The serum and plasma biomarker data will be summarized in a report separate from the CSR. Summary statistics will be presented along with graphic presentations if appropriate.

## **2.8.13 FACS Analysis**

The FACS analysis data will be summarized in a report separate from the CSR. Summary statistics will be presented along with graphic presentations if appropriate.

## **2.8.14 Sputum soluble factor analysis**

The sputum soluble factor analysis data will be summarized in a report separate from the CSR. Summary statistics will be presented along with graphic presentations if appropriate.

## **2.9 Pharmacokinetic evaluations**

Summary statistics of the plasma PK concentration data at different timepoints at Day1, Week 6 and Week 12 for each analyte will be provided along with individual patient listings.

## **2.10 Resource utilization**

Healthcare resource utilization will not be collected in this study.

## **2.11 Health-related Quality of Life**

### **2.11.1 Asthma Quality of Life (AQLQs)**

A 32-item disease specific questionnaire, each answered on a 7-point scale (1 = totally limited/problems all the time, 7 = not at all limited/no problems).

The domain scores will be calculated from the sum of individual question responses as follows:

Activity limitations = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)

Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)

Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)

Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)

Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ is equally weighted and scored along a 7-point scale, where 1 indicates maximal impairment and 7 indicates no impairment. Thus, higher scores indicate better asthma-related HRQOL. There is a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which is the mean score of all 32 items. The resultant overall scores will be between 1 and 7.

The developer suggests no more than 10% of missing data. This means that for a questionnaire of 32 items, no more than 3 items should be missing. Further, for the activity and symptom domains, the recommendation is no more than 1 missing value per domain, and for the emotional function and environmental stimuli domains, no missing responses at all.

The recommended method for handling missing data to reduce the risk of bias is to interpolate (pro-rate) missing values using either previous or subsequent completed questionnaires per domain, in a similar way as described in the data handling section for the analysis of ACQ.

The analyses associated with AQLQ defined below will be reported in CSR.

1.  $\Delta$ AQLQ score

2. proportion of patients with an improvement in AQLQ of  $\geq 0.5$

#### **2.11.1.1 ANCOVA**

Change is considered to be change from baseline to week 6, change from baseline to week 12, change from baseline to week 18 and change from week 12 and week 18.

The AQLQ domains will be summarized by treatments (QAW039 and placebo), analyzed and presented using an ANCOVA model in the same manner as described for primary variable.

#### **Subgroup Analyses:**

We will perform ANCOVA on the AQLQ as mentioned for the primary variable for the above mentioned subgroups.

#### **2.11.1.2 Responder Rate**

It will be done similarly as in the case of the secondary variable but only for improvement from baseline in AQLQ of  $\geq 0.5$  at Visit 4, 5 and 6. The logistic regression model will be fit only if there are sufficient events in each group. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted and only the summary will be presented.

### **2.11.1.3 Normality assumptions and Nonparametric Methods**

It will be done similarly as in the case of the primary variable.

## **2.12 Analyses of other Secondary Objectives**

### **Asthma exacerbations**

Criteria for asthma exacerbations are based on clinic visit spirometry, and investigators clinical judgment. All asthma exacerbations are recorded on the asthma exacerbation episode CRF.

A **severe asthma** exacerbation is defined as treatment with rescue or increase in maintenance systemic corticosteroids for at least 3 days (or equivalent) and hospitalization or emergency department visit (greater than 24 hours) or death due to asthma.

A **moderate asthma** exacerbation is treatment with rescue or increase in maintenance systemic corticosteroids either as an outpatient or in emergency department visits (less than or equal to 24 hours).

Every event of moderate/severe asthma exacerbation leading to discontinuation will be summarized for the three periods- the run-in period, double blind treatment period, and double blind treatment period and Wash-out period.

The total number of moderate/severe asthma exacerbations will be summarized along with the number of weeks for all the three treatment periods- the run-in period, double blind treatment period, and double blind treatment period and Wash-out period. For the Run-in period we will present it for all patients. For the double-blind treatment period and the combined the double-blind treatment period and wash-out period we will present it separately for the two treatment arms.

The number of days at risk for a time-period is defined as number of days from treatment start date to last date of the corresponding treatment period or discontinuation date for discontinuers.



## **2.12.1 Proportion of Exacerbations**

### **2.12.1.1 Logistic regression**

The proportion of patients with  $\geq 1$  moderate/severe asthma exacerbation (leading to discontinuation) during the 12 week double-blind treatment period, the 6 week washout period, the 30 days follow up period and the combined period(12 week treatment+6 week washout+ 30 days follow-up) will be presented and analyzed using logistic regression, provided there is sufficient events in each group for each analysis. As a rule of thumb for each covariate in a logistic regression at least 10 events are needed in each group. If there are insufficient events in each group this analysis will not be conducted.

The model will include parameters for treatment, maintenance OCS use at screening (Yes/No) and Bronchoscopy at screening (yes/no).

An estimate of the odds ratio between treatment groups, together with a 95% confidence interval and p-value, will be presented.

### **2.12.2 Time to first exacerbation**

The time to first asthma exacerbation will be defined as the start date of the exacerbation as recorded on the asthma exacerbation CRF.

Time to first moderate/severe asthma exacerbation during the 12 week double-blind treatment period and the 6 week washout period of QAW039 compared to Placebo will be analysed in the FAS by fitting a Cox regression model including parameters for treatment, maintenance OCS use at screening (Yes/No), Bronchoscopy at screening (yes/no).

Patients with no moderate/severe asthma exacerbations (or no exacerbation in the all exacerbation analysis) will be censored at last visit during the course of the study (including the follow up period).

The hazard ratio of QAW039 /Placebo will be computed, along with associated 95% confidence intervals.

Kaplan-Meier analysis stratified by treatment group will be also presented and displayed graphically.

Time to first severe/moderate asthma exacerbation was analyzed with a Cox proportional hazards regression model.

The null-hypothesis was

$$H_0: \lambda_Q(t) / \lambda_P(t) = 1$$

versus the alternative

$$H_a: \lambda_Q(t) / \lambda_P(t) \neq 1$$

where  $\lambda(t)$  is the hazard function for the failure time of patients treated with QAW039 (Q) and placebo (P), respectively.

The SAS procedure PHREG was used with the following code:

```
proc phreg data=... ;  
model TIMEOTO*CNSR(1) = TRT01P ROCMNT BRO ATHEB /rl ties=exact;  
run;
```

where

TIMEOTO = Censoring or event day

CNSR = Censoring flag

TRT01P = Treatment group (planned)

ROCMNT = maintenance OCS use

BRO= Bronchoscopy at baseline

The model fit of the primary model will be diagnosed by plotting Schoenfeldt residuals against time for the primary model.

All analyses associated with exacerbation described above will be reported in CSR.

## **2.13 Safety evaluation**

The standard frequency tables on treatment-emergent events will be used to quantify the safety topics of interest after the start of study drug administration. They will provide the number and percentage of subjects experiencing each safety topic of interest. Exposure time-adjusted analyses will also be provided.

The relative risk will be calculated with 95% confidence intervals for QAW with placebo as reference. The incidence rate and 95% confidence interval per treatment group will be presented as appropriate.

In addition, listings will be provided presenting which subjects experienced which risk, together with timing of onset relative to study medication, event duration, age, and gender. Medical history and co-medication will be listed for those patients with risk of interest.

All summary tables in this section used the safety analysis set.

All analysis planned in this section will be reported in the CSR.

## **2.13.1 AE of special interest**

### **2.12.1.1 The risk of liver toxicity (SPP risk, Routine risk)**

#### **(1) Cases defined by lab parameters**

The liver function tests (LFT) under consideration include the following serum blood chemistry lab parameters: ALT, AST, ALT, and TBIL. The lab standard tables and figures, such as summary table of change from baseline (including mean, SD, median, IQR, min, and max), shift table with respect to normal reference range, and box plots, will be produced over time.

In addition, to evaluate potential indicators of drug-induced liver injury or dysfunction, patients with newly occurring elevations in LFT at any time post-baseline are summarized and listed based on the following thresholds in lab tests.

- ALT or AST > 3x, 5x, 8x, 10x, 20x ULN
- ALP > 1.5x, 2x, 3x ULN
- TBL > 1.5x, 2x, 3x ULN
- ALP > 3x ULN concurrently with TBL > 2x ULN
- Potential Hy's law cases : (ALT or AST > 3x, 5x, 8x, 10x, 20x ULN) concurrently with TBL > 1.5x, 2x ULN
- Potential Hy's law cases: (ALT or AST > 3x ULN) concurrently with both TBL > 2x ULN & ALP < 2x ULN

This is to identify if there is any evidence of increases in AST or ALT, beyond expected adjustment time and to investigate whether they are accompanied by a similar (delayed) increase over time in Total Bilirubin. For a criterion with combined components, such as lab criteria for Hy's Law which has at least 3 components, each condition has to happen exactly at the same time to meet the criteria. A case is considered as newly occurring if the baseline condition does not meet the clinically notable criterion but clinically notable at post-baseline. For patients with missing value in baseline for at least one component, post-baseline values meeting the notable criterion will be considered as newly occurring.

Matrix graphs of maximum /ULN-normalized liver function test values will be also produced. This is a matrix display of maximum post-baseline /ULN-normalized values in form of scatter plots of all 6 pairs LFTs, i.e. ALT, AST, ALT, and TBIL. These plots allow one to visualize multivariate relationships by a matrix of bivariate distributions and to identify, for example, Hy's law cases.

For all subjects with liver values (AST, ALT, ALP, TBL) matching any of above thresholds single subject profile graphs will be generated showing all AST, ALT, ALP, TBL lab values reported for this study and the time of study treatment.

#### **(2) Cases identified through SMQ**

In addition to liver function tests, adverse events of hepatic disorders will be also summarized. The cases will be identified through SMQ search on "Drug related hepatic disorders - comprehensive search (SMQ)", which is a level 2 child SMQ under the level 1 "Hepatic disorders (SMQ)".

The number and percentage of subjects with AEs will be summarized by SMQ level for all the hierarchies (child SMQs) under level 1 “Hepatic disorders (SMQ)” to provide an overview. The data will be then summarized by SMQ and preferred term for only events under level 2 “Drug related hepatic disorders - comprehensive search (SMQ)”. This is to identify if there is any evidence of a clinically significant imbalance in the overall Level2 SMQ or any of its child SMQs.

#### 2.12.1.2 Other AE of special interest

The following AE’s of special interest will also be summarized in the table with number and percentage of subjects with AEs by SMQ levels:

- 1) Tachyarrhythmia (incl supraventricular and ventricular tachyarrhythmias) broad SMQ (code: 20000054)
- 2) Cardiac Failure SMQ (code: 20000004)
- 3) Increase in platelet counts Using HLT of “Platelet analyses” (coded as 10035523).

Numbers and percentages of patients with change from baseline in heart rate in categories of <-30, -30 to -20, -20 to -10 to -5, -5 to 0, 0 to 5, 5 to 10, 10 to 20, 20 to 30, >30 are also summarized as an analysis of risk of Tachycardia.

## 2.13.2 Other safety evaluation

### 2.13.2.1 Adverse events

Adverse events that start during the study but before the time of the first administration of study drug (e.g. screening period) will be classified as a prior adverse event.

An event of asthma exacerbation will be included in the adverse events analysis.

Asthma related adverse events will be identified using SMQ broad search. Asthma exacerbations will be included in all the adverse event related analysis. Use SMQ code 20000025 (Asthma/bronchospasm (SMQ)) for identifying Asthma related AE’s.

Frequency tables (number and percentage of patients) of the incidence of adverse events will be produced for the following:

- Overall by system organ class and preferred term
- Overall by system organ class, preferred term and maximum severity
- Suspected drug-related adverse events by system organ class and preferred term
- Serious adverse events by system organ class and preferred term
- Adverse events leading to permanent discontinuation of study-drug by system organ class and preferred term
- Asthma related adverse events by system organ class and preferred term, using SMQ broad search, (SMQ code 20000025 - Asthma/bronchospasm (SMQ)).

- Other significant AE's (project specific- Liver toxicity, cardiac findings and increase in platelet count)
- Prior adverse events, if the number of prior adverse events is low, listings will be used instead of summaries.

Listings will be produced for the following, with preferred term, system organ class, seriousness, severity, relationship to study drug, action taken, start and end dates and times and whether continuing at final visit:

- All adverse events
- Serious adverse events
- Adverse events causing study drug discontinuation
- Adverse events requiring dose adjustment or interruption
- Adverse events requiring significant additional therapy (this is combination of concomitant medications and / or non-drug therapy)
- Adverse events related to asthma

A summary of deaths according to the affected primary system organ class and preferred term for the investigator-reported principal cause of death will be presented by primary system organ class, preferred term, and treatment groups regardless of study drug relationship.

Any deaths within 30 days of last dose will be listed with dates and study days of death and last dose, and principal cause of death with associated coded terms.

### **2.13.2.2 Laboratory data**

All the laboratory samples were processed through the Central Laboratory. Laboratory data consist of hematology, biochemistry and urinalysis measurements. All data will be listed with abnormal values flagged. The following sub-sections will describe the method of summary.

Baseline for laboratory parameters is the last available measurement prior to first dose of study medication.

#### **2.13.2.2.1 Summary of absolute values**

For all continuous laboratory parameters, the absolute laboratory values, including the worst case post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits), will be summarized with standard descriptive statistics by parameter, scheduled visit and time-point, and treatment. An example of the direction of interest for worst case post-baseline for selected hematology and biochemistry parameters is shown in Table 2-6. For continuous urinalysis parameters the direction of interest is always High.

For categorical urinalysis laboratory parameters, a frequency table of results will be produced by laboratory parameter, scheduled visit and time-point, and treatment. Worst-case post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits) will also be included.

Patient profile plots can be produced for hematology and biochemistry continuous laboratory parameters, with a line for each patient plotting the result against time. There will be a separate plot for each parameter and each treatment group.

#### 2.13.2.2.2 Summary of change from baseline

For continuous laboratory parameters, the change from baseline at each scheduled visit and time-point, and the change from baseline to the worst case post-baseline values (including values from post-baseline unscheduled and premature discontinuation visits) will be summarized by laboratory parameter, scheduled visit and time-point, and treatment with standard descriptive statistics.

#### 2.13.2.2.3 Shift tables

Shift tables for laboratory parameter will be provided in order to compare a patient's baseline value to the value at each time point at each study visit, relative to the normal reference range for each lab parameter. For the shift tables, normal reference ranges provided by the central lab will be used to evaluate whether a particular laboratory test value for each time point at each visit is normal, low, high or non-available relative to the baseline value also categorized as normal, low, high, or non-available. These summaries will be presented by laboratory test, visit, time point, and treatment group.

In addition, shift tables relative to the normal reference ranges will be used to summarize the change from baseline to the most extreme post-dose value for each laboratory parameter. For each laboratory test, the patients will be classified into one of the four mutually exclusive groups (low, normal, high, and low+high), defined as follows:

- ◆ Low: at least one post-baseline value below the normal range and none above the normal range
- ◆ High: at least one post-baseline value above the normal range and none below the normal range
- ◆ Normal: all the post-baseline values within the normal range
- ◆ Low+High: at least one post-baseline value below the normal range and at least one above the normal range

Categorical parameters in the urinalysis panel will also be summarized with shift tables showing the shift from one categorical result to another. The shift from baseline to most extreme post-dose value will also be summarized, with the least to most extreme scale assumed to be negative, trace, +, ++, +++, +++++.

#### 2.13.2.2.4 Notable values

For selected laboratory tests, the number and percentage of patients with newly occurring or worsening laboratory abnormalities meeting the clinically notable criteria will be summarized by laboratory parameter, post-baseline visit, time point and treatment. An additional section will be included for abnormalities occurring at any time-point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Patients with any newly occurring or worsening value meeting the clinically notable criteria will be counted under the applicable criteria.

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value which is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For patients with missing value in baseline, any post-baseline notable value will be considered as newly occurring.

Guidelines for clinically notable criteria for laboratory tests are based on the FDA Guidelines for adults in SI units. For those parameters where ranges are available, the criteria for clinically notable results are presented in Tables 2-1 and 2-2 as an example.

Listings of patients with notable laboratory values will be provided by laboratory parameter, treatment group, and patient number.

**Table 2-1 Direction of interest for worst case value for laboratory parameters**

<b>Laboratory Parameter</b>	<b>Direction of interest for worst case value</b>
<b>A. Hematology</b>	
Basophils	High
Eosinophils	High
Hematocrit	Low and High
Hemoglobin	Low and High
Lymphocytes	low and high
Monocytes	High
Neutrophils	low and high
Platelets	Low and High
RBC	Low and High
WBC total	Low and high
<b>B. Chemistry</b>	
Albumin	Low
Sodium	Low and High
Alk. Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Gamma GT	High
Glucose (random)	Low and high
Potassium	Low and high
Total protein	Low and High

Table 2-2 Clinical notable criteria for selected laboratory tests



Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
<b>Hematology</b>		
Hematocrit (v/v))		
Male	0.37	
Female	0.32	
Hemoglobin (g/L)		
Male	115	
Female	95	
Thrombocytes (x10E <sup>9</sup> /L)	75	700
WBC's (x10 <sup>9</sup> /L)	2.8	16.0
<b>Chemistry</b>		
Alkaline Phosphatase (U/L)	-	3xULN
Total Bilirubin (mcmol/L)	-	34.2
Creatinine (mcmol/L)		176.8
Potassium (mmol/L)	3	6
Glucose (mmol/L)	2.78	9.99
SGOT (U/L)	-	3 x ULN
SGPT (U/L)	-	3 x ULN
BUN/Serum Urea (mmol/L)		9.99
Sodium (mmol/L)	125	160
Albumin (g/L)	25	-
Total protein (g/L)	40	95
Gamma GT (U/L)		3 x ULN

v = volume, ULN = upper limit of normal

### 2.13.2.3 Vital signs

#### 2.13.2.3.1 Summary of absolute values

Data from the vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be summarized by treatment at the scheduled visits and time-points. The maximum and minimum systolic blood pressure, diastolic blood pressure, and pulse rate post-baseline (including values from post-baseline unscheduled and premature discontinuation visits) can also be summarized by treatment. Absolute body weight will be summarized by scheduled visit.

Vital signs will also be summarized by categories:

- pulse rate: < 40 bpm, 40 – 90 bpm, and > 90 bpm
- systolic blood pressure: < 90 mm Hg, 90 – 140 mm Hg, and > 140 mm Hg
- diastolic blood pressure: < 50 mm Hg, 50 – 90 mm Hg, and > 90 mm Hg.

### 2.13.2.3.2 Summary of change from baseline

The change from baseline to each scheduled post-baseline visit will be summarized similarly as the laboratory parameters where baseline and post-baseline values are both available. The summary will be presented by vital sign parameter, scheduled visit and time-point, and treatment with standard descriptive statistics.

### 2.13.2.3.3 Notable absolute values and change from baseline

The number and percentage of patients with newly occurring or worsening notable values, including notable change from baseline, will be summarized by vital sign parameter, post-baseline visit and treatment group. An additional section will be included for abnormalities occurring at any time-point over the treatment period, considering all post-baseline data from scheduled, unscheduled and premature discontinuation visits. Notable absolute values and notable changes from baseline for each vital sign parameter are defined in Table 2-3 as an example (The notable criteria may be changed depending on the lab used).

For a patient to meet the criterion of a newly clinically notable occurrence, the patient needs to have a baseline value which does not meet the criteria for categorizing a value as notable. For a patient to meet the criterion of a worsening occurrence, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For patients with a missing value at baseline, post-baseline values meeting the notable criterion will be considered as newly occurring.

**Table 2-3 Clinical notable criteria for vital signs**

Vital sign parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
Notable value considering newly occurring or worsening cases		
Systolic blood pressure (mmHg)	< 75	> 200
Diastolic blood pressure (mmHg)	< 40	> 115
Pulse rate (bpm)	< 40	> 130
Notable change from baseline		
Systolic blood pressure (mmHg)	≤ 90 and decrease from baseline by ≥ 20	≥ 180 and increase from baseline by ≥ 20
Diastolic blood pressure (mmHg)	≤ 50 and decrease from baseline by ≥ 15	≥ 105 and increase from baseline by ≥ 15
Pulse rate (bpm)	≤ 50 and decrease from baseline by ≥ 15	≥ 120 and increase from baseline by ≥ 15
Weight (kg)	Decrease ≥ 7% from baseline	Increase ≥ 7% from baseline

### 2.13.2.4 Electrocardiogram ( ECG)

If more than one ECG is taken at a scheduled time point the ECG values will be averaged for the quantitative ECG assessments and analysis. For qualitative assessments, if multiple ECG values were taken, the worst case will be chosen for all summaries.

#### 2.13.2.4.1 Summary of absolute values

The following quantitative variables will be summarized by treatment at each scheduled post-dose visit and time point: ventricular rate, QT interval, RR interval, PR interval, QRS duration, heart rate, and Fridericia's QTc. The maximum QTc (including values from post-baseline unscheduled and premature discontinuation visits) will also be summarized.

QTc will also be summarized by categories:  $\leq 450$  msec,  $> 450 - 480$  msec,  $> 480 - 500$  msec,  $> 500$  msec.

#### 2.13.2.4.2 Summary of change from baseline

The changes from baseline will be summarized by ECG parameter, schedule visit and time point where baseline and post baseline values are both available.

#### 2.13.2.4.3 Overall ECG interpretation

The Overall ECG interpretation is the qualitative ECG assessment. ECGs will be centrally reviewed by a cardiologist. If the central cardiologist reported that an ECG was abnormal, then the investigator commented in the CRF as to whether the ECG abnormality was "normal", "clinically insignificant abnormality" or "clinically significant abnormality". The overall interpretation is based on the evaluation provided by the investigators and the central readings, respectively.

Shift tables will be provided to compare a patient's overall ECG interpretation at screening to the interpretation at the end of the study.

#### 2.13.2.4.4 ECG abnormalities

Using the morphologic determinations, the number and percentage of patients with qualitative ECG abnormality will be summarized *overall during the study period as well as for each visit/ timepoint*.

The abnormality will be summarized by baseline condition (NO/YES, i.e. newly occurring cases, or persistent/recurrent cases) for each evaluation type and finding. The qualitative ECG abnormality will be determined by abnormality of Rhythm, Arrhythmia, Conduction, Morphology, Myocardial infarction, ST segment, T wave abnormalities, and abnormal U wave for example. A patient with multiple occurrence of an abnormality will be counted only once for that treatment.

#### 2.13.2.4.5 Notable QTc values

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value which is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value. For patients with a missing value at baseline, post-baseline values meeting the notable criterion will be considered as newly occurring. The number and percentage of patients who have newly occurring or worsening clinically notable values, or notable changes from baseline, will be presented by post-baseline visit. Notable values will be summarized for Fridericia's QTc. Data from unscheduled visits and from premature discontinuation visits will be included. A listing of all newly occurring or worsening abnormalities will be provided. The clinically notable ranges for selected ECG parameters and notable changes from baseline are show in Table 2-7 as an example.

**Table 2-4 Clinical notable criteria for selected ECG parameters**

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTc (msec)	> 450 for male and >470 for female
QTc (msec)	> 500
Notable change from baseline	
QTc	30 – 60
QTc	> 60

#### 2.14 Interim analyses

RAP M3 for Interim Analysis is documented in a separate document.

#### 2.15 Determination of Sample Size

Table 2-1 provides the sample sizes required for each respective outcome measure (the primary and secondary variables) in order to achieve an 80% power to detect the minimally important difference at a two-tailed 5% significance level.

This study is aimed to power for a 50% reduction in sputum eosinophil percentage. This is equivalent to an absolute reduction in log10 (sputum eosinophil percentage) of  $\log_{10}2 = 0.301$  (Inman et al, 2002, Barnes et al, 2011). The minimally important differences for the primary and key secondary endpoints are listed in Table 9-1.

**Table 2-5 Sample size calculations for primary and secondary endpoints**

Endpoint	Assumption		N per treatment group
	SD*	Minimally	BT# comparison

		important difference	2-group T-test	WMW <sup>\$</sup> rank-sum
$\Delta^\dagger$ in sputum eosinophil percentage on log <sub>10</sub> scale	0.333	0.301¥	21	23
$\Delta^\dagger$ in ACQ	0.385	0.5€	11	13

$\Delta^\dagger$  = change from baseline at week 12

SD<sup>\*</sup> = Standard deviation for the endpoint to be analyzed

BT<sup>#</sup> = between-treatment

WMW<sup>\$</sup> = Wilcoxon/Mann-Whitney rank sum test

¥ (Inman et al, 2002)

€ (Juniper et al, 2005)

With 30 patients per arm to be randomized, it is expected that 24 patients per arm will complete week 12 assessment, assuming the dropout rate during the course of treatment phase (12 weeks) is 20%. With this sample size, the primary and secondary endpoints achieve  $\geq 80\%$  power to detect minimally important difference between QAW039 and placebo, as specified in Table 2-1.

## Appendix 16.1.9 Documentation of statistical methods

### Introduction

This appendix gives details about statistical methods in addition to that provided in Section 9.7 of the main report text. All analyses were performed by using SAS Version 9.3. Inferential analyses were pre-planned and were conducted at a two-sided significance level of 5%. However, statistical tests for secondary and exploratory variables were considered to be exploratory in nature only.

### Major protocol deviations

The following protocol deviations were considered as major and were lead to exclusion of patients/ data from the per-protocol analysis of efficacy:

Have not demonstrated either reversible airway obstruction or airways hyper-reactivity within the last 5 years, or at screening

Received other treatment than originally randomized to

### Rules for calculations related to ACQ

The ACQ measured asthma symptom control and consisted of 7 items: 5 on symptom assessment, 1 on rescue bronchodilator use and 1 on airway calibre (FEV<sub>1</sub> % predicted). All 7 questions of the ACQ were equally weighted. Items 1-6 were scored along a 7-point response scale, where 0 = good controlled and 6 = poor controlled. Question 7 dealt with FEV<sub>1</sub> % predicted pre-bronchodilator. In case the values of FEV<sub>1</sub> % predicted pre-bronchodilator were also available from the central spirometry reading in addition to the ACQ Q7 from CRF, the central reading was used to derive the ACQ score. The value of ACQ Q7 was used only if the central reading was not available. The 7th item on % predicted FEV<sub>1</sub> (pre-bronchodilator) was scored by clinic staff on a 7-point scale (0 – > 95- 99%; 1 – 90-95%; 2 – 80-89%; 3 – 70-79%; 4 – 60-69%; 5 – 50-59%; 6 – < 50%).

The average score of the 7 questions at each visit was calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and the missing item was neither question 1 nor question 7.

If a measure of FEV<sub>1</sub> % predicted pre-bronchodilator was missing in the central spirometry data, then we got it from the ACQ Q7 in CRF. The ACQ score was then calculated as the sum of scores divided by the number of questions that were answered by the patient at the visit, as long as there were at least 6 questions answered and preferable not question 1 (night time awakenings) or 7 (FEV<sub>1</sub> % predicted).

For a missing individual item, the recommended method for handling missing data to reduce the risk of bias was to interpolate using either previous or subsequent completions of the questionnaire. For instance,

Item	Visit 1	Visit 2
1	4	6
2	3	5
3	0	0
4	4	4
5	0	0
6	2	missing
7	5	6

Total visit 1 score for items answered on both visits was  $4+3+0+4+0+5=16$  (A)

Total visit 2 score for items answered on both visits was  $6+5+0+4+0+6=21$  (B)

Item 6 score at visit 1=2

Item 6 score at visit 2=  $B/A * 2=21/16*2=2.63$

The ACQ score for visit 1 was  $(4+3+0+4+0+2+5)/7=2.57$

The ACQ score for visit 2 was  $(6+5+0+4+0+2.63+6)/7=3.38$

It should be noted that a post-treatment missing data could only be imputed using a post treatment visit, and a missing value at baseline (visit 3) could only be interpolated using a value from Visit 2. That is, if the missing was at baseline (visit 3), then we could only do backward interpolation using Visit 2 and if we had missing data on Visit 4, we could only do forward interpolation using Visit 5. If Visit 5 had data missing then we could do forward as well as backward interpolation using either Visit 6 or Visit 4.

### **Rules on calculations related to Asthma Quality of Life (AQLQs)**

AQLQ was a 32-item disease specific questionnaire, each answered on a 7-point scale (1 = totally limited/problems all the time, 7 = not at all limited/no problems).

The domain scores were calculated from the sum of individual question responses as follows:

Activity limitations = Mean of Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32 (11 items)

Symptoms = Mean of Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30 (12 items)

Emotional function = Mean of Items 7, 13, 15, 21, 27 (5 items)

Environmental stimuli = Mean of Items 9, 17, 23, 26 (4 items)

Overall Score = Mean of Items 1 to 32 (32 items)

Each item of the AQLQ was equally weighted and scored along a 7-point scale, where 1 indicated maximal impairment and 7 indicates no impairment. Thus, higher scores indicated better asthma-related HRQOL. There was a mean score calculated for each of the four domains, as well as an overall quality-of-life score, which was the mean score of all 32 items. The resultant overall scores were between 1 and 7.

The developer suggested no more than 10% of missing data. This means that for a questionnaire of 32 items, no more than 3 items should be missing. Further, for the activity and symptom domains, the recommendation was no more than 1 missing value per domain. For the emotional function and environmental stimuli domains, no missing responses at all.

The recommended method for handling missing data to reduce the risk of bias was to interpolate (pro-rate) missing values using either previous or subsequent completed questionnaires per domain, in a similar way as described in the previous section for the analysis of ACQ.



**Clinical notable criteria for selected laboratory tests**

Laboratory parameter (unit)	Lower bound of clinically notable range	Upper bound of clinically notable range
<b>Hematology</b>		
Hematocrit (v/v)		
Male	0.37	
Female	0.32	
Hemoglobin (g/L)		
Male	115	
Female	95	
Thrombocytes (x10 <sup>9</sup> /L)	75	700
WBC's (x10 <sup>9</sup> /L)	2.8	16.0
<b>Chemistry</b>		
Alkaline Phosphatase (U/L)	-	3xULN
Total Bilirubin (mcmol/L)	-	34.2
Creatinine (mcmol/L)		176.8
Potassium (mmol/L)	3	6
Glucose (mmol/L)	2.78	9.99
SGOT (U/L)	-	3 x ULN
SGPT (U/L)	-	3 x ULN
BUN/Serum Urea (mmol/L)		9.99
Sodium (mmol/L)	125	160
Albumin (g/L)	25	-
Total protein (g/L)	40	95
Gamma GT (U/L)		3 x ULN

v = volume, ULN = upper limit of normal

## Statistical methodology and assumptions

- **Mixed model analysis**

The mixed model used for analysis of various endpoints was as follows:

change from baseline of the endpoint = intercept + baseline + treatment + OCS (Yes/No) + bronchoscopy (Yes/No) + error.

The SAS procedure MIXED was used with the following SAS code:

```
proc mixed data=... order = internal;  
by avisitn;  
class trt01pn BRONCBL OCSUSEN;  
model chg = trt01pn BRONCBL OCSUSEN base/outpred = pred residual ddfm = kr;  
LSMEANS trt01pn/cl diff;  
run;
```

where chg = change from baseline value  
trt01pn = planned treatment  
base = baseline value  
OCSUSEN = 1 if OCS use; 0 if no OCS use  
BRONCBL = 1 if bronchoscopy yes; 0 if bronchoscopy no  
avisitn = visit number

Results were presented with least squares mean and standard error for treatment effects and least squares mean, standard error, associated two-sided 95% confidence interval, and two-sided p-value for the treatment contrast.

The normality assumption was checked with a Q-Q plot of residuals for each treatment group separately. No checks for the equality of treatment group variances and homogeneous regression slopes were performed. If the normality assumption was not fulfilled, a nonparametric analysis was performed.

- **Cox regression analysis**

Time to first moderate and severe COPD exacerbation was analyzed with a Cox proportional hazards regression model.

The SAS procedure PHREG was used with the following code:

```
proc phreg data=... ;  
CLASS usubjid trt01pn OCSUSEN BRONCBL ;  
model time*CENSORN(0) = trt01pn OCSUSEN BRONCBL / r1 ties=exact;  
where BRONCBL ne . and OCSUSEN ne . and paramcd = "Combined";  
hazardratio trt01pn ;  
Contrast 'H1' trt01pn 1 / estimate=exp ;  
run;
```

where time = time to first moderate and severe COPD exacerbation  
CENSORN = 0 if data was censored; 1 if event happened  
Trt01pn = planned treatment

OCSUSEN = 1 if OCS use; 0 if no OCS use  
BRONCBL = 1 if bronchoscopy yes; 0 if bronchoscopy no

Results were presented with the adjusted hazard ratio and associated 95% confidence interval and two-sided p-value for the treatment effect. P-values were obtained from the Wald chi-squared statistic testing the null-hypothesis that the parameter estimate for the respective treatment effect is 0 (then the hazard ratio is  $\exp(0) = 1$ ).

In addition, unadjusted Kaplan-Meier estimates were produced with the SAS procedure LIFETEST.

Time to premature discontinuation was also analyzed with a Cox proportional hazards regression model.

- **Mixed Model Repeated Measures (MMRM)**

The following MMRM model was used for analysis of primary and secondary endpoints:

Change from baseline of the endpoint = intercept + treatment + baseline OCS (Yes/No) + bronchoscopy (Yes/No) + visit + treatment\*visit + baseline \*visit + error.

An unstructured covariance matrix for the within-patient error was used.

The SAS procedure MIXED was used with the following code:

```
proc mixed data=.... order=internal;
where avisitn in (4,5,777) and (paramcd = ...) and fasfl = 'Y';
class ocsusec trt01pn BRONCBL avisitn subjid;
model chg = trt01pn ocsusec BRONCBL base avisitn avisitn*trt01pn base*avisitn/ddfm =
kr;
repeated avisitn/subject = subjid type = un;
lsmeans avisitn*trt01pn/diff cl;
estimate "visit 4_QAW vs placebo" trt01pn 1 -1 trt01pn*avisitn 1 0 0
-1 0 0 /cl;
estimate "visit 5_QAW vs placebo" trt01pn 1 -1 trt01pn*avisitn 0 1 0
0 -1 0 /cl;
estimate "visit 777_QAW vs placebo" trt01pn 1 -1 trt01pn*avisitn 0 0 1
0 0 -1 /cl;
run;
```

where chg = change from baseline value  
trt01pn = planned treatment  
base = baseline value  
OCSUSEN = 1 if OCS use; 0 if no OCS use  
BRONCBL = 1 if bronchoscopy yes; 0 if bronchoscopy no  
avisitn = visit number

Results were presented with least squares mean and standard error for treatment effects and least squares mean, standard error, associated two-sided 95% confidence interval, and two-sided p-value for all relevant treatment contrasts.

## **Summary of Changes**

### **Amendment 1**

#### **Document History – Changes compared to previous version of RAP module 3.**

20/1/2014

Removed inappropriate baseline definition for sputum eosinophil

Removed the contents associated with CSR addendum as all outputs contained in this document will be included in core CSR

Added imputation rule for sputum eosinophil value 0s.

20/4/2014

Added analysis for per-protocol analysis

Added description of MMRM for primary and secondary analysis

20/5/2014

Added PK analysis with summary statistics and listings

**AirPROM-Statistical analysis plan (to be read in conjunction with full Novartis Protocol and Statistical Analysis Plan)**

**A double-blind, placebo-controlled, study examining the effect of orally administered QAW039 on sputum eosinophil levels and other efficacy outcomes in patients with sputum eosinophilia and persistent asthma**

Author(s): Rachid Berair, Sherif Gonem, Jim Wild, Wim Vos, Christopher Newby and Christopher Brightling

Version number : v01

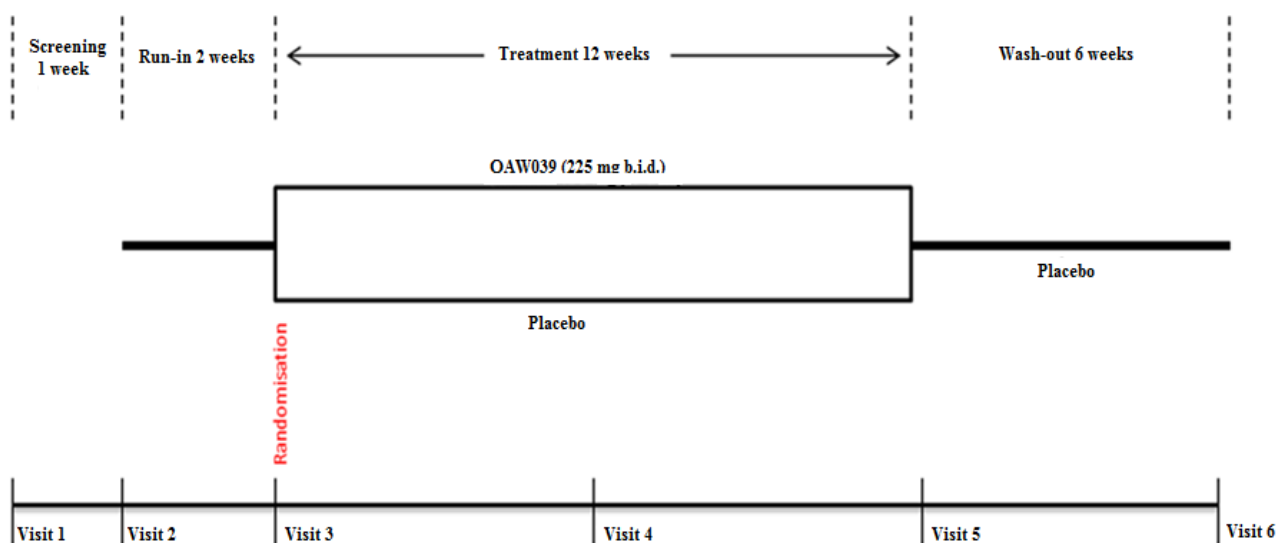
Document date : July 2013

## 1. Study Design

This is a single-centre double-blind, placebo-controlled, parallel-group randomised study examining the effect of orally administered QAW039 225 mg b.i.d for 12 weeks as add-on therapy in adults with asthma (GINA treatment steps 2-5) and a sputum eosinophilia ( $\geq 2\%$ ).

Visit schedule summarised in Figure 1. For detailed protocol refer to main study protocol. After signing informed consent (Visit 1), and screening (Visit 2)(inclusion and exclusion criteria as per main study protocol), patients will undergo a 2-week placebo run-in period. At the baseline visit (visit 3) all eligible patients will be randomized to QAW039 (225 mg b.i.d.) or placebo for 12 weeks. Patients will be assessed after 6 weeks of treatment (visit 4) and at the end of the 12-week treatment period (visit 5), all patients will receive placebo during a 6 week washout period (visit 6). Visits to assess safety and efficacy will be at weeks 6, 12, and 18 weeks post-randomization i.e. visits 4, 5, and 6 with efficacy objectives focussed on the end of the treatment period at week 12 versus baseline (i.e. visit 3 versus visit 5).

**Figure 1:** study design



## 2. Study assessments and efficacy & exploratory endpoints/outcomes

Study assessment	Pre or post BD	Measured endpoints/outcomes
Spirometry	Pre/post BD	FEV <sub>1</sub> (L and % predicted), FVC (L and % predicted) and FEV <sub>1</sub> /FVC (%)
Body plethysmography	Pre-BD	RV (L and % predicted), VC (L and % predicted), TLC (L and % predicted), RV/TLC (%), Va (L and % predicted) and Va/TLC (%).
Gas transfer	Pre-BD	Kco (mmol.min <sup>-1</sup> .kPa.L <sup>-1</sup> and % predicted) and DLco (mmol.min <sup>-1</sup> .kPa and % predicted).
IOS	Pre-BD	R5 (kPa.L <sup>-1</sup> .s), R20 (kPa.L <sup>-1</sup> .s), R5-R20 (kPa.L <sup>-1</sup> .s), X5 (kPa.L <sup>-1</sup> .s) and AX (kPa.L <sup>-1</sup> )
MBW	Pre-BD	LCI, S <sub>cond</sub> (L <sup>-1</sup> ), S <sub>acin</sub> (L <sup>-1</sup> ), LCI <sub>vent</sub> , LCI <sub>ds</sub> and FRC <sub>MBW</sub> (L)
Sputum analysis	N/A	Sputum differential cell count (sputum eosinophils (%), sputum neutrophils (%), sputum macrophages (%), sputum lymphocytes (%), sputum epithelial cells (%)); and total Cell Count x10 <sup>6</sup> /g of sputum. Sputum levels of Eotaxin-1, IL-5, IL-13, IL-8, ECP, prostaglandins and leukotrienes; and TNF-α
HRCT	post-BD	<u>Morphometry</u> : luminal area (LA), total area (TA) and wall (WA) corrected for BSA and %WA (WA/TA) and respective volumes for: RB1-RB10, LB1-LB10 as individual measures and means of each lung, RB1 reported independently as benchmarked to other large studies, mean data for 5th and 6th generation airways, Pi10 and Po20. <u>Densitometry</u> : total lung MLD E/I, total lung MILD, total lung MELD, total lung Perc15, upper third MLD E/I, upper third MILD, upper third MELD, upper third Perc15, middle third MLD E/I, middle third MILD, middle third MELD, middle third Perc15, lower third MLD E/I, lower third MILD, lower third MELD, lower third Perc15, upper lobes MLD E/I, upper lobes MILD, upper lobes MELD, upper lobes Perc15, lower lobes MLD E/I, lower lobes MILD, lower lobes MELD, lower lobes Perc15, right lung MLD E/I, right lung MILD, right lung MELD, right lung Perc15, left lung MLD E/I, left lung MILD, left lung MELD and left lung Perc15. Parametric response mapping. <u>Functional Respiratory Imaging</u> : (specific) airway volumes, (specific) airway resistances, lung volumes and associated measures of hyperinflation at both functional residual capacity (FRC) and total lung capacity (TLC) at lung and lobar level.
He-3 MRI	Pre BD	mean ADC, std ADC, proximal mean r, peripheral mean r, global mean r, global std r
He-3 MRI	Pre/post BD	proximal, peripheral and global VDP; proximal, peripheral and global VD#, global VV CV mean, CV std TRM, ΔVV TRM, ΔVV% global, TLV global PDP, global mean PTT, global std PTT
Bronchial biopsies	N/A	RBM thickness (μm), intact epithelium (%), partial epithelium (%), denuded epithelium (%), ASM area (%), gland (%), epithelium (%), eosinophils, neutrophils, mast cells (tryptase and chymase-positive), CD3-positive /mm <sup>2</sup> lamina propria, /mm <sup>2</sup> epithelium, /mm <sup>2</sup> ASM, goblet cells (PAS staining and/or MUC5AC)/mm <sup>2</sup> intact epithelium, /mm RBM, RBM-ASM distance (μm), vessels/mm <sup>2</sup> lamina propria and mean Chalkley count, CRTh2-positive cells/mm <sup>2</sup> epithelium, /mm <sup>2</sup> lamina propria, epithelial CRTh2-positive cells/mm RBM, fibrocytes/mm <sup>2</sup> lamina propria and fibrocytes/mm <sup>2</sup> ASM.
FeNO <sub>50</sub>	Pre-BD	FeNO <sub>50</sub> (ppb).
ACQ	N/A	ACQ-7 score (questions 1-7) and ACQ-6 (questions 1-6 only). ACQ in those with poor control at baseline ≥1.5.
AQLQs	N/A	AQLQ score, AQLQ symptoms domain score, AQLQ activity limitation domain score, AQLQ emotional domain score and AQLQ environmental domain score.
Blood tests (not safety bloods)	N/A	White blood cell count with differential, ECP, eotaxin-1, IL-5, IL-13, total IgE, hsCRP, TNF-α, MCP-1 and IL-8.

Abbreviations: ACQ = Asthma Control Questionnaire; ADC = apparent diffusion coefficient; AQLQ = Asthma Quality of Life Questionnaire; ASM = airway smooth muscle; BD=bronchodilator; BSA = body surface area; CE = contrast enhanced CV = coefficient of variation of ventilation heterogeneity over the whole lungs; DLco = CO transfer factor; ECP = Eosinophilic cationic protein; E/I = expiratory/inspiratory; FeNO<sub>50</sub>=fractional exhaled nitric oxide;FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; FRC=functional residual capacity, FRCmbw = functional residual capacity from multiple breath washout; hsCRP = high-sensitivity C-reactive protein; Kco = CO transfer coefficient; LA= lumen area; LCI = lung clearance index; LCI<sub>ds</sub> = dead space component of lung clearance index; LCI<sub>vent</sub> = specific ventilation inequality component of lung clearance index; MBW=multiple breath washout; MELD = mean expiratory lung density; MILD = mean inspiratory lung density; MLD = mean lung density; N/A= not applicable; PDP = global perfusion defect percent; ppb = parts per billion; Pi10=WA for hypothetical airway with an internal perimeter of 10mm; Po20= WA and LA for hypothetical airway with an outer perimeter of 20mm; PTT = perfusion transit time; r = fractional ventilation; RV = residual volume; std = standard deviation; TA = total area; TLC = total lung capacity; TLV = total lung volume; TNF = tumour necrosis factor; TRM = treatment response mapping; TV = total volume; Va = alveolar volume; VC = vital capacity; VD# = ventilation defect number; VDP = ventilation defect percent; VV = ventilation volume; ΔVV = ventilated volume change; ΔVV% = ventilated volume change; WA = wall area; %WA = percentage wall area; WV = wall volume; %WV = percentage wall volume.



### 3. Study objectives

The primary objective of this study is to demonstrate a statistically significant reduction in the sputum eosinophil count after treatment with QAW039 for 12 weeks compared to placebo.

The secondary objectives include:

- To demonstrate that QAW039 provides significantly superior control of asthmatic symptoms as measured by the asthma control questionnaire (ACQ) compared to placebo in the group as a whole (and in those with poor control at baseline defined by  $ACQ \geq 1.5$ ).
- To assess safety and tolerability of QAW039.

The exploratory objectives include:

- To demonstrate that QAW039 provides significant improvement in standard physiological markers including pre- and post-bronchodilator  $FEV_1$ , as well as specific small airway markers measured with multiple breath washout (MBW) and impulse oscillometry, namely  $S_{acin}$ , R5-R20 and AX, compared to placebo.
- To explore whether the efficacious effect of QAW039 therapy persists following the cessation of therapy.
- To explore whether quantitative computed tomography (CT) biomarkers at baseline predict response to therapy with QAW039.
- To explore changes in air trapping, as evaluated by quantitative computed tomography (CT), after 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in health-related quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ) after 12 weeks of treatment with QAW039 versus placebo.
- To explore changes in blood mediators and transcriptomic profile by RNAseq following 12 weeks of treatment with QAW039 versus placebo. Further analyses led by Professor Ivo Gut.
- To explore the effect of QAW039 on ventilation heterogeneity, as measured by hyperpolarised helium-3 MRI (He-3 MRI), compared to placebo. Further analyses to be undertaken by University of Sheffield led by Professor Wild.
- To explore whether QAW039 attenuates eosinophilic airway inflammation as measured by bronchial biopsies, compared to placebo.
- To explore whether QAW039 attenuates airway inflammation and features of remodelling in bronchial biopsies (including but not limited to the assessment of histological features of inflammatory and goblet cell number, reticular basement membrane thickness and assessment of collagen deposition) compared to placebo.
- To assess the change in parameters generated by Functional Respiratory Imaging (FRI): (specific) airway volumes, (specific) airway resistances, lung volumes and associated measures of hyperinflation at both functional residual capacity (FRC) and total lung capacity (TLC) following treatment with QAW039 versus placebo. Analyses to be undertaken by AirPROM partner Fluida and further details are provided in annex I.
- Responder analyses to determine predictors of response defined as a continuous variable for all subjects in the active arm for relative percentage change in sputum eosinophil count, ACQ, and  $FEV_1$  (both pre and post bronchodilator) and responders versus non-responders defined as  $>50\%$  relative change in sputum eosinophil count,  $>0.5$  ACQ, and  $>120$ ml  $FEV_1$  (both pre- and post-bronchodilator).
- Genome wide analysis with expression quantitative trait loci (eQTL) associated with baseline characteristics and response. Led by Professor Tobin and Gut see Annex II for further details.
- Development and validation of multi-scale models in AirPROM as per AirPROM description of work ([www.airprom.eu](http://www.airprom.eu))

### 3. Data analysis

Statistical analyses will be performed using SPSS 20 (IBM Corporation, Somers, New York, USA) Prism 6 (GraphPad Software Inc., La Jolla, California, USA) and in R (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>).

The full analysis data set (FAS) or intention-to-treat (ITT) will include all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment they received. All participants who are randomized will be included in the ITT population, and missing data due to withdrawals or otherwise will be imputed using the last observation carried forward. Participants who completed the study up to the post-treatment visit (Visit 5) without major protocol deviations will be included in the per-protocol population (PP). Outcomes will be assessed primarily in the PP population and supported by analysis of the ITT population or FAS.

The primary outcome of the study is the change in sputum eosinophil percentage between the baseline visit (Visit 3) and the post-treatment visit (Visit 5). As sputum eosinophil percentage is known to follow a log-normal distribution, the analysis will be based on a  $\log_{10}$ -transformed scale. To observe a between group post intervention 50% difference in sputum eosinophil percentage, (equivalent to an absolute reduction in  $\log_{10}$  sputum eosinophil percentage of 0.301) with 80% at a 5% level requires 21 subjects in each group. With 30 patients per arm to be randomized, we expect 24 patients to complete the post-treatment assessments, assuming a 20% dropout rate during the course of the treatment phase.

To address the objectives in section 2, outcomes will be assessed at weeks 6, 12, and 18 weeks post-randomization i.e. visits 4, 5, and 6 compared to visit 3 with analysis of endpoints primarily focussed on the end of the treatment period at week 12 versus baseline (i.e. visit 3 versus visit 5). Analyses will be undertaken for all the endpoints listed in Table 1. Following checking for normality assumption using a Q-Q plot of residuals, Shapiro-Wilk and Kolmogorov-Smirnov test, between-group and within-group comparisons will be made for the mean change between baseline values (visit 3) and values at week 6 (visit 4), week 12 (visit 5), and week 18 (visit 6), with the use of unpaired and paired t-tests, respectively, for parametric distributions and the Mann–Whitney U test and Wilcoxon signed-rank test for nonparametric distributions. Between-group comparisons will be carried out using unpaired tests, while paired tests will be used in within-group comparisons. Proportions will be compared with the use of Fisher's exact test.

Responder analysis will determine predictors in responder versus non-responder groups for the efficacy outcomes sputum eosinophils, ACQ and pre- and post-bronchodilator FEV<sub>1</sub>. Response will also be considered as a continuous variable and correlated with baseline values and change in other outcomes i.e. delta versus delta associations. In addition to this an unsupervised cluster responder statistical model will be carried out. This model will use multiple outcomes of the trial to determine if specific latent responder clusters can be determined. The derived cluster membership can then go on to be deep phenotyped using the rest of the variables to determine specific biomarkers that relate to the clusters and thus can predict the drug response for patients.

Structural equation modelling will be carried out on the baseline data to obtain models that contain casual links between variables. Information of the causal links will be found from the literature and will be verified in the structural equation modelling along with existing structural equation models using previous data, in order to create a predictive casual model of clinical outcomes of asthma at baseline. The parameters of the structural equation model can then be tested after treatment with placebo and drug to determine the parameters that have changed furthering evidence of disease mechanism changes. The results once established can then be tested in a simpler manner through hypothesis testing.

For other AirPROM outcomes and multi-scale modelling refer to ([www.airprom.eu](http://www.airprom.eu)) and the attached Annex.