Effects of a novel targeted-release formulation of budesonide vs. placebo in IgA nephropathy: The NEFIGAN randomised clinical trial

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Summary

Background

IgA nephropathy (IgAN) is postulated to be associated with mucosal immune system dysfunction, manifesting as renal IgA deposition leading to impairment and end-stage renal disease (ESRD) in 20–40% of patients over 10–20 years. The NEFIGAN trial investigated a novel targeted-release formulation of budesonide (TRF-budesonide), designed to deliver drug to the distal ileum in IgAN patients.

Methods

This was a randomised, double-blinded, placebo-controlled trial, comprised of 6-month run-in, 9-month treatment, and 3-month follow-up phases. All patients had persistent proteinuria despite optimised renin-angiotensin system (RAS) blockade. A total of 150 randomised patients were treated (safety set). Of these, 149 patients were eligible for the full analysis set: n=48 received 16 mg/day TRF-budesonide , n=51 received 8 mg/day, and n=50 received placebo. ClinicalTrials.gov number NCT01738035.

Findings

At 9 months, mean UPCR (primary endpoint) had decreased by -24·4% with TRF-budesonide (-27·3% with 16 mg/day [p=0·0092], non-significant -21·5% with 8 mg/day [p=0·0290]), relative to +2·7% with placebo. The effect was sustained throughout follow-up; mean UPCR decreased by -32·0% from baseline at 12 months for 16 mg/day vs. +0·5% for placebo. Changes in estimated glomerular filtration rate (eGFR), 24-hour protein excretion, urine albumin creatinine ratio, and 24-hour albumin excretion were consistent with the UPCR

data. Over 9 months, eGFR was stable with TRF-budesonide but decreased -9·8% with placebo (TRF-budesonide vs. placebo: p=0·0010). There were dose-dependent trends in the incidence of solicited corticosteroid-related adverse events and discontinuations, although the incidence of all adverse events was comparable for the three treatment groups. Two of 13 serious adverse events were possibly related to TRF-budesonide: deep vein thrombosis (16 mg/day) and unexplained deterioration in renal function in follow-up.

Interpretation

TRF-budesonide, added to optimised RAS blockade, reduced proteinuria and maintained eGFR in IgAN patients. Both these effects are indicative of a reduced risk of future progression to ESRD. These results suggest that TRF-budesonide has potential to become the first IgAN-specific treatment targeting intestinal mucosal immunity upstream of disease manifestation.

Funding

Pharmalink AB

Introduction

Primary immunoglobulin A (IgA) nephropathy (IgAN) is the most prevalent chronic glomerular disease worldwide, with patients often diagnosed as young adults.[1] Approximately 20–40% of patients progress to end-stage renal disease (ESRD) within 10–20 years of diagnosis.[2–4] Major risk factors for progression to ESRD are persistent proteinuria, hypertension, and reduced glomerular filtration rate (GFR).[1,3,5,6] KDIGO guidelines for glomerulonephritis recommend renin-angiotensin system (RAS) blockade utilizing angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line treatment for IgAN patients with proteinuria >1 g/day (recommendation level 1B), and suggest up-titration as far as tolerated up to the maximum recommended dose (MRD) to achieve proteinuria <1 g/day (recommendation level 2D).[7] For patients with persistent proteinuria >1 g/day and GFR >50 mL/min/1·73 m^2 despite 6 months' optimised RAS blockade, KDIGO suggest 6 months' treatment with high-dose systemic corticosteroids (recommendation level 2C).[7] However, use of high-dose systemic corticosteroids is associated with increased risks of adverse events and sequelae including serious infections, hypertension, weight gain, diabetes, and osteoporosis.[8–10] The benefit of systemic immunosuppression, in addition to the intervention of dietary restrictions and polypharmacy upon optimised RAS blockade has recently been questioned in the STOP-IgAN trial.[11] Notwithstanding, there is an unmet need for a targeted treatment with a favourable risk-benefit profile in IgAN patients at risk of progression to ESRD.

Evidence suggests a role for the mucosal immune system in the pathogenesis of IgAN.[1,12,13] In IgAN patients, mucosal B lymphocytes located in Peyer's patches are thought to be primed to produce IgA1 that is galactose deficient (Gd-IgA1), which in the circulation can form large immune complexes with anti-glycan IgG antibodies.[1,14–16] These complexes may bind to

glomerular mesangial cells and stimulate cell proliferation, release of inflammatory mediators that promote proteinuria, and fibrotic remodelling, ultimately leading to loss of renal function.[1,15] This pathogenesis suggests that local immunosuppression of mucosal B lymphocyte activation and proliferation in Peyer's patches could attenuate Gd-IgA1 production,[17] thereby reducing subsequent pathophysiological changes, assessed as a reduction in protein excretion by the kidneys.

A novel, oral, targeted-release formulation of the glucocorticosteroid budesonide (TRF-budesonide; NEFECON™ [Pharmalink AB, Stockholm, Sweden]) was developed to release drug in the distal ileum, where Peyer's patches reside at high density. The safety profile of TRF-budesonide was anticipated to be superior to high-dose systemic corticosteroids because of its extensive first pass metabolism: less than 10% of budesonide enters systemic circulation.[18] In a previous exploratory phase 2a trial, 16 IgAN patients received TRF-budesonide (8 mg/day). Treatment over 6 months resulted in a statistically significant reduction in proteinuria and was well-tolerated.[19] The objective of the current phase 2b trial was to evaluate the efficacy and safety of two doses of TRF-budesonide in IgAN patients at risk of progressing to ESRD due to persistent proteinuria despite optimised RAS blockade therapy.

Methods

Trial design

The NEFIGAN trial was randomised, double-blinded, and placebo-controlled in patients with biopsy-confirmed primary IgAN and overt proteinuria considered at risk of progressing to ESRD. This phase 2b trial was conducted at 62 sites across 10 European countries (Belgium, Czech Republic, Denmark, Finland, Germany, Italy, Spain, Sweden, The Netherlands, UK; see the Supplementary Appendix). Concerned competent authorities and ethics committees for participating centres approved the trial, which was conducted from December 2012 to June 2015 in accordance with Good Clinical Practice and the Declaration of Helsinki, 2008.

Patients

Male and female patients aged ≥18 years with biopsy-confirmed primary IgAN and overt proteinuria were eligible for the run-in phase. All patients provided written informed consent prior to enrolment. Inclusion criteria for randomisation to treatment included eGFR ≥45 mL/min/1·73 m^2 and a urine protein creatinine ratio (UPCR) ≥0·5 g/g or urinary total protein ≥0·75 g/day, levels considered to increase risk of progressing to ESRD.[20] The approach of using either 24-hour protein excretion or UPCR to determine eligibility was applied to overcome collection errors and deviations from normal creatinine excretion (eg, physically active and muscular males), respectively, thus minimising the risk of unintentionally excluding patients. Eligibility criteria are presented in Table S1.

Procedures

Trial medication was an oral capsule formulation of TRF-budesonide (NEFECON™; Pharmalink AB, Stockholm, Sweden) or a placebo, designed to provide sustained release of

active compound that was delayed until the capsule reached the distal ileum,[21] targeting the site where Peyer's patches reside at high density.

After screening, eligible patients were enrolled into a 6-month run-in phase, a 9-month treatment phase, and a 3-month follow-up phase; patient eligibility was assessed prior to run-in and treatment phases. During run-in, RAS blockade was optimised by up-titrating ACEIs and/or ARBs to a MRD or maximum tolerated dose (MTD) (in keeping with established clinical practice), to a target blood pressure <130/80 mmHg, UPCR <0·5 g/g, and urine protein <0·75 g/day. At the end of run-in, patients with persistent proteinuria (UPCR ≥0·5 g/g or proteinuria ≥0·75 g/day) despite optimised RAS blockade, estimated GFR (eGFR [CKD-EPI serum creatinine equation[22]]) or measured GFR ≥45 mL/min/1·73 m^2, and blood pressure ≤160/100 mmHg were eligible for randomisation to treatment. Run-in phase directives are detailed in the Supplementary Appendix.

An independent Data and Safety Monitoring Board (DSMB) monitored all safety issues and reviewed data at interim analysis.

Randomisation and masking

Patients were stratified according to baseline UPCR (≤0·9 g/g and >0·9 g/g) at Month 0 (baseline). Allocation of patients to treatment groups was done by randomisation using a computer algorithm method of permuted blocks. Within each block, patients were allocated in a 1:1:1 ratio to TRF-budesonide 16 mg/day, 8 mg/day, or placebo. All patients continued optimised RAS blockade treatment throughout the trial. Randomisation was performed by Pharma Consulting Group AB, Uppsala, Sweden.

The trial was double-blind. Therefore, throughout the trial and the analyses, allocation to treatment groups was unknown to each patient, all trial staff (including the investigators and other staff who performed the randomisation and analyses), the sponsor, and the DSMB.

To ensure blinding, placebo capsules were used with the same appearance and route of administration as the active capsules. Patients self-administered blinded capsules, once daily, 1 hour before breakfast during the treatment phase. During follow-up (Months 9–12), patients who received TRF-budesonide 16 mg/day during Months 0–9 were tapered to 8 mg/day for 2 weeks while all other patients (ie, those who received TRF-budesonide 8 mg/day or placebo during Months 0–9) received placebo to maintain blinding. No further trial medication was administered after tapering.

Treatment code envelopes were provided for each randomised patient. In case of emergency, the code envelope could be opened. Any unblinded patient had to be withdrawn from the trial.

Outcomes

The primary outcome was mean change from baseline in UPCR over the 9-month treatment phase. The primary analysis compared mean change from baseline in UPCR at 9 months between TRF-budesonide-treated patients (16 mg/day and 8 mg/day combined) and placebo-treated patients.

Secondary outcomes, assessed at various time points, comprised of mean changes from baseline in UPCR at 12 months, eGFR, 24-hour urine protein excretion, urine albumin creatinine ratio (UACR), and 24-hour urine albumin excretion, which were calculated from measured 24-hour urine samples. The tertiary outcome, the presence or absence of microhaematuria, was assessed by dipstick.

Standardised questionnaires were used at each visit to ask patients about the presence of specific gastrointestinal-related and corticosteroid-related adverse events. All solicited and spontaneously-reported adverse events were recorded from screening until the end of trial, and coded using the Medical Dictionary for Regulatory Activities (Version 16·0E). Vital signs, clinical chemistry, and haematology parameters were assessed.

Statistical analysis

Individual patient data from other relevant studies[23,24] were used to estimate UPCR variability and the expected change from baseline at 9 months for placebo. Based on these studies, the estimated geometric mean ratio of 9-month/baseline UPCR values was 0·88 (log standard deviation [SD]: 0·597). The corresponding geometric mean ratio for TRF-budesonide was estimated from a previous exploratory phase 2a trial[19] as 0·60 (log SD: 0·488). Sample size calculations were based on the hypothesis that the true difference between TRF-budesonide (16 mg/day and 8 mg/day combined) and placebo in log UPCR change from baseline was log(0·60) - log(0·88) corresponding to an absolute difference of (1-0·6) - (1-0·88) = 28%. Thus, a trial with 150 patients (50 per treatment arm) provided more than 90% power to detect this level of treatment effect for TRF-budesonide (16 mg/day and 8 mg/day combined) vs. placebo at the one-sided 2·5% alpha level.

The primary outcome (mean change from baseline in UPCR over the 9-month treatment phase) was assessed on the full analysis set (FAS), defined as all randomised patients who took at least one dose of trial medication and had at least one post-dose efficacy measurement (modified intention-to-treat analysis). A formal interim analysis of the primary outcome governed by the DSMB was prospectively planned and triggered when 90 patients completed 9 months' treatment. As highlighted by an anonymous reviewer of the manuscript before publication, it is important to realise that this was not a simple analysis of the 9-month data

point in the first 90 patients. Rather, using modern mixed modelling methodology accepted by both the US Food and Drug Administration (FDA) and European Medicine Agency (EMA), the interim analysis included all patients who were randomised at the time the 90th patient had completed 9 months' treatment, even if some of these patients had data only up to the 1, 3, or 6-month time point. The number of patients included in the interim analyses was therefore 149, of whom 90 had a 9-month measurement, with the remainder having some data at an earlier time point of 1, 3, or 6 months. The mixed modelling analysis was conducted by analysing the patients' proteinuria profile over time up to the 9-month time point. From this, the treatment effect and p-value at 9 months were extracted to provide the interim analysis result. This approach, which was pre-planned, offers more power than a simple analysis of the 9-month data point in the first 90 patients. The aim of the interim analysis was to ascertain whether the primary hypothesis could be rejected as well as to ensure patient safety and to exclude futility. The threshold for significance for TRF-budesonide (16 mg/day and 8 mg/day) vs. placebo on the primary outcome was 1·58% one-sided; futility could also be declared if predictive power was ≤5%. The alpha level applied at final analysis was 1·52% one-sided to ensure an overall Type I error rate of 2·5% one-sided.

It was prospectively planned that if statistical significance for the primary outcome was met during the interim analysis, the trial would continue, thereby allowing all patients to complete the trial and the analysis of additional endpoints on final data. All secondary and tertiary endpoints were thus analysed during the final analysis after all patients had completed the trial.

The following post-hoc analysis was defined after the interim analysis, and before the final database lock: The treatment effects on UPCR and eGFR CKD-EPI as a function of baseline UPCR and eGFR.

All efficacy data were analysed using MMRM analysis with fixed effect terms for baseline log UPCR, randomised treatment group, UPCR stratification level (UPCR ≤0·9 g/g and >0·9 g/g), visit, and visit by treatment group interaction. Subject and region were included as random effects. Region was defined on the country level, although Denmark was combined with Sweden (region = Scandinavia) and Belgium with the Netherlands (region = Benelux) due to small patient numbers per country. Restricted maximum likelihood estimation was used and inference on the fixed effects was based on robust (sandwich) variance estimation.

Statistical analyses were performed using SAS® (Version 9·3).

This trial is registered with ClinicalTrials.gov, number NCT01738035.

Role of the funding source

The sponsor oversaw all study processes. Alex Mercer is an employee of the sponsor, who contributed to the study design, provided study oversight, participated in data analysis, data interpretation, and writing of the report. Both placebo and TRF-budesonide treatments were provided by the sponsor. Following database lock and unblinding, the sponsor and all investigators had access to analyses performed on trial data. The corresponding author was responsible for submitting the manuscript for publication.

Results

In total, 297 patients were screened between December 11, 2012, and December 26, 2013, and 207 patients were enrolled into the run-in phase. Following run-in, all patients eligible for randomisation to treatment were receiving either a MTD or MRD of ACEIs and/or ARBs. A total of 150 randomised patients received blinded trial medication; 149 comprised the FAS (one patient was unable to swallow capsules) (Figure 1 and Table S2). Trial drug exposure is described in the Supplementary Appendix. Treatment groups (TRF-budesonide 16 mg/day, 8 mg/day, and placebo) were well-balanced regarding demographic and baseline characteristics, with all patients using RAS blockade therapy (Table 1). Patients maintained optimised RAS blockade treatment throughout the trial. In a minority of patients, changes in dose or drug were made in RAS blockade (17 [11%] patients]) or diuretics (10 [7%] patients]). The frequencies of changes were comparable across the TRF-budesonide and placebo treatment groups (Table S3 and S4).

In the pre-planned interim analysis shown in Figure 2a, the primary outcome of geometric LS mean UPCR at 9 months was reduced from baseline by 24·4% (-0·2119 g/g) in all TRF-budesonide-treated patients combined vs. an increase of 2·7% (0·0244 g/g) in placebo-treated patients and the difference was statistically significant (p=0·0066) (Figure 2a; Note: all point estimates and 95% CIs are presented in Table S5). Hence, the primary objective of the trial was met and the corresponding null hypotheses rejected. Geometric LS mean changes from baseline were -27·3% for TRF-budesonide 16 mg/day and -21·5% for 8 mg/day. The difference in UPCR at 9 months was statistically significant for TRF-budesonide 16 mg/day vs. placebo (p=0·0092), but not 8 mg/day vs. placebo (p=0·0290), which did not meet the adjusted p-value at interim analysis (p≤0·0158).

Change in UPCR from baseline at 9 months in the final analysis, when all patients had completed the trial (Figure 2b and Table S5), was consistent with the change at 9 months in the interim analysis (Figure 2a and Table S5).

Secondary and tertiary endpoints and post-hoc analyses were performed in the final analysis.. Exploratory post-hoc analysis of the reduction in UPCR at 9 months vs. baseline showed that TRF-budesonide had a consistent effect on the relative change in UPCR regardless of baseline UPCR levels (Figure S1). Upon completion of the 3-month follow-up, after cessation of trial medication, the geometric LS mean reduction was sustained in the TRF-budesonide 8 mg/day group (-22·6% change from baseline) and continued to decrease in the 16 mg/day group (-32·0% change from baseline) vs. an increase of 0·5% for placebo (Figure 2b and Table S5). Compared to placebo, the changes in UPCR at 12 months in both active treatment groups were statistically significant (16 mg/day vs. placebo, p=0·0005; 8 mg/day vs. placebo, p=0·0101) (Table S5).

Changes from baseline at 9 months and at 12 months in 24-hour urine protein excretion, UACR, and 24-hour urine albumin excretion (Table S6) were consistent with the UPCR data (Table S5). In the final analysis, changes in geometric LS mean (95% CI) from baseline at 9 months in the 16 mg/day group vs. placebo were: UPCR 0·717 g/g (0·556–0·924; p-value not estimated); 24-hour urine protein excretion 0·693 g (0·529–0·907; p=0·0040); UACR 0·676 g/g (0·502–0·911; p=0·0053); 24-hour urine albumin excretion 0·656 g (0·484–0·889; p=0·0035).

eGFR remained stable in the TRF-budesonide groups but decreased in the placebo-treated group during the treatment phase in the final analysis, as shown by percent changes at 9 months (Figure 3a) and by absolute mean changes in eGFR from baseline across the 12 months (Figure 3b and Table S6). Mean percent change from baseline in eGFR at 9 months

was -9·8% for placebo, +0·6% for 16 mg/day, and -0·9% for 8 mg/day (Figure 3a). Comparisons with placebo achieved statistical significance at 9 months (16 mg/day vs. placebo: p=0·0026; 8 mg/day vs. placebo: p=0·0064). Exploratory post-hoc analyses suggested that stabilisation of eGFR in TRF-budesonide-treated groups was independent of baseline UPCR and eGFR values, and that the degree of eGFR reduction in the placebo-treated group appeared related to the magnitude of baseline UPCR (Figure S1). eGFR levels in the TRF-budesonide 16 mg/day group were sustained throughout the trial (mean percent change from baseline at 12 months: -0·7 vs. -10·9% for placebo; p=0·0134). Another post-hoc analysis demonstrated that the magnitude of decline in eGFR was comparable in placebo-treated patients receiving RAS blockade therapy at the MRD (mean [SD] -4·9 mL [12·685]) vs. at the MTD (-4·4 mL [9·187]).

When assessed as a tertiary outcome in the final analysis, the proportion of patients with microhaematuria in the TRF-budesonide 16 mg/day group decreased from 87·5% (n=42 of 48) at baseline to 43·8% (n=21 of 48) at 9 months, and was statistically significant vs. placebo (74·0% [n=37 of 50] of placebo-treated at 9 months, 95% CI 0·072–0·675, OR 0·221, p=0·0041) but remained unchanged in the 8 mg/day- and placebo-treated groups.

There were no deaths and no patient progressed to ESRD. Fourteen patients (TRF-budesonide 16 mg/day, n=3; 8 mg/day, n=4; placebo, n=7) reported treatment-emergent adverse events associated with worsening of renal function and/or received high-dose systemic corticosteroid therapy.

Eleven patients reported 13 treatment-emergent serious adverse events (Table S7). Two were considered possibly related to TRF-budesonide by investigators blinded to trial medication: deep vein thrombosis (16 mg/day), and unexplained worsening of renal function, reported during follow-up after tapering from 16 mg/day to 8 mg/day. Two serious adverse events in

the placebo-treated group were considered possibly related to trial medication: both cases of increased proteinuria, one with a decline in renal function (see the Supplementary Appendix for details on adverse event reporting).

The total incidence of treatment-emergent adverse events was similar across treatment groups (Table 2). The most frequently reported adverse event, nasopharyngitis, was reported by similar percentages of patients in each group. There were no statistically significant changes from baseline in body weight, blood pressure, or glycated haemoglobin A1 (HbA_{1c}) values in either TRF-budesonide group vs. placebo at end of treatment (Table S8, post-hoc analysis). Two patients receiving TRF-budesonide, both with a body mass index of 36 kg/m^2 at baseline, exhibited increases in HbA_{1c} into the diabetic range (≥48 mmol/mol) at the end of treatment or during follow-up (Table S7 footnote for details). There were no other clinically relevant changes in clinical chemistry variables in any treatment group (see the adverse event reporting section of the Supplementary Appendix for the list of clinical chemistry variables investigated). The incidence of gastrointestinal-related adverse events was similar in TRF-budesonide-treated and placebo-treated patients (Table S9).

Solicited corticosteroid-related adverse events were more frequently reported by TRF-budesonide-treated patients (Table S10). Eighteen patients experienced adverse events that led to discontinuation of treatment (n=11 in the 16 mg/day group, n=5 in the 8 mg/day group, n=2 in the placebo group). The majority of patients who discontinued in the TRF-budesonide groups experienced corticosteroid-related adverse events (Table S11).

Discussion

We report the results of the NEFIGAN trial in which 9 months' treatment with TRF-budesonide resulted in a statistically significant reduction in UPCR vs. placebo in patients with primary IgAN. This primary outcome was met in a pre-specified interim analysis of data from the FAS population. The effect of TRF-budesonide was shown to be dose- and time-dependent. Upon completion of the 3-month follow-up, after cessation of trial medication, the mean percent reduction in UPCR was sustained in the TRF budesonide 8 mg/day group and continued to decrease in the 16 mg/day group. The reductions in UPCR were consistent with changes in 24-hour urine protein and albumin excretion and UACR, which were all sustained during the 3-month follow-up. This persistence of effect following cessation of treatment is suggestive of a disease-modifying effect.

Patients entering the treatment phase of this trial were at risk of progression to ESRD due to persistent proteinuria despite optimised RAS blockade (mean of 1·8 g/day and median of 1·2 g/day urine protein excretion). The further reduction in proteinuria was achieved by targeting an alternative pharmacological mechanism, and was attributable to TRF-budesonide, irrespective of baseline UPCR, eGFR, and time since diagnosis of IgAN (Figure S1d). Our findings support the generally accepted hypothesis that mucosal immune system dysfunction has a significant role in the pathogenesis of IgAN, as TRF-budesonide targets the region of the gastrointestinal tract where Peyer's patches reside at high density. There is a growing body of evidence and general acceptance that a reduction in proteinuria is associated with a reduced risk of ESRD in IgAN patients, and time-averaged (TA)-proteinuria is predictive of renal survival in IgAN patients: the rate of decline of renal function and subsequent risk of renal failure are associated with higher levels of TA-proteinuria.[5,20] A recent meta-analysis of IgAN trials by Inker et al.[25] used contemporary statistical methodology to assess the possible

surrogacy of the effect of treatment intervention (RAS blockade, fish oil, immunosuppression, and steroids) on proteinuria at 9 months to predict the effect of the intervention on ESRD clinical outcome. The analysis showed a statistically significant association, suggesting that an improvement in proteinuria at 9 months for drug compared to control would be positively associated with an improvement in longer term ESRD outcome. For patients in the 16mg/day TRF-budesonide group, proteinuria in the form of UPCR and 24-hour urine protein excretion both decreased by approximately 30%, compared to the placebo-treated group (Figure 2a, and Tables S5 and S6). This level of proteinuria reduction is comparable to that conferred by RAS blockade in IgAN patients,[25] and in other chronic kidney disease indications including diabetic nephropathy.[26] In a meta-analysis study by Lambers Heerspink et al.,[26] a statistically significant association was evident between proteinuria reduction and ESRD outcomes. Lambers Heerspink et al.[26] noted that for each 30% reduction in proteinuria by drugs that intervene in the RAS, the risk of ESRD decreased by 32% (95% CI -55–+2). Based on data presented by Inker et al. on IgAN, a treatment-induced decrease in proteinuria of 30% would result in a comparable reduction in the risk of ESRD.[25]

eGFR declined in the placebo-treated group but remained stable in the TRF-budesonide groups following 9 months' treatment, an effect that persisted throughout follow-up in the 16 mg/day group. Stabilisation of eGFR in IgAN patients is likely to predict a favourable outcome. It should be noted that all patients were on a MRD or MTD of and ACEI and/or ARB (as assessed by their investigator). Thus RAS blockade therapy remained optimised throughout the trial, with no dose changes during the treatment phase, except in a small number of individuals (dose of RAS blockade was increased for 5/150 patients and decreased for 6/150 patients), distributed across the 3 treatment groups (see Table S4). Despite the maintenance of rigorous RAS blockade, the rapid rate of loss of eGFR observed in the

placebo-treated group was greater than that seen in the recently reported STOP-IGAN study[11] but consistent with other studies of IgAN in patients receiving optimised RAS blockade, albeit with generally higher levels of baseline proteinuria.[24,27] A post-hoc analysis demonstrated that the eGFR reduction in the placebo-treated group was related to baseline proteinuria, indicating that the response of this group of patients is consistent with the expectation that higher levels of proteinuria are associated with greater loss of eGFR in IgAN (Figure S1b). As histological data are not available for the patients in all of these studies, it is difficult to speculate on the contribution of histopathological changes to the rate of eGFR decline. However, the deterioration in eGFR illustrates that this patient population is at risk of disease progression, current standard-of-care therapy is insufficient, and there is a need for further intervention in IgAN patients with persistent proteinuria.

High-dose systemic corticosteroids and other potent immunosuppressive treatments have been studied in a number of randomised controlled trials with varying results.[28] A consequence of these trials has been the necessity to test interventions with a background of optimised standard-of-care RAS blockade, as has been conducted in this trial. This has also been applied in the TESTING trial, a randomised controlled trial evaluating high-dose systemic corticosteroid therapy vs. placebo (recruitment was stopped early and randomised treatment discontinued due to safety concerns, interim results published)[29], and in the STOP-IgAN trial.[11] The STOP-IgAN trial assessed the potential benefit of systemic immunosuppression in addition to the intervention of dietary restrictions and polypharmacy upon optimised RAS blockade, and is the first study in IgAN to employ such comprehensive supportive care. No difference in the rate of decrease in eGFR was observed between groups over the 3-year period of the STOP-IgAN trial.[11] The slow annual loss of eGFR in the intensive supportive care group (1·6 mL/min/1·73 m^2) in the STOP-IgAN trial contrasts with the more rapid rate of loss of eGFR demonstrated in other studies, including ours, in which

we applied a 6-month run-in phase to optimise RAS blockade. In our study, 62% of patients received the MRD of ACE and/or ARB drugs (Table 1) and, on average, patients received 79% of the MRD. In the placebo-treated group, 68% of patients received the MRD of RAS blockade (Table 1). In comparison, in the STOP-IgAN trial, 76% of patients in the supportive care group were on a MRD of an ACEI or ARB. Whether this difference in RAS blockade is sufficient to account for the different rates of loss of renal function or whether other factors such as polypharmacy and the more rigorous application of dietary restrictions in the STOP-IgAN trial (including limited salt intake) played a greater role cannot be discerned from the available data. In the current trial, a post-hoc analysis demonstrated that eGFR was unlikely to be affected substantially by whether patients received the MRD or MTD of RAS blockade therapy, as the magnitude of decline in eGFR was comparable in placebo-treated patients at the MRD (mean [SD] -4·9 mL [12·685]) vs. at the MTD (-4·4 mL [9·187]).

TRF-budesonide 16 mg/day resulted in a statistically significant reduction in the presence of microhaematuria at 9 months vs. placebo. Although the prognostic significance of haematuria disappearance in IgAN has not been prospectively investigated, clinical and experimental studies suggest that haematuria is associated with glomerular and tubulointerstitial damage in IgAN and other glomerular diseases.[30,31]

In the present trial, TRF-budesonide appeared to be safe and generally well-tolerated, although there was a dose-dependent trend in the incidence of solicited corticosteroid-related adverse events and in discontinuations due to these events (see Tables S9 and S10). Budesonide, administered as a targeted-release oral dosage form, is subject to high first-pass metabolism, resulting in low systemic exposure (approximately 10% of administered dose).[18] Some degree of systemic exposure is reflected in reduced cortisol excretion (data not shown) and the aforementioned dose-dependent trend in the incidence of solicited

corticosteroid-related adverse events. However, several studies have reported higher incidences of diabetes mellitus or impaired glucose tolerance, hypertension, and weight gain in high-dose systemic corticosteroid-treated patients.[11,32] Furthermore, increased incidences of serious and fatal infections were documented with high-dose systemic corticosteroid therapy with or without additional immunotherapy in the STOP-IgAN trial (1 in 55 patients) and TESTING trial (12 in 236 patients, including 2 deaths).[11,29] In contrast, no serious infections were attributed to TRF-budesonide in the NEFIGAN trial and there were no statistically significant changes in blood pressure, HbA_{1c}, or body weight with TRF-budesonide vs. placebo. There was a trend for numerically higher systolic and diastolic blood pressure levels in the TRF-budesonide 16 mg group at the end of treatment compared to baseline values, but this was not statistically significant (Table S8). The NEFIGAN trial data indicate that TRF-budesonide may elicit fewer and less severe systemic effects and has a preferable tolerability profile than previously reported for high-dose systemic corticosteroid regimens, when used to treat IgAN patients at risk of progression to ESRD, many of whom are young adults.[11,32] However, this needs to be confirmed in larger studies than the current phase 2b trial.

Proteinuria is a major risk factor for renal failure in IgAN.[3,5] As addressed by Rauen et al.,[11] in the past, clinically significant proteinuria has been arbitrarily defined as an excretion level greater than 1 g/day (KDIGO guidelines).[7] However, evidence from epidemiology studies indicate that IgAN patients with proteinuria of 0·5 to 1 g/day are at increased risk of renal failure.[20,33] Thus, to evaluate TRF-budesonide in a clinically relevant high-risk IgAN population, a proteinuria threshold of either 0·75 g/day or 0·5 g/g UPCR (on a 24-hour collection) was selected. A threshold level of 0·75 g/day was similarly applied in the recently reported STOP-IgAN trial.

This trial is one of the largest randomised controlled trials conducted in IgAN in which RAS blockade was optimised prior to adjunct therapy. The primary objective of this trial was to assess the effect of TRF-budesonide on UPCR at 9 months, a proteinuria-based measure and surrogate endpoint for renal failure. While both a reduction in UPCR and stabilisation of eGFR were demonstrated, it will be necessary to quantify the magnitude of relative risk reduction associated with TRF-budesonide-treatment in IgAN patients at risk of progression to ESRD in a larger trial of longer duration. Another limitation of the present trial is that the patient population treated was almost exclusively Caucasian, thus the results also need to be confirmed in other populations. In addition, allowing entry of patients into the study regardless of time since biopsy meant that there was a lack of availability of recent histopathology data for all patients prior to randomisation. This prevented the implementation of a stratification strategy to discount imbalance of renal histology scores as a potential confounder. There are also no published pharmacokinetic data for TRF-budesonide in patients with IgAN. Patients with severe hepatic impairment were excluded from the study but it is unknown if IgAN patients may be subject to higher systemic exposure due to increased mucosal GI absorption. There is evidence of increased exposure of budesonide in chronic inflammatory bowel disease (range 11-21% vs. 9-12% in healthy volunteers) but that systemic exposure normalises after 8 weeks of treatment[34].

This trial demonstrated that 9 months' treatment with TRF-budesonide resulted in reduced proteinuria and stabilised eGFR in IgAN patients at risk of progression to ESRD. The observed effect was additive to optimised RAS blockade and supports the use of TRF-budesonide as adjunct therapy in IgAN patients with persistent proteinuria. TRF-budesonide has the potential to become the first disease-specific treatment for IgAN, with a risk-benefit profile supportive of its use early in the course of disease.

Research in context

Evidence before this trial

We searched PubMed up to April 26, 2016, for published papers about TRF-budesonide using the following search terms (with no language restrictions): "targeted-release", "budesonide", "TRF-budesonide", and "NEFECON". We identified one relevant paper. In 2011, Smerud and colleagues[19] reported an open-label, uncontrolled, exploratory phase 2a trial, in which 16 IgAN patients received TRF-budesonide. Treatment over 6 months resulted in a statistically significant reduction in proteinuria and was well tolerated.[19]

Added value of this trial

To date, the current phase 2b trial is the only randomised, double-blinded, placebo-controlled trial to investigate and demonstrate that TRF-budesonide, additional to optimised RAS blockade, reduced proteinuria and stabilised eGFR in IgAN patients at risk of progression to ESRD. At 9 months, mean UPCR had decreased by 24·4% in all TRF budesonide-treated patients combined vs. an increase of 2·7% in placebo-treated patients (combined TRF budesonide vs. placebo: p=0·0066). The effect was sustained throughout follow-up; mean UPCR decreased by 32·0% from baseline at 12 months for 16 mg/day vs. 0·5% for placebo. Changes in eGFR, 24-hour protein excretion, UACR, and 24-hour albumin excretion were consistent with the UPCR data. Over 9 months, eGFR was stable with TRF-budesonide but decreased 9·8% with placebo (combined TRF-budesonide vs. placebo: p=0·0010). These effects are indicative of a reduced risk of future progression to ESRD.

Implications of all the available evidence

TRF-budesonide has the potential to become the first IgAN-specific treatment targeting intestinal mucosal immunity upstream of disease manifestation, reducing the risk of progression to ESRD.

Contributors

Bengt C. Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, John Feehally, Jürgen Floege, Alan G. Jardine, Francesco Locatelli, Bart D. Maes, Alex Mercer, Manuel Praga, Søren S. Sørensen, and Vladimir Tesar designed the study. Bengt C. Fellström, Jonathan Barratt, Johan W. de Fijter, Jürgen Floege, Gerd Hetzel, Bart D. Maes, Fernanda Ortiz, Manuel Praga, Søren S. Sørensen, Vladimir Tesar and Lucia Del Vecchio were study investigators. Bengt C. Fellström was the principal investigator. All authors contributed to data interpretation, writing, manuscript review and approval of the final version.

Data collection was performed by Crown CRO Oy and Pharma Consulting Group AB. Statistical analysis was performed by Scandinavian Development Services AB. Kevin Carroll of KJC Statistics Ltd provided statistical input and medical writing. Heather Cook of PharmaLogic Consulting AB contributed to the study design, submissions for approval to concerned regulatory agencies, data interpretation and writing of the report. Ellen Robertshaw and Justin Cook of Niche Science and Technology Ltd and Michael Riley of Trilogy Writing and Consulting GmbH provided medical writing services, financed by the sponsor Pharmalink AB.

Declaration of interests

Bengt C. Fellström, Jonathan Barratt, Heather Cook, Rosanna Coppo, Francesco Locatelli, Johan de Fijter, Jürgen Floege, Bart Maes, Manuel Praga, and Vladimir Tesar had a consultancy agreement in place with Pharmalink AB and received payment for their services.

Bengt C. Fellström is also a shareholder (<1% of all shares) in Pharmalink AB. Alex Mercer is an employee of Pharmalink AB. All other authors have no major financial conflicts of interest to be disclosed.

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519 # References

520 1. Wyatt RJ and Julian BA. IgA nephropathy. *N Engl J Med*. 2013; **368**: 2402–2414

521 2. Manno C, Strippoli GF, D'Altri C, Torres D, Rossini M, Schena FP. A novel simpler
522 histological classification for renal survival in IgA nephropathy: a retrospective study.
523 *Am J Kidney Dis*. 2007; **49**: 763–775

524 3. Berthoux F, Mohey H, Afiani A. Natural history of primary IgA nephropathy. *Semin*
525 *Nephrol*. 2008; **28**: 4–9

526 4. Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year
527 analysis of 1,012 patients at a single center in Japan. *PLoS One.* 2014; **9**: e91756

528 5. Reich HN, Troyanov S, Scholey JW, Cattran DC; Toronto Glomerulonephritis
529 Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc*
530 *Nephrol*. 2007; **18**: 3177–3183

531 6. Zhang C, Zeng X, Li Z, Wang Z, Li S. Immunoglobulin A nephropathy: current
532 progress and future directions. *Transl Res*. 2015; **166**: 134–144

533 7. KDIGO Guidelines: Chapter 10: Immunoglobulin A nephropathy. *Kidney Int Suppl*.
534 2012; **2**: 209–217.

535 8. Lv J, Zhang H, Chen Y, et al. Combination therapy of prednisone and ACE inhibitor
536 versus ACE-inhibitor therapy alone in patients with IgA nephropathy: a randomized
537 controlled trial. *Am J Kidney Dis*. 2009; **53**: 26–32

538 9. Manno C, Torres DD, Rossini M, Pesce F, Schena FP. Randomized controlled clinical
539 trial of corticosteroids plus ACE-inhibitors with long-term follow-up in proteinuric
540 IgA nephropathy. *Nephrol Dial Transplant*. 2009; **24**: 3694–3701

541 10. Pozzi C, Andrulli S, Del Vecchio L, et al. Corticosteroid effectiveness in IgA
542 nephropathy: long-term results of a randomized, controlled trial. *J Am Soc Nephrol*.
543 2004; **15**: 157–163

544 11. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression
545 in IgA nephropathy. *N Engl J Med*. 2015; **373**: 2225–2236

546 12. Kiryluk K, Li Y, Scolari F, et al. Discovery of new risk loci for IgA nephropathy
547 implicates genes involved in immunity against intestinal pathogens. *Nat Genet*. 2014;
548 **46**: 1187–1196

549 13. Lai KN. Pathogenesis of IgA nephropathy. *Nat Rev Nephrol*. 2012; **8**: 275–283

550 14. Smith AC, Molyneux K, Feehally J, Barratt, J. O-glycosylation of serum IgA1
551 antibodies against mucosal and systemic antigens in IgA nephropathy. *J Am Soc*
552 *Nephrol*. 2006; **17**: 3520–3528

553 15. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. *J Am*
554 *Soc Nephrol*. 2011; **22**: 1795–1803

555 16. Tomana M, Novak J, Julian BA, Matousovic, K, Konecny, K, Mestecky, J.
556 Circulating immune complexes in IgA nephropathy consist of IgA1 with galactose-
557 deficient hinge region and antiglycan antibodies. *J Clin Invest*. 1999; **104**: 73–81

558 17. Yeo SC, Liew A, Barratt J. Emerging therapies in immunoglobulin A nephropathy.
559 *Nephrology (Carlton)*. 2015; **20**: 788–800

18. Edsbäcker S, Wollmer P, Nilsson Å, Nillson M. Pharmacokinetics and gastrointestinal transit of budesonide controlled ileal release (CIR) capsules. *Gastroenterology*. 1993; **104**: A695

19. Smerud HK, Bárány P, Lindström K, et al. New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol Dial Transplant*. 2011; **26**: 3237–3242

20. Le W, Liang S, Hu Y, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant*. 2012; **27**: 1479–1485

21. Watts P, and Smith A. TARGIT technology: coated starch capsules for site-specific drug delivery into the lower gastrointestinal tract. *Expert Opin Drug Deliv*. 2005; **2**: 159–167

22. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; **150**: 604–612

23. Praga M, Gutiérrez E, González E, Morales E, Hernández E. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol*. 2003; **14**: 1578–1583

24. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. *Kidney Int*. 2010; **77**: 543–549

25. Inker LA, Mondal H, Greene T, et al. Early change in urine protein as a surrogate end point in studies of IgA nephropathy: an individual-patient meta-analysis. *Am J Kidney Dis*. 2016 Mar 29. doi: 10.1053/j.ajkd.2016.02.042. [Epub ahead of print]

582 26. Lambers Heerspink HJ, Tighiouart H, Sang Y, et al. GFR decline and subsequent risk
583 of established kidney outcomes: a meta-analysis of 37 randomized controlled trials.
584 *Am J Kidney Dis*. 2014; **64**: 860–866

585 27. Woo KT, Chan CM, Tan HK, et al. Beneficial effects of high-dose losartan in IgA
586 nephritis. *Clin Nephrol.* 2009; **71**: 617–624

587 28. Floege J, Eitner F. Current therapy for IgA nephropathy. *J Am Soc Nephrol.* 2011; **22**:
588 1785–1794

589 29. Lv J, Zhang H, Perkovic V, on behalf of the TESTING Study Group. The Therapeutic
590 Evaluation of Steroids in IGA Nephropathy Global (TESTING) Study.
591 http://www.abstracts2view.com/era/view.php?nu=ERA16L1_3394. Accessed on 01
592 Sep 2016.

593 30. Vivante A, Calderon-Margalit R, Skorecki K. Hematuria and risk for end-stage
594 kidney disease. *Curr Opin Nephrol Hypertens*. 2013; **22**: 325–330

595 31. Moreno JA, Yuste C, Gutiérrez E, et al. Haematuria as a risk factor for chronic kidney
596 disease progression in glomerular diseases: A review. *Pediatr Nephrol*. 2016; **31**:
597 523–533

598 32. Lv J, Xu D, Perkovic V, et al. Corticosteroid therapy in IgA nephropathy. *J Am Soc*
599 *Nephrol*. 2012; **23**: 1108–1116

600 33. Nam KH, Kie JH, Lee MJ, et al. Optimal proteinuria target for renoprotection in
601 patients with IgA nephropathy. *PLoS One.* 2014; **9**: e101935.

602

603 34. Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules
604 for Crohn's disease. *Clin Pharmacokinet.* 2004; **43**:803–821.

Table 1: **Patient demographics and baseline characteristics* (full analysis set)**

Variable		Placebo (N=50)	TRF-budesonide 8 mg/day (N=51)	TRF-budesonide 16 mg/day (N=48)	Total (N=149)
Age (years)		38·9 (12·0)	40·6 (13·0)	37·5 (11.9)	39·0 (12·3)
Sex, n (%)	Male	35 (70·0)	37 (72·5)	33 (68·8)	105 (70·5)
BMI (kg/m^2)		27·5 (5·37)	26·5 (4·39)	27·8 (5·17)	27·3 (4·99)
Weight (kg)		85·2 (18·89)	80·9 (14·46)	86·7 (16·89)	84·2 (16·89)
Race, n (%)	Asian	1 (2·0)	0	1 (2·1)	2 (1·3)
	Caucasian	48 (96·0)	49 (96·1)	47 (97·9)	144 (96·6)
	Other	1 (2·0)	2 (3·9)	0	3 (2·0)
Ethnicity, n (%)	Hispanic/Latino	3 (6·0)	11 (21·6)	7 (14·6)	21 (14·1)
	Non-Hispanic/Non-Latino	47 (94·0)	40 (78·4)	41 (85·4)	128 (85·9)
Blood pressure (mmHg)	Systolic	128·1 (11·87)	127·7 (13·56)	126·7 (11·62)	127·5 (12·33)
	Diastolic	80·2 (10·13)	80·3 (9·66)	78·1 (9·59)	79·6 (9·78)
UPCR (g/g), median (IQR)		0·83 (0·52–1·59)	0·81 (0·56–1·16)	0·79 (0·54–1·31)	0·81 (0·54–1·27)
24-hour protein excretion (g), median (IQR)		1·23 (0·98–3·19)	1·14 (0·87–1·83)	1·32 (0·86–2·14)	1·2 (0·89–2·07)
UACR (g/g), median (IQR)		0·72 (0·42–1·32)	0·71 (0·46–1·04)	0·69 (0·43–1·16)	0·71 (0·44–1·12)
24-hour albumin excretion (g), median (IQR)		1·07 (0·81–2·24)	0·99 (0·68–1·58)	1·08 (0·75–1·84)	1·03 (0·76–1·81)
eGFR CKD-EPI (creatinine formula) (mL/min/1·73 m^2)		76·5 (23·2)	74·1 (25·8)	83·8 (25·9)	78·3 (25·1)
Patients with microhaematuria, n (%)		40 (80·0)	32 (62·7)	42 (87·5)	114 (76·5)
Time from diagnosis to start of treatment (days), median (IQR)		1101 (294–2870)	1972 (623–4188)	1218.5 (497·5–2573)	1499 (496–3162)
Patients who made lifestyle changes during the run-in phase, n (%)†		16 (32·0)	18 (35·3)	14 (29·2)	48 (32·2)
Patients previously treated with corticosteroids/immunosuppressants, n (%)		7 (14·0)	14 (27·5)	6 (12·5)	27 (18·1)
Patients on ACEI alone, n (%) [% on MRD]		21 (42·0) [28·0]	25 (49·0) [21·6]	26 (52·4) [29·2]	72 (48·3) [26·2]
Patients on ARB alone, n (%) [% on MRD]		16 (32·0) [20·0]	14 (27·5) [15·7]	14 (29·2) [18·8]	44 (29·5) [18·1]
Patients on ACEI and ARB, n (%) [% on MRD of one or both]		13 (26·0) [20·0]	12 (23·5) [21·6]	8 (16·7) [12·5]	33 (22·1) [18·1]
Patients on MRD of ACEI and/or ARB, n (%)		34 (68·0)	30 (58·8)	29 (60·4)	93 (62·4)

*Unless otherwise indicated, values are expressed as mean (standard deviation).
†Including salt intake, fluid intake, protein intake, fish oil intake, smoking, exercise.

ACEI=angiotensin-converting-enzyme inhibitor. ARB=angiotensin receptor blocker. BMI=body mass index. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration Equation. IQR=interquartile range. MRD=maximum recommended dose. UACR=urine albumin creatinine ratio. UPCR=urine protein creatinine ratio.

Table 2: **Treatment-emergent adverse events reported by ≥5% of all patients by preferred term (safety set)***

	Placebo (N=50)		TRF-budesonide 8 mg/day (N=51)		TRF-budesonide 16 mg/day (N=49)		Total (N=150)	
Preferred Term	**n (%)**	**e**	**n (%)**	**e**	**n (%)**	**e**	**n (%)**	**e**
Any AE	42 (84)	162	48 (94)	270	43 (88)	305	133 (88)	737
Nasopharyngitis	10 (20)	14	8 (16)	16	10 (20)	16	28 (19)	46
Acne‡	3 (6)	3	8 (16)	9	9 (18)	10	20 (13)	22
Joint swelling	2 (4)	2	8 (16)	8	9 (18)	14	19 (13)	24
Cushingoid‡	3 (6)	3	5 (10)	5	8 (16)	8	16 (11)	16
Insomnia‡	2 (4)	2	6 (12)	6	8 (16)	9	16 (11)	17
Diarrhoea	7 (14)	9	1 (2)	1	5 (10)	5	13 (9)	15
Dyspepsia†	4 (8)	5	2 (4)	2	7 (14)	9	13 (9)	16
Headache	3 (6)	4	3 (6)	3	6 (12)	6	12 (8)	13
Alopecia‡	2 (4)	2	4 (8)	5	4 (8)	4	10 (7)	11
Back pain	1 (2)	1	6 (12)	8	3 (6)	3	10 (7)	12
Mood swings‡	2 (4)	2	3 (6)	3	5 (10)	5	10 (7)	10
Oedema peripheral	2 (4)	3	2 (4)	3	6 (12)	9	10 (7)	15
Blood creatine phosphokinase increased	3 (6)	3	3 (6)	4	3 (6)	3	9 (6)	10
Hirsutism‡	1 (2)	1	3 (6)	3	5 (10)	5	9 (6)	9
Hypertension	1 (2)	1	3 (6)	3	5 (10)	5	9 (6)	9
Muscle spasms	2 (4)	3	5 (10)	5	2 (4)	2	9 (6)	10
Abdominal pain†	1 (2)	1	4 (8)	4	3 (6)	4	8 (5)	9
Nausea	1 (2)	1	4 (8)	4	3 (6)	5	8 (5)	10
Upper respiratory tract infection	3 (6)	3	2 (4)	3	3 (6)	3	8 (5)	9

*Table displays adverse events reported by ≥5% of the total patient population.
†Gastrointestinal-related adverse events solicited by questionnaire at every visit.
‡Corticosteroid-related adverse events solicited by questionnaire at every visit.
AE=adverse event. n=number of patients. e=number of events.

Figure 1: **Patient CONSORT diagram**

Flow diagram of all patients screened, enrolled, and randomised with reasons for withdrawal. *FAS corresponds to the modified intention-to-treat analysis set.

ACEI=angiotensin-converting enzyme inhibitors. AE=adverse event. ARBs=angiotensin receptor blockers. CTP=clinical trial protocol. FAS=full analysis set. SAE=serious adverse event.

Figure 2: **Change in UPCR from baseline**

Panel A shows the percent change in UPCR from baseline in patients after receiving placebo or TRF-budesonide (16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day) for 9 months at the interim analysis (primary outcome). The comparisons of TRF-budesonide 16 mg/day and 8 mg/day combined and 16 mg/day with placebo were statistically significant, but not 8 mg/day vs. placebo (p=0·0290). Panel B shows the absolute mean change in UPCR from baseline in patients receiving TRF-budesonide 16 mg/day, 8 mg/day, or placebo over the 9-month treatment phase (solid line) and 3-month follow-up phase (dashed line). UPCR=urine protein creatinine ratio. Data are expressed as mean±standard error of the mean. In both panels, the changes in UPCR are based on data from all 149 patients in the FAS.

Figure 3: **Change in eGFR from baseline**

Panel A shows the percent change in eGFR CKD-EPI from baseline in patients after receiving placebo or TRF-budesonide (16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day) for 9 months. The comparisons of TRF-budesonide 16 mg/day and 8 mg/day combined, 16 mg/day, and 8 mg/day with placebo were statistically significant. Panel B shows the absolute mean change in eGFR CKD-EPI from baseline in patients receiving TRF-budesonide 16 mg/day, 8 mg/day or placebo over the 9-month treatment phase (solid line) and 3-month follow-up phase (dashed line). CKD-EPI=Chronic Kidney Disease

Epidemiology Collaboration Equation. eGFR=estimated glomerular filtration rate. Data are expressed as mean±standard error of the mean. In both panels, the changes in UPCR are based on data from all 149 patients in the FAS.

Figure 1

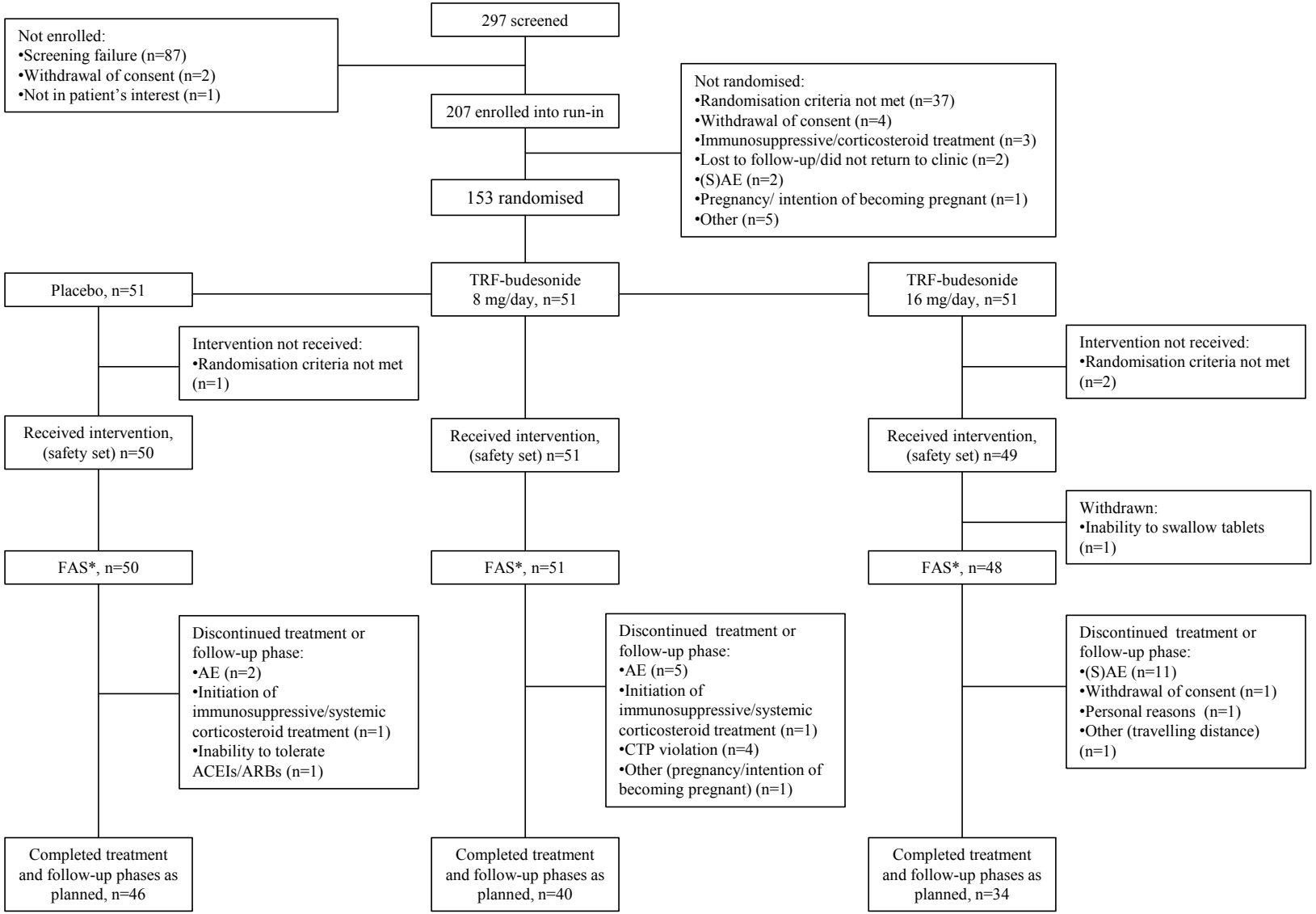
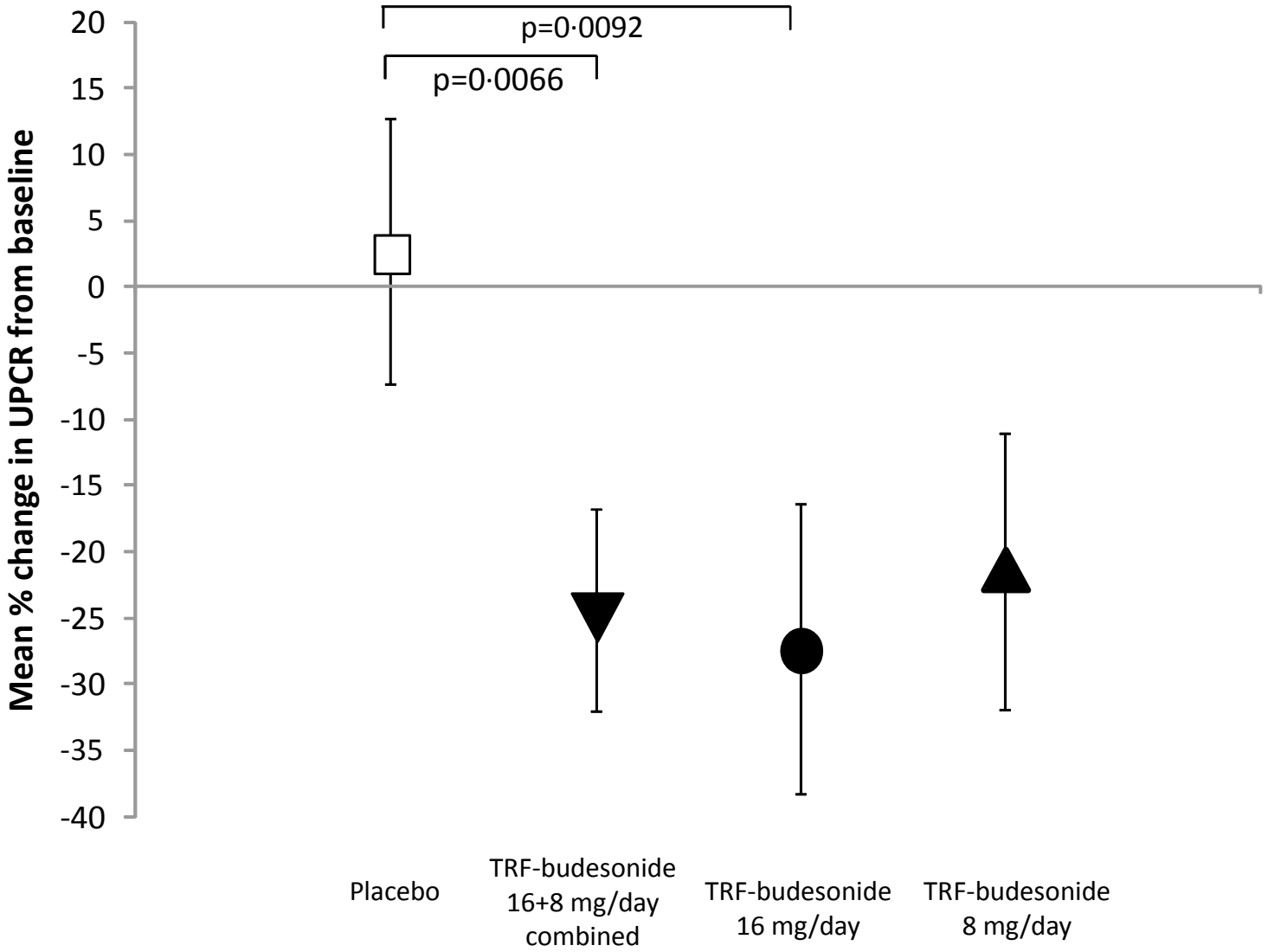

297 screened
Not enrolled:
•Screening failure (n=87)
•Withdrawal of consent (n=2)
•Not in patient's interest (n=1)
207 enrolled into run-in
Not randomised:
•Randomisation criteria not met (n=37)
•Withdrawal of consent (n=4)
•Immunosuppressive/corticosteroid treatment (n=3)
•Lost to follow-up/did not return to clinic (n=2)
•(S)AE (n=2)
•Pregnancy/ intention of becoming pregnant (n=1)
•Other (n=5)
153 randomised
Placebo, n=51
TRF-budesonide 8 mg/day, n=51
TRF-budesonide 16 mg/day, n=51
Intervention not received:
•Randomisation criteria not met (n=1)
Intervention not received:
•Randomisation criteria not met (n=2)
Received intervention, (safety set) n=50
Received intervention, (safety set) n=51
Received intervention, (safety set) n=49
Withdrawn:
•Inability to swallow tablets (n=1)
FAS*, n=50
FAS*, n=51
FAS*, n=48
Discontinued treatment or follow-up phase:
•AE (n=2)
•Initiation of immunosuppressive/systemic corticosteroid treatment (n=1)
•Inability to tolerate ACEIs/ARBs (n=1)
Discontinued treatment or follow-up phase:
•AE (n=5)
•Initiation of immunosuppressive/systemic corticosteroid treatment (n=1)
•CTP violation (n=4)
•Other (pregnancy/intention of becoming pregnant) (n=1)
Discontinued treatment or follow-up phase:
•(S)AE (n=11)
•Withdrawal of consent (n=1)
•Personal reasons (n=1)
•Other (travelling distance) (n=1)
Completed treatment and follow-up phases as planned, n=46
Completed treatment and follow-up phases as planned, n=40
Completed treatment and follow-up phases as planned, n=34

Figure 2

A


p=0·0092
p=0·0066
Mean % change in UPCR from baseline
20
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
Placebo
TRF-budesonide 16+8 mg/day combined
TRF-budesonide 16 mg/day
TRF-budesonide 8 mg/day

B

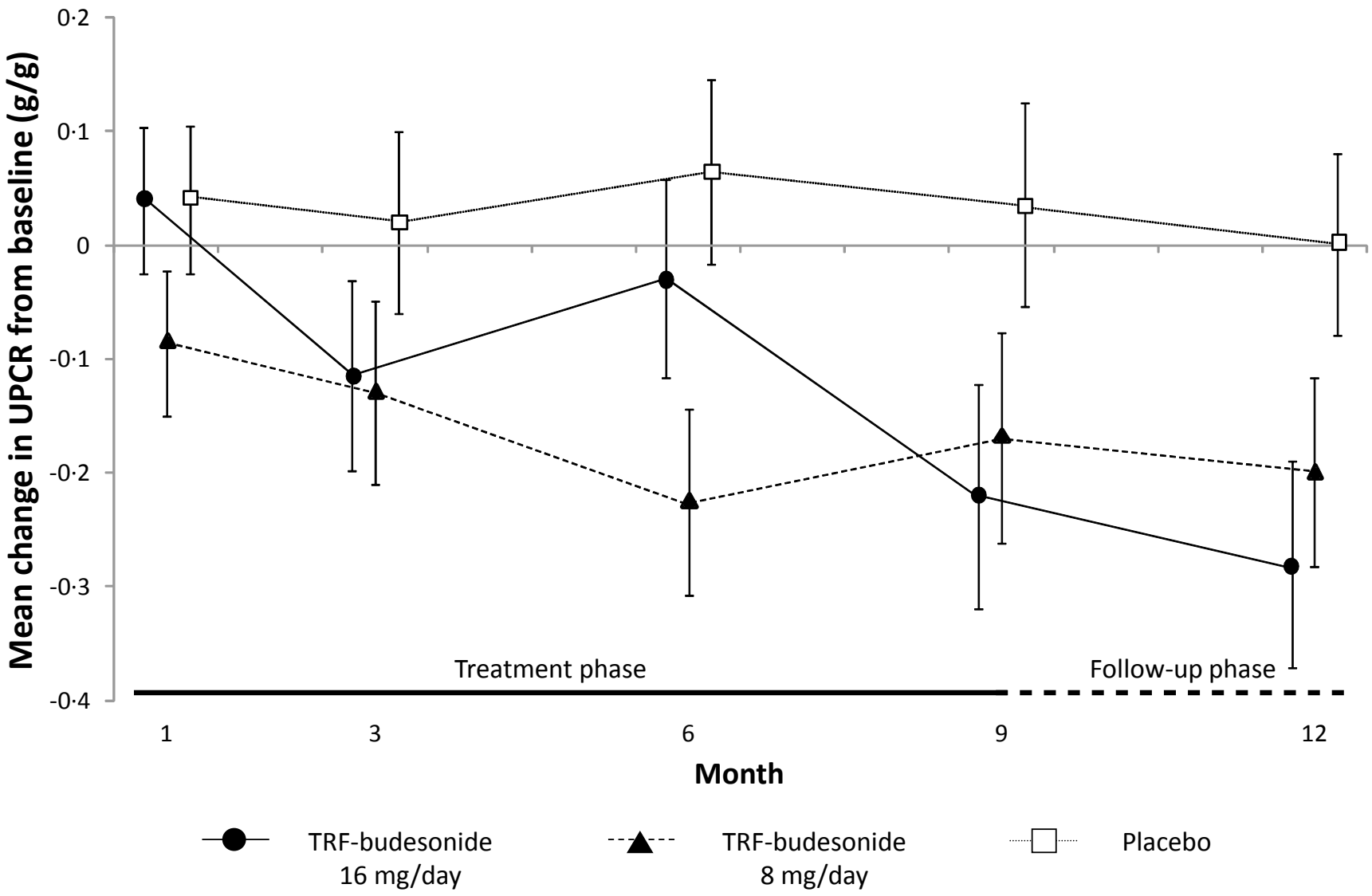
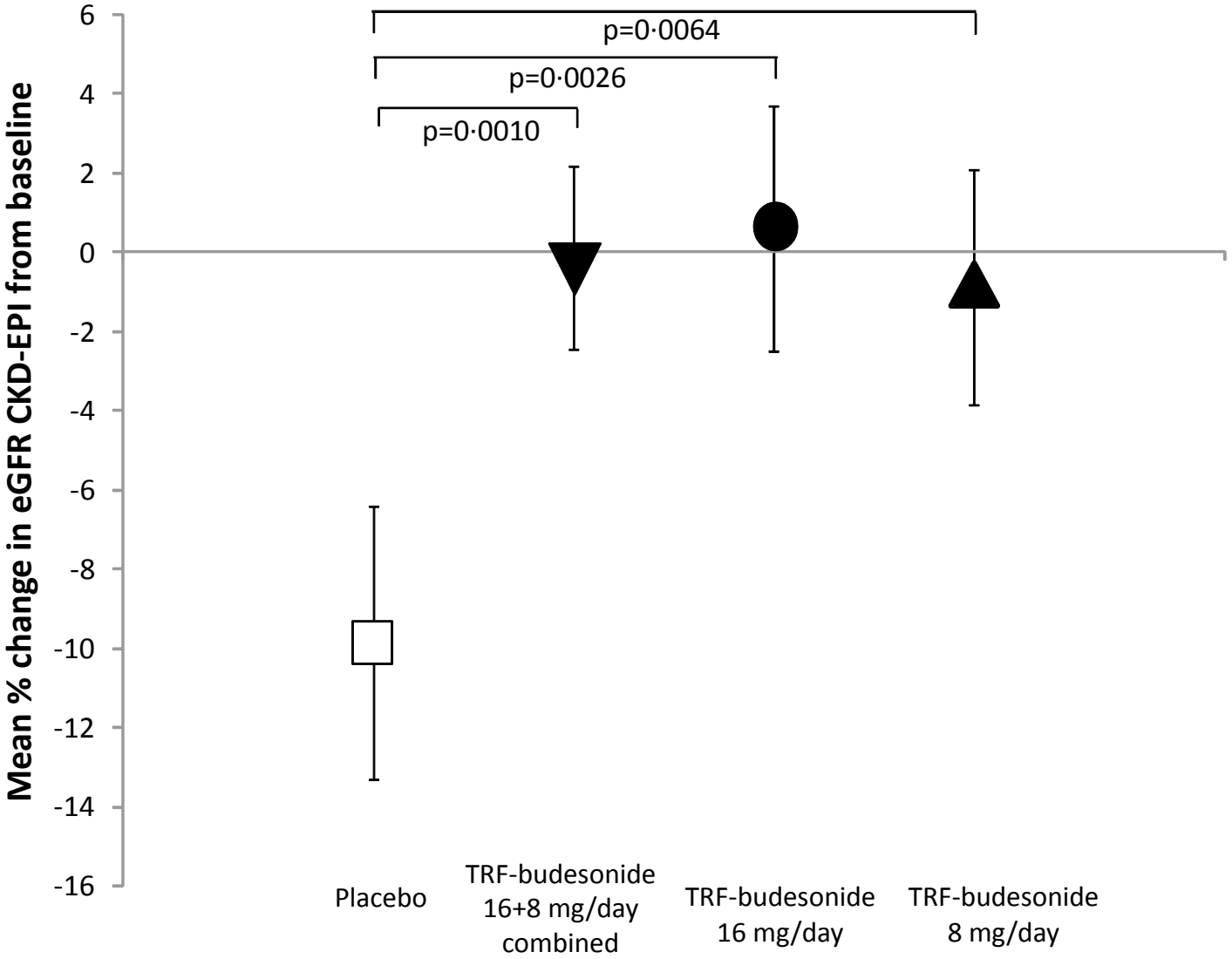
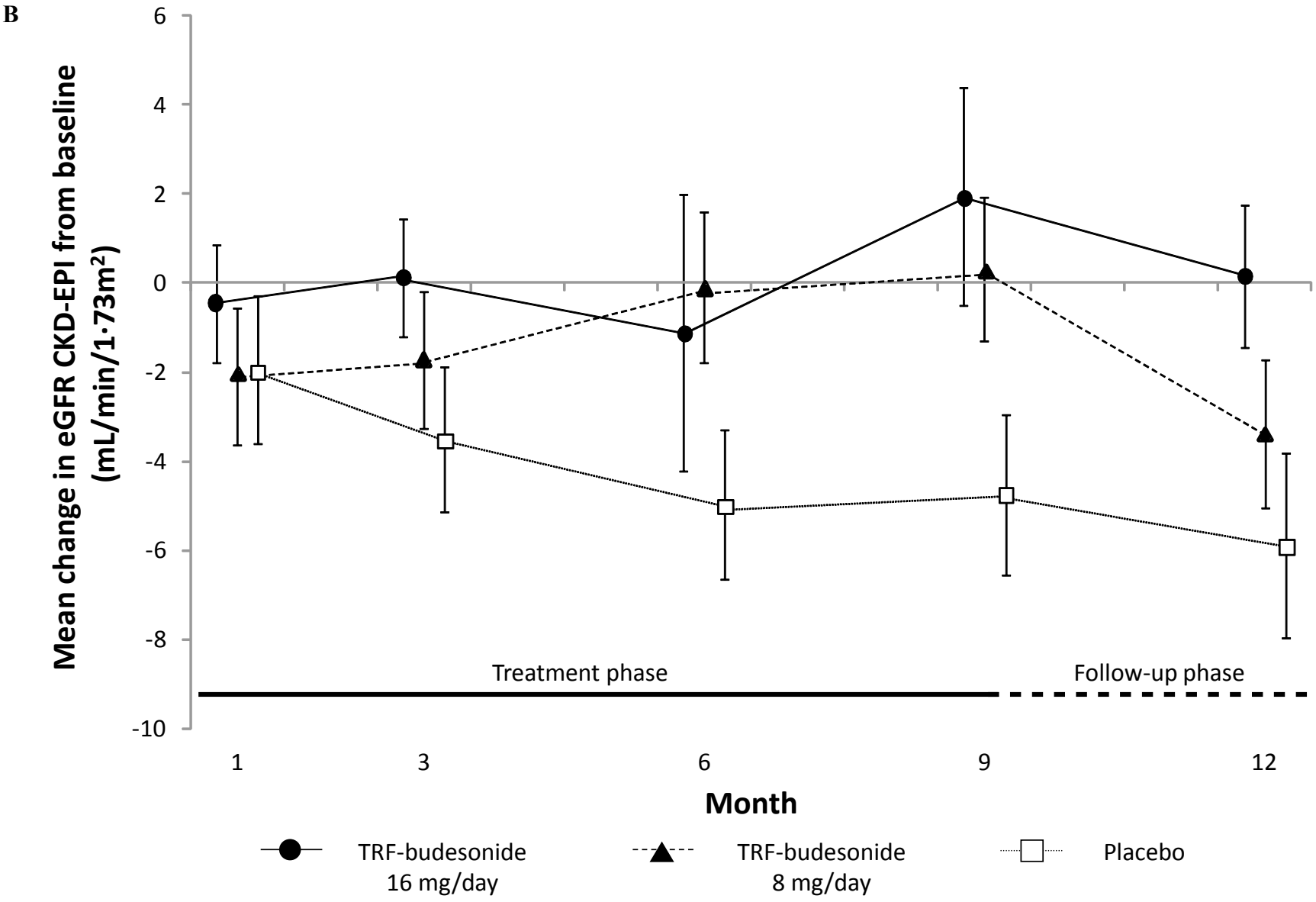

0·2
0·1
0
-0·1
-0·2
-0·3
-0·4
Mean change in UPCR from baseline (g/g)
Treatment phase
Follow-up phase
1
3
6
9
12
Month
TRF-budesonide 16 mg/day
TRF-budesonide 8 mg/day
Placebo

Figure 3

A


p=0·0064
p=0·0026
p=0·0010
Mean % change in eGFR CKD-EPI from baseline
6
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
Placebo
TRF-budesonide 16+8 mg/day combined
TRF-budesonide 16 mg/day
TRF-budesonide 8 mg/day

B


Mean change in eGFR CKD-EPI from baseline (mL/min/1·73m²)
6
4
2
0
-2
-4
-6
-8
-10
Treatment phase
Follow-up phase
1
3
6
9
12
Month
TRF-budesonide 16 mg/day
TRF-budesonide 8 mg/day
Placebo