Letter to the Editor

We thank Dr Gough for his comments regarding our manuscript entitled “Achieving Glycaemic Control with Concentrated Insulin in Patients with Type 2 Diabetes.” We have addressed each comment separately below.

1. We accept that although degludec U200 and glargine U300 can be described as highly concentrated basal insulins, degludec U100 cannot be described as such. This inaccuracy has now been corrected in the manuscript.

2. We agree that ““the stabilising action of low concentrations of phenol and increased albumin binding resulting in the formation of hexamers following subcutaneous injection” does not clearly indicate the process of multihexameric formation following injection which occurs as phenol diffuses away and also agree that albumin plays a relatively small role. However, we do not entirely agree that the pharmacokinetics of degludec have been misrepresented with regard to amino acid changes as they are clearly stated in the article entitled “Design of the Novel Protraction Mechanism of Insulin Degludec, an Ultra-long-Acting Basal Insulin“ (Jonassen et al, Pharm Res 2012;29(8):2104-2014) and quoted as follows:- “In conclusion, it is possible to engineer insulin analogues that can self-associate into a multihexameric state after injection. This was accomplished by attaching a C16 or C18 dicarboxylic acid via a γ-glutamic acid spacer to the ε-amino group of the B29 lysine residue of desB30 human insulin. As shown herein, this capability is critically dependent on the specific composition of the fatty acid and spacer complex, and therefore shared by few insulin analogues. The resultant PD profile of this mechanism is highly promising from the perspective of developing an improved basal insulin fulfilling the criteria of more than 24-hour duration of action with little variability over the day and from day-to-day, and providing an option for co-formulation with rapid-acting insulin.” In the article on “Impact of the mode of protraction of basal insulin therapies on their pharmacokinetic and pharmacodynamic properties and resulting clinical outcomes” (Heise and Mathieu, Diab Obes Metab 2017;19(1):3-12), insulin degludec is described as “an analogue in which threonine has been removed at B30, and B29 has been acetylated with a 16-carbon fatty diacid via a glutamic acid spacer” representing amino acid changes.

3. With regard to the statement regarding increased window of administration of 4-6 hours, a number of studies demonstrate that a 4-6 hour window of administration is acceptable for both degludec and glargine U300. A Japanese study of patients with type 2 diabetes showed that taking insulin degludec 2 hours before and after the usual time was equally safe and effective as taking degludec at a fixed time every day (Kadowaki et al, Efficacy and safety of once-daily insulin degludec dosed flexibly at convenient times vs fixed dosing at the same time each day in a Japanese cohort with type 2 diabetes: A randomized, 26-week, treat-to-target trial, J Diabetes Investig. 2016 Sep;7(5):711-7). Similarly, the EDITION 1 and 2 studies for glargine U300 (Riddle et al Efficacy and Safety of Flexible Versus Fixed Dosing Intervals of Insulin Glargine 300 U/mL in People with Type 2 Diabetes, Diabetes Technol Ther. 2016 Apr;18(4):252-7) showed that dose administration 3 hours before and after usual time has no effect on glycaemic efficacy or safety.

4. The advice regarding insulin degludec initiation in patients already on insulin therapy was taken from the US version of the SmPC (2015, updated Nov 2018, https://www.novo-pi.com/tresiba.pdf) which states that in adults with type 1 or type 2 diabetes who are already on insulin therapy "Start TRESIBA® at the same unit dose as the total daily long or intermediate-acting insulin unit dose." We accept that the SmPC (EU) (last revised July 2018) https://www.ema.europa.eu/en/documents/product-information/tresiba-epar-product-information_en.pdf states that a 20% reduction is recommended when transferring patients with type 2 diabetes on twice daily insulin or insulin glargine U300 or with type 1 diabetes for basal insulin or the basal component of a continuous subcutaneous insulin infusion. The reason for the discrepancy between the two SmPCs is not clear.

5. This is a pragmatic review and therefore pricing was discussed as it is an important factor when considering prescribing especially in poorer health economies. We accept that pricing is dynamic and subject to review.

6. Systematic reviews and meta-analyses were discussed in section 5.5 and are the highest level of evidence when comparing studies. However we accept that differences in study design and conduct and participant characteristics can make comparison between studies challenging.

Yours sincerely

Sudesna Chatterjee

Kamlesh Khunti

Melanie Davies CBE