Response to Swinnen et al.

Dear Editor:

Interpretation of data from the comparison of two insulins in a clinical trial setting is challenging when the insulins are studied in different dosing regimens and their titration is performed using different algorithms. In a recent article, Swinnen et al.¹ attempt to justify their design of L2T3, namely, the comparison of twice-daily detemir to once-daily glargine. However, differences in dosing regimens and the complexity of titration algorithms have the potential to impact all aspects of the results, including efficacy, safety, and patient-reported outcomes. Caution should be exercised when designing such a study, and even more caution should be exercised when interpreting the results.

Swinnen et al. acknowledge that the benefits of insulin glargine and insulin detemir compared to those of neutral protamine Hagedorn (NPH) insulin had been established at the time the L2T3 study was designed.^{2–4} However, the authors questioned the efficacy of detemir in a once-daily regimen based on the results of one regulatory submission study⁵ and one other study, by Hermansen et al.,² that evaluated detemir and NPH in twice-daily dosing regimens. While the regulatory submission study did demonstrate a greater decrease in hemoglobin A1c (HbA1c) with NPH and a similar decrease in fasting plasma glucose, less weight gain, and a lower risk of minor and nocturnal hypoglycemia with detemir, Hermansen et al.² showed similar efficacy and confirmed less weight gain and a lower risk of overall and nocturnal hypoglycemia with detemir. It is important to consider several other published studies supporting the once-daily use of detemir, including pharmacokinetic/pharmacodynamic studies^{6,7} and randomized clinical trials in type 1 and type 2 diabetes.^{8–10} The labeling for detemir allowed for once- or twice-daily dosing at the time of the design of the study. It is regrettable that Swinnen et al. did not include a third arm in order to compare insulin glargine (once daily) to insulin detemir (once and twice daily).

Swinnen et al. further reference a study of once-daily detemir versus once-daily NPH by Philis-Tsimikas et al.¹¹ and, despite the similar efficacy observed in this study, raise doubts as to “whether such a strategy will help as many people achieve good control as NPH or glargine once daily.” They highlight final HbA1c values of 7.4% for both detemir and NPH as a concern. In fact, the overall changes in HbA1c from beginning to end of the study and the insulin doses used at the end of the study were similar to those observed in Riddle et al.,³ and Philis-Tsimikas et al.¹¹ used a less aggressive insulin titration schedule. It is important to note that four separate studies with insulin glargine demonstrated comparable end points, with final HbA1c values above 7%.^{12–15}

Swinnen et al. also reference studies in which patients using detemir “required” a second daily injection^{16,17} but do not explain the study designs in these investigations. Rosenstock et al.¹⁶ required only patients using detemir—not those using glargine, because of labeling restrictions—to add a second daily dose if prespecified, pre-dinner titration targets were not achieved. In fact, a post hoc evaluation of this study indicated that a similar percentage of glargine patients would have required twice-daily dosing if the same titration schedule was applied to those patients using glargine.¹⁸ However, it cannot be known if patients injecting insulin glargine twice daily would have experienced the same effect on blood glucose as those patients injecting insulin detemir twice daily. A subanalysis of the 45% of patients who remained on once-daily insulin detemir in this study demonstrated equivalent efficacy, safety, and dosing between detemir and glargine and spurred the design of future trials that have studied detemir exclusively in a once-daily regimen in patients with type 2 diabetes taking oral antidiabetes drugs.^{11,19}

While Swinnen et al. attempt to justify the rationale behind the twice-daily dosing regimen for detemir in L2T3, a discussion of what has been learned since the design of the study was not provided. Specifically, the authors make no mention of the numerous studies supporting the once-daily use of detemir, including randomized controlled trials and large observational studies^{11,16,19–24} and clamp and continuous glucose monitoring studies demonstrating comparable time-action profiles between detemir and glargine.^{25,26} In fact, according to the 2009 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, “detemir can be used with 1 injection per day in patients with type 2 diabetes; excellent reproducibility of absorption profile within individuals; possibly less weight gain than with other insulins.”²⁷ Current labeling for detemir in the countries participating in L2T3, including Europe, Canada, and Australia,^{28–30} recommends the use of detemir once daily in combination with oral antidiabetes drugs for the treatment of type 2 diabetes. While an exhaustive discussion of more recent data cannot be expected, some reference to current literature should have been provided, as it is important to acknowledge what has been learned since the design of L2T3 in order to place its design and anticipated results into perspective.

Finally, although it has previously been demonstrated in patients with type 1 diabetes prior to the design of L2T3,³¹ Swinnen et al. also fail to acknowledge the now well-established concept that twice-daily dosing regimens of any basal insulin elevate the dose compared to once-daily regimens, with limited additional impact on glycemic control.^{16,32} The addition of a second basal dose also is likely to adversely

impact hypoglycemia rates, weight gain, the prevalence of injection site reactions, and overall quality of life, including treatment satisfaction.³¹ This learning is important to share when discussing the design of L2T3 to ensure the results are discussed in proper perspective.

In summary, only one study has evaluated insulin detemir and insulin glargine in a head-to-head comparison as an add-on to oral therapy in type 2 diabetes.¹⁶ The L2T3 study will contribute to the literature concerning the treatment of type 2 diabetes with basal insulin; however, any differences between insulin detemir and insulin glargine would have been more clearly identified had the analogs been studied in identical dosing regimens. It is reasonable to assume that any observed differences in outcomes between the two analogs in the L2T3 study may be a result of the different dosing regimens, especially with respect to dosage, hypoglycemia, and patient-reported outcomes, as well as the inherent differences between the analogs. The results from the L2T3 study, together with those from an ongoing study comparing insulin detemir and insulin glargine in identical, once-daily dosing regimens (the Effect of Insulin Determir and Insulin Glargine on Blood Glucose Control in Subjects with Type 2 Diabetes [EFFICACY™] trial [identified as NCT00909480 at <http://www.clinicaltrials.gov>]), will provide valuable information about the use of these analogs in the treatment of type 2 diabetes and will benefit the diabetes community.

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Author Disclosure Statement

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