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Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study

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Abstract

Aims: To assess the efficacy, insulin dose, safety and immunogenicity when people with type 1 diabetes mellitus switched between MYL-1501D and reference insulin glargine (Lantus®; Sanofi-Aventis US LLC, Bridgewater, New Jersey).

Materials and methods: Eligible participants from INSTRIDE 1 who completed 52 weeks of reference insulin glargine treatment were randomized 1:1 to the reference sequence (n = 63; reference insulin glargine for 36 weeks) or to the treatment-switching sequence (n = 64; MYL-1501D [weeks 0–12], reference insulin glargine [weeks 12–24] and MYL-1501D [weeks 24–36]). Change in glycated haemoglobin (HbA1c) from baseline to week 36 was the primary efficacy endpoint used to demonstrate equivalence between the two treatment sequences. Secondary endpoints included: change in fasting plasma glucose (FPG), self-monitored blood glucose (SMBG) and insulin dose; immunogenicity; and adverse events, including hypoglycaemia.

Results: Mean changes in HbA1c (least squares [LS] mean [SE]) from baseline to week 36 were −0.05 (0.032) and −0.06 (0.034) for the treatment-switching and reference sequences, respectively (LS mean difference 0.01 [95% CI −0.085 to 0.101]). Treatment sequences were comparable in terms of secondary endpoints, including FPG, SMBG and insulin dose, and the safety and immunogenicity profiles of the two sequences were similar.

Conclusions: Switching participants between MYL-1501D and reference insulin glargine demonstrated equivalent efficacy and similar safety and immunogenicity, showing that people taking reference insulin glargine can safely switch to MYL-1501D.

KEYWORDS

insulin glargine, biosimilar, switch, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic condition in which autoimmune destruction of pancreatic β cells leads to insulin deficiency and hyperglycaemia.[1] The major goal of T1DM management is to achieve control of glycaemic variables, including glycated haemoglobin (HbA1c) and self-monitored blood glucose (SMBG).[2] Glycaemic control helps reduce microvascular complications such as retinopathy,

nephropathy and neuropathy, and may reduce the risk of cardiovascular disease.[3,4] Insulin is the primary therapy for individuals with T1DM, and most receive multiple daily insulin injections (basal-bolus regimens) or continuous insulin infusion.[2] Insulin glargine (Lantus®; Sanofi-Aventis US LLC, Bridgewater, New Jersey), a long-acting human insulin analogue, allows once-daily basal use in people with T1DM.[5]

Biologics such as insulin analogues are costly, limiting global access.[6,7] Biosimilars, also known as follow-on biologics (FOBs) in the United States, are associated with cost savings and may help improve access to treatment.[8] Both the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have provided guidelines for the development of biosimilars and FOBs, indicating that a biosimilar should be highly similar to the biologic reference product, with no clinically meaningful differences between the biosimilar and reference product in terms of safety, purity and potency.[9,10] Non-inferiority to a licensed reference product is necessary for obtaining EMA[9] or FDA[10] approval as a biosimilar or FOB insulin or insulin analogue.

MYL-1501D, which has an amino acid sequence identical to that of reference insulin glargine,[11] has recently been approved by the EMA[12] as a biosimilar and is being developed as an FOB to insulin glargine in the United States. Determination of biosimilarity was based in part on the results of two phase 3 studies, INSTRIDE 1 and INSTRIDE 2, which demonstrated similar safety and efficacy of MYL-1501D and reference insulin glargine in patients with T1DM and type 2 diabetes mellitus, respectively (ClinicalTrials.gov identifiers: NCT02227862 and NCT02227875, respectively).[13,14] The primary objective of the INSTRIDE 3 study was to assess whether patients with T1DM can switch between MYL-1501D and reference insulin glargine through testing equivalence after 36 weeks between two treatment sequences (ie, patients who remain on reference insulin glargine vs. those who switch between MYL-1501D and reference insulin glargine).

2 | MATERIALS AND METHODS

2.1 | Study design

This was a multicentre, open-label, randomized, parallel-group, phase 3 study comparing the efficacy and safety of MYL-1501D with those of US-sourced reference insulin glargine (Lantus) in patients with T1DM (ClinicalTrials.gov identifier: NCT02666430). Individuals who successfully completed 52 weeks of reference insulin glargine treatment in the INSTRIDE 1 study (NCT02227862)[13] and provided written informed consent were eligible. Individuals were excluded if they had a history of clinically significant infections, had moderate insulin resistance (requiring basal plus prandial insulin of ≥1.5 U/kg/d), or planned to receive elective surgery requiring hospitalization or another investigational drug during the study period.

Participants were randomized in a 1:1 ratio to one of two treatment sequences. The reference insulin glargine sequence group continued reference insulin glargine for 36 weeks. The MYL-1501D (treatment-switching) sequence group received MYL-1501D for weeks 0 to 12, reference insulin glargine for weeks 12 to 24, and MYL-1501D for weeks 24 to 36 (Figure S1). After week 36, all participants resumed their baseline treatment and had a safety follow-up visit at week 40. Both treatments were administered as subcutaneous injections via prefilled disposable pens, with initial study doses of MYL-1501D and reference insulin glargine administered at a dose adapted to the actual blood glucose levels of the participants. Participants also received disposable pens for subcutaneous injection of insulin lispro (Humalog®; Eli Lilly and Company, Indianapolis, Indiana) at mealtimes. During the study, including across treatment periods, titration of both MYL-1501D and reference insulin glargine was minimized but allowed for safety concerns (ie, if required, doses were titrated to ensure good diabetes control). Use of other antidiabetic medications was prohibited during the study period.

The primary endpoint used to demonstrate equivalence between the two treatment sequences was change in HbA1c from baseline to week 36. Secondary endpoints included change from baseline in fasting plasma glucose (FPG), eight-point self-monitored blood glucose (SMBG) profile and insulin dose per unit body weight, and immunogenicity at week 36, in addition to occurrence of hypoglycaemic events (30-day rate), nocturnal hypoglycaemic events, and adverse events (AEs). Two conventional radioimmunoprecipitation assays were used for the assessment of antidrug antibodies—one that detects antidrug antibodies against MYL-1501D and one that detects antidrug antibodies against reference insulin glargine—and the proportion of participants with a treatment-emergent antibody response (TEAR) was determined. TEAR measured whether a participant's antidrug antibody status changed during the study, identifying a relative increase in binding higher than that expected from analytical and biological variability alone. For participants without detectable antibodies at baseline, TEAR was defined as a change to a detected insulin antibody binding level of at least 1.00% or 1.15% post-baseline for the reference insulin glargine and MYL-1501D assays, respectively; for participants with detectable antibodies at baseline, TEAR was defined as a ≥ 30% relative increase in insulin antibody binding from baseline for both assays.

Hypoglycaemic events were defined as SMBG ≤3.9 mmol/L (70 mg/dL), and nocturnal hypoglycaemia was defined as hypoglycaemia that occurred from the time the participant went to bed at night until he or she woke up. Hypoglycaemic events included severe hypoglycaemia, documented symptomatic hypoglycaemia, asymptomatic hypoglycaemia, probable symptomatic hypoglycaemia, relative hypoglycaemia, and nocturnal hypoglycaemia. Severe hypoglycaemia was defined as hypoglycaemic events that required assistance to actively administer carbohydrate, glucagon or other resuscitative actions resulting in neurological recovery, regardless of availability of a blood glucose measurement. Participants recorded all hypoglycaemic events from week 0 until the end-of-treatment visit. Hypoglycaemic event rate per participant per 30 days calculated between two visits was defined as the total number of episodes between two visits divided by the number of days between the visits, multiplied by 30 days.

The study was conducted in accordance with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Council for Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and with applicable local regulatory requirements and laws. The protocol was reviewed and approved by independent ethics committees/institutional review boards in accordance with local legal regulations. All participants provided written informed consent before study enrolment.

2.2 | Statistical analysis

The primary endpoint analysis was performed using the modified intention-to-treat population (mITT; all randomized participants who had at least one baseline and one post-baseline HbA1c value between weeks 24 and 36). Analysis of covariance was used to produce a 95% confidence interval (CI) for the difference between the two treatment sequence groups for the mean change from baseline in HbA1c. Equivalence of MYL-1501D to reference insulin glargine was established if the 95% CIs were within ±0.4% equivalence limits. Secondary endpoint analyses were performed using the intention-to-treat population, which included all randomized participants who had a baseline visit and at least one post-baseline visit. Treatment sequence group comparisons for secondary efficacy analysis were performed using a mixed-effects model approach. Safety analyses included participants who were randomized and took at least one dose of study drug. The hypoglycaemic event rate was analysed using a similar mixed-effects model method for treatment comparisons. For categorical data, treatment comparisons were performed using Fisher's exact or the chi-squared test.

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

Overall, 127 participants were randomized: 64 to the MYL-1501D treatment sequence group and 63 to the reference insulin glargine treatment sequence group. A total of 119 participants (93.7%) completed the study. The discontinuation rate for the total study population was 6.3% (8/127), with similar rates in the MYL-1501D and reference insulin glargine sequence groups (4.7% vs 7.9%, respectively; $P = 0.49$). The most common reason for study discontinuation was withdrawal of consent (5/8, 62.5%), followed by loss to follow-up (2/8, 25.0%) and AEs (1/8, 12.5%).

Baseline participant characteristics were similar between the treatment sequence groups (Table 1). The majority of participants were men (n = 77, 60.6%) and white (n = 120, 94.5%), and their mean age was 44.0 years. Across both treatment sequences, the mean (SD) baseline body mass index was 26.9 (4.3) kg/m^2 and the mean (SD) duration of T1DM was 20.8 (11.1) years. Baseline disease characteristics were also well balanced between the treatment sequence groups. Across both treatment sequences, the mean (SD) FPG and HbA1c were 9.7 (3.8) mmol/L (174.8 [68.5] mg/dL) and 61.2 (10.5) mmol/mol or 7.8 (1.0)%, respectively.

TABLE 1 Baseline participant demographics and characteristics

Parameter	Participants, n (%)	
	MYL-1501D sequence (N = 64)	Reference IG sequence (N = 63)
Age, mean (SD), years	44.8 (11.4)	43.2 (12.7)
Men, n (%)	41 (64.1)	36 (57.1)
Women, n (%)	23 (35.9)	27 (42.9)
Race, n (%)		
Asian	2 (3.1)	0
Black	2 (3.1)	2 (3.2)
Hispanic	1 (1.6)	0
White	59 (92.2)	61 (96.8)
Geographic region, n (%)		
Europe	30 (46.9)	27 (42.9)
North America	34 (53.1)	36 (57.1)
Weight, mean (SD), kg	80.7 (16.5)	82.4 (15.3)
BMI, mean (SD), kg/m^2	26.7 (4.2)	27.1 (4.4)
Duration of diabetes, mean (SD), years	21.4 (12.9)	20.2 (9.0)
FPG, mean (SD)		
mmol/L	9.8 (3.5)	9.5 (4.1)
mg/dL	176.6 (63.1)	171.2 (73.9)
HbA1c, mean (SD)		
mmol/mol	60.0 (10.9)	62.5 (10.0)
%	7.6 (1.0)	7.9 (0.9)
Baseline insulin dose, U/kg		
Basal	0.31 (0.12)	0.36 (0.18)
Mealtime	0.37 (0.16)	0.36 (0.15)
Total daily	0.68 (0.24)	0.72 (0.25)

BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IG, insulin glargine.

3.2 | Efficacy

The least squares (LS) mean (SE) change in HbA1c from baseline to week 36 was −0.05 (0.032) for the MYL-1501D sequence group and −0.06 (0.034) for the reference insulin glargine sequence group, with an LS mean difference of 0.01 (95% CI −0.085 to 0.101; Figure 1A). The study met its primary objective by demonstrating that the change in HbA1c from baseline to week 36 in the MYL-1501D treatment sequence was equivalent to the change in the reference insulin glargine treatment sequence, with the 95% CI within ±0.4%

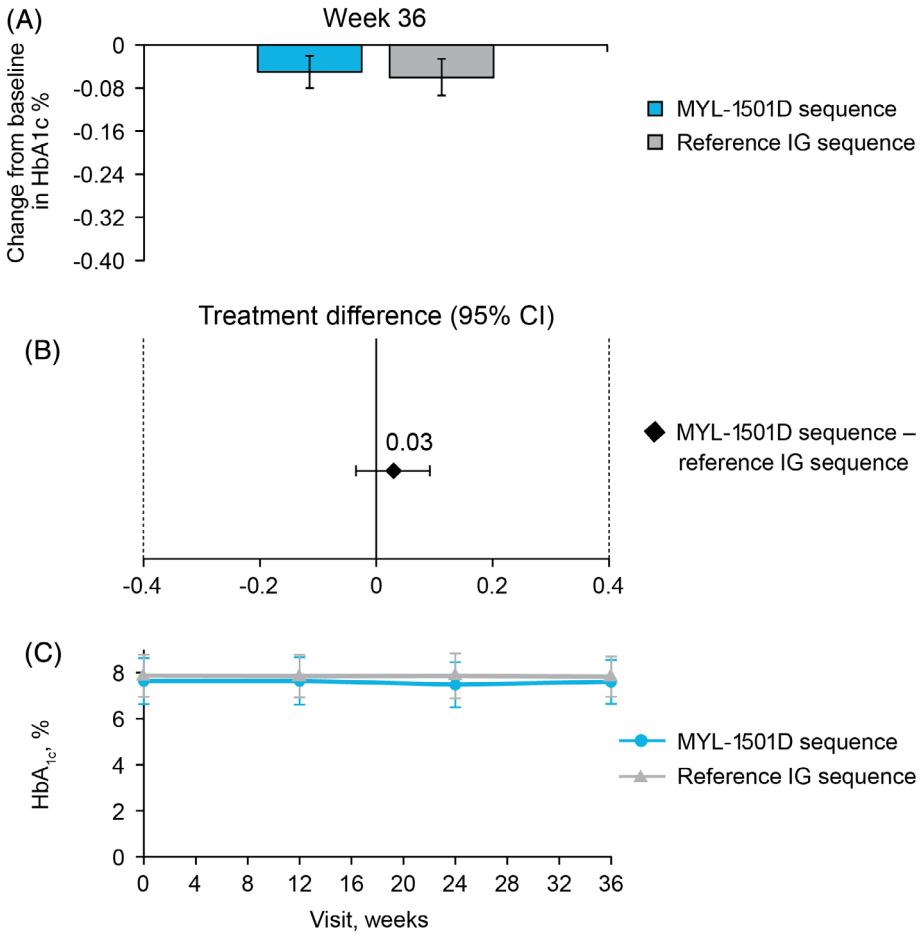

FIGURE 1 **A,** Least squares mean change in glycated haemoglobin (HbA1c; %) from baseline at week 36, **B,** least squares mean difference in HbA1c (%) from baseline at week 36 between the MYL-1501D and reference insulin glargine (IG) treatment sequences showing the confidence interval (CI) for equivalence (equivalence was declared if the 95% CI was within the prescribed acceptance range of ±0.4), and **C,** mean change in HbA1c (%) over time by treatment sequence. Error bars in panel A represent the standard error and in panel C represent the standard deviation

equivalence limits (Figure 1B). Throughout the study, HbA1c remained relatively stable for both treatment sequences, with no statistically significant changes from baseline (*P* values >0.05) or between treatment sequences at any time point throughout the three treatment periods (Figure 1C). In both treatment sequence groups, FPG and SMBG remained relatively stable throughout the three treatment periods, with no clinically significant changes from baseline or between treatment groups throughout the study (Figures S2A and S2B, respectively). For a summary of all endpoints at week 36, see Table S1.

The mean (SD) daily basal insulin dose was slightly higher in the reference insulin glargine treatment sequence (0.36 [0.17] U/kg) than in the MYL-1501D treatment sequence (0.32 [0.13] U/kg) at week 36 (Figure 2). In addition, the mean baseline basal insulin dose was higher in the reference insulin glargine treatment sequence (0.36 [0.18] U/kg) than in the MYL-1501D treatment sequence (0.31 [0.12] U/kg). In the MYL-1501D treatment sequence, which started at a slightly lower daily basal insulin baseline value than the reference insulin glargine treatment sequence, there were statistically significant increases from the baseline mean daily basal insulin dose (0.31 U/kg), but these changes were observed primarily in the first 4 weeks (mean dose at week 4, 0.32 U/kg; change from baseline, 0.01 U/kg; *P* = 0.022) and remained relatively stable thereafter (mean dose at

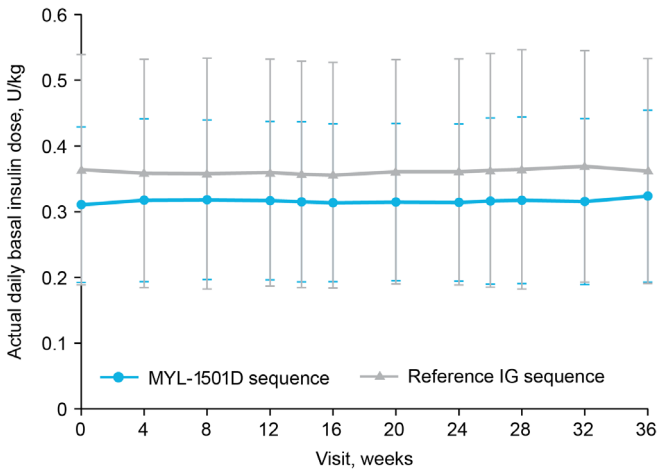

FIGURE 2 Mean actual MYL-1501D or reference insulin glargine (IG) daily basal insulin dose over time. Error bars represent the standard deviation

week 24, 0.31 U/kg; mean dose at week 36, 0.32 U/kg). There was also a single statistically significant treatment difference in change in daily basal insulin dose at week 36 (treatment period 3) between the MYL-1501D and reference insulin glargine treatment sequence

groups (0.019 U/kg; 95% CI 0.007 to 0.031; $P = 0.002$) owing to a small increase from baseline in the MYL-1501D treatment sequence (0.016 U/kg; $P = 0.004$). However, given the magnitude of these changes and the slightly lower baseline basal insulin requirement in the MYL-1501D treatment sequence, none of these changes was considered clinically meaningful. No statistically significant change from baseline in daily basal insulin dose was seen in the reference insulin glargine treatment sequence group. Similarly, for daily mealtime insulin dose, there was a single statistically significant treatment difference between the MYL-1501D and reference insulin glargine treatment sequence groups in treatment period 2 at week 20 (−0.028 U/kg, 95% CI −0.054 to −0.002; $P = 0.038$) owing to a small decrease from baseline in daily mealtime insulin dose in the MYL-1501D sequence (−0.026 U/kg; $P = 0.009$); this difference in daily mealtime insulin dose between treatment sequences was not considered clinically meaningful. The actual total daily insulin dose remained relatively stable throughout the entire treatment period, and there were no statistically significant treatment differences in total daily insulin dose change from baseline at any time point between the MYL-1501D and reference insulin glargine treatment sequence groups.

3.3 | Safety

Rates of treatment-emergent AEs (TEAEs) were similar between the MYL-1501D (41/64, 64.1%) and reference insulin glargine sequence groups (42/63, 66.7%; Table 2) during the 36-week treatment period. The most common TEAE was infection, which included upper respiratory tract infection and influenza. The intensity of most TEAEs was mild (grade 1) or moderate (grade 2), with five participants experiencing grade ≥ 3 TEAEs (two participants in each treatment sequence group had grade 3 events, and one participant in the reference insulin glargine sequence group experienced a grade 5 injury resulting from a car vs pedestrian motor vehicle accident that was unrelated to treatment). No participant discontinued treatment because of a treatment-related TEAE. Three participants (two in the MYL-1501D sequence and one in the reference insulin glargine sequence) reported local and/or systemic allergic reactions, and none of the events were considered related to study treatment. Overall incidences of any hypoglycaemic event or nocturnal hypoglycaemic events were comparable between the two treatment sequences, with no significant difference observed between treatment sequences at any visit (Figure 3A,B). The 30-day adjusted event rates for anytime and nocturnal hypoglycaemic events were also similar for both the MYL-1501D and reference insulin glargine treatment sequences (Figure 3C,D). Although numerically there tended to be more nocturnal hypoglycaemic events in the MYL-1501D treatment sequence, there were no statistically significant differences between treatment sequences, and the trend held during treatment period 2, when participants in the MYL-1501D treatment sequence were receiving reference insulin glargine. No severe hypoglycaemic events occurred at any time point in the study.

Overall, immunogenicity profiles were comparable between the MYL-1501D and reference insulin glargine treatment sequences. The MYL-1501D and reference insulin glargine assays were highly correlated for both cross-reactive and total antibodies (both $r \geq 0.99$). The TEAR rate is a relevant measure by which to assess immunogenicity, and the incidence of TEAR was 14.1% in the MYL-1501D treatment sequence and 14.3% in the reference insulin glargine treatment sequence. The differences between the two treatment sequences were not statistically significant in the reference insulin glargine assay (Figure S3); similar results were observed for the MYL-1501D assay (data not shown).

TABLE 2 Summary of treatment-emergent adverse events[a]

	Participants, n (%)	
	MYL-1501D sequence (N = 64)	Reference IG sequence (N = 63)
≥1 TEAE	41 (64.1)	42 (66.7)
≥1 grade 3, 4 or 5 TEAE	2 (3.1)	3 (4.8)
Participants who discontinued because of TEAEs	0	1 (1.6)
TEAEs occurring in ≥2% of participants in either sequence		
Upper respiratory tract infection	7 (10.9)	5 (7.9)
Nasopharyngitis	3 (4.7)	4 (6.3)
Influenza	3 (4.7)	2 (3.2)
Seasonal allergy	3 (4.7)	1 (1.6)
Viral gastroenteritis	2 (3.1)	2 (3.2)
Muscle strain	2 (3.1)	2 (3.2)
Sinusitis	2 (3.1)	1 (1.6)
Diarrhoea	2 (3.1)	1 (1.6)
Upper abdominal pain	2 (3.1)	0
Rash	2 (3.1)	0
Fatigue	2 (3.1)	0
Stress	2 (3.1)	0
Diabetic retinopathy	1 (1.6)	4 (6.3)
Oropharyngeal pain	1 (1.6)	2 (3.2)
Bronchitis	1 (1.6)	2 (3.2)
Herpes zoster	0	3 (4.8)
Back pain	0	2 (3.2)
Nasal congestion	0	2 (3.2)

IG, insulin glargine; TEAE, treatment-emergent adverse event.
[a]An adverse event was defined as treatment-emergent if the onset (or worsening of a pre-existing condition) occurred after the first administration of study drug.

4 | DISCUSSION

The study met its primary endpoint by demonstrating that the change from baseline to week 36 in HbA1c in participants who switched

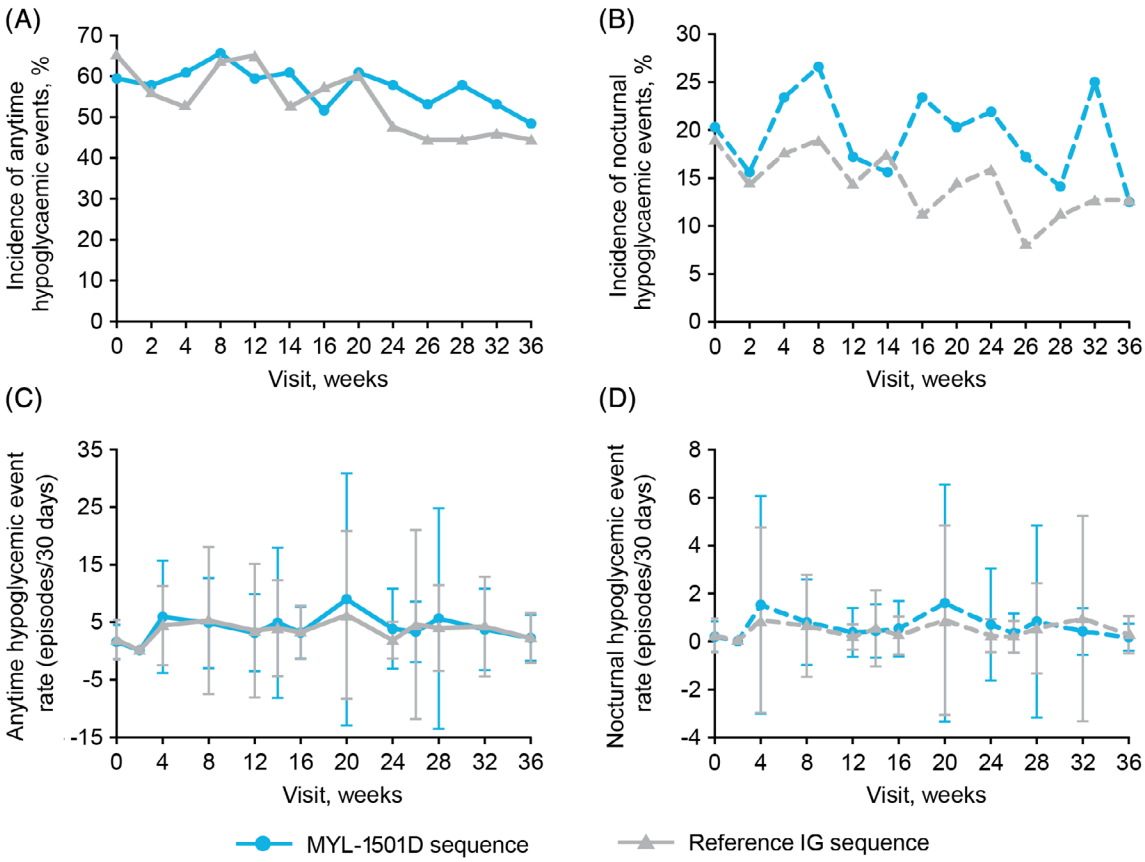

FIGURE 3 Incidence of **(A)** anytime and **(B)** nocturnal hypoglycaemic events and mean actual **(C)** anytime and **(D)** nocturnal hypoglycaemic event rates (number of episodes per 30 days) by visit and treatment sequence. Error bars represent the standard deviation. IG, insulin glargine

between MYL-1501D and reference insulin glargine was equivalent to that observed in participants who received reference insulin glargine for the duration of the trial, with the 95% CI within ±0.4% equivalence limits. In addition, both treatment sequences were comparable in terms of secondary endpoints, including FPG, SMBG and insulin dose. Importantly, for the MYL-1501D sequence, there were no significant changes in efficacy variables when participants switched treatments during treatment periods 2 and 3.

The MYL-1501D and reference insulin glargine sequences had comparable total insulin doses throughout the study. However, it should be noted that, at baseline, the daily basal insulin dose was lower in the MYL-1501D treatment sequence compared with the reference insulin glargine sequence. Although there were small increases from baseline in the daily basal dose for the treatment-switching sequence, primarily in the first 4 weeks, the change of 0.01 U/kg was considered not clinically meaningful when considering the mean weight of the participants (80.7 kg) or the lower baseline basal insulin value in the treatment-switching vs reference insulin glargine sequence. Additionally, the small treatment differences between the treatment-switching sequence and reference insulin glargine sequence at week 36 for daily basal insulin dose and at week 20 for daily mealtime insulin dose were also not considered clinically meaningful, and the total daily insulin dose was comparable for the two treatment sequences throughout the study. Having comparable insulin doses between treatment sequences is important when considering switching treatments. MYL-1501D was well tolerated in participants with T1DM through week 36 of the study. Incidences of reported TEAEs were similar between treatment sequences and in line with those observed in INSTRIDE 1 and INSTRIDE 2.[13,14] The overall incidence of any hypoglycaemic event was similar between the MYL-1501D and reference insulin glargine treatment sequences, with no statistically significant differences overall or at any visit; similarly, the 30-day adjusted hypoglycaemic event rates were also similar between treatment sequences. Although there were numerically more nocturnal hypoglycaemic events in the MYL-1501D treatment sequence compared with the reference insulin glargine treatment sequence, this trend was probably not related to treatment because the trend was consistent across all three treatment periods, including when participants were receiving reference insulin glargine. Overall, the safety results support the safety results of INSTRIDE 1 and INSTRIDE 2 and indicate that the two sequence groups in the present study had equivalent safety profiles throughout the study at the end of the treatment period,[13,14] and switching treatments had no impact on TEAEs, hypoglycaemic events, immunogenicity profiles, or other safety variables.

Changes from baseline in terms of the incidence of TEAR were similar between the treatment-switching and reference insulin glargine treatment sequences. These results suggest that both insulin glargine preparations demonstrated similar immunogenic potential,

and switching patients from MYL-1501D to reference insulin glargine and back to MYL-1501D did not impact immunogenicity; these results further confirm the similar safety profiles of MYL-1501D and reference insulin glargine demonstrated in earlier studies.[13,14] The TEAR findings of the present study were similar to the immunogenicity and safety results of a study comparing another insulin glargine biosimilar (LY2963016) and reference insulin glargine in which the proportion of participants with detectable TEAR was similar between treatment groups, providing additional evidence to support the development and use of biosimilars or FOBs for therapeutics such as insulin.[15]

A possible limitation of the present study was the open-label design. The study was conducted with an open-label design because MYL-1501D and reference insulin glargine have different packaging, thus preventing participant and investigator blinding. To minimize bias in the evaluation of critical endpoints, analyses of efficacy (HbA1c) and safety (immunogenicity) were blinded. This study was a continuation of INSTRIDE 1, and patients entering the present study had received 52 weeks of reference insulin glargine before study entry. The 12 weeks of exposure in each of the three treatment periods was considered adequate to assess the efficacy with respect to HbA1c as well as to compare the safety and immunogenicity profiles between the treatment sequence groups. These results suggest that MYL-1501D and reference insulin glargine have similar efficacy and safety profiles over a 36-week period.

In a review article by Dowlat et al[16] overviewing the current regulatory framework around demonstration of interchangeability with biosimilars, the authors proposed several endpoints for this purpose between a biosimilar insulin analogue and its reference product, including evaluating glycaemic control, changes in insulin doses and incidence and severity of hypoglycaemia. INSTRIDE 3 included several of these proposed endpoints to test equivalence between the MYL-1501D and reference insulin glargine treatment sequences, including eight-point SMBG and FPG profiles to assess glycaemic control, as well as changes in insulin dose and incidence and severity of hypoglycaemia. The findings from this switch study demonstrate that the safety and efficacy profiles in participants who switched between MYL-1501D and reference insulin glargine were equivalent to those in participants who received reference insulin glargine for the duration of the study and that MYL-1501D is safe and efficacious.

In conclusion, the INSTRIDE 3 study met its primary endpoint by demonstrating that the change from baseline to week 36 in HbA1c in participants switching between MYL-1501D and reference insulin glargine was statistically equivalent to that observed in participants receiving reference insulin glargine over a 36-week period. Overall, both treatment sequences were well tolerated, with no meaningful differences in immunogenicity. Together, the results of this study show that switching patients between MYL-1501D and reference insulin glargine resulted in similar efficacy and safety.

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PRIOR PRESENTATION

These data were previously presented in part at the 3rd World Congress on Clinical Trials in Diabetes, December 3–4, 2018, Vienna, Austria.

CONFLICT OF INTEREST

T.C.B. has received clinical research support from AstraZeneca, Eli Lilly, Lexicon, Merck, Mylan, Novo Nordisk and Sanofi. A.B., Y.R., P.A., B.S. and R.M. are paid employees of Mylan Inc. and may hold stock or stock options in the company. S.A. is a paid employee of Biocon Research Ltd and may hold stock or stock options in the company.

AUTHOR CONTRIBUTIONS

T.C.B. contributed to the analysis and interpretation of data and critically revising the manuscript for important intellectual content. A.B. contributed to the conception of the study, the design of the study, the analysis and interpretation of data, and critically revising the manuscript for important intellectual content. Y.R. contributed to the conception of the study, the design of the study, the acquisition, analysis and interpretation of the data, and drafting the manuscript. P.A. contributed to the interpretation of data and critically revising the manuscript for important intellectual content. B.S. contributed to the conception of the study, the design of the study, the acquisition, analysis and interpretation of the data, drafting the manuscript, and critically revising the manuscript for important intellectual content. R.M. X. contributed to the interpretation of data and critically revising the manuscript for important intellectual content. S.A. contributed to the interpretation of data and critically revising the manuscript for important intellectual content. All authors approved the manuscript for publication.

REFERENCES

1. American Diabetes Association, Classification and diagnosis of diabetes. 2. Classification and Diagnosis of Diabetes. *Diabetes Care*. 2017; 40(suppl 1):S11-S24.
2. American Diabetes Association. Glycemic targets. *Diabetes Care*. 2017;40(suppl 1):S48-S56.
3. Diabetes Control and Complications Trial Research Group, Nathan DM, Genuth S, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329 (14):977—986.
4. Nathan DM, Cleary PA, Backlund JY, et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.
5. Lantus [package insert]. *Bridgewater*. Sanofi-Aventis US LLC: NJ; 2015.
6. Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits*. 2013;6:469-478.
7. McCamish M, Woollett G. Worldwide experience with biosimilar development. *MAbs*. 2011;3:209-217.

8. Mellstedt H, Niederwieser D, Ludwig H. The challenge of biosimilars. *Ann Oncol*. 2008;19:411-419.
9. European Medicines Agency. Biosimilars in the EU: information guide for healthcare professionals. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Accessed July 12, 2018.
10. US Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. https://www.fda.gov/media/82647/download. Accessed November 22, 2017.
11. Verma M, Hazra P, Iyer H, et al. Basalog® is similar to Lantus® in producing glycemic control in patients with type 1 diabetes mellitus on multiple daily insulin regimens. *Int J Diabetes Dev Cties*. 2011;31:26-31.
12. European Medicines Agency. Committee for Medicinal Products for Human Use summary of positive opinion for Semglee. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-semglee_en.pdf. Accessed February 27, 2018.
13. Blevins TC, Barve A, Sun B, Ankersen M. Efficacy and safety of MYL-1501D vs insulin glargine in patients with type 1 diabetes after 52 weeks: results of the INSTRIDE 1 phase III study. *Diabetes Obes Metab*. 2018;20:1944-1950.
14. Blevins TC, Barve A, Sun B, et al. Efficacy and safety of MYL-1501D versus insulin glargine in patients with type 2 diabetes after 24 weeks: results of the phase III INSTRIDE 2 study. *Diabetes Obes Metab*. 2019;21:129-135.
15. Ilag LL, Deeg MA, Costigan T, et al. Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus® insulin glargine in patients with type 1 or type 2 diabetes mellitus. *Diabetes Obes Metab*. 2016;18:159-168.
16. Dowlat HA, Kuhlmann MK, Khatami H, Ampudia-Blasco FJ. Interchangeability among reference insulin analogues and their biosimilars: regulatory framework, study design and clinical implications. *Diabetes Obes Metab*. 2016;18:737-746.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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