Research: Treatment

Hypoglycaemia is reduced with use of inhaled Technosphere® Insulin relative to insulin aspart in type 1 diabetes mellitus

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Abstract

Aim To evaluate the effect of final HbA1c levels on the incidences of hypoglycaemia in participants with type 1 diabetes treated with inhaled Technosphere® Insulin or subcutaneous insulin aspart, reported in alignment with the International Hypoglycaemia Study Group recommendations.

Methods In the randomized, phase 3, multicentre AFFINITY-1 study, adults (N = 375) who had type 1 diabetes for ≥ 12 months and an HbA1c level of 58–86 mmol/mol (7.5–10.0%) were randomized to receive basal insulin plus either inhaled Technosphere Insulin or subcutaneous insulin aspart. This was a post-hoc regression analysis on a subset (N = 279) of the randomized AFFINITY-1 cohort for whom baseline and end-of-treatment HbA1c values were reported. Primary outcome measures were incidence and event rates for levels 1, 2 and 3 hypoglycaemia, respectively defined as blood glucose levels of ≤ 3.9 mmol/l, < 3.0 mmol/l or requiring external assistance for recovery.

Results Participants treated with Technosphere Insulin experienced statistically significantly fewer level 1 and 2 hypoglycaemic events and a lower incidence of level 3 hypoglycaemia than participants treated with insulin aspart. The lower rate of hypoglycaemia with Technosphere Insulin was observed across the range of end-of-treatment HbA1c levels. Technosphere Insulin was associated with higher rates of hypoglycaemia 30–60 min after meals, but significantly lower rates 2–6 h after meals.

Conclusions Participants using Technosphere Insulin experienced clinically non-inferior glycaemic control and lower hypoglycaemia rates across a range of HbA1c levels compared with participants receiving insulin aspart. ClinicalTrials.gov: NCT01445951.

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Introduction

Glycaemic control is important for people with diabetes mellitus because it helps reduce microvascular complications such as retinopathy, nephropathy and neuropathy [1], and may reduce the risk of cardiovascular disease [2]. However, hypoglycaemia and the fear of hypoglycaemia are barriers to effective insulin therapy and may prevent people with diabetes from achieving glycaemic targets [3]. Rapid-acting insulins, such as insulin lispro, insulin aspart and insulin glulisine, help people with diabetes achieve better prandial glucose control than regular human insulin. However, rapid-acting insulins are often not fast-acting enough to match physiological needs, particularly if they are not appropriately timed before the meal, and they may put people with diabetes at risk of both early postprandial hyperglycaemia and late postprandial hypoglycaemia [4,5].

Technosphere® Insulin (MannKind Corporation, Westlake Village, CA, USA), a dry-powder formulation of
What’s new?

- Hypoglycaemia and fear of hypoglycaemia are barriers to effective insulin therapy and may prevent people with diabetes from achieving glycaemic targets.
- Administration of inhaled Technosphere® Insulin at mealtime provides comparable glycaemic control and lower rates of hypoglycaemia across a range of HbA1c levels compared with subcutaneous insulin aspart in people with type 1 diabetes mellitus.
- The ultra-rapid time-action profile of Technosphere Insulin offers the flexibility to dose at the beginning of or 20 min after starting a meal, and allows for the convenience of between-meal dosing with a lower risk of hypoglycaemic events compared with subcutaneous rapid-acting insulin analogues.

recombinant human insulin adsorbed onto Technosphere microparticles for oral inhalation, is an ultra-rapid-acting insulin that has a faster onset (~12 min) and shorter, dose-dependent duration of action (typically ≤3 h across typical dose ranges) compared with currently available subcutaneously injected rapid-acting insulin analogues, such as fast-acting insulin aspart injection (Fiasp®; Novo Nordisk, Inc, Plainsboro, NJ, USA), which has an onset of action of ~20 min and a duration of action of at least 5–6 h [6,7].

The 24-week, phase 3 AFFINITY-1 study (ClinicalTrials.gov identifier, NCT01445951) in participants with type 1 diabetes demonstrated that prandial Technosphere Insulin provides glycaemic control that is non-inferior to prandial insulin aspart [8]. Since publication of the AFFINITY-1 trial, the International Hypoglycaemia Study Group has suggested that hypoglycaemia in clinical trials be categorized as level 1 (defined as a blood glucose level of ≤3.9 mmol/l), level 2 (blood glucose <3.0 mmol/l) or level 3 hypoglycaemia (defined as severe cognitive impairment that requires outside assistance for recovery) [9]. This proposal has subsequently been accepted or adopted by the American Diabetes Association, European Association for the Study of Diabetes and European Medicines Agency [9–11]. To interpret the data collected during AFFINITY-1 from the perspective of these new recommendations, the primary objective of this post-hoc regression analysis was to compare the incidence and event rates for levels 1, 2 and 3 hypoglycaemia on the basis of final HbA1c levels measured at 24 weeks in participants with type 1 diabetes treated with inhaled Technosphere Insulin or subcutaneous insulin aspart.

Participants and methods

Study design and population

AFFINITY-1 was a phase 3, randomized, multicentre, 24-week trial, and the study design and methodology have been described previously [8]. Adults aged ≥18 years who had type 1 diabetes for ≥12 months and an HbA1c level of 58–86 mmol/mol (7.5–10.0%) were randomized to receive Technosphere Insulin plus basal insulin or insulin aspart plus basal insulin. The ratios of men to women were similar for participants in both treatment groups (Technosphere Insulin: 44.3% vs. 55.7%; insulin aspart: 43.3% vs. 56.7%, respectively). Participants continued their pre-enrolment basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn insulin) throughout the study. Doses of basal insulin were determined during a 4-week titration period, with doses titrated every 3 days to reach a fasting plasma glucose target range of 5.6–6.7 mmol/l. The mean daily dose of basal insulin increased from 31.8 and 29.0 units at week 1 to 37.1 and 31.6 units at week 24 for the Technosphere Insulin and insulin aspart treatment groups, respectively. Doses of prandial subcutaneous insulin aspart were administered 5–10 min before a meal, and doses of Technosphere Insulin, provided via an inhaler, were administered immediately before a meal or up to 20 min after starting a meal. Doses were adjusted weekly during the first 12 weeks of the study to reach a premeal self-monitored blood glucose (SMBG) average target range of 5.6–6.7 mmol/l for insulin aspart and a 90-min post-meal SMBG average target range of 6.1–8.9 mmol/l for Technosphere Insulin.

In addition to regular testing of blood glucose, seven-point SMBG curves were obtained at least three times during the week preceding visits at weeks 0, 12 and 24. Reported hypoglycaemia data included the exact date and time of the hypoglycaemic event, the date and time of blood glucose readings, and meals, symptoms, treatments (if any) and any other specific circumstances. A post-hoc analysis was performed on a subset of the AFFINITY-1 cohort for whom an end-of-treatment HbA1c value was known.

Any SMBG value of ≤3.9 mmol/l or any symptomatic events corrected with carbohydrate ingestion were categorized as level 1 hypoglycaemia. Any SMBG value of <3.0 mmol/l was categorized as level 2 hypoglycaemia. Events requiring the assistance of another person to actively administer carbohydrates or glucon to or take other corrective actions were categorized as level 3 hypoglycaemia [12].

Statistical analyses

The frequency of hypoglycaemia was modelled as a negative binomial distribution with mean μ and reciprocal dispersion factor ν. The logarithm of μ, ln(μ), was modelled as a linear function of the continuous variable HbA1c and indicator variables representing treatment (Technosphere Insulin or insulin aspart), basal insulin (insulin glargine, insulin detemir or neutral protamine Hagedorn insulin) and region (North America, Latin America or Eastern Europe). Hypoglycaemia incidence was tabulated and significance was evaluated by
binomial regression using the same indicator variables used for event rates. For the evaluation of level 3 hypoglycaemia over a 6-h postprandial range, there were too few events to model all the terms in the negative binomial model. Instead, these data were analysed using a binomial distribution based on a common frequency so that the probability of an event in each group was proportional to the exposure to that treatment divided by the total exposure of all participants in the post-hoc population. A 5% significance level was used throughout; no adjustment was made for multiplicity of statistical tests.

Ethical approval

Written informed consent was obtained from all participants before screening. The study protocol and informed consent form were reviewed by the Independent Ethics Committee or Institutional Review Board for each centre. This study was conducted according to the ethical principles of the Declaration of Helsinki.

Results

Participant characteristics

The population in the post-hoc analysis resembles the randomized population as shown in Fig. 1. The original hypoglycaemia analysis was performed on the full safety population, which was defined as participants who had at least one dose of study treatment, and the full analysis set, which was defined as all randomized participants, was evaluated for efficacy [8]. Final HbA1c was a clinical endpoint, so the efficacy was evaluated with a mixed-effect model repeat measurement approach, and pattern mixture sensitivity analyses were performed to evaluate the impact of early participant discontinuations and missing data on the results. The between-group difference of 2 mmol/mol (0.2%) [95% confidence intervals (CI) 0 to 4 mmol/mol, 0.02% to 0.36%] satisfied the predetermined non-inferiority criterion in the original AFFINITY-1 study of 4 mmol/mol (0.4%); therefore, these differences were not considered clinically significant.

For this post-hoc analysis of the effect of final HbA1c on hypoglycaemia, the final HbA1c was not the endpoint but a covariate. The HbA1c distribution in the post-hoc population was shown to be representative of the original safety population by comparing HbA1c results from the post-hoc and original analyses (Table 1). Additionally, both the full safety population and the post-hoc analysis population recorded SMBG readings at comparable frequency and experienced hypoglycaemic events at comparable rates (Table 2). Participants excluded from the post-hoc analysis accounted for < 10% of total drug exposure; hence, the mean recorded values per day did not shift appreciably. Regardless of treatment, excluded participants tended to under-report SMBG values to the same extent (Technosphere Insulin, 4.8 readings per day; insulin aspart, 5.0 readings per day). Compared with the original analysis, the post-hoc analysis excluded more of the low-reporting participants in the Technosphere Insulin group, thus reducing the statistical significance of the difference in reporting rate between treatments.

FIGURE 1 Participant disposition. ANCOVA, analysis of covariance; MMRM, mixed-effect model repeat measurement; TI, Technosphere Insulin.

*Participants in the MedTone Inhaler group were not included in the original primary efficacy endpoint analysis of AFFINITY-1 and were not included in this post-hoc analysis.
Hypoglycaemia

Participants receiving Technosphere Insulin experienced significantly fewer level 1 and 2 hypoglycaemic events than participants receiving insulin aspart (Table 2; Fig. 2). The observed rate of level 1 hypoglycaemia was 30.8% lower for participants receiving Technosphere Insulin compared with participants receiving insulin aspart (9.7 vs. 14.0 events per participant-month, respectively; P < 0.001). The observed rate of level 2 hypoglycaemia was 38.0% lower for participants receiving Technosphere Insulin compared with participants receiving insulin aspart (3.2 vs. 5.2 events per participant-month, respectively; Fig. 2; P < 0.001). Participants receiving Technosphere Insulin experienced fewer level 3 hypoglycaemic events than participants receiving insulin aspart (0.076 vs. 0.154 events per participant-months, respectively), corresponding to an observed 50.4% lower rate in level 3 hypoglycaemia, although this difference did not achieve statistical significance (P = 0.052). These results for the post-hoc population are consistent with the original analysis of the full safety population.

The effects of treatment and final HbA1c on hypoglycaemia event rate were separated by negative binomial regression. The results were in agreement with those listed in Table 2. Of the 30.8% reduction in level 1 hypoglycaemia (Fig. 3a), the effect of Technosphere Insulin vs. insulin aspart reduced the rate by ~27%, and the difference of 2 mmol/mol in average final HbA1c reduced the rate by another 4%. The geometric mean ratio for treatment effect was 0.74 (95% CI 0.63, 0.86), and the geometric mean ratio for the 2 mmol/mol difference was 0.95 (95% CI 0.93, 0.97). Similarly, for level 2 hypoglycaemia (Fig. 3b), the treatment effect reduced the event rate by ~36%, and the difference in HbA1c contributed another 4% reduction. The geometric mean ratios for the treatment and HbA1c effects were 0.64 (95% CI 0.51, 0.79) and 0.96 (95% CI 0.94, 0.99), respectively. Finally, for level 3 hypoglycaemia, the negative binomial model estimated a reduction in level 3 event rates of ~44%, based on a geometric mean ratio of 0.56 (95% CI 0.32, 0.96); the HbA1c term was not statistically significant (Fig. 3c).

In addition to the overall lower frequency of hypoglycaemia, the use of Technosphere Insulin was associated with a difference in the timing of hypoglycaemia (Fig. 4). Events associated with Technosphere Insulin tended to occur earlier than with insulin aspart, so the event rates for level 1 and level 2 hypoglycaemia were significantly lower after the first 2 h (Fig. 4a,b). The higher rates of level 1 and level 2 hypoglycaemia occurring 30–60 min after dosing with Technosphere Insulin were consistent with its known time-action profile. The same general pattern was observed for level 3 hypoglycaemia, with a statistically significant difference over one interval (60–90 min post dose).

Discussion

This post-hoc regression analysis was performed on a representative subset of participants from the AFFINITY-1 study for whom an end-of-treatment HbA1c value was known. Participant withdrawal due to personal circumstances was the main reason for study discontinuation among participants in the insulin aspart and Technosphere Insulin groups. Of the 44 participants receiving Technosphere Insulin who withdrew from the study, one withdrew because of hypoglycaemia, indicating that hypoglycaemia was not the driving factor behind the difference in dropout rates between treatment groups.

During the course of this 24-week study, participants receiving the ultra-rapid-acting inhaled insulin Technosphere Insulin (immediately before or up to 20 min after the start of a meal) experienced significantly fewer rates of hypoglycaemia with non-inferior glycaemic control compared with participants receiving subcutaneous insulin aspart (5–10 min before

Table 1 Population comparison: original vs. post-hoc analysis

|                   | Technosphere® Insulin | Insulin aspart | Treatment difference |
|-------------------|-----------------------|----------------|----------------------|
| **Original analysis (MMRM)** |                       |                |                      |
| Randomized, N     | 174                   | 171            |                      |
| Per protocol, N   | 130                   | 147            |                      |
| Mean HbA1c, mmol/mol (%) | 63 (7.9)             | 63 (7.9)       |                      |
| **Adjusted mean change** |                   |                |                      |
| Baseline          | –2 (–0.2)             | –5 (–0.4)      | 2 (0.2)              |
| End of treatment  | –4, –1 (–0.33, –0.09)  | –6, –3 (–0.52, –0.28) | 0, 4 (0.02, 0.36) |
| **Post-hoc analysis (ANCOVA)** |                   |                |                      |
| N                 | 131                   | 148            |                      |
| Mean HbA1c, mmol/mol (%) | 64 (8.0)             | 63 (7.9)       |                      |
| **Mean change**   | –2 (–0.2)             | –4 (–0.4)      | 2 (0.2)              |
| Baseline          | –0, 0 (–0.43, –0.02)  | –6, –2 (–0.38, –0.21) | 0, 4 (0.01, 0.36) |

ANCOVA, analysis of covariance; CI, confidence interval; MMRM, mixed-effect model repeat measurement.
In particular, participants receiving Technosphere Insulin experienced statistically significantly fewer level 1 and 2 hypoglycaemic events than participants receiving insulin aspart. Level 2 glucose concentrations (defined as a blood glucose level of <3.0 mmol/l) can cause defective glucose counter-regulation and impaired awareness of hypoglycaemia, and people who experience frequent hypoglycaemia at these levels may not experience hypoglycaemic symptoms, thus increasing the risk of level 3 hypoglycaemia and potential mortality [9,12]. The development of prandial insulins with flexible treatment regimens is a potential strategy for reducing risk factors for hypoglycaemia [3].

A critical need when using prandial insulin therapy is to provide appropriate glycaemic control at mealtime while avoiding late prandial hypoglycaemia [4]. Late post-prandial hypoglycaemic events can occur several hours after meals and most likely occur as a consequence of the long duration of action of subcutaneous rapid-acting insulin analogues. The incidence of hypoglycaemia was slightly higher within the first 1.5 h after meals in participants receiving Technosphere Insulin than in those receiving insulin aspart, but this is most likely the result of the rapid onset of action of Technosphere Insulin, which peaks ~35–55 min post dose [6]. At later time points after the initial 1.5 h, however, substantially fewer hypoglycaemic events were observed in participants receiving Technosphere Insulin than in those receiving insulin aspart (2–6 h after meals), and this translated to a lower overall rate of postprandial hypoglycaemia.

Table 2 Summary of Hypoglycaemic Incidence and Events

| Parameter                  | Technosphere Insulin (n = 174) | Insulin aspart (n = 171) | Per cent difference between Technosphere Insulin and insulin aspart values | P-value |
|----------------------------|---------------------------------|--------------------------|---------------------------------------------------------------------------|---------|
| Original analysis SMBG     |                                 |                          |                                                                           |         |
| Recorded values, n         | 128 593                         | 151 939                  | NA                                                                        | NA      |
| Total exposure, participant-days | 24 554                         | 27 347                   | NA                                                                        | NA      |
| Recorded values per participant-day | 5.2                             | 5.6                      | -5.7                                                                      | 0.02    |

Hypoglycaemia classification

| Incidence, n (%) | 167 (96.0) | 170 (99.4) | -3.4 | 0.06 |
| Events, n        | 7919       | 12,571     | NA   | NA   |
| Events per participant-month | 9.8             | 14.0        | NA   | < 0.001 |
| Incidence, n (%) | 32 (18.4)  | 30 (29.2)  | -37.0 | 0.02  |
| Events, n        | 65         | 130        | NA   | NA   |
| Events per participant-month | 0.081             | 0.145       | -44.1 | 0.10  |

| Level 1‡ Incidence, n (%) | 131 (100) | 148 (100) | 0  | 1.00  |
| Events, n               | 7120       | 11,661     | NA  | NA    |
| Events per participant-month | 9.7             | 14.0        | -30.8 | < 0.001 |
| Incidence, n (%)        | 126 (96.2) | 144 (97.3) | -1.1 | 0.58  |
| Events, n               | 2365       | 4331       | NA  | NA    |
| Events per participant-month | 3.2             | 5.2         | -38.0 | < 0.001 |
| Incidence, n (%)        | 27 (20.6)  | 48 (32.4)  | -36.4 | 0.03  |
| Events, n               | 76         | 128        | NA  | NA    |
| Events per participant-month | 0.076             | 0.154       | -50.4 | 0.05  |

NA, not applicable; SMBG, self-monitored blood glucose; TI, Technosphere Insulin.
‡All hypoglycaemia was defined as any SMBG value of ≤3.9 mmol/l or any symptomatic events corrected with carbohydrate ingestion.
§Level 1 hypoglycaemia was defined as any SMBG value of ≤3.9 mmol/l or any symptomatic events corrected with carbohydrate ingestion.
¶Level 2 hypoglycaemia was defined as any SMBG value of <3.0 mmol/l.
§Level 3 hypoglycaemia was defined as events requiring the assistance of another person to take corrective actions.

a meal). In particular, participants receiving Technosphere Insulin experienced statistically significantly fewer level 1 and 2 hypoglycaemic events than participants receiving insulin aspart. Level 2 glucose concentrations (defined as a blood glucose level of <3.0 mmol/l) can cause defective glucose counter-regulation and impaired awareness of hypoglycaemia, and people who experience frequent hypoglycaemia at these levels may not experience hypoglycaemic symptoms, thus increasing the risk of level 3 hypoglycaemia and potential mortality [9,12]. The development of prandial insulins with flexible treatment regimens is a potential strategy for reducing risk factors for hypoglycaemia [3].

A critical need when using prandial insulin therapy is to provide appropriate glycaemic control at mealtime while avoiding late postprandial hypoglycaemia [4]. Late post-prandial hypoglycaemic events can occur several hours after meals and most likely occur as a consequence of the long duration of action of subcutaneous rapid-acting insulin analogues. The incidence of hypoglycaemia was slightly higher within the first 1.5 h after meals in participants receiving Technosphere Insulin than in those receiving insulin aspart, but this is most likely the result of the rapid onset of action of Technosphere Insulin, which peaks ~35–55 min post dose [6]. At later time points after the initial 1.5 h, however, substantially fewer hypoglycaemic events were observed in participants receiving Technosphere Insulin than in those receiving insulin aspart (2–6 h after meals), and this translated to a lower overall rate of postprandial hypoglycaemia.

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hypoglycaemia. The temporal pattern in postprandial hypoglycaemia in the Technosphere Insulin group is consistent with the established rapid kinetics of inhaled Technosphere Insulin. In euglycaemic clamp studies, the first measurable effect of Technosphere Insulin occurs at ~12 min; its effect quickly peaks at 35–55 min and returns to baseline sooner than injected insulins [6,7,13]. Additionally, maximal glucose disposal occurs within 45 min of Technosphere Insulin administration, in contrast to within ~2–3 h of insulin aspart administration (MannKind Corporation, unpublished data).

**FIGURE 2** Summary of level 1, level 2 and level 3 hypoglycaemia incidences and events after treatment with TI or insulin aspart. *P < 0.05. Pt, participant; TI, Technosphere® Insulin.

**FIGURE 3** Hypoglycaemic event rates as a function of HbA1c. Distribution of (a) level 1, (b) level 2 and (c) level 3 hypoglycaemia events (rate per participant-month) across the range of HbA1c values at the end of treatment with either TI or insulin aspart. Pt, participant; TI, Technosphere® Insulin.
This ultra-rapid time–action profile of Technosphere Insulin may contribute to its reduced risk of hypoglycaemic events compared with rapid-acting analogues, such as insulin aspart, particularly in the late postprandial period, across a range of HbA1c levels. These results are further supported by the recent STAT study, a pilot study comparing Technosphere Insulin and insulin aspart in participants with type 1 diabetes who monitored glucose via continuous glucose monitoring (Dexcom G5®; Dexcom, Inc, San Diego, CA, USA). In the STAT study, participants treated with Technosphere Insulin demonstrated as much or more time in the glycaemic target range of 3.9–10.0 mmol/l than those treated with insulin aspart and significantly less time in hypoglycaemia [< 3.3 mmol/l; mean (SD): Technosphere Insulin, 0.7 (0.5)%; insulin aspart, 2.1 (0.4)%; P = 0.02; and < 2.8 mmol/l; mean (SD): Technosphere Insulin, 0.3 (0.2)%; insulin aspart, 0.9 (0.2)%; P = 0.04], providing further support that Technosphere Insulin improves early postprandial glycaemic control with a lower risk of hypoglycaemia [15].

A limitation of the AFFINITY-I study is that participants in the Technosphere Insulin and insulin aspart groups had different glycaemic targets. Participants randomized to the insulin aspart group targeted average premeal SMBG values of 5.6–6.7 mmol/l, and participants randomized to the Technosphere Insulin group targeted average 90-min postmeal SMBG values of 6.1–8.9 mmol/l [8]. These differences between treatment groups limit the ability to make a direct comparison. Additionally, the use of continuous glucose monitors, such as those used in the STAT study, may have provided more comprehensive information about postprandial hypoglycaemia than SMBG values alone. Another study limitation of the AFFINITY-I analysis is that the mean baseline and end-of-treatment HbA1c levels were higher for participants receiving Technosphere Insulin than those receiving insulin aspart, although the treatment difference was not clinically significant and non-inferiority between treatments was achieved. Participants receiving Technosphere Insulin reported fewer level 1, level 2 and level 3 hypoglycaemic events than participants receiving insulin aspart, indicating that Technosphere Insulin not only achieves non-inferior postprandial glycaemic control but also has a hypoglycaemic advantage when taken at the start of a meal.

The results of this regression analysis, which controlled for achieved HbA1c values, suggest that use of Technosphere Insulin in a multidose insulin regimen may permit treatment intensification with less risk of provoking hypoglycaemia. The ultra-rapid time–action profile of Technosphere Insulin offers participants the flexibility to take Technosphere Insulin at the beginning of or within 20 min of starting a meal. Its short duration of action limits effects in the late post-meal period and may limit the risk of ‘insulin stacking’, thus allowing for greater flexibility and convenience of between-meal dosing with a lower risk of hypoglycaemic events compared with subcutaneous insulin aspart [8,15]. Furthermore, switching participants from subcutaneous rapid-acting insulin analogues to Technosphere Insulin may benefit those who have already reached their HbA1c goals by reducing the frequency of hypoglycaemic events.
In summary, administration of inhaled Technosphere Insulin as a prandial therapy at mealtime provides glycaemic control comparable with that of commonly used subcutaneous rapid-acting insulin analogues, such as insulin aspart, with a potentially lower risk of hypoglycaemic events in participants with type 1 diabetes. These promising results suggest the need for additional studies with comparable glucose targets in both treatment groups.

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Competing interests

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Frank M. Pompilio was employed with MannKind Corporation during the composition and submission of this manuscript; he is no longer affiliated with MannKind Corporation.

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