REDUCED HYPOGLYCAEMIA IS OBSERVED WITH INHALED INSULIN VERSUS SUBCUTANEOUS INSULIN ASPART IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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INTRODUCTION

- Technosphere® Insulin Inhalation Powder (TI) is a dry powder formulation of recombinant human insulin adsorbed onto fumaryl diketopiperazine microparticles for oral inhalation in patients with diabetes mellitus.
- TI has been shown to have a more rapid absorption and elimination profile compared with subcutaneous regular human insulin.[1]
- The AFFINITY 1 Study (ClinicalTrials.gov Identifier: NCT01445951) was a randomized, open-label, noninferiority study of 24 weeks' duration comparing prandial TI versus subcutaneous insulin aspart added to basal insulin in patients with type 1 diabetes mellitus (T1DM).[2]
- In the AFFINITY 1 Study, TI was shown to be noninferior to subcutaneous insulin aspart with regards to improvement in glycated hemoglobin A_{1c} (HbA_{1c}) levels.[2]
- Lower hypoglycaemia event rates were also observed with TI compared with insulin aspart.[2]

OBJECTIVES

- To conduct a post hoc analysis of hypoglycaemia rates from the AFFINITY 1 Study and investigate the impact of supplemental dosing of TI and insulin aspart on rates of hypoglycaemia.
- To investigate hypoglycaemia rates in the titration and maintenance phases of the study.

METHODS

Study Design and Patients

- This was a post hoc analysis conducted in a modified safety population of the AFFINITY 1 Study (those patients with T1DM who received ≥ 1 normal dose of TI or insulin aspart, and who also had baseline HbA_{1c} data available; N = 339).
- In the AFFINITY 1 Study, patients in the TI group were instructed to administer 1 supplemental dose (a fixed dose of 10 Units TI) if their 90-minute postprandial blood glucose (BG) measurement was ≥ 180 mg/dL; those patients who achieved a 90-minute postprandial BG measurement of ≥ 110 to < 160 mg/dL and who also had 2 of 3 pre-next-meal BG measurements ≥ 160 mg/dL were instructed to regularly use a supplemental dose 90 minutes after the meal. Patients in the insulin aspart group were not instructed to administer supplemental doses on the basis of their postprandial BG values; however, correction doses were allowed by protocol.
- We determined annualised hypoglycaemia rates in the modified safety population (as described above), patients taking ≥ 1 post-meal supplemental dose (TI, n = 111; insulin aspart, n = 91), and patients not taking a supplemental dose (TI, n = 61; insulin aspart, n = 76).
- The impact of supplemental dosing frequency on hypoglycaemia was also investigated in patients receiving 1-5, 6-20, 21-60, and > 60 supplemental doses during the study.
  - any hypoglycaemic event that occurred ≥ 1 hour after the supplemental dose and also on the same day as the supplemental dose was included in the analysis
- Hypoglycaemia rates during study weeks 0-12 (titration phase) and study weeks 12-24 (maintenance phase) were also assessed.
  - during the titration phase, prandial doses in each group were adjusted weekly; patients randomized to TI targeted average 90-minute post-meal BG levels between 110 and 160 mg/dL and patients randomized to insulin aspart targeted average pre-next-meal BG values between 100 and 120 mg/dL

Endpoints

- Hypoglycaemia was defined as
  - total: all hypoglycaemic events (any symptomatic or asymptomatic hypoglycaemic event)
  - confirmed: any hypoglycaemic event with a BG value ≤ 49 mg/dL
  - nocturnal: any hypoglycaemic event occurring between midnight and 06:00 am
  - severe: any hypoglycaemic event for which the patient required assistance

Statistical Analyses

- Descriptive statistics were used to compare baseline characteristics of patients treated with TI and insulin aspart.
- Continuous variables were compared using Student t-tests and categorical variables were compared using χ^2 tests.
- Annualised hypoglycaemia event rates were determined (total number of hypoglycaemic events divided by total exposure) and adjusted for baseline HbA_{1c} level (exploratory adjustment for end of treatment HbA_{1c} was also conducted); negative binomial regression was used to compare results between TI and insulin aspart.

RESULTS

Patients and Baseline Characteristics

- Baseline characteristics of the 339 patients included in the post hoc analysis are shown in **Table 1**.
- There was no statistically significant difference in the mean number of supplemental doses taken between the TI and insulin aspart treatment arms (34.1 vs 26.6 doses, respectively; $P = 0.1907$).

Table 1. Baseline Patient Characteristics (Modified Safety Population; N = 339).

Characteristic	TI (n = 172)	Insulin Aspart (n = 167)	*P* Value
Age in years	36.9 (12.4)	39.2 (12.5)	0.0871
Male, n (%)	75 (43.6)	72 (43.1)	0.9275
Body mass index, kg/m^2	25.9 (4.4)	25.2 (4.1)	0.1292
Weight, kg	75.2 (15.5)	72.4 (15.3)	0.0893
HbA_{1c}, %	7.98 (0.77)	7.88 (0.75)	0.2431
T1DM duration, years	15.9 (10.1)	16.7 (10.0)	0.5055

Data represent mean (standard deviation) unless otherwise specified.

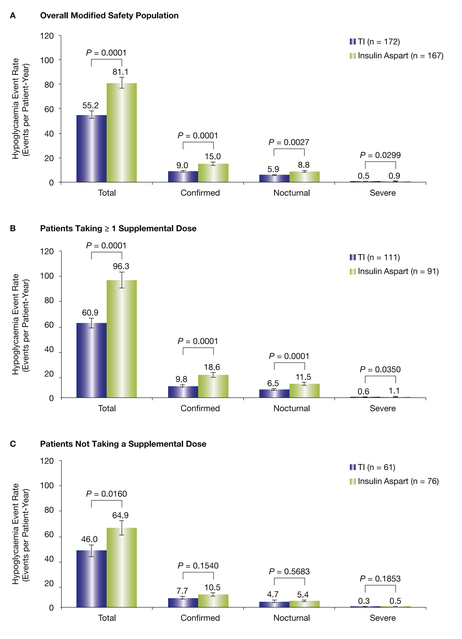
Hypoglycaemia in the AFFINITY 1 Study

- Lower hypoglycaemia events rates were seen for TI versus insulin aspart in the modified safety population (**Figure 1A**).
  - the differences observed were statistically significant for all types of hypoglycaemia assessed (total, 55.2 vs 81.1 events per patient-year, $P = 0.0001$; confirmed, 9.0 vs 15.0 events per patient-year, $P = 0.0001$; nocturnal, 5.9 vs 8.8 events per patient-year, $P = 0.0027$; and severe 0.5 vs 0.9 events per patient-year, $P = 0.0299$)
- An exploratory analysis adjusting for end of treatment HbA_{1c} level had no impact on these results.
- Similarly, in patients taking ≥ 1 supplemental dose, a lower hypoglycaemia event rate was observed in patients treated with TI compared with insulin aspart (**Figure 1B**).
  - the differences observed were statistically significant for all types of hypoglycaemia assessed (total, 60.9 vs 96.3 events per patient-year, $P = 0.0001$; confirmed, 9.8 vs 18.6 events per patient-year, $P = 0.0001$; nocturnal, 6.5 vs 11.5 events per patient-year, $P = 0.0001$; and severe, 0.6 vs 1.1 events per patient-year, $P = 0.0350$)
- In patients not taking a supplemental dose, lower rates of hypoglycaemia were observed in patients treated with TI compared with insulin aspart, but the difference was statistically significant only for total hypoglycaemia (46.0 vs 64.9 events per patient-year; $P = 0.0160$) (**Figure 1C**).

Impact of Supplemental Dosing Frequency on Hypoglycaemia

- Within both the TI and the insulin aspart treatment arms, confirmed hypoglycaemia rates ≥ 1 hour after supplemental dosing were higher in patients who had a higher supplemental dose frequency (**Figure 2**).

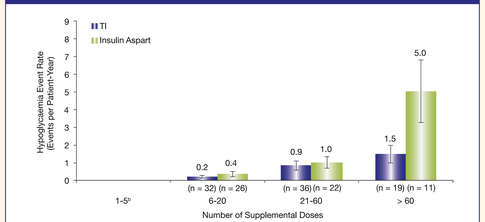
Figure 1. Hypoglycaemia Event Rates in the Overall Modified Safety Population (A), Patients Taking ≥ 1 Supplemental Dose (B), and Patients Not Taking a Supplemental Dose (C).



Error bars represent SE.
SE, standard error.

- 0.2 versus 0.9 versus 1.5 confirmed hypoglycaemia events per patient-year for patients receiving 6-20, 21-60, and > 60 supplemental doses in the TI treatment arm, respectively
  - these differences were statistically significant between patients receiving 6-20 versus 21-60 supplemental doses ($P = 0.0059$) and 6-20 versus > 60 supplemental doses ($P = 0.0001$), but not between patients receiving 21-60 versus > 60 supplemental doses ($P = 0.1588$)
- 0.4 versus 1.0 versus 5.0 confirmed hypoglycaemia events per patient-year for patients receiving 6-20, 21-60, and > 60 supplemental doses in the insulin aspart treatment arm, respectively
  - these differences were not statistically significant between patients receiving 6-20 versus 21-60 supplemental doses ($P = 0.1293$), but were between patients receiving 6-20 versus > 60 ($P = 0.0001$) and 21-60 versus > 60 supplemental doses ($P = 0.0146$)

Figure 2. Confirmed Hypoglycaemia Event Rates in the TI and Insulin Aspart Treatment Groups According to Number of Supplemental Doses Taken.[a]



[a]No statistically significant differences were observed in rates of confirmed hypoglycaemia between the TI and insulin aspart treatment arms in patients receiving 6-20 and 21-60 supplemental doses ($P = 0.2674$ and $P = 0.8017$, respectively). In patients receiving > 60 supplemental doses there was a significantly higher rate of hypoglycaemia observed in the insulin aspart treatment arm compared with the TI treatment arm ($P = 0.0083$). [b]Event rates for patients receiving 1-5 supplemental doses were not estimable for confirmed hypoglycaemia.

- There was no statistically significant difference observed in rates of confirmed hypoglycaemia between the TI and insulin aspart treatment arms in patients receiving 6-20 and 21-60 supplemental doses. In patients receiving > 60 supplemental doses there was a significantly higher rate of hypoglycaemia observed in the insulin aspart treatment arm compared with the TI treatment arm ($P = 0.0083$).

Hypoglycaemia in the Titration and Maintenance Phases of the AFFINITY 1 Study

- In the modified safety population, within the TI treatment arm, there was no statistically significant difference in the rate of hypoglycaemia (all types) during the titration phase compared with the maintenance phase (**Table 2**).
- In the modified safety population, within the insulin aspart treatment arm, higher rates of total and confirmed hypoglycaemia were observed during the titration phase compared with the maintenance phase; these differences were statistically significant (total, 90.5 vs 75.2 events per patient-year, $P = 0.0308$; and confirmed, 17.5 vs 13.1 events per patient-year, $P = 0.0297$) (**Table 2**).
- In patients taking a supplemental dose, within both treatment arms, there was no statistically significant difference in the rate of hypoglycaemia (all types) during the titration phase versus the maintenance phase (**Table 2**).
- In patients taking a supplemental dose, significantly lower rates of total, confirmed, and nocturnal hypoglycaemia were observed in the TI treatment arm compared with the insulin aspart treatment arm, during both the titration and maintenance phases.
- In patients not taking a supplemental dose, within the TI treatment arm, there was no statistically significant difference in the rate of hypoglycaemia (all types) during the titration phase compared with the maintenance phase (**Table 2**).
- In patients not taking a supplemental dose, within the insulin aspart treatment arm, higher rates of total and confirmed hypoglycaemia were observed during the titration phase versus the maintenance phase; these differences were statistically significant (total, 79.8 vs 57.2 events per patient-year, $P = 0.0064$; and confirmed, 14.1 vs 8.4 events per patient-year, $P = 0.0056$) (**Table 2**).

LIMITATIONS

- This study methodology was a non pre specified post hoc analysis.
- Correction for multiple comparisons is warranted.
- However, the data reported here do provide more detail and demonstrate consistency regarding the hypoglycaemia benefits observed with TI compared with insulin aspart.

Table 2. Hypoglycaemia Event Rates During the Titration and Maintenance Phases of the Study.

	Hypoglycaemia, Events per Patient-Year (SE)				
	Titration Phase	*P* Value (Between Treatment Arms)	Maintenance Phase	*P* Value (Between Treatment Arms)	*P* Value (Within Treatment Arm)
Overall modified safety population					
Total TI	57.9 (3.5)		56.2 (3.8)		0.7550
Total insulin aspart	90.5 (5.4)	0.0001	75.2 (4.6)	0.0028	0.0308
Confirmed TI	9.7 (1.0)		8.8 (1.0)		0.5373
Confirmed insulin aspart	17.5 (1.6)	0.0001	13.1 (1.3)	0.0083	0.0297
Nocturnal TI	6.2 (0.7)		5.9 (0.7)		0.7710
Nocturnal insulin aspart	9.4 (0.9)	0.0031	8.3 (0.8)	0.0296	0.3737
Severe TI	0.6 (0.1)		0.4 (0.1)		0.2203
Severe insulin aspart	0.9 (0.2)	0.2259	0.9 (0.2)	0.0197	0.8131
Patient taking a supplemental dose					
Total TI	62.0 (3.9)		64.3 (4.8)		0.7066
Total insulin aspart	102.1 (7.9)	0.0001	95.8 (7.7)	0.0003	0.5660
Confirmed TI	10.1 (1.2)		10.6 (1.5)		0.7970
Confirmed insulin aspart	21.1 (2.6)	0.0001	18.5 (2.4)	0.0037	0.4462
Nocturnal TI	7.0 (0.9)		6.8 (1.0)		0.8974
Nocturnal insulin aspart	12.5 (1.5)	0.0001	11.6 (1.5)	0.0064	0.6767
Severe TI	0.6 (0.2)		0.6 (0.2)		0.9722
Severe insulin aspart	1.3 (0.4)	0.0866	1.1 (0.4)	0.1667	0.6311
Patient not taking a supplemental dose					
Total TI	50.7 (6.1)		46.8 (5.7)		0.6355
Total insulin aspart	79.8 (6.8)	0.0001	57.2 (5.0)	0.2034	0.0064
Confirmed TI	8.9 (1.7)		6.7 (1.3)		0.2924
Confirmed insulin aspart	14.1 (1.8)	0.0381	8.4 (1.1)	0.3280	0.0056
Nocturnal TI	4.9 (0.9)		4.9 (0.9)		0.9788
Nocturnal insulin aspart	6.5 (0.9)	0.2148	5.4 (0.8)	0.6921	0.3471
Severe TI	0.6 (0.3)		0.1 (0.1)		0.0604
Severe insulin aspart	0.5 (0.2)	0.7419	0.7 (0.2)	0.0154	0.5461

CONCLUSIONS

- These data show that there was a consistently lower hypoglycaemia rate in patients with T1DM treated with TI versus insulin aspart, including in those patients taking supplemental doses.
- This lower hypoglycaemia rate persisted during both the titration and maintenance phases of the study.
- The more rapid-acting profile of TI was not associated with a statistically significant increase in supplemental dosing compared with insulin aspart.

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