

Reduced Incidence and Frequency of Hypoglycemia in an Integrated Analysis of Pooled Data from Clinical Trials of Subjects with Type 2 Diabetes Using Prandial Inhaled Technosphere® Insulin

Daniel Lorber¹, Campbell P. Howard², Hao Ren², Alicia Rossiter², Anders H. Boss²

¹Diabetes Care and Information Center of New York, Flushing, NY; ²MannKind Corporation, Valencia, CA

ABSTRACT

Objective: Insulin human [rDNA] Inhalation Powder (AFREZZA™ or Technosphere® Insulin) is an ultra rapid-acting insulin with a pharmacokinetic profile that may result in a lower rate of postprandial hypoglycemia when used as a prandial insulin. We explored this hypothesis by carrying out an integrated analysis of the pooled data from 6 Phase 2/3 clinical trials in subjects with type 2 diabetes mellitus inadequately controlled (HbA1c ≥6.6% and ≤12.0%) despite insulin with or without oral antihyperglycemic therapy.

Methodology: Subjects were randomized to treatment regimens to achieve predefined glycemic goals: AFREZZA (n=1795) or sc insulin (n=942), which included BPA 70/30, or insulin aspart and "usual care," with insulin adjustments according to investigator discretion in 5 trials in which structured titration regimens were not enforced and 1 trial with forced titration. When experiencing hypoglycemic-like symptoms, subjects were instructed to confirm the event with a blood glucose reading. Subjects experiencing a severe hypoglycemic episode were required to report the details of third-party assistance (if needed), the presence of neurologic symptoms, and the specifics of treatment.

Result: Mean baseline characteristics were similar for AFREZZA and sc insulin (age 56.2, 55.6 years; disease time since diagnosis 10.8, 12.4 years; Baseline HbA1c 8.82%, 8.84%; BMI 31.07, 31.07 kg/m²). Subjects treated with AFREZZA experienced statistically significantly fewer hypoglycemic episodes in regard to both incidence and frequency compared with subjects treated with sc insulins. For incidence, significantly fewer subjects reported hypoglycemia with AFREZZA: 31.8% vs 49.6% for total hypoglycemia (OR 0.466; p<0.0001), 31.6% vs 49.4% for mild/moderate hypoglycemia (OR 0.466; p<0.0001), and 2.8% vs 7.5% for severe hypoglycemia (OR 0.359; p<0.0001). For frequency, AFREZZA also had significantly fewer events, evaluated by event rate (number of events per 100 subject-months): 23.87 vs 38.78 for total hypoglycemia (p<0.0001); 23.16 vs 37.32 for mild/moderate hypoglycemia (p<0.0001); and 0.66 vs 1.37 for severe hypoglycemia (p<0.0184).

Conclusion: AFREZZA, often in combination with a basal insulin, consistently reduced the incidence and frequency of both mild/moderate and severe hypoglycemic events under conditions of comparable glycemic control.

BACKGROUND AND AIMS

- ✦ Fear of hypoglycemia is a common deterrent to the initiation of insulin in patients with type 2 diabetes (T2DM).¹ Once insulin therapy is initiated, concerns about risk of hypoglycemia as well as the actual episodes themselves often limit insulin dosing, thereby preventing adequate blood glucose (BG) control.²
- ✦ A recent report found that insulin-treated patients with T2DM experience ~16.4 episodes of hypoglycemia per year, with 0.35 of these episodes per patient per year (~5 episodes per year) being considered severe hypoglycemic events.³
- ✦ New treatments are needed for patients with T2DM that lower the risk for hypoglycemia, thus allowing for more effective insulin titration and improved glycemic control.
- ✦ MannKind Corporation is developing the Technosphere® Insulin Inhalation System (AFREZZA™) for the control of hyperglycemia in adult patients with diabetes. Once inhaled, AFREZZA dissolves immediately upon contact with the lung surface and the insulin is rapidly absorbed into the systemic circulation with a time to maximum observed concentration (t_{max}) of approximately 14 minutes in subjects with type 2 diabetes. As a result of the rapid absorption, the metabolic effects of AFREZZA achieve maximum effect substantially earlier than has been reported for other insulins. In clinical studies, the majority of the glucose-lowering effect of AFREZZA is delivered in the first 3 hours postdose, thereby reducing the risk for and the incidence of hypoglycemia.

METHODOLOGY

- ✦ Subjects were randomized to the following treatment regimens and insulin adjustments were made according to investigator discretion in 5 trials and forced titration in 1 trial: AFREZZA (n=1795) or subcutaneous (sc) insulin (n=942), which included biphasic aspart (BPA) 70/30 BID, insulin aspart TID, and "usual antidiabetic care with insulin."
- ✦ Subjects in the AFREZZA group received AFREZZA 3-4 times per day before meals or snacks, alone or in combination with sc insulin glargine QD.
- ✦ Mild/moderate hypoglycemia was defined as a BG <63 mg/dL (3.5 mmol/L) or hypoglycemia-like symptoms.
- ✦ Severe hypoglycemia was defined as a BG ≤36 mg/dL (2.0 mmol/L) or when all 3 of the following occurred simultaneously – subject required the assistance of another person; AND subject exhibited at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness); AND a measured BG ≤49 mg/dL (2.7 mmol/L), or, in the absence of a BG measurement, clinical symptoms were reversed by oral carbohydrates, sc glucagon or intravenous glucose administration. Or in some smaller trials, events that required glucagon injections, glucose infusions, or third party assistance.
- ✦ An integrated analysis of hypoglycemia using pooled data from the active-controlled Phase 2/3 trials (similarity of trial design and continuous exposure to study treatment of >14 days) was performed comparing AFREZZA with sc insulin comparators.

RESULTS

Baseline Characteristics

At Baseline, both treatment groups were similar with respect to age, BMI, HbA1c, and duration of type 2 diabetes (Table 1).

Incidence of Hypoglycemia

Subjects treated with AFREZZA had a lower incidence of hypoglycemia than sc insulin comparators in all assessed categories, with statistically significant differences for total, mild/moderate, and severe hypoglycemia, including those events with a BG ≤49 mg/dL (≤2.7 mmol/L) and ≤36 mg/dL (≤2.0 mmol/L) (Table 2).

	AFREZZA (n=1795)	SC Insulin Comparators (n=942)
Age (years)	56.2 (8.7)	55.6 (8.9)
Time Since Diagnosis (years)	10.8 (6.7)	12.4 (7.3)
Baseline HbA1c (%)	8.8 (1.3)	8.8 (1.3)
BMI (kg/m ²)	31.1 (4.8)	31.1 (4.9)

Table 2. Incidence of Hypoglycemia in T2DM, AFREZZA vs SC Insulin Comparators (Safety Population)

	AFREZZA vs SC Insulin Comparators		AFREZZA vs SC Insulin Comparators		
	AFREZZA (n=1795)	SC Insulin Comparators (n=942)	Odds Ratio	95% CI	p Value
Mild/Moderate	567 (31.6)	465 (49.4)	0.466	[0.395, 0.550]	<0.0001
Severe	50 (2.8)	71 (7.5)	0.359	[0.247, 0.520]	<0.0001
Total	570 (31.8)	467 (49.6)	0.466	[0.395, 0.550]	<0.0001
With Cognitive Neurological Symptom	7 (0.7)	13 (1.7)	0.429	[0.170, 1.080]	0.0724
With Glucose ≤49 mg/dL (≤2.7 mmol/L)	301 (16.8)	270 (28.7)	0.501	[0.414, 0.607]	<0.0001
With Glucose ≤36 mg/dL (≤2.0 mmol/L)	47 (2.6)	70 (7.4)	0.372	[0.258, 0.537]	<0.0001

Hypoglycemia Event Rates

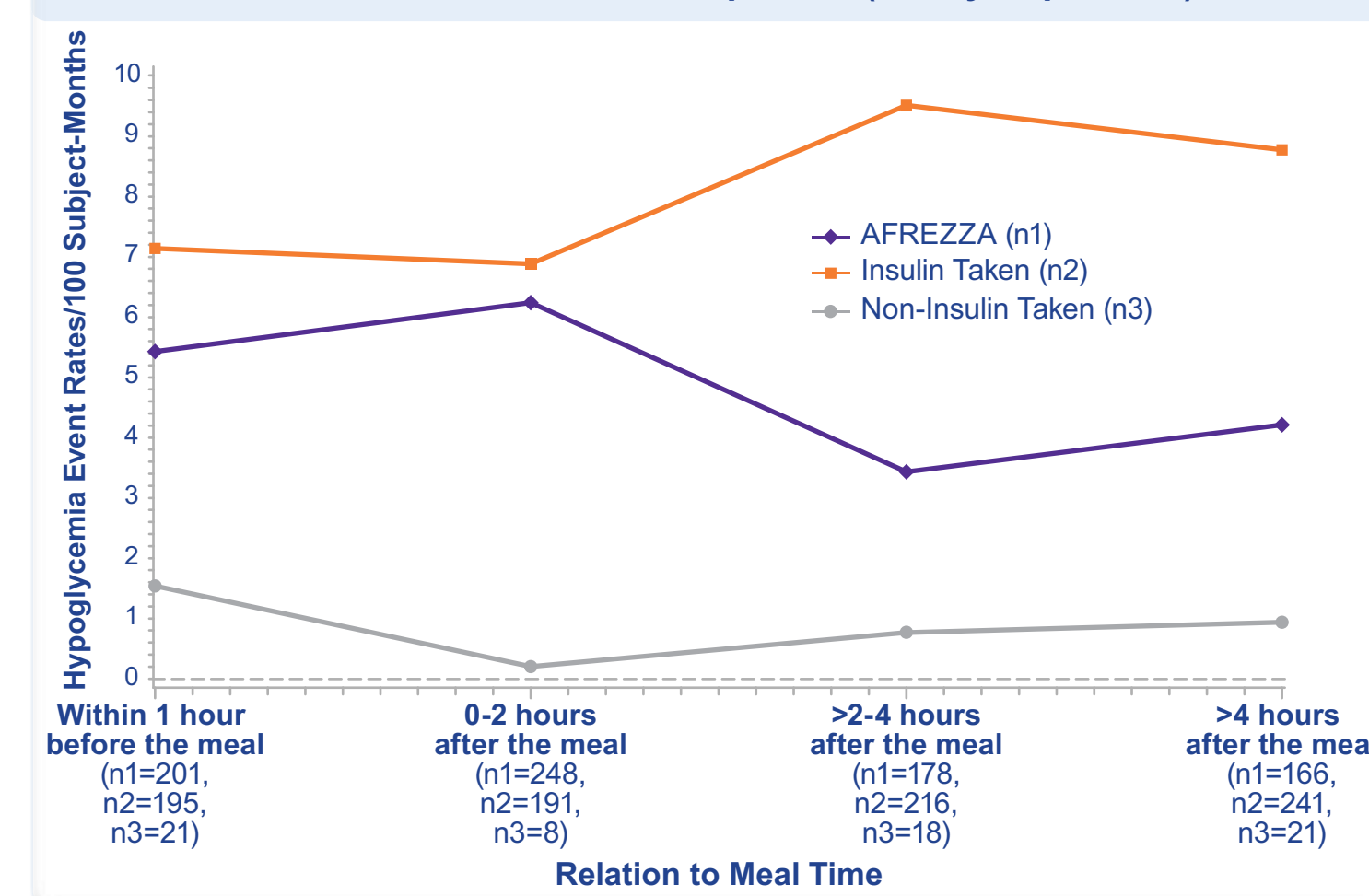
Subjects treated with AFREZZA had significantly lower hypoglycemia event rates than sc insulin comparators with respect to total, mild/moderate, and severe hypoglycemia, as well as subjects with BG ≤36 mg/dL (≤2.0 mmol/L).

For the category of subjects at risk for cognitive neurological symptoms, analyses covered only some of the Phase 3 studies – where the safety data bases could be queried for this category. For other categories of hypoglycemia, event rates were calculated from all pooled, active controlled studies, so the number of subjects at risk was larger (Table 3, right).

Hypoglycemia Event Rates in Relation to Meal Time

The AFREZZA time-action profile translates into a lower risk of hypoglycemic events overall in subjects with T2DM, with a considerably lower risk of hypoglycemia at the ">2 hours after a meal" time period (Figure 1).

Figure 1. Mild/Moderate Hypoglycemia Event Rates in Relation to Meal Time, AFREZZA vs SC Insulin Comparator (Safety Population)



RESULTS (CONTINUED)

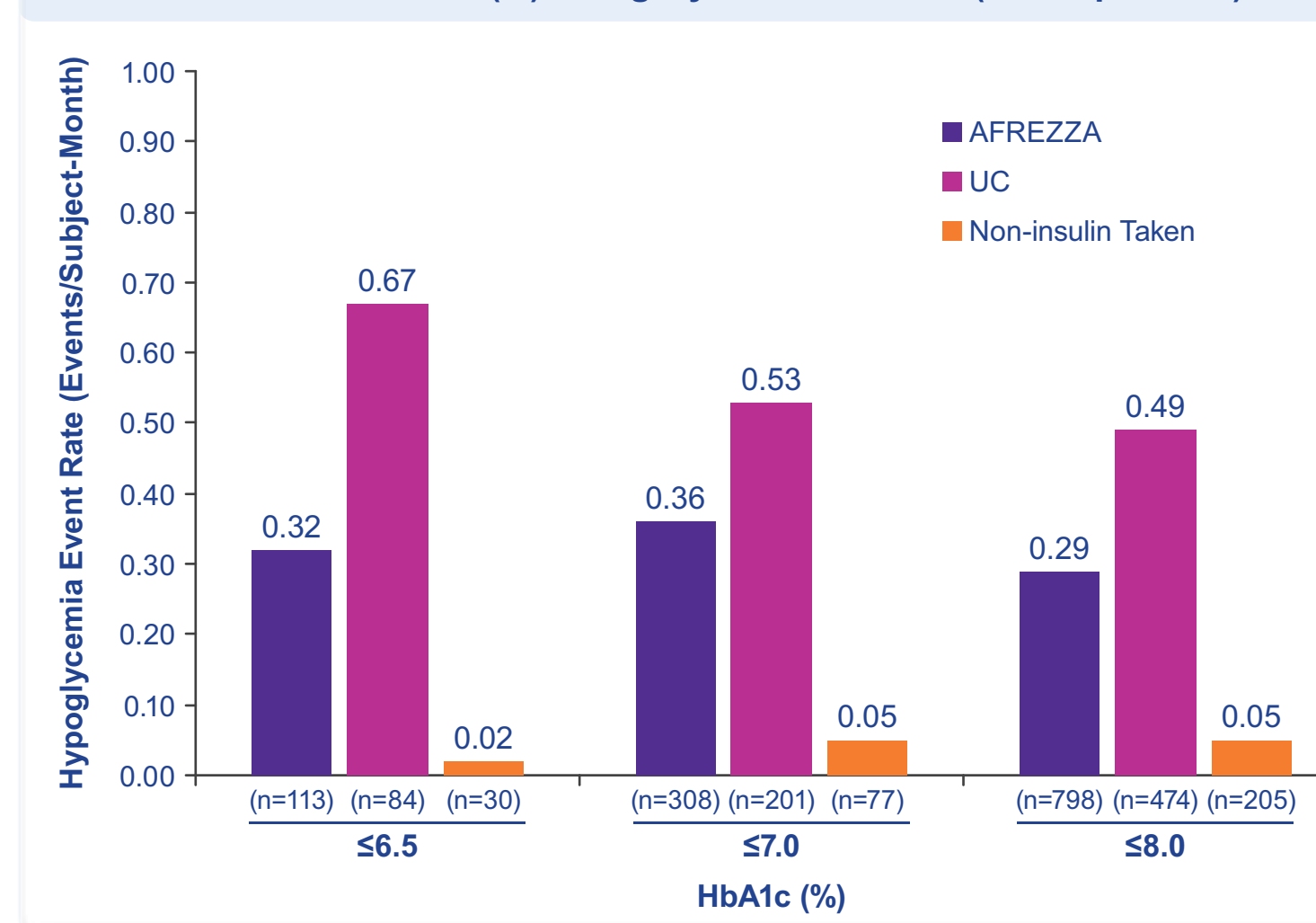
Hypoglycemia Event Rate Based on End-of-Trial HbA1c Category and Treatment

✦ Event rates of total hypoglycemia, when stratified by end-of-trial HbA1c levels, were always markedly lower in subjects treated with AFREZZA vs sc insulin comparators (Figure 2).

✦ Thus, at equivalent levels of HbA1c control, AFREZZA has a markedly improved hypoglycemic risk profile compared to sc insulin comparators.

Category	AFREZZA + Basal Insulin (n=1795)	SC Insulin Comparators (n=942)	AFREZZA + Basal Insulin p Value
Total			
No. of Subjects at Risk	1795	942	
No. of Subjects w/Events (%)	570 (31.8)	467 (49.6)	
No. of Events	3653	4862	
Exposure Time (subject-month)	15305.2	12536.9	
Event Rate (per 100 subject-month)	23.9	38.8	<0.0001
Mild/Moderate			
No. of Subjects at Risk	1795	942	
No. of Subjects w/Events (%)	567 (31.6)	465 (49.4)	
No. of Events	3545	4679	
Exposure Time (subject-month)	15305.2	12536.9	
Event Rate (per 100 subject-month)	23.2	37.3	<0.0001
Severe			
No. of Subjects at Risk	1795	942	
No. of Subjects w/Events (%)	50 (2.8)	71 (7.5)	
No. of Events	101	172	
Exposure Time (subject-month)	15305.2	12536.9	
Event Rate (per 100 subject-month)	0.66	1.37	0.0184
Cognitive Neurological Symptoms			
No. of Subjects at Risk	979	787	
No. of Subjects w/Events (%)	7 (0.7)	13 (1.7)	
No. of Events	7	19	
Exposure Time (subject-month)	12763.8	11675.8	
Event Rate (per 100 subject-month)	0.05	0.16	
Glucose ≤36 mg/dL (≤2.0 mmol/L)			
No. of Subjects at Risk	1795	942	
No. of Subjects w/Events (%)	47 (2.6)	70 (7.4)	
No. of Events	97	167	
Exposure Time (subject-month)	15305.2	12536.9	
Event Rate (per 100 subject-month)	0.63	1.33	0.0187

Figure 2. Event Rate of Hypoglycemia for Subjects Based on End-of-Trial HbA1c (%) Category and Treatment (ITT Population)



DISCUSSION

In Subjects with T2DM:

- ✦ The incidence and frequency of severe hypoglycemic events were significantly lower with AFREZZA than with sc insulin comparator regimens in subjects with T2DM.
- ✦ The incidence and frequency of nonsevere (mild/moderate) hypoglycemic events were significantly lower with AFREZZA than with sc insulin comparator regimens in subjects with T2DM.
- ✦ The incidence and frequency of total hypoglycemic events were significantly lower with AFREZZA than with sc insulin comparator regimens in subjects with T2DM.
- ✦ There were fewer nocturnal hypoglycemic events, for both severe and mild/moderate, in subjects treated with AFREZZA than with sc insulin comparator regimens: 2.2 vs 4.6 per 100 subject-months, respectively, for mild/moderate event rates and 0.1 vs 0.2 per 100 subject-months, respectively, for severe event rates.

CONCLUSION

- ✦ Under conditions of comparable HbA1c control, the incidence and frequency of hypoglycemic events in AFREZZA-treated subjects were significantly lower than the sc insulin comparator treatment in subjects with T2DM.

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Contact: Campbell Howard ✦ 201.983.5033 ✦ choward@mannkindcorp.com
MannKind Corporation ✦ 61 South Paramus Road ✦ Paramus, NJ 07652