

Hypoglycemia in Patients with Type 1 Diabetes Mellitus Incorporating Prandial Inhaled Technosphere® Insulin into Their Usual Diabetes Treatment Regimen vs Continuing Their Usual Diabetes Management

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ABSTRACT

Objective: Insulin human [rDNA origin] Inhalation Powder (AFREZZA™ or Technosphere® Insulin) is an ultra rapid-acting inhaled insulin with a pharmacokinetic profile well suited for control of postprandial plasma glucose. This is to report the results of prespecified secondary safety endpoints from MKC-T1 030, a prospective, multisite parallel-group study comparing the efficacy and safety of prandial AFREZZA vs usual diabetes care (UC) in patients with type 1 diabetes mellitus and inadequate glycemic control (HbA1c >6.6% and <12.0%) despite subcutaneous insulin therapy.

Methodology: Subjects with type 1 diabetes were randomly assigned to a 2-year diabetes treatment regimen consisting of prandial AFREZZA plus subcutaneous basal insulin (AFREZZA group, n=267) or usual diabetes treatment regimens of any insulin (subcutaneous basal and/or prandial), the UC group (n=271). Insulin doses were adjusted according to investigator discretion to achieve glycemic goals established by the American Diabetes Association and the American Association of Clinical Endocrinologists; they were not instructed to follow a protocol-specified insulin dose titration regimen. Prespecified endpoints included change in HbA1c, change in body weight, and frequency of defined mild, moderate, and severe hypoglycemia.

Result: Mean baseline characteristics were similar between the AFREZZA and UC groups: mean age 40.0, 39.4 years; diabetes duration 15.7, 15.1 years; Baseline HbA1c 8.7%, 8.5%; and BMI 26.3, 26.3 kg/m², respectively. The average daily dose in the AFREZZA group was 138.3±61.6 U (roughly 20% bioavailability relative to rapid-acting analog). Basal insulin therapies were similar in both groups. At the 2-year time point, there was comparable reduction in HbA1c (by 0.29% and 0.31% in the AFREZZA and UC groups, respectively). AFREZZA resulted in weight loss, while UC resulted in weight gain (-0.59 vs +1.38 kg, respectively; p=0.0007). Overall event rates were 0.86/subject-month for the AFREZZA group (2.36 severe events/100 subject-months) vs 0.70 for the UC group (3.76 severe).

Conclusion: Diabetes treatment regimens containing prandial AFREZZA resulted in HbA1c reductions that were comparable, weight loss, and less hypoglycemia in patients with type 1 diabetes mellitus and inadequate glycemic control compared with conventional diabetic regimens utilizing subcutaneous prandial insulin.

INTRODUCTION

Technosphere® insulin is a rapid-acting inhaled insulin with pharmacokinetics well suited for control of postprandial plasma glucose.¹ As part of the evaluation of the efficacy and safety of AFREZZA in this larger type 1 population, glycemic control was prespecified as a secondary endpoint in a 2-year study whose primary endpoint was pulmonary safety. This study was powered to achieve this primary endpoint, but not the secondary glycemic-related endpoint.

The Safety Population included all randomized subjects who received at least one dose of insulin. The Intent-To-Treat (ITT) Population included all subjects who were in the Safety Population, had a baseline value, and at least one postbaseline value of the primary variable (FEV₁). The Per Protocol (PP) Population was defined as all subjects in ITT Population who completed the trial, had FEV₁ measurement at 24 months, and were deemed to be protocol-compliant. (Table 1)

The secondary endpoints included differences between the groups in changes in HbA1c and incidence and frequency of defined mild, moderate, and severe hypoglycemia. The protocol defined mild or moderate hypoglycemia as occurring when the subject experienced any of the 3 parameters listed below:

- hypoglycemia-like symptoms (eg, lightheadedness, palpitations, sweats, tremulousness, and headache) and a BG measurement of <63 mg/dL (3.5 mmol/L); or
- in the absence of a BG measurement, hypoglycemia-like symptoms that were relieved with carbohydrate intake or self-administered glucagon injections; or
- any BG measurement <49 mg/dL (2.7 mmol/L) and >36 mg/dL (2.0 mmol/L).

Note: BG <36 mg/dL defined the event as severe hypoglycemia

The protocol defined severe hypoglycemia when the subject experienced the 3 parameters listed below:

- the subject required the assistance of another person, and
- the subject exhibited at least 1 cognitive neurological symptom (memory loss, confusion, uncontrollable behavior, irrational behavior, unusual difficulty in awakening, seizure, loss of consciousness), and
- measured BG was <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, any measured BG <36 mg/dL (2.0 mmol/L) with or without symptoms.

Table 1. Randomization of Subjects with Type 1 Diabetes			
Study Population	AFREZZA n (%)	Usual Care n (%)	Total n (%)
Safety	267 (99.3)	271 (100.0)	538 (99.6)
Intent-To-Treat	200 (74.3)	246 (90.8)	446 (82.6)
Per Protocol	114 (42.4)	181 (66.8)	295 (54.6)

METHODS

Subjects recruited had type 1 diabetes for more than 2 years, were currently treated with insulin, were men or women between 18 and 80 years of age with BMI <42 kg/m², FEV₁ >70% of predicted, DLCO >70% of predicted, and TLC >80% of predicted, and had HbA1c >6.6% and <12.0%. Subjects with significant renal, hepatic or pulmonary disease, Grade 3 or 4 congestive heart failure, myocardial infarction within the past 6 months, unstable angina, history of malignancy or severe complications of diabetes were excluded.

STUDY MEDICATIONS AND TREATMENTS

Subjects were randomized to either incorporate AFREZZA into their usual antihyperglycemic regimen (the AFREZZA group) or continue their usual antihyperglycemic regimen over 2 years (the UC group). Investigators were asked to follow the established guidelines of the American Diabetes Association and the American Association of Clinical Endocrinologists; although one was recommended, they were not mandated to follow a protocol-specified insulin dose titration regimen. AFREZZA was administered via the MedTone® Inhaler. The active ingredient, human insulin in a dry powder formulation, was packaged as AFREZZA in pre-metered single dose cartridges containing 15 or 30 Units of insulin (estimated equivalency to be 5 and 10 IU of rapid acting analog, respectively) at each meal. All subjects received diet and exercise advice and were treated according to established guidelines.

RESULTS

Patient Demographics and Baseline Characteristics

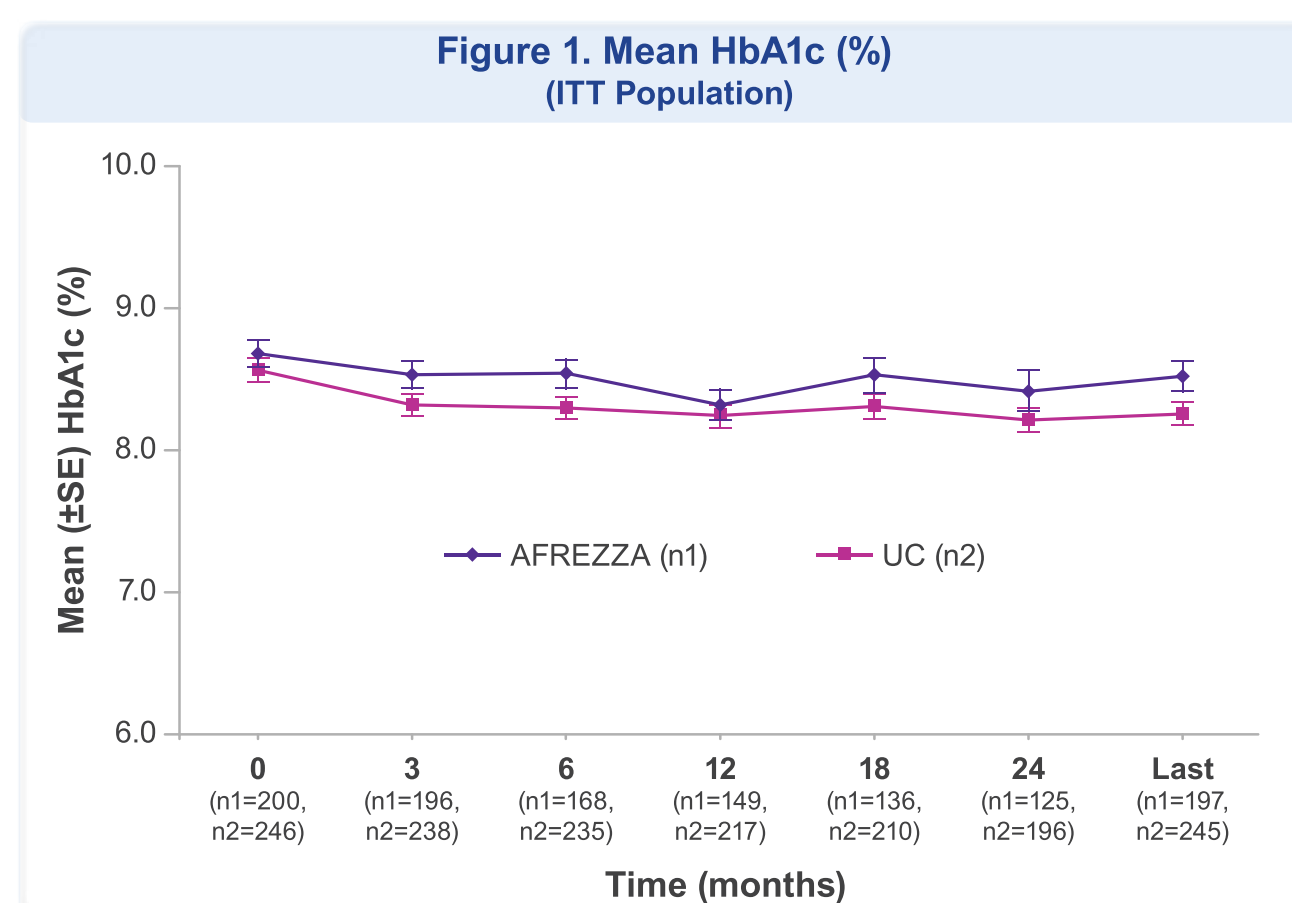
Of 3741 subjects with type 1 and type 2 diabetes screened, 267 type 1 diabetics were randomized to AFREZZA and 271 to UC. In the Safety Population, demographic and baseline characteristics were comparable between the AFREZZA and UC groups (Table 2).

Table 2. Patient Demographics and Baseline Characteristics				
Demographic/Characteristic		AFREZZA (n=267)	Usual Care (n=271)	Between Group Comparison p Value
Age (years)	Mean (SD)	40 (11.9)	39.4 (11.9)	0.541 [2]
Gender, n (%)	Male	154 (57.7)	152 (56.1)	0.728 [1]
	Female	113 (42.3)	119 (43.9)	
Race	Caucasian	254 (95.1)	255 (94.1)	0.868
	Other	13 (4.9)	16 (5.9)	
	Weight (kg)	Mean (SD)	78.26 (15.485)	
BMI (kg/m ²)	Mean (SD)	26.33 (4.217)	26.33 (4.141)	0.9909 [1]
Baseline HbA1c (%)	Mean (SD)	8.7 (1.31)	8.5 (1.31)	0.2172 [1]
Duration of Diabetes (years)	Mean (SD)	15.7 (11.17)	15.1 (9.90)	
Mean Total Daily Dose of Insulin at Study Entry	Mean (SD)	54.1 IU (24.8)	55.7 IU (2.5)	

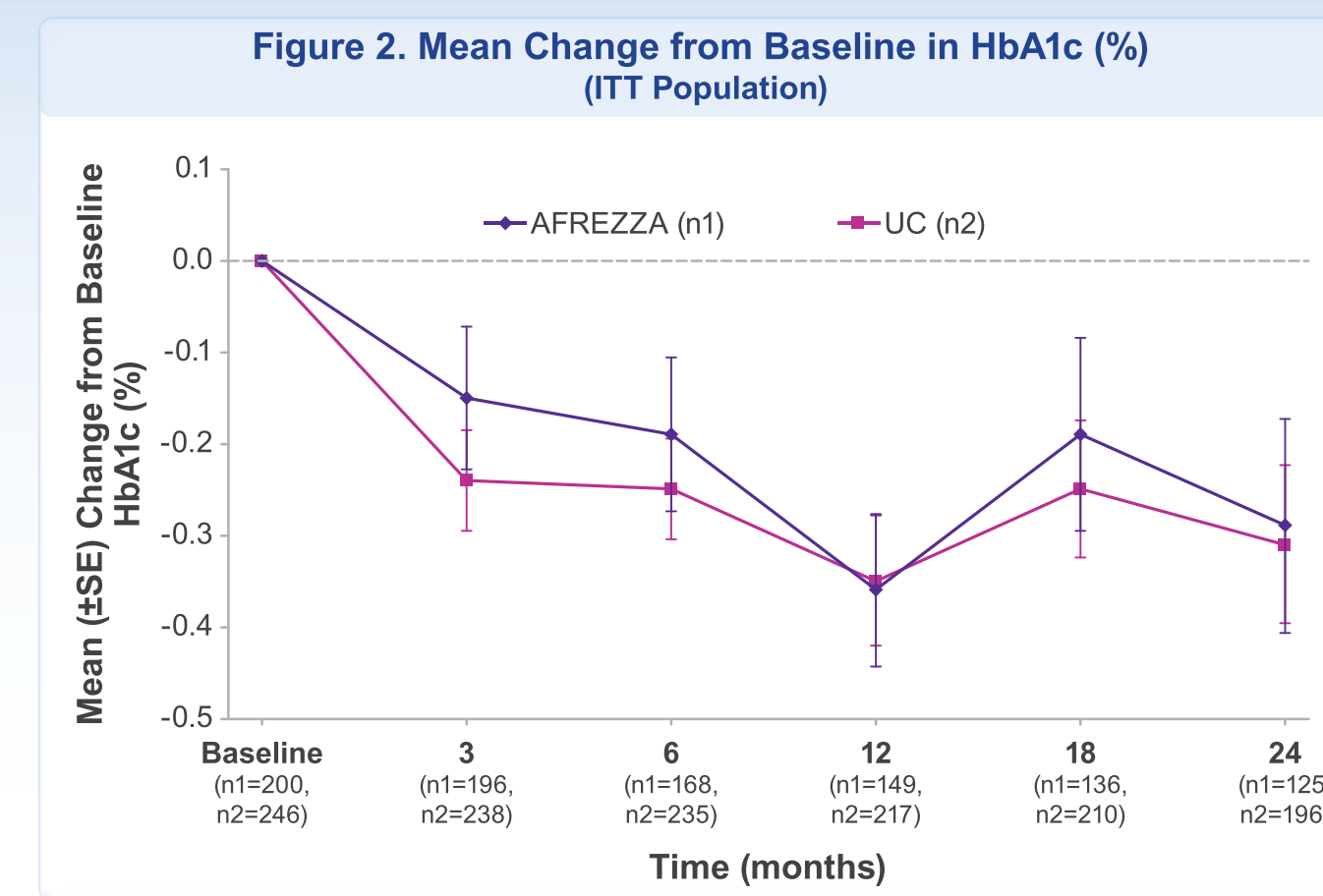
[1] Fisher's Exact Test
 [2] Two sample t test

Glycemic Control

For the ITT Population, glycemic control was achieved and maintained the same level over time, and was comparable between the AFREZZA and UC groups. Mean HbA1c change from Baseline to last measurement was -0.15% in the AFREZZA group compared to -0.30% in the UC group; for subjects who completed the trial, the change from Baseline was -0.29% in the AFREZZA group and -0.31% in the UC group. HbA1c is summarized by reported value (Figure 1) and change from Baseline (Figure 2) for the ITT Type 1 population.



RESULTS (CONTINUED)



Hypoglycemia

The incidence of hypoglycemia in the Safety Population trended lower in the AFREZZA group than in the subset of patients in the UC group who were receiving insulin therapy; this included a lower incidence of all hypoglycemic events (61.8% vs 66.05%), mild/moderate hypoglycemic events (61.42% vs 65.68%), and severe hypoglycemic events (15.73% vs 17.34%). Over the first three months of the study, while subjects were titrating the dose of AFREZZA, total hypoglycemic event rates on AFREZZA were higher (1.40 per subject month on AFREZZA and 0.83 per subject month on UC); after Month 3 and over the next 21 months, event rates were comparable (0.77 per subject month on AFREZZA and 0.68 per subject month on UC).

There were 2.36 severe hypoglycemic events/100 subject months in the AFREZZA group and 3.76 in the UC group.

Severe event rates were lower throughout all ranges of the subjects' final HbA1c value (Figure 3 and Table 3).

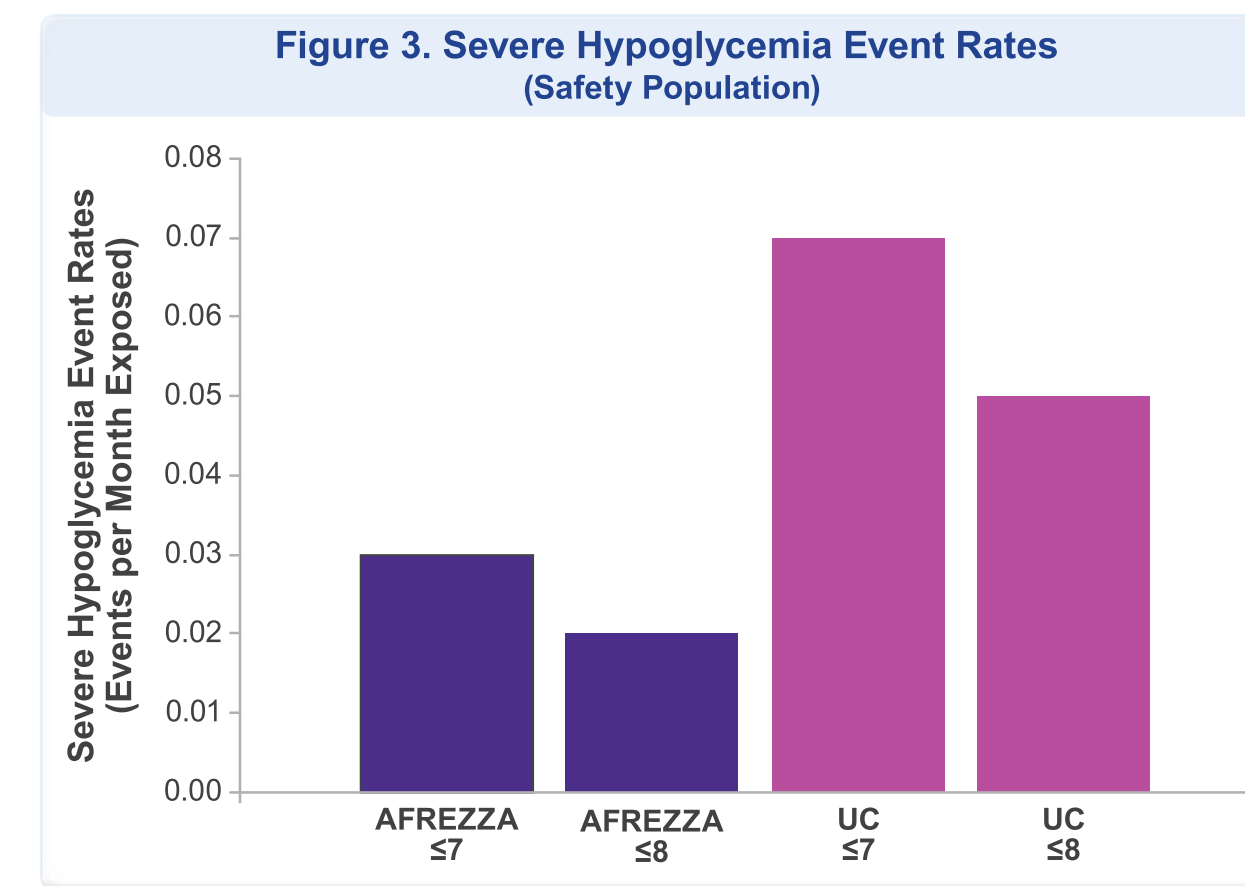
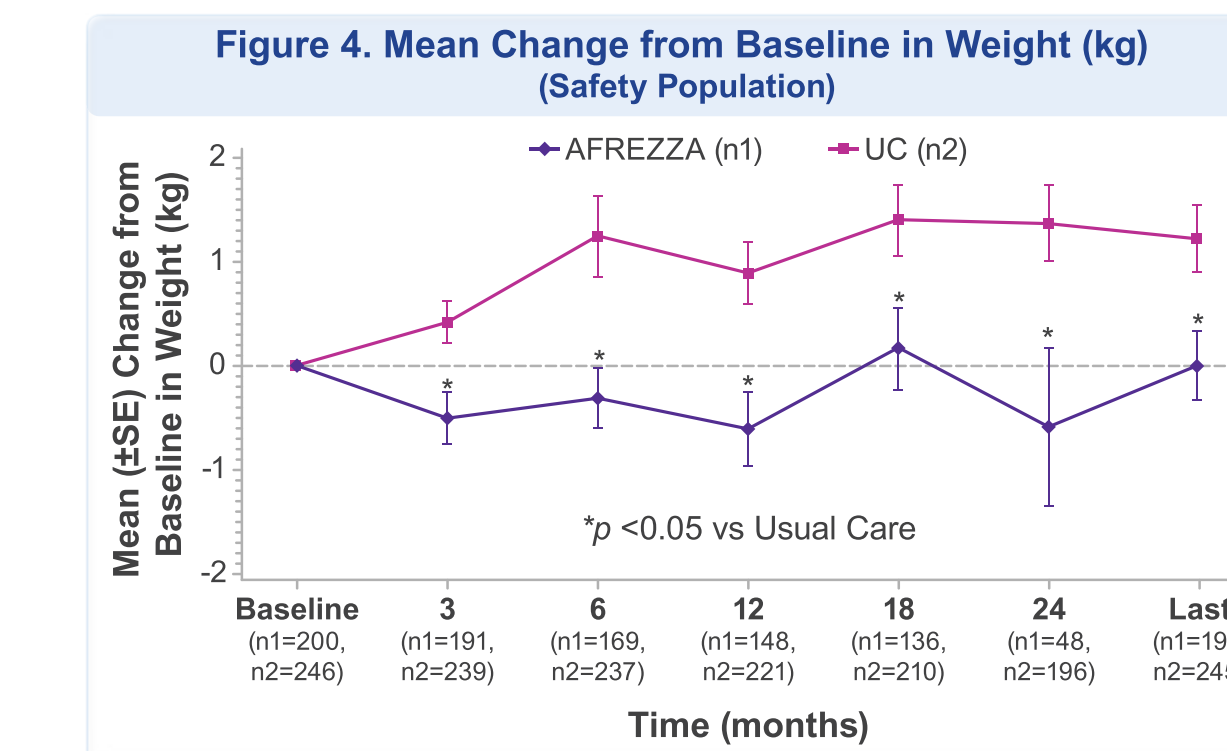


Table 3. Severe Hypoglycemia Event Rates		
Category	AFREZZA	UC
Subjects with HbA1c ≤ 7.0 at End of Study		
Number of Subjects at Risk	25	39
Number of Subjects with Events (%)	10	11
Number of Events	16	56
Exposure Time (subject-month)	483.5	752.6
Event Rate	0.03	0.07
Subjects with HbA1c ≤ 8.0 at End of Study		
Number of Subjects at Risk	88	119
Number of Subjects with Events (%)	20	28
Number of Events	31	128
Exposure Time (subject-month)	1571.6	2387.1
Event Rate	0.02	0.05

RESULTS (CONTINUED)

Changes in Body Weight

In subjects with type 1 diabetes, there was generally weight loss in the AFREZZA group (ranging between from -0.61 kg to +0.08 kg) and weight gain in the UC group (ranging between from +0.40 kg to +1.38 kg), with a statistically significant difference between the groups at each time point (Figure 4).



CONCLUSIONS

As compared with subjects receiving usual care, subjects who incorporated AFREZZA into their therapeutic regimen demonstrated:

- Comparable HbA1c reduction
- Fewer hypoglycemia events
- No weight gain

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