Effect of Afrezza on Glucose Dynamics During HCL Treatment

Alfonso Galderisi,[1,2] Nathan Cohen,[3] Peter Calhoun,[3] Kristen Kraemer,[1] Marc Breton,[4] Stuart Weinzimer,[1] and Eda Cengiz[1,5]

Diabetes Care 2020;43:2146–2152 | https://doi.org/10.2337/dc20-0091

OBJECTIVE

A major obstacle in optimizing the performance of closed-loop automated insulin delivery systems has been the delay in insulin absorption and action that results from the subcutaneous (SC) route of insulin delivery leading to exaggerated postmeal hyperglycemic excursions. We aimed to investigate the effect of Afrezza inhaled insulin with ultrafast-in and -out action profile on improving postprandial blood glucose control during hybrid closed-loop (HCL) treatment in young adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS

We conducted an inpatient, three-way, randomized crossover standardized meal study to assess the efficacy and safety of Afrezza at a low (A_L) and a high (A_H) dose as compared with a standard SC rapid-acting insulin (aspart) premeal bolus during Diabetes Assistant (DiAs) HCL treatment. Participants received two sequential meals on three study days, and premeal insulin bolus was determined based on home insulin-to-carbohydrate ratio for each meal (rounded up to the closest available Afrezza cartridge dose for A_H and down for A_L). The primary efficacy outcome was the peak postprandial plasma glucose (PPG) level calculated by pooling data for up to 4 h after the start of each meal. Secondary outcomes included hyperglycemic, hypoglycemic, and euglycemic venous glucose metrics.

RESULTS

The mean ± SD PPG for the rapid-acting insulin control arm and A_H was similar (185 ± 50 mg/dL vs. 195 ± 46 mg/dL, respectively; $P = 0.45$), while it was higher for meals using A_L (208 ± 54 mg/dL, $P = 0.04$). The A_H achieved significantly lower early PPG level than the control arm (30 min; $P < 0.001$), and improvement in PPG waned at later time points (120 and 180 min; $P = 0.02$) coinciding with the end of Afrezza glucodynamic action.

CONCLUSIONS

Afrezza (A_H) premeal bolus reduced the early glycemic excursion and improved PPG during HCL compared with aspart premeal bolus. The improvement in PPG was not sustained after the end of Afrezza glucodynamic action at 120 min.

Postprandial blood glucose is a key contributor to overall glycemic control (1,2) and acts as an independent cardiovascular risk factor (2). The essential need for optimizing postprandial glucose in type 1 diabetes is still unmet. While forefront diabetes technology based on hybrid closed-loop (HCL) systems has been proven to be effective in managing overnight and fasting blood glucose levels, it has shown limited efficacy in minimizing postmeal excursions and thus optimizing overall glycemic control (3,4). The delay in insulin absorption, as well as its prolonged action, is a major obstacle to attaining postmeal glycemic control.

[1]Department of Pediatrics, Yale School of Medicine, New Haven, CT
[2]Department of Women's and Children's Health, University of Padova, Padova, Italy
[3]Jaeb Center for Health Research, Tampa, FL
[4]Center for Diabetes Technology, University of Virginia, Charlottesville, VA
[5]Bahcesehir University School of Medicine, Istanbul, Turkey

Corresponding author: Alfonso Galderisi, alfonso.galderisi@yale.edu and alfonso.galderisi@unipd.it

Received 13 January 2020 and accepted 15 June 2020

Clinical trial reg. no. NCT03234491, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.12514949.

Delayed subcutaneous (SC) absorption of rapid-acting insulin analogs prevents current HCL systems from effectively replacing the first-phase physiologic insulin action (3–10 min from a meal), which is essential to control the early blood glucose rise (3). Strategies aimed at slowing down carbohydrate absorption or accelerating insulin action have been proposed to overcome these barriers in HCL systems (5–9) as well as to inhibit paradoxical glucagon response observed in type 1 diabetes (10,11). The adjunctive use of an SC injection of pramlintide at meal time, a synthetic analog of the peptide amylin, has been shown to reduce postprandial hyperglycemia by slowing gastric emptying and suppressing glucagon secretion (7,10). Insulin infusion site warming devices, such as the InsuPatch, have been shown to accelerate the glucodynamic action of a standardized bolus dose of aspart insulin by 35 min but failed to improve postprandial hyperglycemia when small quantities of insulin are delivered by an HCL system (5,6). Faster-acting aspart insulin, a modified formulation of aspart insulin, has been shown to have faster appearance in circulation and greater glucose-lowering effect during the first 2 h from administration than aspart (12,13). However, faster-acting aspart insulin was associated with higher 1-h postprandial glucose than aspart when used with a fully closed-loop (CL) system (14).

More recently, Afrezza inhaled insulin (MannKind Corporation, Valencia, CA) has been shown as a safe option in adults to overcome suboptimal glycemic control related to the delayed absorption of rapid-acting SC analogs, namely, mitigating postprandial hyperglycemia (15) and preventing late hypoglycemia given Afrezza's faster-in and faster-out action profile (16). Afrezza insulin plasma concentrations have been shown to reach peak levels ~12–15 min after dosing and return to baseline within 3 h from the administration, which is significantly faster than the rapid-acting insulin action profile (17).

Afrezza is a recombinant human regular insulin adsorbed onto Technosphere microparticles (18) delivered to the lungs using a breath-powered inhaler. Premeal bolus of Technosphere insulin by an older version of the inhalation delivery device during CL treatment has been shown to modestly improve time in target range during the subsequent 5 h as compared with CL without bolus at a low titration dose (16).

The current study is aimed at investigating the optimal premeal single dose of Afrezza during HCL basal insulin delivery as compared with an SC aspart insulin equivalent dose in young adults with type 1 diabetes. We hypothesized that Afrezza given before a meal to mimic physiologic first-phase insulin release would attenuate the magnitude and rate of rise of glucose levels following a meal and achieve greater % time spent within target blood glucose range compared with CL therapy with SC premeal aspart insulin bolus and will be safe to use during HCL treatment.

RESEARCH DESIGN AND METHODS

Study Design

We conducted an open-label, randomized, three-way crossover study to compare the peak postprandial glucose levels during HCL therapy using aspart insulin (control) versus Afrezza at two different doses (Afrezza high dose [A_H] and low dose [A_L]). The premeal insulin bolus was determined based on each participant's insulin-to-carbohydrate ratio for that given meal (breakfast and lunch).

On CL study days using Afrezza, subjects received a premeal Afrezza dose based on their insulin-to-carbohydrate ratio rounded down to the closest Afrezza dose, A_L, and during the other admission the dose was rounded up to the corresponding Afrezza dose, A_H. The equivalent doses of Afrezza and aspart were based on a 1:1 ratio (U.S. Food and Drug Administration [FDA] approved the dosing regimen in 2014 [19,20]) rounded up or down to the closest multiple of 4, as necessary, using cartridges of Afrezza insulin at the fixed doses of 4, 8, or 12 units. Participants were given a premeal SC insulin dose for the control HCL visit for comparison. The study procedure and meals were otherwise identical. The study protocol was approved by the Human Investigations Committee of the Yale School of Medicine (NCT03234491). Investigational device exemption was obtained for the use of HCL in the current trial (IDE G170076).

Participants provided written informed consent to participate in the study.

Study Participants

Eligible participants were young adults (aged 18–30 years) diagnosed with type 1 diabetes for >1 year and with an HbA_{1c} ≤10% (measured by DCA Vantage Analyzer; Siemens Medical Equipment, Malvern, PA).

Exclusion criteria were unstable insulin dosing parameters (requiring daily adjustments in insulin sensitivity factor, insulin-to-carbohydrate ratio, and basal rates), history of severe hypoglycemia or diabetic ketoacidosis (DKA) during the past 6 months, history of recurrent DKA defined as more than three episodes of admissions for DKA during the past 12 months, hypoglycemia unawareness, insulin total daily dose <0.1 units/kg/day and >3 units/kg/day, history of pulmonary disease, history of abnormal spirometry or chest X-ray suggestive of lung disease, smoking, allergy or known hypersensitivity for Afrezza or drugs with similar chemical structure, use of a device that may pose electromagnetic compatibility issues and/or radiofrequency interference with the Dexcom continuous glucose monitor (CGM) (implantable cardioverter defibrillator, electronic pacemaker, neurostimulator, intrathecal pump, and cochlear implants), active gastroparesis requiring current medical therapy, known bleeding diathesis or dyscrasia, any disease or exposure to any medication which may impact glucose metabolism, and pregnancy for female participants. A forced expiratory volume in 1 s (FEV_1) <70% and/or forced vital capacity (FVC) <70% than predicted were additional exclusion criteria (21).

Study Visits

Participants were randomly assigned, on each of the three study day admissions, to *1*) HCL with rapid-acting insulin analog (aspart) premeal bolus, *2*) HCL with premeal dose rounded down, or *3*) HCL with premeal dose rounded up to the higher dose of inhaled insulin. Participants were admitted in the evening on the day before the meal test for CL setup and sensor insertion. A Dexcom G5 Platinum sensor (Dexcom, San Diego, CA) was inserted in the SC space of the anterior abdominal wall, and a new insulin infusion set was placed on the contralateral side of the abdomen. The home insulin pump was replaced with the study pump (t:slim insulin pump; Tandem Diabetes Care, San Diego, CA). Both devices were components of the study HCL platform—Diabetes Assistant (DiAs)—previously described (22–27). Participants were started on CL mode after dinner to achieve target glucose in the morning. The algorithm implemented on the DiAs remained unchanged across the three study admissions and did not receive a meal announcement during the two inhaled insulin sessions. Time for active insulin was set at 5 h. Inhalation maneuver training and retraining using the Afrezza BluHale system were completed

during the screening visit and during the evening prior to each study visit.

After the overnight stay in a Yale New Haven Hospital hotel facility, participants were admitted to the Yale New Haven Hospital Research Unit at 0700 h and an intravenous catheter was placed into an arm vein for blood sampling. On each study day admission, subjects completed two standardized meal studies 4 h apart on the same day. Premeal insulin dosing was considered $t = 0$.

Three separate meal menus with the identical carbohydrate and nutrient amount were designed by the metabolic kitchen nutritionist. The total carbohydrate content was 70–80 g per meal, lipid 14–15 g, protein 25–30 g, and energy 540–570 kcal; therefore, the meal composition was the same between breakfast and lunch as well as across the three meal study visits. Each subject had the option of selecting meals from these menus prior to the first study visit and was not allowed to change the meal menu choice during the following visits.

Insulin bolus was considered $t = 0$; the meal started immediately after the initiation of insulin bolus dose and was consumed within 15 min from the bolus completion.

Plasma glucose levels were measured at the bedside by the YSI 2300 glucose analyzer (YSI Life Sciences, Yellow Springs, OH) every 5 min for the first 90 min, then every 10 min for the following 90 min, and every 15 min for the last 60 min, for a total duration of 240 min (4 h). Serum insulin levels were measured with identical intervals using Millipore ELISA assay (EMD Millipore Corporation, Burlington, MA).

CGM was calibrated 15 min prior to the first meal. CL system activity was verified, and plasma ketones were measured (Precision Xtra Blood Ketonemeter, Abbot Diabetes Care, Alameda, CA) in the morning before the beginning of the meal study. Spirometry testing was conducted at the beginning and end of the meal test to measure FEV_1 and FVC. The target premeal blood glucose was 70–180 mg/dL.

For each of the three study days, meal carbohydrate, lipid, and protein contents were standardized for each visit. The premeal bolus was calculated and verified by the research staff based on the home insulin-to-carbohydrate ratio.

Patients who were not on CGM were started on the Dexcom G5 Platinum sensor 4 weeks before the first study admission for verification of home insulin-to-carbohydrate ratio. Patients on HCL were maintained on HCL, and individual ratios were derived from the CL mode treatment of the 4 weeks preceding the first study admission.

At the end of the first 4-h meal assessment period, a second meal study was conducted, with premeal insulin bolus type identical as per randomization. Blood glucose and insulin collection timing followed the same protocol as the morning meal. At the end of the second 4-h meal assessment period, the CL system was inactivated, and subjects were discharged on home insulin regimen.

Hypoglycemia (YSI glucose values <80 mg/dL) was treated with 16 g fast-acting carbohydrate if participants were experiencing symptoms of hypoglycemia. For YSI glucose values <70 mg/dL, all subjects were given hypoglycemia treatment regardless of the symptoms.

Safety Assessment

Spirometry (FEV_1 and FVC) test was performed at the screening visit and at the beginning and at the end of each study visit, according to American Thoracic Society and European Respiratory Society recommendations (21). Prior to each session and during the study day, participants were queried for any respiratory symptoms.

Statistical Analysis

The primary outcome of the study was the peak postprandial glucose levels during 4 h after the meal bolus. Secondary outcomes included mean glucose, % time in target range (70–180 mg/dL), % time in the hypoglycemic (<70 mg/dL) and hyperglycemic (>180 mg/dL) range, coefficient of variation, and mean glucose at prespecified time points (30, 60, 90, 120, and 180 min from the meal bolus).

All venous glucose metrics were calculated by pooling all readings for up to 4 h after the start of the meal. CGM data were used to impute missing readings, and descriptive statistics appropriate to the distribution were reported for each venous glucose metric. Efficacy analyses were limited to subjects who completed the study and meals with at least 3 h of venous glucose data available prior to imputation with CGM data. A repeated-measures linear mixed model adjusting for the venous glucose level at the start of the meal, meal type (i.e., breakfast or lunch), period, and number of venous glucose measurements available during the postprandial period was used to compare treatment arms for each of the venous glucose metrics. The model accounted for the correlation between meals from the same subject and meals on the same day. Skewed outcomes were transformed using Van der Waerden scores prior to fitting of the model. Line graphs displaying the distribution of the venous glucose levels, serum insulin levels, and basal insulin infusion rates every 10 min throughout the course of the postprandial period also were created. Sensitivity analyses were conducted with use of the CGM data, as well as pooling of data up to 3 h after the start of the meal and up to the start of the next meal. Exploratory subgroup analyses also were performed by meal type. For the primary analysis, a permutation test was used to account for multiplicity. The false discovery rate was controlled using the adaptive Benjamini-Hochberg procedure for secondary outcomes.

The power calculation for the current study was performed on a subject level. Assuming a 5% significance level, a reduction of 39 mg/dL in peak glucose, and a SD of 47 mg/dL, 15 participants needed to be enrolled in order to attain 80% power.

RESULTS

Baseline Characteristics of the Study Cohort

In total, 11 subjects completed the study out of 15 who were randomized. Baseline demographic and clinical characteristics of the 15 randomized subjects and the 11 subjects in the efficacy analyses are shown in Table 1. Among the 15 who enrolled, mean $\pm$ SD age was 20 $\pm$ 3 years, 8 (53%) of the 15 subjects were male, and 14 (93%) were white. All participants were on continuous subcutaneous insulin infusion (8 of 15 on HCL, 6 on sensor-augmented pump, and 1 on continuous subcutaneous insulin infusion without a CGM) at the screening visit.

C-peptide was tested for all subjects, and all the participants had undetectable C-peptide levels (C-peptide <0.1 pmol/L).

Similar demographics and characteristics were found for the subjects included in the efficacy analysis. Of the four subjects who dropped out, two completed a single meal study visit and the other two did not complete any meal study visits. Efficacy analyses included 64 meals from 11 completers. Two control meals consumed by a subject who completed the study were excluded from analyses due to a lack of sufficient venous glucose data available (<3 h of venous glucose data available); a sensitivity analysis was performed that included these two meals and yielded similar results.

Table 1—Baseline characteristics of the study cohort

	Randomized subjects ($N = 15$)	Analyzed subjects ($N = 11$)
Age (years)[a]		
Mean ± SD	20 ± 3	21 ± 4
Range	18–30	18–30
Male sex, *n* (%)	8 (53)	6 (55)
Race/ethnicity, *n* (%)		
White non-Hispanic	14 (93)	11 (100)
Hispanic or Latino	1 (7)	0 (0)
Diabetes duration (years)		
Mean ± SD	6 ± 5	7 ± 5
Range	0–19	0–19
BMI (kg/m^2), mean ± SD	24 ± 4	24 ± 4
Total daily insulin (units/day)	48 (43, 57)	48 (43, 55)
Basal insulin (%)	43 (28, 49.5)	38.7 (27, 49.5)
HbA_{1c} (%)	7.3 (6.8, 8.0)	7.3 (6.8, 7.6)

Data are median (quartiles) unless otherwise indicated. [a]Includes one participant aged 30 years, which exceeded the maximum age limit of 29 years. A protocol deviation was logged for the inclusion of this participant.

Primary and Secondary Analyses

Results from the primary analysis and secondary analyses are shown in Table 2. The mean ± SD peak postprandial venous glucose level in the aspart premeal bolus (control arm), A_L, and A_H groups were 185 ± 50 mg/dL, 208 ± 54 mg/dL, and 195 ± 46 mg/dL, respectively. After adjustment for glucose level at the start, meal type, period, and number of glucose measurements, the mean peak in the control group was lower than for the A_L arm ($P = 0.04$) but was similar to that for the A_H arm ($P = 0.45$).

The median % time in range was similar in the control, A_L, and A_H arms (83% vs. 80% vs. 84%, respectively; $P = 0.40$ for control arm vs. A_L; $P = 0.98$ for control arm vs. A_H). The coefficient of variation also did not differ between the control group and the A_L group (26% ± 13% vs. 24% ± 10%; $P = 0.67$) or the A_H group (26% ± 13% vs. 25% ± 9%; $P = 0.70$). For mean glucose, the median for the control group was slightly lower vs. A_L (130 vs. 152 mg/dL; $P = 0.15$) but similar to that of the A_H (130 vs. 134 mg/dL; $P = 0.57$). Additionally, the median values of mean serum insulin also were similar in the control, A_L, and A_H arms (41 vs. 38 vs. 49 μU/mL, respectively; $P = 0.40$ for control arm vs. A_L; $P = 0.61$ for control arm vs. A_H).

In the control group, 9 (45%) of 20 meals included two or more consecutive YSI readings <70 mg/dL compared with 4 (18%) of 22 meals in the A_L group and 7 (32%) of 22 meals in the A_H group.

Hyperglycemia, as measured by % time >180 mg/dL, was similar across the three groups. In the control group, the median for this metric was 9% time (quartiles 0, 33) vs. 11% time (0, 53) in the A_L group ($P = 0.40$) and 8% time (0, 39) in the A_H group ($P = 0.81$). Similar results were observed for other hyperglycemic venous glucose metrics.

A trend was observed for the glucose values at fixed time points. Glucose values closer to the start of the meal (i.e., prior to 60 min) tended to be higher in the control arm compared with the Afrezza arms, while the opposite effect was observed for later time points. At 30 min from the start of the meal, the mean ± SD glucose values were 157 ± 36 mg/dL in the control arm, 130 ± 40 mg/dL ($\Delta = 19$; $P = 0.15$) in A_L group, and 118 ± 42 mg/dL $\Delta = 44$; $P < 0.001$) in the A_H group. However, at 180 min from the start of the meal, the glucose values were 122 ± 58 vs. 162 ± 47 mg/dL ($P = 0.15$) and 159 ± 49 mg/dL ($P = 0.02$), respectively. These values suggest a beneficial effect of Afrezza immediately following the meal bolus, which diminished over time.

Sensitivity Analyses

Sensitivity analyses involving CGM data and varying analysis windows were performed (Supplementary Table 1). The results of these analyses paralleled the results of the main analyses described above. In general, glucose values as measured by CGM had greater variability compared with the venous glucose values. This resulted in a lower median CGM-based % time in range and a higher mean peak glucose in all three treatment arms compared with the results based on the venous glucose data. However, relative differences between the control group and the A_L and A_H groups remained the same. Results for the outcomes calculated up to 3 h after the start of the meal and up to the start of the next meal were consistent with the results from the main analyses.

The same analyses described above were performed separately for breakfast and lunch (Table 3). All subgroup analyses were conducted separately within each of the two strata; no tests for treatment–by–meal type interactions were conducted. Overall, the control arm was comparable with the A_L and A_H arms with respect to mean peak glucose at lunch (184 ± 52 vs. 181 ± 42 vs. 180 ± 35 mg/dL, respectively; $P = 0.30$ for control arm vs. A_L; $P = 0.99$ for control arm vs. A_H). At breakfast, the mean peak glucose values were slightly lower for the control arm compared with A_L (186 ± 51 vs. 234 ± 54 mg/dL; $P = 0.06$) and A_H (186 ± 51 vs. 211 ± 51 mg/dL; $P = 0.24$).

With pooling of data across all meals in each arm, the mean basal infusion rates were 1.2, 1.5, and 1.4 units per hour in the control, A_L, and A_H arms, respectively. At breakfast, the respective values were 1.2, 1.6, and 1.5 compared with 1.3, 1.5, and 1.4 units per hour at lunchtime.

Figure 1 displays the distribution of the venous glucose values, serum insulin values, and basal insulin infusion rates by treatment arm over time throughout the course of the meal study visit. Typically, the control arm tended to have higher glucose levels immediately following the meal but lower glucose levels toward the end of the meal. The only exception was at breakfast for the control group versus A_L arm where the control arm had similar or lower mean glucose levels over the entire 4 h. Overall glucose control at breakfast was considerably better in the control arm compared with the Afrezza arms, as evidenced by the lower median mean glucose value and higher median % time in range (Table 3). Interestingly, the control arm had similar overall glucose control for breakfast and lunch, while the Afrezza arms had better glucose control at lunch.

Safety Analyses

None of the participants had severe hypoglycemia, and no CL system failure was experienced during the meal study visits. All of the participants tolerated Afrezza well, and none and had any respiratory issues, acute bronchospasm, hypersensitivity reactions, or clinically relevant decline in pulmonary function.

Table 2—Primary and secondary outcomes following in-clinic meal

	Control ($N = 20$ meals)	A_L ($N = 22$ meals)	A_H ($N = 22$ meals)	$P_{(\text{control vs. } A_L)}$	$P_{(\text{control vs. } A_H)}$
Primary outcome					
Peak postprandial glucose level (mg/dL)	185 ± 50	208 ± 54	195 ± 46	0.04	0.45
Overall glucose control					
Mean glucose (mg/dL)	130 (109, 145)	152 (132, 177)	134 (121, 169)	0.15	0.57
Coefficient of variation (%)	26 ± 13	24 ± 10	25 ± 9	0.67	0.70
% time in target range (70–180 mg/dL)	83 (63, 97)	80 (47, 100)	84 (61, 94)	0.40	0.98
Glucose levels at prespecified times					
At the start of the meal	127 ± 36	128 ± 38	136 ± 33	NA	NA
At 30 min from the start of the meal	157 ± 36	130 ± 40	118 ± 42	0.15	<0.001
At 60 min from the start of the meal	164 ± 43	162 ± 59	130 ± 56	0.72	0.40
At 90 min from the start of the meal	144 ± 55	180 ± 66	149 ± 64	0.15	0.61
At 120 min from the start of the meal	127 ± 64	186 ± 63	167 ± 58	0.07	0.02
At 180 min from the start of the meal	122 ± 58	162 ± 47	159 ± 49	0.15	0.02
Hypoglycemic outcomes					
% time <70 mg/dL	2.9 (0.0, 9.4)	0.0 (0.0, 0.0)	0.0 (0.0, 6.3)	0.97	0.57
Meals with ≥2 consecutive YSI <70 mg/dL[a]	9 (45)	4 (18)	7 (32)	NA	NA
Meals with ≥2 consecutive YSI <54 mg/dL[a]	0 (0)	1 (5)	1 (5)	NA	NA
Meals with carbohydrate rescue[a]	6 (30)	1 (5)	2 (9)	NA	NA
Hyperglycemic outcomes					
% time >140 mg/dL	53 (14, 69)	55 (34, 75)	36 (22, 74)	0.40	0.81
% time >180 mg/dL	9 (0, 33)	11 (0, 53)	8 (0, 39)	0.40	0.81
Mean serum insulin (μU/mL)	41 (31, 51)	38 (29, 54)	49 (42, 68)	0.40	0.61

Data are *n* (%), means ± SD, or median (quartiles). [a]Hypoglycemic events and carbohydrate rescues were post hoc outcomes, so *P* values were not computed for these metrics.

CONCLUSIONS

In young adults with type 1 diabetes, pre-meal A_H had an effect similar to that of a rapid-acting insulin analog on glycemic peak and time in glycemic range during the 4 h following meal challenge, when used with the HCL system. Conversely, the A_L resulted in a higher glucose peak and a % time in target range akin to that of aspart bolus over 4 h after meal.

The A_H effectively replaced first-phase insulin response by lowering glucose levels 30 min from the meal compared with aspart bolus. Neither the A_L nor the A_H increased the risk for late hypoglycemia during the 4 h after each meal.

The two major novelties of this trial are the three-arm crossover study design that

Table 3—Primary and secondary outcomes by meal type

	Control ($N = 10$ meals)	A_L ($N = 11$ meals)	A_H ($N = 11$ meals)	$P_{(\text{control vs. } A_L)}$	$P_{(\text{control vs. } A_H)}$
Breakfast					
Peak postprandial glucose level (mg/dL)	186 ± 51	234 ± 54	211 ± 51	0.06	0.24
Mean glucose (mg/dL)	135 (113, 149)	173 (148, 191)	162 (128, 169)	0.23	0.65
Coefficient of variation (%)	27 ± 14	24 ± 9	24 ± 7	0.61	0.69
% time in target range (70–180 mg/dL)	88 (65, 94)	48 (31, 100)	69 (59, 91)	0.24	0.67
% time <70 mg/dL	2.9 (0.0, 6.3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.57	0.65
Meals with ≥2 consecutive YSI <70 mg/dL[a]	4 (40)	0 (0)	2 (18)	NA	NA
Meals with ≥2 consecutive YSI <54 mg/dL[a]	0 (0)	0 (0)	0 (0)	NA	NA
Meals with carbohydrate rescue[a]	4 (40)	0 (0)	0 (0)	NA	NA
% time >140 mg/dL	63 (28, 73)	69 (53, 88)	69 (33, 79)	0.58	0.83
% time >180 mg/dL	8 (0, 32)	52 (0, 66)	31 (3, 41)	0.23	0.65
Mean serum insulin (μU/mL)	39 (35, 51)	37 (30, 60)	52 (43, 59)	0.58	0.65
Lunch					
Peak postprandial glucose level (mg/dL)	184 ± 52	181 ± 42	180 ± 35	0.30	0.99
Mean glucose (mg/dL)	115 (104, 140)	132 (113, 152)	125 (115, 141)	0.53	0.82
Coefficient of variation (%)	25 ± 13	25 ± 12	26 ± 11	0.53	0.83
% time in target range (70–180 mg/dL)	75 (59, 100)	91 (66, 100)	91 (69, 100)	0.76	0.69
% time <70 mg/dL	3.1 (0.0, 9.4)	0.0 (0.0, 9.4)	0.0 (0.0, 12.5)	0.58	0.74
Meals with ≥2 consecutive YSI <70 mg/dL[a]	5 (50)	4 (36)	5 (45)	NA	NA
Meals with ≥2 consecutive YSI <54 mg/dL[a]	0 (0)	1 (9)	1 (9)	NA	NA
Meals with carbohydrate rescue[a]	2 (20)	1 (9)	2 (18)	NA	NA
% time >140 mg/dL	36 (0, 56)	34 (25, 56)	28 (13, 44)	0.53	0.84
% time >180 mg/dL	13 (0, 34)	0 (0, 28)	0 (0, 9)	0.72	0.67
Mean serum insulin (μU/mL)	44 (30, 52)	40 (29, 54)	47 (35, 69)	0.58	0.83

Data are *n* (%), means ± SD, or median (quartiles). [a]Hypoglycemic events and carbohydrate rescues were post hoc outcomes, so *P* values were not computed for these metrics.

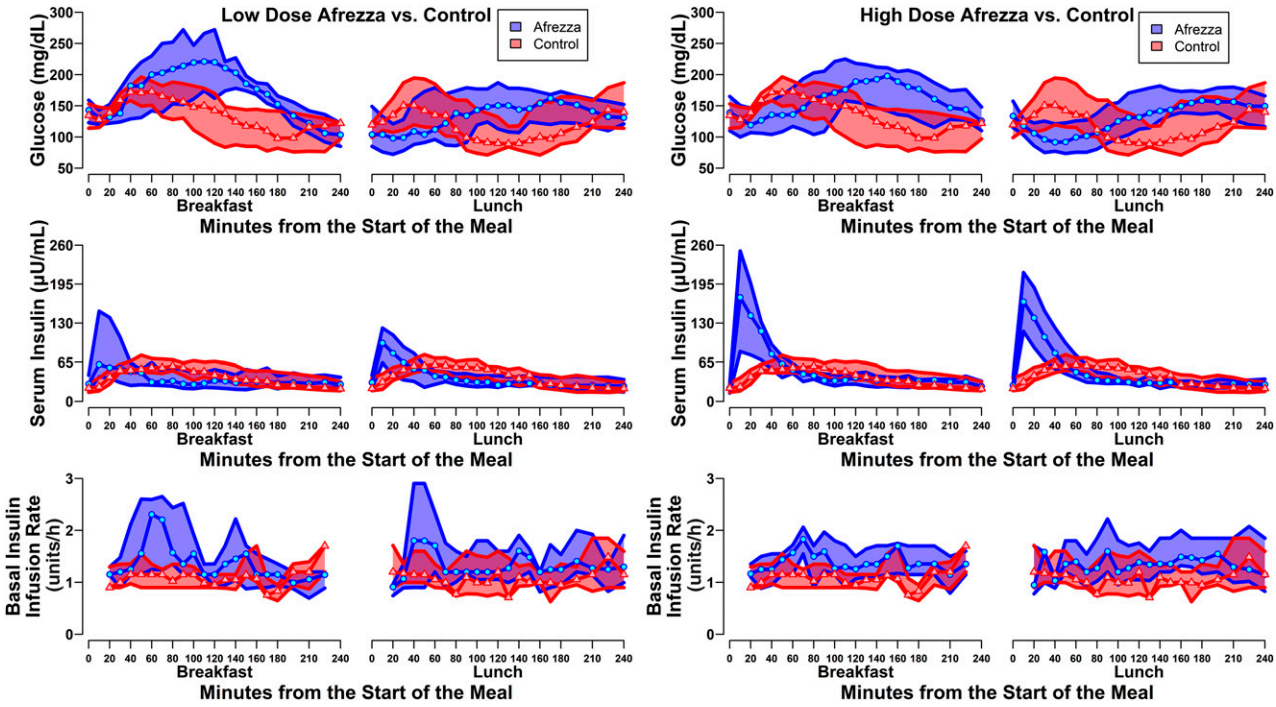

Figure 1—Comparison of venous glucose levels (upper panels), serum insulin (middle panels), and basal insulin infusion rates (lower panels) over time between the Afrezza arms and the control arm.

included two different titration doses of Afrezza versus aspart and the contemporary adoption of HCL for basal rate adjustment during each meal session.

The choice of two doses (A_H and A_L) results from the 4-unit increase limit of the Afrezza cartridges. Our findings support the use of A_H (rounded up) in light of its equivalence to the aspart bolus as well as its more pronounced effect on the 30-min glucose value compared with aspart. Notably, the rapid-acting insulin analog–to–Afrezza conversion ratio that is used to calculate Afrezza dose derived from the SC insulin–to–carbohydrate ratio was revised by the FDA during the study and was updated from 1:1 to 1:1.5 in 2017. We used the 1:1 ratio during the study for consistency given that the 1:1 ratio conversion was approved in the original protocol. The Afrezza dose calculation using a 1:1 conversion ratio led to an underestimation of the required premeal Afrezza dose both for the A_H and the A_L premeal dosing. Nevertheless, despite the disadvantage, premeal A_H dosing succeeded in controlling early postprandial plasma glucose (PPG) during HCL and was safe to use as a premeal dose in the context of HCL basal insulin delivery.

Supplemental Afrezza dosing after 1 h or 2 h from a meal, according to postprandial glucose, has been shown to increase time in target range in the absence of an increase in hypoglycemic events (28). However, the contemporary use of HCL for basal insulin adjustment was expected to overcome supplemental bolusing with the ultimate intent of simplifying meal daily management and increase therapeutic compliance in an outpatient setting.

We did not observe clinically significant changes in lung functional test (FEV_1 and FVC) from baseline nor any adverse clinical events in response to inhaled insulin, including minor symptoms such as cough, previously described in outpatient trials (15).

The inclusion of two sequential meals on the same study day, with the same nutrient composition, is a point of strength of the current study. The use of an actual meal in place of mixed-meal standard beverages makes our observations generalizable to real-life conditions, due to the more pronounced effect of delayed gastric emptying on solid, as opposed to liquid, meals (29,30).

As compared with the aspart group, whose % time in range remained consistent across the two meals (88% time vs. 75% time), both the A_L and the A_H groups exhibited a pronounced increase in the median % time in range (48–91% time and 69–91% time for A_L and A_H, respectively) in the absence of a difference in mean serum insulin between the two meals. In the absence of adaptive intervention on the model predictive control algorithm to account for Afrezza bolus, the basal insulin delivery differed across the three study admissions, with a more pronounced insulin delivery during the Afrezza admission than the control day. However, similar serum insulin levels throughout the 4-h postmeal period support the hypothesis that Afrezza use does not affect daily individual insulin requirements. In spite of the FDA-suggested conversion rate of 1:1.5, a proper adjustment of basal insulin delivery during the postmeal phase, as with HCL, is expected to improve postprandial glucose without increasing serum insulin and, as a consequence, the risk for hypoglycemia and the long-term weight gain that might be expected.

The lack of adaptive premeal intervention on the model predictive control algorithm for Afrezza meals is another limitation in optimization of Afrezza premeal bolusing. Indeed, we expect post hoc analysis from the insulin delivery rate to inform individualized model predictive control (MPC) controllers for Afrezza insulin boluses. Due to unannounced Afrezza meal boluses, the MPC-driven insulin delivery may have contributed to optimizing glycemic control for the second meal by way of increasing time in range for both A_H and A_L at lunch.

Nevertheless, integrating Afrezza with HCL systems may provide an effective method to mitigate early PPG control in the outpatient setting.

Four subjects were excluded in the primary analysis, which could affect generalizability and reduce statistical power. However, the mean peak glucose levels for A_H and control groups were similar (195 vs. 185 mg/dL, respectively).

Our study demonstrated that only the "rounded-up" premeal Afrezza (A_H) dose achieved postmeal time in range similar to that of aspart and effectively replaced first-phase insulin secretion by blunting the 30-min glucose values as compared with the aspart during HCL treatment.

In summary, HCL treatment with premeal Afrezza insulin bolus is safe and well tolerated and provides superior early PPG control compared with aspart premeal bolus. The higher glucose levels in the later part of the meal suggest that the current CL system needs to be adjusted to mitigate late postprandial hyperglycemia to account for the fast-out glucodynamic action profile.

Funding. This work has been supported by JDRF International under grants 2-APF-2019-737-A-N and JDRF 3-SRA-2016-244-M-R, the National Institutes of Health under grant 1DP3DK106826-01, the National Center for Research Resources and the National Center for Advancing Translational Science (Clinical and Translational Science Award UL1 RR024139), the International Society for Pediatric and Adolescent Diabetes (ISPAD Fellowship 2016), and Robert E. Leet and Clara Guthrie Patterson Trust Award (to A.G.).

Duality of Interest. M.B. has received research support from Tandem Diabetes Care, Dexcom, Novo Nordisk, and Sanofi; has received honorarium and consulting fees from Tandem and Dexcom; and is an author on patents owned by the University of Virginia and relevant to the subject matter. S.W. is a speaker for Insulet and Tandem; served as consultant for Eli Lilly, Sanofi, and Zealand; and received grant support (to institution) from Medtronic. E.C. is a speaker for Novo Nordisk and serves on the advisory board for Novo Nordisk, MannKind, Adocia, and Lexicon. A.G. received research support from Dexcom. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. E.C. designed the study. A.G., K.K., S.W., and E.C. enrolled the patients. A.G. and E.C. conducted the clinical study and collected patients' data. N.C. and P.C. analyzed the data. M.B. was the study engineer in charge of the HCL system and reviewed the manuscript. A.G., N.C., and E.C. drafted the manuscript. A.G., N.C., P.C., K.K., S.W., M.B., and E.C. contributed to data interpretation and critical review of the manuscript. E.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 13th International Conference on Advanced Technologies & Treatments for Diabetes, Madrid, Spain, 19–22 February 2020.

References

1. Akturk HK, Rewers A, Joseph H, Schneider N, Garg SK. Possible ways to improve postprandial glucose control in type 1 diabetes. Diabetes Technol Ther 2018;20:S224–S232
2. Ceriello A, Hanefeld M, Leiter L, et al. Postprandial glucose regulation and diabetic complications. Arch Intern Med 2004;164:2090–2095
3. Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. Diabetes Obes Metab 2012;14:780–788
4. Cengiz E. Closer to ideal insulin action: ultra fast acting insulins. Panminerva Med 2013;55:269–275
5. Cengiz E, Weinzimer SA, Sherr JL, et al. Faster in and faster out: accelerating insulin absorption and action by insulin infusion site warming. Diabetes Technol Ther 2014;16:20–25
6. Cengiz E, Weinzimer SA, Sherr JL, et al. Acceleration of insulin pharmacodynamic profile by a novel insulin infusion site warming device. Pediatr Diabetes 2013;14:168–173
7. Weinzimer SA, Sherr JL, Cengiz E, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. Diabetes Care 2012;35:1994–1999
8. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. Diabetes Care 2008;31:934–939
9. Sherr JL, Patel NS, Michaud CI, et al. Mitigating meal-related glycemic excursions in an insulin-sparing manner during closed-loop insulin delivery: the beneficial effects of adjunctive pramlintide and liraglutide. Diabetes Care 2016;39:1127–1134
10. Galderisi A, Sherr J, VanName M, et al. Pramlintide but not liraglutide suppresses meal-stimulated glucagon responses in type 1 diabetes. J Clin Endocrinol Metab 2018;103:1088–1094
11. Fredheim S, Andersen ML, Pörksen S, et al. The influence of glucagon on postprandial hyperglycaemia in children 5 years after onset of type 1 diabetes. Diabetologia 2015;58:828–834
12. Heise T, Hövelmann U, Brøndsted L, Adrian CL, Nosek L, Haahr H. Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart. Diabetes Obes Metab 2015:682–688
13. Heise T, Zijlstra E, Nosek L, Rikte T, Haahr H. Pharmacological properties of faster-acting insulin aspart vs insulin aspart in patients with type 1 diabetes receiving continuous subcutaneous insulin infusion: a randomized, double-blind, crossover trial. Diabetes Obes Metab 2017;19:208–215
14. Dovc K, Piona C, Yeşiltepe Mutlu G, et al. Faster compared with standard insulin aspart during day-and-night fully closed-loop insulin therapy in type 1 diabetes: a double-blind randomized crossover trial. Diabetes Care 2020;43:29–36
15. Bode BW, McGill JB, Lorber DL, Gross JL, Chang PC, Bregman DB; Affinity 1 Study Group. Inhaled technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. Diabetes Care 2015;38:2266–2273
16. Zisser H, Dassau E, Lee JJ, Harvey RA, Bevier W, Doyle FJ III. Clinical results of an automated artificial pancreas using technosphere inhaled insulin to mimic first-phase insulin secretion. J Diabetes Sci Technol 2015;9:564–572
17. Heinemann L, Baughman R, Boss A, Hompesch M. Pharmacokinetic and pharmacodynamic properties of a novel inhaled insulin. J Diabetes Sci Technol 2017;11:148–156
18. Rosenstock J, Franco D, Korpachev V, et al.; Affinity 2 Study Group. Inhaled Technosphere insulin versus inhaled Technosphere placebo in insulin-naïve subjects with type 2 diabetes inadequately controlled on oral antidiabetes agents. Diabetes Care 2015;38:2274–2281
19. Center for Drug Evaluation and Research: application number: 022472Orig1s000: summary review [Internet]. Available from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022472Orig1s000SumR.pdf. Accessed 1 March 2017
20. MannKind Corporation. Afrezza – Highlights of prescribing information [Internet], 2020. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022472lbl.pdf. Accessed 1 March 2017
21. Miller MR, Hankinson J, Brusasco V, et al.; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–338
22. Keith-Hynes P, Guerlain S, Mize B, et al. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. J Diabetes Sci Technol 2013;7:1416–1426
23. Kovatchev BP, Breton MD, Keith-Hynes PT, Patek SD. The Diabetes Assistant (DiAs). Unified platform for monitoring and control of blood glucose levels in diabetic patients. U.S. patent WO/2012/178134. 27 December 2012
24. Kovatchev BP, Renard E, Cobelli C, et al. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. Diabetes Care 2013;36:1851–1858
25. Kovatchev BP, Renard E, Cobelli C, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 2014;37:1789–1796
26. Place J, Robert A, Ben Brahim N, et al. DiAs web monitoring: a real-time remote monitoring system designed for artificial pancreas outpatient trials. J Diabetes Sci Technol 2013;7:1427–1435
27. Kovatchev B, Cheng P, Anderson SM, et al. Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. Diabetes Technol Ther 2017;19:18–24
28. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled Technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. Diabetes Technol Ther 2018;20:639–647
29. Lyrenås EB, Olsson EH, Arvidsson UC, Orn TJ, Spjuth JH. Prevalence and determinants of solid and liquid gastric emptying in unstable type I diabetes. Relationship to postprandial blood glucose concentrations. Diabetes Care 1997;20:413–418
30. Meier JJ, Gallwitz B, Salmen S, et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. J Clin Endocrinol Metab 2003;88:2719–2725