Protocol Title: ABC [Afrezza with Basal Combination]: A Phase 4 Study of Mealtime Control with Afrezza in Adult Subjects with Type 1 Diabetes Mellitus in Combination with an Automated Insulin Pump or Insulin Degludec

Brief Title: Afrezza With Basal Combination (ABC)

Protocol Number: MKC-TI-192

Clinical Phase: Phase 4

Protocol Version and Date: Version 2.0, 20 June 2022

Sponsor: MannKind Corporation, 30930 Russell Ranch Road, Suite 300, Westlake Village, CA 91362

NCT Number: NCT05243628

Clinical Study Protocol

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This study will be performed in compliance with Good Clinical Practice, the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

SIGNATURE PAGE

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The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol. The undersigned agree that the trial will be carried out in accordance with the clinical study protocol, Good Clinical Practice, with the Declaration of Helsinki (with amendments), and with the laws and regulations of the countries in which the study takes place.

Any modifications of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor Approval:

Signature: _____ Date: _____

Name: Kevin Kaiserman, MD

Title: Vice President, Medical Affairs and Safety
MannKind Corporation

Investigator Agreement:

I have read the clinical study protocol and agree the trial will be carried out in accordance with Good Clinical Practice, with the Declaration of Helsinki (with amendments), and with the laws and regulations of the countries in which the study takes place.

Signature: _____ Date: _____

Name (print): _____

Site Name: _____

Site Address: _____

REVISION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	MannKind	Kevin Kaiserman	01Feb2022	Original version
1.1	Johanna Ulloa	Kevin Kaiserman	04Mar2022	(1) Updated CGM language to clarify that reports will be downloaded for Medtronic CGM and pumps and reports/data will be downloaded for Dexcom CGM and Tandem pump. (2) Updated meter language to clarify that all subjects will receive a study-provided glucose meter (minimally) for collection of hypoglycemia events. (3) Updated Table 3 to review/download unblinded CGM at V2, collect glucose meter data at V14 and EOT, and clarified that insulin degludec injection supplies are only for Afrezza + Insulin Degludec group. (4) Removed placement of Dexcom G6 PRO from Section 3.7.2. (5) Clarified in section 3.8.1.1 that blinded CGM at baseline can be worn for up to 20 days during a 28-day screening window. (6) Clarified in section 3.7.2.1 that confirmation of glucose being ≥70mg/dl will happen 15 minutes before start of the meal. (7) Updated history of diabetes definition in section 3.8.2.1 to only include date of clinical diagnosis of T1DM, start date of current insulin treatments, and treatment name. (8) Incorporated vital signs as an optional procedure during the physical examination. (9) Updated statistical processing tools in section 5.3.
2.0	Jennifer Pleitez	Kevin Kaiserman	20June2022	(1) Inclusion criteria 4 revised to ensure that subjects are using the AID automated mode function (2) Added Table 4 to identify visits that require CGM/pump report/data; added one additional report to retrieve (10d prior to V9) (3) Clarified that post-meal insulin correction doses and the insulin to use for correction dose of each Afrezza treatment group. (4) Added requirement to train participants on CGM use (5) Inserted instruction to take carbs or glucagon should a subject accidentally take Afrezza with a meal announcement. (6) Inserted instruction to train subject on appropriate use of glucagon for emergency situations; language added to ensure subject has glucagon available in the event of hypoglycemia. (7) Inserted text to ensure that participants are trained to identify and manage any events of hypo and hyperglycemia. Provided specific instruction to manage DKA if glucose is >250 mg/dL (8) Added that subjects who experience respiratory symptoms that are not associated with an upper respiratory infection (URI) should undergo additional pulmonary function test to monitor clinically relevant decline. (9) Inserted text to define the clinically relevant decline in pulmonary function. (10) Inserted criteria or discontinuing the study (11) Added details of post study interview

SYNOPSIS

Protocol Title:	ABC [Afrezza with Basal Combination]: A Phase 4 Study of Mealtime Control with Afrezza in Adult Subjects with Type 1 Diabetes Mellitus in Combination with an Automated Insulin Pump or Insulin Degludec
Protocol Number:	MKC-TI-192
Sponsor:	MannKind Corporation
Investigator(s)/Study Center(s):	This study will be conducted by Investigators at two or more study centers located in the United States.
Phase of Development:	Phase 4
Objectives:	**Primary Objective:** • To evaluate the change in glycated hemoglobin (HbA1c) from baseline to end of study in adults ≥18 years of age with type 1 diabetes mellitus (T1DM) for each of the three following groups: o Afrezza + AID: Afrezza for bolus (mealtime) in combination with use of a continuous subcutaneous insulin infusion (CSII) pump with an automated insulin delivery (AID) algorithm using a rapid-acting insulin analog (RAA) for basal and correction insulin coverage o Afrezza + Insulin Degludec: Afrezza for bolus (mealtime and correction) in combination with insulin degludec for basal insulin coverage o AID Control: CSII pump with an AID algorithm using an RAA for all bolus (mealtime and correction) and basal insulin coverage **Secondary Objectives:** • To evaluate the safety of study treatment based on hypoglycemia event rate and severe hypoglycemia incidence rate in adults ≥18 years of age with T1DM for each of the three following groups: o Afrezza + AID o Afrezza + Insulin Degludec o AID Control • To evaluate the impact of study treatment on overall glycemic control when comparing baseline versus end of treatment period as measured by core continuous glucose monitoring (CGM) metrics: o Change in percent time in range (TIR), defined as time spent with glucose in the range of 70 to 180 mg/dL o Change in percent time below range (TBR), defined as time spent with glucose <70 mg/dL

	○ Change in percent time spent with glucose <54 mg/dL ○ Change in percent time above range (TAR), defined as time spent with glucose >180 mg/dL ○ Change in percent time spent with glucose >250 mg/dL ○ Change in glycemic variability as measured by coefficient of variation (CV) The above metrics will be evaluated in adults ≥18 years of age with T1DM for each of the three following groups: ○ Afrezza + AID ○ Afrezza + Insulin Degludec ○ AID Control
Study Design:	MKC-TI-192 is a Phase 4, 90-day, randomized, three-arm, multicenter clinical trial evaluating the treatment paradigm and efficacy of Afrezza in controlling postprandial glucose in adult subjects (≥18 years of age) with T1DM. Subjects will be randomized to one of three treatment groups (two Afrezza groups and one control group): • Afrezza + AID: Subjects in this group will use Afrezza for their bolus (mealtime) insulin and a CSII pump with an AID algorithm using RAA for their basal and correction insulin coverage. • Afrezza + Insulin Degludec: Subjects in this group will use Afrezza for their bolus (mealtime and correction) insulin and insulin degludec for basal insulin coverage. • AID Control: Subjects in this group will use a CSII pump with an AID algorithm using RAA for all bolus (mealtime and correction) and basal insulin coverage (control group). The study is composed of up to 5 clinic visits (screening, 3 treatment visits, and an end-of-treatment visit) and 9 telephone visits: • **Visit 1 (Screening):** Informed consent will be obtained and screening procedures performed. Laboratory values will be collected for HbA1c, creatinine and thyroid-stimulating hormone (TSH); a documented normal TSH or creatinine level within 6 months of screening can be used in lieu of testing. A baseline forced expiratory volume in one second (FEV_1) measurement will be obtained. A Dexcom G6 Professional (G6 Pro) blinded CGM device will be placed on each subject. Subjects will continue to use their own CGM device in addition to the blinded CGM. • **Visit 2 (Randomization & Meal Challenge):** At least 10 days (+ 4 days) after Visit 1, subjects will return for Visit 2. At this visit, the Investigator will evaluate for appropriate use of the blinded sensor and will download the blinded CGM data (CSV file). If sensor wear time is inadequate, sensor wear can be

repeated once and this becomes an unscheduled visit. The subject will return to the clinic 10 days (+ 4 days) later, and if the sensor wear is adequate and all eligibility criteria are met, be randomized to study treatment and proceed to the meal challenge and other Visit 2 assessments.

Subjects will be randomized in a 2:2:1 ratio to the following treatment groups, with the goal of 25 subjects enrolled:

- Afrezza + AID (N=10)
- Afrezza + Insulin Degludec (N=10)
- AID Control (N=5)

In order to achieve balanced representation of Medtronic 670G/ 770G and Tandem Control IQ AID users for each group, the randomization will target for a minimum number of subjects who use each AID system as follows:

- Within each Afrezza group (Afrezza + AID, Afrezza + Insulin Degludec):
  - 3 subjects using Medtronic 670G/770G
  - 3 subjects using Tandem Control IQ AID
- Within the AID Control group:
  - 2 subjects using Medtronic 670G/770G
  - 2 subjects using Tandem Control IQ AID

Subjects will come to the clinic fasting with no manual insulin bolus administered within the prior 4 hours. CGM reports and pump reports will be downloaded from V1 to V2 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from V1 to V2 using Clarity for Dexcom CGM and t:connect for Tandem pumps. The site will de-identify all reports and data. Subjects will undergo a 2-hour meal tolerance test in the clinic. The Afrezza + Insulin Degludec and the Afrezza + AID groups will receive an Afrezza initial dose that is 2 times the calculated RAA dose (based on their insulin-to-carbohydrate ratio [I:CHO] calculated prandial dose) rounded down to the nearest 4-unit dose of Afrezza, but not exceeding 24 units of Afrezza. The Afrezza dose will be administered at the start of the meal challenge. The AID Control group will administer bolus insulin 10 ± 5 minutes (per label) prior to the meal, per Investigator discretion. The start of the meal will define t=0. Subjects in the Afrezza + Insulin Degludec group will continue on AID throughout the meal tolerance test and then transition to insulin degludec at the discretion of the Investigator. Basal insulin doses and time of administration in all study subjects will be documented. Subjects should have glucagon available for use in the event of hypoglycemia

	and should not be discharged until hypoglycemia is resolved. • **Visits T3, T4, T5, T6, T7, T8 (Telephone):** Between Visits 2 and 9 in the clinic, several telephone visits will be conducted. During these visits, the Investigator will titrate insulin dosages, ask about changes to concomitant medications, record any adverse events (AE) and hypoglycemic events, and answer any questions/concerns raised by the subject. • **Visit 9 (Clinic):** This visit will be conducted at least 30 days (+ 7 days) after Visit 2. CGM reports and pump reports will be downloaded from V2 to V9 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from V2 to V9 using Clarity for Dexcom CGM and t:connect for Tandem pumps. The site will de-identify all reports and data. The Investigator will titrate insulin dosages. Basal insulin dosages will be documented. • **Visits T10, T11, T12 (Telephone):** Between Visits 9 and 13 in the clinic, three telephone visits will be conducted. During these visits, the Investigator will titrate dosages and answer any questions/concerns raised by subjects. • **Visit 13 (Clinic):** This visit will occur 8 to 10 days prior to Visit 14. CGM reports and pump reports will be downloaded from V9 to 30 days after V9 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from V9 to 30 days after V9 using Clarity for Dexcom CGM and t:connect for Tandem pumps. The site will de-identify all reports/data. The Investigator will place a Dexcom G6 Pro blinded sensor on subjects in all groups. The Investigator will titrate insulin dosages. Additionally, Afrezza + AID and Afrezza + Degludec groups will be asked to log meal announcements and Afrezza doses in the final 10 days. • **Visit 14 (Clinic):** At least 90 days following Visit 2 (+ 7 days), subjects will return for HbA1c measurement and safety assessments, including a final FEV_1 measurement. The Investigator will download the blinded CGM data (CSV file) from the prior sensor wear. Additionally, CGM reports and pump reports will be downloaded from 30 days before V14 to V14 and from V13 to V14 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from 30 days before V14 to V14 and from V13 to V14 using Clarity for Dexcom CGM and t:connect for Tandem pumps. The site will de-identify all reports and data. Basal insulin dosages will be documented.
Planned Sample Size:	25 subjects (10 in each Afrezza group, 5 in AID Control group)

Medical Condition or Disease Under Investigation:	T1DM
Subject Selection Criteria:	**Inclusion Criteria** *At screening:* 1. Subjects ≥18 years of age at the time of signing the informed consent form 2. Clinical diagnosis of T1DM 3. ≥7.0% and <11.0% HbA1c 4. Treatment with a CSII pump with an AID algorithm (Medtronic 670G/770G or Tandem Control IQ) for at least 3 months, including use of the AID automated mode function. 5. Ability to pay for their own RAA used in the insulin pump or injections, either through co-pay or self-pay, for the duration of the study (see acceptable insulin analogs below) 6. Willingness to follow study procedures including discontinuing their insulin pump and transitioning to insulin degludec injections plus Afrezza **Exclusion Criteria** *At screening:* 1. A recent history of asthma (defined as using any medications to treat within the last year), chronic obstructive pulmonary disease (COPD), or any other clinically important pulmonary disease (e.g., cystic fibrosis, bronchopulmonary dysplasia), or significant congenital or acquired cardiopulmonary disease 2. History of serious complications of diabetes (e.g., active proliferative retinopathy or symptomatic autonomic neuropathy) 3. History of hypersensitivity to insulin or any of the Afrezza excipients 4. On dialysis 5. Respiratory tract infection within 14 days before screening (subject may return 14 days after resolution of symptoms for rescreening) 6. Exposure to any investigational drug in the past 30 days or an investigational device in the past 2 weeks 7. Adrenal insufficiency, active use of steroids or planned steroid use 8. Hypothyroidism not controlled, as defined by TSH outside the upper limit of the reference range by >1.5 × in the last 6 months, according to the local laboratory reference range 9. Hyperthyroidism not controlled, as defined by TSH below the

	normal reference range, according to the local laboratory 10. Use of antiadrenergic drugs (e.g., beta blockers and clonidine) 11. Any concurrent illness (other than diabetes mellitus) not controlled by a stable therapeutic regimen 12. History of a significant eating disorder (e.g., anorexia or bulimia nervosa) 13. Current drug or alcohol abuse or a history of drug or alcohol abuse that, in the opinion of the Investigator or the Sponsor, would make the subject an unsuitable candidate for participation in the study 14. History of smoking (includes cigarettes, cigars, pipes, vaping devices, and marijuana) in the 6 months before screening 15. Female subject who is pregnant, breast-feeding, intends to become pregnant, or is of child-bearing potential and not using adequate contraceptive methods as required by local regulation or practice (may include sexual abstinence) 16. An event of severe hypoglycemia, as reported by the patient, within the last 180 days before screening 17. An episode of diabetic ketoacidosis requiring hospitalization within the last 180 days before screening 18. Exposure to Afrezza in the 30 days before screening 19. Abnormal TSH, or creatinine levels above 2.0 mg/dL
Study Treatment(s):	Subjects randomized to the Afrezza + AID group (N=10) or the Afrezza + Insulin Degludec group (N=10) will receive Afrezza in this study. The AID Control group (N=5) will continue AID with their currently prescribed RAA.
AID Systems:	Acceptable AID systems in this study are Medtronic 670G/770G and Tandem Control IQ AID. The randomization will target for a minimum of 3 subjects each who use Medtronic 670G/770G and Tandem Control IQ AID in each of the Afrezza groups, and a minimum of 2 subjects each who use Medtronic 670G/770G and Tandem Control IQ AID in the AID Control group.
Test Product, Dose, and Mode of Administration:	**Test product:** Afrezza® [insulin human] inhalation powder **Active ingredient:** Human insulin, recombinant DNA origin **Dose regimen:** Individualized **Mode of Administration:** Oral inhalation
Basal and RAA Insulin Therapy Dose, and Mode of Administration:	**Basal insulin analog:** Insulin degludec **Infused rapid-acting: Insulin aspart** (Novolog® or Fiasp®) or **insulin lispro** (Humalog®, Admelog®, or Lyumjev®) for basal insulin coverage (insulin pump/AID users)

	Dose regimen: Individualized **Mode of Administration:** Subcutaneous injection or infusion
Duration of Treatment:	90 days
Criteria for Evaluation:	This study will evaluate the efficacy and safety of Afrezza combined with basal insulin or AID with insulin pump therapy, based on the endpoints outlined below: **Efficacy Endpoints** • Change in HbA1c from baseline to end of study **Safety Endpoints** • Event rates and incidence of Level 1 (<70 mg/dL) and Level 2 (<54 mg/dL) hypoglycemic events as confirmed by self-monitored blood glucose (SMBG) • Event rates and incidence of severe hypoglycemic events, defined as events requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions • Incidence and severity of AEs: treatment-emergent AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), and device complaints • Change in FEV_1 from screening to end of study
Statistical Methods:	**Sample Size Determination** Twenty-five subjects are planned to complete this proof-of-concept study. Subjects who discontinue from the study within the first 4 weeks will be replaced. Subjects who discontinue from the study after 4 weeks will not be replaced. If possible, HbA1c measurements will be obtained for subjects who discontinue after 4 weeks of participation. The sample size of 25 subjects was not determined using statistical methods. **Analysis Populations** All randomized subjects in the clinical study will be included in the Intent-To-Treat (ITT) Population. ITT subjects who have no major protocol deviations that would have an impact on the primary endpoint assessment will be included in the Per-Protocol (PP) Population. **Descriptive Summary of Efficacy** HbA1c values will be summarized at baseline and end of study for the ITT Population. CGM values and metrics will be summarized by visit. A summary table with descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be provided. CGM data will also be presented graphically.

	Descriptive Summary of Safety The incidence of hypoglycemia confirmed by SMBG (total and severe) and the percentage time (by CGM) with glucose below 70 mg/dL and below 54 mg/dL will be reported. Nocturnal is defined as midnight to 0600 and severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. The number and percentage of subjects with treatment-emergent AEs will be tabulated by system organ class and preferred term by relationship to treatment and by severity. A summary table by study visit with descriptive statistics for FEV_1 at screening and end of study will be provided. The FEV_1 data will also be presented graphically.

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FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AID	automated insulin delivery
BMI	body mass index
CGM	continuous glucose monitor
CI	confidence interval
COVID-19	coronavirus 2019
CRF	case report form
CSII	continuous subcutaneous insulin infusion
CV	coefficient of variation
DKA	diabetic ketoacidosis
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
HbA1c	glycated hemoglobin
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
I:CHO	Insulin to Carb Ratio
ITT	intent to treat
IRB	institutional review board
MDI	multiple daily injection(s)
PPG	postprandial glucose
PPGE	postprandial glucose excursion
RAA	rapid-acting insulin analog
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation

Abbreviation	Definition
SC	subcutaneous
SMBG	self-monitored blood glucose
SOP	standard operating procedure
TAR	time above range
TBR	time below range
TEAE	treatment-emergent adverse event
TI	Technosphere Insulin
TIR	time in range
TSH	thyroid-stimulating hormone
T1DM	type 1 diabetes mellitus
URI	Upper Respiratory Infection

DEFINITIONS OF TERMS

Enrollment: The date when the subject has consented to participate in the study and eligibility criteria are met.

ITT: Intent to Treat

PP: Per Protocol

Start of the study: The study starts on the date that the informed consent form is signed for the first subject.

End of the study: The study ends with the last visit of the last subject participating in the study.

1 INTRODUCTION

1.1 Background

According to the latest estimates, >1.6 million Americans have type 1 diabetes mellitus (T1DM) (CDC 2020). Importantly, the incidence of T1DM is increasing at an annual rate of approximately 1.9% (Divers et al. 2020).

T1DM is a chronic autoimmune disorder characterized by a destruction of the insulin-producing β-cells of the pancreatic islets, leading to insulin deficiency, subsequent hyperglycemia and the need for exogenous insulin therapy. T1DM is associated with increased microvascular and macrovascular disease, reduced life span and significant healthcare-related costs (Foster et al. 2019, Rawshani et al. 2018, Livingstone et al. 2015, Tao et al. 2010).

In order to delay or prevent complications associated with diabetes, it is critical that patients adhere to their diabetes treatment regimen. The therapeutic objective for diabetes management is to match the endogenous pattern of insulin secretion as closely as possible without causing hypoglycemia (Pettus et al. 2016). Use of intensified, basal-bolus insulin therapy is considered standard of care for treatment of patients with T1DM (ADA 2021b).

Despite advances in glucose monitoring and insulin delivery technologies, a significant proportion of individuals with type 1 diabetes are not achieving their glycemic targets (Foster et al. 2019). Nonadherence to prescribed insulin regimens is high and remains a major driver of poor glucose control (Riaz et al. 2014). Among patients treated with a multiple daily insulin injection (MDI) regimen, 1 in 5 (~20%) mealtime injections are intentionally missed, leading to challenges in achieving effective glycemic control (Peyrot et al. 2010). Reasons for omitting insulin injections include interference with daily activities, injection pain, and embarrassment. However, nonadherence to mealtime and correction dosing is also problematic among insulin pump users (Burdick et al. 2004).

Technosphere® Insulin inhalation powder (TI inhalation powder) provides an alternative to injectable insulin for prandial glucose control. TI inhalation powder and the Gen2 Inhaler were approved as Afrezza® (insulin human) inhalation powder and Afrezza Inhaler by the United States FDA on 27 June 2014 to improve glycemic control in adult patients ≥18 years of age with diabetes mellitus and has been registered by the Brazilian Health Regulatory Agency (ANVISA) as of 03 June 2019. Afrezza is an ultra-rapid-acting insulin that is administered by oral inhalation using a breath-powered inhaler. Afrezza particles have a median diameter of approximately 2 to 2.5 µm, a size appropriate for inhalation into the lung. Following inhalation, Afrezza particles dissolve immediately at the physiologic pH of the lung, and insulin is absorbed systemically. After administration of Afrezza in adults, the maximum serum insulin concentration occurs in approximately 12 to 15 minutes (versus 45 to 60 minutes for a rapid-acting insulin analog [RAA] via subcutaneous route) and returns to near baseline levels in approximately 180 minutes (versus about 5 hours for RAA) (Afrezza IB).

This unique ultra-rapid time-action profile allows for simpler and more flexible mealtime dosing, lessens the potential for inter-prandial hypoglycemia, and enables additional postprandial dosing to decrease mealtime glycemic excursions, when needed, based on the patient's self-measured glucose levels.

1.2 Study Rationale

Approximately 40% to 60% of patients with T1DM use continuous subcutaneous insulin infusion (CSII) devices, commonly referred to as insulin pumps (Umpierrez et al. 2018, Miller et al. 2015). CSII devices are computerized devices programmed to deliver an RAA under the skin continuously throughout the day via a catheter attached to a person's abdomen. When used in tandem with continuous glucose monitoring (CGM) this is a closed-loop system. Hybrid closed-loop systems are characterized by the coexistence of algorithm-driven automated insulin delivery (AID) for basal insulin coverage combined with manual mealtime bolus insulin doses.

The current study aims to evaluate mealtime use of Afrezza in adults ≥18 years of age with T1DM who currently use AID. In this study, Afrezza-treated subjects will use two different methods for basal insulin delivery (subcutaneous [SC] injection of long-acting insulin or an AID system with RAA) compared to a control group (without Afrezza) of patients on an AID system with RAA.

Subjects will administer their initial Afrezza dose based on the subject's current insulin-to-carbohydrate (I:CHO) ratio multiplied by 2 and rounded down to the nearest Afrezza dose size, subject to Investigator discretion, but not exceeding 24 units of Afrezza. Pooled Afrezza trial data suggests that subjects achieve similar glycemic control with a dose ratio of 1.5- to 2-fold the equivalent unit value of a subcutaneous insulin analog in head-to-head comparisons (Kendall et al. 2020, Grant et al. 2019), which is significantly higher than the dose conversion in the label. Additionally, a proof-of-concept study was done with 20 patients demonstrating improved postprandial glucose excursions (PPGE) with the higher dose of Afrezza compared to the current label (Afrezza 2020). This higher initial conversion dose of Afrezza will be used for the first dose under medical supervision in the clinic.

1.3 Risks and Benefits

1.3.1 Afrezza

Clear benefits of Afrezza include faster onset of insulin response, ability to administer insulin at mealtimes, lower risk of hypoglycemia and fewer injections compared to subjects using RAAs injected subcutaneously for post-prandial control.

The following safety risks have been identified through evaluation of all currently available data with Afrezza:

Important identified risks

- Bronchospasm in subjects with underlying chronic obstructive lung disease
- Severe hypoglycemia

- Hyperglycemia during initiation of treatment due to inadequate conversion of RAA dose

Important potential risks

- Diabetic ketoacidosis
- Hyperglycemia during acute illness or change of treatment
- Lung cancer: Data are insufficient to determine whether Afrezza has an effect on lung or respiratory tract tumors. In subjects with active lung cancer, a prior history of lung cancer, or in subjects at risk for lung cancer, the Investigator considers whether the benefits of Afrezza use outweigh this potential risk.

Further information on the benefits and risks of Afrezza are provided in the Investigator's Brochure (IB) and the Afrezza prescribing information (Afrezza 2020).

1.3.2 Insulin Degludec

Subjects who are randomized to treatment with Afrezza in combination with a basal insulin will discontinue using their insulin pump and inject insulin degludec for basal insulin coverage. During the transition period, there is a risk of increased hyperglycemia and/or hypoglycemia while the basal insulin dose is optimized. To mitigate the risk to subjects in this study, subjects will be provided training in the clinic and frequent telephone visits will occur in the first 21 days after randomization.

See the prescribing information for Tresiba for a complete list of risks (Tresiba 2019).

1.3.3 Continuous Glucose Monitoring

CGM will be used in this study to enable real-time display of glucose values. Subjects will wear a blinded Dexcom G6 Professional (Dexcom G6 Pro) between screening and randomization and during the last 10 days of the study, in addition to their own personal CGM. Subjects will be provided training in the clinic for how to operate the Dexcom G6 Pro. Additionally, subjects will measure their glucose throughout the study using an unblinded CGM system (sensors, transmitter) and glucose meters, if required.

Subjects will also be instructed to measure glucose values using a blood glucose meter (self-monitored blood glucose [SMBG] value), as required by their personal CGM system, and to confirm glucose levels when their CGM is <70mg/dL and anytime their CGM reading does not match their symptoms or expectations.

Use of CGM is associated with a low risk for developing a local skin infection at the site of the CGM sensor placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies. CGM sensors may fracture in situ on rare occasions. In the rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain subjects should consult with the Investigator or prescribing physician for the best course of action. If there is no portion of the

broken sensor wire fragment visible above the skin, attempts to remove it without medical guidance are not advised.

For a complete list of risks for Dexcom G6, refer to the Dexcom G6 Pro User Guide (Dexcom 2020). For a complete list of risks for the subject's personal CGM that they will continue to use during the study, refer to the corresponding user guide.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To evaluate the change in HbA1c from baseline to end of study in adults ≥18 years of age with T1DM for each of the three following groups:
  - Afrezza + AID: Afrezza for bolus (mealtime) in combination with use of a CSII pump with an AID algorithm using a RAA for basal and correction insulin coverage
  - Afrezza + Insulin Degludec: Afrezza for bolus (mealtime and correction) in combination with insulin degludec for basal insulin coverage
  - AID Control: CSII pump with an AID algorithm using an RAA for all bolus (mealtime and correction) and basal insulin coverage

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety of study treatment based on hypoglycemia event rate and severe hypoglycemia incidence rate in adults ≥18 years of age with T1DM for each of the three following groups:
  - Afrezza + AID
  - Afrezza + Insulin Degludec
  - AID Control
- To evaluate the impact of study treatment on overall glycemic control when comparing baseline versus end of treatment period as measured by core CGM metrics:
  - Change in percent time in range (TIR), defined as time spent with glucose in the range of 70 to 180 mg/dL
  - Change in percent time below range (TBR), defined as time spent with glucose <70 mg/dL
  - Change in percent time spent with glucose <54 mg/dL
  - Change in percent time above range (TAR), defined as time spent with glucose >180 mg/dL
  - Change in percent time spent with glucose >250 mg/dL
  - Change in glycemic variability as measured by coefficient of variation (CV)
- The above metrics to be evaluated on each of the three following groups in adults ≥18 years of age with T1DM for each of the three following groups:
  - Afrezza + AID
  - Afrezza + Insulin Degludec
  - AID Control

3 INVESTIGATIONAL PLAN

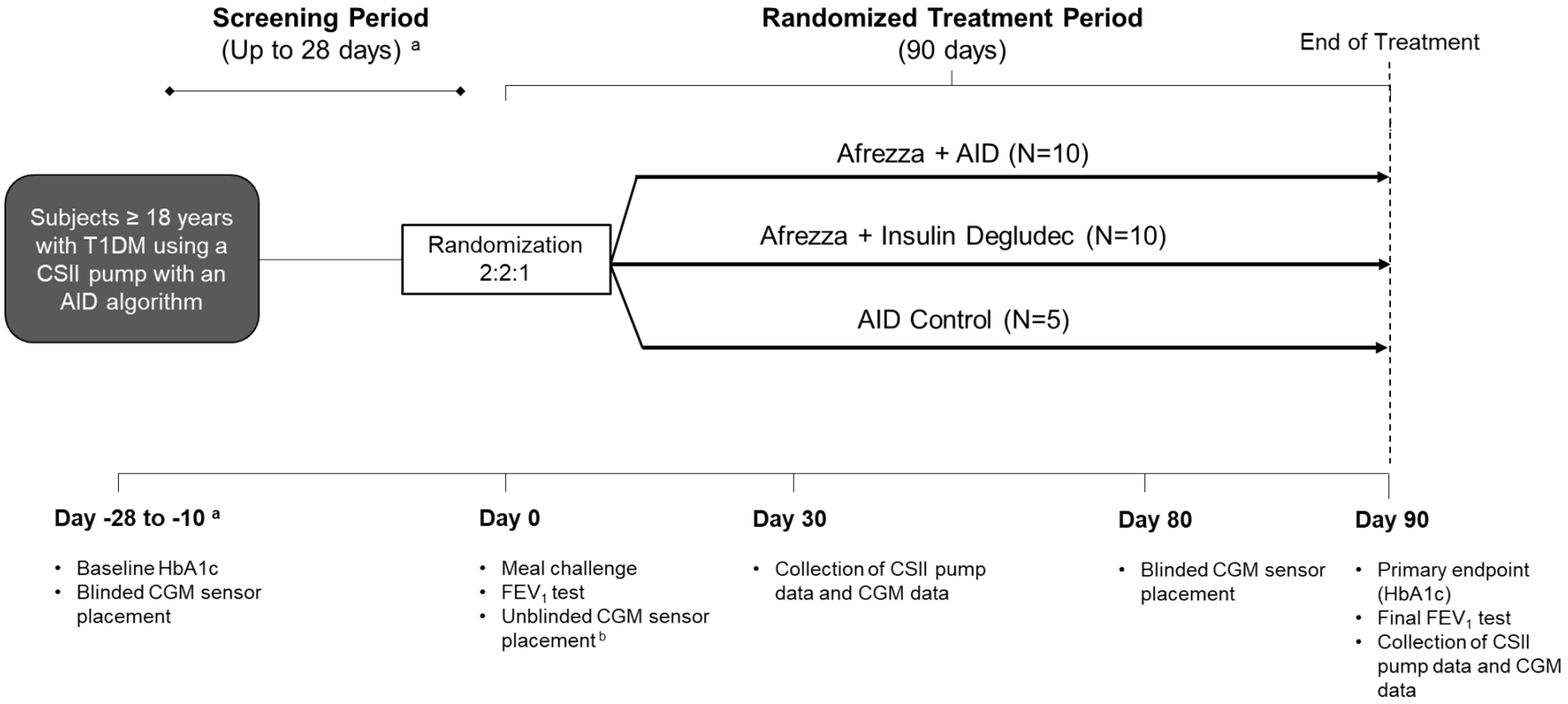
3.1 Overall Study Design and Plan

MKC-TI-192 is a Phase 4, 90-day, randomized, three-arm, multicenter clinical trial evaluating the treatment paradigm and efficacy of Afrezza in controlling postprandial glucose in adult subjects (≥18 years of age) with T1DM. Subjects will be randomized to one of three treatment groups (two Afrezza groups and one control group):

- Afrezza + AID: Subjects in this group will use Afrezza for their bolus (mealtime) insulin and a CSII pump with an AID algorithm using RAA for their basal and correction insulin coverage.
- Afrezza + Insulin Degludec: Subjects in this group will use Afrezza for their bolus (mealtime and correction) insulin and insulin degludec for basal insulin coverage.
- AID Control: Subjects in this group will use a CSII pump with an AID algorithm using RAA for all bolus (mealtime and correction) and basal insulin coverage (control group).

See Figure 1 for a schematic of the study design.

Figure 1: MKC-TI-192 Study Schematic



AID=automated insulin delivery, CGM=continuous glucose monitor, CSII=continuous subcutaneous insulin infusion, FEV_1= forced expiratory volume in 1 second, HbA1c=glycated hemoglobin A1c, T1DM=type 1 diabetes mellitus

a. The Screening Visit should be scheduled 10 days (+ 4 days) before the subject's expected date of randomization. Subjects will be provided with a blinded Dexcom G6 Professional CGM device at the Screening Visit, which they will use in addition to their own CGM device during the Screening Period. At Visit 2, blinded CGM data will be downloaded and CGM sensor wear evaluated. If CGM sensor wear time is inadequate, per the discretion of the Investigator, the Screening Period can be extended and sensor wear can be repeated once. The subject will return to the clinic 10 days (+ 4 days) later and, if sensor wear is adequate and all eligibility criteria met, be randomized to study treatment and proceed with the meal challenge.

b. Only applies to subjects in the Afrezza + Insulin Degludec group who use a Medtronic 670G/770G system.

The study is composed of up to 5 clinic visits (screening, 3 treatment visits, and an end-of-treatment visit) and 9 telephone visits:

- **Visit 1 (Screening):** At the Screening Visit, informed consent will be obtained and screening procedures performed. Laboratory values will be collected for HbA1c, creatinine and thyroid-stimulating hormone (TSH); a documented normal TSH or creatinine level within 6 months of screening can be used in lieu of testing. A baseline forced expiratory volume in one second (FEV_1) measurement will be obtained. A Dexcom G6 Pro blinded CGM device will be placed on each subject. Subjects will continue to use their own CGM device in addition to the blinded CGM.
- **Visit 2 (Randomization & Meal Challenge):** At least 10 days (+ 4 days) after Visit 1, subjects will return for Visit 2. At this visit, the Investigator will evaluate for appropriate use of the blinded sensor and will download the blinded CGM data (CSV file). If sensor wear time is inadequate, sensor wear can be repeated once and this becomes an unscheduled visit. The subject will return to the clinic 10 days (+ 4 days) later, and if the sensor wear is adequate and all eligibility criteria are met, be randomized to study treatment and proceed to the meal challenge and other Visit 2 assessments.
  Subjects will be randomized in a 2:2:1 ratio to the following treatment groups, with the goal of 25 subjects enrolled:
  - Afrezza + AID (N=10)
  - Afrezza + Insulin Degludec (N=10)
  - AID Control (N=5)

  In order to achieve balanced representation of Medtronic 670G or 770G and Tandem Control IQ AID users for each group, the minimum subject numbers will be as follows:
  - At least 5 subjects using Medtronic 670G or 770G
  - At least 5 subjects using Tandem Control IQ

Subjects will come to the clinic fasting with no manual insulin bolus administered within the prior 4 hours. CGM reports and pump reports will be downloaded from V1 to V2 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from V1 to V2 using Clarity for Dexcom CGM and t:connect for Tandem pumps (

). The site will de-identify all reports and data. Subjects will undergo a 2-hour meal tolerance test in the clinic. The Afrezza + Insulin Degludec and the Afrezza + AID groups will be administered an Afrezza initial dose that is 2 times the calculated RAA dose (based on their insulin-to-carbohydrate ratio [I:CHO] calculated prandial dose) rounded down to the nearest 4-unit dose of Afrezza, but not exceeding 24 units of Afrezza. The Afrezza dose will be administered at the start of the meal challenge. The AID Control group will administer bolus insulin 10 ± 5 minutes (per label) prior to the meal, per Investigator discretion. The start of the meal will define t=0. Subjects in the Afrezza + Insulin Degludec will continue on AID throughout the meal tolerance test and then transition to insulin degludec at the discretion of the Investigator. Basal insulin doses and time of administration in all study subjects will be documented. Subjects should have glucagon available for use in the event of hypoglycemia and should not be discharged until hypoglycemia is resolved.

- **Visits T3, T4, T5, T6, T7, T8 (Telephone):** Between Visits 2 and 9 in the clinic, several telephone visits will be conducted. During these visits, the Investigator will titrate insulin dosages, ask about changes to concomitant medications, record any AEs and hypoglycemic events, and answer any questions/concerns raised by the subject.
- **Visit 9 (Clinic):** This visit will be conducted at least 30 days (+7 days) after Visit 2. CGM reports and pump reports will be downloaded from V2 to V9 and from 10 days prior to V9 to V9 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from V2 to V9 and from 10 days prior to V9 to V9 using Clarity for Dexcom CGM and t:connect for Tandem pump). The site will de-identify all reports and data. The Investigator will titrate insulin dosages. Basal insulin dosages will be documented.
- **Visits T10, T11, T12 (Telephone):** Between Visits 9 and 13 in the clinic, three telephone visits will be conducted. During these visits, the Investigator will titrate dosages and answer any questions/concerns raised by subjects.

Visit 13 (Clinic): This visit will occur 8 to 10 days prior to Visit 14. CGM reports and pump reports will be downloaded from V9 to 30 days after V9 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from V9 to 30 days after V9 using Clarity for Dexcom CGM and t:connect for Tandem pumps (

). The site will de-identify all reports/data. The Investigator will place a Dexcom G6 Pro blinded sensor on subjects in all groups. The Investigator will titrate insulin dosages. Additionally, Afrezza + AID and Afrezza + Degludec groups will be asked to log meal announcements and Afrezza doses in the final 10 days.

Visit 14 (Clinic): At least 90 days following Visit 2 (+ 7 days), subjects will return for HbA1c measurement and safety assessments, including a final FEV_1 measurement. The Investigator will download the blinded CGM data (CSV file) from the prior sensor wear. Additionally, CGM reports and pump reports will be downloaded from 30 days before V14 to V14 and from V13 to V14 using Carelink for Medtronic CGM and pumps, CGM reports/data and pump reports/data will be downloaded from 30 days before V14 to V14 and from V13 to V14 using Clarity for Dexcom CGM and t:connect for Tandem pumps (

). The site will de-identify all reports and data. Basal insulin dosages will be documented. See Section 3.7 for information on the assessments to be performed at these visits.

3.2 Study Duration

The length of the entire study (from first subject enrolled to the last subject last visit) is expected to be 180 days. The end of the clinical study is defined as the day the last subject completes his/her last visit.

3.3 Selection of Study Population

The population sought for this study is adult subjects ≥18 years of age with T1DM. Twenty-five subjects are planned to complete the study. Subjects who discontinue from the study within the first 4 weeks will be replaced. Subjects who discontinue from the study after 4 weeks will not be replaced. If possible, HbA1c measurements will be obtained for subjects who discontinue after 4 weeks of participation.

3.3.1.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to participate in the study:

At screening:

1. Subjects ≥18 years of age at the time of signing the informed consent form
2. Clinical diagnosis of T1DM
3. ≥7.0% and <11.0% HbA1c
4. Treatment with a CSII pump with an AID algorithm (Medtronic 670G/770G or Tandem Control IQ) for at least 3 months, including use of the AID automated mode function
5. Ability to pay for their own RAA used in the insulin pump or injections, either through co-pay or self-pay, for the duration of the study (See acceptable insulin analogs in Section 3.4.2)
6. Willingness to follow study procedures including discontinuing their insulin pump and transitioning to insulin degludec injections plus Afrezza

3.3.1.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria at screening will not be enrolled in the study.

At screening:

1. A recent history of asthma (defined as using any medications to treat within the last year), chronic obstructive pulmonary disease (COPD), or any other clinically important pulmonary disease (e.g., cystic fibrosis, bronchopulmonary dysplasia), or significant congenital or acquired cardiopulmonary disease
2. History of serious complications of diabetes (e.g., active proliferative retinopathy or symptomatic autonomic neuropathy)
3. History of hypersensitivity to insulin or any of the Afrezza excipients
4. On dialysis
5. Respiratory tract infection within 14 days before screening (subject may return 14 days after

resolution of symptoms for rescreening)

6. Exposure to any investigational drug in the past 30 days or an investigational device in the past 2 weeks
7. Adrenal insufficiency, active use of steroids or planned steroid use
8. Hypothyroidism not controlled, as defined by TSH outside the upper limit of the reference range by >1.5 × in the last 6 months, according to the local laboratory reference range
9. Hyperthyroidism not controlled, as defined by TSH below the normal reference range, according to the local laboratory
10. Use of antiadrenergic drugs (e.g., beta blockers and clonidine)
11. Any concurrent illness (other than diabetes mellitus) not controlled by a stable therapeutic regimen
12. History of a significant eating disorder (e.g., anorexia or bulimia nervosa)
13. Current drug or alcohol abuse or a history of drug or alcohol abuse that, in the opinion of the Investigator or the Sponsor, would make the subject an unsuitable candidate for participation in the study
14. History of smoking (includes cigarettes, cigars, pipes, vaping devices, and marijuana) in the 6 months before screening
15. Female subject who is pregnant, breast-feeding, intends to become pregnant, or is of child-bearing potential and not using adequate contraceptive methods as required by local regulation or practice (may include sexual abstinence)
16. An event of severe hypoglycemia, as reported by the patient, within the last 180 days before screening
17. An episode of diabetic ketoacidosis (DKA), as determined by the Investigator, requiring hospitalization within the last 180 days before screening
18. Exposure to Afrezza in the 30 days before screening
19. Abnormal TSH or creatinine levels above 2.0 mg/dL

Subjects who are unable to comply with the requirements of the study or who, in the opinion of the Investigator, should not participate in the study are not eligible. In addition, any subjects for whom Afrezza is contraindicated, based on the Afrezza prescribing information (Afrezza 2020), should not be enrolled in the study.

3.3.1.3 Removal of Subjects from Therapy or Assessment

A subject will be considered to have completed the study when the subject completes the treatment visits and the end-of-treatment visit assessments.

If a subject discontinues from the study before completing all protocol-specified visits, an early-termination visit should be conducted as soon as possible to have the assessments shown in the Schedule of Assessments (Table 3).

Participation in the study is strictly voluntary. A subject or legally authorized representative has the right to withdraw from the study at any time and for any reason. If he/she chooses to withdraw, the Investigator must be informed immediately. The Investigator has the right to

terminate participation of any subject at any time if the Investigator deems it in the subject's best interest. The Investigator should discuss the subject's withdrawal with the medical monitor beforehand, if possible. If not possible, the Investigator should discuss the withdrawal with the medical monitor within 24 hours of being informed of the decision.

For any subject who fails to return to the site, the Investigator should make every effort to contact the subject (e.g., contact the subject's family or private physician, review available registries or health care database) and to determine their health status. Attempts to contact the subject must be documented in the subject's study records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, and a copy of the letter).

Subjects withdrawn from the study must not be re-included in the study. Their inclusion numbers must not be reused. Subjects withdrawn within the first 4 weeks will be replaced. However, subjects withdrawn from the study after 4 weeks will not be replaced. If possible, HbA1c measurements will be obtained for subjects who are withdrawn after 4 weeks of participation.

3.3.1.3.1 Reasons for Discontinuation

The reason and circumstances for early termination will be documented in the subject's case report form (CRF). The reason for any early discontinuation should be indicated on this form. The primary reason for a subject's early study termination should be selected from the following standard categories of early termination:

- *Adverse Event (AE):* Clinical or laboratory events occur that, in the medical judgment of the Investigator could affect the subject's safety or well-being if treatment is continued. This includes serious (Section 4.1.2) and nonserious AEs regardless of relation to the study drug.
- *Withdrawal of Consent*: The subject desires to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the subject gives a reason for withdrawing, it should be recorded in the CRF.
- *Treatment Noncompliance:* The subject fails to comply with the prescribed dosing of the study treatment after multiple attempts have been made to obtain compliance.
- *Major Protocol Violation*: The subject's findings or conduct fails to meet the protocol entry criteria or fails to adhere to the protocol requirements that are deemed to affect subject safety or the integrity of the study data.
- *Pregnancy:* If a subject becomes pregnant, she will be discontinued from the study.
- *Smoking:* The subject begins smoking or vaping, including smoking marijuana.
- *DKA:* The subject has 2 events of DKA.
- *Lost to Follow-up*: The subject stops coming for visits and study personnel are unable to contact the subject.
- *Other*: The subject discontinues from the study for a reason other than those listed above, such as termination of study by Sponsor.

If a subject discontinues from the study due to the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic, information should be captured on the CRF so this information can be summarized in the clinical study report at the end of the study, in line with the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19

Public Health Emergency (FDA 2021). The reason for discontinuation should be recorded on the CRF as SARS-CoV-2/COVID-19, if applicable, and include as many details as possible.

For example, specific reasons may include, but are not limited to:

- The subject exhibits symptoms consistent with COVID-19 within the last 10 days (yes/no).
- The subject has a positive test result for SARS-CoV-2 (yes/no).
- The subject has neither symptoms nor a positive test but has chosen to discontinue treatment due to COVID-19 concerns.

3.3.1.3.2 Replacement of Subjects

Subjects who discontinue from the study within the first 4 weeks will be replaced. However, subjects who discontinue from the study after 4 weeks will not be replaced. If possible, HbA1c measurements will be obtained for subjects who discontinue after 4 weeks of participation.

3.4 STUDY TREATMENT

3.4.1 Test Product, Dose, and Mode of Administration

The test product is defined as Afrezza administered using the inhaler (Table 1). Afrezza consists of single-use plastic cartridges filled with a white powder containing insulin, which is administered via oral inhalation using the Afrezza Inhaler only.

Afrezza Inhalation Powder is a dry powder supplied as 4-, 8-, or 12-unit cartridges.

The Afrezza Inhaler is breath-powered by the subject. When the subject inhales through the device, the powder is aerosolized and delivered to the lung.

Table 1: Test Product (Afrezza)

Test Product	
Trade Name	Afrezza®
Nonproprietary Name	Technosphere® Insulin inhalation powder and Gen2C inhalation system
Manufacturer	MannKind Corporation
Active Ingredient	Human insulin, recombinant DNA origin
Formulation	Inhalation powder Each milligram of formulation contains 3.0 units of human insulin.
Route	Oral inhalation The inhaler is breath-powered by the subject. When the subject inhales through the device, the powder is aerosolized and delivered to the lung.
Dose(s)	Individualized
Storage (Not in Use)	Refrigerated at 2°C to 8°C (36°F to 46°F): Until expiration date Note: The inhaler should be at room temperature for 10 minutes before use.

Test Product	
Storage (In Use)	• Room temperature storage 25°C (77°F) • Excursions permitted to 15 to 30°C (59°F to 86°F) • Sealed (unopened) blister card: Must be used within 10 days • Opened strip: Must be used within 3 days
Packaging	Blister card containing 15 cartridges. Two blister cards are overwrapped in a foil pouch.
Strength(s)	Pre-metered single-dose 4-, 8-, and 12-unit cartridges will be provided.
Lot and Batch Numbers	Will be recorded in the study master file and provided in the final clinical study report

3.4.2 Basal and Rapid-Acting Insulin Therapy Dose and Mode of Administration

Subjects in the Afrezza + Insulin Degludec group will be treated with insulin degludec administered subcutaneously for basal insulin coverage.

Subjects in the Afrezza + AID Control group will be treated with infused rapid-acting: insulin aspart (Novolog® or Fiasp®) or insulin lispro (Humalog®, Admelog®, or Lyumjev®) for basal insulin coverage (insulin pump/AID users). The dose regimen will be individualized.

Subjects in the AID Control group will be treated with infused rapid-acting: insulin aspart (Novolog or Fiasp) or insulin lispro (Humalog, Admelog, or Lyumjev) for basal insulin and prandial/correction insulin coverage (insulin pump/AID users). The dose regimen will be individualized.

3.4.3 Afrezza Training

At Visit 2, subjects in Afrezza groups (Afrezza + Insulin Degludec and Afrezza + AID) will receive Afrezza inhalation training using the BluHale system, which consists of an Afrezza Inhaler, an empty cartridge, and a pressure-sensing jacket that slips onto each inhaler. The jacket is designed for repeated use on multiple inhalers and does not require sterilization between subjects. Therefore, subjects may use the same jacket during training. Empty cartridges will be provided for training and practice. Subjects must demonstrate the ability to adequately perform the inspiratory maneuver utilizing the empty cartridge to continue in the study.

If, in the opinion of the Investigator, a subject cannot adequately perform the inspiratory maneuver after the second repeated training, the subject will be withdrawn from the study.

3.4.4 Dosage Schedule

Subjects in the Afrezza groups (Afrezza + Insulin Degludec and Afrezza + AID) will administer their first dose of Afrezza at Visit 2, at the start of the meal challenge. Afrezza will be dosed at 2 × the calculated RAA dose rounded down to the nearest 4-unit dose (based on their I:CHO dose calculated for mealtime), but not exceeding 24 units of Afrezza. The Afrezza dose will be administered at the start of the meal challenge. The start of the meal will define t=0. After the

meal challenge and at subsequent visits, Afrezza will be titrated to glycemic effect per Investigator discretion.

Table 2: Starting Dose of Afrezza for Subjects in the Afrezza Groups

RAA Dose (Units)	Afrezza Dose (Units)
<4	4
4	8
5	
6	12
7	
8	16
9	
10	20
11	
≥12	24*

RAA=rapid-acting insulin analog (e.g., insulin aspart or insulin lispro)

*The initial mealtime dose (taken at Visit 2 in the Afrezza + AID and Afrezza + Insulin Degludec groups) should not exceed 24 units of Afrezza.

Note: Aside from the initial mealtime dose cap mentioned (24 units of Afrezza), there is no maximum dose of Afrezza and the required total mealtime dose for the subject during the study may differ from the examples provided in this table.

Following the initial dose of Afrezza and throughout the study, post-meal insulin correction doses can be taken no sooner than 60 to 90 minutes after a previous dose of Afrezza if the subject's glucose value is >160mg/dL, or per investigator discretion. Subjects in the Afrezza+AID group will correction dose with RAA while subjects in the Afrezza+Tresiba group will correction dose with Afrezza.

3.4.5 Treatment Assignment

Subjects in this study will be assigned a unique subject ID. Once screening procedures are complete and eligibility is confirmed, eligible subjects will be enrolled and randomized to treatment at Visit 2.

All subjects in the Afrezza groups will receive Afrezza at Visit 2 and continue this treatment through Visit 14. Subjects in the AID Control group will not receive Afrezza and will continue using their CSII pump with AID algorithm and RAA throughout the study.

3.4.6 Drug Packaging and Blinding

This is an open-label clinical study. Neither clinical site personnel nor subjects will be blinded to treatment.

3.4.7 Drug Inventory and Accountability

The Investigator or designee is responsible for maintaining Afrezza and inhaler accountability records to ensure appropriate distribution throughout the clinical study. The Investigator should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all Afrezza and inhalers received at the site before final disposition. At the end of the study, or as directed, all Afrezza and inhalers, including unused, partially used, and empty containers will be discarded.

3.4.8 Treatment Compliance

It is expected that subjects will be compliant with all dosing instructions and subjects will administer the initial dose of Afrezza under clinical supervision at the study site.

3.4.9 Prior and Concomitant Illnesses and Treatments

3.4.9.1 Prior and Concomitant Illnesses

All illnesses present at screening will be considered to be prior illnesses (medical history). The subject's history of diabetes should be recorded at screening on the CRF. Subjects will also be questioned about drug and environmental allergies, family pulmonary disease history, and their smoking status/exposure to pulmonary toxins. The Investigator (or their designee) should document all other significant illnesses that the subject has experienced within 6 months of screening as medical history on the CRF.

After enrollment, any new or worsening illnesses should be documented as AEs on the CRF.

3.4.9.2 Concomitant Treatments

Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the CRF. The entry must include the dose, regimen, route, indication, and dates of use.

Concomitant treatments, defined as treatments taken after enrollment, include all nonstudy treatments that are taken by subjects at any time during the clinical study, including prescription drugs, herbal supplements, or over-the-counter medications, should be recorded as concomitant medications.

Antiadrenergic drugs (e.g., beta blockers and clonidine) are prohibited during the study. Subjects should continue their prestudy antihyperglycemic medications but no changes to their medications should be made between Visits 1 and 2. The initiation of drugs or herbal preparations known to modify glucose metabolism that may, in the opinion of the Investigator, interfere with the clinical study results should be discussed with the medical monitor.

3.5 Assessments

Unless otherwise indicated, all assessments will be performed by the Investigator or a qualified designee.

3.6 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 3).

Table 3: Schedule of Assessments

Study Period	**Screen**	**Treatment Period**												**ET** [c]
In-clinic Visit (V) Telehealth Visit (T)	V1	V2	T3	T4	T5	T6	T7	T8	V9	T10	T11	T12	V13	V14	
Day	Up to 28 Days Before Random. [a]	0	1	2	4	7	14	21	30	37 [b]	44 [b]	51 [b]	80	90 (EOT)	
Visit Window (Days)		--	--	--	--	±2	±2	±2	+7	±2	±2	±2	+2	+7	
Informed consent	X														
Eligibility criteria confirmed	X	X													
Demographics and medical history	X														
Randomization		X													
Physical examination, including weight and height	X													X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status and evaluation of pulmonary toxin exposure	X													X	X
Adverse events [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
COVID-19 screening [e]	X														
Hypoglycemic events [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c (central laboratory)	X													X	X [c]
Pregnancy test [g]	X														
TSH test [h]	X														
Serum creatinine [h]	X														

Study Period	**Screen**	**Treatment Period**												**ET** [c]
In-clinic Visit (V) Telehealth Visit (T)	V1	V2	T3	T4	T5	T6	T7	T8	V9	T10	T11	T12	V13	V14	
Day	Up to 28 Days Before Random. [a]	0	1	2	4	7	14	21	30	37 [b]	44 [b]	51 [b]	80	90 (EOT)	
Visit Window (Days)		--	--	--	--	±2	±2	±2	+7	±2	±2	±2	+2	+7	
FEV_1 measurement	X													X	X
Dispensing and placement of blinded CGM sensors	X												X		
Instruction of subject on blinded CGM procedures	X												X		
Review of blinded CGM readings and compliance		X													
Removal and download of blinded CGM		X												X	
Review/download unblinded CGM data [i]		X							X				X	X	X
Review/download pump data [i]		X							X				X	X	X

Study Period	**Screen**	**Treatment Period**												**ET** [c]
In-clinic Visit (V) Telehealth Visit (T)	V1	V2	T3	T4	T5	T6	T7	T8	V9	T10	T11	T12	V13	V14	
Day	Up to 28 Days Before Random. [a]	0	1	2	4	7	14	21	30	37 [b]	44 [b]	51 [b]	80	90 (EOT)	
Visit Window (Days)		--	--	--	--	±2	±2	±2	+7	±2	±2	±2	+2	+7	
Remind subjects in the Afrezza + AID group to NOT enter carb intake/meal announcements into their insulin pump [j]			X	X	X	X	X	X	X	X	X	X	X		
Training on use of the study-provided glucose meter	X														
Dispense glucose meter and supplies	X														
Provide additional glucose test strips and lancets, as necessary		X							X				X		
Collect and review glucose meter data		X							X				X	X	X
Instruct subject on logging of meal announcements and Afrezza doses, as applicable		X[j]											X		
Collect information on meal announcements and Afrezza doses, as applicable														X	

Study Period	**Screen**	**Treatment Period**												**ET** [c]
In-clinic Visit (V) Telehealth Visit (T)	V1	V2	T3	T4	T5	T6	T7	T8	V9	T10	T11	T12	V13	V14	
Day	Up to 28 Days Before Random. [a]	0	1	2	4	7	14	21	30	37 [b]	44 [b]	51 [b]	80	90 (EOT)	
Visit Window (Days)		--	--	--	--	±2	±2	±2	+7	±2	±2	±2	+2	+7	
First dose of Afrezza (Afrezza groups) or dose of RAA (AID Control group) with standardized meal		X													
Titration of all insulins to glycemic effect			X	X	X	X	X	X	X	X	X	X	X		
Afrezza Groups Only															
Training for use and storage of Afrezza		X													
Training, as needed, on CGM use including but not limited to the use of alerts, interpretation of trends, interfering substances, contraindications, etc		X	X	X	X	X	X	X	X	X	X	X	X		
Dispense Afrezza inhalers and cartridges, as necessary		X							X				X		

Study Period	**Screen**	**Treatment Period**												**ET** [c]
In-clinic Visit (V) Telehealth Visit (T)	V1	V2	T3	T4	T5	T6	T7	T8	V9	T10	T11	T12	V13	V14	
Day	Up to 28 Days Before Random. [a]	0	1	2	4	7	14	21	30	37 [b]	44 [b]	51 [b]	80	90 (EOT)	
Visit Window (Days)		--	--	--	--	±2	±2	±2	+7	±2	±2	±2	+2	+7	
Disbursement/ placement of unblinded CGM sensors [k]		X							X						
Training on use of unblinded CGM [k]		X													
Assess the need for Afrezza correction dosing based on CGM profile			X	X	X	X	X	X	X						
Dispense insulin degludec and injection supplies, as necessary (Afrezza + Insulin Degludec group only)		X							X						
Record basal insulin dosages (Afrezza + Insulin Degludec group only)		X							X				X	X	
Collect Afrezza unused inhalers and cartridges as well as any unopened bottles of insulin degludec														X	X

AID=automated insulin delivery, CGM=continuous glucose monitoring, COVID-19=coronavirus 2019, EOT=end of treatment, ET=early termination, FEV_1=forced expiratory volume in 1 second, HbA1c=glycated hemoglobin A1c, RAA=rapid-acting insulin analog, Random=randomization, Screen=screening, SMBG=self-monitored blood glucose, TSH=thyroid-stimulating hormone.

a. The Screening Visit should be scheduled 10 days (+ 4 days) before the subject's expected date of randomization. When subjects return for Visit 2, blinded CGM data will be downloaded and CGM sensor wear evaluated. If CGM sensor wear time is inadequate, per the discretion of the Investigator, the Screening Period can be extended (this becomes an unscheduled visit) and sensor wear can be repeated once. The subject will return to the clinic 10 days (+ 4 days) later and, if sensor wear is adequate and all eligibility criteria met, be randomized to study treatment and proceed with the meal challenge and Visit 2 assessments. Visit 2 should be within 4 days of the end of the final sensor wear data (i.e., the CGM sensor with adequate wear time).

b. The timing of telephone visits T10, T11, and T12 is relative to Visit 9 (T10 should occur 7 days [±2 days] from Visit 9, T11 is 14 days [±2 days] from Visit 9, and T12 is 31 days [±2 days] from Visit 9).

c. A sample should be collected for HbA1c at the ET visit if the subject discontinues the study after 4 weeks of participation.

d. Any adverse event that occurs after the subject enrolls in the study (consent date) will be recorded.

e. Subjects will be asked to provide a recent negative COVID-19 test (if available), confirm they have no symptoms of COVID-19, or provide evidence of COVID-19 vaccination.

f. Subjects should use their study provided blood glucose meter to take an SMBG value if their CGM reading is <70 mg/dL or if their CGM reading does not match their symptoms or expectations. Hypoglycemic episodes will be defined as all SMBG measurements <70 mg/dL. See Section 3.9.2.6.

g. A negative urine pregnancy test is required for enrollment, from all female subjects of child-bearing potential. After enrollment, additional pregnancy tests may be conducted as needed at the discretion of the Investigator.

h. A documented normal level within 6 months of screening can be used in lieu of testing.

i. CGM reports and pump reports will be downloaded from V1 to V2 at V2, V2 to V9 and 10 days before V9 to V9 at V9, V9 to 30 days after V9 at V13, and 30 days before V14 to V14 and V13 to V14 at V14 using Carelink for Medtronic CGM and pumps. CGM reports/data and pump reports/data will be downloaded from V1 to V2 at V2, V2 to V9 and 10 days before V9 to V9 at V9, V9 to 30 days after V9 at V13, and 30 days before V14 to V14 and V13 to V14 at V14 using Clarity for Dexcom CGM and t:connect for Tandem pumps. The site will de-identify all reports and data.

j. Subjects in the Afrezza + AID group will be instructed not to enter carb intake/meal announcements in the pump system. In the event that they accidentally enter carb intake/meal announcement for a certain meal, they should NOT dose Afrezza for that same meal. If they accidentally take Afrezza with a meal announcement, carbs or glucagon should be administered. For subjects in the Afrezza + AID group, the site will confirm at every visit (phone or in person) to make sure they are not entering carb intake/meal announcements in the pump system.

k. Only applies to subjects in the Afrezza + Insulin Degludec group who use a Medtronic 670G/770G system.

Table 4: CGM/Pump Reports and Data to be Downloaded

Reports/Data to be Downloaded	V2	V9	V13	V14
Blinded G6 PRO Data	X			X
V1 to V2 CGM/pump report/data	X			
V2 to V9 CGM/pump report/data		X		
V9 minus 10 Days to V9 CGM/pump report/data		X		
V9 to V9 plus 30 Days CGM/pump report/data			X	
V14 minus 30 Days to V14 CGM/pump report/data				X
V13 to V14 CGM/pump report				X
Study Meter Download	X	X	X	X

3.7 Study Procedures

Subject consent will be obtained at screening before any clinical study procedures are performed.

Procedures will be performed at the visits indicated in the Schedule of Assessments (Table 3). A detailed description of each assessment can be found in Sections 3.9.1 (efficacy) and 3.9.2 (safety).

3.7.1 Screening (V1)

Subject consent will be obtained upon screening before any study procedures are performed.

The following will also be performed at Visit 1:

- Record demographics and medical history (see Section 3.9.2.1)
- Perform physical examination (see Section 3.9.2.2)
- Record height and weight (see Section 3.9.2.3)
- Record vital signs (see Section 3.9.2.4), as deemed appropriate by investigator
- Record concomitant medications
- Record smoking status and pulmonary toxin exposure
- Measure and record FEV_1
- Collect blood and urine for laboratory tests (see Section 3.9.2.8)
- Perform COVID-19 screening assessment
- Place Dexcom G6 Pro CGM device in blinded mode

3.7.2 Randomization (V2)

When subjects return for Visit 2, blinded CGM data will be downloaded and CGM sensor wear evaluated. If CGM sensor wear time is inadequate, per the discretion of the Investigator, the Screening Period can be extended and sensor wear can be repeated once (this becomes an unscheduled visit). The subject will return to the clinic 10 days (+4 days) later and, if sensor wear is adequate and all eligibility criteria met, be randomized to study treatment and proceed with the meal challenge and Visit 2 assessments. Visit 2 should be within 4 days of the end of the final sensor wear data (i.e., the CGM sensor with adequate wear time).

The following procedures will be performed at Visit 2:

- Enrollment (if eligibility criteria are met)
- Record concomitant medications
- Record current basal insulin dosages
- Remove blinded Dexcom G6 Pro CGM

Download and de-identify data from Dexcom G6 Pro device (

-)

Download and de-identify of unblinded CGM reports and pump reports for Medtronic CGM and pumps (

-)

Download and de-identify of unblinded CGM reports/data and pump reports/data for Dexcom CGM and t:connect for Tandem pumps (

-)
- Subjects randomized to study treatment (Afrezza + Insulin Degludec, Afrezza + AID, or AID Control)
- Disbursement/placement of unblinded CGM sensor (only applies to subjects in the Afrezza + Insulin Degludec group who use a Medtronic 670G/770G system)
- Conduct 2-hour, in-clinic meal tolerance test
- Subjects will take their first dose of Afrezza or their dose of RAA with standardized meal challenge as described in Section 3.7.2.1.
- Record AEs
- Record any hypoglycemic episodes (see Section 3.9.2.6)
- Provide additional subject training, as needed, on CGM use, including but not limited to the use of alerts, interpretation of trends, interfering substances, and contraindications.
- Provide study treatment instructions to the subject. Subjects in the Afrezza + AID group should be instructed NOT to enter carb intake/meal announcements into their insulin pump during the study, to avoid the risk of an automated insulin bolus (i.e., to avoid stacking insulin). In the event that they accidentally enter carb intake/meal announcement for a certain meal, they should NOT dose Afrezza for that same meal. In the event they accidentally enter carb intake/meal announcement for a certain meal and take a dose of Afrezza for that same meal, they should ingest carbohydrates or administer glucagon and contact the study team as soon as possible.
- Provided adequate training on the appropriate use of glucagon emergency kits to all subjects.

3.7.2.1 Meal Challenge

Subjects will come into the clinic in a fasting state for Visit 2, with exception of treating hypoglycemia. Fasting will be defined as no intake of drink or food, with exception of water, for ≥6 hours before the clinic visit. Subjects will also be instructed not to administer manual bolus doses of insulin during the 4 hours immediately preceding the meal challenge. If the subject requires a manual bolus insulin dose to correct hyperglycemia within the 4 hours prior to the scheduled visit, the meal challenge will need to be rescheduled.

The CGM glucose value will be confirmed 15 minutes before the start of the meal. If the subject's CGM value is ≥70 mg/dL, the subject can start the meal challenge 15 minutes later. If the subject's CGM value is <70 mg/dL, the Investigator can provide 15 g of fast-acting carbohydrates and reassess the CGM glucose value after 30 minutes and if the subject's new CGM value is ≥70 mg/dL, the subject can start the meal challenge 15 minutes later. The CGM value obtained immediately before the start of the meal (defined as t=0) will serve as the baseline glucose value for that visit.

Subjects in the Afrezza groups will receive training on how to use the Afrezza Inhaler using BluHale technology, as well as how to identify and manage any events of hypo and hyperglycemia.

In addition to CGM, subjects will be instructed to take SMBG measurements 15 minutes before the start of the meal, immediately before the start of the meal (t=0), and at 15, 30, 45, 60, 90, and 120 minutes after the start of the meal challenge.

The meal challenge will consist of 1-2 bottles of Boost nutritional shake (1 bottle is approximately 240 calories, 41 g carbohydrate, 10 g protein, and 4 g fat). The meal is to be fully consumed within 15 minutes. Each Afrezza dose will be administered at the start of the meal challenge. The RAA dose will be administered 10 ± 5 minutes (per label) before the start of the meal challenge, per Investigator discretion.

For Afrezza doses exceeding 12 units, inhalations from multiple cartridges are necessary. To achieve the required total mealtime dose, subjects should use a combination of 4-unit, 8-unit, and 12-unit cartridges.

The blood glucose monitoring values and CGM values (if available) will be entered in the CRF completed at Visit 2. Afrezza subjects will remain under clinical supervision for the 2 hours after their dose of Afrezza. Subjects should have glucagon available for use in the event of hypoglycemia and should not be discharged until hypoglycemia is resolved.

3.7.3 Telephone Visits (T3-T8)

- Telephone Visits 3 to 8 will be conducted as summarized below:
  - T3 phone call on Day 1 (the day after randomization on Day 0)
  - T4 phone call on Day 2
  - T5 phone call on Day 4
  - T6 phone call on Day 7 (± 2 days)
  - T7 phone call on Day 14 (± 2 days)
  - T8 phone call on Day 21 (± 2 days)

At these visits:

- Record changes to concomitant medications
- Record any AEs
- Record hypoglycemic events
- Titrate mealtime, correction and basal insulin dosages
- Answer subjects' questions/concerns
- Remind subjects in the Afrezza + AID group to NOT enter carb intake/meal announcements into their insulin pump during the study, to avoid the risk of an automated insulin bolus (i.e., to avoid stacking insulin).

3.7.4 Clinic Visit (V9)

- Record changes to concomitant medications
- Record any AEs
- Record hypoglycemic events
- Collect and review glucose meter data

Download and de-identify of unblinded CGM reports and pump reports for Medtronic CGM and pumps (

-)

Download and de-identify of unblinded CGM reports/data and pump reports/data for Dexcom CGM and t:connect for Tandem pumps (

-)
- Remind subjects in the Afrezza + AID group to NOT enter carb intake/meal announcements into their insulin pump during the study, to avoid the risk of an automated insulin bolus (i.e., to avoid stacking insulin).
- Titrate mealtime, correction and basal insulin dosages
- Record current basal insulin dosages
- Assess the need for Afrezza correction dosing based on CGM profile (Afrezza groups only)
- Provide subject with any needed supplies (e.g., glucose test strips, Afrezza cartridges)

3.7.5 Telephone Visits (T10-T12)

The timing of telephone Visits T10, T11, and T12 is relative to Visit 9. Visit T10 should occur 7 days (±2 days) from Visit 9, T11 is 14 days (±2 days) from Visit 9, and T12 is 31 days (±2 days) from Visit 9.

At these visits:

- Record changes to concomitant medications
- Record any AEs
- Record hypoglycemic events
- Titrate mealtime, correction and basal insulin dosages
- Answer subjects' questions/concerns

3.7.6 Clinic Visit (V13)

This visit will be conducted at least 30 days (+7 days) after Visit 2.

The following procedures will be performed at Visit 13:

- Record changes to concomitant medications
- Record any AEs
- Record hypoglycemic events
- Collect and review glucose meter data

Download and de-identify of unblinded CGM reports and pump reports for Medtronic CGM and pumps (

-)

Download and de-identify of unblinded CGM reports/data and pump reports/data for Dexcom CGM and t:connect for Tandem pumps (

-)
- Place blinded Dexcom G6 Pro CGM sensors on all subjects
- Titrate mealtime, correction and basal insulin dosages
- Record current basal insulin dosages
- Provide subject with any needed supplies (e.g., glucose test strips, Afrezza cartridges)
- Instruct participants to log meal announcements and Afrezza doses in the final 10 days

3.7.7 Visit 14 / Early-Termination Visit

The following procedures will be performed at Visit 14, or if the subject discontinues early, at the early-termination visit:

- Perform all safety assessments

Download and de-identify data from Dexcom G6 Pro device (

-)

Download and de-identify of unblinded CGM reports and pump reports for Medtronic CGM and pumps (

-)

Download and de-identify of unblinded CGM reports/data and pump reports/data for Dexcom CGM and t:connect for Tandem pumps (

-)
- Collect meal announcements and Afrezza dose log for final 10 days
- Collect blood for laboratory tests (see Section 3.9.2.8)
- Record concomitant medications
- Record current basal insulin dosages
- Measure and record FEV_1
- Record AEs

3.8 Post Study Interview

An optional post-study interview may be conducted for those subjects who opt-in to participate, as indicated in the Informed Consent Form. The goals of the post-study interview are to gain insight into the subject's experience living with diabetes, their experience in the study (both positive and negative), and learn about how being in the study has affected their quality of life.

Sites will share the subject's contact information with the interviewer once the subject has opted in to participate. Responses to the questions will be summarized and shared with the Sponsor.

3.9 Procedures for Subjects Who Prematurely Withdraw from the Study

Any subject who discontinues treatment prematurely should have an early-termination visit conducted as soon as possible to complete the assessments indicated in Table 3.

3.9.1 Efficacy Assessments

3.9.1.1 Continuous Glucose Monitoring

Subjects will wear a blinded CGM at baseline for up to 20 days during an up to 28-day screening period and during the last 10 days of the study. Additionally, subjects will measure their glucose throughout the study using an unblinded CGM system (sensors, transmitter). Subjects will be instructed at Visit 2 in the operation of their CGM device.

3.9.1.2 Self-Monitored Blood Glucose

Confirmatory blood glucose values for CGM readings <70 mg/dL should be self-measured by the subject using a study-provided blood glucose meter and corresponding supplies (lancets, test strips, etc.). Subjects will also be instructed to use their blood glucose meter to take an SMBG value if they suspect DKA accompanied by a CGM value >250 mg/dL, or if their CGM reading does not match their symptoms or expectations, to make treatment decisions.

3.9.2 Safety Assessments

3.9.2.1 Medical History and Demographics

A detailed medical history should be taken to assess whether or not subjects meet the inclusion/exclusion criteria, including history of diabetes (i.e., date of clinical diagnosis of T1DM, start date of current insulin treatments and treatment name). In addition, subjects will be

queried about drug and environmental allergies, family pulmonary disease history, and their smoking status.

Demographic data, including age (years), race, ethnicity, and gender (male, female, other, or "decline to state") will also be collected.

3.9.2.2 Physical Examinations

A physical examination, including general appearance, ear, nose, throat, lung, and cardiac auscultation will be performed at Visit 1.

Abbreviated physical examinations will be performed as deemed appropriate by the Investigator for safety reasons; these abbreviated physical examinations will include, but are not limited to, general appearance, vital signs, mental status, respiratory and cardiovascular systems, and other evaluations, as needed.

All changes identified as clinically noteworthy must be recorded in an AE page of the CRF.

3.9.2.3 Height and Weight

Height, in centimeters, should be measured when the subject's shoes are off, feet together, and arms by the sides. Heels, buttocks, and upper back should also be in contact with the wall when the measurement is made.

Body weight, in kilograms, should be obtained with the subject wearing undergarments or very light clothing and no shoes, and with an empty bladder. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The same scale should be used throughout the study and calibrated on a regular basis as recommended by the manufacturer.

The body mass index (BMI) value will be calculated based on the height and weight.

3.9.2.4 Vital Signs

Vital signs may include body temperature, respiratory rate, pulse, and sitting systolic and diastolic blood pressures, as deemed appropriate by investigator.

3.9.2.5 Pulmonary Function Tests

Subjects will undergo FEV_1 testing according to American Thoracic Society and European Respiratory Society recommendations in the clinic. Subjects who experience respiratory symptoms that are not associated with an upper respiratory infection (URI) should undergo additional pulmonary function test to monitor clinically relevant decline (Section 4.1.3) per investigator's discretion in accordance with the Afrezza USPI. FEV_1 values will be recorded in the CRF

3.9.2.6 Hypoglycemic Events

A hypoglycemic episode is defined as any event with SMBG <70 mg/dL (i.e., Level 1 hypoglycemia) or SMBG <54 mg/dL (i.e., Level 2 hypoglycemia) (ADA 2021a) on the study-provided glucose meter. Severe hypoglycemic events are defined as events requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycemic events will be documented as SAEs in the CRF. Nonsevere hypoglycemic events will not be documented as AEs but will be recorded in the hypoglycemia page of the CRF.

After the standardized meal challenge at Visit 2, subjects will be monitored for signs of hypoglycemia. Subjects exhibiting signs of hypoglycemia will be treated as appropriate (e.g., provided with a snack or glucose). The type of treatment given and time will be recorded and subjects will remain in-clinic until hypoglycemia is resolved.

In the event that the subject accidentally enters carb intake/meal announcement for a certain meal and also doses with Afrezza, carbohydrates or glucagon should be administered. The subject should be instructed to contact the Investigator and site staff as soon as possible following the event to ensure prompt review and to give the Investigator the opportunity to address any further necessary measures for correction.

3.9.2.7 Hyperglycemic Events and Diabetic Ketoacidosis (DKA)

Investigators will educate subjects on recognizing and managing hyperglycemia and DKA using their CGM and study provided glucose meter, taking additional insulin and/or checking ketones as required. To ensure subject safety, subjects will be removed from the study if they have two events of DKA. Events of DKA are considered AESIs (Section 4.1.3) for which diagnostic criteria in Section 4.1.3.1 must be met.

At the time of suspected DKA accompanied by a CGM value of >250 mg/dL, the subject's blood glucose should be measured using the study-provided glucose meter to confirm.

- If glucose is > 250 mg/dL for more than 4 consecutive hours and continues >250 mg/dL after the subject has taken insulin and ingested water, ketones should be measured. If serum ketones are >1.5mmol/L or urine ketones are "moderate" or greater, the subject should contact the site staff and/or their physician as soon as possible for further guidance and ketones should be tested every hour until serum ketones are <1.5mmol/L or urine ketones are less than "moderate". Symptoms should be treated in accordance with standard of care instructions from the Investigator.
- If glucose is > 250 mg/dL and the subject is vomiting or feels ill, ketones should be measured. If serum ketones are >1.5mmol/L or urine ketones are "moderate" or greater, the subject should contact the site staff and/or their physician as soon as possible for further guidance and ketones should be tested every hour until serum ketones are

<1.5mmol/L or urine ketones are less than “moderate”. Symptoms should be treated in accordance with standard of care instructions from the Investigator.

3.9.2.8 Clinical Laboratory Tests

The clinical site will collect blood samples for HbA1c, creatinine and TSH from subjects at Visit 1. Samples for HbA1c will be forwarded to the central laboratory for analysis. Samples for creatinine and TSH will be tested by a local laboratory; however, a documented normal TSH or creatinine within 6 months of screening can be used in lieu of testing. Urine pregnancy tests (for β-human chorionic gonadotropin) will be performed locally for women of child-bearing potential only.

3.9.2.9 Adverse Events

All AEs occurring after enrollment and through the duration of the study will be recorded. See Section 4 for additional information.

3.9.3 Appropriateness of Measurements

All assessments to be used in this study are commonly used and generally recognized as relevant in diabetes studies.

4 ADVERSE EVENT REPORTING

Throughout the course of the study, all AEs will be monitored and recorded in an AE page of the CRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the study drug. If AEs occur, the first concern will be the safety of the study subjects. All AEs will be followed until resolved or stable and the outcome documented in the CRF.

4.1 Definitions and Criteria

4.1.1 Adverse Events

Per ICH E2A, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The intensity of each AE will be determined according to the following criteria:

- Mild: no modification of daily activities and does not require corrective/symptomatic treatment.
- Moderate: hinders normal daily activities and/or requires corrective/symptomatic treatment.
- Severe: prevents daily activities and requires corrective/symptomatic treatment.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs, but the action taken to treat a particular medical condition. They should be recorded as treatment of the AEs.

4.1.2 Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy tumors [histologically different from primary tumor])

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe. Similarly, a severe AE is not necessarily serious (e.g., nausea of several hours' duration may be rated as severe but may not be considered serious).

4.1.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern, specific to the investigational medicinal product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

For AESIs, the Sponsor must be informed immediately (i.e., within 24 hours), per the SAE notification guidelines described in Section 4.2.3.

The following AEs are considered AESIs:

- Acute bronchospasm
- Clinically relevant decline in pulmonary function (>20% decline from baseline percent predicted FEV_1 OR respiratory symptoms not associated with URI
- Hypersensitivity reactions, including anaphylaxis, which can occur with insulin products, including Afrezza
- DKA

4.1.3.1 Diagnostic Criteria for Diabetic Ketoacidosis

The following diagnostic criteria must be met to be considered a DKA event (ADA 2004):

- Arterial blood pH <7.30 or serum bicarbonate <15 mEq/L
- Blood glucose >250 mg/dL (or >13.9 mmol/L)
- Serum ketones or large/moderate urine ketones
- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Treatment provided in a health care facility

4.1.4 Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or that has worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded in the AE pages of the CRF:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study drug
- Has accompanying or inducing symptoms or signs
- Is judged by the Investigator as clinically significant

4.1.5 Assessing Relationship

The Investigator will classify every AE according to its relationship to study drug, study device, or study-related procedure. The AE relationship categories that will be used are listed below:

Related:

- An AE that occurs at a reasonable time interval after administration of the investigational

product, use of the device, or procedure

- An AE that follows a known response pattern to the investigational product, use of the device, or procedure
- An AE that improves after stopping the investigational product, use of the device, or procedure and reappears after repeated exposure to the investigational product, device, or procedure. Depending on the nature of the AE, rechallenge may not be possible.

Probably related:

- An AE that occurs at a reasonable time interval after administration of the investigational product, use of the device, or procedure
- An AE that follows a known response pattern to the investigational product, use of the device, or procedure, where an alternative explanation (e.g., a concomitant drug or concurrent disease) is less likely

Possibly related:

- An AE that occurs at a reasonable time interval after administration of the investigational product, use of the device, or procedure
- An AE that follows a known response pattern to the investigational product, use of the device, or procedure, but could have been produced by the subject's clinical status or by other therapies

Unlikely related:

- An AE for which sufficient information exists to indicate that the etiology is unrelated to the investigational product, use of the device, or procedure
- An AE for which another etiology is specified

Not related:

- An AE without a temporal relationship to the investigational product (e.g., an AE occurring in a subject who has not received investigational product), use of the device, or procedure
- An AE for which another cause is known

4.2 Reporting Procedures and Requirements

4.2.1 Adverse Events

Any AEs occurring from the date that the subject consents to participate in the study until they exit the study will be recorded.

The Investigator should document all AEs in the subjects' source documentation, on the AE CRF, and the SAE report (if the AE is serious). AEs of hypoglycemia that meet SAE criteria should be documented in the AE CRF and SAE report.

The Investigator should specify the date of the onset of the AE, the intensity (see definitions in Section 4.1.1), action taken with respect to the study drug, corrective treatment/therapy given, additional investigations performed, outcome, and the relationship to study drug (Section 4.1.5)

Whenever possible, the diagnosis or syndrome should be reported instead of individual associated symptoms (e.g., record "influenza" if this is the diagnosis instead of "fever" and "chills").

Every AE and serious AE should be followed until resolved, or resolved with sequelae, or considered stable in the opinion of the Investigator. To the extent possible, event resolution information will be obtained by means of due diligence (see the site operations manual).

If the severity of an AE increases, a new AE CRF must be completed for that AE. The date of change would be included as the end date for the original AE and the start date for the new AE of greater severity.

4.2.2 Adverse Events of Special Interest

As soon as possible (desired within 24 hours of Investigator or study coordinator awareness), the investigational center staff must report all AESIs (including DKA) to the Sponsor. For these events, the AE CRF will be completed with all known details as soon as possible, this will serve as notification to the Sponsor. If the study database cannot be accessed due to technical problems, contact the Sponsor and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE CRF.

Source documents that support the event (e.g., clinic notes, hospital admission and discharge records, lab reports, EMT reports, ER/Urgent Care) should be provided to the Sponsor. All source documents/medical records should be redacted. Each source page should be identified with the subject ID.

4.2.3 Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (within 24 hours) is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with all applicable regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB), and Investigators.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the subject and considered by the Investigator to be caused by the investigational product with a reasonable possibility should also be reported.

4.2.4 Procedures for Documenting Pregnancy During Study

If a female subject becomes pregnant during the study, the Investigator will notify the medical monitor immediately following pregnancy confirmation. A subject who becomes pregnant over the course of this study will be discontinued from study drug and followed for safety outcomes until 30 days beyond resolution of the pregnancy. Pregnancy is not in and of itself an AE.

However, if any adverse findings in a child or fetus of a subject exposed to the study drug occur before conception or during pregnancy, these should be reported as AEs.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Data Management Considerations

Paper CRFs will be employed for this study. Completed CRFs for this study will be forwarded to the Sponsor or its representative where editing and construction of a validated database will occur. Data will be quality checked, double-entered, and verified before entry into the database. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the Sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using the latest version of the WHO Drug Global Dictionary. Data management details will be outlined in a separate data management plan.

5.2 Statistical Considerations

Any deviations from the analyses described below will be documented prior to database lock, which will be described in the clinical study report.

5.3 General Considerations

All statistical processing will be performed using the most current version of statistical software (such as MiniTab, MATLAB, or Microsoft Excel) at the time of the analysis. Summary tables (descriptive statistics and/or frequency tables) will be provided for screening and/or baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data.

Individual data will be listed and sorted by treatment, subject ID, visit, and time point.

Database lock will occur upon the completion of the study.

5.4 Primary Endpoint

This study will evaluate the efficacy and safety of Afrezza combined with basal insulin or AID with insulin pump therapy, based on the change in HbA1c from baseline to the end of study.

5.4.1 Safety Endpoints

- Event rates and incidence Level 1 (<70 mg/dL) and Level 2 (<54 mg/dL) hypoglycemic events as confirmed by SMBG
- Event rates and incidence of severe hypoglycemic events, defined as events requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
- Incidence and severity of AEs: TEAEs, SAEs, AESIs, and device complaints
- Change in FEV_1 from screening to end of study

5.5 Randomization

This study is an open-label, randomized, three-arm study. Subjects will be randomized 2:2:1 to the Afrezza + AID, Afrezza + Insulin Degludec, and AID Control groups.

The randomization will target for a minimum of 3 subjects each who use Medtronic 670G/770G and Tandem Control IQ AID in each of the Afrezza groups, and a minimum of 2 subjects each who use Medtronic 670G/770G and Tandem Control IQ AID in the AID Control group.

5.6 Sample Size Justification

The sample size (25 subjects completing the study) was not determined using statistical methods as there is no statistical significance that will be derived.

5.7 Analysis Populations

The following analysis populations will be used:

- **Intent-To-Treat (ITT) Population**, defined as all subjects assigned to study treatment. The ITT Population will be the primary efficacy population.
- **Per-Protocol (PP) Population**, defined as all ITT subjects who have no major protocol deviations that would have an impact on the primary endpoint assessment during the 90-day randomized treatment period.

5.8 Protocol Deviations

Major protocol deviations (number and percentage of subjects) will be summarized for the ITT Population. All protocol deviations will be reviewed by clinical and statistical personnel to identify important deviations (those anticipated to have an impact on efficacy or safety findings) before the primary database lock.

5.9 Subject Disposition

Disposition of subjects will be summarized for ITT Population. Number and percentage of subjects completed or discontinued from the study will be summarized by visit and/or study period. Reasons for discontinuation will also be summarized.

5.10 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including usual insulin doses, will be summarized descriptively for the ITT Population. Summary statistics will include frequency and percentage, means, SD, minimum, and maximum as appropriate.

5.11 Medical History

Medical history data will be collected at the Screening Visit. The number and percentage of subjects with each medical history preferred term and system organ class will be summarized for ITT Population.

5.12 Concomitant Medications

All nonstudy medications will be coded with the current version of the WHO Drug Global Dictionary. Concomitant medications refer to nonstudy medications that have been used on or after administering the first dose of study drug. Among the concomitant medications, new concomitant medications refer to medications that are started after administering the first dose of study drug.

The number and percentage of subjects administering concomitant medications and new concomitant medications will be summarized by Anatomic Therapeutic Chemical Classification System Level 4 category and preferred term for the ITT Population.

5.13 Treatment Exposure and Compliance

Descriptive statistics will be used to summarize subject dosing information including the basal, bolus, and total insulin doses by visit.

A by-subject listing of study drug administration will also be provided.

5.14 Descriptive Summary of Efficacy

HbA1c values will be summarized at baseline and end of study for the ITT Population. CGM values and metrics will be summarized by visit. A summary table with descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). CGM data will also be presented graphically.

5.15 Descriptive Summary of Safety

The incidence of hypoglycemia (total, nocturnal, and severe) and percentage time below 70 mg/dL and below 54 mg/dL will be reported. Nocturnal is defined as midnight to 0600 and severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

The number and percentage of subjects with treatment-emergent AEs will be tabulated by system organ class and preferred term by relationship to treatment and by severity.

A summary table by study visit with descriptive statistics for FEV_1 at screening and end of study will be provided. The FEV_1 data will also be presented graphically.

6 STUDY MANAGEMENT

6.1 Ethics and Consent

6.1.1 Regulations and Guidelines

The study will be performed in accordance with this protocol state and federal laws, and ICH guidelines for Good Clinical Practice.

6.1.2 Institutional Review Board

The clinical trial documents, including this protocol, will be reviewed by the relevant IRB before the start of the study.

Conduct of the trial must be approved by an appropriately constituted IRB. Approval is required for the study protocol, protocol amendment(s), ICF(s), subject information sheets, and any advertising materials. No investigational product will be shipped to a site until written IRB authorization has been received by the Sponsor or its representative.

6.1.3 Informed Consent

For each trial subject, written consent will be obtained before any protocol-related activities are performed. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time without any resulting disadvantage. They will receive all information that is required by local regulations and ICH guidelines.

All subjects will be insured against injury caused by their participation in the study according to legal requirements. They will be informed about the insurance and the resulting obligations on their part.

6.1.4 Data Protection

The Sponsor will ensure the confidentiality of a subject's medical information in accordance with all applicable laws and regulations.

Personal data generated within the scope of this study must be available for inspection upon request by representatives of the Sponsors' monitors, representatives, and collaborators.

6.1.5 Discontinuation of the Study by the Sponsor

The Sponsor reserves the right to discontinue the study at this site or at all sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation pertaining to the study and study drug must be returned to the Sponsor or its representative.

The study may also be discontinued at the discretion of the Sponsor if:

- Two subjects in the Afrezza+AID group and two subjects in the Afrezza+degludec group are discontinued from the study due to DKA

  OR

- Two subjects in the Afrezza+AID group and two subjects in the Afrezza+degludec group are discontinued from the study due to severe hypoglycemia

6.1.6 Study Documentation

The Investigator will acknowledge that he/she has received a copy of the Afrezza IB and assures the Sponsor that he/she will comply with the protocol. No changes in this protocol can be made without the Sponsor's written approval.

6.2 Data Management and Quality Control

6.2.1 Case Report Forms

The Investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

All clinical data will be captured in a validated database or CRF.

The Investigator site staff will enter and edit the data via a secure network, with secure access features (username and password) and/or on a paper CRF. A complete audit trail will be maintained. The Investigator will approve the data using an electronic and/or physical signature, and this approval will be used to confirm the accuracy of the data recorded. CRFs will be used for all subjects. The subject data will be accessible from the Investigator's site throughout the trial. The CRF must be kept current to reflect subject status at each phase during the course of the trial. The CRF will not capture personalized data. The Investigator must make a separate confidential record of personalized details (name and initials) on the subject identification and enrollment log.

It is the responsibility of the Investigator of the respective site to ensure that all subject discontinuations or changes in study or other medications entered in the subject's CRF are also made on the subject's medical records. The CRFs for any subject leaving the study should be completed at the time of the final visit or shortly thereafter.

6.3 Study Monitoring and Quality Assurance

This study will be performed in compliance with the Sponsor's standard operating procedures (SOPs) or with the contract research organization's SOPs, if applicable, and with regulations set forth by the FDA, ICH, and other significant regulatory authorities. Compliance will be achieved through study-specific audits of clinical sites and review of data. The Investigator or their qualified designee will enter the information required by the protocol on CRFs provided by the

Sponsor. Site monitors should visit each clinical site at a frequency documented in the monitoring plan to review CRFs for completeness and accuracy. Any discrepancies found between source documents and completed CRFs should be queried and appropriate clinical site personnel should address and or correct those discrepancies.

Computerized and manual procedures should be used to review and check data from CRFs and data from external sources for omissions, apparent errors, and values that may require further clarification from the clinical site. Data queries will be addressed by appropriate clinical personnel in the CRF. Only authorized personnel can make corrections to CRF in the clinical database and all corrections are documented in the CRF audit trail.

6.4 Retention of Records

The Investigator must arrange for retention of study records at the site. The Investigator should take measures to prevent accidental or premature destruction of these documents for the duration of the retention period.

The Investigator and institution must agree to provide direct access to all study-related materials, study staff, facilities, and source documents for study monitors, auditors, or regulatory inspectors.

6.5 Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its representative.

6.6 Financial Disclosure

The Investigator will be required to disclose any financial equity interests in the Sponsor and any conflicts of interest.

6.7 Publications and Disclosure Policy

This clinical study will be registered on ClinicalTrials.gov no later than 21 days after the first subject is enrolled, in compliance with applicable regulatory requirements.

As a multicenter trial, the Sponsor intends to publish clinical data from all centers participating in the investigation. Authorship and manuscript composition will reflect joint cooperation between multiple Investigators, sites, and the Sponsor's personnel. Authorship will be established before writing of the manuscript.

In conformity with International Committee of Medical Journal Editors (ICMJE 2019) recommendations, Investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those Investigators may be included in a collective

authorship (e.g., “Clinical Investigators”) or acknowledged individually with their contribution(s) specified.

Individual Investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, provided that the Sponsor is given ample opportunity to review and authorize the disclosure of data for any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the Sponsor authorizes the presentation of the data prior to disclosure.

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