Clinical Study Protocol

Protocol Title:	DOS [Dosing Optimization Study]: Open-label, Single-arm, Proof-of-Concept Dosing Study of Afrezza® in Adult Subjects 18 Years and Older with Type 1 or Type 2 Diabetes Mellitus
Protocol Number:	MKC-TI-191
Clinical Phase:	Phase 4
Protocol Version and Date:	Original, 15 March 2021
NCT	04849845
Sponsor:	MannKind Corporation 30930 Russell Ranch Road, Suite 300 Westlake Village, CA 91362

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

Protocol Title: DOS [Dosing Optimization Study]: Open-label, Single-arm, Proof-of-Concept Dosing Study of Afrezza® in Adult Subjects 18 Years and Older with Type 1 or Type 2 Diabetes Mellitus

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: _____

SYNOPSIS

Protocol Title:	DOS [Dosing Optimization Study]: Open-label, Single-arm, Proof-of-Concept Dosing Study of Afrezza® in Adult Subjects 18 Years and Older with Type 1 or Type 2 Diabetes Mellitus
Protocol Number:	MKC-TI-191
Sponsor:	MannKind Corporation
Investigator(s)/Study Center(s):	This study will be conducted by Investigators at 2 or more study centers located in the United States.
Phase of Development:	Phase 4
Objectives:	**Primary Objective:** • To evaluate the efficacy of Afrezza administered at 2 different doses, combined with basal insulin, in adults 18 years and older with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) as measured by: o Mean change from baseline postprandial glucose based on self-monitored blood glucose (SMBG) from immediately before administering Afrezza (t=0; baseline) to 15, 30, 45, 60, 90 and 120 minutes after Afrezza dosing in conjunction with a standardized meal challenge **Secondary Objective:** • To evaluate the safety of Afrezza administered at 2 different doses, combined with basal insulin, in adults 18 years and older with T1DM or T2DM, as measured by: o Event rates and incidence of Level 1 (<70 mg/dL) and Level 2 (<54 mg/dL) hypoglycemic events within the 120 minutes after Afrezza dosing o 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 within the 120 minutes after Afrezza dosing o Change in percent predicted forced expiratory volume in 1 second (FEV_1) before Afrezza dosing to 120 minutes after Afrezza dosing o Incidence and severity of adverse events (AEs): treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs)
Study Design:	MKC-TI-191 is a Phase 4, single-arm, multicenter, proof-of-concept clinical trial evaluating the efficacy and safety of Afrezza, administered according to the current Afrezza prescribing

	information (PI) compared to a titrated dose, in combination with a basal insulin in adult subjects (≥18 years of age) with T1DM or T2DM. Eligible subjects will be on a stable regimen consisting of a basal-bolus insulin therapy prior to screening. The study is composed of up to 4 clinic visits (screening, 2 treatment visits, and a follow-up visit): • **Screening (Visit 1):** Informed consent will be obtained and eligibility confirmed. Eligible subjects will be enrolled at Visit 1. • **Visit 2:** The first dose of Afrezza will be based on the dose of subcutaneous rapid-acting insulin analog (RAA) that the subject would normally take, converted according to the guidelines provided in the current Afrezza PI. If the subject's normal RAA dose is <4 units, the subject will be asked to consume enough nutritional shake, per their normal insulin:carbohydrate ratio, to cover an RAA dose of ≥4 units such that their Afrezza dose at Visit 3 is higher than the dose taken at Visit 2. After completing the standardized meal challenge, the Investigator will decide, based on the subject's glucose excursion at Visit 2, if the subject should proceed to Visit 3 where a second dose of Afrezza will be administered. • **Visit 3:** The second dose of Afrezza will be based on the dose of subcutaneous RAA that the subject would normally take, converted by multiplying their RAA dose by 2 and rounding down to the nearest Afrezza cartridge size. • **Follow-up (Visit 4):** Subjects will return for safety assessments 24 to 72 hours after their last dose of Afrezza. **Treatment Period** Subjects will come into the clinic in a fasting state for Visits 2 and 3, 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. At the beginning of each visit, before their dose of Afrezza, subjects will have FEV_1 measurements taken in the clinic. Before each dose of Afrezza, subjects will be trained on proper inhalation technique with BluHale® PRO. Each meal challenge will consist of 1 to 2 bottles of nutritional shake to be fully consumed within 15 minutes. The nutritional shake will contain approximately 240 calories, 41 g carbohydrate, 10 g protein, and 4 g fat per bottle. Each Afrezza dose will be administered at the start of the meal challenge. The subject's SMBG value must be between 100 and 200 mg/dL without requiring a correction dose of bolus insulin in order to receive the Afrezza dose and complete the meal challenge. Subjects

	using an insulin pump will be instructed to make sure their insulin pump is not in automated insulin delivery mode for the 3 hours before and during Visits 2 and 3. Subjects will also be instructed not to inject correction doses of bolus insulin during the 6 hours immediately preceding each Afrezza dose. If the subject requires a bolus insulin injection to correct hyperglycemia within the 6 hours prior to the scheduled visit, the meal challenge will need to be rescheduled. An SMBG measurement will be taken 15 minutes before the expected dose of Afrezza so the Investigator can assess if the subject is within the required SMBG range (100 to 200 mg/dL). If the subject's SMBG value is <100 mg/dL at the start of the visit, the Investigator can provide 15 g of fast-acting carbohydrates and remeasure SMBG after 30 minutes to determine if the subject should proceed to the meal challenge. The SMBG value obtained immediately before each dose of Afrezza (t=0) will be used to determine if the subject can proceed to the meal challenge and will serve as the baseline value for that visit. Subjects will be monitored by the Investigator for at least 2 hours after administering each dose of Afrezza. The subject will be instructed not to ingest additional food for the 2 hours they are in the clinic for observation, with exception of treating hypoglycemia; any treatment for hypoglycemia (e.g., snack or glucose) will be documented. Subjects will take SMBG measurements 15 minutes before their Afrezza dose and at t=0 (baseline), 15, 30, 45, 60, 90, and 120 minutes with respect to their Afrezza dose, where t=0 corresponds to the time immediately before administering their dose of Afrezza. Additional SMBG measurements may be taken per Investigator discretion. Subjects will have an FEV_1 measurement after completion of each standardized meal challenge (120 minutes after the Afrezza dose) at Visits 2 and 3. **Follow-up Visit** Subjects will be asked to return to the clinic within 24 to 72 hours after their last dose of Afrezza for safety assessments, including a final FEV_1 measurement.
Planned Sample Size:	20 subjects (number of subjects to complete the study)
Medical Condition or Disease Under Investigation:	T1DM and T2DM, with no more than 50% of subjects having T2DM

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 or T2DM (per the Investigator) and on a stable basal-bolus insulin regimen **Exclusion Criteria** *At screening:* 1. History of asthma, chronic obstructive pulmonary disease, or any other clinically important pulmonary disease (e.g., cystic fibrosis, bronchopulmonary dysplasia), use of any medications to treat such conditions within the last year, or significant congenital or acquired cardiopulmonary disease 2. History of serious complications of diabetes (e.g., active proliferative retinopathy or symptomatic autonomic neuropathy) 3. On dialysis 4. Respiratory tract infection within 14 days before screening (subject may return 14 days after resolution of symptoms for rescreening) 5. Treatment with any investigational drug in the past 30 days or an investigational device in the past 2 weeks 6. Any disease other than diabetes or initiation of any new medication that, in the judgment of the Investigator, could have a direct impact on glycemic control during the study 7. Use of antiadrenergic drugs (e.g., beta blockers and clonidine) 8. Any concurrent illness (other than diabetes mellitus) not controlled by a stable therapeutic regimen 9. History of a significant eating disorder (e.g., anorexia or bulimia nervosa) 10. 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 11. History of smoking (includes cigarettes, cigars, pipes, vaping devices, and marijuana) in the 6 months before screening 12. Female subject who is pregnant, breastfeeding, 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) 13. An event of severe hypoglycemia, as judged by the Investigator, within the 90 days before screening

	14. An episode of diabetic ketoacidosis requiring hospitalization within the 90 days before screening 15. Exposure to Afrezza in the 30 days before screening
Study Treatment(s):	All subjects will receive Afrezza in this study.
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 Insulin Therapy Dose, and Mode of Administration:	**Basal insulin analog:** The subject's personal basal insulin. The dose and type of basal insulin should not be changed between Visits 1 and 3. **Dose regimen:** Individualized **Mode of Administration:** Subcutaneous injection or via pump. Note: Pumps cannot be in automated insulin delivery mode for the 3 hours before or during Visits 2 and 3.
Duration of Treatment:	Two individual doses of Afrezza will be administered during this study, during Visits 2 and 3, with a standardized meal challenge.
Criteria for Evaluation:	This study will evaluate the efficacy and safety of Afrezza administered according to new dosing guidelines, combined with basal insulin, based on the endpoints outlined below: **Efficacy Endpoint** • Change in SMBG from immediately before administering the dose of Afrezza (t=0; baseline) to 15, 30, 45, 60, 90 and 120 minutes after Afrezza dosing **Safety Endpoints** • Event rates and incidence Level 1 (<70 mg/dL) and Level 2 (<54 mg/dL) hypoglycemic events • 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, and AESIs • Change in FEV_1 from t=0 to 120 minutes after Afrezza dosing
Statistical Methods:	**Sample Size Determination** Twenty subjects are planned to complete the study. Subjects who do not complete the study may be replaced. The sample size of 20 subjects was not determined using statistical methods, but rather was chosen based on clinical considerations. **Analysis Populations**

	All subjects in the clinical study who receive a dose of Afrezza will be included in analyses. **Analysis of Efficacy Endpoints** SMBG values will be summarized by visit. A summary table with descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by time point relative to Afrezza dosing will be provided. SMBG data will also be presented graphically. **Analysis of Safety Endpoints** The incidence of hypoglycemia (total, nocturnal, and severe) and number of hypoglycemic episodes will be summarized. Summary tables providing frequency counts and the percentage of subjects within each category will be provided for Level 1 hypoglycemia (SMBG <70 mg/dL) and Level 2 hypoglycemia (SMBG <54 mg/dL). Exposure-adjusted incidence rates and exposure-adjusted event rates will be calculated and summarized. The number and percentage of subjects with TEAEs 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 all time points will be provided. The FEV_1 data will also be presented graphically.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
BMI	body mass index
CGM	continuous glucose monitor
COVID-19	coronavirus 2019
CRF	case report form
DKA	diabetic ketoacidosis
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ITT	intent to treat
IRB	institutional review board
PI	prescribing information
RAA	rapid-acting insulin analog
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
SMBG	self-monitored blood glucose
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TI	Technosphere Insulin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus

DEFINITIONS OF TERMS

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

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

Diabetes constitutes one of the fasting growing global health emergencies. The prevalence of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are rising, with nearly half a billion people living with diabetes worldwide (IDF 2019). Among adults aged 20-79 years, an estimated 463.0 million adults worldwide have diabetes (~9.3% of all adults in this age group).

In both T1DM and T2DM, the therapeutic objective is to optimally control blood glucose levels and this objective is fundamentally the same in all subjects with diabetes, with individual circumstances and needs dictating what those optimal levels should be. In order to delay or prevent complications associated with diabetes, it is critical that patients adhere to their diabetes treatment regimen. Among patients treated with a multiple daily injection regimen of insulin, 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.

Technosphere® Insulin inhalation powder (TI inhalation powder) provides an alternative to injectable insulin. TI inhalation powder and the Gen2 Inhaler were approved as Afrezza® (insulin human) inhalation powder and Afrezza Inhaler by the United States Food and Drug Administration (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 [SC] route) and returns to near baseline levels in approximately 180 minutes (versus about 5 hours for RAA) (Afrezza IB 2021).

This unique ultra-rapid time-action profile allows for simpler and more flexible mealtime dosing, lessens the potential for interprandial 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

The current study aims to evaluate 2 different doses of Afrezza in adults ≥ 18 years of age. Subjects will administer an Afrezza dose based on the current prescribing information (PI) with a meal challenge, and then proceed to a second meal challenge where a second Afrezza dose will be administered based on the subject's RAA dose multiplied by 2 and rounded down to the nearest Afrezza cartridge size, subject to Investigator discretion.

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 SC insulin analog in head-to-head comparisons (Kendall et al. 2020, Grant et al. 2019). Thus, the Sponsor has chosen to evaluate 2 different doses of Afrezza to assess whether a higher dose results in improved postprandial glucose control.

1.3 Risks and Benefits

A clear benefit of Afrezza is fewer injections compared to subjects using RAAs injected subcutaneously.

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 (DKA)
- 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) (Afrezza IB 2021).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To evaluate the efficacy of Afrezza administered at 2 different doses, combined with basal insulin, in adults 18 years and older with T1DM or T2DM as measured by:
    - Mean change from baseline in postprandial glucose based on self-monitored blood glucose (SMBG) from immediately before administering the dose of Afrezza (t=0; baseline) to 15, 30, 45, 60, 90 and 120 minutes after Afrezza dosing in conjunction with a standardized meal challenge

2.2 Secondary Objective

The secondary objective of this study is:

- To evaluate the safety of Afrezza administered at 2 different doses, combined with basal insulin, in adults 18 years and older with T1DM or T2DM, as measured by:
    - Event rates and incidence of Level 1 (<70 mg/dL) and Level 2 (<54 mg/dL) hypoglycemic events within the 120 minutes after Afrezza dosing
    - 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 within the 120 minutes after Afrezza dosing
    - Change in percent predicted forced expiratory volume in 1 second (FEV_1) from before Afrezza dosing to 120 minutes after Afrezza dosing
    - Incidence and severity of adverse events (AEs): treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs)

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

MKC-TI-191 is a Phase 4, single-arm, multicenter clinical trial evaluating the efficacy and safety of Afrezza, administered according to the current Afrezza PI compared to a titrated dose, in combination with a basal insulin in adult subjects (≥18 years of age) with T1DM or T2DM.

Eligible subjects will be on a stable regimen consisting of a basal-bolus insulin therapy prior to screening.

The study is composed of up to 4 clinic visits (screening, 2 treatment visits, and a follow-up visit):

- **Screening (Visit 1):** Informed consent will be obtained and eligibility confirmed. Eligible subjects will be enrolled at Visit 1.
- **Visit 2:** The first dose of Afrezza will be based on the dose of SC RAA that the subject would normally take, converted according to the guidelines provided in the current Afrezza PI. If the subject's normal RAA dose is <4 units, the subject will be asked to consume enough nutritional shake, per their normal insulin:carbohydrate ratio, to cover an RAA dose of ≥4 units such that their Afrezza dose at Visit 3 is higher than the dose taken at Visit 2. After completing the standardized meal challenge, the Investigator will decide, based on the subject's glucose excursion at Visit 2, if the subject should proceed to Visit 3 where a second dose of Afrezza will be administered.
- **Visit 3:** The second dose of Afrezza will be based on the dose of SC RAA that the subject would normally take, converted by multiplying their RAA dose by 2 and rounding down to the nearest Afrezza cartridge size.
- **Follow-up Visit (Visit 4):** Subjects will return for safety assessments, including a final FEV_1 measurement, 24 to 72 hours after their last dose of Afrezza.

See Section 3.5 for information on the assessments to be performed at these visits.

3.2 Study Duration

Two individual doses of Afrezza will be administered during the study, during Visits 2 and 3. The duration of each subject's participation in the trial is expected to be approximately 2 weeks.

The end of the clinical study is defined as the day the last subject completes his/her last visit. The length of the entire study (from the first subject enrolled to the last subject last visit) is expected to be approximately 3 months.

3.3 Selection of Study Population

The population sought for this study is adult subjects ≥18 years of age with T1DM or T2DM. No more than 50% of subjects enrolled will have T2DM. Twenty subjects are planned to complete the study. Subjects who do not complete the study may be replaced.

Specific inclusion and exclusion criteria are detailed in Section 3.3.1 and Section 3.3.2.

3.3.1 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 or T2DM (per the Investigator) and on a stable basal-bolus insulin regimen

3.3.2 Exclusion Criteria

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

1. History of asthma, chronic obstructive pulmonary disease, or any other clinically important pulmonary disease (e.g., cystic fibrosis, bronchopulmonary dysplasia), use of any medications to treat such conditions within the last year, or significant congenital or acquired cardiopulmonary disease
2. History of serious complications of diabetes (e.g., active proliferative retinopathy or symptomatic autonomic neuropathy)
3. On dialysis
4. Respiratory tract infection within 14 days before screening (subject may return 14 days after resolution of symptoms for rescreening)
5. Treatment with any investigational drug in the past 30 days or an investigational device in the past 2 weeks
6. Any disease other than diabetes or initiation of any new medication that, in the judgment of the Investigator, could have a direct impact on glycemic control during the study
7. Use of antiadrenergic drugs (e.g., beta blockers and clonidine)
8. Any concurrent illness (other than diabetes mellitus) not controlled by a stable therapeutic regimen
9. History of a significant eating disorder (e.g., anorexia or bulimia nervosa)
10. 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
11. History of smoking (includes cigarettes, cigars, pipes, vaping devices, and marijuana) in the 6 months before screening
12. Female subject who is pregnant, breastfeeding, 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)
13. An event of severe hypoglycemia, as judged by the Investigator, within the 90 days before screening
14. An episode of DKA requiring hospitalization within the 90 days before screening

15. Exposure to Afrezza in the 30 days before screening

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 PI (Afrezza 2020), should not be enrolled in the study.

3.3.3 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 follow-up 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 2).

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-enrolled in the study. Their identification numbers must not be reused.

3.3.3.1 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:* 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.

- *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:* The subject becomes pregnant.
- *Smoking:* The subject begins smoking or vaping, including smoking marijuana.
- *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/coronavirus 2019 (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.

3.3.4 Replacement of Subjects

Subjects who discontinue from the study will not be replaced.

3.4 Treatments

3.4.1 Details of Study Treatments and Storage Conditions

The test product is defined as Afrezza [insulin human] inhalation powder administered using the inhaler (Table 1).

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 aerolized and delivered to the lung.
Dose(s)	Individualized; See Section 3.5.2.2.1.1 (Visit 2) and Section 3.5.2.2.2.1 (Visit 3) for guidelines.
Storage (Not in Use)	Refrigerated at 2°C to 8°C (36°F to 46°F) Note: The inhaler should be at room temperature for 10 minutes before use.
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

In addition, subjects will take their personal basal insulin while enrolled in the study. The dose and type of basal insulin should not be changed between Visits 1 and 3.

Basal insulin therapy administered via either SC injection or pump will be permitted, but pumps cannot be in automated insulin delivery mode for the 3 hours before or during Visits 2 or 3.

3.4.2 Dosage Schedule

Subjects will administer Afrezza at Visits 2 and 3, at the start of a meal challenge, according to the dosing guidelines provided in Section 3.5.2.2.1.1 (Visit 2) and Section 3.5.2.2.2.1 (Visit 3).

3.4.3 Treatment Assignment

All subjects in this study will receive Afrezza at Visits 2 and 3.

Subjects in this study will be assigned a unique subject identification number. Once screening procedures are complete, eligible subjects will be enrolled.

3.4.4 Drug Packaging and Blinding

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

3.4.5 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. Investigators 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.

3.4.6 Treatment Compliance

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

3.4.7 Prior and Concomitant Illnesses and Treatments

3.4.7.1 Prior and Concomitant Illnesses

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. Investigators (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 in the CRF.

3.4.7.2 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 3. 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.

3.5.1 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 2).

Table 2: Schedule of Assessments

Clinic Visit	Screening	Treatment Period		Follow-up	Early Termination
	Visit 1 [a]	Visit 2	Visit 3	Visit 4	
Day	Up to 7 days before Visit 2	1	Day 4	Day 7	
Visit Window		NA	+/- 2 days	+/- 2 days	
Informed consent	X				
COVID-19 screening assessment [b]	X				
Demographics and medical history	X				
Eligibility criteria confirmed and subject registration	X				
Vital signs measurement	X				
Complete physical examination and record height and weight	X				
Record concomitant medications	X	X	X	X	X
Smoking status and evaluation of pulmonary toxin exposure	X				
Laboratory assessments					
HbA1c	X				
Urine pregnancy test [c]	X				
Education, treatment, and clinic assessments					
Training on the use of Afrezza with BluHale PRO		X	X		
Dose of Afrezza with standardized meal [d]		X	X		
SMBG measurements [e]		X	X		
CGM readings, if applicable [f]		X	X		
FEV_1 measurement	X	X [g]	X [g]	X	X
Collect and review glucose meter data		X	X		
Record AEs	X [h]	X	X	X	X
Record any hypoglycemic episodes [i]		X	X		
Provide discharge instructions to the subject		X	X		

AE=adverse event, BMI=body mass index, CGM=continuous glucose monitor, COVID-19=coronavirus 2019, CRF=case report form, FEV_1=forced expiratory volume in 1 second, HbA1c=glycated hemoglobin A1c, SMBG=self-monitored blood glucose.

Note: Subjects should arrive to the clinic in a fasting state for Visits 2 and 3, with exception of treating hypoglycemia. Fasting is defined as no intake of drink or food, with exception of water, for ≥6 hours before the clinic visit.

a. Visits 1 and 2 may be consolidated into a single clinic visit, provided the subject is in a fasting state and able to complete all assessments required for both visits.

b. 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.

c. 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.

d. The subject's SMBG value must be between 100 and 200 mg/dL without requiring a correction dose of bolus insulin in order to receive the Afrezza dose and complete the meal challenge.
e. Subjects should use their Sponsor-provided blood glucose meter to take SMBG values: 15 minutes before their Afrezza dose, immediately before administering their dose of Afrezza (t=0; baseline) and at 15, 30, 45, 60, 90 and 120 minutes after Afrezza dosing. Additional SMBG measurements may be taken per Investigator discretion.
f. If the subject is wearing a CGM, they will be asked to write down their CGM value every time they take an SMBG measurement in the clinic. These CGM values will be entered in the CRF completed at Visit 2 and Visit 3.
g. At the beginning of Visits 2 and 3, before their dose of Afrezza, subjects will have FEV_1 measurements taken in the clinic. After completion of the standardized meal challenge (120 minutes after Afrezza dose), subjects will have another FEV_1 measurement before leaving the clinic.
h. Any AE that occurs after the subject enrolls in the study (consent date) will be recorded.
i. Hypoglycemic episodes will be defined as all SMBG measurements <70 mg/dL. See Section 3.5.5.6.

3.5.2 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 2). A detailed description of each assessment can be found in Sections 3.5.4 (efficacy) and 3.5.5 (safety).

3.5.2.1 Screening (Visit 1)

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

The following will be performed at Visit 1:

- Record demographics and medical history (see Section 3.5.5.1)
- Record vital signs (see Section 3.5.5.4)
- Perform complete physical examination (see Section 3.5.5.2)
- Record height and weight (see Section 3.5.5.3)
- Record concomitant medications (see Section 3.4.7.2)
- Record smoking status and pulmonary toxin exposure
- Measure and record FEV_1
- Collect blood and urine for laboratory tests (see Section 3.5.5.7)
- Perform COVID-19 screening assessment
- Enrollment (if eligibility criteria are met)

Visits 1 and 2 may be consolidated into a single clinic visit, provided the subject is in a fasting state and able to complete all assessments required for both visits.

3.5.2.2 Treatment Period

Subjects will come into the clinic in a fasting state for Visits 2 and 3, 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 must have an SMBG value between 100 and 200 mg/dL without requiring a correction dose of bolus insulin in order to receive each Afrezza dose and complete the meal challenges.

Subjects using an insulin pump will be instructed to make sure their insulin pump is not in the automated insulin delivery mode for the 3 hours before and during treatment visits. Subjects will also be instructed not to inject correction doses of bolus insulin during the 6 hours immediately preceding each Afrezza dose. If the subject requires a bolus insulin injection to correct hyperglycemia within the 6 hours prior to the scheduled visit, the meal challenge will need to be rescheduled. An SMBG measurement will be taken 15 minutes before the expected dose of Afrezza so the Investigator can assess if the subject is within the required SMBG range (100 to 200 mg/dL). If the subject's SMBG value is <100 mg/dL, the Investigator can provide 15 g of fast-acting carbohydrates and remeasure SMBG after 30 minutes to determine if the subject should proceed to the meal challenge. The SMBG value obtained immediately before each dose of Afrezza (t=0) will be used to determine if the subject can proceed to the meal challenge and will serve as the baseline value for that visit.

Each meal challenge will consist of 1 to 2 bottles of nutritional shake to be fully consumed within 15 minutes. The nutritional shake will contain approximately 240 calories, 41 g carbohydrate, 10 g protein, and 4 g fat per bottle. Each Afrezza dose will be administered at the start of the meal challenge.

3.5.2.2.1 Visit 2

The following procedures will be performed at Visit 2:

- Record concomitant medications (see Section 3.4.7.2)
- Complete training on the Afrezza inhaler using BluHale® PRO
- Measure and record FEV_1 before Afrezza dose
- Take first dose of Afrezza with standardized meal challenge according to Section 3.5.2.2.1.1
- Measure and record FEV_1 after completion of the meal challenge
- Record AEs
- Collect and review glucose meter data
- Record any hypoglycemic episodes (see Section 3.5.5.6)
- Provide discharge instructions to the subject

3.5.2.2.1.1 Standardized Meal Challenge and Afrezza Dosing at Visit 2

The Afrezza dose to be taken at Visit 2 will be based on the dose of RAA that the subject would normally take, converted according to the guidelines provided in the current Afrezza PI as shown in Table 3.

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.

Table 3: Dose of Afrezza at Visit 2

RAA Dose (Units)	Afrezza Dose (Units)
Up to 4	4
5	8
6	
7	
8	
9	12
10	
11	
12	
13	16
14	
15	
16	
17	20
18	
19	
20	
21	24
22	
23	
24	

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

Note: There is no maximum dose of Afrezza and the required total mealtime dose may differ from the examples provided in this table.

The dose of Afrezza will be administered at the start of the meal challenge. The subject must consume 1 to 2 bottles of nutritional shake within 15 minutes for the meal challenge and take SMBG measurements 15 minutes before their Afrezza dose, immediately before administering the Afrezza dose (t=0; baseline) and at 15, 30, 45, 60, 90, and 120 minutes after Afrezza dosing. The subject will remain under clinical supervision for the 2 hours after their dose of Afrezza.

If the subject is wearing a continuous glucose monitor (CGM), they will be asked to write down their CGM value every time they take an SMBG measurement in the clinic. These CGM values will be entered in the CRF completed at Visit 2.

After completing the standardized meal challenge, the Investigator will decide, based on the subject's glucose excursion at Visit 2 if the subject should proceed to Visit 3 where a titrated dose of Afrezza will be administered according to Table 4.

3.5.2.2.2 Visit 3

The following procedures will be performed at Visit 3:

- Record concomitant medications (see Section 3.4.7.2)
- Complete refresher training on the Afrezza inhaler using BluHale PRO
- Measure and record FEV_1 before Afrezza dose
- Take the dose of Afrezza with standardized meal challenge according to Section 3.5.2.2.1.1
- Measure and record FEV_1 after completion of the meal challenge
- Record AEs
- Collect and review glucose meter data
- Record any hypoglycemic episodes (see Section 3.5.5.6)
- Provide discharge instructions to the subject

3.5.2.2.2.1 Standardized Meal Challenge and Afrezza Dosing at Visit 3

The Afrezza dose to be taken at Visit 3 will be based on the dose of RAA that the subject would normally take, converted by multiplying their RAA dose by 2 and rounding down to the nearest Afrezza cartridge size as shown in Table 4. If the subject's normal RAA dose is <4 units, the subject will be asked to consume enough nutritional shake, per their normal insulin:carbohydrate ratio, to cover an RAA dose of ≥4 units such that their Afrezza dose at Visit 3 is higher than the dose taken at Visit 2.

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.

Table 4: Dose of Afrezza at Visit 3

RAA Dose (Units)	Afrezza Dose (Units)
<4	4
4	8
5	
6	12
7	
8	16
9	
10	20
11	
12	24
13	
14	28
15	
16	32
17	
18	36
19	
20	40
21	
22	44
23	
24	48

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

Note: There is no maximum dose of Afrezza and the required total mealtime dose may differ from the examples provided in this table.

The dose of Afrezza will be administered at the start of the meal challenge. The subject must consume 1 to 2 bottles of nutritional shake within 15 minutes for the meal challenge and take SMBG measurements 15 minutes before their Afrezza dose, immediately before administering the Afrezza dose (t=0; baseline) and at 15, 30, 45, 60, 90, and 120 minutes after Afrezza dosing. The subject will remain under clinical supervision for the 2 hours after their dose of Afrezza.

If the subject is wearing a CGM, they will be asked to write down their CGM value every time they take an SMBG measurement in the clinic. These CGM values will be entered in the CRF completed at Visit 3.

3.5.2.3 Follow-up (Visit 4) / Early-Termination Visit

The following procedures will be performed at Visit 4, or if the subject discontinues early, at the early-termination visit:

- Record concomitant medications (see Section 3.4.7.2)
- Measure and record FEV_1
- Record AEs

3.5.3 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 2 and Section 3.5.2.3.

3.5.4 Efficacy Assessment

3.5.4.1 Self-Monitored Blood Glucose

Subjects will measure their blood glucose using the Sponsor-provided blood glucose meter and corresponding supplies (lancets, control solutions, test strips, etc.). Subjects will be instructed at both Visits 2 and 3 to take SMBG values 15 minutes before their Afrezza dose, immediately before administering their dose of Afrezza (t=0; baseline), and at 30, 45, 60, 90 and 120 minutes after Afrezza dosing. Additional SMBG measurements may be taken per Investigator discretion.

3.5.5 Safety Assessments

3.5.5.1 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 (e.g., age at onset of diabetes, start and stop dates of previous insulin treatments, treatment name, dose[s], frequency and method of dose delivery, date of clinical diagnosis of T1DM or T2DM). In addition, subjects will be queried about drug and environmental allergies, family pulmonary disease history, and any change in their smoking status.

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

3.5.5.2 Physical Examinations

A complete 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, 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.

3.5.5.3 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.

3.5.5.4 Vital Signs

Vital signs will include body temperature, respiratory rate, pulse, and sitting systolic and diastolic blood pressures. Vital sign measurements will be recorded with the subject in a sitting position for 5 minutes before the measurement is taken.

3.5.5.5 Pulmonary Function Tests

Subjects will undergo pulmonary function tests (spirometry) according to American Thoracic Society and European Respiratory Society recommendations in the clinic.

The FEV_1 values will be recorded in the CRF.

3.5.5.6 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). 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 challenges at Visit 2 and Visit 3, 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) and the type of treatment given and time will be recorded. If a subject experiences hypoglycemia, SMBG measurements should be performed every 15 minutes until hypoglycemia is resolved.

3.5.5.7 Clinical Laboratory Tests

The clinical site will collect blood samples for HbA1c from subjects at Visit 1 and samples will be forwarded to the central laboratory for analysis. Urine pregnancy tests (for β-human chorionic gonadotropin) will be performed locally for women of child-bearing potential only.

3.5.5.8 Adverse Events

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

3.5.6 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 at any dose:

- 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 (e.g., an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious). Furthermore, 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 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 4.2.2.

The following AEs are considered AESIs:

- Acute bronchospasm
- Clinically relevant decline in pulmonary function (>20% decline from baseline percent predicted FEV_1 accompanied by respiratory symptoms)
- Hypersensitivity reactions, including anaphylaxis, which can occur with insulin products, including Afrezza
- DKA

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 when the subject enrolls in the study (consent date) until they exit the study will be recorded.

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

The Investigator should specify the date of the onset of the AE, the intensity (see definitions in Section 4.1), 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 SAE 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 page in the 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 and Severe Hypoglycemia

As soon as possible (desired within 24 hours of Investigator or study coordinator awareness), the investigational center staff must report all events of severe hypoglycemia and AESIs (including DKA) to the Sponsor. For these events, the AE page of the 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 page in the CRF.

Source documents that support the event (e.g., clinic notes, hospital admission and discharge records, lab reports, emergency medical technician reports, emergency room/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 identification number.

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.

4.3 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 before conception or during pregnancy 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 WHODrug Global. 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.

5.2.1 General Considerations

All statistical processing will be performed using the most current version of SAS® software (SAS Institute Inc, Cary, NC) 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 identification number, visit, and time point.

Database lock will occur upon the completion of the study.

5.2.2 Randomization

This study is an open-label, single-arm study (not randomized).

5.2.3 Sample Size Justification

The sample size (20 subjects completing the study) was not determined using statistical methods, but rather was chosen based on clinical considerations.

5.2.4 Analysis Populations

All subjects in the clinical study who receive a dose of Afrezza will be included in the analyses reported at the end of the study.

5.2.5 Protocol Deviations

Major protocol deviations (number and percentage of subjects) will be summarized. 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.

5.2.6 Subject Disposition

Disposition (the 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.

5.2.7 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including usual basal and bolus insulin doses, at screening will be summarized descriptively. Summary statistics will include frequency and percentage, means, standard deviation, minimum, and maximum as appropriate.

5.2.8 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.

5.2.9 Concomitant Medications

All nonstudy medications will be coded with the current version of WHODrug Global. 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.

5.2.10 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.

5.2.11 Efficacy Analyses

SMBG values will be summarized by visit. A summary table with descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by time point relative to Afrezza dosing will be provided. SMBG data will also be presented graphically.

5.2.12 Safety Analyses

The incidence of hypoglycemia (total, nocturnal, and severe) and number of hypoglycemic episodes will be summarized. Summary tables providing frequency counts and the percentage of subjects within each category will be provided for Level 1 hypoglycemia (SMBG <70 mg/dL)

and Level 2 hypoglycemia (SMBG <54 mg/dL). Exposure-adjusted incidence rates and exposure-adjusted event rates will be calculated and summarized.

The number and percentage of subjects with TEAEs 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 all time points 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), informed consent forms(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.

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.

6.2 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.

6.3 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.

6.4 Data Management and Quality Control

6.4.1 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.

The Investigator site staff will enter and edit the data via a secure network, with secure access features (username and password). A complete audit trail will be maintained. The Investigator will approve the data using an electronic signature, and this approval will be used to confirm the accuracy of the data recorded. Data for all subjects will be recorded in CRFs. 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.

6.4.2 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.

6.5 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.

6.6 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.

6.7 Financial Disclosure

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

6.8 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.

7 REFERENCES

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SIGNATURE PAGE

Protocol Title: DOS [Dosing Optimization Study]: Open-label, Single-arm, Proof-of-Concept Dosing Study of Afrezza® in Adult Subjects 18 Years and Older with Type 1 or Type 2 Diabetes Mellitus

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: DocuSigned by: Kevin Kaiserman E6963882D53149C... Date: 3/18/2021

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: 28 Mar 2021

Name (print): Mark P. Christiansen, MD

Site Name: Diablo Clinical Research, Inc.

Site Address: 2255 Ygnacio Valley Road, Suite M,
Walnut Creek, CA 94598