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

SAP Document Version: Version 1.0

SAP Note: Redacted sections describe Data Management procedures for the study. Only Statistical sections are presented.

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

NCT Number: NCT05243628

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Data Management & Statistical Analysis Plan

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 Identifier	MKC-TI-192
Protocol Version	1.1
Sponsor/Local Sponsor	MannKind Corporation
Document Version	1.0

1. Version History

Version	Summary of Change(s)	Author
1.0	Initial Version	Jennifer Pleitez & Joseph Hanna

2. Purpose

[redacted]

The purpose of this Statistical Analysis Plan (SAP) is to detail procedures and methods for executing the evaluation of primary and secondary endpoints. The study is not powered for statistical analysis.

3. Scope

This DMP & SAP cover study-related tasks and deliverables for the above referenced study. It describes how data will be collected, processed, QC'ed, stored, and analyzed.

4. Definitions & Acronyms

The following table lists the study terms specific-to and only used in this document

Term	Definition
A1c / HbA1c	Hemoglobin HbA1c

AE	Adverse Event
AID	Automatic Insulin Delivery
CGM	Continuous Glucose Monitor/Monitoring
CRF	Case Report Form
CSR	Clinical Study Report
DM	Data Manager
DMP	Data Management Plan
RAA	Rapid-acting insulin analogue
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMBG	Self-monitoring of blood glucose
(e)TMF	(electronic) Trial Master File

5. Data Storage

Database	Database Owner	Description of Data Stored
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6. Data Collection and Processing

[redacted]

6.1 Data Locks

[redacted]

7. Randomization

7.1 Randomization List Generation

The DM will create a master randomization list; however, no formal validation will be performed. Subject assignments will be predetermined and distributed ahead of time to ensure enrollment stratification and criteria are met. Microsoft Excel's "rand" function will be used to generate and assign a study arm group for each subject in the study in advanced with the following criteria:

1. A total of 25 subjects
2. Three study arms:
   a. Afrezza + AID (total of 10 subjects)
   b. Afrezza + Degludec (total of 10 subjects)
   c. AID Control (total of 5 subjects)
3. Study arms 1 and 3 must have a minimum of 3 subjects each from AID systems at screening:
   a. Medtronic 670G/770G
   b. Tandem Control IQ
4. Site 001 will have 12 subjects
5. Site 002 will have 13 subjects
6. The total number of subjects in each study arm will be approximately split evenly between sites.

Throughout enrollment, the data manager may rearrange randomization assignments manually if criterion 3 is not being met.

The sites will not have visibility to which study arm they will be assigned ahead of subject randomization.

If a subject drops after randomization and the site intends to enroll another subject to meet their total enrollment goal (criteria 4 and 5), the study arm assignment for that subject will be moved to the bottom of the list or wherever appropriate to ensure the criteria are met.

7.2 Randomization Assignment

As subjects are randomized into the study, the subject ID, AID system at screening, and status (active enrollment or dropped) will be tracked on the master randomization list.

7.3 Study Site Randomization Procedures

After clinical sites confirm subject eligibility at Visit 2, they will e-mail the Sponsor at ABCStudy@mannkindcorp.com, requesting randomization assignment with:

- The subject ID
- The subject's AID system at screening

The Sponsor must reply as soon as possible with the assigned study arm from the master randomization list, such that the site may continue the visit.

8. Statistical Analysis

8.1 Study Objectives

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

The secondary objectives of this study are to:

Evaluate the safety of study treatment based on hypoglycemia event rate, based on SMBG (self-monitored blood glucose testing), 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

Evaluate the impact of study treatment on overall glycemic control when comparing baseline versus end of treatment period as measured by core CGM metrics based on G6 Pro data:

- 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

8.2 Statistical Methods

8.2.1 Sample Size Determination

The sample size (25 subjects completing the study) was not determined using statistical methods.

8.2.2 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.

In general, any data for endpoint analysis collected outside the allowed study visit window may be considered missing for the PP population. Participants with early termination will be included in ITT analyses, as applicable, based on the amount of data collected relevant to the analysis. A summary of data exclusion and rationale will be included in the CSR.

8.2.3 Descriptive Summary of Efficacy

HbA1c values will be summarized at baseline and end of study. 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.

8.2.4 Descriptive Summary of Safety

The incidence (number of events) 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.

8.3 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.

Signatures for

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