STATISTICAL ANALYSIS PLAN

MKC-TI-155 Part I

Open-label, Single-arm, Multiple-dose Safety, Titration, and Pharmacokinetic Trial of Afrezza® in Pediatric Patients Ages 4 to 17 Years With Type 1 Diabetes Mellitus

NCT02527265

Prepared by: Lin Chen

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Author: Lin Chen

SIGNATURES

The undersigned have approved this Statistical Analysis Plan for use in this study.

John Krueger, MBA (Date)
Vice President, Clinical Development
Mannkind Corporation

Marisa Jones, PharmD (Date)
Clinical Research Specialist, Clinical Development
Mannkind Corporation

Ping-Chung Chang (Date)
Director of Biostatistics and Programming
PPD

Lin Chen (Date)
senior Biostatistician,
PPD

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1 INTRODUCTION

1.1 Study Background

AFREZZA® inhalation powder (hereafter referred to as AFREZZA®) consists of recombinant human insulin adsorbed onto fumaryl diketopiperazine (FDKP), a novel excipient which, at acidic pH, self-assembles into particles, and polysorbate 80. AFREZZA® 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 and FDKP are absorbed systemically.

AFREZZA® is currently available in cartridges labeled as "4 units", "8 units", and "12 units". The actual contents are 10 units human insulin in a "4 unit cartridge", 20 units in an "8 unit cartridge", and 30 units in a "12 unit cartridge".

AFREZZA® received Food and Drug Administration (FDA) approval for the treatment of adults 18 years or older with type 1 diabetes mellitus (T1DM) or type 2 diabetes. In subjects with T1DM, AFREZZA® must be used with a long-acting basal insulin formulation. After administration of AFREZZA® in adults, the maximum serum insulin concentration occurs in approximately 12 to 15 minutes (versus 45 to 60 minutes for rapid-acting analog [RAA] insulin via subcutaneous [SC] route) and returns to near baseline levels in approximately 180 minutes (versus about 5 hours for RAA) (1).

MKC-TI-155 Part 1 (2) is designed to assess the pharmacokinetics (PK), safety, and tolerability of AFREZZA® in children with T1DM ages 4 to 17 years who are on a stable regimen of basal-bolus insulin therapy administered by multiple daily injections (MDI). The study is intended to gain initial experience with AFREZZA® regarding its safety profile, to compare its PK properties to that previously reported in adults and to determine the ability to dose titrate and administer supplemental doses in children from 4-17 years of age. The data from this study will help determine the appropriate age range for inclusion, and recommended dosing for a 1-year pediatric efficacy and safety study (MKC-TI-155 Part 2). The study design for Part 2 is in development.

1.2 Changes from Protocol

There is no deviation from the original statistical analyses described in the protocol.

2 STUDY OBJECTIVES

The objectives of the study, MKC-TI-155 Part 1, are to:

- Assess the safety and tolerability of AFREZZA® in children ages 4 to 17 years with T1DM
- Assess PK following a prandial dose of AFREZZA® in children ages 4 to 17 years with T1DM

- Assess the ability to titrate the prandial and supplemental doses of AFREZZA® at each meal using postprandial self-monitored blood glucose (SMBG) values obtained 120 to 150 minutes after each prandial dose of AFREZZA® in children ages 4 to 17 years with T1DM

3 STUDY DESIGN

3.1 Overview of Study Design

MKC-TI-155 Part 1 will be a single-arm, multi-center, open-label, uncontrolled study to evaluate PK, safety, and ability to titrate AFREZZA® in children ages 4 to 17 years with T1DM, who were previously on a regimen of basal-bolus insulin therapy administered by multiple daily injections (MDI).

The structure of the study is as follows:

- Single dose PK at breakfast
- 4-week titration period starting at lunch after PK evaluation
- Optional 52-week safety extension

The screening period is up to 3 weeks. On Day 1, eligible subjects will receive a single dose of AFREZZA® prior to PK sampling. There will be 3 different doses of AFREZZA® for the PK study. The AFREZZA® dose (4, 8, or 12 units) will be based on the dose of SC RAA that the subject would usually receive for a breakfast containing a predetermined level of carbohydrate, comprising approximately 50% of the total caloric content. After this starting dose, each subject will be titrated with AFREZZA® TI according to the titration rules given in the protocol (2).

After the 4-week titration period, subjects will have the option to continue in a 52-week extension study at the Investigator's discretion. For subjects who opt not to continue treatment with AFREZZA®, a follow-up visit will occur approximately 1 week after the end of AFREZZA treatment for safety assessments (duration of 1 day). For subjects who participate in the extension study, an end-of-study follow-up visit will be conducted 4 weeks after the 52-week treatment period.

The study will be conducted sequentially in age groups beginning with Cohort 1. Approximately 46 subjects will be enrolled sequentially into 3 age cohorts:

- **Cohort 1: 13 to 17** years**;** approximately 18 subjects distributed across 4, 8, and 12 unit starting dose groups. Before proceeding to Cohort 2, at least 14 subjects must be dosed (i.e., must complete Visit 2). Of those, at least 6 subjects must receive the 8 unit dose.
- **Cohort 2: 8 to 12 years;** approximately 14 subjects distributed across 4 and 8 unit starting dose groups (the sample size may be adapted after taking the PK data from Cohort 1 into

account). Before proceeding to Cohort 3, at least 6 subjects must have completed Visit 15, and all subjects in Cohort 2 must have been evaluated for PK.

- **Cohort 3: 4 to 7 years;** approximately 14 subjects will be treated and assessed for AFREZZA® with a starting dose of 4 units. The sample size may be adapted after evaluating the PK data from Cohort 1 and Cohort 2.

3.2 Study Population

Approximately 46 subjects will be enrolled in Part 1 of the study (18 subjects for 13 to 17-year-old cohort, 14 subjects for 8 to 12-year-old cohort, and 14 subjects for 4 to 7-year-old cohort).

3.3 Sample Size Considerations

For the purpose of sample size calculation, total standard deviations (SD_{Total}) of 0.250 to 0.750 for inhaled insulin were used, based on the SD_{Total} observed for AFREZZA® in adults.

Table 1 shows the maximum imprecision (in terms of the 95% confidence interval) for AFREZZA® that will be obtained within an age cohort with 80% assurance, for a total number of subjects varying from 6 to 18, and a true SD_{Total} of 0.250, 0.425, 0.450, 0.725, and 0.750 for log(CL/F).

Table 1 Maximum imprecision for geometric mean estimates of Cl/F – Figures applicable for one cohort

Confidence level: 95%; Assurance: 80%		
Total SD on log scale	Total number of subjects	Maximum imprecision (%)
0.250	6	27.2
	8	21.9
	10	18.8
	14	15.2
	18	13.1
0.425	6	41.6
	8	34.3
	10	29.9
	14	24.5
	18	21.2
0.450	6	43.5
	8	35.9
	10	31.3
	14	25.7
	18	22.3
0.725	6	60.1
	8	51.2
	10	45.4
	14	38.0
	18	33.4
0.750	6	61.3
	8	52.4
	10	46.5
	14	39.0
	18	34.3

Imprecision is in terms of the relative distance (%) of the lower 95% confidence limit from the observed geometric mean.
Study design: 1-treatment parallel groups.

In order to control the maximum imprecision of 95% confidence interval for the geometric mean estimate of CL/F within 40%, a total of 14 subjects in the first cohort will be required to achieve at least 80% power, assuming an SD_{Total} of 0.725 as the most conservative approach. For Cohort

2 and Cohort 3, the sample size may be adjusted to enable taking the PK variability in previous cohorts into account.

3.4 Randomization

N/A

4 STUDY ENDPOINTS AND COVARIATES

4.1 PK Endpoints

- Insulin C_{max} (maximum observed concentration after correction for baseline)
- Insulin $AUC_{0\text{-}tlast}$ (area under the baseline-corrected concentration-time curve from time 0 to the last measurable concentration)
- Insulin t_{max} (time to C_{max})
- Insulin apparent clearance (CL/F)
- Insulin apparent volume of distribution (Vss/F)
- Fumaryl diketopiperazine (FDKP) elimination half-life ($t_{1/2}$)
- Insulin AUC (area under the serum concentration versus time curve extrapolated to infinity according to the following equation:

$$AUC = AUC_{last} + C_{last}/\lambda z$$

4.2 Safety Endpoints

- Adverse events, serious adverse events, treatment-emergent adverse events
- Adverse Events of Special Interest (AESI), which include the following events:
    - Acute bronchospasm
    - Verified Clinically relevant decline in pulmonary function
    - Hypersensitivity reactions, including anaphylaxis, which can occur with insulin products, including AFREZZA®
    - Diabetic ketoacidosis
- Vital sign measurements

- Abnormal clinical laboratory assessments
- Hypoglycemia: asymptomatic, symptomatic, nocturnal, and severe hypoglycemia according to the 2014 International Society for Pediatric and Adolescent Diabetes guideline (3)
- Anti-insulin antibodies

4.3 Predetermined Covariates and Prognostic Factors

N/A

5 DEFINITIONS

5.1 Study Day 1

Study Day 1 is defined as the date of the first study dose.

5.2 Baseline

Baseline values are defined as the last measurements collected on or prior to Study Day 1 before dosing, unless otherwise specified.

5.3 Relative Day

Relative days will be calculated as follows only when the full assessment date is known; partial dates will have missing relative days:

- For days on or after Study Day 1:

  Relative Day = Date of Assessment – Study Day 1 + 1

- For days prior to Study Day 1:

  Relative Day = - (Study Day 1 – Date of Assessment)

5.4 Study Period

Two study periods are defined: an approximately 4-week titration period (Visit 2 – Visit 16, including PK assessments at Day 1) followed by an optional 52-week extension period (Visit 17 – Visit 29). Participants in the titration period are defined as subjects who take at least one dose of study drug in the titration period and participants in the extension period are defined as subjects who complete the titration period and opt to participate in the extension study.

Start date of the titration period is defined as Study Day 1. For subjects who do not participate in the extension period, end date of the titration period is defined as the last visit/contact date; for

subjects who participate in the extension period, end date of the titration period is defined as the date of Visit 15.

Start and end date of the extension period are defined for subjects who participate in the extension period only. Start date is defined as date of Visit 15 +1 day, and end date is defined as the last visit/contact date.

5.5 Study Drug Exposure

For each subject, information regarding study drug exposure will be derived from the eCRF and study drug dosing eDiary data. Here is a summary:

- First dose date is defined as the date the first study drug dose is taken, as shown in the eCRF ('AFREZZA® dosing' page at Visit 2).
- Last dose date is defined as the date the last study drug dose is taken, as shown in the eDiary.
- Period-specific treatment start date:
  - Treatment start date in the titration period is defined as Study Day 1.
  - Treatment start date in the extension period is defined for subjects who participate in the extension period only, as the date the first study drug dose is taken after the date of Visit 15.
- Period-specific treatment end date:
  - Treatment end date in the titration period is defined as:
    - The date the last study drug dose is taken, for subjects who do not participate in the extension period;
    - The date the last study drug dose is taken prior or on the date of Visit 15, for subjects who participate in the extension period
  - Treatment end date in the extension period is defined for subjects who participate in extension period only, as the date the last study drug dose is taken.
- Total Exposure time (days) is defined as last study dose date – first study dose date +1.
- Period-specific exposure time (days) is defined as period-specific treatment end date – period-specific treatment start date +1.
- Total daily dose is defined as the sum of all doses of AFREZZA® taken during a day.
- Prandial dose at a meal is defined as the sum of the pre-meal dose and the post-meal dose given at that meal. Per protocol, subjects should take a dose at beginning of each meal, and the post-meal dose will be given as needed to keep the blood glucose level in control.

5.6 Change from Baseline

Change from Baseline = Values at specified post-baseline visit – baseline value

5.7 Incidence Rate

- For analyses based on the entire study, incidence rate = Number of subjects with a specific event / Total number of subjects in analysis population
- For period-specific analyses, incidence rate = Number of subjects with a specific event occurred in the study period / Total number of subjects in analysis population who participant in the study period.

5.8 Event Rate – Observation Time-Adjusted Frequency

- For analyses based on the entire study, Event Rate = Number of events occurred during the entire study/ Total observation time in the entire study in subject-year (or subject-month). For period-specific analyses, Event Rate = Number of events occurred in the study period/ total observation time in the study period in subject-year (or subject-month)
- Event Rate in a time interval = Number of events occurred during the time interval/ Total observation time in the time interval in subject-year (or subject-month)
- Total observation time in subject-year = Sum of observation time (in days) over all applicable subjects in the analysis population/ 365.25. Observation time could be calculated for the entire study, for a study period, or for a time interval, depending on the specific analysis.
- Total observation time in subject-month = Sum of observation time (in days) over all applicable subjects in the analysis population/ 30.4375.
- For different types of events, i.e., adverse events or hypoglycemic events, observation time is defined differently (see corresponding sections for more details).

5.9 Age

For each subject, age will be defined as: Age (in years) = (date of informed consent form (ICF) signed – birth date +1)/365.25, and round down to the first decimal place.

5.10 BMI

BMI at a given visit will be calculated as

Weight (in kg) measured at this visit/height (in m) measured at screening ^2.

5.11 Duration of T1DM

Duration of T1DM is defined as:

Duration of T1DM (in years) = (Date of ICF signed – date of diagnosis +1)/365.25.

Incomplete T1DM diagnosis date will be imputed as follows:

- If only year available, impute as 01-Jul of the year;
- If year and month are available, impute as 15th of the month.

For subjects with missing T1DM diagnosis date, the duration of T1DM will set to be missing.

5.12 Cohorts

There are three age cohorts in the study: Cohort 1(13 to 17 years), Cohort 2 (8 to 12 years) and Cohort 3 (4 to 7 years). Data will be summarized based on the cohort the subject enrolled into.

6 ANALYSIS POPULATION

6.1 Safety

All subjects in the study who receive a dose of AFREZZA® will be included in the safety population.

All analyses, except for PK analyses will be performed on the Safety Population.

6.2 PK (Pharmacokinetic)

All subjects without any major deviations related to study drug administration (no sneezing or coughing right after AFREZZA® inhalation on Day 1), and for whom any PK parameters are available, will be included in the PK population.

All PK analyses will be performed on the PK Population.

7 INTERIM ANALYSES

Interim analyses (IA) will be conducted on a cohort by cohort basis upon the completion of each cohort's PK and 4-week Titration Phase of this protocol. Tables/listings/figures produced for the IA will be a subset of those produced for the final analysis. The same analysis methods will be used, with the exception that only data collected in the titration phase will be included. Tables/listings/figures to be included in the interim analyses are indicated in Appendix 3.

Pharmacokinetics and safety data will be reviewed on a rolling basis by the Sponsor and the DMC in order to allow enrollment in Cohorts 2 and 3. Tables/listings/figures to be included in the DMC package are indicated in Appendix 3.

8 STATISTICAL METHODS

8.1 General Considerations

In this study, unless otherwise specified, all analyses will be performed in a descriptive manner by age cohort (including 'Cohort 1', 'Cohort 2', 'Cohort 3' and 'Total'). The 'Total' group will include all subjects in the analysis population.

Where appropriate, all dimensions will be summarized in metric units, but listings will, in addition, represent values as collected.

For continuous variables, the number of subjects, mean, standard deviation, median, minimum, and maximum values will be displayed, as appropriate according to the type of data. The minimum and maximum will be displayed to the same number of decimal places that the data were recorded to. The mean and median will have 1 extra decimal place and the standard deviation will have 2 extra decimal places. The geometric mean and coefficient of variation (CV) will have 2 extra decimal places. Confidence interval (of the mean) will have the same decimal precisions as the mean.

For categorical variables, frequency counts and percentages of total for each category will be presented; missing values will be treated as a separate category, where appropriate. Percentage will be presented in 1 decimal place.

Visit specific data (e.g., 7-point SMBG or pulmonary function tests) will be summarized by analysis visit, which is defined based on the visit windows specified in Section 0

Non-visit specific data (e.g., hypoglycemic events or daily dose) will be summarized by study period and/or by time interval. See relevant sections for more details.

8.1.1 Data Handling/Imputation Methods

8.1.1.1 Missing Data Imputation

Unless otherwise specified, missing data other than start date of adverse events (AE) or start/end date of concomitant medications (CM) will not be imputed.

The imputation rules for start date of Aes and start/end date of CMs are as follows:

Adverse Events

- Start date
  - If the start date is completely missing, the start date is set to the date of first dose.
  - If the year is present and the month and day are missing or the year and day are present and the month is missing:

    If year = year of first dose, then set month and day to month and day of first dose

If year < year of first dose, then set month and day to December 31.

If year > year of first dose, then set month and day to January 1st.

- If the month and year are present and the day is missing:

  If year = year of first dose and

    If month = month of first dose then set day to day of first dose date

    If month < month of first dose then set day to last day of month

    If month > month of first dose then set day to 1st day of month

  If year < year of first dose then set day to last day of month

  If year > year of first dose then set day to 1st day of month

- For all other cases, set the start date to the date of first dose

Concomitant Medications

- Start date
  - If the start date is completely missing, then the start date will not be imputed.
  - If the year is present and the month and day are missing or the year and day are present and the month is missing:

    Set month and day to January 1st.

  - If the year and month are present and the day is missing:

    Set day to 1st day of month.

- End date
  - If the end date is completely missing, then the end date will not be imputed.
  - If the year is present and the month and day are missing or the year and day are present and the month is missing:

    Set month and day to December 31.

  - If the year and month are present and the day is missing:

    Set day to last day of the month.

8.1.1.2 Visit Window

Visit windows are defined for visit-specific parameters as following:

Table 2 Visit Window

Parameter	Study Period	Analysis Visit	Target Relative Day (s)*	Visit Window (Relative Days)*
HbA1c, Anti-insulin antibody	Screening	Screening	-21 to -7	[Day of ICF signed, - 1]
	Titration	Week 4 (Visit 15, EOT)	29	[22, 36]
	Extension	Month 12 (Visit 28, EOT)	Start day of the extension period + 365	[Start day of the extension period + 337, End day of the extension period + 393]
FEV_1	Screening	Screening	-21 to -7	[Day of ICF signed, - 1]
	Titration	Day 1	1	No visit window, data collected on that day will be summarized by nominal time point
		Week 2 (Visit 9)	15	[8, 21]
		Week 4 (Visit 15, EOT)	29	[22, Treatment end day of the titration period]
		Follow-up	36	[Treatment end day of the titration period + 1, End day of the titration period]. Only subjects who opt not to participate in the extension period should have this visit.
	Extension	Month 3	Start day of the extension period + 91	[Start day of the extension period + 77, Start day of the extension period + 105]
		Month 6	Start day of the extension period + 183	[Start day of the extension period +169 , Start day of the extension period +197]
		Month 9	Start day of the extension	[Start day of the extension period +260, Start day of the extension period +288]

Parameter	Study Period	Analysis Visit	Target Relative Day (s)*	Visit Window (Relative Days)*
			period + 274	
		Month 12 (Visit 28, EOT)	Start day of the extension period + 365	[Start day of the extension period + 351 , Treatment end day of the extension period]
		Follow-up	Start day of the extension period + 396	[Treatment end day of the extension period +15, End day of the extension period]
Vital Signs and 7-Point SMBG	Screening	Screening	-21 to -7	[Day of ICF signed, - 1]
	Titration	Day 1	1 (for Vital Signs only)	No visit window, data collected on that day will be summarized by nominal time point
		Week 1 (Visit 5)	8	[5, 11]
		Week 2 (Visit 9)	15	[12, 18]
		Week 3 (visit 12)	22	[19, 25]
		Week 4 (Visit 15, EOT)	29	[26, Treatment end day of the titration period]
		Follow-up (for Vital Signs only)	36	[Treatment end day of the titration period +4, End day of the titration period]. Only subjects who opt not to participate in the extension period should have this visit.
	Extension	Month 3	Start day of the extension period + 91	[Start day of the extension period + 77, Start day of the extension period + 105]
		Month 6	Start day of the extension period + 183	[Start day of the extension period +169 , Start day of the extension period + 197]
		Month 9	Start day of the extension period + 274	[Start day of the extension period +260 , Start day of the extension period +288]

Parameter	Study Period	Analysis Visit	Target Relative Day (s)*	Visit Window (Relative Days)*
		Month 12 (Visit 28, EOT)	Start day of the extension period + 365	[Start day of the extension period +351 , Treatment end day of the extension period]
		Follow-up (for Vital Signs only)	Start day of the extension period + 396	[Treatment end day of the extension period + 15, End day of the extension period]

* Start/end day is calculated as the corresponding start/end date – Study Day 1 +1.

- Data will be assigned to analysis visits using the date of measurement and the visit windows (see Table 2 above).
- If multiple measurements are collected within the same visit window, (1) for Screening visit, the last measurement will be used for analyses; (2) for post-baseline visits, the measurement that is closest to the target relative day will be used for analyses. In the event of a tie, the later measurement will be selected for analyses.
- In addition to the analysis visits listed in the table above, a visit of 'Early Termination' will also be included, for both the titration period and the extension period. For subjects with early discontinuation, data collected at the Early Termination visit will be summarized and presented at that visit, no matter whether the data has fallen into the visit window of any other visit or not (i.e., for example, if the value from Early Termination visit also falls into the visit window of Week 4, it will be summarized both with the Week 4 data, and with the other data collected at the Early Termination visit). By doing so, special attention can be drawn to the data collected at Early Termination, so if there is any particular safety data pattern associated with early discontinuation, it could be more easily recognized.
- Values which are not collected at Early Termination visits and do not fall into any of the visit windows will not be included in by-visit data summary, but will be presented in subject-listings
- If measurements are taken at multiple scheduled time points on the same day, data will be summarized based on nominal time points. Data collected at unscheduled time points will not be used for analyses.
- Visit specific parameters which are not included in Table 2, e.g., urine cotinine tests and pregnancy tests, will not be summarized by visit and will only be presented in subject-listings.

8.1.2 Protocol Deviations

- Protocol deviation is defined as any unapproved change, deviation, or departure from the study design or procedures defined in the protocol.
- Major protocol deviation is defined as one that affects the integrity of the study data (integrity means completeness, accuracy and reliability of the data), and/or affects subject rights, safety or well-being. Major protocol deviations will be evaluated on a case-by-case basis. Categorization of protocol deviations will be reviewed periodically throughout the study, as well as before each formal analysis, by PPD and MannKind.
- Before study database lock, major protocol deviations related to study drug administration which impact subject eligibility in the PK Population will be identified, such as sneezing or coughing right after AFREZZA® inhalation on Day 1.
- All and major protocol violations will be summarized by category by cohort, as well as presented by a subject-level listing.

8.1.3 Subject Disposition

Number and percentage of subjects will be presented by cohort for the following categories:

- Screened Subjects
- Enrolled Subjects
- Safety Subjects
- PK subjects
- Subjects completed the titration period
- Subjects participated in the extension period
- Subjects completed the extension period
- Early Withdrawn Subjects during the titration period
- Early Withdrawn Subjects during the extension period

Detailed withdrawal reasons will be summarized separately for titration period and extension period and will also be presented in this table by cohort. Here is a summary of possible withdrawal reasons:

- Adverse Event
- Death
- Lack of Efficacy
- Lost to Follow-up
- Non-Compliance with Study Drug
- Physician Decision
- Pregnancy
- Protocol Violation
- Study Terminated by Sponsor
- Subject begins Smoking
- Withdrawal by Subject
- Other

A detailed subject listing will also be presented.

8.2 PK Analyses

PK population will be used in all PK analyses.

At visit 2, PK blood samples as well as blood glucose values will be collected at multiple time points pre- and post-dose according to the table below:

Table 3 Schedule of the PK Visit Table

Day	**D1**																			
Time (minute)	**-30**	**-25**	**-15**	**0**	**5**	**10**	**15**	**18**	**20**	**30**	**45**	**55**	**60**	**90**	**120**	**125**	**180**	**240**	**245**	**250**
Indicative clock time	7:30 am	7:35 am	7:45 am	8:00 am	8:05 am	8:10 am	8:15 am	8:18 am	8:20 am	8:30 am	8:45 am	8:55 am	9:00 am	9:30 am	10:00 am	10:05 am	11:00 am	12:00 pm	12:05 pm	12:10 pm
Blood glucose via glucose meter reading[a]	**X**																			
Glucose value via local or central laboratory[b]				**G00**						**G01**			**G02**	**G03**	**G04**		**G05**	**G06**		
Study treatment administration																				
AFREZZA® inhalation				**X** [c]																**X** [e]
Meal				**X** [d]																**X** [e]
Pharmacokinetics																				
Human insulin	**S00**		**S01**	**S02**	**S03**	**S04**	**S05**		**S06**	**S07**	**S08**		**S09**	**S10**	**S11**		**S12**	**S13**		
FDKP				**SF00**			**SF01**				**SF02**				**SF03**			**SF04**		

Abbreviations: FEV_1,forced expiratory volume in 1 second; FDKP, fumaryl diketopiperazine;

a. If the FPG value is ≥80 mg/dL at Visit 2, the subject will undergo a 4-hour PK assessment after eating his/her usual breakfast and receiving his/her breakfast dose of AFREZZA®.

b. Glucose value via local or central laboratory: glucose reading to be done locally via a table top glucose meter (e.g., YSI) at Investigator site. Central laboratory will be used only if local reading (i.e., table top glucose meter) is not available.

c. Subject will inhale a dose of AFREZZA® under the supervision of the Investigator after the glucose sample has been taken and immediately before the first mouthful of food. The AFREZZA® dose will be calculated based on the conversion table. The AFREZZA® dosing time will be recorded in the electronic case report form (e-CRF).

d. Subject will receive a breakfast containing a predetermined level of carbohydrate, comprising approximately 50% of the total caloric content The starting and ending time of breakfast will be recorded in the e-CRF.

e. At the conclusion of the PK test, plasma glucose concentration will be assessed and subjects will receive a lunch. The lunch should correspond in size and composition to the subject's usual lunch, and should be accompanied by an AFREZZA® dose corresponding to the subject's usual dose of prandial insulin with an adjustment (if necessary) based on the results of the glucose profile during the PK test and the pre-lunch plasma glucose value.

PK parameters, as well as baseline-corrected insulin PK concentrations, will be computed by MannKind. The calculation methods will be described in a separate document (PK Analysis Plan for MKC-TI-155 Part 1).

The parameters will include, but may not be limited to, the following:

- Insulin C_{max} (maximum observed concentration after correction for baseline)
- Insulin $AUC_{0\text{-}tlast}$ (area under the baseline-corrected concentration-time curve from time 0 to the last measurable concentration)
- Insulin t_{max} ($_{time}$ to reach C_{max})
- Apparent total body $_{clearance}$ (CL/F) and apparent volume of distribution (Vss/F) of insulin
- FDKP elimination $_{half}$-life ($t_{1/2}$)
- Insulin AUC (area under the serum concentration versus time curve extrapolated to infinity) according to the following equation:

$$AUC = AUC_{last} + C_{last}/\lambda z$$

In summary tables/figures, concentrations below limit of quantification (BLQ) will be imputed as ½ * Lower Limit of Quantification (LLQ). In subject-listings, these values will be presented as BLQ

Table presentation

Baseline-corrected insulin concentrations and concentrations of FDKP will be summarized by PK dose, nominal time point and cohort. The number of subjects, mean, SD, geometric mean, CV, median, minimum, and maximum values will be displayed. Each PK parameter will be summarized by PK dose and cohort. In addition to the aforementioned descriptive statistics, 95% CI of the geometric mean will also be computed and presented, based on assumption of log-normal distribution of the parameters.

Blood glucose values and change from baseline (defined as the glucose value collected at 0 min pre-dose) will be summarized and presented by nominal time point and cohort.

Graphical Presentation

Mean +/- Standard error (SE) of baseline-corrected insulin concentrations and concentrations of FDKP will be plotted against nominal time by PK dose and cohort. In addition, individual patient profile plot of concentration vs. actual time will also be provided.

Blood glucose values collected at the PK visit will be plotted against nominal time by cohort. Similar individual patient plot will be created.

Subject Listings

PK concentrations and PK parameters for insulin and FDKP, as well as blood glucose values measured at PK visit, will be listed by (in the order of) cohort, PK dose, investigator site, and subject.

8.3 Safety Analyses

8.3.1 Adverse Event

Definition

Adverse Event (AE)

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality.

General

All adverse events will be described with cohort, start date, resolution date, seriousness, severity (mild, moderate, severe), outcome of AE (recovered/resolved, recovering/ resolving, recovered/resolved with sequelae, not recovered/resolved, death related to AE, and unknown), relationship to study treatment (definite, probable, possible, unlikely, and not related), action taken with investigational medicinal product (dose increased dose, dose not changed, dose reduced, dose interrupted, dose withdrawn, not applicable, and unknown), other action taken (treatment given and withdrawn from the trial).

Coding

Adverse events will be coded by the system organ class and preferred terms specified in the MedDRA (version 20.1) dictionary.

Classification

Prior Adverse Event

A prior adverse event is defined as adverse event whose start date is before the date of the first dose of study drug.

A subject listing will be presented for all the prior adverse events.

Treatment-Emergent Adverse Event (TEAE)

An adverse event is treatment-emergent if the start date is on or between the date of the first dose of study drug and the date of the last dose of study drug plus 30 days (inclusive). Worsening of a pre-treatment event during the trial is also treatment emergent.

Follow-up Adverse Event

A follow-up adverse event is defined as adverse event whose start date is between the date of the last dose of study drug plus 30 days (exclusive) and the date of the last visit day of the follow-up period.

A subject listing will be presented for all the follow-up adverse events.

Special Adverse Event

The following special treatment-emergent adverse event will be identified and reported from the adverse event database.

- Acute bronchospasm
- Verified clinically relevant decline in pulmonary function
- Hypersensitivity reactions, including anaphylaxis, which can occur with insulin products, including AFREZZA
- Diabetic ketoacidosis

Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that suggests a significant hazard or side effect, regardless of the Investigator or sponsor's opinion of the relationship to the IMP, study related procedures or device. This includes, but is not limited to an event that:

- Is fatal;
- Is life threatening (places the trial subject at immediate risk of death);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect; or
- Is an important medical event*

  * Important medical events are those events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the trial subject or require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

Most Common Treatment-Emergent Adverse Event

Most common treatment-emergent adverse events are defined as the TEAEs which occurred in ≥5% subjects in any cohort during the entire study.

Table Presentation

Summary tables will be reported by cohort and study period (titration period, extension period, and entire study). Number and percentage of subjects with Aes, number of Aes and event rate in person-year accounting for the observation time will presented for the following categories:

- Overall summary including: all TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEAEs, severe TEAEs, moderate TEAEs, mild TEAEs, TEAEs leading to subject discontinuation from the trial, and TEAEs leading to death
- TEAEs by system organ class and preferred term
- TEAEs by preferred term only
- TEAEs by relationship to study drug by system organ class and preferred term
- TEAEs by severity by system organ class and preferred term
- Most Common TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Serious TEAEs by relationship to study drug by system organ class and preferred term
- TEAEs leading to discontinuation by system organ class and preferred term
- TEAEs leading to death by system organ class and preferred term
- TEAEs leading to temporary treatment interruption by system organ class and preferred term
- TEAEs of special interest by system organ class and preferred term
- TEAEs of special interest by relationship to study drug by system organ class and preferred term

For percentage calculation, number of subjects in each cohort in the safety population will be used as denominator for the summaries for the entire study and the titration period. For the extension period, number of subjects in safety population who participate in extension period (see definition in Section 5.4) will be used as denominator.

Observation time for TEAE is defined as:

- For the entire study: min(last visit/contact date, last dose date +30) – Study Day 1 + 1
- For the titration period:
  - min(last visit/contact date, last dose date +30) – Study Day 1 + 1, for subjects who do not participate in the extension period
  - date of Visit 15 – Study Day 1 +1, for subjects who participate in the extension study
- For the extension period: min(last visit/contact date, last dose date +30) – date of Visit 15, for subjects who participate in the extension period only.

Subject Listing

Individual data listings will be provided for the following, by (in the order of) cohort, investigator site and subject:

- All adverse events
- Treatment emergent adverse events
- Prior adverse events and follow-up adverse events
- Serious treatment-emergent adverse events
- Treatment-emergent adverse events leading to discontinuation from the trial
- Treatment-emergent adverse events leading to death
- Treatment-emergent adverse events leading to temporary treatment interruption
- Treatment-emergent adverse events of special interest

8.3.2 Deaths

Any deaths occurred in the trial will be reported. An individual subject listing will also be presented with details of death listed, by (in the order of) cohort, investigator site and subject.

8.3.3 Hypoglycemic Event

Definitions:

Hypoglycemic event:

The general symptoms of hypoglycemia most subjects experience include 1 or more of the following: headache, dizziness, general feeling of weakness, drowsiness, confusion, pallor, irritability, trembling, sweating, lightheadedness, shaky, increased appetite, rapid heartbeat and a

cold, clammy feeling. In severe cases, seizure, loss of consciousness, or even coma can occur.

All hypoglycemic events will be recorded on the Hypoglycemia eCRF page. In addition, severe hypoglycemia episodes and other hypoglycemia episodes which meet the criteria of SAE will also be records as SAEs in the AE page and safety complementary e-CRF.

Non-severe Hypoglycemic event

Non-severe hypoglycemic event is defined according to the ISPAD Clinical Practice Consensus Guidelines 2014 (3) as follows:

- SMBG levels <70 mg/dL and/or
- Symptoms of hypoglycemia that are relieved by the administration of carbohydrates

Severe Hypoglycemic event

Severe hypoglycemic event in children is defined according to the ISPAD Clinical Practice Consensus Guidelines 2014 (3) as an event associated with a seizure, coma, or loss of consciousness and will be considered an SAE.

Asymptomatic Hypoglycemic event

Asymptomatic hypoglycemic event is defined as an episode not accompanied by typical symptoms of hypoglycemia, but with a measured plasma glucose concentration < 70 mg/dL

Symptomatic hypoglycemic event

Symptomatic hypoglycemic event is defined as an episode accompanied with typical symptoms of hypoglycemia, with or without measured plasma glucose concentration, which is relieved by the administration of carbohydrates

Nocturnal hypoglycemic event

Nocturnal hypoglycemic event is defined as a hypoglycemia episode which occurs overnight during sleep.

Documented hypoglycemic event

Documented hypoglycemic event is defined as an episode with measured plasma glucose concentration <70 mg/dL. If such an episode is also accompanied by typical hypoglycemic symptoms, then it is defined as a symptomatic documented hypoglycemic event; otherwise, it is defined as an asymptomatic documented hypoglycemic event.

Table Presentation

Summary tables will be reported by cohort and study period (titration period, extension period, and entire study). Only hypoglycemic events occurred on treatment (i.e., with start date between the first dose date and last dose date, both inclusive) will be included. Number and percentage of subjects with hypoglycemic events, number of hypoglycemic events, and event rate in subject-month accounting for observation time will be presented for the following categories:

- All hypoglycemic events
- Asymptomatic hypoglycemic events
- Symptomatic hypoglycemic events
- Nocturnal hypoglycemic events
- Severe hypoglycemic events
- Documented hypoglycemic events
- Symptomatic documented hypoglycemic events
- Asymptomatic documented hypoglycemic events

For percentage calculation, number of subjects in each cohort in the safety population will be used as denominator for the summaries for the entire study and the titration period. For the extension period, number of subjects in safety population who participate in extension period will be used as denominator.

For calculation of event rate, observation time is defined as treatment exposure time (total exposure time and period-specific exposure time for the corresponding analysis respectively, see definition in Section 5.5).

In addition, causality of hypoglycemic events will be summarized (for the entire study only). Number and percentage of subjects experiencing hypoglycemic events in each causality category will be presented by cohort.

Graphical Presentation

Only hypoglycemic events occurred on treatment will be included. The following graphs will be presented by cohort and overall:

- Day profile of hypoglycemic events

Event rate (in subject-month) will be calculated at 1 week interval for the titration period and at 1 month interval the extension period, and plotted against time since the start of the study period. Onset date of the event will be used to determine the time interval. Weeks since the start of the study period will be calculated as int((date – start date of the study period+1)/7). Months since the start of the period will be calculated as int((date – start date of the study period+1)/30.4375).

The last interval in each study period, i.e., Week 4 for the titration period and Month 12 for the extension period, will extend to the treatment end date of the study period, for subjects whose treatment duration is longer than 4 weeks or 12 months, for the two study periods respectively.

To derive event rate, observation time (in months) for a time interval will be calculated as

> The number of days in the time interval which are between first dose date and last dose date (both inclusive)/30.4375.

Observation time will first be calculated for each individual subject, and then summed across all applicable subjects in the safety population.

- Time profile of hypoglycemic events in relation to pre-meal dosing

For each week in the titration period and each month in the extension period, event rate of hypoglycemia (in subject-month) will be calculated at 1 hour interval (i.e., [0,1] h, (1,2) h, (2, 3) h, and (3, 4h)) relative to the pre-meal insulin dosing time. A bar plot will be created with hypoglycemic events occurred following each pre-meal dose presented as a separate bar. Only hypoglycemic events occurred within 4 hours following a pre-meal dose will be included in this analysis.

To derive event rate, observation time for an hour (e.g., 0-1 h after breakfast) in a time interval (e.g., Week 1 in titration period) will be calculated as

> The number of days in the time interval which are between first dose date and last dose date (both inclusive) /30.4375.

Observation time will first be calculated for each individual subject, and then summed across all applicable subjects in the safety population.

Subject Listings

For all hypoglycemic events and all severe events, detailed information of every event will be listed, by (in the order of) cohort, investigator site and subject.

8.3.4 Cough

Cough will be reported as an adverse event on the AE page.

Graphical Presentation

- Day profile of cough

This figure will be created in the same way as the 'Day profile of hypoglycemic events' figure. Event rate of cough (in subject-month) will be calculated at 1 week interval during the titration period and at 1 month interval for the extension period. Only cough occurred between the first dose date and the last dose date will be included in this analysis

Subject Listings

All cough events will be listed, by (in the order of) cohort, investigator site and subject, and start date.

8.3.5 Pulmonary Function Testing

Schedule and parameters

Spirometry tests will be performed at screening, visits 2, 9, 15, and 16 in the titration period, visits 19, 22, 25, 28, and 29 in the extension period, as well as at the early termination visits in both periods. At each visit, Forced Expiratory Volume in 1 second (FEV_1) will collected. At Visit 2, FEV_1 will be collected at several time points: -25 min, 18 min, 55 min, 125 min and 245 min relative to the time of first dose.

Table presentation

FEV_1 value and change from baseline will be summarized descriptively by cohort and analysis visit/nominal time point. For each post-baseline visit/time point, number and percentage of subjects with verified clinically relevant decline in pulmonary function from baseline (as indicated on the eCRF) will be presented by cohort. For percentage calculations, the total number of subjects in each cohort who attend the visit will be used as denominators.

Verified clinically relevant decline in pulmonary function will be captured as AE. A continuous decline will be captured as a single AE. The start date of this event is defined as the date when the criterion of clinically relevant decline (i.e., >15% decrease from baseline) is met for the first time, and the end date of this event is defined as the date when the criterion is no longer met. Each event will be assigned to a study period based on the start date. Duration (in days) of an event will be calculated as end date – start date + 1, and summarized by cohort and study period.

Subject Listings

For spirometry tests, detailed information of every measurement will be listed, by (in the order of) cohort, investigator site, subject and visit/time point.

8.3.6 Laboratory Data

Schedule and parameters

- Hematology, biochemistry, urinalysis, urine drug screen, fasting serum C-peptide, and serology test will be performed at screening visit only

- Urine cotinine and urine β -HCG (for females with childbearing potential) will be measured at screening visit, at visits 2, 6, 9, 12, 15 and 16 in the titration period, and at visits 19, 22, 25, 28 and 29 in the extension period, as well as the early termination visits in both study periods.

- HbA1c will be measured at screening visit and at end of treatment visit/early termination visit in both study periods

List of Hematology and Chemistry Laboratory Tests

	Biochemistry					
Hematology	**Plasma/serum electrolytes**	**Metabolism**	**Liver Status**	**Kidney Status**	**Specialty Tests**	**Serology**
Hemoglobin	Sodium	Albumin	Total and conjugated bilirubin	Blood Urea nitrogen (BUN)	HbA_{1c}	Hepatitis B antigen
Hematocrit	Potassium	Total Protein	Alkaline phosphatase	Creatinine Uric acid	Fasting serum C-peptide	Hepatitis C antibodies
Red blood cells	Chloride	Total cholesterol	Alanine aminotransferase			anti-HIV-1 and anti-HIV-2 antibodies
White blood cells with differential	Calcium	Low-density lipoprotein	Aspartate aminotransferase			
Neutrophils	Phosphorus	Triglycerides				
Lymphocytes	Carbon dioxide					
Monocytes						
Eosinophils						
Basophils						
Platelets						

Urinary Laboratory Tests

Urinalysis	Specialty tests	Urine Drug Screen
Albumin/creatinine ratio	Urine pregnancy test[a]	Amphetamines/methamphetamines
Ketones	Cotinine	Benzodiazepines
Glucose		Cannabinoids
Erythrocytes		Benzoylecgonine
Leukocytes		Opiates
pH		Barbiturates
Urobilinogen		
Nitrates		
Specific gravity		

a: Only for women of childbearing potential

Table presentation

For HbA1c:

Value and change from baseline will be summarized by cohort and analysis visit.

For fasting serum C-peptide:

Value at screening visit will be summarized by cohort, and presented as part of the 'Demographics and baseline characteristics' table.

Subject Listings

The results of all lab measurements, including hematology, biochemistry, urinalysis, HbA1c, fasting serum C-peptide, serology, urine drug screen, urine cotinine, and urine pregnancy test, will be listed, by parameter and by (in the order of) cohort, investigator site, subject and visit.

Graphical Presentation

For HbA1c, a Mean (SE) plot representing mean and SE for each cohort at each analysis visit will be provided.

8.3.7 Vital Signs

Schedule and Parameters

Vital signs assessments will be made at screening, at visits 2, 6, 9, 12, 15 and 16 in the titration period, and at visits 19, 22, 25, 28 and 29 in the extension period, as well as at the early termination visits in both periods. Height will be collected at screening only. The following parameters will be collected at all visits: respiratory rate, sitting blood pressure (systolic blood pressure and diastolic blood pressure), pulse rate, temperature, and body weight. At Visit 2, these parameters will be collected at two time points: pre-dose and post-dose.

All the measurements will be presented in international units. If measurements are collected in different units, a conversion will be made first before presentation. Below is the summary of conversion between different units.

Conversion	Formula
From lbs to kg in weight	Weight (kg) = Weight (lbs) x 0.45
From inch to meter in length	Length (meter) = Length (inch) x 2.5
From F to C in temperature	Temp (C) = {Temp (F) -32} x 5/9

Table presentation

For each parameter, descriptive statistics will be provided by cohort and analysis visit/time point. Change from baseline to all post-baseline visits/time points will be provided by cohort, except for height.

Subject Listings

Detailed information of every measurement will be listed, by (in the order of) cohort, investigator site, subject and visit/time point.

Graphical Presentation

For BMI, a Mean (SE) plot representing mean and SE for each cohort at each analysis visit will be provided.

8.3.8 ECG

Schedule and Parameters

ECG assessments will be made at screening. The parameters to be collected are: the result of sinus rhythm test, PR Interval, QRS, QT Interval, Ventricular Rate and QTc Interval.

Table presentation

For each parameter, descriptive statistics will be provided by cohort.

ECG results will also be recorded as: Normal, Abnormal Not Clinically Significant and Abnormal Clinically Significant. Summary table presenting number and percentage of subjects in each category will be provided. For percentage calculations, the total number of subjects with in each cohort in the safety population will be used as denominators. Number of subjects with missing values will be presented as a separate category.

Subject Listings

Detailed information of every measurement will be listed, by (in the order of) cohort, investigator site and subject.

8.3.9 Physical Exam

Full physical examination, including assessments of 11 body systems and Tanner stage of pubertal development, will be performed at screening. Abbreviated physical examination will be performed at visits 2, 6, 9, 12, 15, 16 in the titration periods, visits 19, 22, 25, 28 and 29 in the extension period, as well as the early termination visits in both periods. During abbreviated physical examination, the investigator will check if there any clinically significant changes from the previous evaluation

Detailed information of every measurement will be listed, by (in the order of) cohort, investigator site, subject and visit.

8.3.10 Anti-insulin antibody

Schedule and Parameters

Anti-insulin antibody will be measured at screening visit and at end of treatment visit/early termination visits in both study periods.

Table presentation

Results of anti-insulin antibody measurements will be presented in three categories: ‘Positive’, ‘Negative’ and ‘Not Done’ (ND). Shift table presenting change from baseline to each post-baseline analysis visit in the above categories will be provided. At each post-baseline visit, only subjects who attend both the baseline visit and the post-baseline visit will be included in the summary.

Subject Listings

Detailed information of every measurement will be listed, by (in the order of) cohort, investigator site, subject and visit.

8.4 Other Endpoints

Unless otherwise specified, safety population will be used in all the following analyses.

8.4.1 Demographics and Baseline Characteristics

Demographic characteristics including gender, race, ethnicity and date of birth will be collected at screening visit. Age (at the time of signed informed consent) will be derived using date of birth and informed consent signed date. Descriptive statistics will be provided by cohort for the above along with screening assessments including height, weight, BMI, Tanner stage, duration of T1DM and fasting serum C-peptide at screening.

The above summaries will be conducted for Safety and PK populations. For percentage calculations, the total number of subjects in each cohort in the analysis population will be used as denominators.

All the demographics and baseline disease data will also be listed, by (in the order of) cohort, investigator site and subject.

8.4.2 Extent of Study Drug Exposure

Detailed dosing information of AFREZZA® will be collected from the first dose to the last dose through the trial. Information of doses given during the PK Visit is captured on the eCRF, while other dosing information is captured on the eDiary.

Table Presentation

Dosing information at the PK Visit will be summarized by cohort, and presented in a subject-level listing.

For total exposure time, both numerical and categorical summaries will be provided by cohort and study period. For AFREZZA® doses collected on the eDiary, the following will be derived and summarized by cohort. For Cohort 1 and Cohort 2, additional summaries will be provided by starting dose, as appropriate.

- Average total daily dose of AFREZZA® at weekly intervals for the titration period, and at monthly intervals for the extension period. For each time interval, only data collected in the 2nd half of the interval (i.e., within 3 days prior to the each clinic visit in the titration period and within 2 weeks prior to each visit in the extension period) will be included in the summary. If a visit is performed, the actual visit date will be used to determine the time frame; if a visit is not performed, the target visit date will be used to determine the time frame. Average total daily dose is defined as the average of all total daily doses taken within a time frame. For each time interval, average total daily dose will be calculated for each subject first, and then summarized by cohort.

- Average prandial dose of AFREZZA® by meal at weekly intervals for the titration period, and at monthly intervals for the extension period, calculated using the same method as described above

Moreover, the use of post-meal (i.e., supplemental) doses will be presented in a summary table, by cohort and study period. Both subject-level summary (number and percentage of subjects

taking at least one post-meal dose) and dose-level summary (e.g., number of post-meal doses indicated, number of doses given, etc.) will be provided.

Graphic Presentation

Average total daily dose of AFREZZA® and average prandial dose of AFREZZA® by meal will be plotted over time to illustrate dose change throughout the study.

8.4.3 Concomitant Medications

Concomitant medications are defined as those that are started prior to first study medication dose and ongoing after, or those that started after first study medication dose. Summary table presenting number and percentage of subjects for each concomitant medication taken will be provided by cohort for the entire study. For percentage calculation, number of subjects in each cohort in the safety population will be used as denominator. In addition, detailed medication information will be listed.

Prior medications are defined as those that are stopped prior to first study medication dose, and will be presented in the same manner as concomitant medications.

Prior and concomitant medications will be coded using the WHO Drug Dictionary (version 2017 Q3). Medications will be summarized by ATC level 4 category and preferred term. Medications which cannot be coded will be summarized in a category named 'Not Codable'.

8.4.4 Medical history

Medical history information will be collected at the screening visit. A summary table will show the number and percentage of subjects with a medical history in each body system based on the safety population. The information will also be listed, by (in the order of) cohort, investigator site, and subject.

8.4.5 Fasting pre-breakfast SMBG and post-prandial SMBG

Schedule and Parameters

Fasting pre-breakfast SMBG and post-prandial SMBG at each meal will be measured daily throughout the study.

Table presentation

For each of the four parameters (fasting pre-breakfast SMBG and post-prandial SMBG at breakfast, lunch and dinner), average will be calculated at weekly intervals for the titration period and at monthly intervals for the extension period for each subject, and summarized by cohort. Same as for total daily dose and prandial dose, only data collected in the 2nd half of each interval (i.e., within 3 days prior to the each clinic visit in the titration period and within 2 weeks prior to each visit in the extension period) will be included in the analysis.

Baseline is defined as the average of all values collected prior to Visit 2. Change from baseline for a post-baseline time interval will be calculated as average of SMBG in the post-baseline time interval – baseline for each subject, and then summarized by cohort.

Graphical Presentation

For each of the four parameters, a Mean (SE) plot will be provided, presenting weekly average in the titration period and monthly average in the extension period (along with standard error) by cohort.

8.4.6 7-point SMBG

Schedule and Parameters

7-point SMBG (pre-meal and 120-150 minutes post-dose at breakfast, lunch and dinner as well as at bedtime) will be collected at screening visit, visits 6, 9, 12, 15 in the titration period, and visits 19, 22, 25, 28 in the extension period.

Table presentation

For each of the 7 parameters (pre-meal and 120-150 minutes post-dose 7-point SMBG at breakfast, lunch and dinner as well as at bedtime), average will be calculated at weekly intervals for the titration period and at monthly intervals for the extension period for each subject, and summarized by cohort. For each of these intervals, all data collected from the date of the previous on-site visit (including) to 1 day before the current visit for each visit are included in the summary.

Baseline is defined as the average of all values collected prior to Visit 2. Change from baseline for a post-baseline time interval will be calculated as average of 7-point SMBG in the post-baseline time interval – baseline for each subject, and then summarized by cohort.

Subject Listings

Detailed information of every measurement will be listed, by (in the order of) cohort, investigator site, subject and visit.

Graphical Presentation

For each of 7 parameters, a Mean (SE) plot will be provided, presenting weekly average in the titration period and monthly average in the extension period (along with standard error) by cohort.

8.4.7 Mean of 7-point SMBG

Schedule and Parameters

The mean of 7-point SMBG is defined as the area under the 7-point SMBG profile divided by the measurement time (i.e., time of the last point – time of the first point), and will be calculated using the trapezoidal method. It will not be calculated if more than 3 points in the profile are missing.

Table presentation

Mean of 7-point SMBG and change from baseline in mean of 7-point SMBG will be calculated and summarized by cohort and visit. In addition, 7-point SMBG data will be summarized by cohort, visit and time point.

Subject Listings

Detailed information of every measurement will be listed, by (in the order of) cohort, investigator site, subject and visit.

Graphical Presentation

For mean of 7-point SMBG, a Mean (SE) plot representing mean and SE for each cohort at each scheduled visit will be provided. In addition, a figure will be created to present the mean curve of 7-point SMBG (mean +/- SE at each time point over nominal time points), at screening, Visit 15 and Visit 28, by cohort.

8.4.8 Insulin to carbohydrate ratio

Insulin to carbohydrate ratio for each meal will be captured at the screening visit, and at end of treatment/early termination visit for the titration period. Data will be listed, by (in the order of) cohort, investigator site, subject and visit.

8.4.9 Substance Use

Pre-trial usage of tobacco and alcohol will be captured at screening. Data will be listed, by (in the order of) cohort, investigator site, and subject.

9 CHANGES FROM PREVIOUS VERSIONS

REVISION NUMBER	AUTHOR	EFFECTIVE DATE	CHANGES:	REASON:
1.1	Yi Qu	2017/10/20	Remove all description regarding the 2 previous subjects from the Sanofi study.	The 2 subjects will not be included in the any of the analyses
1.1	Yi Qu	2017/10/20	Present PK concentrations/parameters by dose	The PK concentrations and parameters of insulin and FDKP are affected by the dose of AFREZZA®
1.1	Yi Qu	2017/10/20	Change 'clinically relevant decline' in pulmonary function to 'verified clinically relevant decline', and add a table to summarize the duration of verified clinically relevant decline.	Clinically relevant decline will be verified by the sites. The duration of such decline is of interest
1.1	Yi Qu	2017/10/20	Add a table to present the use of post-meal dose.	It is of interest to see how frequently post-meal (i.e., supplemental) doses need to be given
1.1	Yi Qu	2017/10/20	Adjust visit windows	From clinical point of view, it doesn't make sense to use very large windows
1.1	Yi Qu	2017/10/20	Add 'Early Termination' visit to the by-visit summary tables	To draw special attention to data collected at the early termination visit. If there is some particular data pattern associated with subject discontinuation, it could be more easily recognized.
1.1	Yi Qu	2017/10/20	Create a summary table for 'documented hypoglycemia' (defined as glucose < 70 mg/dl), including the subcategories of asymptomatic/symptomatic documented hypoglycemia	This category of hypoglycemia is of interest from medical point of view.
1.1	Yi Qu	2017/10/20	When calculating average dose/SMBG at weekly interval in the titration period and at monthly interval in the extension period, only include data collected in the 2nd half of the interval (i.e., within 3 days prior to the each clinic visit in the titration period and within 2 weeks prior to each visit in the extension period) in the analysis.	These values are more of interest from clinical point of view.

REVISION NUMBER	AUTHOR	EFFECTIVE DATE	CHANGES:	REASON:
3.0	Lin Chen	2019/12/10	Add the imputation rules of incomplete T1DM diagnosis date for the calculation of duration of T1DM	As analysis needed
3.0	Lin Chen	2019/12/10	Add "Drug-related serious TEAEs" item for TEAE overall summary	To show the number and percentage of subjects who has any drug-related serious TEAEs in the AE overall summary table
3.0	Lin Chen	2019/12/10	Correct the derivation of time profile of hypoglycemia to be "The number of days in the time interval which are between first dose date and last dose date (both inclusive) /30.4375"	Correct the derivation error.
3.0	Lin Chen	2019/12/10	Use "Benzoylecgonine"to replace Cocaine" in the table of Urinary Laboratory tests	It was captured in the CRF of "Benzoylecgonine", not "Cocaine".
3.0	Lin Chen	2019/12/10	Add "the result of sinus rhythm test" in the summarization of ECG parameters as it is captured in the EDC.	Updated as EDC data
3.0	Lin Chen	2019/12/10	Add the section 8.4.6 "7-point SMBG" , at the same time, change the old 8.4.6 "7-point SMBG" to be 8.4.7 "Mean of 7-point SMBG	Add some analyses for the 7-point SMBG parameters and keep those analyses we proposed for Mean of 7-point SMBG
3.0	Lin Chen	2019/12/10	Appendix 3 has been updated	Updated as the shell updates

10 REFERENCES

1. Investigator's Brochure: Technosphere Insulin Inhalation System. MannKind Corporation Version 10.0. 31 Jul 2012.
2. Clinical Study Protocol AMENDMENT 2: MKC-TI-155: Open-label, single-arm, multiple-dose safety, titration, and pharmacokinetic study of AFREZZA® in pediatric subjects ages 4 to 17 years with type 1 diabetes mellitus
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APPENDIX 1 LIST OF LAB UNITS

Panel/Test	Conventional Units	SI Units
Albumin / Creatinine Ratio	mg/mmol Creatinine	mg/mmol Creatinine
C Peptide	ng/mL	nmol/L
Chemistry / ALT	U/L	U/L
Chemistry / AST	U/L	U/L
Chemistry / Albumin	g/dL	g/L
Chemistry / Alkaline Phosphatase	U/L	U/L
Chemistry / BUN	mg/dL	mmol/L
Chemistry / Bicarbonate	mEq/L	mmol/L
Chemistry / Bilirubin, Direct	mg/dL	mcmol/L
Chemistry / Bilirubin, Total	mg/dL	mcmol/L
Chemistry / Calcium	mg/dL	mmol/L
Chemistry / Chloride	mEq/L	mmol/L
Chemistry / Cholesterol, Total	mg/dL	mmol/L
Chemistry / Creatine Phosphokinase (CPK)	U/L	U/L
Chemistry / Creatinine	mg/dL	mcmol/L
Chemistry / Lactate Dehydrogenase	U/L	U/L
Chemistry / Phosphorous	mg/dL	mmol/L
Chemistry / Potassium	mEq/L	mmol/L
Chemistry / Protein	g/dL	g/L
Chemistry / Sodium	mEq/L	mmol/L
Chemistry / Triglyceride	mg/dL	mmol/L
Chemistry / Uric Acid	mg/dL	mmol/L
Creatinine, Urine	mg/dL	mmol/L
Glucose	mg/dL	mmol/L

Panel/Test	Conventional Units	SI Units
HDL	mg/dL	mmol/L
Hematology / Basophils	K/cu mm	x 10^9/L
Hematology / Eosinophils	K/cu mm	x 10^9/L
Hematology / Hematocrit	%	%
Hematology / Hemoglobin	g/dL	g/L
Hematology / Lymphocytes	K/cu mm	x 10^9/L
Hematology / MCH	pg	pg
Hematology / MCHC	g/dL	g/dL
Hematology / MCV	fl	fl
Hematology / MPV	fl	fl
Hematology / Monocytes	K/cu mm	x 10^9/L
Hematology / Platelet	K/cu mm	x 10^9/L
Hematology / RBC	x 10^6/cu mm	x 10^12/L
Hematology / RDW	%	%
Hematology / Total Neutrophils	K/cu mm	x 10^9/L
Hematology / WBC	K/cu mm	x 10^9/L
Hemoglobin A1c	%	%
LDL	mg/dL	mmol/L

APPENDIX 2 GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Classification
BMI	Body Mass Index
BLQ	Below Limit of Quatification
CM	Concomitant Medications
CRF	Case Report Form
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FDKP	Fumaryl Diketopiperazine
FEV_1	Forced Expiratory Volume in 1 Second
ICF	Informed Consent Form
IA	Interim Analyses
LLQ	Lower Limit of Quantification
MDI	Multiple Daily Injections
PK	Pharmacokinetic
RAA	Rapid-Acting Analog
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SMBG	Self-Monitored Blood Glucose
TEAE	Treatment-Emergent Adverse Event
T1DM	Type 1 Diabetes Mellitus

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APPENDIX 4 SHELLS FOR TABLES, FIGURES, AND LISTINGS

Please see the files: MKC-TI-155 Part1_Listing_Shells.doc

MKC-TI-155 Part1_Table_Figure_Shells.doc