CLINICAL STUDY PROTOCOL AMENDMENT 3: MKC-TI-155

Study Title:	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
Study Number:	MKC-TI-155 Part 1
Study Phase:	2
Product Name:	AFREZZA® (insulin human) Inhalation Powder (Technosphere® Insulin Inhalation Powder)
IND Number:	061729
Indication:	Diabetes Mellitus
Sponsor:	MannKind Corporation One Casper Street Danbury, CT 06810
Sponsor Contact:	David J. Klein MD, PhD Senior Director, Clinical Development Office: 203-790-3174 dklein@mannkindcorp.com
Original Date **Amendment 1 Date:**	11 February 2014 (TDR 14323 V2) 13 February 2017
Amendment 2 Date:	11 May 2017
Amendment 3 Date:	14 February 2018

NAMES AND ADDRESSES OF

CLINICAL OPERATIONS STUDY TEAM LEADER	Name:	David Gash
	Address:	MannKind Corporation One Casper Street Danbury, CT 06810
	Tel:	973-744-5292
	E-mail:	dgash@mannkindcorp.com
MEDICAL MONITOR	Name:	David J. Klein MD, PhD
	Address:	MannKind Corporation One Casper Street Danbury, CT 06810
	Tel:	203-790-3174
	E-mail:	dklein@mannkindcorp.com
CLINICAL STUDY MANAGEMENT	Name:	PPD
	Address:	929 North Front Street Wilmington, NC 28401-331
	Tel:	1-910-251-0081
	Fax:	1-910-762-5820
SPONSOR'S MEDICAL DIRECTOR	Name:	David J. Klein MD, PhD
	Address:	MannKind Corporation One Casper Street Danbury, CT 06810
	Tel:	203-790-3174
	E-mail:	dklein@mannkindcorp.com
SPONSOR	Company:	MannKind Corporation
	Address:	One Casper Street Danbury, CT 06810

CLINICAL STUDY SUMMARY

The AFREZZA pediatric study MKC-TI-155 consists of 2 parts:

- Part 1 is a Phase 2, open-label, single-arm, multiple-dose safety, titration, and pharmacokinetic (PK) study of AFREZZA in pediatric subjects ages 4 to 17 years with type 1 diabetes mellitus (T1DM).
- Part 2 is a Phase 3, 52-week, open-label, randomized, multinational, clinical study evaluating the efficacy and safety of AFREZZA (insulin human) inhalation powder in combination with a basal insulin versus insulin aspart in combination with a basal insulin in pediatric subjects with type 1 or type 2 diabetes mellitus. The design of the Phase 3 study may be modified based on the results from Part 1. Design for the Phase 3 study is in development (Section 18.3 - Appendix C).

STUDY NUMBER	MKC-TI-155 Part 1
COMPOUND:	AFREZZA® (insulin human) Inhalation Powder
STUDY TITLE	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
INVESTIGATOR/STUDY LOCATION	United States
PHASE OF DEVELOPMENT	2
STUDY OBJECTIVES	• 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 dose of AFREZZA at each meal using postprandial self-monitored blood glucose values obtained 120 to 150 minutes after each prandial dose of AFREZZA in children ages 4 to 17 years with T1DM
STUDY DESIGN	Part 1 of the study 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). On Day 1, 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 subcutaneous (SC) rapid-acting analog (RAA) that the subject would usually receive with breakfast. During the 4-week titration period following the PK visit, each subject will be titrated with AFREZZA according to the titration

	rules given. The study will be conducted sequentially in age cohorts beginning with Cohort 1 and then proceeding to Cohort 2 and Cohort 3 in parallel. Approximately 46 subjects will be enrolled 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 and Cohort 3, at least 14 subjects must be dosed (complete PK Visit 2). Of those, at least 6 subjects must receive at least the 8 unit dose. **Cohort 2: 8 to 12 years**; approximately 14 subjects distributed across 4, 8, and 12 unit starting dose groups, as derived from the insulin:carb ratio – Figure 1 (the sample size may be adapted after taking the PK data from Cohort 1 into account).. **Cohort 3: 4 to 7 years**; approximately 14 subjects will be treated and assessed for AFREZZA with a starting dose of distributed across 4, 8, and 12 unit starting dose groups, as derived from the insulin:carb ratio – Figure 1. The sample size may be adapted after evaluating the PK data from Cohort 1 and Cohort 2. The study consists of: • Up to 3-week screening period • PK assessment period: 1 day, after a single dose of AFREZZA® • Dose titration period: approximately a 4-week period with multiple doses of AFREZZA • A follow-up visit will occur approximately 1 week after the end of AFREZZA treatment for safety assessments (duration 1 day) **Stopping rules** • Administration of AFREZZA in any dose group(s) of an age cohort may be halted if the Sponsor or data safety monitoring committee (DMC) considers a dose group or age cohort to be unsafe or that it is unreasonable to continue. • The study may also be stopped if the Sponsor or DMC considers it not appropriate to proceed to the next age cohorts based on safety, PK, or titration data.
STUDY POPULATION	
Main selection criteria	**Inclusion criteria** 1. Written consent or oral assent from the pediatric subject and

	written informed consent from the parent(s) or legal guardian and a witness, as required by both state and federal laws and the local Institutional Review Board; 2. Children aged ≥4 and ≤17 years (enrolled into 3 age cohorts: 13 to 17, 8 to 12, and 4 to 7 years); 3. Clinical diagnosis of T1DM and using insulin for at least 1 year; 4. Currently receiving a regimen of basal/bolus insulin administered by MDI for at least 6 weeks prior to enrollment; 5. Subjects with pre-breakfast self-monitored blood glucose values between 80 and 250 mg/dL for 5 of 7 documented daily readings obtained in the week prior to Visit 2 (readings to be taken using glucometer provided at Screening Visit 1) and reported via the e-Diary; 6. Subjects on a regimen of insulin via continuous SC insulin infusion may be enrolled if they satisfy all other enrollment criteria and are willing to convert to MDI for the duration of the study, beginning 6 weeks prior to enrollment. They must continue to meet all enrollment criteria after converting to the MDI regimen; 7. Total daily insulin dose ≤1.5 units/kg/day with a minimum of 3 units of RAA at every meal. 8. Hemoglobin A1c (HbA1c) 7.0% to 10.0% at the time of screening; 9. Fasting serum C-peptide ≤0.3 ng/mL; 10. Forced expiratory volume in 1 second (FEV_1) ≥70% of National Health and Nutrition Examination Survey (NHANES) III predicted for children ≥8 years of age or Wang predicted for children <8 years of age; 11. Forced vital capacity ≥70% of NHANES III predicted for children ≥8 years of age or Wang predicted for children <8 years of age; 12. Subjects of childbearing potential must use "highly effective" methods of contraception. These include, for example, a state after surgical sterilization, hormonal intrauterine devices (coil), oral hormonal contraceptives, sexual abstinence or a surgically sterilized partner. "Highly effective" methods are considered those with a low failure rate (i.e., less than 1% undesired pregnancies per year). During the entire trial females of childbearing potential

	must use two contraceptive methods which are independent from each other, e.g. an intrauterine contraceptive coil or oral hormonal contraceptive plus a vaginal diaphragm or a condom coated with a spermicidal substance. The use of a condom in combination with spermicidal creams, however, is not sufficiently reliable. **Exclusion criteria:** 1. Body mass index below 25th or above 95th percentile for age and gender according to Centers for Disease Control and Prevention growth charts: https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm 2. History of physician diagnosis of asthma or any other clinically important pulmonary disease, or use of any medications to treat such conditions within the last year; 3. Allergy or known hypersensitivity for AFREZZA or to drugs with similar chemical structure; 4. Unstable diabetes control, defined as 2 or more episodes of severe hypoglycemia (i.e., an episode associated with a seizure, coma, or loss of consciousness) or any hospitalization or emergency room visit for poor diabetes control, ketoacidosis, hypoglycemia, or hyperglycemia within the preceding 3 months from screening; 5. Serum creatinine ≥ the upper limit of normal for age; 6. Respiratory tract infection within 30 days before screening or between screening and initiation of treatment period; subject may return 4 weeks after resolution of the infection for rescreening; 7. Evidence of any complication of diabetes (proliferative retinopathy, autonomic neuropathy, nephropathy, etc), or likelihood of requiring laser photocoagulation, vitrectomy, or other specific treatment for diabetic retinopathy in the coming year; 8. Smoking of tobacco or other substances or positive urine cotinine testing (>100 ng/mL); 9. Positive urine drug screen; 10. Positive urine pregnancy test for female subjects of childbearing potential; 11. Inability to perform study procedures including pulmonary function testing;

	12. Exposure to any investigational product(s) in the past 3 months or 5 half-lives, whichever is more; 13. History of eating disorder; 14. Any disease or exposure to any medication which, in the judgment of the principal Investigator, may impact glucose metabolism; 15. Any concurrent medical or major psychiatric condition that makes the subject unsuitable for the clinical study or impairs the subject's ability to participate in the study.
Total expected number of subjects	Approximately 46 subjects will be enrolled in the 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).
STUDY TREATMENTS	
Investigational medicinal product	AFREZZA® (insulin human) Inhalation Powder and Inhaler
Formulation	Recombinant DNA origin Each milligram of formulation contains 3.0 units of human insulin
Route of administration	Inhalation
Dose regimen	At the beginning of each meal
Non-investigational medicinal product	Basal insulin (e.g., insulin glargine)
Formulation	Long acting insulin analog
Route of administration	Subcutaneous injection
Dose regimen	Daily dose as instructed by Physician
ENDPOINTS	**Pharmacokinetic 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 (V_{ss}/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:
	$AUC = AUC_{last} + C_{last}/\lambda_z$
	Safety endpoints:
	• Adverse events, serious adverse events, treatment-emergent adverse events
	• Adverse Events of Special Interest (AESI), which include the following events:
	  • Acute bronchospasm
	  • 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
	• Anti-insulin antibodies

ASSESSMENT SCHEDULE	The schedule of study-related procedures/assessments is detailed in the study flow chart.
STATISTICAL CONSIDERATIONS	**Sample size determination:** Sample size calculation is based on a total standard deviation (SD_{Total}) of 0.725 for the log-transformed apparent total body clearance (CL/F). The sample size is planned to target the maximum imprecision of the 95% confidence interval for the geometric mean estimates of CL/F in each age cohort within 40%, with at least 80% power. A sample size of 14 subjects in the first cohort will provide at least 80% power in order to target the maximum imprecision of the 95% confidence interval of the geometric mean estimates within 40%, 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. **Analysis population:** All subjects in the clinical study who receive a dose of

	AFREZZA will be included in the safety population. 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. **Pharmacokinetic analysis:** All analyses will be performed in a descriptive manner based on the PK population. **Safety analyses:** Analyses will be performed in a descriptive manner by age cohort. The safety analysis will be conducted on the safety population and will be based on the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables and plots if appropriate). Individual values will be flagged for potentially clinically significant abnormalities and treatment-emergent adverse events will be tabulated (counts and percent). The details of the analyses for the study will be specified in the Statistics and Analysis Plan (SAP) for the study.
DURATION OF STUDY PERIOD (per subject)	The total duration of the study will be approximately 6 to 8 weeks per subject through the 4-week titration period.
STUDY COMMITTEES	Data Monitoring Committee: an independent group of experts will be responsible for monitoring the safety of the subjects enrolled in the clinical trial on an on-going basis in order to provide, in a timely fashion, appropriate recommendations to the Sponsor.

1 FLOW CHARTS

1.1 STUDY FLOW CHART FOR PK AND TITRATION PHASE

Phase	Screening	PK	Titration period												End of Titration	Follow-up	Early Termination[a]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Day	D–21 to D–7	D1	D2	D4	D6	D8	D10	D12	D15	D17	D19	D22	D24	D26	D29	D36	
Visit window (days)			0	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	
Visit at clinical site	X	X				X			X			X			X	X	X
Telephone contact			X	X	X		X	X		X	X		X	X			
Informed consent/Assent	X																
Review inclusion/ exclusion criteria	X	X															
Enrollment	X																
Medical/ surgical history	X																
Demography	X																
HbA1c	X														X		X
Fasting serum C-peptide	X																

Phase	Screening	PK	Titration period												End of Titration	Follow-up	Early Termination[a]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Day	D–21 to D–7	D1	D2	D4	D6	D8	D10	D12	D15	D17	D19	D22	D24	D26	D29	D36	
Visit window (days)			0	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	
Serology test[b]	X																
Full physical examination including Tanner stage, body weight and height, body temperature	X																
Abbreviated physical examination, body weight		X				X			X			X			X	X	X
Vital signs	X	X				X			X			X			X	X	X
12-lead ECG	X																
Urine drug screen, alcohol breath, or plasma test	X																
Urine cotinine	X	X				X			X			X			X	X	X
Urine β-HCG (females of childbearing potential)[c]	X	X				X			X			X			X	X	X
Spirometry (FEV_1)[d]	X	X							X						X	X	X

Phase	Screening	PK	Titration period												End of Titration	Follow-up	Early Termination[a]
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Day	**D–21 to D–7**	**D1**	**D2**	**D4**	**D6**	**D8**	**D10**	**D12**	**D15**	**D17**	**D19**	**D22**	**D24**	**D26**	**D29**	**D36**	
Visit window (days)			**0**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 3**	
Hematology, biochemistry, urinalysis	**X**																
Concomitant medications	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse event collection	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
BG and SMBG																	
Blood glucose samples during 4 hr PK[e]		**X**															
Remind subject to obtain 7 Fasting SMBGs in week prior to Visit 2, PK	X																
Dispense glucose meter, test strips[f]	**X**																
Training on both the study supplied Glucose Meter and e-diary	**X**																
Remind subject to obtain 7-point glucose data for	**X**				**X**			**X**			**X**			**X**			

Phase	Screening	PK	Titration period												End of Titration	Follow-up	Early Termination[a]
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Day	D–21 to D–7	D1	D2	D4	D6	D8	D10	D12	D15	D17	D19	D22	D24	D26	D29	D36	
Visit window (days)			0	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	
next site visit [g]																	
Blood glucose via glucose meter reading		X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review subject's 7-point glucose data						X			X			X			X		
AFREZZA® and basal insulin																	
BluHale inspiratory training		X															
Training on use and storage of AFREZZA® inhaler and cartridge		X															
Dispense new Afrezza inhalers and cartridges as necessary [i]		X				X			X			X			X		
Breakfast and lunch at site		X															
AFREZZA® inhalation		X															
Dose titration			X	X	X	X	X	X	X	X	X	X	X	X	X		

Phase	Screening	PK	Titration period												End of Titration	Follow-up	Early Termination[a]
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Day	**D–21 to D–7**	**D1**	**D2**	**D4**	**D6**	**D8**	**D10**	**D12**	**D15**	**D17**	**D19**	**D22**	**D24**	**D26**	**D29**	**D36**	
Visit window (days)			**0**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 1**	**± 3**	
based on SMBG values																	
Provide nutritional information		**X**															
Prescription for usual prandial RAA															**X**		**X**
Pharmacokinetics																	
Insulin PK sampling for 4 hours		**X**															
FDKP PK sampling for 4 hours		**X**															
Anti-insulin antibody	**X**														**X**		**X**

Abbreviations: β-HCG, beta human chorionic gonadotropin; BG, blood glucose; ECG, electrocardiogram; FDKP, fumaryl diketopiperazine; HbA1c, glycated hemoglobin A1c; PK, pharmacokinetic(s); RAA, rapid-acting analog; SMBG, self-monitored blood glucose.

a. Early termination is defined as withdrawal or discontinuation at any point between AFREZZA® administration on Day 1 (Visit 2) and end of 28-day titration.
b. Tests for hepatitis B antigen, hepatitis C antibodies, anti-HIV-1, and anti-HIV- 2.
c. Urine β-HCG test to be done in female subjects of childbearing potential in Cohorts 1 and 2.
d. Spirometry: on Day 1 Spirometry test will be conducted at approximately –25, 18, 55, 125, and 245 minutes.
e. Blood glucose sample for 4 hours: glucose reading to be done locally via a table top glucose meter (eg, YSI) at Investigator site. Central laboratory will be used only if local reading (i.e., table top glucose meter) is not available.
f. Additional test strips may be provided as needed at Visits 6, 9, 12, 15 and every 3 months during the extension treatment period.

g. Once per week in the week prior to the next clinic visit, subjects will obtain 7-point glucose data (pre-meal and 120-150 minutes post-dose at breakfast, lunch, dinner, and pre-bedtime). On these days, the starting and ending time for each meal will be recorded in the e-Diary, in addition to the dosing time.
h. If the fasting plasma glucose (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®.
i. One inhaler, which may be used for up to 15 days, and replacements will be available if necessary.

1.2 SCHEDULE FOR DAY 1

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
Concomitant medications	<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	>
Adverse event collection	<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	>
Blood glucose via glucose meter reading[a]	X																			X
Glucose value via local or central laboratory[b]				**G00**						**G01**			**G02**	**G03**	**G04**		**G05**	**G06**		
Spirometry (FEV_1)		X						X				X				X			X	
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 that is typical for that subject based on his/her usual patterns of eating and activity. 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.

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3 LIST OF ABBREVIATIONS

AE	:	adverse event
AESI	:	adverse event of special interest
AUC	:	area under the serum concentration versus time curve extrapolated to infinity
$AUC_{0\text{-tlast}}$	:	area under the baseline-corrected concentration-time curve from time 0 to the last measurable concentration
CL/F	:	apparent total body clearance
C_{max}	:	maximum observed concentration after correction for baseline
CSR	:	clinical study report
DMC	:	data safety monitoring committee
e-CRF	:	electronic case report form
FDA	:	Food and Drug Administration (USA)
FDKP	:	fumaryl diketopiperazine
FEV_1	:	forced expiratory volume in 1 second
GCP	:	Good Clinical Practice
HbA1c	:	glycated hemoglobin A1c
ICH	:	International Council for Harmonisation
IMP	:	investigational medicinal product
ISPAD	:	International Society for Pediatric and Adolescent Diabetes
MDI	:	multiple daily injections
NHANES	:	National Health and Nutrition Examination Survey
NIMP	:	non-investigational medicinal product
PK	:	pharmacokinetic(s)
RAA	:	rapid-acting analog
SAE	:	serious adverse event
SAP	:	statistical analysis plan
SC	:	subcutaneous
SD_{Total}	:	total standard deviation
SMBG	:	self-monitored blood glucose
T1DM	:	type 1 diabetes mellitus
t_{max}	:	time to C_{max}
V_{ss}/F	:	apparent volume of distribution

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

In type 1 diabetes mellitus (T1DM), the therapeutic objective is to optimally control blood glucose levels and this objective is fundamentally the same in all subjects with T1DM. However, individual circumstances and needs dictate what those optimal levels should be. Children and adolescents with T1DM are dependent on insulin for survival (1), (2), (3), (4). Children and adolescents experience phases of growth and pubertal development associated with substantial changes in metabolism and, consequently, insulin requirements (5), (6).

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 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) (7).

Because of its more rapid kinetics, AFREZZA® may be potentially more useful as a first-phase prandial insulin replacement than injectable prandial insulins. Basing AFREZZA® dosing on self-monitored blood glucose (SMBG) readings done 120 to 150 minutes post-dose takes both the pre-meal glucose and the rise of blood glucose after a meal into account, and represents a new treatment and monitoring paradigm. Postprandial or “follow-on” AFREZZA® dosing following meals based on these postprandial SMBG readings may also offer the possibility to correct postprandial glucose elevations without the “stacking” of insulin.

4.2 RATIONALE

MKC-TI-155 Part 1 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 the ability to dose-titrate in children. 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 (Section 18.3– Appendix C).

4.3 POTENTIAL BENEFITS

The potential benefits of AFREZZA® over current treatment modalities with SC insulin include an improved compliance to treatment and a reduced incidence of hypoglycemia with similar overall glycemic control as assessed by glycated hemoglobin A1c (HbA1c) levels.

4.4 IMPORTANT POTENTIAL RISKS AND ASSESSMENT PLAN

Safety of AFREZZA® has not been evaluated in children. The potential risk(s) of AFREZZA® based on the results of the studies done in adults may include the following (Table 1):

Table 1 Risk and Assessment/Mitigation plan

Risk	Assessment/mitigation plan
Important Identified risks	
Bronchospasm in patients with chronic obstructive pulmonary disease	
The long-term safety and efficacy of AFREZZA® in subjects with chronic lung disease has not been established. Acute bronchospasm has been observed in subjects with asthma and chronic obstructive pulmonary disease (COPD) using AFREZZA®. Because of the risk of acute bronchospasm, AFREZZA® is contraindicated in subjects with chronic lung disease such as asthma or COPD. The FDA-approved label has a boxed warning explaining the risk of acute bronchospasm in subjects with chronic lung disease.	Subjects with asthma or any other clinically important pulmonary disease will not be enrolled in the study.
Severe hypoglycemia	

Risk	Assessment/mitigation plan
In T1DM, the incidence of mild/moderate hypoglycemia was significantly lower in TI Inhalation Powder-treated subjects than in those treated with sc insulin comparator. The incidence of severe hypoglycemia was comparable between treatment groups (24.2% for TI Inhalation Powder and 28.3% for sc insulin comparator). Event rates for severe hypoglycemia were also comparable between the 2 groups (5.63 per 100 subject-month and 6.39 per 100 subject- month, respectively). Event rates per 100 subject-month for mild/moderate and severe hypoglycemia were not significantly different between the 2 groups.	Blood glucose will be monitored using self-monitored blood glucose. Dose titration and supplement dose instruction will be given to subjects.
Hyperglycemia during initiation of treatment	
During the clinical development program, some subjects treated with TI Inhalation Powder presented with events of hyperglycemia. Most of these events were reported during the first 4 weeks of treatment initiation and were associated with insufficient titration. As is the case during initiation of any insulin therapy, blood glucose concentrations should be closely monitored on an individual basis and dose adjustments should be made as necessary during initiation of TI Inhalation Powder.	Blood glucose will be monitored using self-monitored blood glucose. Dose titration and supplement dose instruction will be given to subjects.
Important potential risks	
Diabetic Ketoacidosis	
In clinical studies in adults with type 1 diabetes mellitus, diabetic ketoacidosis was more common in subjects receiving AFREZZA® (0.43%; n=13) than in subjects receiving comparators (0.14%; n=3). In subjects at risk for diabetic ketoacidosis, such as those with an acute illness or infection, increase the frequency of glucose monitoring and consider delivery of insulin using an alternate route of administration if indicated.	Blood glucose will be monitored using self-monitored blood glucose. Dose titration and supplement dose instruction will be given to subjects.
Lung Cancer	

Risk	Assessment/mitigation plan
In clinical studies in adults, 2 cases of lung cancer, 1 in controlled studies and 1 in uncontrolled studies (2 cases in 2750 subject-years of exposure), were observed in participants exposed to AFREZZA®, while no cases of lung cancer were observed in comparators (0 cases in 2169 subject-years of exposure). In both cases, a prior history of heavy tobacco use was identified as a risk factor for lung cancer. Two additional cases of lung cancer (squamous cell) occurred in non-smokers exposed to AFREZZA® and were reported by investigators after clinical study completion. These data are insufficient to determine whether AFREZZA® has an effect on lung or respiratory tract tumors.	Cotinine is test at screening as part of entry criteria and monitored throughout the study.
Dyspnea	
Dyspnea is an uncommon AE occurring in 1.7% and 0.1% of TI Inhalation Powder subjects and comparator-treated subjects with T1DM, respectively, and in 1.2% and 0.4% of TI Inhalation Powder and comparator-treated subjects with T2DM, respectively. A relatively higher incidence of dyspnea in TI Inhalation Powder-treated subjects may have been influenced by the open-label design of these trials. It is possible that subjects receiving an inhaled product were more self-aware and reported more signs and symptoms than did those on usual sc injection or oral treatments.	All adverse events will be collected and monitored throughout the study
Hyperglycemia during acute illness or change of treatment	
TI Inhalation Powder may be used during intercurrent illnesses, including upper respiratory tract infection. At such times, more frequent monitoring of blood glucose concentrations and dose adjustment may be required. If administration by inhalation is not feasible, substitution with an injectable insulin may be needed. It is important that a patient's insulin be continued. Transfer from TI Inhalation Powder treatment to other insulin therapies requires close monitoring of blood glucose	Blood glucose will be monitored using self-monitored blood glucose. Dose titration and supplement dose instruction will be given to subjects.

Risk	Assessment/mitigation plan
concentrations to reduce the risk of hypoglycemia or hyperglycemia during the transition period. These changes should be made under close medical supervision and the frequency of blood glucose monitoring should be increased. Concomitant oral antidiabetic treatment may need to be adjusted.	
Additional safety consideration:	
Decline in FEV1	
In clinical studies excluding subjects with chronic lung disease and lasting up to 2 years, AFREZZA® treated subjects experienced a small (40 mL [95% confidence interval (CI): -80, -1]) but greater forced expiratory volume in 1 second (FEV_1) decline than comparator-treated subjects. The FEV_1 decline was noted within the first 3 months, and persisted for the entire duration of therapy (up to 2 years of observation). In this population, the annual rate of FEV_1 decline did not appear to worsen with increased duration of use. The effects of AFREZZA® on pulmonary function for treatment duration longer than 2 years have not been established.	To enter the study, subjects must have $FEV_1 \geq 70\%$ of National Health and Nutrition Examination Survey (NHANES) III predicted for children ≥8 years of age or Wang predicted for children <8 years of age, and forced vital capacity (FVC) ≥70% of NHANES III predicted for children ≥8 years of age or Wang predicted for children <8 years of age. Spirometry (FEV_1) will be done to assess pulmonary function at the screening visit and at 5 time points during pharmacokinetic assessment before and after AFREZZA® dose at Visit 2 to evaluate any acute change in lung function after dosing. In addition, FEV_1 assessment will take place at Visits 9, 15, and the follow up visit (Visit 16), and/or Early Termination Visit.

5 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 SMBG values obtained 120 to 150 minutes after each prandial dose of AFREZZA® in children ages 4 to 17 years with T1DM

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

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 MDI.

The structure of the study is as follows:

- Single dose PK at breakfast
- 4-week titration period starting at lunch after PK evaluation

On Day 1, 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 with breakfast (Section 8.1.3). After this starting dose, each subject will be titrated with AFREZZA® TI according to the titration rules given.

The study will begin with Cohort 1 then proceed to Cohort 2 and Cohort 3 in parallel. Approximately 46 subjects will be enrolled 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 subsequent cohorts, at least 14 subjects must be dosed (i.e., complete PK Visit 2). Of those, at least 6 subjects must receive at least the 8 unit dose.
- **Cohort 2: 8 to 12 years**; approximately 14 subjects distributed across 4 ,8 and 12 unit starting doses, as derived from the insulin:carb ratio – Figure 1.The sample size may be adapted after evaluating the PK data from Cohort 1.
- **Cohort 3: 4 to 7 years**; approximately 14 subjects will be treated and assessed for AFREZZA® distributed across 4, 8, and 12 unit starting doses, as derived from the insulin:carb ratio table – Figure 1.. The sample size may be adapted after evaluating the PK data from Cohort 1 and Cohort 2.

6.2 STOPPING RULES

Administration of AFREZZA® in any dose group(s) of an age cohort may be halted if the Sponsor or data safety monitoring committee (DMC) considers a dose group or age cohort to be unsafe or that it is unreasonable to continue.

The study may also be stopped if the Sponsor or DMC considers it not appropriate to proceed to the next age cohorts based on safety, PK, or titration data.

6.3 DURATION OF STUDY PARTICIPATION FOR EACH SUBJECT

The study consists of:

- Up to a 3-week screening period
- PK assessment period: 1 day, after a single dose of AFREZZA®
- Dose titration period: approximately a 4-week period with multiple daily doses of AFREZZA®
- A follow-up visit will occur approximately 1 week after the end of AFREZZA® treatment for safety assessments (duration of 1 day)

The total duration of the study through the 4-week titration period and follow-up will be approximately 6 to 8 weeks per subject.

6.4 DETERMINATION OF END OF CLINICAL STUDY (ALL SUBJECTS)

The end of the clinical study is defined as the day the last subject completed his/her last visit planned in the protocol.

6.5 INTERIM ANALYSIS

An interim analyses will be conducted on a cohort by cohort basis as each cohort completes PK and 4-week Titration Phase of this protocol.

Pharmacokinetics and safety data for Cohort 1 will be reviewed on a rolling basis by the Sponsor and the DMC in order to allow enrollment into Cohorts 2 and 3 as described in Section 6.1.

7 SELECTION OF PARTICIPANTS

7.1 NUMBER OF SUBJECTS PLANNED

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).

7.2 INCLUSION CRITERIA

Eligible subjects must meet all the following inclusion criteria for Part 1 of the study:

1. Written or oral assent from the pediatric subject and written informed consent from the parent(s) or legal guardian and a witness, as required by both state and federal laws and the local Institutional Review Board;
2. Children aged ≥4 and ≤17 years (enrolled into 3 age cohorts: 13 to 17, 8 to 12, and 4 to 7 years);
3. Clinical diagnosis of T1DM and using insulin for at least 1 year;
4. Currently receiving a regimen of basal/bolus insulin administered by MDI for at least 6 weeks prior to enrollment.
5. Subjects with pre-breakfast SMBG values between 80 and 250 mg/dL for 5 of 7 documented daily readings obtained in the week prior to Visit 2 (reading to be taken using glucometer provided at Screening Visit 1) and reported via the e-Diary;
6. Subjects on a regimen of insulin via continuous SC insulin infusion may be enrolled if they satisfy all other enrollment criteria and are willing to convert to MDI for the duration of the study, beginning 6 weeks prior to enrollment. They must continue to meet all enrollment criteria after converting to the MDI regimen;
7. Total daily insulin dose ≤1.5 units/kg/day with a minimum of 3 units of RAA at every meal.
8. HbA1c 7.0% to 10.0% at the time of screening;
9. Fasting serum C-peptide ≤0.3 ng/mL;
10. Forced expiratory volume in 1 second (FEV_1) ≥70% of National Health and Nutrition Examination Survey (NHANES) III predicted for children ≥8 years of age or Wang predicted for children <8 years of age (8), (9);
11. Forced vital capacity ≥70% of NHANES III predicted for children ≥8 years of age or Wang predicted for children <8 years of age (8), (9);
12. Subjects of childbearing potential must use “highly effective” methods of contraception. These include, for example, a state after surgical sterilization, hormonal intrauterine devices (coil), oral hormonal contraceptives, sexual abstinence or a surgically sterilized partner.

"Highly effective" methods are considered those with a low failure rate (i.e., less than 1% undesired pregnancies per year). During the entire trial females of childbearing potential must use two **contraceptive methods which are independent from each other**, e.g. an intrauterine contraceptive coil or oral hormonal contraceptive plus a vaginal diaphragm or a condom coated with a spermicidal substance. The use of a condom in combination with spermicidal creams, however, is not sufficiently reliable.

7.3 EXCLUSION CRITERIA

Subjects who have met all the above inclusion criteria listed in Section 7.2 will be screened for the following exclusion criteria:

1. Body mass index below 25th or above 95th percentile for age and gender according to Centers for Disease Control and Prevention growth charts https://www.cdc.gov/growthcharts/html_charts/bmiagerev.htm
2. History of physician diagnosis of asthma or any other clinically important pulmonary disease, or use of any medications to treat such conditions within the last year;
3. Allergy or known hypersensitivity to AFREZZA® or to drugs with similar chemical structure;
4. Unstable diabetes control, defined as 2 or more episodes of severe hypoglycemia (i.e., an episode associated with a seizure, coma, or loss of consciousness) or any hospitalization or emergency room visit for poor diabetes control, ketoacidosis, hypoglycemia, or hyperglycemia within the preceding 3 months from screening;
5. Serum creatinine ≥ the upper limit of normal for age;
6. Respiratory tract infection within 30 days before screening or between screening and initiation of treatment period; subject may return 4 weeks after resolution of the infection for rescreening;
7. Evidence of any complication of diabetes (proliferative retinopathy, autonomic neuropathy, nephropathy, etc), or likelihood of requiring laser photocoagulation, vitrectomy, or other specific treatment for diabetic retinopathy in the coming year;
8. Smoking of tobacco or other substances or positive urine cotinine testing (>100 ng/mL);
9. Positive urine drug screen;
10. Positive urine pregnancy test for female subjects of childbearing potential;
11. Inability to perform study procedures including pulmonary function testing;
12. Exposure to any investigational product(s) in the past 3 months or 5 half-lives, whichever is more;
13. History of eating disorder;
14. Any disease or exposure to any medication which, in the judgment of the principal

Investigator, may impact glucose metabolism;

15. Any concurrent medical or major psychiatric condition that makes the subject unsuitable for the clinical study or impairs the subject's ability to participate in the study.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

8.1.1 AFREZZA (Insulin Human) inhalation powder and inhaler

AFREZZA consists of single-use plastic cartridges filled with a white powder containing insulin, which is administered via oral inhalation using the AFREZZA Inhaler only.

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

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

8.1.2 AFREZZA inhalation training

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

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

8.1.3 Initial dose for PK assessment

Dosing is individualized for each subject. For PK assessment, the AFREZZA dose for the breakfast will be calculated based on the dosage chart (Figure 1). AFREZZA should be taken under Investigator's supervision, immediately before the first bite of breakfast. The starting and ending time of breakfast will be recorded.

A standardized meal will be provided to the subjects for their first dose of Afrezza. Carbohydrate should account for 50% of the meal content up to a maximum of 70 grams of carbohydrate. Each cohort will likely fall in the following ranges for grams of carbohydrate at the initial breakfast:

Cohort 1: 50 - 70g;
Cohort 2: 40 - 60g; and,
Cohort 3: 30 - 40g.
The appropriate dose of Afrezza will be determined by using the subjects insulin/carbohydrate ratio in conjunction the with carb content of the meal per Figure 1.

Figure 1 Dosage chart to determine AFREZZA unit cartridges

Breakfast Carbs (g)	Breakfast Carbohydrate Ratio (units of insulin/g Carb)				
	1/5*	1/7	1/10	1/12	1/15
40	12	8	4	4	4
50	16**	8	8	4	4
60	16**	12	8	8	4
70	20**	12	12	8	8

*Consider dosing at 1:7 ratio recommendation in insulin resistant subjects
**Consider lowering carbohydrate intake since supplemental dose (second cartridge inhalation) may be indicated.

8.1.4 Dose titration

AFREZZA® should be taken at the beginning of the meal. An individualized postprandial dose will be administered 120 to 150 minutes after the initial dose if the SMBG exceeds 180 mg/dL. For dose titration, initial doses for lunch and dinner on Day 1 will also be determined based on the conversion table (Figure 1).

Throughout the study, doses for each of the following 3 days' meals will be titrated at the end of the current 3-day period based on the median SMBG (120 to 150 minutes post-dose) (Table 2). In other words, the subject will measure his/her 120 to 150 minute post-lunch SMBG for 3 days. The median dose (not the average dose, but the middle – between highest and lowest - of the 3 test values) will be used for dose adjustment per Table 2. This new dose should be used for the next 3 days. This process will be duplicated for both the post breakfast and dinner SMBG values.

Table 2 Recommended AFREZZA dose adjustments

Median 120-150 minute PPG value (mg/dL)	AFREZZA dose adjustment for that meal
<110	Decrease dose by 4 units
110-180	Maintain current dose
>180	Increase dose by 4 units

8.1.5 Postprandial dosing (follow-on doses)

If a subject's SMBG is greater than or equal to 180 mg/dL, 120 to 150 minutes after the prandial dose, the subject should take an additional, individualized postprandial or follow-on dose. The dose should be sufficient to reduce blood glucose below 120 mg/dL based on the subject's individualized dose-response.

8.1.6 Additional dosing of AFREZZA for snacks

Additional AFREZZA dosing may or may not be required with snacks. The need for a dose and the size of the dose depends on the size and content of the snack and the individual's dose-response.

8.1.7 Basal insulin dose adjustment

The basal insulin dose should be adjusted, as necessary, to achieve a fasting SMBG of 80 to 130 mg/dL.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCTS

During the study, all subjects will receive daily injections of basal long-acting insulin.

8.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

In MKC-TI-155 Part 1, subjects will be assigned to their cohort based on their age.

8.4 PACKAGING AND LABELING

AFREZZA will be provided in 4, 8, and 12 unit cartridges with AFREZZA inhalers.

Empty AFREZZA cartridges are provided for training with the AFREZZA inhaler.

AFREZZA will be packaged and labeled per the FDA-approved prescribing information and for clinical trial use.

8.5 STORAGE CONDITIONS AND SHELF LIFE

AFREZZA should be refrigerated (2ºC to 8ºC or 36ºF to 46ºF). When in transit by a commercial carrier, the product may be shipped refrigerated or frozen (–25ºC to –15ºC or –13ºF to 5ºF). See Site Operations Manual for further information.

8.5.1 AFREZZA inhalation powder

When not in use: it should be stored in refrigerator at 2°C to 8°C (36°F to 46°F). Sealed (unopened) foil packages may be stored at 2°C to 8°C (36°F to 46°F) until the expiration date. **If a foil package is not refrigerated, the contents must be used within 10 days.**

When in use: it should be stored at room temperature at 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Sealed (unopened) blister cards and strips must be used within 10 days, and **opened strips must be used within 3 days.**

8.5.2 AFREZZA inhaler

Store at 2°C to 25°C (36°F to 77°F): excursions permitted. Inhaler may be stored refrigerated, but should be at room temperature before use.

8.5.3 Handling

Before use, cartridges should be at room temperature for 10 minutes.

8.6 RESPONSIBILITIES

The Investigator, the clinical site pharmacist, or other personnel allowed to store and dispense investigational medicinal product (IMP) will be responsible for ensuring that the IMP used in the clinical study is securely maintained in a temperature-controlled environment as specified by the Sponsor.

All IMP shall be dispensed in accordance with the protocol, and it is the Investigator's responsibility to ensure that up to date and accurate records of IMP issued and returned are maintained.

Any IMP-related quality issues should be recorded and reported to the Sponsor by the means of a procedure on product technical complaint forms (refer to Site Operations Manual).

A potential defect in the quality of IMP provided by the Sponsor may initiate a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP provided by the Sponsor to a third party, allow the IMP provided by the Sponsor to be used other than as directed by this clinical study protocol, or dispose of IMP provided by the Sponsor in any other manner.

8.7 CONCOMITANT TREATMENT

A concomitant medication is any treatment used by the subject at the same time they are using the study IMP. Any treatment which is continued during the study and/or initiated or changed during the study must be recorded in source data and in the electronic case report form (e-CRF), including the name of the medication, indication for which the medication is being given, daily dosage, and duration of use.

During the study, all subjects will receive daily injections of basal long-acting insulin.

With the exception of ibuprofen and over the counter cold remedies, the use of any other concomitant medications (including herbal supplements) in the period from 2 weeks before the screening visit to the conclusion of the subject's participation in this study should be discussed with the Sponsor's medical monitor.

Subjects who have an intercurrent illness (including respiratory tract infections) will be treated at the discretion of the Investigator or a designee. After consultation with the Sponsor medical monitor, the subject may be discontinued from the study treatment.

During intercurrent illnesses, including upper respiratory tract infection, it is important that a subject's insulin be continued. At such times, more frequent monitoring of blood glucose concentrations and dose titration may be required. AFREZZA may be continued unless, in the judgment of the Investigator, temporary substitution with injectable insulin is needed.

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 Sponsor's medical monitor. Dose adjustment and increased frequency of glucose monitoring may be required when AFREZZA is co-administered with drugs that may increase risk of hypoglycemia (ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs [e.g., octreotide], and sulfonamide antibiotics).

8.8 TREATMENT ACCOUNTABILITY AND COMPLIANCE

At each contact with the subject, either by telephone or during on-site visits, the Investigator or his/her delegate must ask the subject about administered doses of IMP and non-investigational medicinal product (NIMP).

Treatment units are returned by the subject at each on-site visit. The Investigator or delegate has to inspect IMP remaining in the returned packs and compare it to the dosing records documented in the subjects' diaries. Discrepancies have to be addressed with the subject for clarification of actual treatment administration. However, as subjects with T1DM require insulin, the level of glycemia as reflected by SMBG and HbA1c is a sensitive marker of adherence to insulin treatment.

The Investigator or delegate fills the treatment log form per subject and records the dosing information on the appropriate page(s) of the e-CRF.

The monitor will check the e-CRF data by comparing them with the subject's diary entries, treatment log forms, and unused treatment kits.

8.9 RETURN AND/OR DESTRUCTION OF TREATMENTS

Investigational medicinal product reconciliation must be performed at the site by the Investigator and the monitoring team using treatment log forms and documented on the center IMP inventory countersigned by the Investigator and the monitoring team.

A written authorization for destruction will be given by the clinical study team once the IMP reconciliation is achieved. This destruction can be performed at site depending on IMP specificities and local requirements or IMP can be returned to the Sponsor for destruction.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

All protocol-defined biological safety analysis, except SMBG, will be performed by a Central Laboratory. Detailed information on samples drawing, management, and analysis will be provided in a specific Central Lab Specifications (CLS).

9.1 PHARMACOKINETICS

All insulin PK parameters will be based on baseline-corrected insulin concentration. The baseline insulin concentration due to residual basal insulin will be estimated from the pre-dose blood samples. Insulin concentrations will be determined by validated radioimmunoassay. The FDKP serum levels will be determined by LC-MS and anti-insulin antibodies will be determined by radioimmunoprecipitation assay.

9.1.1 Sampling times

The sampling times for blood collection can be found in the Flow Chart 1.2.

9.1.2 Number of PK samples

The number of samples per subject and by study is indicated in Table 3.

Table 3 Number of serum samples

	AFREZZA® insulin	FDKP	Anti-insulin antibody
By subject	14	5	2[a]
Total for study (n subjects)	14 × 46 = 644	5 × 46 = 230	2 × 46 = 92

a. Anti-insulin antibody samples to be collected at screening and end of treatment/early termination.

9.1.3 Sample handling procedure

The sample handling procedure is summarized in Table 4.

Special procedures for collection, storage, and shipment will be provided in the CLS.

Table 4 Summary of handling procedures

	AFREZZA® Insulin	FDKP	Anti-insulin antibody
Blood sample volume	2 mL	2 mL	2 mL
Serum aliquot split	1 aliquot	1 aliquot	1 aliquot
Serum storage conditions	–70°C	–70°C	–20°C
Serum shipment conditions	Dry ice	Dry ice	Dry ice

9.1.4 Bioanalytical methods

A brief outline of the bioanalytical assay is provided in Table 5 below.

Table 5 Summary of bioanalytical methods

Analyte	AFREZZA® Insulin	FDKP	Anti-insulin antibody
Matrix	Serum	Serum	Plasma
Analytical technique	Radioimmunoassay	LC-MS/MS	Radioimmunoprecipitation
Lower limit of quantification	8 µU/mL	1 ng/mL	NA
Assay volume	100 µL serum	200 µL serum	250 µL plasma

9.1.5 Pharmacokinetic parameters

The following PK parameters will be calculated, using non-compartmental methods using baseline-corrected serum insulin concentrations obtained after AFREZZA single dose. 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})
- Insulin AUC (area under the serum concentration versus time curve extrapolated to infinity) according to the following equation:

$$AUC = AUC_{last} + C_{last}/\lambda_z$$

- Apparent total body clearance (CL/F) and apparent volume of distribution (V_{ss}/F) calculated by standard non-compartmental methods
- Fumaryl diketopiperazine elimination half-life ($t_{1/2}$)

9.2 SAFETY

9.2.1 Baseline demographic characteristics

Baseline demographic characteristics at screening will consist of:

1. Age (years)

2. Height (cm): 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.

3. Body weight (kg): 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.

4. Body mass index

5. Race and/or ethnicity

6. Gender

9.2.2 Medical history

Medical history along with subject demographics will be obtained at screening, 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).

Determination of the relevance of the medical history, and its impact on subject eligibility, will be made by the Investigator or designee. The Investigator may consult with the Sponsor medical monitor if necessary.

9.2.3 Screening assessment

Informed Consent/Assent will be obtained prior to performing any screening procedures. The safety assessment at screening will be performed according to the Flow Chart 1.1 and will include:

- Assessment of inclusion and exclusion criteria

- Physical examination (at screening): full physical examination, including ear, nose, throat, lung and cardiac auscultation, recording of Tanner stages of pubertal development and excluding genitourinary and rectal examinations

- Oral body temperature, body weight, and height

- Vital signs (respiratory rate, sitting blood pressure, and pulse measurements) will be recorded with the subject in a sitting position for 5 minutes before the measurement is taken.

- HbA1c

- Fasting serum C-peptide
- Laboratory tests:
    - Serology tests: hepatitis B antigen, hepatitis C antibodies, anti-HIV-1 and anti-HIV-2 antibodies
    - Anti-Insulin Antibody
    - Pregnancy test: females of childbearing potential
    - Urine cotinine
    - Urine drug screening: amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates
    - Alcohol breath or plasma test
    - Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets
    - Biochemistry:
        1. Plasma/serum electrolytes: sodium, potassium, chloride, calcium, phosphorus, carbon dioxide
        2. Liver function: aspartate aminotransferase, alanine transaminase, alkaline phosphatase, total and conjugated bilirubin
        3. Renal function: blood urea nitrogen, creatinine, uric acid
        4. Metabolism: albumin, total proteins, total cholesterol, low-density lipoprotein, triglycerides
        5. Potential muscle toxicity: creatinine phosphokinase, lactate dehydrogenase
    - Urinalysis: albumin/creatinine ratio, ketones, glucose, erythrocytes, and leucocytes count, pH, urobilinogen, nitrates, specific gravity
- A standard 12-lead electrocardiogram recorded after at least 10 minutes in a supine position
- FEV_1 testing: Spirometry (FEV_1) will be done to assess pulmonary function. Another pulmonary function test may be done after consultation with a pediatric pulmonologist if the subject is unable to perform spirometry
- Adverse events (AEs) spontaneously reported by the subject or observed by the Investigator will be monitored
- Prior/concomitant medications reported by the subject or by the Investigator will be

recorded

9.2.4 Safety assessment during the study

Safety assessments during the study will be done according to the Flow Chart 1.1 and will include, but is not limited to:

- Physical examination: the abbreviated physical examinations will include, but not limited to, general appearance, mental status, respiratory and cardiovascular systems, and other evaluations deemed appropriate by the Investigator for safety reasons
- Body weight (kg)
- Vital signs (respiratory rate, sitting blood pressure, and pulse measurements) will be recorded after the subject has been sitting for 5 minutes
- Laboratory tests:
  - Urine pregnancy test: females of childbearing potential
  - Urine cotinine
- Adverse events spontaneously reported by the subject or observed by the Investigator will be monitored
- FEV_1 testing: Spirometry will be done to assess pulmonary function. Another pulmonary function test may be done after the consultation of a pediatric pulmonologist if the subject is unable to perform spirometry
- Concomitant medications reported by the subject or by the Investigator will be recorded

9.2.5 Self-measured blood glucose (SMBG)

Blood glucose values will be self-measured by the subject using the Sponsor-provided blood glucose meter and corresponding supplies (lancets, control solutions, test strips, etc). Subjects will enter their SMBG data in the Sponsor-provided e-Diary.

Post-dose SMBG will be used to adjust the bolus insulin. The frequency of monitoring, including ad hoc values, can be adjusted by the Investigator.

All SMBG values will be used by the Investigator to monitor glycemia.

9.2.6 Mandatory SMBG

9.2.6.1 Fasting pre-breakfast SMBG

Fasting pre-breakfast SMBG will be measured daily during the study and used, among other things, to titrate basal insulin doses.

9.2.6.2 Routine SMBG monitoring

In addition to performing fasting SMBG every morning before breakfast, subjects or parents will perform SMBG monitoring 120-150 minutes post-dose at each meal. AFREZZA® doses will be adjusted based on these measurements (Table 2).

9.2.6.3 7-point SMBG profiles

Once during the screening period in the week prior to the PK visit (Visit 2) and once per week during the treatment period 7-point glucose data (pre-meal and 120-150 minutes post-dose at breakfast, lunch, and dinner as well as at bedtime) will be obtained via SMBG readings. These data will be reviewed by the site and may be used to prescribe a regular supplemental post-meal AFREZZA® dose as per Section 8.1.5.

On these days, the starting and ending time for each meal will be reported in the e-Diary and in the e-CRF.

9.2.6.4 Self-monitored blood glucose during symptomatic hypoglycemia

Whenever the subjects feel hypoglycemic symptoms, glucose should be measured by the subject (or others, if applicable) if possible. Subjects should be instructed to measure plasma glucose levels prior to carbohydrate intake/administration of glucose whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate carbohydrate/glucose rescue prior to confirmation.

Subjects have to document hypoglycemic events appropriately in their diaries and contact the Investigator as soon as possible following severe events for review and for decision on any necessary measures to be taken.

All hypoglycemia episodes will be documented on the “hypoglycemia specific form” in the e-CRF. This includes all symptomatic hypoglycemia events and asymptomatic hypoglycemia.

Hypoglycemia events fulfilling the criteria of a serious adverse event (SAE) will be documented on the SAE form in the e-CRF.

9.2.7 Recording of SMBG into the e-CRF

All mandatory SMBG readings will be recorded in the e-CRF. Subjects will record SMBG readings in the e-Diary. Refer to the Site Operations Manual regarding SMBG data upload.

9.2.8 Recording of insulin doses into the e-CRF

To assess the change in daily AFREZZA and basal insulin dose, appropriate documentation of administration times and doses in corresponding pages of the e-CRF is requested.

Subjects will document the doses and times of administration of AFREZZA® and basal insulin in the e-Diary on a daily basis.

9.3 OTHER ASSESSMENT

Information on the ability to use the AFREZZA inhalation device will be collected in the e-Diary.

10 SUBJECT SAFETY

The Investigator is the primary person responsible for taking all clinically relevant decisions on safety issues.

If judged necessary, the opinion of a specialist should be sought in a timely manner (e.g., acute renal failure, convulsions, skin rashes, angioedema, cardiac arrest, electrocardiographic modifications, etc).

10.1 ADVERSE EVENT MONITORING

All events will be managed and reported in compliance with all applicable regulations and included in the final clinical study report (CSR).

10.2 DEFINITIONS OF ADVERSE EVENTS

10.2.1 Adverse event

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.

- **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.

10.2.2 Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event:

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 patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, that do not result in inpatient hospitalization, or the development of drug dependence or drug abuse.

10.2.3 Adverse event of special interest

An AESI is an adverse event (serious or nonserious) of scientific and medical concern, specific to the IMP 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 SAE notification guidelines described in Section 10.3.2, even if not fulfilling a seriousness criterion as an SAE.

The following adverse events are considered AESIs:

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

10.2.4 Hypoglycemia

10.2.4.1 Definitions and reporting for hypoglycemia and severe hypoglycemia

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.

The definitions used in this protocol are based on the Clinical Practice Consensus Guidelines 2014 of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (10). In the adult population, severe hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. In childhood, this definition is problematic as most young children require assistance to correct even mild hypoglycemia. As a result, in the pediatric population, severe hypoglycemia is generally defined as an event associated with severe neuroglycopenia usually resulting in loss of consciousness, coma, or seizure.

10.2.4.2 Non-severe hypoglycemic episodes

Non-severe hypoglycemia is defined according to the ISPAD Clinical Practice Consensus Guidelines 2014 (10) as follows:

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

All episodes of hypoglycemia that meet this definition of non-severe hypoglycemia are to be recorded in the e-Diary, and will be reported on the hypoglycemia page in the e-CRF.

10.2.4.3 Severe hypoglycemic episodes

Severe hypoglycemia in children is defined according to the ISPAD Clinical Practice Consensus Guidelines 2014 (10) as an event associated with a seizure, coma, or loss of consciousness and will be considered an SAE (see below). If glucose measurements are not available during such an event, the neurological recovery attributable to the restoration of glucose to normal will be considered sufficient evidence that the event was induced by a low glucose concentration.

The following episodes of hypoglycemia require reporting in the AE page and safety complementary e-CRFs and the hypoglycemia e-CRF. This applies for:

- Hypoglycemia associated with coma or loss of consciousness, or
- Hypoglycemic seizure, or
- Hypoglycemia that meets other conditions for an SAE, as defined under "Serious Adverse Event" in Section 10.2.2

The Investigator will adjudicate episodes of hypoglycemia reported in the e-Diary that appear to meet the criteria for SAEs. If the Investigator judges that the episode is not an SAE, it will be corrected on a data clarification form in the e-Diary and will not be recorded in an SAE e-CRF.

10.2.4.4 Guidelines for treating hypoglycemia

A subject exhibiting signs of hypoglycemia will be treated as appropriate by the Investigator, parent, or other caregiver.

10.2.5 Cough

Cough as an isolated symptom will be reported as an AE in the e-CRF. For cough associated with a defined clinical entity (e.g., upper respiratory tract infection), the appropriate diagnosis associated with the cough will be recorded in the AE e-CRF.

10.3 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.3.1 General guidelines for reporting adverse events

All AEs, regardless of seriousness or relationship to IMP/NIMP, occurring between consent/assent and the end of the study will be recorded.

AEs are to be recorded as defined by the protocol on the corresponding e-CRF for subjects who are enrolled and for those who fail screening.

For screen failed subjects, recording in the e-CRF is only performed in case of an SAE occurring during the screening period or in case of an AE when some study-specific screening procedures expose the subject to safety risks. Whenever possible, diagnosis or syndrome should be reported instead of individual associated symptoms (e.g., record "Influenza" not fever, chills, etc). The Investigator should specify the date of onset, intensity (see definitions in Section 10.2.1), action taken with respect to IMP/NIMP, corrective treatment/therapy given, additional investigations performed, outcome, and Investigator's opinion as to whether there is a reasonable possibility that the AE was caused by the IMP/NIMP.

In order to ensure the safety of the subjects, the Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until no further improvement is expected, or until death. Follow-up of the AE resolution/status will end at the follow-up visit. If necessary, SAEs will be followed beyond the last planned visit per protocol until resolution, no further improvement is expected, or death. Additional investigations of the SAE may be requested by the Sponsor.

When treatment is prematurely discontinued, an early termination (ET) visit should be conducted as soon as possible. Laboratory, vital sign, or electrocardiogram abnormalities are to be recorded as AEs only if:

- Laboratory and/or vital signs not specifically addressed elsewhere in the protocol change $\geq 10 \times$ the upper or the lower limits of normal and are undesired, and are a change from the pre-enrollment assessment values, and/or
- Are symptomatic, and/or

- Are clinically significant
- Require either corrective treatment or additional assessments, or a specialist consultation, and/or
- Lead to IMP/NIMP discontinuation or modification of dosing, and/or
- Meet criterion for an SAE, and/or
- Are an AESI.

10.3.2 Guidelines for reporting SAEs

In the case of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the SAE information in the appropriate screens of the e-CRF. The electronic data capture system will automatically send the notification to the safety team after approval by the Investigator within the e-CRF or after a standard delay.
- SEND (by fax) copies of all procedures, examinations, and medications administered and the dates on which these were administered or performed. Care should be taken to ensure that the subject's identity is redacted and the subject's identifiers in the clinical study are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

  PPD 24 hour safety hotline fax number: +1-888-529-3580

  +1-919-654-3836

- All further data updates of the subject's SAE should be recorded in the e-CRF as it becomes available, along with further documentation of procedures, examinations, and medications administered. Laboratory data, concomitant medication, subject study status, etc. should be sent (by fax) to the safety team within 24 hours of knowledge. In addition, an effort should be made to further document SAE within the week (7 days) following initial notification.

A back-up plan is used (using paper flow) when the e-CRF system does not work.

Back-up plan

- SEND (by fax) within 24 hours, the signed and dated page(s) corresponding to those in the CRF to PPD SAE report form collection along with all of the documentation requested above. Follow-up instruction (above) should be implemented either by back-up plan or e-CRF:

  PPD 24 hour safety hotline phone number: +1-888-483-7729

  PPD 24 hour safety hotline fax number: +1-888-529-3580

  +1-919-654-3836

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 IMP with a reasonable possibility should be reported to the safety team.

10.3.3 Guidelines for reporting adverse events of special interest

For AESIs, (see Section 10.2.3), the Sponsor is to be informed immediately (i.e., within 24 hours), as per the SAE notification guidelines described in Section 10.3.2, even if a seriousness criterion is not met.

10.4 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least possibly related to the IMP (suspected unexpected serious adverse reaction) to the Health Authorities and Institutional Review Boards as required and to the Investigators
- All SAEs that are expected and at least possibly related to the IMPs to the Health Authorities, according to local regulations

Any AE not listed as an expected event in the investigator's brochure or in this protocol will be considered as unexpected.

The Sponsor will report all safety observations made during the conduct of the study in the CSR.

11 HANDLING OF SUBJECT WITHDRAWAL

11.1 LIST OF TREATMENT WITHDRAWAL CRITERIA

- The subject fails to comply with prescribed dosing of the study treatment or any study-related procedures after multiple attempts made to obtain compliance.
- An AE or SAE occurs that could affect the subject's safety or well-being if treatment is continued.
- The subject begins using another investigational product, the Investigator and study monitors should discuss together whether the added agent requires AFREZZA discontinuation.
- The subject becomes pregnant.
- The subject begins smoking.
- Major protocol violations that, upon consultation between the Investigator and the medical monitor, are deemed to affect subject safety or the integrity of the study data.

11.2 REASONS FOR TREATMENT WITHDRAWAL

The subject, parents, or legally authorized representatives can withdraw from the study at any time, without giving a reason. The Investigator can also decide if it is in the subject's best interest to discontinue participation in the study. The Investigator should discuss the subject's withdrawal with a medical monitor beforehand, if possible. If not possible, the Investigator should discuss the withdrawal with a medical monitor within 24 hours of being informed of the decision.

11.3 TREATMENT WITHDRAWAL FOLLOW-UP PROCEDURE

For subjects who withdraw from the study for any reason, the Investigator will advise them about other treatment alternatives. All study treatment withdrawals should be recorded by the Investigator on the appropriate e-CRF screens.

Subjects are to be assessed using the procedure planned for the Early Termination visit. For a complete list of procedures scheduled for the ET visit please refer to the Flow Chart 1.1.

For any subject who fails to return to the site, the Investigator should make every effort to re-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, including at least his/her vital status. Attempts to contact the subject must be documented in the subject's study records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, and a copy of the letter).

Subjects withdrawn from the study must not be re-included in the study. Their inclusion numbers must not be reused.

12 STUDY PROCEDURES

12.1 VISIT SCHEDULE

MKC-TI-155 Part 1 consists of:

- A 7 to 21-day screening period
- A 1-day in-clinic PK assessment
- A 28-day outpatient study of the safety and ability to titrate AFREZZA in children ages 4 to 17 years with T1DM

All visits to the clinical site should take place in the morning at approximately the same time. For telephone-call visits, the subject is called by the Investigator or qualified designee at a pre-scheduled time.

A timeframe of ±1 days using the day of Visit 2 as reference is acceptable. The post-treatment follow-up Visit 16 should occur 1 week ± 3 days after the last treatment.

If a visit date is changed, the next visit should take place according to the original schedule.

If a subject withdraws consent to participate in the study, or his/her physician decides participation is no longer in the subject's best interest, an end of treatment visit should be conducted to evaluate the subject's health status as soon as possible if the subject is willing and in the physician's opinion able to do so.

For a complete list of procedures scheduled for each study visit, please refer to the Study Flow Charts (1.1 and 1.2). The following sections provide additional details about how some of the procedures will be performed.

12.1.1 Screening period

Screening procedures for subjects on MDIs will be carried out between 7 to 21 days prior to inclusion. The screening visit will include all the investigations listed in the Flow Chart 1.1 and detailed in Section 9.2. Subjects may have any screening parameter re-checked 2 times.

The subjects and their parent or legally authorized representative will receive information on the study objective(s) and procedures from the Investigator. Prior to any action related to the study, the informed consent document will have to be signed by the subject's parent or legally authorized representative, and the subject, if able, to understand the nature, scope, and possible consequences of the clinical study.

On safety grounds, pregnant females must not participate in this clinical trial because the trial procedures may pose unforeseeable risks for the mother and the unborn child. For this reason,

only females who take appropriate contraceptive measures may participate in this clinical trial (See Inclusion Criteria #12).

This study consists of 3 age-related subject cohorts. A blood or urine pregnancy test will be carried out for female participants in Cohort 1 (ages 13-17) and Cohort 2 (ages 8-12) at the beginning of the clinical trial and also several times during the course of the trial. However, early-stage pregnancies can only be reliably detected a few days after conception. Female participants in Cohort 3 (ages 4-7) will not have pregnancy tests performed.

Subjects who meet all the inclusion criteria (Section 7.2) and none of the exclusion criteria (Section 7.3) will be eligible for the study.

Subjects will receive a glucose meter, supplies and training for use during the study. Subjects will also receive an Electronic Diary (e-diary) and be trained in its use. Instructions will be given on how and when to take blood glucose readings during the screening period and how to enter those reading into the e-diary.

The PK visit will be scheduled and the subject will be reminded to bring their e-Diary to the PK visit. Five of seven fasting SMBG values obtained during the week prior to the PK visit must be between 80 and 250 mg/dL. Only the week (7 days) before the Day 2 visit values qualifies the subject for the study. Subjects will also be asked to refrain from vigorous physical activity within 24 hours of Visit 2 (Day 1), to fast overnight, to maintain their hydration (water only), to take any basal insulin the night before Visit 2, and to take no other medication in the morning of the PK visit.

12.1.2 PK assessment period (Visit 2)

Subjects who successfully completed screening will participate in Visit 2/PK visit. Study staff will confirm subject fasted overnight for at least 8 hours (only water is permitted), and the last dose of basal insulin was administered the night before Visit 2. Subjects should test their glucose by meter at home prior to coming into the clinic for Visit 2. If their glucose is less than 80 mg/dL, they should call the clinic and reschedule their Visit 2 PK Visit.

Upon arriving at the clinic on the morning of Visit 2, subjects will have the following assessments performed before they receive the first dose of AFREZZA:

- **Blood glucose determination:** Fasting pre-breakfast SMBG on the day of Visit 2 must be ≥80 mg/dL for the subject to participate in the PK assessment. However, if the SMBG value is >250 mg/dL, a urine sample will be checked for the presence of ketones using dipstick. If more than trace ketones are detected, the subject will not be permitted to proceed. The subject may return up to 2 more times on separate days to attempt to satisfy the SMBG criteria.
- Abbreviated physical exam and vital signs prior to Afrezza dosing.
- Urine pregnancy testing

- Urine cotinine
- **FEV_1 evaluation by spirometry:** Successive spirometry tests will be performed approximately 25 minutes before and 18, 55, 125, and 245 minutes after administration of AFREZZA to evaluate for possible acute changes in FEV_1 related to dosing.

Inhalation maneuver training: the BluHale system consists of an AFREZZA inhaler, an empty cartridge, and a pressure-sensing jacket that slips onto the inhaler. The jacket is designed for repeated use on multiple inhalers and does not require sterilization between subjects. Therefore, subjects may use the same jacket during training. Empty cartridges will be provided for training and practice. Subjects must demonstrate the ability to adequately perform the inspiratory maneuver utilizing the empty cartridge to continue in the study.

If, in the opinion of the Investigator, a subject cannot adequately perform the inspiratory maneuver after a second training, the subject will be withdrawn from the study. The Site Operations Manual (SOM) provides a more detailed description of the BluHale Inspiratory System.

Breakfast and AFREZZA dosing: subjects will receive a breakfast that is based on their assigned cohort and their Insulin/Carbohydrate ratio. (See Section 8.1.3 Initial dose for PK assessment) The meal will be provided by the clinical site. At the beginning of the meal, immediately before the first mouthful of food, the subject will inhale a dose of AFREZZA. The AFREZZA dose will be calculated based on the dosage table (Figure 1). The starting and ending time of breakfast will be recorded.

Post dosing assessment: the subject will then remain at the clinical study site for approximately 6 hours. The following procedures will be performed:

- 4-hour blood PK sample collection for insulin and FDKP. See Table 3 for number of samples and Flow Chart 1.2 for sampling times.
- Subjects will be monitored for signs of hypoglycemia. Blood glucose measurements will be taken during the course of the PK assessment visit according to the period Flow Chart 1.2, preferably by table top glucose analyzers present in the Investigator's facility (e.g., Beckman or YSI). If blood glucose measurement cannot be done in the Investigator's facility, blood samples need to be sent for central laboratory measurement. A subject exhibiting signs of hypoglycemia will be treated as appropriate. A snack will be given (e.g., 6 oz of milk) if any glucose measured during the PK test is <75 mg/dL.
- Following the 4-hour PK test, plasma glucose will be assessed, after which the subject will receive another dose of AFREZZA, followed by lunch. The lunch should correspond in size and composition to the subject's usual lunch. The AFREZZA dose should correspond to the subject's usual dose of prandial insulin. Consideration should be given to adjusting the lunchtime AFREZZA dose based on plasma glucose readings during the PK test and the pre-lunch plasma glucose value.

Instructions for dose titration period

- The initial dose of AFREZZA for each meal will be determined based on the subject's usual RAA dose for those meals and the glucose profile during the PK test; the doses will be recorded on a subject reminder card that the subject will take with them.

- The subjects/parents will be instructed to administer AFREZZA at the beginning of each meal and to perform and record (e-Diary) an SMBG assessment at 120 to 150 minutes after each mealtime dose. Subjects will also be instructed to record the start and ending times of each meal and the AFREZZA® dosing time.

- Pre-breakfast SMBG values will be obtained (for basal insulin adjustments) and recorded for this visit as well as for the duration of the study.

- Study site staff will explain to subjects/parents how to titrate the prandial dose for each meal based on the 120 to 150 minute post-dose SMBG values.

- Study site staff will explain to subjects/parents how to determine the appropriate postprandial or follow-on dose based on the value of 120 to 150 minute post-dose SMBG.

- Instructions will be provided on proper use and storage of AFREZZA® (inhaler and cartridges), and subjects/parents will be reminded to bring all cartridges back to the site with them at their next visit.

- Nutritional information will be provided (e.g., including carbohydrate content of meals and its impact on insulin requirements). Subjects will receive information about the importance of maintaining stable carbohydrate content of meals throughout this study.

- Glucose meter test strips and Afrezza cartridges will also be provided.

Discharge

Subjects will be discharged from the clinic after the completion of PK sampling (4 hours), lunch, an abbreviated physical examination and vital signs.

12.1.3 Dose titration period

AFREZZA® will be taken at the beginning of each meal.

The 28-day dose titration period will consist of 13 visits (Visits 3 to 15), which includes 4 site visits (Visit 6, 9, 12, and 15) and 9 telephone contacts (Visits 3, 4, 5, 7, 8, 10, 11, 13, and 14) primarily to adjust dosage and assess safety and tolerability.

A follow-up visit (Visit 16) will be performed approximately 1 week after the end of the AFREZZA® treatment period for safety assessments.

12.1.3.1 Telephone contact (Visits 3, 4, and 5)

Subjects will be contacted by the site via telephone 24 hours after Visit 2, primarily to record any AEs and concomitant medications and to ensure dosing and SMBG procedures are understood and are not problematic.

Subjects will be contacted by the site 3 times by telephone prior to the next clinic visit (Visit 6). The phone calls will be made 1 day after Visit 2, and 3 and 5 days after Visit 2 (within the protocol defined visit windows of ±1 day). Mealtime AFREZZA dose will be adjusted per the Investigator's discretion and recommendations described in Section 8.1.4, Section 8.1.5, and Section 8.1.6).

Basal insulin dose will also be adjusted as necessary by the Investigator based on the subject's pre-breakfast SMBG value according to Section 8.1.7.

At Visit 5, subjects will be instructed to obtain 7-point glucose data (pre-meal and 120-150 minutes post-dose at breakfast, lunch, and dinner as well as pre-bedtime, during one 24-hour day) prior to Visit 6. Subjects will also be reminded to bring their remaining drug supply and used cartridges to the next clinical site visit.

12.1.3.2 Clinical site visits (Visits 6, 9, and 12)

Subjects will return to the clinical site 2 to 4 days after the previous telephone contact (Visits 5, 8, and 11, respectively) for clinical assessment and further dose adjustment. The subjects' prandial doses will be adjusted for each meal according to Table 2 and their basal doses according to section 8.1.7 The subject will bring their remaining drug supply and used cartridges. Site staff will review unused IMP to assess compliance and need for additional IMP supply. Subjects will receive IMP and glucose test strips sufficient for approximately another 8 days. The Investigator will review the e-Diary with the subject to evaluate compliance with dosing and SMBG assessment requirements and to review hypoglycemic events. The Investigator will adjudicate episodes of hypoglycemia reported in the e-Diary that appear to meet the criteria for SAEs. If the investigator judges that the episode is not an SAE, it will be corrected on a data clarification form in the e-Diary and will not be recorded on an SAE e-CRF.

Subjects will be assessed according to the Flow Chart 1.1. Assessments include but are not limited to the following:

- Urine pregnancy test for females of childbearing potential
- Review of concomitant medications and AEs
- Vital sign measurements
- Abbreviated physical examination (general appearance, mental status, respiratory and cardiovascular systems, and other evaluations deemed appropriate by the Investigator for safety reasons)
- Body weight
- Urine cotinine
- Spirometry (Visit 9)

- Blood glucose via glucose meter reading
- Glucose test strips and AFREZZA® cartridges/inhalers provided (if necessary)
- Dose titration based on SMBG values
- 7-point glucose data will be reviewed and may be utilized to adjust dosing

12.1.3.3 Telephone contact (Visits 7, 8, 10, 11, 13, and 14)

There will be a safety/dose titration telephone contact after site Visits 6, 9, and 12. Adverse events and concomitant medications will be reviewed, and the subjects' prandial doses will be adjusted for each meal according to Table 2 and their basal doses according to Section 8.1.7. Subjects will also be instructed to obtain 7-point glucose data (pre-meal and 120-150 minutes post-dose at breakfast, lunch, and dinner as well as pre-bedtime during one 24-hour day) prior to the next visit.

12.1.3.4 End of titration (Visit 15)

Subjects will return to the site 3 ± 1 days after the last telephone contact at Visit 14. During this visit (Visit 15), FEV_1 will be assessed, and post-dose SMBG values since the last visit and current AFREZZA® doses will be reviewed. Subjects will be discharged from the clinic after an abbreviated physical examination (evaluating general appearance, mental status, respiratory and cardiovascular systems, and any other evaluations deemed necessary by Investigator).

Subjects will be assessed according to the Flow Chart 1.1. Assessments include but are not limited to the following:

- Urine pregnancy test for females of childbearing potential
- HbA1c
- Urine cotinine
- Anti-insulin antibody
- Review of concomitant medications and AEs
- Abbreviated physical examination (general appearance, mental status, respiratory and cardiovascular systems, and other evaluations deemed appropriate by the Investigator for safety reasons)
- Body weight
- Vital sign measurements
- Blood glucose via glucose meter reading
- Spirometry or another pulmonary function test for a subject who is unable to perform the spirometry test
- 7-point glucose data will be reviewed
- Subjects will return all study supplies and receive a prescription for usual prandial RAA and for basal insulin

12.1.3.5 Follow-up (Visit 16)

The subjects will return to the site for a follow-up visit 1 week ± 3 days after being off IMP (Visit 15). At which time FEV_1 will be assessed and AEs, glycemic status, and general health based on an abbreviated physical examination will be evaluated. Subjects will be assessed according to the Flow Chart 1.1. Assessments include but are not limited to the following:

- Body weight
- Urine cotinine
- Review of concomitant medications and AEs
- Abbreviated physical examination (general appearance, mental status, respiratory and cardiovascular systems, and other evaluations deemed appropriate by the Investigator for safety reasons)
- Vital sign measurements
- Blood glucose by glucose meter
- Spirometry or another pulmonary function test for a subject who is unable to perform the spirometry test
- Urine pregnancy test for females of childbearing potential

12.1.4 Early termination

Early termination is defined as withdrawal or discontinuation at any point between AFREZZA administration on Day 1 and end of 28-day titration.

Regardless of the reason for early termination, every effort must be made to perform the following end of treatment procedures prior to discharge:

- Body weight
- Review of AEs and concomitant medications
- Abbreviated physical examination
- Vital sign measurements
- Spirometry
- Blood glucose via glucose meter reading
- HbA1c
- Urine pregnancy test for females of childbearing potential
- Urine cotinine
- Prescription for RAA
- Anti-insulin antibodies

Subjects who cannot adequately perform the inhalation maneuver with an empty cartridge at Visit 2 will not be required to have an additional physical examination for early termination. Physical examinations will be performed for subjects who discontinue after receiving 1 or more AFREZZA doses.

After early termination, the Investigator or designee will follow up by telephone within 3 days to determine whether the subject experienced any previously unreported AEs during or subsequent to study participation. If so, the event(s) will be reported (as outlined in Section 10.3) and followed.

The reasons for early treatment termination will be collected in the e-CRF.

12.2 STUDY RECORD KEEPING

All data reported in the e-CRF must be consistent with identified source documents present at the site; any discrepancies must be explained.

Source documents are the original records. To satisfy International Council for Harmonization/Good Clinical Practice (ICH/GCP) guidance, source documentation must meet the following criteria for quality:

1) Attributable. Source documentation must be attributable to a study team member listed on the site delegation of authority log (initialed or signed and dated)

2) Legible. Source documentation must be clearly and completely legible

3) Contemporaneous. Source documentation should be recorded contemporaneously, that is, at the time of the event

4) Original. The information was first captured on the source document

5) Accurate. The source documentation should be accurate and completely describe the event or assessment

In addition, the study source records should be sufficient to document the activities and course of the site's subjects while on study, and all of the study-related events from the site's start-up through close out.

12.2.1 Site essential documents

Site essential documents for the study must be kept by the site in an organized site Investigator's File. These essential documents individually and collectively permit evaluation of the study conduct and the quality of the data produced. These documents serve to demonstrate the site's compliance with the standards of GCP and all applicable regulatory requirements.

All documents should be filed in the Investigator's Site Study File and will be collected by the monitor for filing in the Study Master File (Sponsor's documentation).

Both site and Sponsor files are to be current, complete, and accurately filed (i.e., regulatory authority inspection ready) at all times from study start up through study close out.

13 STATISTICAL CONSIDERATIONS

Statistical analyses described in the following subsections will be performed as outlined in the statistical analysis plan (SAP) for the study. The SAP will be issued prior to database lock and will be included in the CSR for this protocol. If there are any deviations from the original SAP, these will be reported in the CSR, and the SAP will be amended as appropriate. For all analyses, the age cohort of a subject will be determined by their age at inclusion to the study. Individual data will be listed and sorted by age cohort, subject, visit, and time point.

13.1 DETERMINATION OF SAMPLE SIZE

Historical data

Sample size calculation is based on information from a previous study conducted by MannKind Corporation with AFREZZA in adults with T1DM (MKC-TI-177).

The study was a randomized, 2 × 2 crossover study comparing insulin exposure and pharmacodynamic response following a single dose inhalation of AFREZZA versus an equivalent dose of SC RAA.

Determination of sample size

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 6 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 6 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.
PGM=DEVOPS/CPPK_STAT/E0173032/SAMPLE_SIZE/EXPLO/PGM/est_cros_Afrezza_TDR14323.sas
OUT=EXPLO/OUTPUT/est_one_TDR14323_i.rtf (29JAN2015 - 2:00)

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 account for the PK variability in Cohort 1.

13.2 SUBJECT DESCRIPTION

13.2.1 Disposition, demographics, and baseline characteristics of subjects

Subject disposition, demographics, and baseline characteristics will be summarized using descriptive statistics. Number and percentage of subjects taking concomitant medications will be summarized in frequency tables by therapeutic classes and generic terms using the World Health Organization dictionary. The number of subjects with pre-existing medical conditions will be summarized.

A listing of comments in the e-CRF and/or deviation log related to investigational product compliance and dosing, safety, or other comments will be provided.

13.3 ANALYSIS POPULATION

A summary table of count of subjects included in each study population will be provided by age cohort and start dose. All exclusions from any analysis populations will be fully documented in the CSR.

13.3.1 Safety population

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

13.3.2 Pharmacokinetics population

All subjects without any major deviations related to study drug administration, and for whom any PK parameters are available, will be included in the PK population.

Subjects who sneeze or cough right after AFREZZA inhalation for PK profiling will be considered as important deviations related to IMP and will be excluded for PK analysis.

13.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, including usual insulin doses, will be analyzed for all subjects from the safety population per age cohort and overall.

13.4.1 Subject demographic characteristics, medical history, and diagnoses

Continuous variables (age, height, weight and body mass index) daily basal insulin dose, daily prandial SC insulin dose, and qualitative variables (gender, race) will be summarized by descriptive statistics.

Demographic data will also be listed, including history of diabetes.

13.4.2 Baseline pharmacodynamic parameters
Not applicable.

13.4.3 Baseline safety parameters
Safety parameters will be summarized in a descriptive manner for the included subjects.

Baseline for safety parameters will be defined as the last available and evaluable parameter value before and closest to the first IMP dosing for laboratory data, and for vital sign parameters, including body temperature and further safety parameters unless specified differently.

13.5 EXTENT OF STUDY TREATMENT EXPOSURE AND COMPLIANCE
The following listings will be provided and sorted by subject:

- Details of drug dosing (actual treatment received, date and time of IMP administrations, route of administration, intended and actual dose received)
- Subjects receiving IMP from specified batch

The exposure to IMP (i.e., number of doses of IMP and duration of IMP in days, defined by: [end date of administration – start date of administration + 1]) will be summarized categorically (counts and percentages) by age cohort and overall, on the safety and PK population. If appropriate, exposure will also be summarized by start dose.

In addition, dose changes from baseline at the end of treatment for IMP (units and units/kg) will be summarized by age cohort and starting doses group for the safety population.

13.6 PRIOR/CONCOMITANT MEDICATION/THERAPY
Concomitant treatments will be coded according to the World Health Organization-Drug Dictionary (WHO-DD, latest version in use at time of database lock). Subjects who took medications that were stopped before the first IMP dosing and/or subjects who received concomitant treatments with the IMP will be listed.

Non-IMP insulin treatment will be presented separately and doses will be summarized.

13.7 ANALYSIS OF PHARMACODYNAMIC VARIABLES
Not applicable.

13.8 ANALYSIS OF SAFETY DATA

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, graphics) and if needed on statistical analysis (appropriate estimations, hypothesis tests). All the safety analyses will be performed using the safety population.

13.9 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSIS

Not applicable.

13.10 INTERIM ANALYSIS

An interim analyses 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.

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 as described in Section 6.1.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 ETHICAL AND REGULATORY STANDARDS

This clinical study will be conducted by the Sponsor, the Investigators, delegated Investigator staff, and Sub-Investigators in an ethical and humane manner; in accordance with ICH/GCP and all other applicable regulatory requirements; and the protocol, amendments, and study manuals. This clinical study will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first subject enrollment, in compliance with applicable regulatory requirements and with MannKind public disclosure commitments.

15 STUDY MONITORING AND QUALITY

15.1 INVESTIGATOR QUALITY AND REGULATORY RESPONSIBILITIES

The Investigator is required to supervise the conduct of the study at her/his site to ensure compliance with ICH/GCP and all other regulatory requirements; ensure the rights and welfare of subjects at this site are protected; and conduct the study in compliance with the protocol, amendments, and study manuals.

15.1.1 Protocol deviations

Investigators must not intentionally deviate from the protocol except to avert immediate risk of harm to a subject. If the Investigator deviates from the protocol in order to avoid immediate harm to a subject, the PI or delegate should inform MannKind Medical Monitor of the event (date, subject number, and circumstance) by phone or by email within 24 business hours.

All deviations from the protocol, ICH/GCP, or other regulatory requirements will be recorded at the site on a study log or e-CRF; discussed by delegated site staff with the site monitor no later than by the end of the next interim monitoring visit; and will be reported per their local EC and other regulatory requirements.

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.

15.2 SPONSOR QUALITY ASSURANCE AND REGULATORY RESPONSIBILITIES

This study will be performed in compliance with MKC's standard operating procedures (SOPs) for quality for tasks not transferred by contract to a CRO. For tasks contracted to CROs or Vendors, the CRO or Vendors' SOPs will be followed. MKC will provide oversight of all activities contracted through a CRO (e.g., clinical monitoring, data management, project management) through review of clinical monitoring reports; study metrics review; data listings review; tracking study progress against the study timeline); and an audit program conducted at clinical study sites by a third party contracted to MKC.

15.3 DATA MONITORING COMMITTEE

A DMC will be seated for this study. The DMC will remain independent of the clinical investigators and MannKind Corporation in order to avoid potential conflicts of interest. Other than being members of the DMC, members will have no relationship to the study, the design of the protocol, the conduct of the study, or the PIs. The DMC will review safety data on an ongoing basis. The frequency of meetings and the format and content of the data will be specified in the DMC Charter. The DMC will make recommendations to make pertinent changes to the protocol, and/or stop the study at any time if significant concerns regarding safety of the IMP or study procedures should arise.

15.4 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Sub-Investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patient are included earlier than expected

15.5 CLINICAL STUDY RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of the study results to the Investigator.

16 BIBLIOGRAPHIC REFERENCES

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3. Bangstad HJ, Danne T, Deeb L, Jarosz-Chobot P, Urakami T, Hanas R. Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2009;10 Suppl 12:82-99.

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17 INVESTIGATOR'S SIGNATURE

Study Title:	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
Study Number:	MKC-TI-155 Part 1 – Amendment 3
Final Date:	14 February 2018

I have read the protocol of Study MKC-TI-155 Part 1 Amendment 3 as described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Print name:_____

18 APPENDICES

18.1 APPENDIX A

N/A

18.2 APPENDIX B

N/A

18.3 APPENDIX C - PHASE 3 STUDY (PART 2 OF THE AFREZZA PEDIATRIC DEVELOPMENT PROGRAM)