Study Comparing Prandial Insulin Aspart vs. Technosphere Insulin in Patients with Type 1 Diabetes on Multiple Daily Injections: Investigator-Initiated A Real-life Pilot Study—STAT Study

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Abbreviations:

A1c	**Hemoglobin A1c**
AE	**Adverse Event**
AUC	**Area Under The Curve**
CGM	**Continuous Glucose Monitoring**
CBC	**Complete Blood Count**
CMP	**Complete metabolic panel**
CRO	**Contract Research Organization**
DKA	**Diabetic Ketoacidosis**
FEV1	**Forced Expiratory Volume In 1 Second**
FDA	**Food and Drug Administration**
IRB	**Intuitional Review Board**
MDI	**Multiple Daily Injections**
NL	**Novolog®, Insulin Aspart**
SAE	**Serious Adverse Event**
SMBG	**Self-Monitoring of Blood Glucose**
PPBG	**Post-prandial Blood glucose**
PPGE	**Post-prandial Glucose Excursion**
T1D	**Type 1 Diabetes**
TI	**Afrezza®, Technosphere Insulin**

Clinical Trial Summary

Title	**St**udy Comparing Prandial Insulin **A**spart vs. **T**echnosphere Insulin in Patients with Type 1 Diabetes on Multiple Daily Injections: Investigator-Initiated, A Real-life Pilot Study—STAT Study
Trial Location	Multi-center (USA)
Study Objectives	Primary objectives: 1. Improved time in range (70-180 mg/dl) with technosphere insulin (*TI*) on continuous glucose monitoring (CGM) 2. Better post-prandial glucose excursions (PPGE) (1-4 hours after meals) with *TI* Secondary objectives: 1. To assess glucose variability (standard deviation and/or coefficient variation), 2. The area under the curve (AUC) in the post-prandial blood glucose (PPBG) and PPGE, 3. Change in A1c in one-month treatment, 4. To determine above the target (>180 mg/dl) on CGM, and 5. To evaluate hypoglycemia (below the target <70, <60, <50 mg/dl) on CGM
Study Design	Randomized, open-label, parallel, multi-center, prospective, investigator-initiated
Study Population Main Selection Criteria	Inclusion criteria: 1. Signed informed consent before any study-related activities, 2. Male or female aged 18-70 years, 3. Type 1 diabetes mellitus (T1D) duration more than six months,

	4. Treatment with multiple daily injections (MDI) for at least three months before screening visit; stable insulin dose for the last one month, 5. No use of any oral anti-diabetics, any other form of insulin other than mentioned in the protocol, or any other type of injections such as glucagon-like-peptide-1 (GLP-1) analogs, pramlintide or insulin/GLP-1 analog combinations, 6. A1c between 6.5 to 10%, 7. Willingness to routinely collect at least two blood glucose measurements per day to calibrate the CGM. Beyond the calibrations, patients may use CGM for necessary action without having to confirm with fingersticks self-monitoring blood glucose (SMBG), as approved by the Food and Drug Administration (FDA), 8. BMI ≤35 kg/m^2, 9. Ability and willingness to adhere to the protocol including clinical and phone visits and 4-week-long CGM wear, 10. Using insulin glargine or insulin degludec as basal insulin, 11. Able to use and understand CGM data, 12. Willing to complete phone and clinic visits, 13. Patients who eat three main meals in a day (breakfast, lunch, and dinner), 14. Ability to speak, read, and write English, and 15. Patients prandial insulin need must be <18 units per meal Exclusion criteria: 1. Use of any other diabetic medication other than allowed in the protocol, 2. Pregnant or intention to become pregnant during the study, or not using adequate birth control methods,

	3. Severe unexplained hypoglycemia requiring emergency treatment in the previous three months, 4. Use of systemic or inhaled corticosteroids, 5. History of hemoglobinopathies, 6. Diagnosis of anemia, 7. Post-renal transplantation, currently undergoing dialysis, creatinine >2.0 mg/dl or a calculated creatinine clearance of <50 mL/min, 8. Advanced or unstable retinopathy needing laser procedure or vitrectomy, 9. History of pancreatitis, 10. Extensive skin changes/diseases that inhibit wearing a sensor on normal skin, 11. Known allergy to adhesives, 12. Known allergy to study medication, 13. Participation in another investigational study protocol within 30 days before enrollment, 14. Known chronic obstructive pulmonary disease, pulmonary hypertension, asthma, pulmonary fibrosis, or any chronic pulmonary infection, or any systemic disease that primarily affects the lungs. History of any pulmonary nodule will be excluded to participate in the study, 15. Active smokers, 16. Marijuana users, 17. Insulin pump users, 18. Expected acetaminophen use during CGM, 19. Using insulin detemir or NPH as basal insulin, 20. Patients who use more than 18 units per meal, 21. Any other condition, as determined by the investigator, which could make the subject unsuitable for the trial, impairs the

<table>
<tr><td></td><td>subject's suitability for the trial, or impairs the validity of the informed consent.</td></tr>
<tr><td>Total patients</td><td>Up to 75 enrolled for a total of 60 randomized patients to account for dropouts/screen fails</td></tr>
<tr><td>Study Treatment
Investigational medication(s)</td><td>Treatment group: Technosphere insulin (Afrezza®)
TI will be supplied as single-use cartridges of inhaled insulin of 4 or 8 or 12 units each.
Control group: Insulin aspart (Novolog®) {*NL*}
Novolog® will be supplied as 100 U/mL solution for SC injection in the Novolog® Flexpen™ disposable pen.</td></tr>
<tr><td>Routes of administration</td><td>Treatment group: *TI* Inhaler
Control group: Subcutaneous injection of *NL*</td></tr>
<tr><td>Dose regimen and adjustment</td><td>Patients will continue their routine meal and correction coverage, if applicable. Tables are for recommendations only and will be used as guidance. Since this is a real-life pilot study, patients will not be mandated to use corrections in the *NL* group. However, in the *TI* group, patients will use the conversion table from their current prandial insulin dosage as provided (Table 1A). Patients in the *TI* group will be recommended to use additional post-meal *TI* bolus as recommended to optimize PPBG {2-hour correction will be used only if blood glucose is >201 mg/dl and has not decreased by ≥ 50 mg/dl between 1 and 2-hours} (Table 1B).
<table>
<tr><td>Conversion</td><td>Table 1A</td></tr>
<tr><td>Injected mealtime insulin dose</td><td>Technosphere insulin dose</td></tr>
<tr><td>Up to 4 units</td><td>4 units</td></tr>
<tr><td>5-8 units</td><td>8 units</td></tr>
<tr><td>9-12 units</td><td>12 units</td></tr>
<tr><td>13-16 units</td><td>16 units</td></tr>
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<tr><td></td><td>
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<tr><td>17-20 units</td><td>20 units</td></tr>
</table>
<table>
<tr><td>Correction</td><td>Table 1B</td><td></td></tr>
<tr><td>Blood glucose</td><td>1-hour</td><td>2-hour</td></tr>
<tr><td><150 mg/dl</td><td>-</td><td>-</td></tr>
<tr><td>151-200 mg/dl</td><td>4 units</td><td>-</td></tr>
<tr><td>>201 mg/dl</td><td>8 units</td><td>4 units</td></tr>
</table>
</td></tr>
<tr><td>Basal insulin</td><td>Insulin degludec (Tresiba®), insulin glargine (Lantus®, Basaglar®, Toujeo®)</td></tr>
<tr><td>Route of administration</td><td>Subcutaneous injection</td></tr>
<tr><td>Dose regimen</td><td>Patients will continue their current dose basal insulin once or twice a day.</td></tr>
<tr><td>Statistical considerations</td><td>Randomization: Patients will be assigned to TI or NL 1:1 randomization.
Sample size determination: Power Analysis is based on the studies done in patients with diabetes. This sample size will provide 80% power to detect a difference in the primary endpoint of time in the range of 11%, assuming a standard deviation of 15% and 97% power to detect a difference of 1.0 glucose excursion post-prandially, assuming a standard deviation of 1.0.
Analysis population: Statistical analysis will be done after the study is complete. The analysis will be conducted on an intent to treat (ITT) population.</td></tr>
<tr><td>Study duration</td><td>Screening visit followed by randomization visit (up to 7 days)
4-week treatment period (2 phone visits, 2 clinic visits)
1-week follow-up period (1 phone visit)
Total of 6 weeks</td></tr>
</table>

Sponsor: Investigator initiated trial supported by Mannkind, Corp, Valencia, CA.

Project Overview

This is an investigator-initiated, prospective, randomized, multicenter, parallel, open-label, pilot clinical trial evaluating the efficacy of *TI* for PPBG, PPGE, and time-in-range on CGM download in patients with T1D. *TI* is an inhaled, ultra-rapid-acting insulin, approved by the FDA for use in patients with diabetes. This is a pilot, real-life study where patients will continue their routine diabetes care and use post-meal correction dosages as deemed necessary for normalizing PPBG as per the protocol.

This multi-center study will enroll 75 patients with T1D for a total of 60 randomized patients to account for dropouts/screen fails, A1c values between 6.5 to 10%. The patients will be randomized in 1:1 fashion to either *TI* or *NL*. Patients who are randomized into the *NL* arm will continue using their usual prandial insulin dose before meals. Patients who are randomized into the *TI* arm will be instructed to dose before the meals and take necessary corrections at 1- and 2-hours after meals to optimize PPBG (Table 1B). There will be a total of 7 study visits (screening visit, randomization visit, 2 clinic, and 3 phone visits). There will be a 4-week treatment comparison between *TI* and *NL* and 1-week of post-study follow up. (Phone visit; Figure-1). Standard lab tests (A1c, complete metabolic panel {CMP}, complete blood count {CBC}) will be performed at the screening visit.

All patients will use real-time CGM (Dexcom G5®, San Diego, CA), which will be provided at the randomization visit for their day-to-day diabetes care. CGM data will be downloaded at every clinic visit on a secured computer. The data will be analyzed after

the study for different primary and secondary end points. All patients will be allowed to keep the CGM after the study is over for their day-to-day diabetes care.

Primary objective:

1. Improved time in range (70-180 mg/dl) with *TI* on CGM
2. Better PPGE (1-4 hours after meals) with *TI*

Secondary objectives:

1. To assess glucose variability (GV) (standard deviation and/or coefficient variation),
2. The area under the curve (AUC) in the PPBG and PPGE,
3. Change in HbA1c in one-month treatment,
4. To determine above the target (>180 mg/dl) on CGM, and
5. To evaluate hypoglycemia (below the target <70, <60, <50 mg/dl) on CGM.

Research Design

What do we intend to do?

We plan to execute an investigator-initiated, treat-to-target (TTT), multi-center, prospective randomized, parallel, open-label pilot clinical trial evaluating the efficacy of *TI* for lowering PPBG and PPGE in 60 adult patients (18 to 70 years) with T1D when compared with *NL* over a 4-week treatment period. The study protocol is registered with the NCT Government website: ClinicalTrials.Gov. NCT03143816

How are we going to do the work?

The Barbara Davis Center for Diabetes (BDC), primarily a leading T1D clinical and research center equipped for large-scale clinical research, will enroll approximately 15-20 patients (Halis Kaan Akturk, MD). The other four sites are: Atlanta Diabetes Associates (Bruce Bode, MD), USC Westside Center for Diabetes (Anne Peters, MD), AMCR Institute (Timothy Bailey, MD), and Rainier Clinical Research Center (Leslie Klaff, MD, and Ronald Brazg, MD). All other sites will enroll approximately 10-15

patients. Necessary personnel from all sites will attend an investigator's meeting likely in Denver in June 2017, which will be organized and conducted before the trial initiation. All patients will sign an informed consent form approved by the respective institutional review boards (IRB). The study will be coordinated by an external contract research organization (CRO), and all sites will be monitored at least once during the study.

How will the sites communicate?

Throughout the duration of the study, specific events will also be communicated by CRO between secondary sites and the primary investigator site. These events include protocol exemption, and waiver requests including failed inclusion or exclusion criteria. The patients will be screened within 2 weeks for A1c deviation. All serious adverse events (SAEs) will be reported to the CRO and the principal investigator within 24 hours.

What is the study population?

The study population will consist of patients with T1D currently receiving care at all respective study sites as listed on the front page. All investigators will attempt to recruit males and females with T1D from a variety of ethnic groups for participation in this study. Participants selected for this trial will be adult males and females (18-70 years old) with BMI ≤35.0, diabetes duration >6 months, A1c between 6.5–10% with T1D, who have not taken any oral anti-diabetics or any other insulin other than mentioned in the protocol or GLP-1 analog injections or any combination of insulin/GLP-1 analog injections in the last three months (detailed in Appendix 2 and 3). One repeat A1c will be allowed within two weeks of the screening phase. Patients who need more than 18 units of prandial insulin before meals will be excluded from the study. Only patients taking glulisine (Apidra®), lispro (Humalog®), or aspart (Novolog®) as their prandial insulin at baseline will be allowed in the study.

How are patients being selected for the study?

Patients will be randomly selected from the patient population at all sites. First recognized by the investigator, coordinator, or from a computer-generated list based on

entry criteria, patients who qualify will be offered to participate in the study on a first come basis. Patients who appear to fit the inclusion/exclusion criteria as mentioned in Appendix 2 and 3 during prescreening will be screened.

What are the treatment groups?

There are two parallel treatment groups. Beginning the day after visit 2, week 1, patients in the *TI* treatment group will use only *TI* for meals and corrections. Patients in the comparison group will be using *NL* for meals as they use it in real life. All patients will be provided with *TI* and insulin aspart for the duration of the study. All basal insulin (Toujeo®, Lantus®, Basaglar®, Tresiba®) except NPH and detemir (Levemir®) are allowed before and during the study as a part of MDI regimens. Basal insulin will not be provided throughout the study period.

What is your assignment strategy?

The patients will be assigned in a 1:1 fashion to either the *TI* or *NL* group. Sites will be responsible for supplying *TI*, *NL*, and other necessary materials to the patients related to the study. The Barbara Davis Center for Diabetes will be responsible for randomization using a computer system (Janet Snell-Bergeon, PhD). All patients will be provided with a CGM (Dexcom G5®, San Diego, CA) and six sensors for the duration of the study. Patients will be allowed to keep the CGM systems for their personal use after the study. The CGM data will be downloaded and analyzed for different GV indices at all clinical visits.

What are sample size calculations?

Sixty (60) patients will be randomized into the *TI* and *NL* groups, and the study will likely initiate in summer of 2017. Power Analysis is based on the studies done in patients with diabetes. This sample size will provide 80% power to detect a difference in the primary end point of time in the range of 11%, assuming a standard deviation of 15%, and 97% power to detect a difference of 1.0 glucose excursion post-prandially, assuming a standard deviation of 1.0.

What is the schedule of events for the treatment groups?

All patients will participate in a 1-2 hour screening visit 1, week-1. In the same week, patients will be randomized into one of the two treatment groups during baseline visit 2 (week 0). The treatment group will only use *TI* for rapid acting insulin for meals and corrections. The control group will only use *NL* for rapid acting insulin for meals. The patients in the control group will continue to use their respective treatments for four weeks with no predetermined change in dosage or titration. The patients in the *TI* group will use *TI* insulin as prandial insulin and for PPBG correction at 1- and 2-hours after main meals. Three main meals should be at least 4 hours apart from each other. Because the duration of action of *TI* is shorter, but ultra-rapid in onset compared to *NL*, patients in the treatment group can use *TI* insulin for correction dose(s) at 1-hour and 2-hour after the meal dose, if BG is over 150 mg/dl. All patients in the treatment group will use a dose-conversion chart that will be provided at randomization for meals according to their usual prandial insulin dose (Table 1A). The study design is summarized in Figure-1. All patients in the treatment group will be given the option of using correction if PPBG at 1-hour after the meal is between 151-200 mg/dl by 4 units of *TI*, and if PPBG is over 201 mg/dl by 8 units of *TI* (Table 1B). If PPBG does not decrease more than 50 mg/dl, and still over 201 mg/dl at 2-hour after the meal, they will be given the option of using 4 units of *TI* (Table 1B). All patients in the treatment group will be instructed on proper use of the *TI* inhaler. At all clinical visits, all insulin dosages will be recorded. All data will be downloaded and saved on a secured computer. FEV_1 at baseline, after 2-week of treatment and at the end of the study will be done for all patients. Appendix-1 summarizes the schedule of events.

Excluded medications:

The patients who are current smokers or have any other significant pulmonary disease will not be allowed to participate in the study. No marijuana consumption will be allowed during the study (since the effects of acute marijuana inhalations on *TI* absorption are unknown).

All oral anti-diabetics and other forms of insulin and injectable medications other than mentioned in the protocol should not be taken in the last three months.

Medications that affect blood sugar, including oral anti-diabetic medications, are not to be used for the duration of the study. The patients must not be taking inhaled or oral systemic corticosteroids.

Other drugs that interact with *TI* and/or *NL* are to be considered on a case-by-case basis by the investigator, including herbs with hypoglycemic properties.

Visit Descriptions:

Screening, Visit 1 (Week -1):

A screening visit: Visit 1 (Week -1). Informed consent will be obtained before commencement of any trial-related activities, defined as any procedure that would not have been performed during standard care of the subject outside of the study.

During this visit, patients will receive a physical exam, EKG, vitals and medical history, demographics, and a concomitant medications list will be recorded. A blood draw will be performed to assess for A1c (point of care preferred), CMP, and CBC. A urine pregnancy test will be administered for females of childbearing potential. If the patient has a qualified HbA1c done in the last two weeks, it will not be repeated at the screening visit unless the PI deems it necessary. All patients will receive a spirometry (FEV_1) test for screening.

Baseline/Randomization, Visit 2 (Week 0) ± 3 days:

Patients who meet the screening criteria will be randomized into one of two groups and necessary study medication will be dispensed. Instructions will be given on how to use the study medication, *TI*, starting the day following this visit with meals and corrections with doses recommended as seen in Table 1A and 1B, and to basal insulin regimen throughout the trial without any dose change. However, the PI may make

necessary changes in patients' insulin dosages especially keeping patient safety in mind. Any changes that are done by the PI out of the protocol for patient safety will be recorded and considered in statistical analysis.

Patients will have their vitals, weight, any adverse events, and concomitant medications recorded. All patients will start real-time CGM (Dexcom G5®, San Diego, CA) at that visit. All patients will wear CGM throughout the study. They will be allowed to keep the CGM after the study. They will be trained to use CGM if they do not know how or if they are not already on it. Patients will be trained on study paperwork (food, glucose and insulin diaries). Patients will continue to check their blood glucose levels via SMBG as they deem necessary. However, as approved by the FDA, Dexcom G5® data may be used to take necessary action, but all patients must calibrate the sensor two times a day per the label.

All patients in the treatment group will be given the option of using correction if PPBG at 1-hour after the meal is between 151-200 mg/dl by 4 units of *TI* and if PPBG is over 201 mg/dl by 8 units of *TI*. If PPBG does not decrease more than 50 mg/dl and still over 201 mg/dl at 2-hours after the meal, they will be given the option of using 4 units of *TI*. All patients in the treatment group will use the recommended conversion (Table 1A) when they calculate their prandial insulin dose. Since this is a real-life study, patients in the treatment group will be instructed to use *TI* for post-prandial hyperglycemia; however, they will not be mandated. In the control group, patients will continue their current *NL* prandial dose 15 minutes before meals according to their prandial insulin dose. If they use correction, they will correct; however, they will not change their routine pre- and post-prandial management.

Telephone Visits (Visits 3, 5, and 7) ± 3 days (Figure-1):

A phone call will be made by the study site staff to each subject at visits 3, 5, and 7. Although the window is ± 3 days, call time will be arranged in advance during the clinic visit. At this visit, staff will review any adverse events and changes in medications. Compliance to study protocol rules and CGM use will be reviewed.

Visit 4 (Week 2) ± 3 days:

This visit will occur at Week 2. At Visit 4, study site staff will record patients' vitals, weight, review of CGM data, and any adverse events and concomitant medications. Glucose download, insulin use/dose, and sensor glucose data will be discussed with the provider or the study coordinator.

The patients will remain in the same treatment or control group. Basal, bolus, and total daily dose of insulin will be recorded. The patients will receive necessary refills for CGM supplies and study medications. All patients will be reminded about the study protocol and insulin conversion and correction doses (Table 1A and 1B). Patients will get FEV_1 spirometry test. Patients who have decline more than 20% at FEV_1 test at 2-week of treatment will be excluded.

End of study, Visit 6 (Week 4) or Early Termination Visit ± 3 days:

For patients who withdraw at any point during the trial period, this visit will also be offered as an early termination visit (ETV).

Patients who complete treatment will schedule an end of study visit. This will be Visit 6 at Week 4. During this visit, a physical exam will be conducted. Vitals, weight, review of CGM data, adverse events, and concomitant medications will be recorded. Additional blood will be drawn for A1c or point of care A1c will be done. Unused medication will be returned. Active treatment with *TI* will end at this visit.

Basal, bolus, and total daily dose of insulin will be recorded. After the study, patients will be expected to continue their previous therapy. All patients will receive a spirometry (FEV_1) test.

Risks and Justification of Procedures

Technosphere insulin (Afrezza®)

Technosphere insulin (*TI*) (MannKind Corporation, Valencia, CA) is a dry powder formulation of regular human insulin adsorbed onto technosphere microparticles for oral inhalation (1). Upon inhalation, these microparticles can reach the deep lung where they dissolve rapidly because of the physiological pH, allowing absorption of insulin into the systemic circulation with a time to maximum serum insulin concentration of ~12–15 min (2). *TI* is currently approved for the treatment of Type 1 and 2 diabetes. Hypoglycemia is a potential risk of taking any insulin and/or *TI* therapy. Typical symptoms of mild/moderate hypoglycemia include: cold sweats, cool pale skin, nervousness or tremor, anxious feeling, unusual tiredness or weakness, confusion, difficulty concentrating, drowsiness, excessive hunger, and/or transient vision changes (3).

Acute bronchospasm has been observed in patients with asthma and COPD using *TI* (3). *TI* is contraindicated in patients with chronic lung disease. Before starting

TI, detailed medical history, physical exam, and a spirometry (FEV_1) test are mandatory to identify potential lung disease in all patients (3). Patients who had >20% decrease in FEV_1 during treatment will be discontinued from using *TI*.

In patients with T1D receiving basal insulin, HbA1c reduction with *TI* was noninferior to that of aspart, with less hypoglycemia and less weight gain (3). A multi-center randomized clinical trial in patients with Type 2 diabetes showed that patients had significantly lower weight gain and fewer mild-to-moderate and severe hypoglycemic events on *TI* plus insulin glargine than on biaspart insulin (4). Another study in patients with T1D compared insulin NPH to *TI* and *TI* was not inferior for post-prandial blood glucose control and had better results at fasting plasma glucose (5).

Safety Measures:

CRO will oversee safety data throughout the study via reporting of hypoglycemic events, adverse events, and serious adverse events (SAEs). All AEs, reported spontaneously by the patients, as well as those noted by the investigator or study staff, regardless of seriousness, severity, expectedness, or relationship to the study drug, will be recorded on source documents from the time of obtaining the informed consent to 7 days after the last dose of the study drug.

Severe hypoglycemia, a hypoglycemic episode requiring assistance or hospitalization with or without an SMBG or CGM data, is to be reported as a SAE. A hypoglycemic event “requiring assistance” is identified when the subject is unable to treat the event on their own. Any untoward event resulting in hospitalization, an extension of hospitalization, death, or threat of death will also be considered an SAE. All SAEs will be reported to FDA MedWatch by the CRO.

Statistical Analysis Plan

Statistical analysis will be done after the study is complete. The analysis will be conducted on the intent to treat (ITT) population. Sample size and power calculations were based on the pilot study conducted at the BDC (7).

The primary end points are to demonstrate improved time in range (70-180mg/dl) with *TI* on CGM and better PPGE (1-4 hours after meals). The secondary end points are to assess hypoglycemia, measure HbA1c changes, evaluate glucose variability, and to assess above the target (>180mg/dl) on CGM download.

Publication Strategy

Study results may be presented at national and international conferences including: the Scientific Sessions of the American Diabetes Association, European Association for the Study of Diabetes, Advanced Technologies for the Treatment of Diabetes, etc. The PI may submit the study results for publishing to peer-reviewed scientific journals, particularly within the fields of diabetes and endocrinology. All study results and data will be shared with the sponsor.

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Table-1A Injected insulin to technosphere insulin conversion chart at study initiation

Injected mealtime insulin dose	Technosphere insulin dose*
Up to 4 units	4 units
5-8 units	8 units
9-12 units	12 units
13-16 units	16 units
17-20 units	20 units

*Investigators may change the dosage based on patient safety, this table will be used as a guide. Patients who take more than 18 units on insulin aspart per meal will be excluded from the study.

Table-1B Correction doses for technosphere insulin group

Blood glucose	1-hour	2-hour
<150 mg/dl	-	-
151-200 mg/dl	4 units	-
>201 mg/dl	8 units	4 units*

*2-hour correction will be used only if blood glucose is >201 mg/dl and has not decreased by ≥ 50 mg/dl between 1 and 2-hours.

Appendix-1 Schedule of events

Visit	1	2	3	4	5	6		7
Week	-1	0	1	2	3	4		5
Visit Type	Clinic	Clinic	Phone	Clinic	Phone	Clinic		Phone
Assessment	Screening and Baseline	Randomization	Treatment week	Treatment week	Treatment week	Treatment week		Post-study follow up
						Final	Early termination	
Day (±3)	-7	0	7	14	21	28		35
Informed consent-Eligibility criteria	x							
Demographic Data, Medical History	x							
Concomitant medications	x	x	x	x	x	x		
Adverse events			x	x	x	x		x
Physical exam	x	x		x		x		
EKG	x							
Urine pregnancy test if applicable	x							
HbA1c*	x					x		
Complete blood count	x							
Complete metabolic panel	x							
Spirometry(FEV 1)	x			x		x		
Vital signs/weight	x	x		x		x		
Randomization		x						
Record basal,bolus, total insulin dose+	x	x		x		x		
Dispense TI		x		x				
Dispense insulin aspart		x		x				
Dexcom CGM-training and dispense CGM		x						
CGM change/download/ removal				x		x		
Glucose meter download		x		x		x		
TI-NL conversion chart dispense and education		x		x				
Compliance check			x	x	x	x		

*HbA1c test may not be waived at Visit 1 if the patient had an A1C done in the last 2 weeks.
+All insulin (basal and prandial) will be recorded in a diary provided.

Version 3
August 15, 2017

Appendix-2
Inclusion Criteria:

Patients that meet the following criteria will be considered for admission to the study:

1. Signed informed consent before any study-related activities,
2. Male or female aged 18-70 years,
3. Type 1 diabetes mellitus duration more than six months,
4. Treatment with MDI for at least three months before screening visit; stable insulin dose for the last month,
5. No use of any oral anti-diabetics, any other forms of insulin other than mentioned in the protocol, or any other types of injections such as GLP-1 analogs, pramlintide or insulin/GLP-1 analog combinations,
6. A1c between 6.5 to 10%,
7. Willingness to routinely practice at least two blood glucose measurements per day needed to calibrate the CGM. Beyond the calibrations, patients may use CGM for necessary action without having to confirm with fingersticks (SMBG), as approved by the FDA,
8. BMI ≤ 35 kg/m^2,
9. Ability and willingness to adhere to the protocol including clinical and phone visits and 4-week-long CGM wear,
10. Using insulin glargine or insulin degludec as basal insulin,
11. Able to use and understand CGM data,
12. Willing to complete phone and clinic visits,
13. Patients who eat three main meals in a day (breakfast, lunch, and dinner),
14. Ability to speak, read, and write English,
15. Patient's prandial insulin need must be <18 units per meal.

Appendix-3

Exclusion Criteria:

Patients will be excluded from the study if any of the following apply:

1. Use of any other diabetic medication other than allowed in the protocol,
2. Pregnant or intent to become pregnant during the study or not using adequate birth control methods,
3. Severe unexplained hypoglycemia requiring emergency treatment in the previous three months,
4. Use of systemic or inhaled corticosteroids,
5. History of hemoglobinopathies,
6. Diagnosis of anemia,
7. Post-renal transplantation, currently undergoing dialysis, creatinine >2.0 mg/dl or a calculated creatinine clearance of <50 mL/min,
8. Advanced or unstable retinopathy needing laser procedure or vitrectomy,
9. History of pancreatitis,
10. Extensive skin changes/diseases that inhibit wearing a sensor on normal skin,
11. Known allergy to adhesives,
12. Known allergy to study medication,
13. Participation in another investigational study protocol within 30 days before enrollment,
14. Known chronic obstructive pulmonary disease, pulmonary nodule, pulmonary hypertension, asthma, pulmonary fibrosis or any chronic pulmonary infection, or any systemic disease that primarily affects the lungs,
15. Active smokers,
16. Marijuana users,
17. Insulin pump users,
18. Expected acetaminophen use during CGM,
19. Using insulin detemir or NPH as basal insulin,
20. Patients who use more than 18 units per meal,

21. Any other condition, as determined by the investigator, which could make the subject unsuitable for the trial, impairs the subject's suitability for the trial, or impairs the validity of the informed consent

Appendix-4

Discontinuation Criteria:

1. A major change in exercise regimen during study participation,
2. Diabetic ketoacidosis,
3. Development of pancreatitis,
4. Pregnancy,
5. A decline in glucose control or an increase in hypoglycemia which, in the opinion of the PI, is considered to compromise patient safety,
6. Initiation of any other insulin or other injectable or oral form of anti-diabetics during the study other than the mentioned control or intervention group medications,
7. Developing significant shortness of breath or intolerance and cough to inhaled insulin, and/or
8. Decline >20% in FEV_1 test as compared to baseline during *TI* treatment. All patients will receive a spirometry test (FEV_1) at baseline, visit-4 and at the end of the study.
9. Acetaminophen use during CGM (4-week treatment period)

Figure-1 Flow diagram of the study