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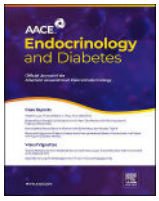

Original Research

Inhaled Insulin Dosing in a Randomized Trial in Adults With Type 1 Diabetes

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ABSTRACT

Objective: Technosphere insulin (TI) is an ultrarapid-acting inhaled insulin available in 4, 8, and 12 U cartridges. The U.S. Prescribing Information recommends converting subcutaneous rapid-acting insulin analogs (RAAs) to TI by rounding up to the nearest 4-U increment. This study aimed to evaluate TI dosing patterns after initiating therapy at a higher conversion dose than in the U.S. Prescribing Information and characterize subsequent titration needs.

Methods: In a multicenter, randomized trial, adults with type 1 diabetes were assigned to TI plus insulin degludec or usual care. TI was initiated at a 2:1 TI-to-RAA unit conversion, rounded down to the nearest cartridge and titrated to glycemic targets. Dosing data were collected at baseline, 17 weeks, and 30 weeks.

Results: Across participants randomized to TI with no missing dosing data for 30 weeks ($N = 35$), mean total daily TI dose increased from 36 U at baseline to 48 U at 17 weeks ($P = .002$) and 52 U at 30 weeks ($P < .001$). By 30 weeks, the TI bolus/basal ratio shifted from ~50%/50% prestudy RAA to ~70%/30% TI ($P < .001$). At 17 weeks, 57% of participants increased their TI dose by >4 U; this increased to 74% at 30 weeks. No new safety signals were identified.

Conclusion: Most participants who initiated TI at a higher conversion dose still required additional TI uptitration for glucose management. This study highlights the need for higher TI unit dosing requirements in clinical practice to support individualized titration to reach glycemic goals.

Introduction

Background on Inhaled Insulin

Technosphere insulin (TI), approved by the U.S. Food and Drug Administration in 2014 as the second inhaled insulin product, is currently the only inhaled insulin commercially available in the United States.[1,2] TI is available in prefilled, single-use cartridges of 4, 8, and 12 U, with higher doses administered by taking multiple cartridges in series.[3] Because the doses are limited to 4 U increments rather than the single-unit (or smaller) increments of standard subcutaneous rapid-acting soluble insulin, the dosing may be viewed as rigid and/or imprecise.[4] It is valuable for clinicians to recognize the distinctive "per-unit" effect of TI based on its unique time–action profile, bioavailability, and the resultant real-world TI dosing so they can use this therapeutic option effectively.[5]

TI is an orally inhaled, dry-powder formulation of insulin delivered via a small breath-powered inhaler.[3] It consists of regular human insulin molecules adsorbed onto small, inert, water-soluble carrier particles of fumaryl diketopiperazine (FDKP) and trace polysorbate 80.[3,6] This rapid-acting insulin is indicated for glycemic control in adult patients with diabetes. It is taken at the start of a meal, with no prebolusing needed.[3] The TI U.S. label has a boxed warning about a risk of acute bronchospasm in patients with chronic lung disease.[3]

Abbreviations: AID, automated insulin delivery; CGM, continuous glucose monitoring; FDKP, fumaryl diketopiperazine; FEV_1, forced expiratory volume in 1 second; PPGE, postprandial glucose excursion; RAA, rapid-acting insulin analog; TI, Technosphere insulin; T1D, type 1 diabetes; USPI, U.S. Prescribing Information.

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Pharmacokinetic and Pharmacodynamic Profile

This formulation of regular insulin delivered via the pulmonary route results in a unique pharmacokinetic and pharmacodynamic profile.[7,8] After oral inhalation through the inhaler, TI particles (2-2.5 μm) travel to the large surface area of the lung and rapidly enter systemic circulation.[8-10] The FDKP and insulin dissociate in the deep lung tissue; FDKP is excreted unchanged primarily in the urine.[8,9] It is worth noting that while some of the powder is seen in the oropharynx and stomach, affecting bioavailability, the delivered dose to the alveoli is equally distributed and the pharmacodynamic effect is reproducible.[8] Euglycemic clamp studies show serum insulin concentrations increase rapidly after TI administration, with the peak insulin concentration occurring at 14 to 18 minutes compared with a subcutaneous injection of insulin lispro at 73 to 95 minutes.[10] The onset of TI occurs at ~12 minutes.[3] Peak activity (~35-55 minutes) and duration (~1.5-4.5 hours) are dose dependent.[3] The rapid absorption of TI leads to a sharp peak with a short duration of action, resembling the incline of insulin uptake with intravenous administration.[8] Similarly, the effect on glucose lowering, expressed as the area under the curve of the glucose infusion rate in response to a dose of TI vs subcutaneous rapid-acting insulin analogs (RAAs), is not unit-for-unit equivalent, mostly owing to the shorter duration of action.[10] A 12 U dose of TI had a area under the curve of the glucose infusion rate (SD) of 397.1 (201.5) mg/kg, whereas an 8 U dose of insulin lispro was 701.1 (355.5) mg/kg.[10] Several studies have noted that the bioeffect and bioavailability of TI are lower than insulin delivered subcutaneously based on the current labeled TI units.[7-11]

TI has several differences from subcutaneous RAA that may provide clinical benefits for patients. Oral inhalation decreases the injection burden of intensive insulin therapy which can be associated with skin and subcutaneous tissue changes like lipohypertrophy.[12,13] The alternate route of administration may also be a favorable option to those with needle aversion or needle phobia.[12] The time–action profile of TI allows for administration at the start of a meal without the need for prebolusing, which is often recommended with subcutaneous insulin administration to optimize mealtime glucose coverage.[14] The early peak activity of TI can help decrease 1-hour and 2-hour postprandial glucose excursions (PPGEs), possibly improving mealtime management by increasing flexibility and spontaneity.[14-16] The short duration of TI action allows for corrective doses to be given 60 to 90 minutes after a previous dose without increasing risk of late hypoglycemia but also may mean additional doses could be needed to maintain glucose levels in the target range between meals.[15]

Current Dosing Guidance and Limitations

The current U.S. Prescribing Information (USPI) includes guidance on converting a subcutaneous mealtime insulin dose to a starting TI dose by rounding up to the closest 4-U increment, then titrating to effect.[3] The insulin exposure and glucose disposal is lower for TI compared with RAA as noted previously, which may result in underdosing if not appropriately titrated.[7,10] An individual's response to a dose of insulin can vary from person to person, so to mitigate the risk of hypoglycemia when switching from one insulin formulation to another, it is reasonable to start conservatively. It is important to understand that the initial conversion of a subcutaneous dose to TI is a starting point and is not necessarily clinically bioequivalent.[7,10] Several trials have shown that to achieve similar glucose control by A1C, TI doses must be titrated to higher units compared with subcutaneous insulin.[15,17] The short duration of action allows a separate correction dose of TI to be administered 60 to 90 minutes after dose with minimal insulin on board, which can help guide titration.[15] With TI titration, PPGEs can be significantly lower at 1 hour compared with RAA dosing.[15] The titrated doses of TI in studies have been 40% to 80% higher than subcutaneous insulin doses, without an increase in hypoglycemia.[18] Initiating TI therapy with a suboptimal dose followed by gradual titration may result in prolonged periods of hyperglycemia.

Highlights

- Initiated Technosphere insulin (TI) at 2:1 rapid-acting insulin analog conversion, rounded down
- Majority of patients required further TI titration beyond initial dose
- Bolus/basal ratio shifted from ~50%/50% on rapid-acting insulin analog to ~70%/30% on TI by week 30
- Higher TI doses were well tolerated with no increase in hypoglycemia
- Study supports higher conversion and individualized TI dosing

Clinical Relevance

Initiating Technosphere insulin at higher-than-recommended doses appears safe and often necessary for optimal glycemic control. This supports individualized dosing and highlights the importance of titration beyond standard conversion guidelines to achieve effective outcomes in type 1 diabetes management.

Studies Evaluating a Higher Conversion Dose

Recent studies have aimed to address the safety and efficacy of converting a subcutaneous insulin dose to a more clinically equivalent TI dose. A study of patients with type 1 diabetes (T1D) and type 2 diabetes compared a mealtime dose of TI based on the USPI (dose 1) and a higher modified dose (dose 2). The higher modified dose was obtained by multiplying the expected subcutaneous RAA dose by 2, then rounding down to the closest 4-U TI dose. Patients were provided the same meal and received TI at the start of each meal on 2 separate occasions (dose 1 and dose 2). Dose 2 resulted in substantially lower PPGEs from 45 to 120 minutes compared with dose 1. A single participant had 2 hypoglycemic events after receiving dose 2.[19] In a study evaluating the safety and efficacy of patients with T1D on TI plus automated insulin delivery (AID) versus AID control, the same higher modified dose described above was used to convert the first mealtime TI dose. The TI plus AID group had substantially lower PPGEs from 45 to 120 minutes compared with the AID-administered RAA control group. One asymptomatic level 1 hypoglycemic event occurred in the TI plus AID group.[16] Another recent study evaluated PPGE in adults with T1D comparing TI and RAA delivered via multiple daily injections or insulin pump. A meal challenge was completed at baseline and at 17 weeks with a standardized meal. TI was initiated with the same higher modified dose described above and given at the time of the meal, while the RAA dose was given 5 to 15 minutes before the meal. Compared with subcutaneous RAA, the initial converted TI resulted in substantially lower PPGEs, and after 17 weeks of titration, PPGEs decreased even further. During the baseline meal challenge, 1 asymptomatic level 1 hypoglycemic event occurred in each group.[17,20,21]

Rationale for the Study

Insulin therapy is given to prevent hyperglycemia and to attempt to achieve a reasonable approximation of normal pancreatic function but avoid hypoglycemia from excess insulin. An insulin with a substantially different time–action profile compared with traditional rapid-acting formulas may require time and clinical experience to fully integrate into practice.[5] Since insulin therapy is personalized, clinicians and patients must understand the individual's response to a dose over time and adapt. Although many TI studies report the mean final total dose,[18] actual cartridge-level doses for meals are not always specified. This information as well as the overall titration of TI may be helpful to guide clinicians. Using the patterns seen in patients using TI, clinicians can apply these data to their patients as they gain their own experience in dosing and titrating TI.

Study Objective

This study aims to describe the characteristics and changes of TI dosing in a subset of clinical study participants who used TI for 30 weeks after initiating TI at a higher modified conversion from subcutaneous RAA.

Methods

INHALE-3 (NCT05904743) was a multicenter, randomized, controlled study evaluating the safety and efficacy of TI in combination with insulin degludec compared with usual care in adults with T1D.[17] Participants were not blinded to treatment. The usual care group consisted of treatment regimens that included multiple daily injections or insulin pump therapy, including AID systems. All procedures were performed in compliance with relevant laws and institutional guidelines, the ethical principles stated in the Declaration of Helsinki, and approved by a central institution review board; privacy rights of participants were observed and informed consent was obtained as detailed in the previously published papers.[17,21] The primary end point evaluated A1C between treatment groups at 17 weeks. Participants could additionally continue on TI for a 13-week study extension period, for a total of ≤30 weeks on therapy. Details regarding the INHALE-3 study protocol, including settings/locations, harms, and type of randomization, can be accessed in the published paper and its supplementary information.[17]

The present analysis focused on a subset of INHALE-3 study participants randomized to the TI plus degludec arm who had complete insulin dosing data at all 3 key time points—baseline, week 17, and week 30. Inclusion in this substudy required nonmissing data for total daily insulin doses and mealtime dosing at each of these time points. A total of 35 participants met these criteria and were included in the final analysis cohort.

At randomization, participants in the TI arm transitioned from their prior insulin therapy to TI using a conversion ratio modified from the existing USPI recommendation, where the TI dose is calculated by multiplying the participant's usual subcutaneous RAA dose by 2 and rounding it down to the nearest available cartridge size (4, 8, or 12 U, or combinations; Table 1). The first dose of TI was administered in clinic with a standardized meal. Participants were then instructed to titrate their TI doses over time based on glycemic response, with adjustments made to achieve individualized glucose targets. Study protocol recommendations for TI correction doses included (1) taking another dose as soon as 60 to 90 minutes after the previous dose, (2) taking 4 U if glucose level is 140 to 200 mg/dL and 8 U if >200 mg/dL, (3) taking 4 U if glucose level was >200 mg/dL overnight, (4) stressing the importance of correction dosing at bedtime, and (5) titrating to higher correction doses as needed. The initial dose of insulin degludec was based on the average daily amount of basal insulin the study participant was currently taking and was titrated from there, with the protocol-specified goal of achieving fasting glucose between 90 and 120 mg/dL without hypoglycemia. Continuous glucose monitoring (CGM) was used throughout the study to support titration and assess glycemic trends.[17]

Table 1
Modified[a] Starting Dose Conversion From RAA for TI Participants

RAA dose, U	TI dose, U
<4	4
4	8
5	
6	12
7	
8	16
9	
10	20
11	
≥12	24[b]

Abbreviations: RAA = rapid-acting insulin analog; TI = Technosphere insulin; USPI = U.S. Prescribing Information.
[a] Compared with the current USPI for TI.
[b] The initial TI dose taken did not exceed 24 U.

At every study visit, clinical investigators reviewed participant-reported dosing, observed glycemic response, and made insulin titration recommendations at their discretion for both groups. For this substudy, participant-reported insulin dosing data were used from baseline, week 17, and week 30 time points. Data included prestudy insulin doses, basal insulin doses, and total daily as well as individual mealtime TI doses.

Changes in total daily bolus insulin were assessed using a threshold of 4 U to reflect the fixed cartridge sizes available for TI (4, 8, and 12 U). This threshold served as a practical analog for identifying meaningful titration changes. Mealtime bolus doses were recorded for breakfast, lunch, and dinner. The investigator-prescribed doses at baseline (day 0) were compared with participant-reported doses at week 30. To better understand typical mealtime dosing patterns in the context of fixed cartridge increments, the distribution of median meal bolus doses (across breakfast, lunch, and dinner) was analyzed at baseline and at week 30. This approach provides insight into the range of TI doses that may be expected in clinical use.

Statistical Methods

This was a descriptive, exploratory analysis of a subset of participants from the INHALE-3 study. Although the analysis was not powered to detect statistically significant differences overall, 2-sided paired *t* tests were conducted where relevant to assess changes over time in insulin dosing, bolus/basal ratios, and glycemic outcomes. Results for difference in dose are presented as summary statistics, including means, SDs, and proportions, where appropriate. Missing data imputation was not performed, as inclusion in the analysis required participants to have complete data across all study visits; therefore, no missing data were present in the analysis subset. Changes in insulin dosing over time were evaluated descriptively to characterize trends in total daily dose, mealtime dosing, and bolus/basal ratios. Owing to the small sample size ($N = 35$), findings should be interpreted with caution and are only intended to inform future hypothesis-driven research.

All analyses were performed using R (v4.4.0), the most current version available at the time of analysis.

Results

A total of 35 participants met the inclusion criteria for this INHALE-3 substudy (Fig. 1). The participant mean age was 46 years, with a baseline A1C of 7.72% (SD ± 1.0; 61 mmol/mol). At study entry, prior to start of TI, 40% of participants were using AID. The mean baseline bolus and basal dose of RAA insulin were 23.9 U/d, with a bolus/basal ratio of approximately 50%/50%. Baseline demographic and clinical characteristics are summarized in Table 2. Details regarding the period of recruitment, participant allocation, and study discontinuation for INHALE-3 can be accessed in the published paper and its supplement.[17]

Following initiation of TI in combination with insulin degludec, the first participant-reported total daily bolus insulin was recorded on study treatment day 4, with a mean of 36 U of TI insulin. This increased to 48 U at week 17 ($P = .002$) and 52 U at week 30 ($P < .001$; Fig. 2). The bolus/basal ratio shifted from 50%/50% using prestudy RAA insulin to 60%/40% with TI on day 4 ($P < .001$), further increased to 65%/35% at week 17 ($P < .001$), and increased to 70%/30% at week 30 ($P < .001$; Fig. 3). Additionally, A1C levels in this subset declined to 7.67% (SD ± 1.0; 60 mmol/mol) at week 17 ($P = .71$) and 7.45% (SD ± 1.1; 58 mmol/mol) at week 30 ($P = .059$).

At week 17, 57% of participants had increased their total daily TI dose by >4 U compared with study treatment day 4, 17% had decreased by >4 U, and 26% remained within 4 U. At week 30, 74% had increased by >4 U, 9% had decreased by >4 U, and 17% remained within 4 U (Table 3). Mean breakfast bolus increased from 9 U to 12 U ($P = .04$), mean lunch bolus increased from 11 U to 13 U ($P = .02$), and mean dinner bolus increased from 12 U to 15 U at week 30 ($P = .12$; Fig. 4).

At baseline, 20% of participants had a median meal bolus of 4 U, which declined to 6% at week 30. In contrast, the proportion of participants with a median meal bolus >8 U increased from 43% at baseline to 55% at week 30 (Fig. 5), indicating that most patients required more than a single 4-U cartridge per meal by the end of the study.

CGM-measured percent time below range (<70 mg/dL) in this subset was not statistically different from baseline, 1.84% (SD ± 2.2), to week 30, 2.14% (SD ± 2.9; $P = .59$).

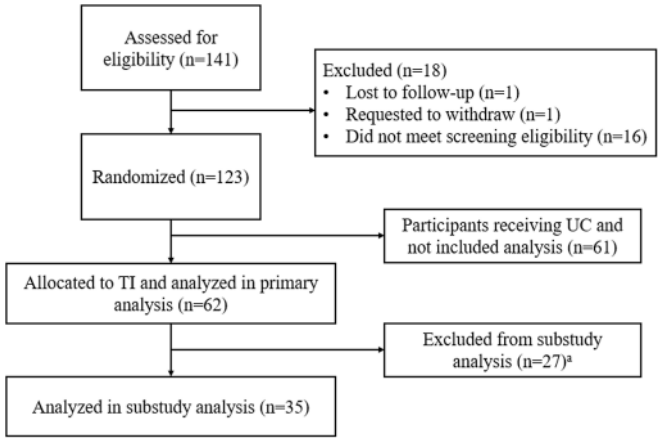

Fig. 1. Screening, allocation, and study completion for substudy analysis. [a]The inclusion criteria for the substudy were not met. Inclusion in this substudy required nonmissing data for total daily insulin doses and mealtime dosing at baseline, week 17, and week 30. *TI = Technosphere insulin; UC = usual care.*

Table 2
Baseline Participant Characteristics, INHALE-3 Substudy

Characteristic	TI + degludec ($N = 35$)
Age, mean ± SD, y	46 ± 15
Sex, female, %	51
Duration of diabetes, mean ± SD, y	25 ± 15
BMI, mean ± SD, kg/m^2	27.9 ± 4.4
Baseline insulin modality, %	
Multiple daily injections	49
Insulin pump, without automation	11
AID pump	40
A1C, mean ± SD, %	7.72 ± 1.0 (61 mmol/mol)
Baseline daily RAA insulin	
Bolus, mean ± SD, U	23.9 ± 12.7
Basal, mean ± SD, U	23.9 ± 12.3
Bolus/basal ratio, mean ± SD, %	50/50 ± 0.5

Abbreviations: AID = automated insulin delivery; BMI = body mass index; RAA = rapid-acting insulin analog; TI = Technosphere insulin.

Discussion

Summary of Key Findings

The rapid onset of action, early peak, and short duration of TI result in a lower overall insulin exposure leading to a less than unit-for-unit conversion from subcutaneous insulin doses. TI can be an effective treatment modality for some patients when titrated to glycemic effect and not limited by the initial conversion. As noted by Hirsch et al,[17] the registrational trial for TI in T1D used a conversion dose that was not clinically bioequivalent to the corresponding RAA dose and a 2:1 TI:RAA conversion reflects a more appropriate initial dose with a greater reduction in postprandial hyperglycemia.[22] Additionally, previous analysis has shown that titrated TI doses can be approximately 1.5 to 2.0 times higher than subcutaneous insulin doses.[18] Starting at a higher conversion dose may decrease the time to start achieving a favorable glucose response. In the reported substudy of INHALE-3 participants, even with starting at a higher conversion dose, further titration occurred toward achieving glycemic control. The mean A1C in the reported substudy improved at the 17 and 30 week time points, similar to the full study TI group.[17,20] The mean dose increased from 36 U to 52 U over the 30 weeks, leading to a final TI bolus/basal ratio of ~70%/30%. Pettus et al[5] also reported the need for higher TI units than RAA units. Failing to understand this difference can lead to underdosing and hyperglycemia; the conversion dose is only a starting point, with ongoing titration needed to achieve glycemic targets.[5] The mealtime doses started and remained at 4 U for some, but by 30 weeks, most of the participants were regularly taking ≥8 U as a mealtime dose, with some taking >28 U. These higher units of TI compared with RAA were not associated with an increased time in hypoglycemia as measured by CGM.

Clinical Interpretation

As clinicians gain a better understanding of how to dose TI, they can become more comfortable in using and titrating it. Although measured in units, TI is not directly comparable with subcutaneous insulin and requires a different approach to dosing.[4] The lungs provide a large vascular surface area that allows the ultrarapid absorption of TI into the systemic circulation, much like the absorption rate seen with intravenous administration of insulin. Similarly, a higher number of TI units compared with subcutaneous units are often necessary to achieve the desired glycemic response. Although the lowest

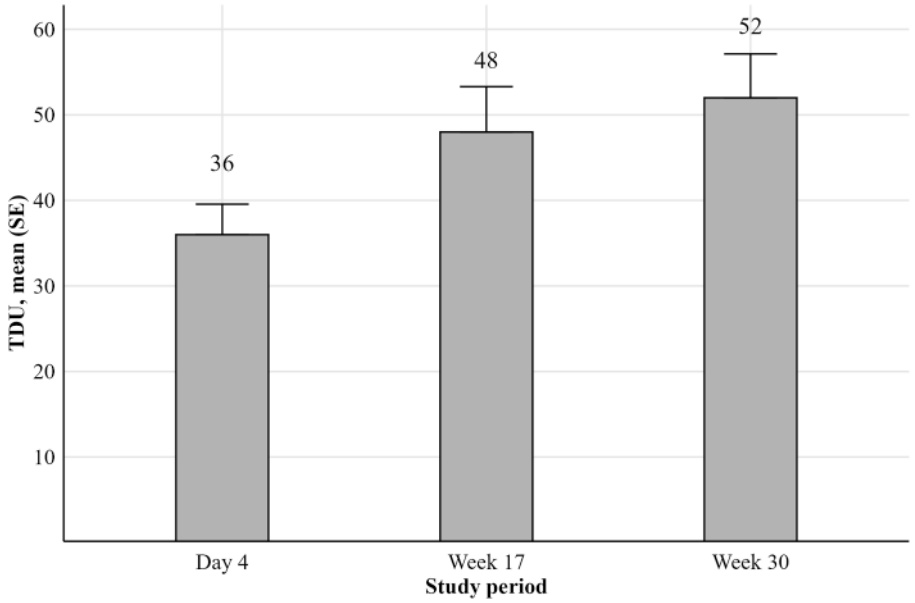

Fig. 2. TI TDU. Mean TDU ± SE used at day 4, week 17, and week 30 among participants randomized to TI. Values are rounded down to the nearest 4-U cartridge size. *TDU = total daily units; TI = Technosphere insulin.*

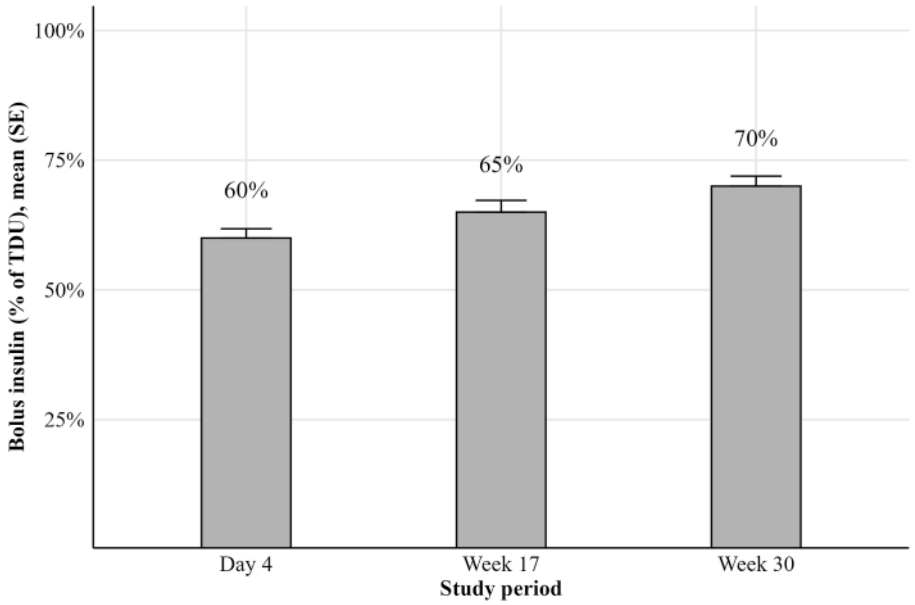

Fig. 3. TI bolus/basal ratio. Percent of total daily TI bolus insulin over time among participants randomized to TI. Values are rounded to the nearest 5% interval. *TDU = total daily units; TI = Technosphere insulin.*

Table 3
Percentage of Participants With Change in Total Daily TI From Day 4

Change in total daily TI	Week 17	Week 30
Increased by >4 U, *n* (%)	20 (57)	26 (74)
Remained within 4 U, *n* (%)	9 (26)	6 (17)
Decreased by >4 U, *n* (%)	6 (17)	3 (9)

Abbreviation: TI = Technosphere insulin.

cartridge increment is a 4-U TI dose, it did not appear to be a barrier for therapy adoption, with the majority of participants ultimately needing an increase for mealtime coverage. TI is administered at the start of a meal without the need for prebolusing. The option to deliver a corrective dose 60 to 90 minutes after the initial mealtime dose—when minimal insulin remains on board—may provide confidence in further uptitration of mealtime doses and/or corrective measures to reduce prolonged hyperglycemia. Owing to its short duration of action, TI doses exert minimal glucose-lowering effects beyond 2 hours, in contrast to RAA, which typically continues to lower glucose for 3 to 5 hours.[10] The shorter action profile of TI may reduce the risk of late-onset hypoglycemia. All these factors affect the need for individualized dosing of TI and the potential for more than just 3 inhalations a day to cover 3 presumed meals.

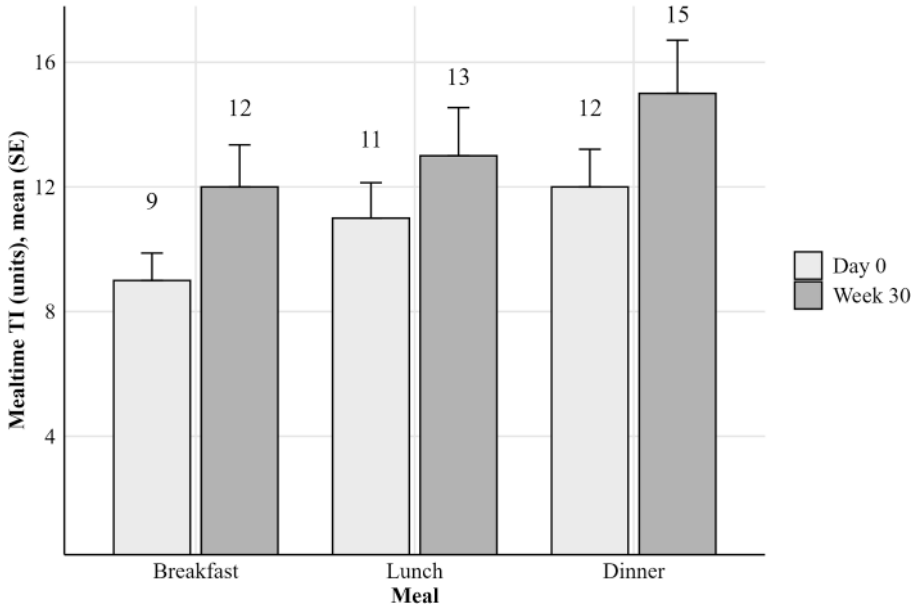

Fig. 4. TI mealtime dosing at day 0 and 30 weeks. Mean TI units by meal type at day 0 and week 30. Mean TI dose is rounded to the nearest whole number. *TI = Technosphere insulin.*

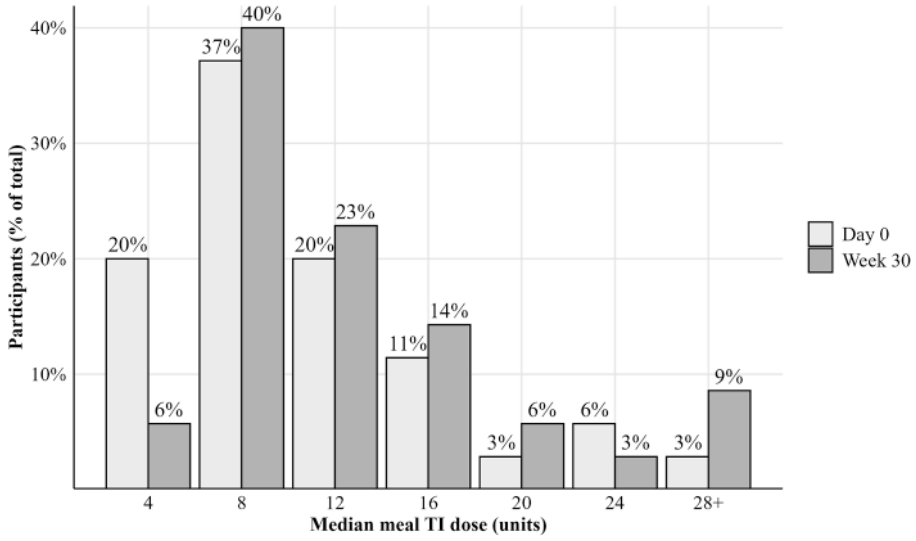

Fig. 5. Distribution of TI dose sizes by participant at day 0 and week 30. Bars represent the percentage of participants at each daily median TI dose level. *TI = Technosphere insulin.*

Safety and Tolerability

This substudy, as in others involving a higher initial conversion dose, showed no new safety signals, as described in the full study results.[17,20] Hypoglycemia is the most common side effect with all insulins, but the use of CGM has dramatically improved detection of hypoglycemia before severe events occur.[23] Even with a higher unit dosing, the TI group compared with usual care showed no statistically significant increase in time in CGM-measured hypoglycemia.[17] Consistent with previous trials, in the full 30-week evaluation, cough was the most common adverse event attributable to TI.[15] Pulmonary function testing via measurement of forced expiratory volume in 1 second (FEV_1) remained stable with no significant difference between the TI plus degludec and the usual care groups.[17,20] An FEV_1 is recommended to check at baseline, 6 months after start, and then annually.[3] If FEV_1 decreases $\geq$20% from baseline, TI discontinuation should be considered.[3]

Implications for Clinical Practice

Insulin therapy is often lifelong owing to beta-cell destruction, principally in patients with T1D but also in patients with type 2 diabetes, as well as other forms of diabetes. Initiating and maintaining insulin therapy is complicated and all encompassing. Insulin is a potentially lethal drug given to patients to self-administer multiple times a day while balancing the risk of hypoglycemia with complications from prolonged hyperglycemia. As noted in Hirsch et al,[17] postmeal hyperglycemia is common and an insulin with a rapid onset and dissipation could provide substantial glycemic control in appropriate patients. The option of TI can

be impactful for many patients owing to its unique administration and time–action profile. The burden of multiple insulin injections can be overwhelming for some, even without needle phobia, leading to intentionally and unintentionally missed doses. After long-term therapy with subcutaneous insulin administration, scar tissue and skin changes can affect quality of life and insulin efficacy. The alternate route of administration that TI provides could help improve medication management in these groups of patients. Mealtime dosing of insulin involves attention to meal composition, carbohydrate amount, and timing to match the peak activity of the insulin with the rising glucose load from a meal. With subcutaneous insulin, doses are optimally taken approximately ≥10 minutes before consuming the meal to account for the peak activity typically around ≥90 minutes after dose, with a duration that can last 3 to 5 hours. Patients are typically advised to avoid taking corrective doses 1 to 3 hours after a subcutaneous insulin injection owing to the risk of insulin stacking, which can occur when moderate levels of insulin remain active and increase the likelihood of hypoglycemia. In contrast, TI is administered at the start of a meal or shortly thereafter, with glucose-lowering effects beginning in approximately 12 minutes and peaking around 35 minutes after dose for 4 U.[3,5] This rapid onset can help manage 1 to 2-hour PPGEs. Additionally, the short duration of action of TI may allow for a corrective dose to be administered 60 to 90 minutes after the initial inhalation, with reduced risk of stacking. Dose planning and PPGEs, particularly noted on CGM, can be a source of frustration for some patients and lead to difficulty with the therapeutic regimen. The flexibility of dosing that TI provides may be an advantage to some patients. Patients who have an unpredictable eating schedule or who are exercising may benefit from an insulin that works quickly and does not have a prolonged effect. Understanding the real-world dosing of TI described in this study can help clinicians gain confidence in titrating and offering this therapy to patients who may be appropriate candidates for its use. Patients must also be informed and educated about the different time–action profile and decreased glucose-lowering activity per unit of TI compared with subcutaneous insulin to promote effective and safe dosing of TI.

Strengths and Limitations

This substudy describes clinically relevant TI dosing data over 30 weeks in a population that is often encountered in clinical practice. The participants, as a whole, improved their A1C over the 30 weeks, but as in the real world, some individuals had a worsening of their A1C after switching to TI plus degludec. TI requires active administration to achieve therapeutic effectiveness.

The substudy employed a descriptive analysis approach without formal hypothesis testing, which means that the results are presented as summary statistics rather than inferential statistics. This limits the ability to draw definitive conclusions about the TI dosing patterns. The sample size is small, with only 35 patients having complete data, which may limit the generalizability of the findings to broader populations. Additionally, the reliance on participant-reported dosing data may introduce potential biases. Future studies with larger sample sizes and rigorous statistical analyses are needed to confirm these findings and provide more robust evidence for clinical practice.

Future Directions

As treatment options expand and technology improves personalized diabetes therapy, larger and additional studies are needed to expand the use of TI. The ability to passively and accurately track doses in conjunction with CGM tracings to help inform an individual's response to TI could be greatly beneficial, particularly enhanced with a future algorithm to actively recommend dosing. Expanding the use in special populations like pregnancy where 1 and 2-hour postprandial targets are more stringent, an insulin that can truly target those time points would be ideal. TI use in patients with gastroparesis or other gastric motility disorders could be studied, focusing on TI dosing in response to delayed or enhanced glucose absorption. TI represents a potential adjunctive option, particularly in combination with other modalities such as AID systems, provided that external administration of insulin with a distinct time–action profile can be appropriately accounted for. The current landscape of insulin therapy aims to provide dynamic and safe insulin coverage. Ultimately, a better understanding of the real-world dosing and titration of TI can help direct current and future applications of this distinctive insulin.

Conclusion

In the era of real-time glucose monitoring with CGM, effective glucose management should be guided by an individual's response to their therapeutic regimen. Even when starting with a higher initial conversion dose, additional TI titration was needed to achieve glycemic targets. Most participants required at least a 4 U increase in TI over the course of the study. The mealtime doses described in the study reinforce the clinical expectation that higher TI units may be required to achieve glycemic goals. This report highlights the importance of characterizing the glycemic response to TI on an individual basis and utilizing that to personalize and optimize glucose regulation.

Disclosure

The authors are employees of MannKind Corporation and hold equity and/or stock in MannKind Corporation. The terms of this arrangement have been reviewed and approved in accordance with MannKind Corporation's policies on objectivity in research. TECHNOSPHERE is a trademark of MannKind Corporation.

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References

1. An inhaled insulin (Afrezza). *JAMA*. 2015;313(21):2176–2177.
2. US Food and Drug Administration. NDA 022472 – Afrezza (insulin human) Inhalation Powder. Silver Spring, MD: US Department of Health and Human Services; 2014.
3. MannKind Corporation. *Afrezza®* (insulin human inhalation powder, for oral inhalation use), Full Prescribing Information, MannKind Corporation, Danbury, CT, 2023.
4. Heinemann L, Baughman R, Boss A, Hompesch M. Pharmacokinetic and pharmacodynamic properties of a novel inhaled insulin. *J Diabetes Sci Technol*. 2017;11(1):148–156.
5. Pettus J, Santos Cavaiola T, Edelman SV. Recommendations for initiating use of Afrezza inhaled insulin in individuals with type 1 diabetes. *Diabetes Technol Ther*. 2018;20(6):448–451.
6. Angelo R, Rousseau K, Grant M, Leone-Bay A, Richardson P. Technosphere insulin: defining the role of Technosphere particles at the cellular level. *J Diabetes Sci Technol*. 2009;3(3):545–554.
7. Heinemann L. Inhaled insulin: dead horse or rising phoenix? *J Diabetes Sci Technol*. 2018;12(2):239–242.
8. Pfützner A, Forst T. Pulmonary insulin delivery by means of the Technosphere drug carrier mechanism. *Expert Opin Drug Deliv*. 2005;2(6):1097–1106.
9. Al-Tabakha MM. Future prospect of insulin inhalation for diabetic patients: the case of Afrezza versus Exubera. *J Control Release*. 2015;215:25–38.
10. Grant M, Heise T, Baughman R. Comparison of pharmacokinetics and pharmacodynamics of inhaled technosphere insulin and subcutaneous insulin lispro in the treatment of type 1 diabetes mellitus. *Clin Pharmacokinet*. 2022;61(3):413–422.

11. Khan AB, Ahmad A, Ahmad S, et al. Comparative analysis of inhaled insulin with other types in type 1 diabetes mellitus: a systematic review and meta-analysis. *Cureus*. 2022;14(4):e23731.
12. Liu H, Shan X, Yu J, Li X, Hu L. Recent advances in inhaled formulations and pulmonary insulin delivery systems. *Curr Pharm Biotechnol*. 2020;21(3):180–193.
13. Ludvigsson J. Insulin adverse events. *Pediatr Endocrinol Rev*. 2020;17(suppl 1):183–190.
14. Haller MJ, Jones MC, Bhavsar S, Kaiserman KB. Time-action profile of technosphere insulin in children with type 1 diabetes. *Diabetes Ther*. 2023;14(3):611–617.
15. Akturk HK, Snell-Bergeon JK, Rewers A, et al. Improved postprandial glucose with inhaled technosphere insulin compared with insulin aspart in patients with type 1 diabetes on multiple daily injections: the STAT study. *Diabetes Technol Ther*. 2018;20(10):639–647.
16. Jacobson C, Kaiserman KB, Ulloa J, et al. Safety and efficacy of inhaled Technosphere® Insulin in the postprandial period with modified initial dose conversion. *Diabetes Ther*. 2025;16(8):1695–1705.
17. Hirsch IB, Beck RW, Marak MC, et al. A randomized trial comparing inhaled insulin plus basal insulin versus usual care in adults with type 1 diabetes. *Diabetes Care*. 2025;48(3):353–360.
18. Kendall DM, Manoukian J, Krueger JA, et al. 1023-P: dose titration and clinical effects of inhaled technosphere insulin compared with mealtime subcutaneous (SC) analog insulin therapy in type 1 diabetes (T1D). *Diabetes*. 2020;69(supplement_1):1023–P.
19. Kaiserman KB, Christiansen M, Bhavsar S, et al. Reduction in postprandial peak glucose with increased technosphere insulin dosage. *J Diabetes Sci Technol*. 2024;18(2):397–401.
20. Beck RW, Bailey RJ, Klein KR, et al. Inhaled Technosphere insulin plus insulin degludec for adults with type 1 diabetes: the INHALE-3 extension study. *Diabetes Technol Ther*. 2025;27(3):170–178.
21. Hirsch IB, Beck RW, Marak MC, et al. A randomized comparison of postprandial glucose excursion using inhaled insulin versus rapid-acting analog insulin in adults with type 1 diabetes using multiple daily injections of insulin or automated insulin delivery. *Diabetes Care*. 2024;47(9):1682–1687.
22. Bode BW, McGill JB, Lorber DL, et al. Inhaled Technosphere insulin compared with injected prandial insulin in type 1 diabetes: a randomized 24-week trial. *Diabetes Care*. 2015;38(12):2266–2273.
23. van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol*. 2016;4(11):893–902.