Glucose Excursion in Response to Inhaled Insulin, INHALE-3 Study

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OBJECTIVE

To evaluate the glycemic profile of inhaled Technosphere Insulin (TI) doses in adults with type 1 diabetes using clinical trial CGM data from the INHALE-3 study.

CONCLUSIONS

- TI doses administered during euglycemia resulted in a stable post-bolus aggregate glycemic profile across participants.
- These findings highlight the rapid onset and short duration of TI action, supporting its role as a uniquely flexible mealtime insulin with minimal late postprandial glycemic excursions.

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INTRODUCTION

Inhaled Technosphere Insulin (TI) is an ultra-rapid acting insulin with a unique pharmacokinetic and pharmacodynamic profile. In studies compared to subcutaneous rapid-acting analogs (RAA), TI demonstrates a significantly faster onset and shorter duration of action, enabling the potential for lower postprandial glucose excursions.

Despite advances in insulin delivery, a substantial proportion of patients with type 1 diabetes do not achieve their glycemic targets, particularly in the postprandial period. RAA insulins often peak too late to effectively control postprandial glucose without the risk for late hypoglycemia.

INHALE-3 was a clinical study conducted to determine efficacy and safety of 17 week exposure to TI therapy in patients with type 1 diabetes compared to usual care regimens, followed by a 13 week extension (Figure 1). In a previously presented analysis of standardized meal challenges comparing TI at initial dose, TI after dose optimization, and usual care, TI demonstrated improved post-prandial control in the 120 minute postprandial period (Figure 2)[1].

TI is approved for use in adults in USA, Brazil, and India, available in three color-coded dosage cartridges: 4U (blue), 8U (green), and 12U (yellow)[2].

METHODS

Study Design

This subanalysis of the INHALE-3 trial included adults with type 1 diabetes randomized to TI plus insulin degludec (up to 30 weeks) or usual care (up to 13 weeks using TI during the study extension). During TI treatment, all participants wore real-time continuous glucose monitors (CGM) and had the option to use an electronic dose logger device used under development to timestamp TI boluses.
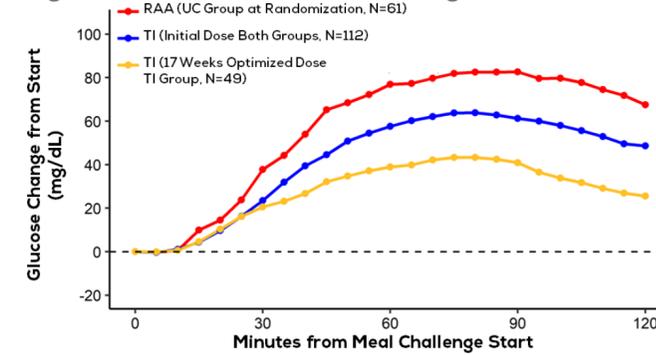
INHALE-3 Inclusion Criteria

- Age ≥18 years
- T1D for ≥6 months
- Stable treatment regimen ≥3 months
- HbA1c <11.0% and ≤20% of participants <7%
- Total daily insulin dose 20-100 units
- ≥70% CGM utilization over 14-day period

Figure 1. INHALE-3 Study Design

Screening	Randomized Treatment (17 Weeks)	Treatment Extension (13 Weeks)

Randomization

TI + Basal (N=62)

Usual Care → Usual Care (N=61) → TI + Basal (N=100)

Figure 2. INHALE-3 Meal Challenges*

- RAA (UC Group at Randomization, N=61)
- TI (Initial Dose Both Groups, N=112)
- TI (17 Weeks Optimized Dose TI Group, N=49)

*Lines represent means. TI initial dose is combining the TI group at randomization and the Usual Care (UC) group using TI at 17 weeks. TI optimized dose is from the TI group at 17 weeks. RAA is the UC group at randomization. RAA was dosed 5–15 minutes prior to or to the start of the meal and TI was dosed immediately prior to the meal.

Statistical Methods

CGM profiles were aligned to TI boluses using criteria to isolate the effects of a single insulin dose:

- No other TI dose occurred within ±180 minutes
- 5-minute CGM data were available and complete from 30 minutes before to 180 minutes after the dose
- Pre-dose CGM values were within 70-180 mg/dL in the 30 minute period before the dose

Individual median CGM profiles were aggregated across participants using percentile bands (5th, 25th, 75th, 95th).

Time in range metrics were derived from post-dose CGM values from 0–180 minutes for each profile. Participant level medians were aggregated to generate cumulative distribution curves for time in range (70-180 mg/dL), time above range (>180 mg/dL) and time below range (<70 mg/dL).

RESULTS

Fifty-four participants (Table 1) had TI boluses and CGM data that met isolation criteria. A total of 1039 TI doses were analyzed (average of 19.2 doses per participant).

Table 1. Participant Demographics

Parameter	N=54
Age, Years Mean (SD)	45 (15)
Sex, % Female	57%
Baseline HbA1c, % Mean (SD)	7.3 (0.8)

The aggregated CGM profile demonstrated minimal glycemic change over 180 minutes post-TI dose with the majority of the distribution remaining within the euglycemic range. The change in median glucose is 6.7 mg/dL from t=0 to t=60 minutes and 16.8 mg/dL from t=0 to t=120 minutes (Figure 3).

In the 180-minute window following insulin administration, 72.2% of participants achieved time in range >70%, 98.1% maintained time below range <4%, and 74.1% kept time above range <25%, consistent ADA glycemic targets (Figure 4).

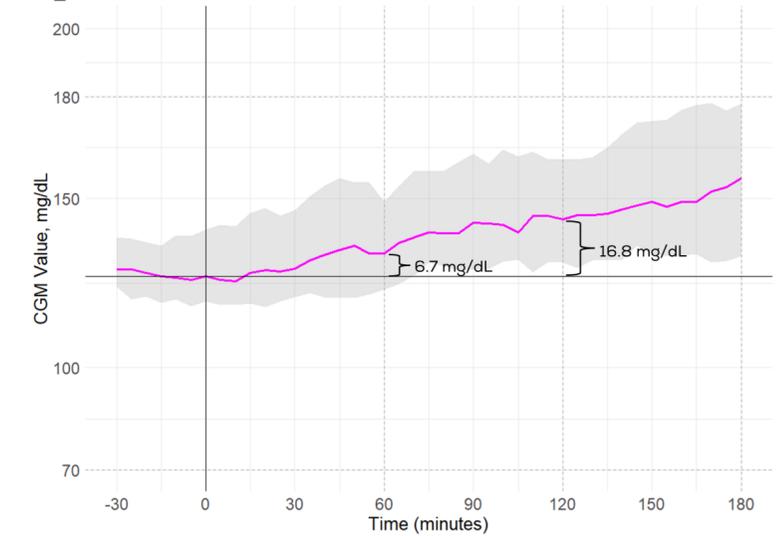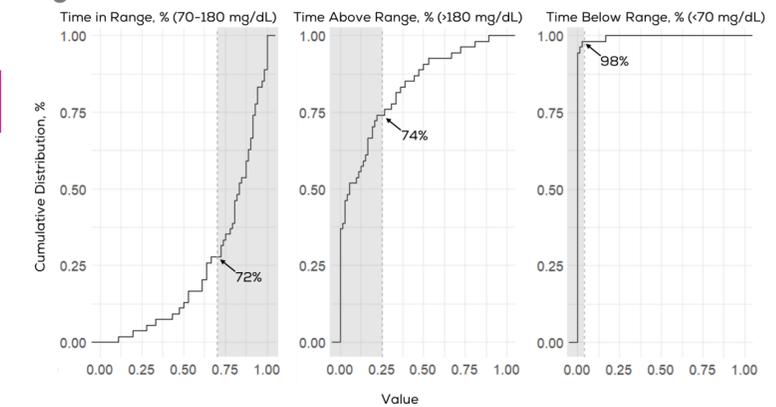### Figure 3. CGM Profile from TI Bolus (Median, IQR)

Figure 4. CGM Cumulative Distributions, t=0-180 min

1. Weinstock RS. Technosphere Insulin Versus Rapid Acting Analogue During Standardized In-clinic Meal Challenges. Oral presentation at: 84th Scientific Sessions of the American Diabetes Association; June 22, 2024; Orlando, FL. Symposium: INHALE-3.
2. Afrezza (insulin human) Inhalation Powder Prescribing Information. MannKind Corporation. Danbury, CT; February 2023.