Inhaled Insulin Dosing in a Randomized Trial in Adults with Type 1 Diabetes (T1D)

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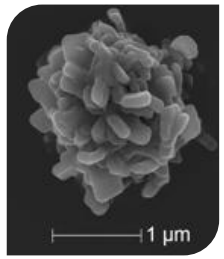
Technosphere Insulin (insulin human) Oral Inhalation Delivery[1]

Technosphere
Microparticles (FDKP)



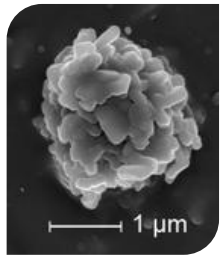
Water

+

Human Regular Insulin Monomers

=

Technosphere *Insulin* (TI)

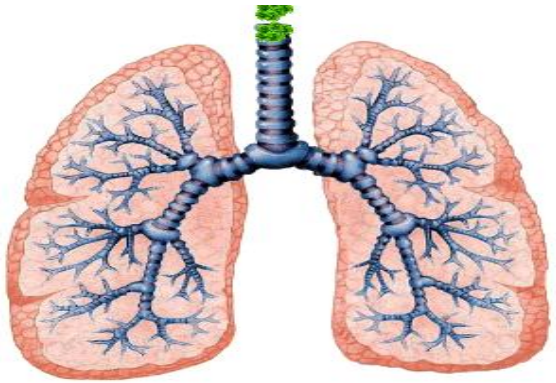


Breath-Powered Oral Inhalation of Dry Powder

pH <6
Technosphere Insulin

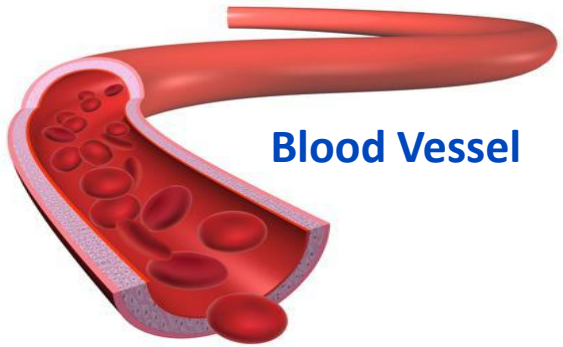
Insulin adsorption onto FDKP particle

Bis-3,6(4-fumarylaminobutyl)-2,5-diketopiperazine



pH >6 (physiologic pH)

- Small particle size travels to deep lung
- Inhaled particles dissolve rapidly across alveolar membrane and separate
- FDKP and insulin are absorbed in the systemic circulation



Insulin | FDKP

[1]Pfützner A, et al. *Expert Opin Drug Deliv*. 2005;2(6):1097-1106.

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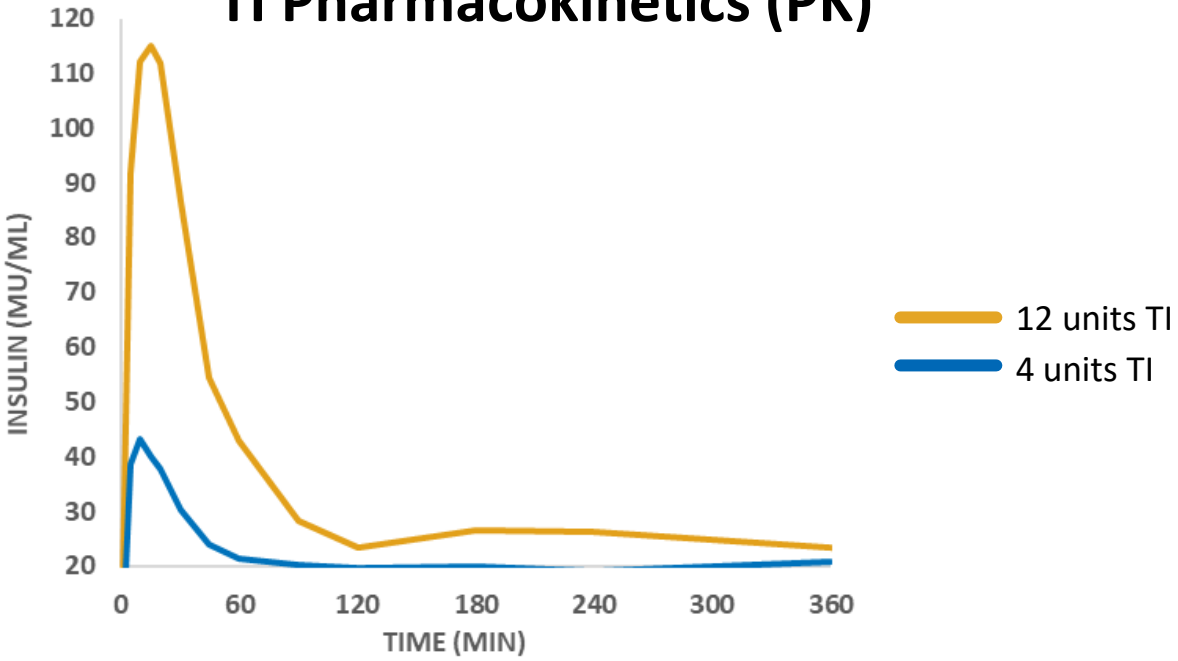
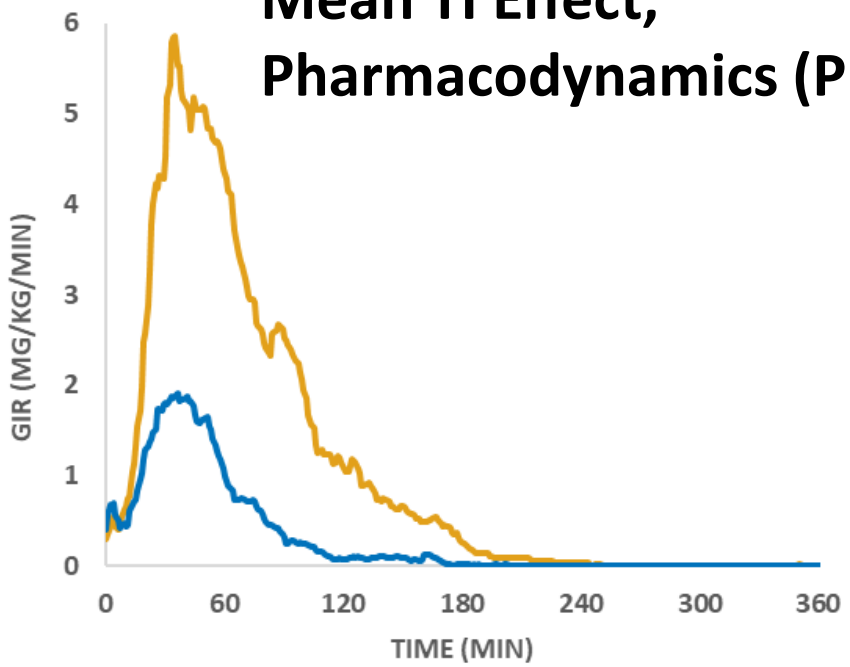
Inhaled Insulin PK/PD Profile[1]

TI Pharmacokinetics (PK)



Mean TI Effect, Pharmacodynamics (PD)



Parameter for Insulin Effect	TI 4 units	TI 12 units	TI 48 units
Time to first measurable effect	~12 minutes	~12 minutes	~12 minutes
Time to peak effect	~35 minutes	~45 minutes	~55 minutes
Time for effect to return to baseline	~90 minutes	~180 minutes	~270 minutes

[1]Afrezza® (insulin human) Inhalation Powder Prescribing Information. MannKind Corporation.

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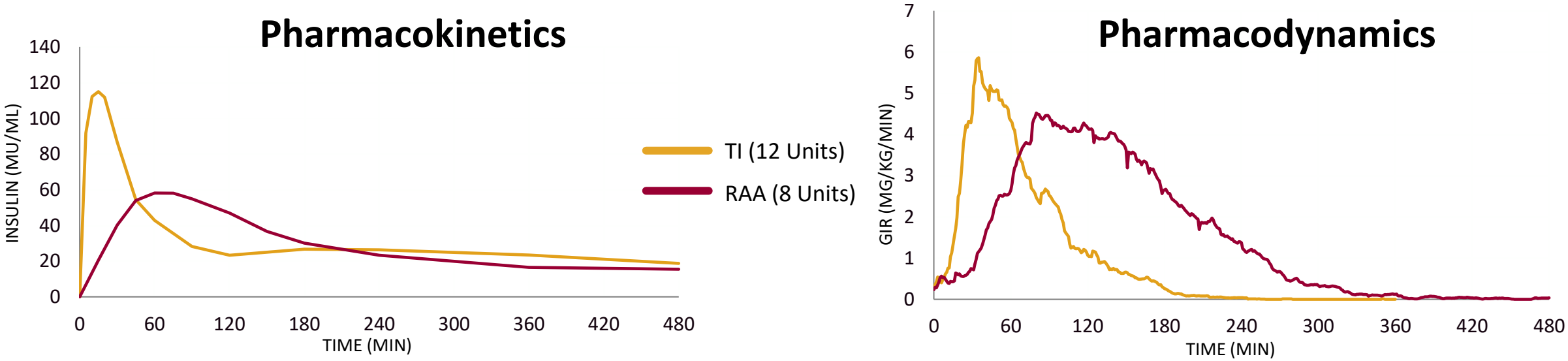
Insulin Effect is a Function of Delivery[1,2]

Inhaled insulin is not unit-to-unit equivalent to subcutaneous rapid-acting insulin (RAA)

- From euglycemic clamp studies: faster insulin absorption is associated with higher peak concentration, but a shorter duration of exposure
- Regular human insulin given IV is 100% bioavailable[3], but overall has a decreased glucose lowering effect due to the short duration compared to subcutaneous administration



- The glucose lowering impact of TI occurs earlier with a shorter duration and lower overall glucose disposal compared to subcutaneous rapid acting insulin
- The GIR (SD) AUC, mg/kg/min for TI (12 Units) is 397.1 (201.5) versus 701.1 (355.5) for RAA (8 Units)
- The shorter duration of activity may allow a separate TI dose to be given 60-120 minutes with minimal insulin on board

[1]Adapted from Heinemann L, et al. *J Diabetes Res*. 2018;2018:4568903. [2]Adapted from Grant M, et al. *Clin Pharmacokinet*. 2022;61(3):413-422. [3]Howey D, Bowsher R, Brunelle R, Woodworth J. *Diabetes*. 1994;43:396–402.

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Dosing of Inhaled Insulin[1]

Mealtime TI Starting Dose Conversion Table

Injected Mealtime Insulin Dose (RAA units)	TI Dose (TI units)
1-4	4
5-8	8
9-12	12
13-16	16
17-20	20
21-24	24

4-Unit Cartridge | 8-Unit Cartridge | 12-Unit Cartridge

(Cartridges not to scale)

- 3 available cartridges sizes
- Doses can be made with combinations of cartridges taken in series
- Titrate to glycemic effect
- After titration, final TI dose can be 40-80% more than RAA doses[2,3]

[1]Afrezza® (insulin human) Inhalation Powder Prescribing Information. MannKind Corporation. [2]Kendall DM, Manoukian J, Krueger JA, et al. *Diabetes*, 2020;69(Supplement_1), 1023-P. [3]Kendall DM, Krueger JA, Abaniel R, et al. Poster presentation at: *American Diabetes Association's 80th Scientific Sessions*; June 2020; Virtual.

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Higher Initial Dose in DOS Study[1]

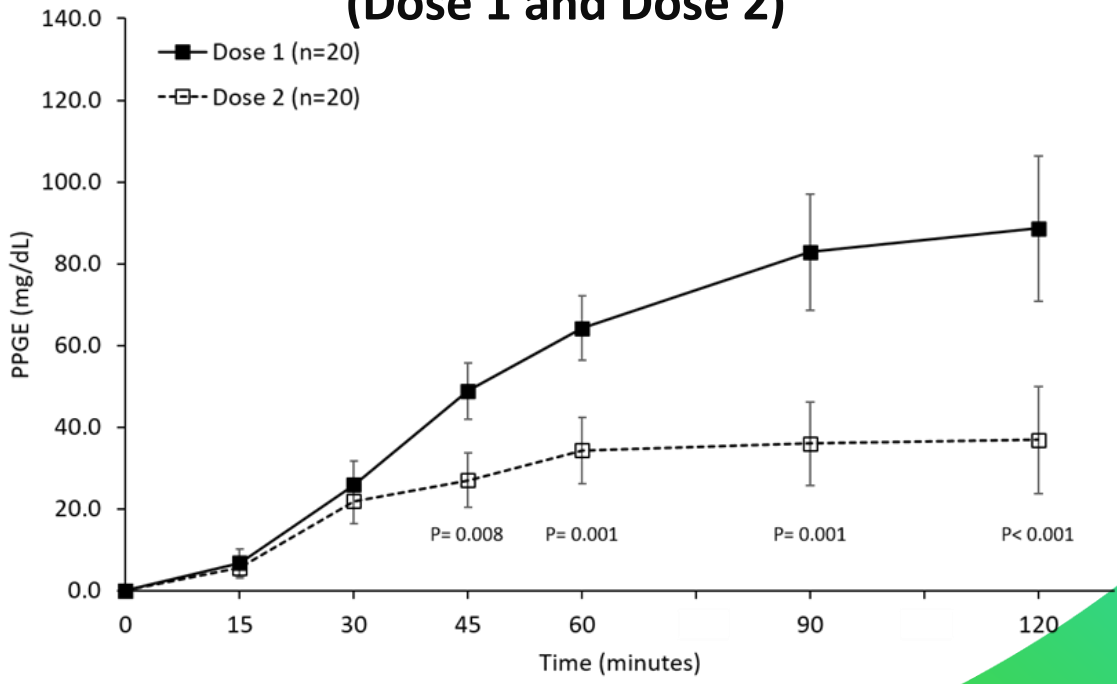
A study of patients with T1D and T2D (n=20) evaluating efficacy and safety of the USPI dose (**dose 1**) compared to a modified initial conversion ratio of ~2:1 for TI and SC RAA (**dose 2**)

- **Dose 2 was shown to have significant reductions** in postprandial glucose excursion (PPGE), from 45 minutes to 120 minutes from start of meal, when compared with Dose 1.
- Two hypoglycemia events were observed in a single subject after receiving Dose 2. No serious adverse events were observed.

Dose 2: Modified Dose Conversion Table

Injected Mealtime Insulin Dose (RAA units)	TI Dose (TI units)
<4	4
4-5	8
6-7	12
8-9	16
10-11	20
12-13	24

Mean PPGE (±SE) in the 2-hour postprandial period (Dose 1 and Dose 2)

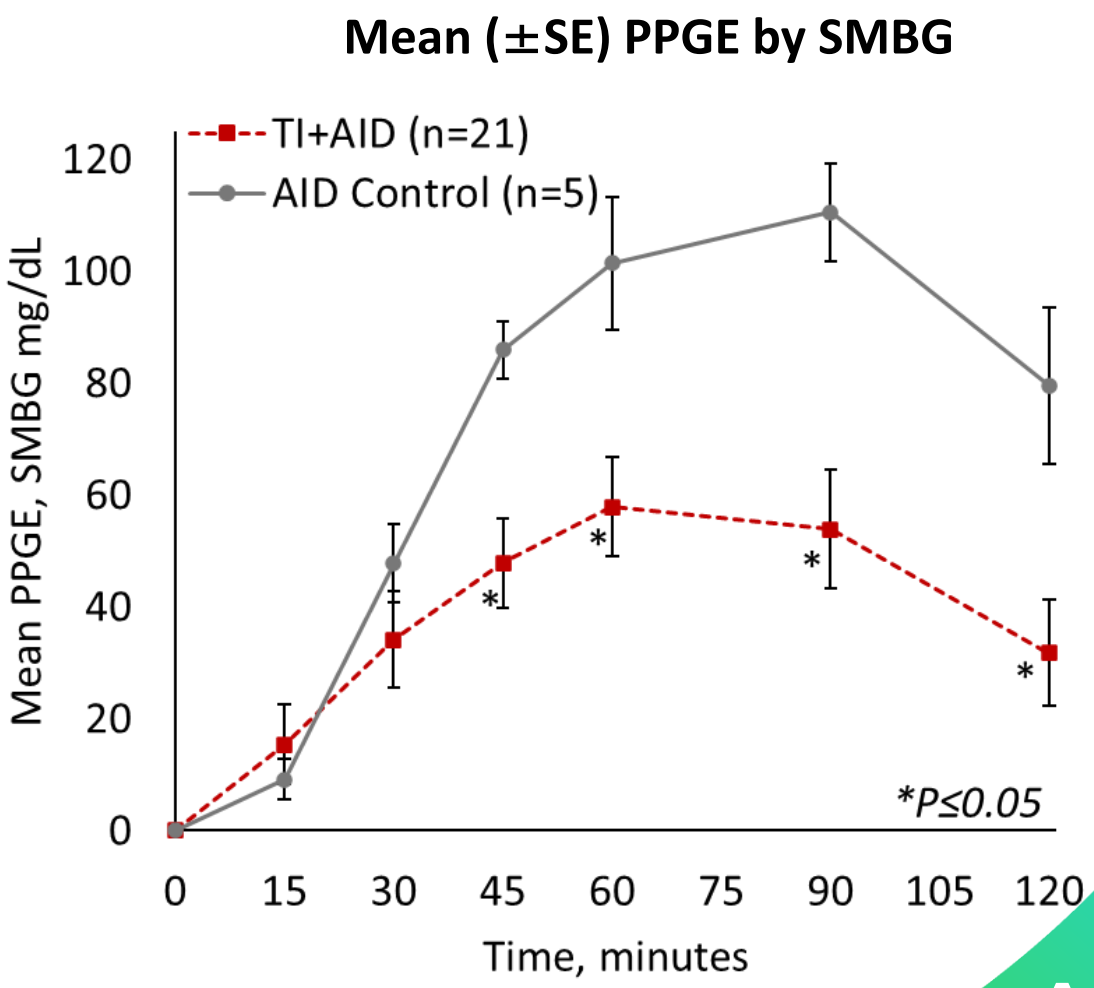


[1]Kaiserman KB, Christiansen M, Bhavsar S, et al. *J Diabetes Sci Technol*. 2022;19322968221110622.

Higher Initial Dose in ABC Study[1]

A study of patients with T1D, evaluating efficacy and safety of TI + automated insulin-delivery (AID) compared with AID-administered RAA control

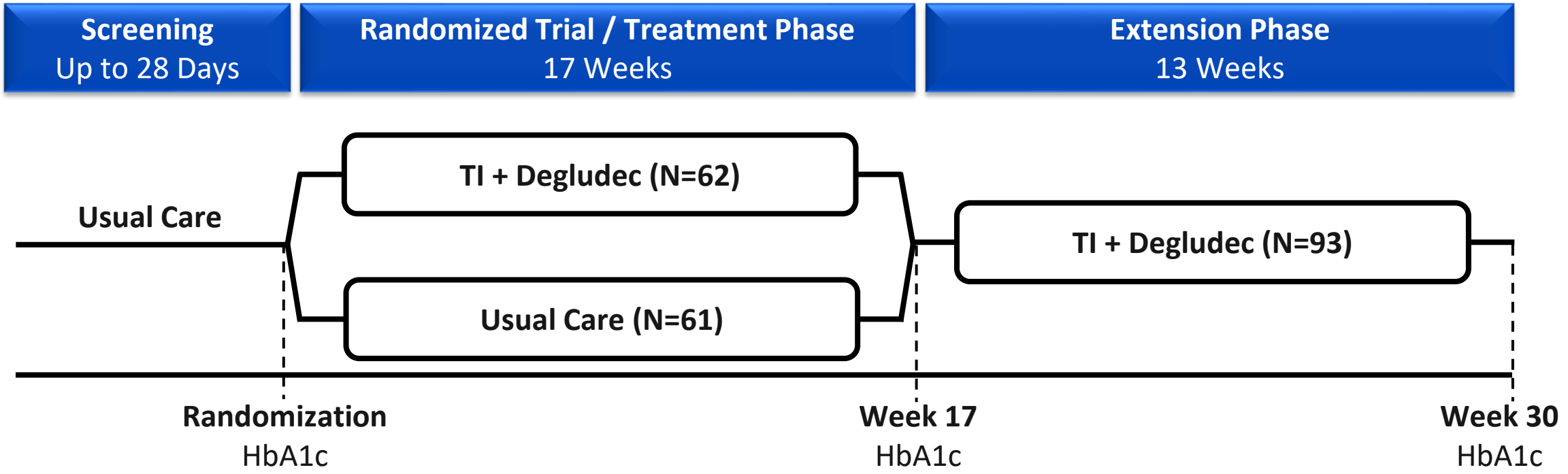
- The TI + AID group received the modified ~2:1 dose of TI, calculated by doubling their usual RAA dose and rounding down to the nearest four-unit cartridge of TI
- **PPGE was significantly reduced** in the TI + AID group at timepoints 45-120 minutes following the meal compared to AID Control ($p \leq 0.05$)
- There was one event of asymptomatic level 1 hypoglycemia in the TI + AID group



[1]Kaiserman K., et al. Oral presentation at: *Advanced Technologies & Treatments for Diabetes Conference*; February 2023; Berlin & Online. http://doi.org/10.1089/dia.2023.2525.abstracts

INHALE-3 Study Design[1]

30-week study comparing TI + Degludec and Usual Care in Type 1 Diabetes



- TI + Degludec started with modified ~2:1 dosing; demonstrated similar HbA1c outcomes compared to Usual Care (UC)
- TI + Degludec patients completed 30 weeks with no missing dosing data (N=35)

[1]Hirsch IB, Beck RW, Marak MC, et al. Diabetes Care. vol 48,00 (2025): 1-8. 2. ClinicalTrials.gov identifier: NCT05904743. Accessed January 17, 2024. https://clinicaltrials.gov/study/NCT05904743

INHALE-3 Patient Characteristics

Patients randomized to TI and completed 30 weeks with no missing dosing data

	TI + Degludec (N=35)
Age (years), Mean (SD)	46.3 (14.6)
Sex – Female, *n* (%)	18 (51%)
Duration of Diabetes (years), Mean (SD)	25.3 (14.9)
BMI (kg/m^2), Mean (SD)	27.9 (4.4)
Baseline Insulin Modality Injections, *n* (%) Pump (without automation), *n* (%) AID (Automated Insulin Delivery) Pump, *n* (%)	 17 (49%) 4 (11%) 14 (40%)
Baseline HbA1c (%), Mean (SD)	7.7 (1.0)
Daily Baseline RAA Insulin (Units) Bolus, Mean (SD) Basal, Mean (SD) Basal:Bolus Ratio, % (SD)	 23.9 (12.7) 23.9 (12.3) 50/50 (0.5)

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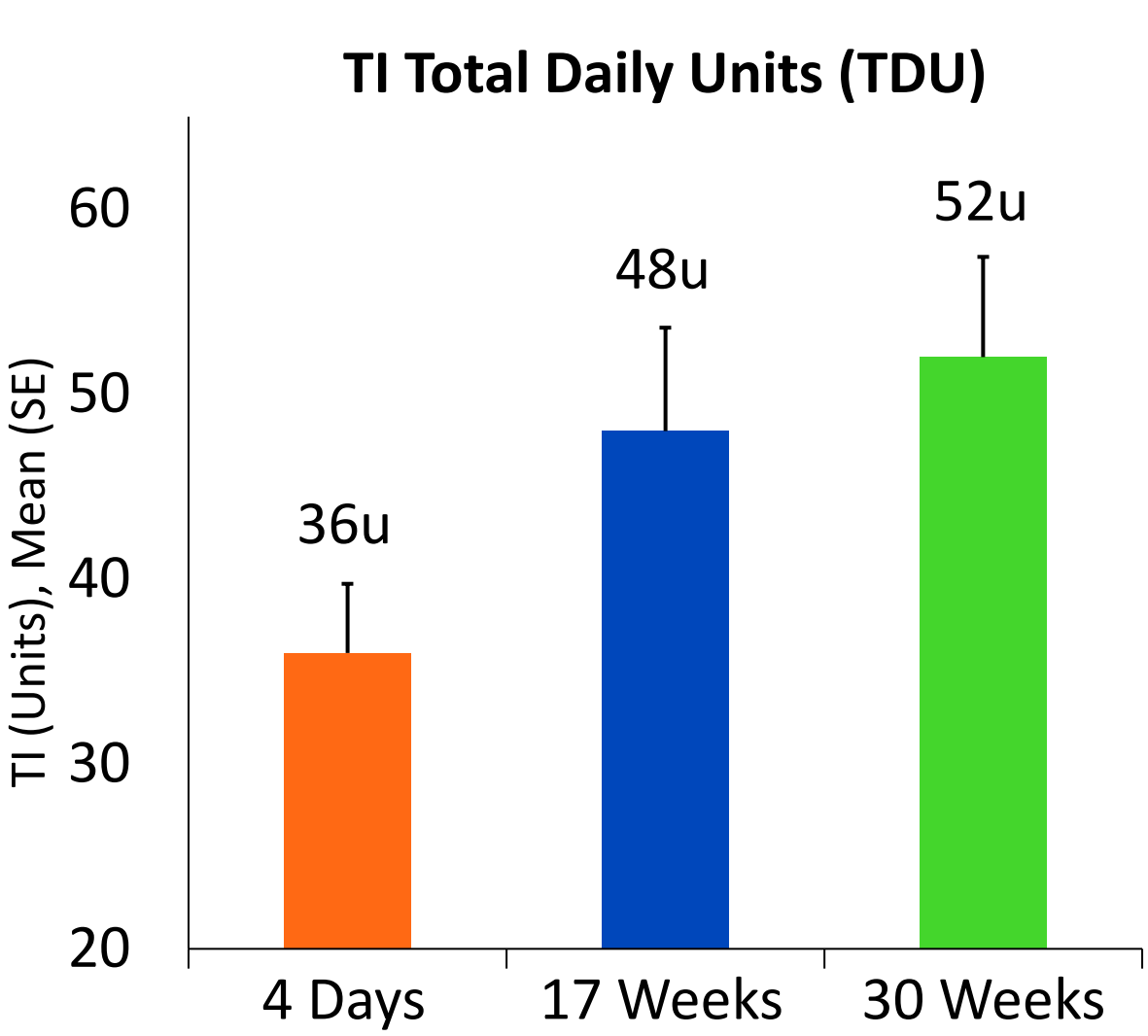
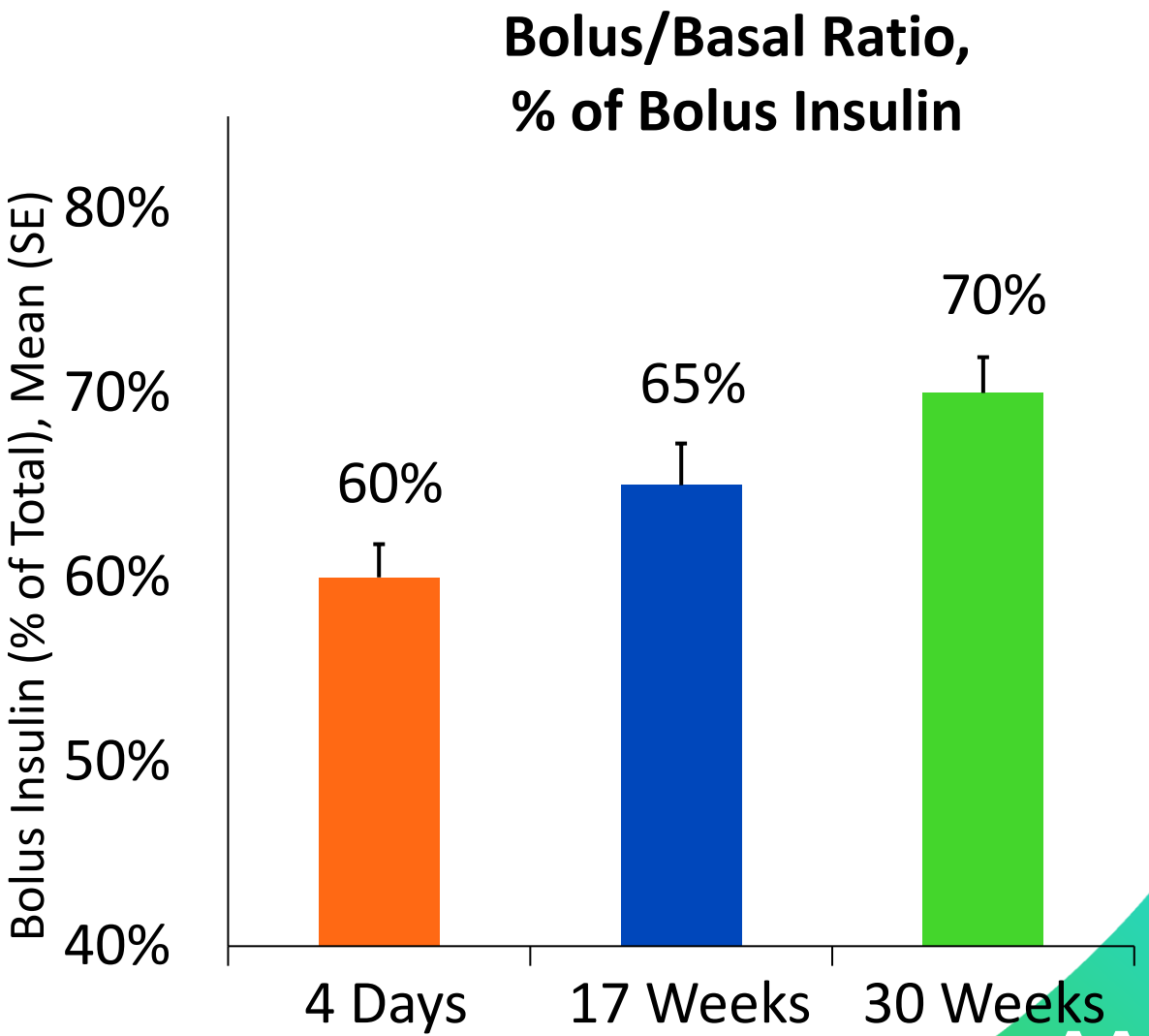
Inhaled Insulin Titration (TI Units)





Average total daily units rounded down to the nearest 4-unit cartridge size. Bolus/Basal ratio rounded to nearest 5 percent interval. N=35 subjects randomized to TI and completed 30 weeks with no missing dosing data.

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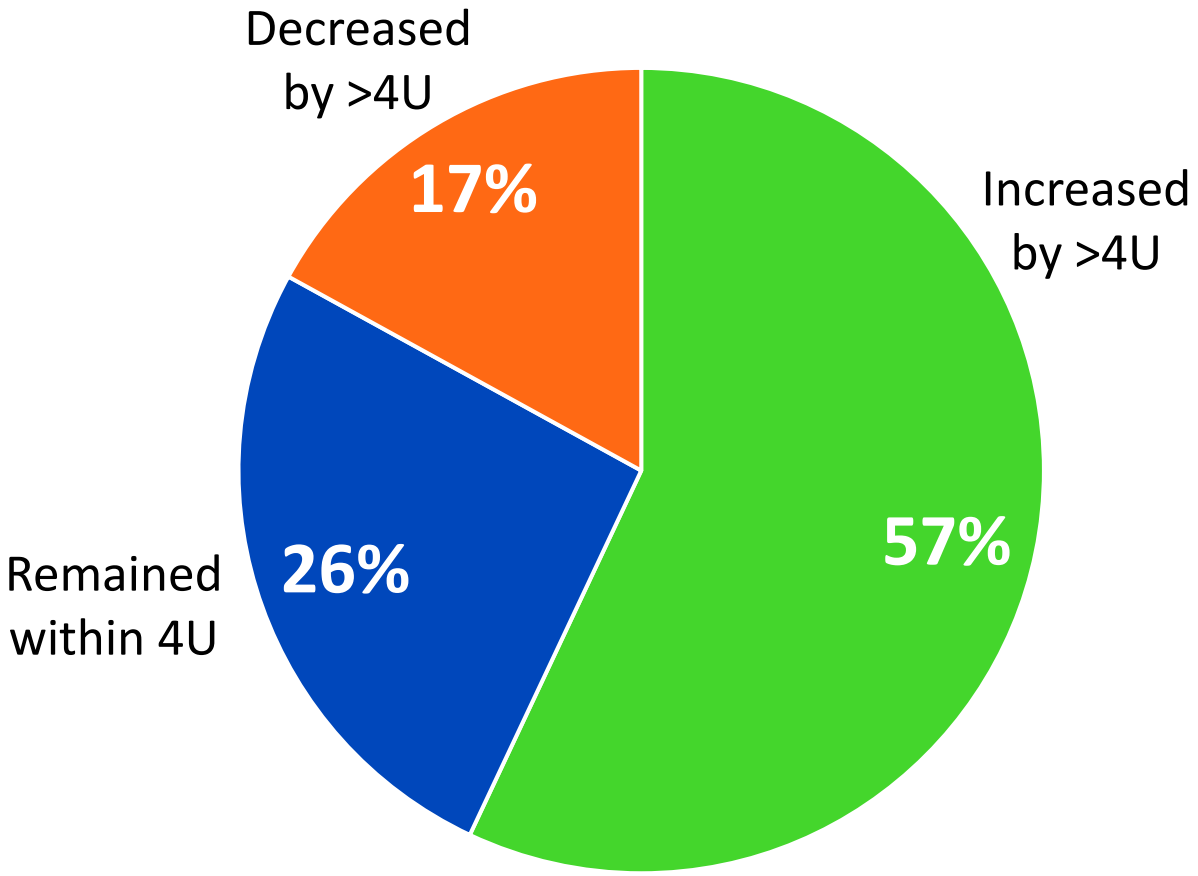
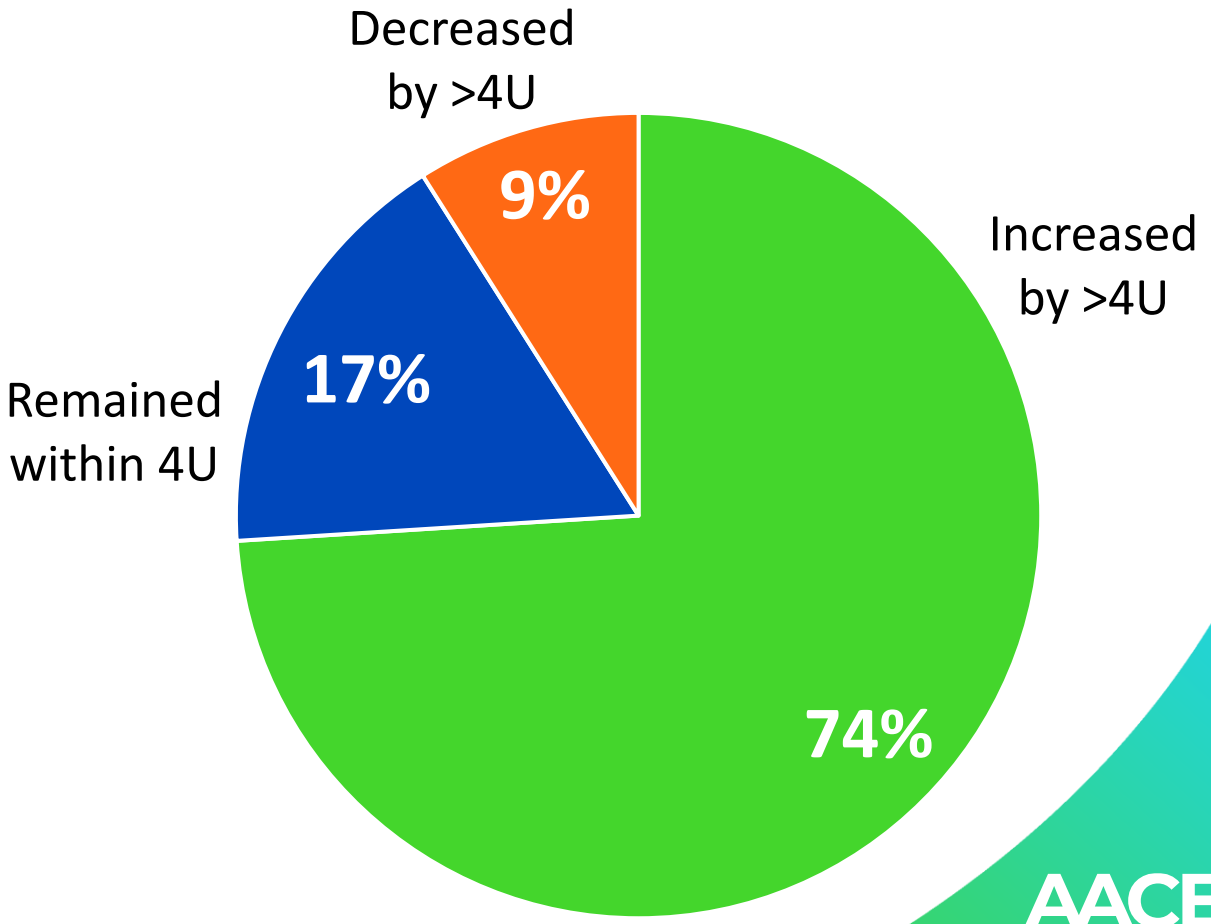
Patients with TI Dose Changes from Day 4 (TDU)

17 Weeks, %



30 Weeks, %



Change from Day 4. Total Daily Units at Day 4 rounded down to 4 unit intervals. N=35 subjects randomized to TI and completed 30 weeks with no missing dosing data

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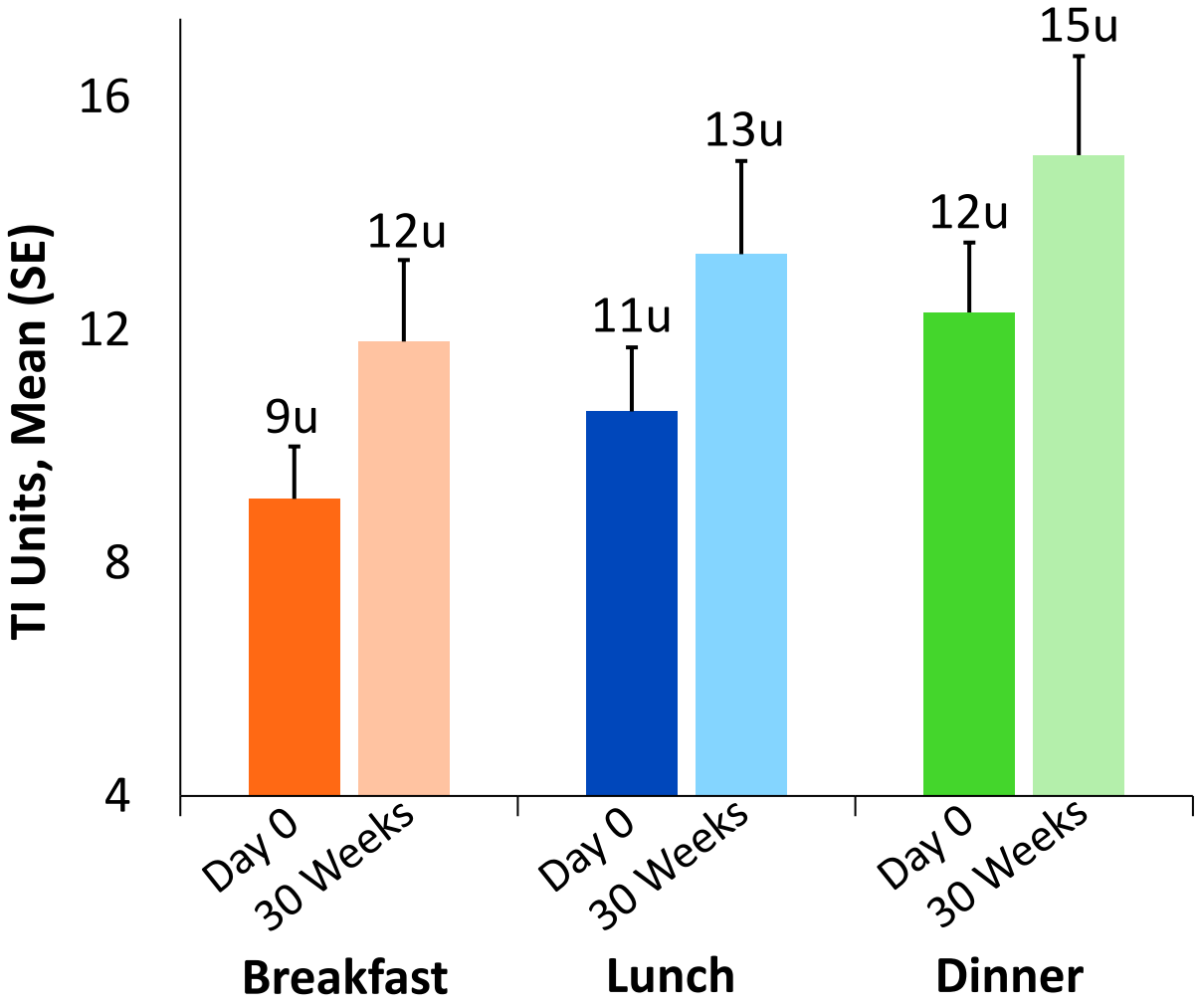
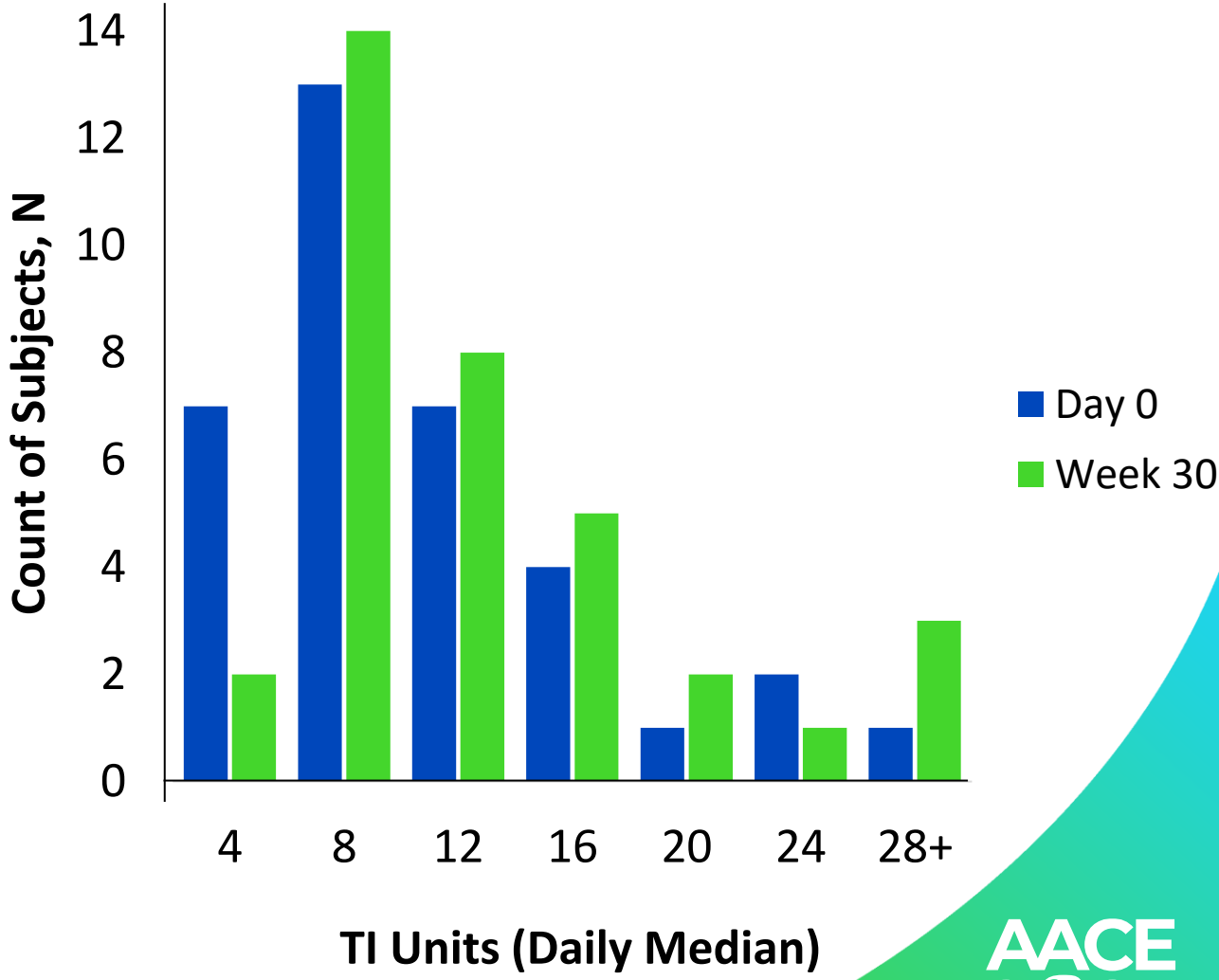
Meal-Time Dosing

TI Dosing by Meal Type



TI Dose Size by Subject



Day 0 was first prescribed dose by the investigator; 30 weeks was the patient-reported current dose at the 30 week visit. Mean dose by meal is the average across all subjects. Median dose by subject is the median meal dose of breakfast, lunch, and dinner. N=35 subjects randomized to TI and completed 30 weeks with no missing dosing data.

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Safety

Across all INHALE-3 patients over the 30-week trial, no new safety signals were identified

Hypoglycemia

- CGM-measured hypoglycemia was similar between groups for glucose <70 mg/dL and <54 mg/dL[1]
- One severe hypoglycemia event was reported in the TI group, which was adjudicated as being unlikely related to TI[1]
- One severe hypoglycemia event was reported during the Extension Phase in the UC to TI group due to delay in starting meal after TI dose[2]

Adverse Events

- Two serious adverse events were reported in the UC group due to hospitalization: one for hyperglycemia/ketosis and one for appendectomy[1]
- The most commonly reported adverse event in the TI group was cough, consistent with previous TI clinical trials. Cough was generally described as brief, at time of inhalation[1-3]

Pulmonary Function

- No statistically significant between-group difference in FEV_1[1]

[1]Hirsch IB, Beck RW, Marak MC, et al. *Diabetes Care*. 2025;48 (3): 353-360. [2]Beck RW, Bailey RJ, Akturk HK, et al. *Diabetes Technol Ther*. 2025 27:3, 161-169. [3]Beck RW, Bailey RJ, Klein KR, et al. *Diabetes Technol Ther*. 2025 27:3, 170-178

Summary

- TI has a unique delivery method, bioavailability, and pharmacodynamics leading to a difference in clinical effect per unit compared to RAA
- Many subjects still needed additional TI titration toward glycemic control goals and a small number needed a decrease or maintained the initial higher conversion dose during the INHALE-3 trial
- No new safety events compared to usual care were reported
- Every patient has individual insulin needs that can change based on meal patterns, physical activity, illness or concurrent medications and this study helps characterize typical TI-based doses

Questions?

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