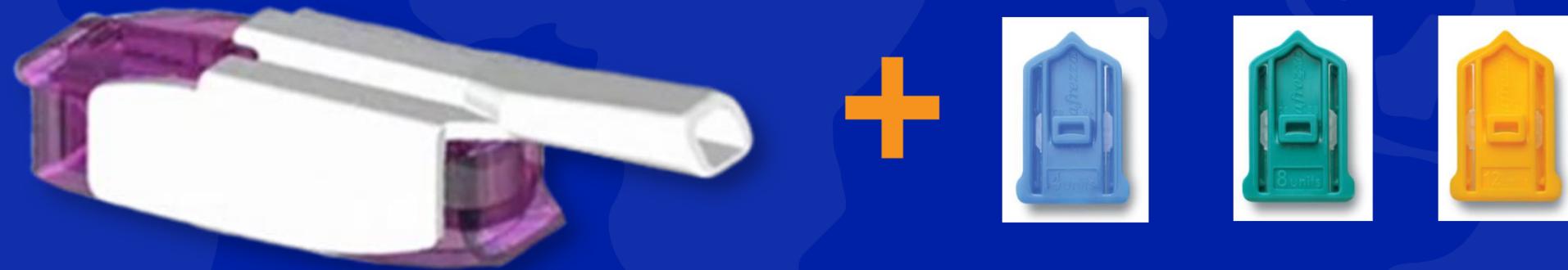


Inhaled Insulin in Pediatrics

Michael Haller, MD



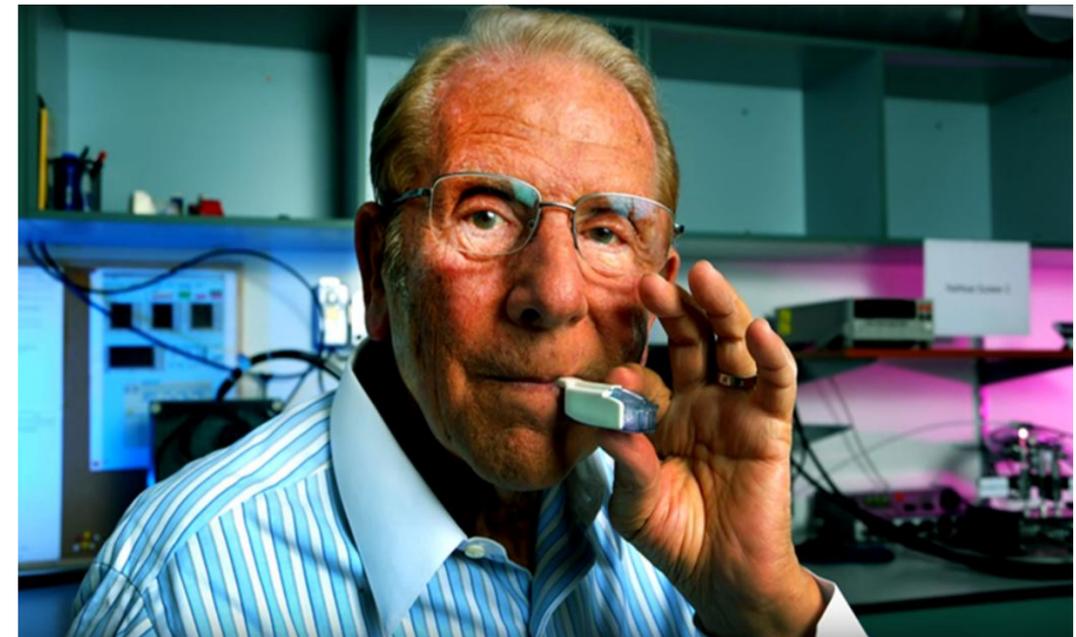
Cartridges not to scale

Disclosures

- MannKind - Consultant and Scientific Advisory Board Member
- SAB Bio - Consultant and Scientific Advisory Board Member
- Sanofi – Consultant

History of Technosphere Insulin

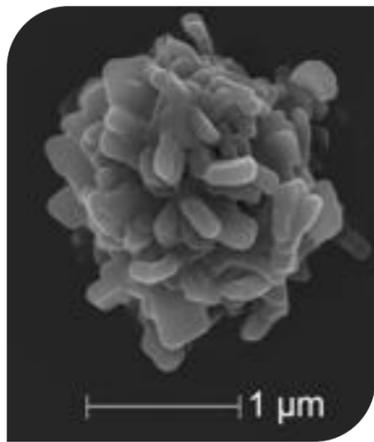
- 1997 - Al Mann - Dry powder insulin to achieve more rapid absorption than possible with SQ injections
- 20+ years... Technosphere Insulin (Afrezza®) to market
- FDA approved in 2014
- Licensed to Sanofi in 2014 and returned to MannKind in 2016



Technosphere Insulin Inhaled Delivery

Technosphere

Microparticles (FDKP)



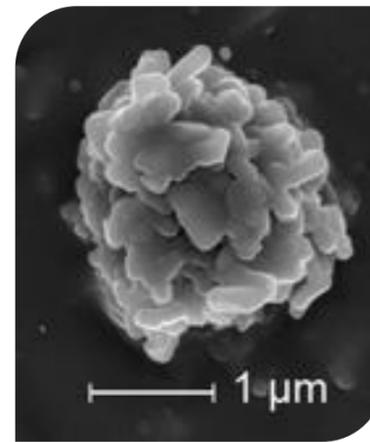
Water

+



Human Regular Insulin

=



pH < 6

Technosphere Insulin:

Insulin adsorption onto

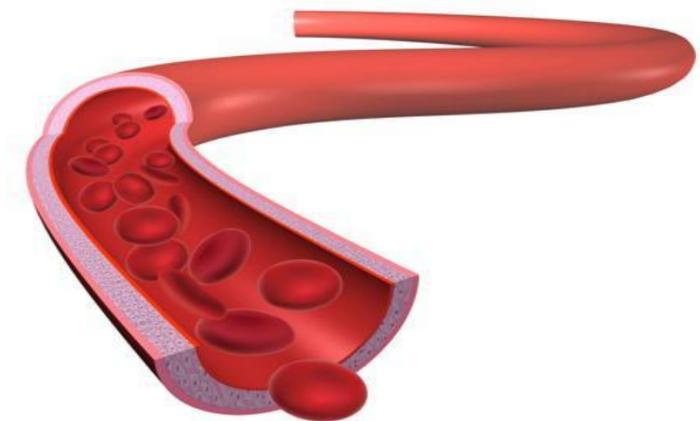
FDKP particle

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

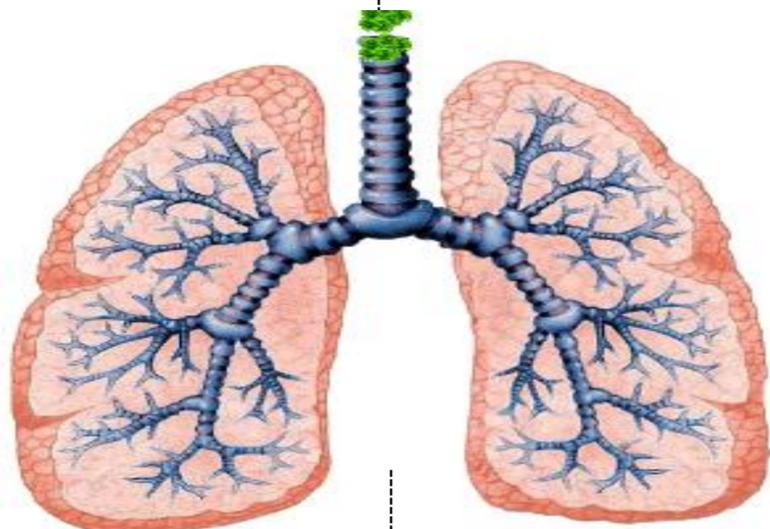
pH > 6 (physiologic pH)

- Inhaled particles dissolve rapidly and separate
- FDKP and insulin are then quickly absorbed across the lung membrane

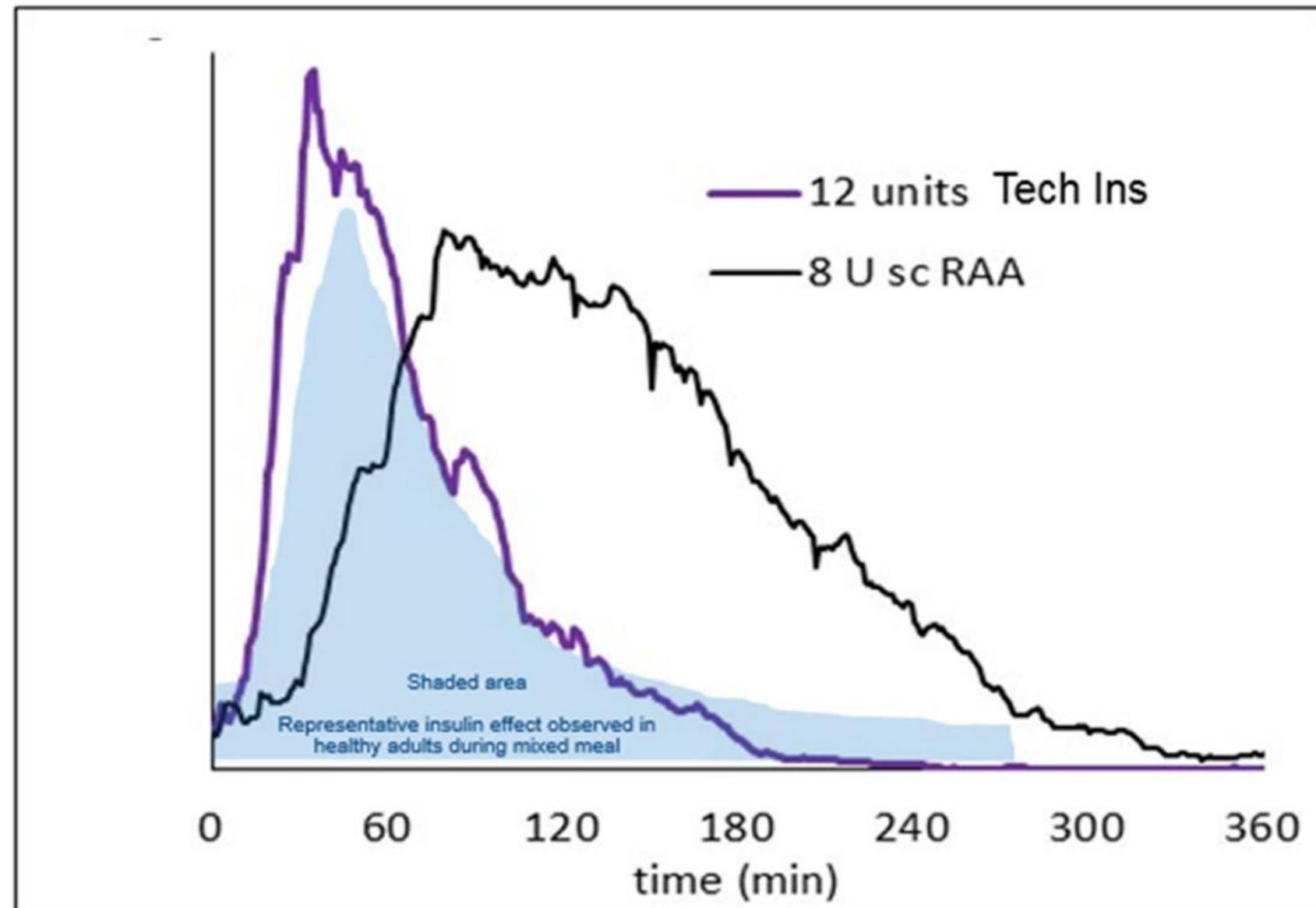
Blood Vessel



Insulin | FDKP

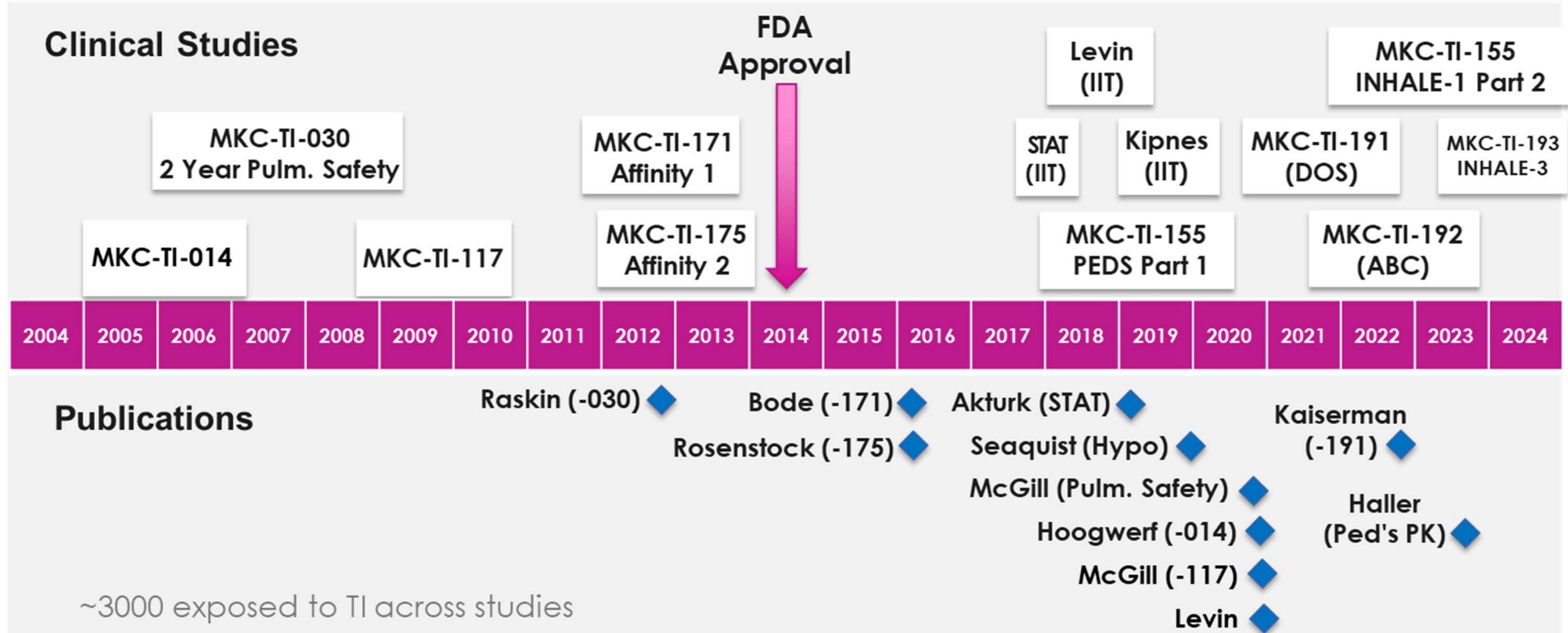


PD: Technosphere Insulin vs Rapid Analogue



- TI maximum serum insulin concentration in 12-15min vs 45-60min for RAA
- TI effect dissipates faster than RAA potentially reducing post-meal hypoglycemia

Technosphere Insulin Clinical Studies



Pivotal T1D Trial – Noninferiority

1266

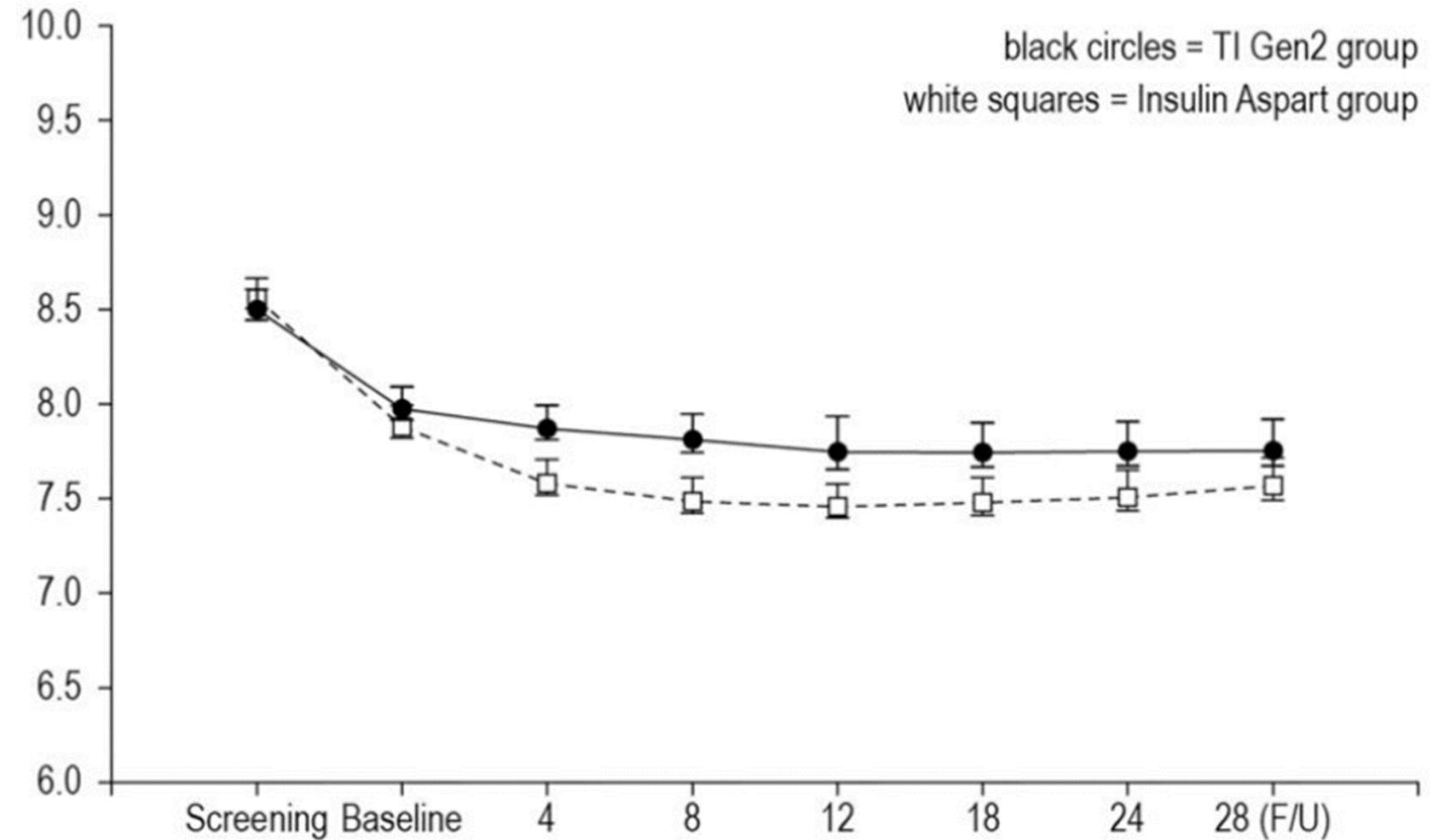
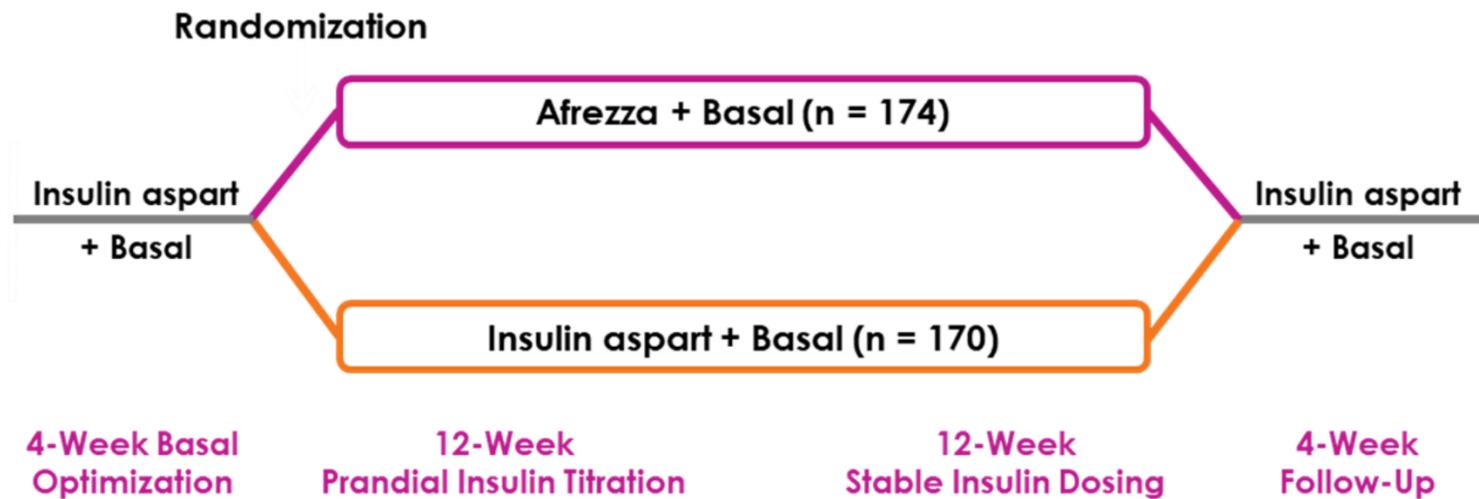
Diabetes Care Volume 38, December 2015



Inhaled Technosphere Insulin Compared With Injected Prandial Insulin in Type 1 Diabetes: A Randomized 24-Week Trial

Diabetes Care 2015;38:2266–2273 | DOI: 10.2337/dc15-0075

Bruce W. Bode,³ Janet B. McGill,⁷
Daniel L. Lorber,³ Jorge L. Gross,⁴
P.-C. Chang,⁵ and David B. Bregman,^{6,7}
for the Affinity 1 Study Group*



Dose Optimization – 2x...3x

Original Article

Reduction in Postprandial Peak Glucose With Increased Technosphere Insulin Dosage

Journal of Diabetes Science and Technology
2024, Vol. 18(2) 397–401
© 2022 Diabetes Technology Society
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/19322968221110622
journals.sagepub.com/home/dst
SAGE

Kevin B. Kaiserman, MD¹, Mark Christiansen, MD²,
Sunil Bhavsar, MS¹, Johanna Ulloa, BSE¹, Brandi Santogatta, BA¹,
Joseph Hanna, BS¹, and Timothy S. Bailey, MD³

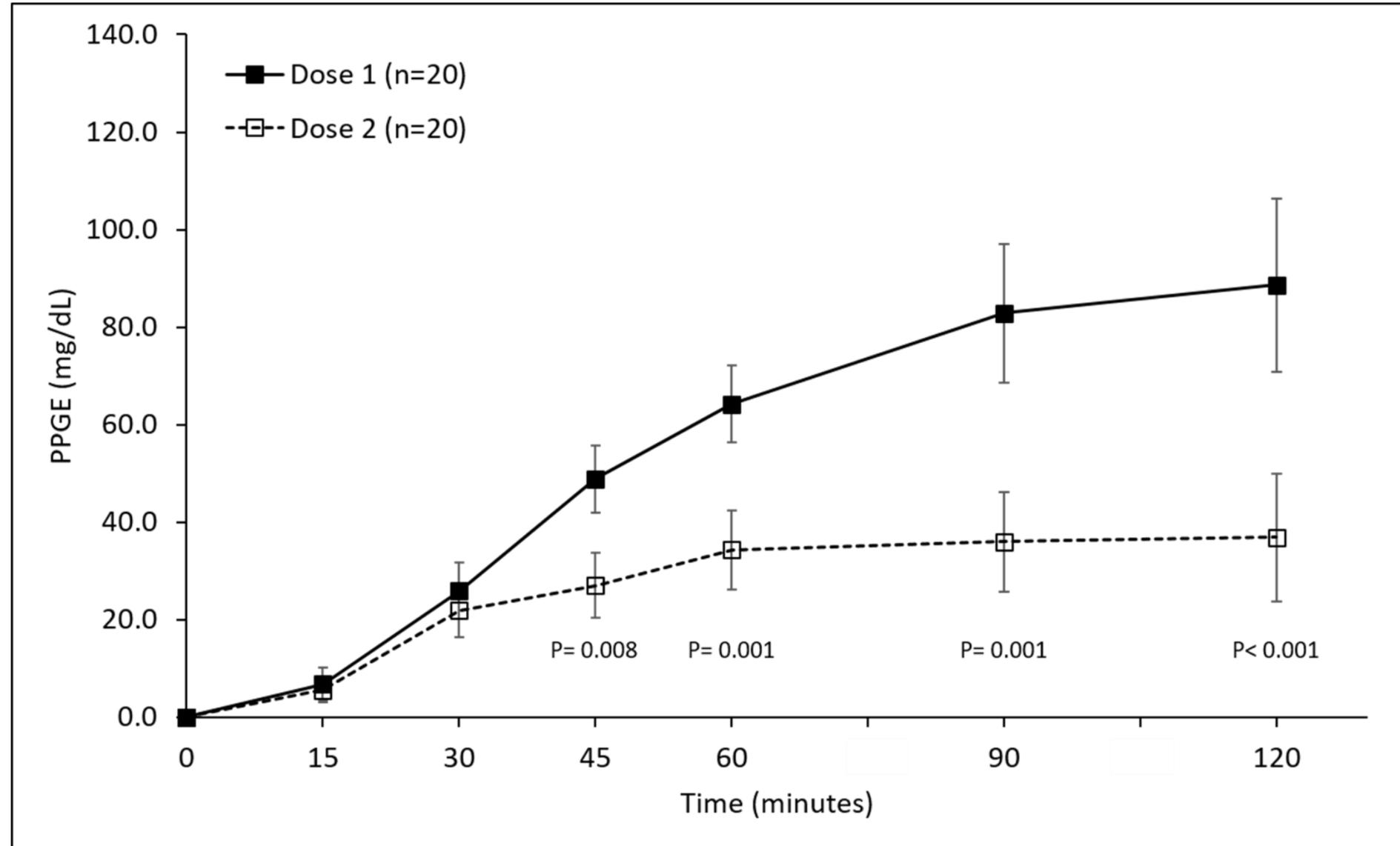
RAA Dose (units)	TI Dose (units)
Up to 4	4
5-8	8
9-12	12
13-16	16

RAA Dose (units)

TI Dose (units)

1-3	4
4-5	8
6-7	12
8-9	16
10-11	20
12-13	24
14-15	28

Dose Optimization – 2x...3x



INHALE-3 -Adults

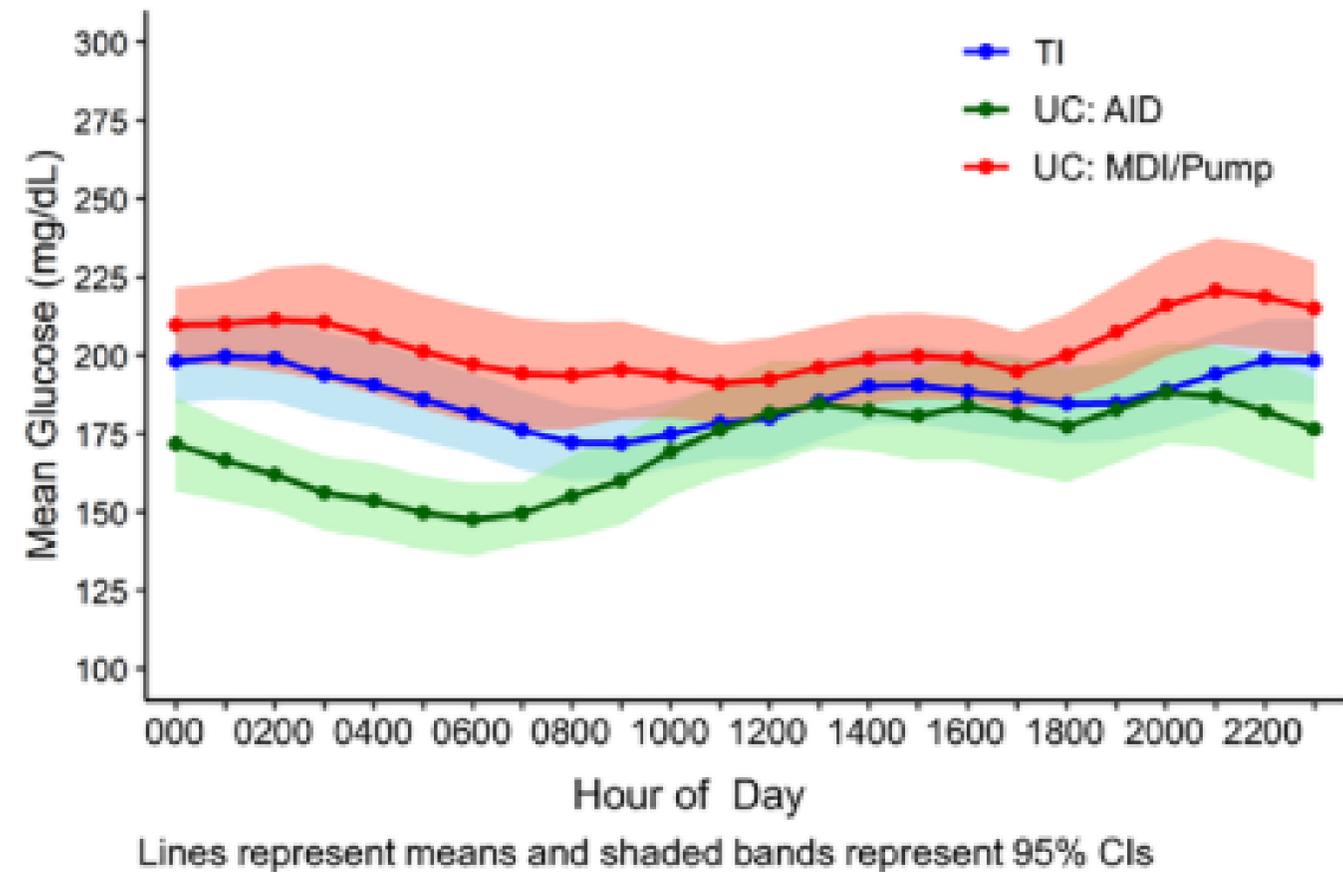
Inhaled Technosphere insulin (TI) has been shown to reduce post-prandial glucose excursions in adults with type 1 diabetes (T1D).



Results

Primary Outcome: Mean HbA_{1c}

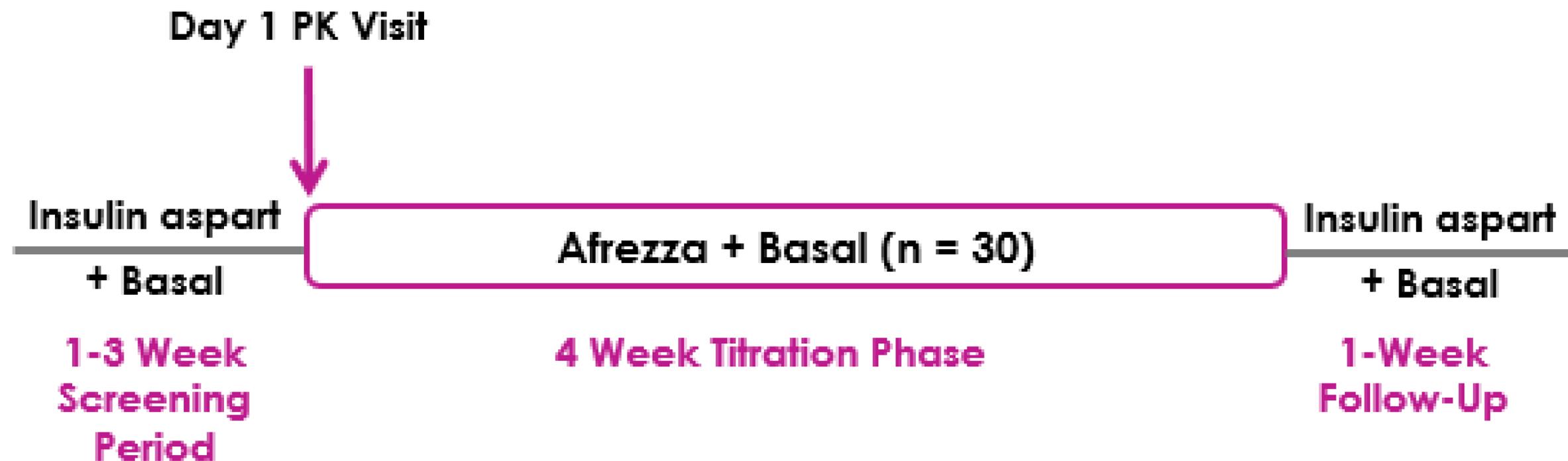
	TI+Degludec (N=122)	Usual Care (N=121)
HbA _{1c} : baseline/17w	7.57%/7.62%	7.59%/7.54%
Trt group diff (95% CI)	0.11% (-0.10 to 0.33)	
P value (non inferiority)	0.01	



Randomized Trial Comparing Inhaled Insulin Plus Basal Insulin Versus Usual Care in Adults With Type 1 Diabetes. *Diabetes Care*. 2024

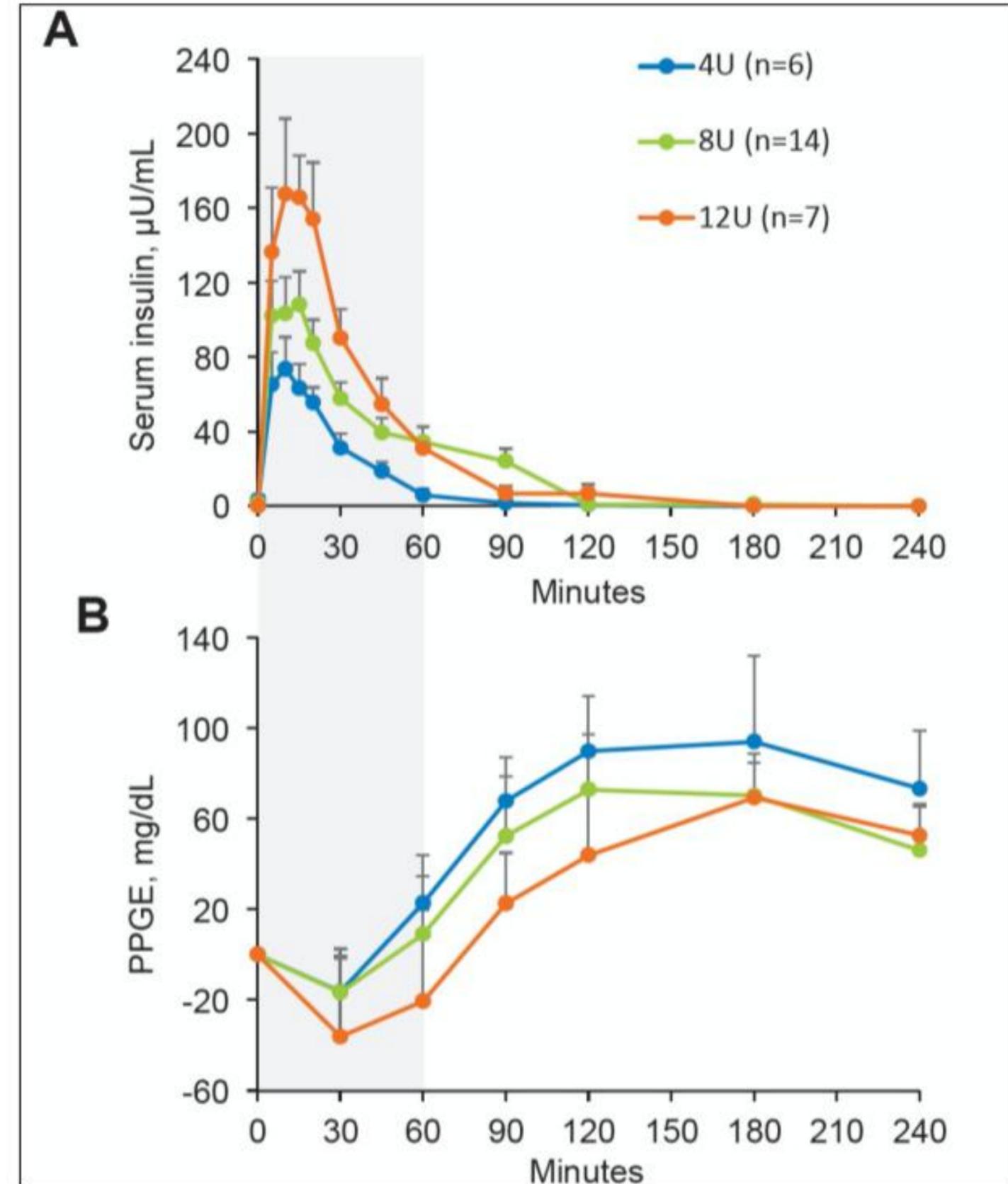
Pediatric Study Part 1

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)



Pilot PK/PD/Safety - Pediatrics

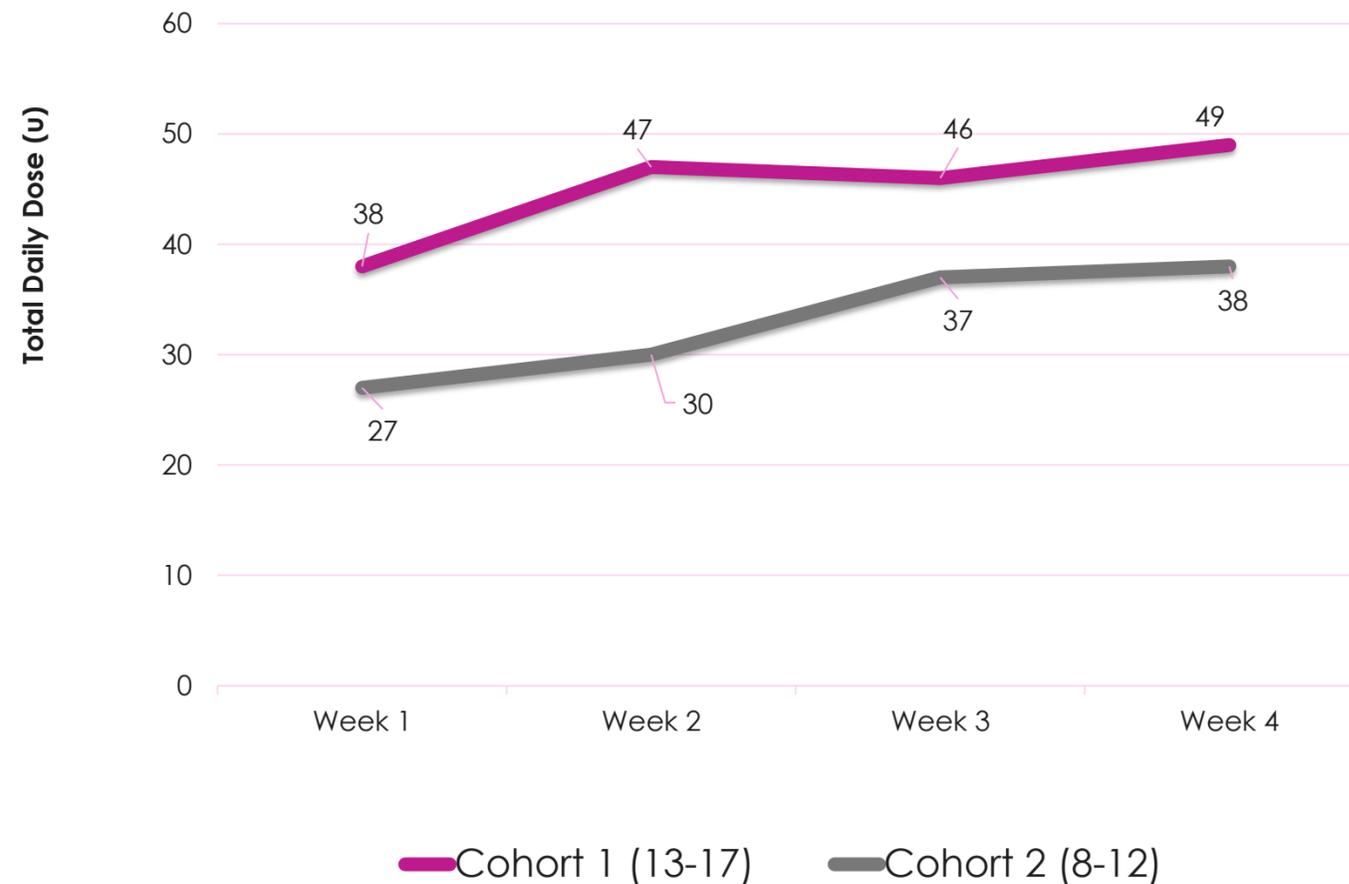
- PK data - 27 subjects
- Mean age, BMI, and duration of T1D were 13.3 ± 2.9 yrs, 20.8 ± 3.6 kg/m², and 4.5 ± 3.2 yrs
Sixteen subjects (59.3%) were female
-
- Twenty-two (81.5%) were White, 2 were Black and 2 were Other Race.
- 1 Level 1 hypo in 3 subjects, 1 Level 2 in 1, No severe hypo



Pediatric Study Part 1: Dosing

- Afrezza dose at end of trial was **1.75x SQ dose**
- 87% of subjects received at least one post-meal correction dose

Total Daily Dose of Afrezza



Pediatric Study Part 1: Safety

- Most common adverse events: hypoglycemia, cough, and URI
- 93% of TEAEs were considered mild or moderate (43/46 events)
- Other TEAE's related to study drug (n):
 - Throat irritation (1), tonsillar hypertrophy (1), vomiting (1), dizziness (1), HA (2), asthenia (1)

TEAE	Cohort 1: 13-17 yrs (n=15)	Cohort 2: 8-12 yrs (n=15)	Total (n=30)	T1DM Adults pooled (n=1026)
Hypoglycemia	10 (67%)	10 (67%)	20 (67%)	96%
Cough	7 (47%)	5 (33%)	12 (40%)	29.4%
URI	1 (7%)	3 (20%)	4 (13%)	13%
DKA	1 (7%)	0%	1 (3%)	0.43%*

Pediatric Study Part 1: Safety

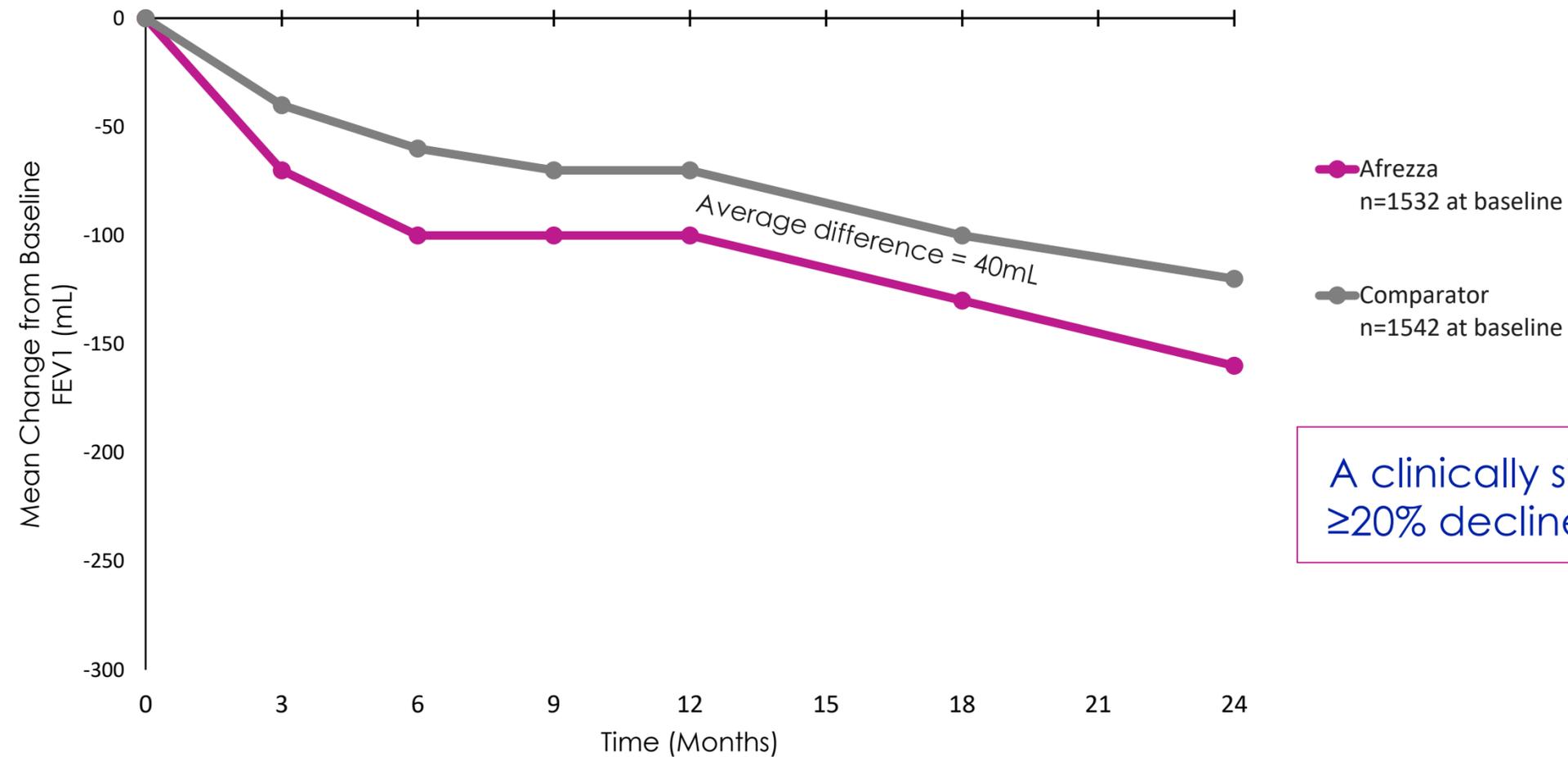
Severe Adverse Events

Cohort	Subject	Demo	Days on Study Drug	Adverse Event	Outcome	Discontinued?	Relationship to Study Drug
Cohort 1	6431003	17/F/O	5	Diabetic Ketoacidosis	Resolved	Yes	Possible
Cohort 2	6421009	12/M/W	4*	Abdominal pain	Resolved	No	Not related
Cohort 2	6461003	10/F/W	28	Stomach Flu	Unknown	LTFU	Unlikely

AE leading to drug discontinuation

Cohort	Subject	Demo	Days on Study Drug	Adverse Event	Duration of AE	Severity	Outcome	Relationship to Study Drug
Cohort 1	6431003	17/F/O	5	Diabetic Ketoacidosis	1 day	Severe	Resolved	Possible
Cohort 1	6431001	17/M/W	11	Cough	26 days	Moderate	Resolved	Possible
Cohort 2	6451003	8/F/W	2	Vomiting, acute cough	3 days	Moderate	Resolved	Definite

Afrezza: Effect on FEV1



A clinically significant difference is $\geq 20\%$ decline, or $\sim 600\text{mL}$ for adults

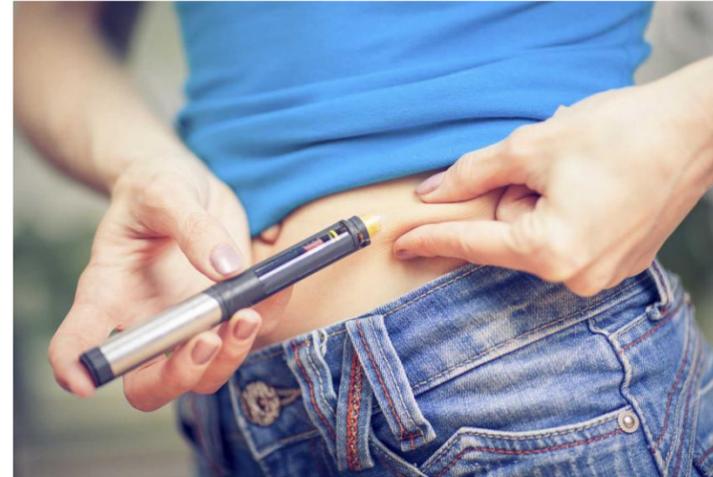
Diabetes and Lung Function

- After age 25, FEV₁ decreases at about 35-40 mL/yr in healthy subjects²
- Diabetes is associated with a further decline in FEV₁ of 25 mL/yr compared to healthy subjects³

Pediatric Pivotal Study

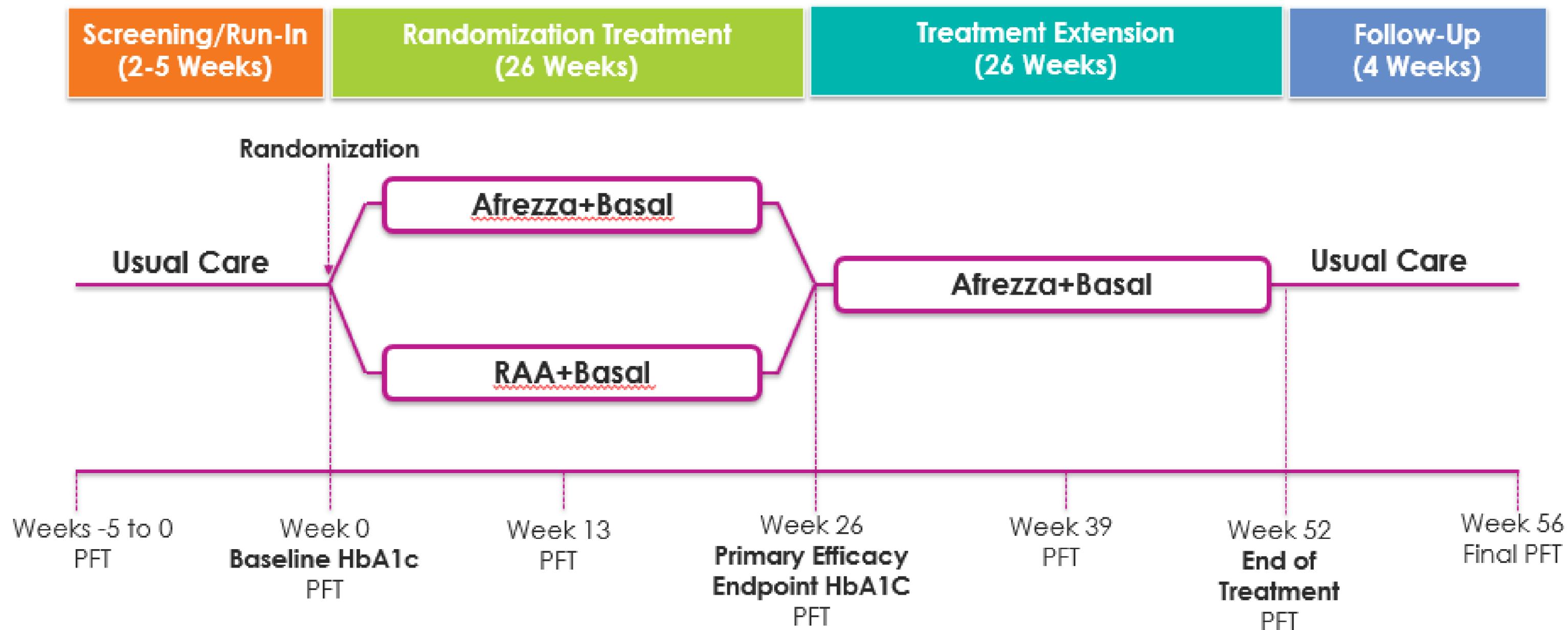


OR

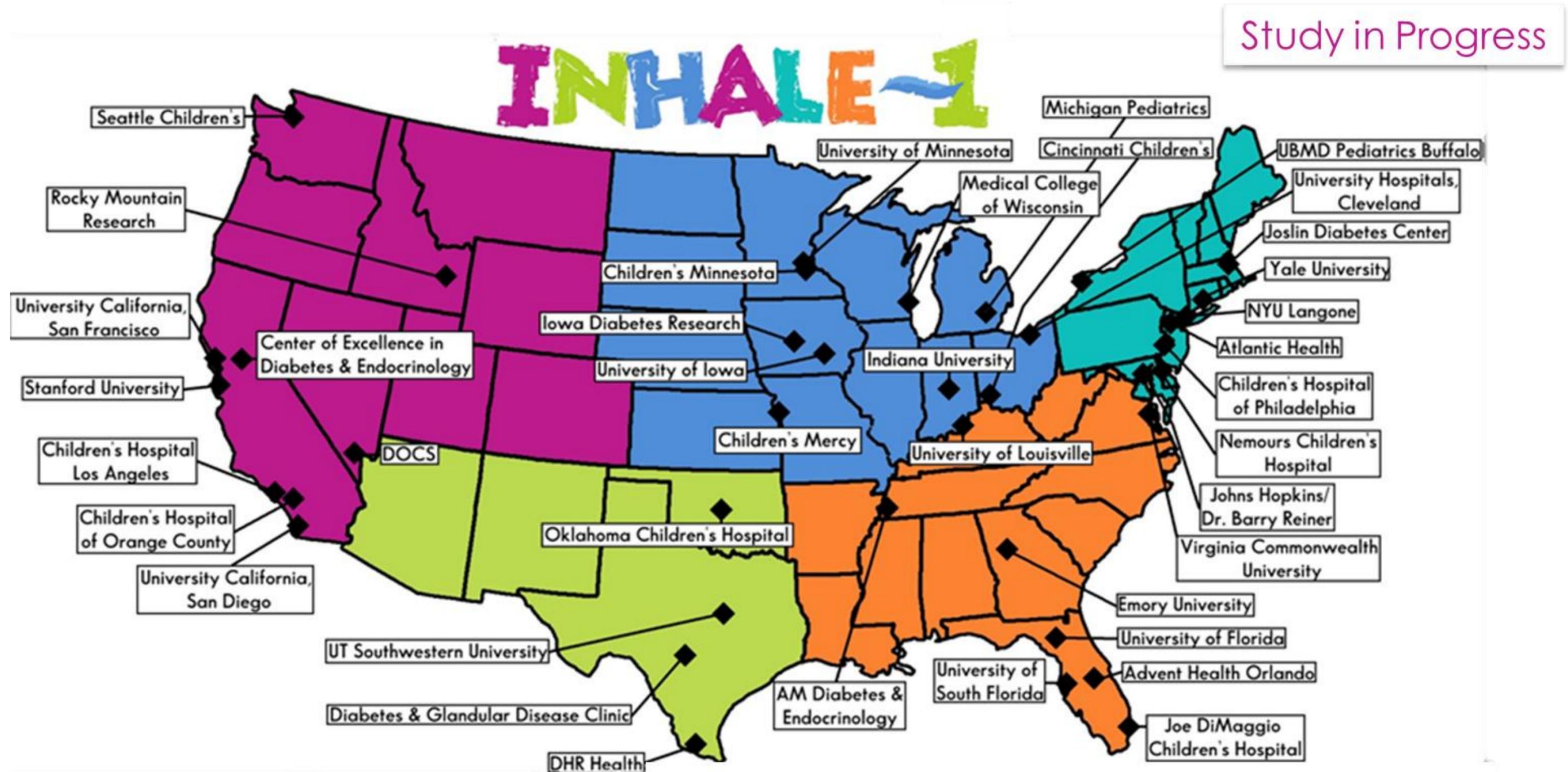


230 youth 4 to 17 years old with insulin-requiring diabetes were assigned to either TI or RAA with basal insulin for 26 weeks, plus CGM.

Pediatric Pivotal Study



Pediatric Pivotal Study



Baseline Characteristics

Characteristics	Afrezza (N=117)	RAA (N=113)	Overall (N=230)
Age (years)			
n	117	113	230
Mean (SD)	12.7 (2.90)	12.4 (3.15)	12.6 (3.03)
SE	0.27	0.30	0.20
Median	13.0	13.0	13.0
Min, Max	6, 17	4, 17	4, 17
Age group, n (%)			
≥4 and <13 years	53 (45.3)	52 (46.0)	105 (45.7)
≥13 and <18 years	64 (54.7)	61 (54.0)	125 (54.3)
Gender, n (%)			
Male	72 (61.5)	70 (61.9)	142 (61.7)
Female	45 (38.5)	43 (38.1)	88 (38.3)
Diabetes type			
Type 1 diabetes mellitus (T1DM)	113 (96.6)	112 (99.1)	225 (97.8)
Type 2 diabetes mellitus (T2DM)	4 (3.4)	1 (0.9)	5 (2.2)
Age at diagnosis of diabetes (years)			
n	117	113	230
Mean (SD)	8.27 (3.390)	8.07 (3.522)	8.17 (3.450)
SE	0.313	0.331	0.227
Median	8.00	8.00	8.00
Min, Max	1.0, 17.0	1.0, 16.0	1.0, 17.0

Baseline Characteristics

	Afrezza (N=117)	RAA (N=113)	Overall (N=230)
HbA1c (%)	117	113	230
n	8.22 (0.866)	8.21 (0.958)	8.21 (0.910)
Mean (SD)	0.080	0.090	0.060
SE	8.10	8.00	8.00
Median	6.7, 10.7	6.3, 11.0	6.3, 11.0
Min, Max			
HbA1c group at baseline			
<8.5%	75 (64.1)	71 (62.8)	146 (63.5)
≥8.5%	42 (35.9)	42 (37.2)	84 (36.5)

Saturday 1130 - D2 - First dose Inhale-1 vs SQ

ADA 2025 - Primary End Point - Non=Inferiority

INHALE-1



4-units 8-units 12-units