

POSTPRANDIAL GLUCOSE FOLLOWING A BOLUS WITH INHALED INSULIN VERSUS USUAL CARE

Results from the INHALE-3 Randomized Trial

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UNPUBLISHED DATA

Disclosures

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee
Dexcom and Mannkind			xx				
Abbott, Roche, Hagar, Vertex		XX					

Study funding provided by MannKind Corporation

Background

- Post-meal hyperglycemia is difficult to prevent with subcutaneous rapid-acting analogue (RAA) insulin.
- Even with automated insulin delivery (AID) systems, most patients have substantial hyperglycemia, averaging 6-7 hrs/day with glucose levels >180 mg/dL.¹

Background

- **Technosphere Insulin inhalation powder¹**
(marketed as Afrezza; MannKind Corporation, Danbury, CT) has a much more rapid onset of action, which more closely mirrors insulin release from a normal pancreas.
 - Maximum serum insulin concentration achieved in 12-15 min compared with 45-60 min for subcutaneous RAA
 - Effect dissipates faster than RAA potentially reducing post-meal hypoglycemia²



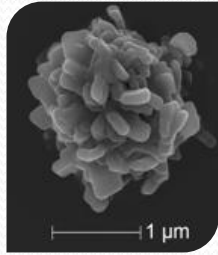
RAA, Rapid-Acting Analogue Insulin

1. Afrezza® (insulin human) Inhalation Powder Prescribing Information. MannKind Corporation.
2. Seaquist ER et al. *Diabet Med.* 2020;37(5):752-759.

Technosphere Insulin Inhaled Delivery

Technosphere

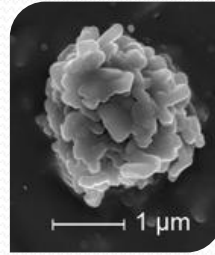
Microparticles (FDKP)



Water



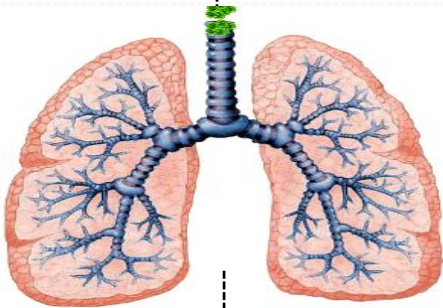
Human Regular Insulin



pH < 6

Technosphere Insulin:
Insulin adsorption onto
FDKP particle

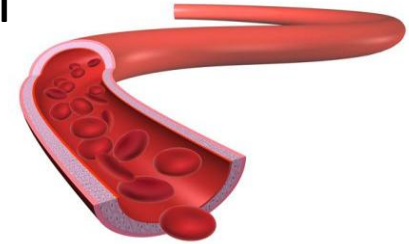
Bis-3,6(4-fumarylaminobutyl)-2,5-diketopiperazine (FDKP)



pH > 6 (physiologic pH)

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

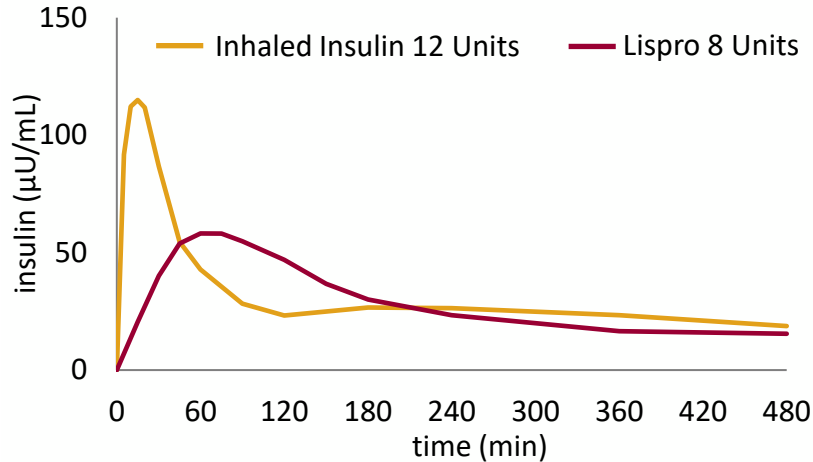
Blood Vessel



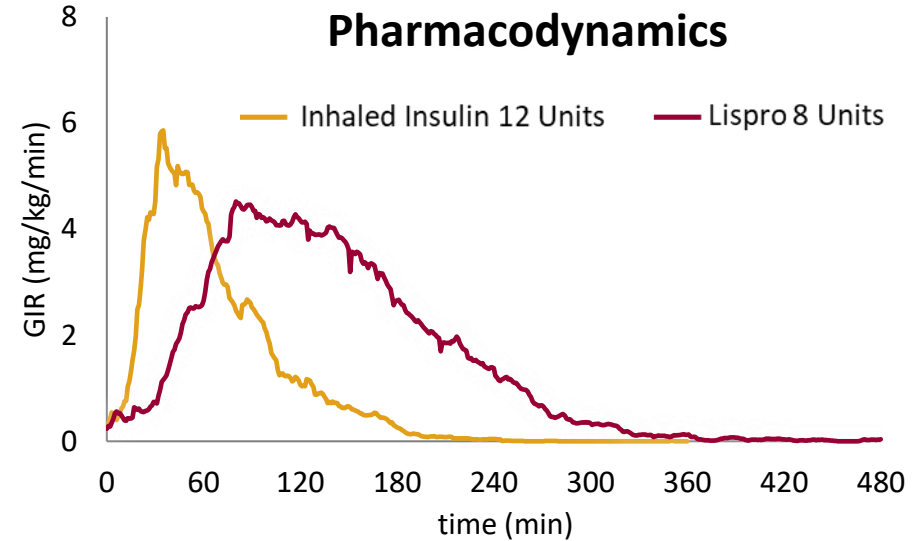
Insulin | FDKP

Pharmacokinetics of Technosphere Insulin Versus Rapid Acting Insulin Analogues

Pharmacokinetics



Pharmacodynamics



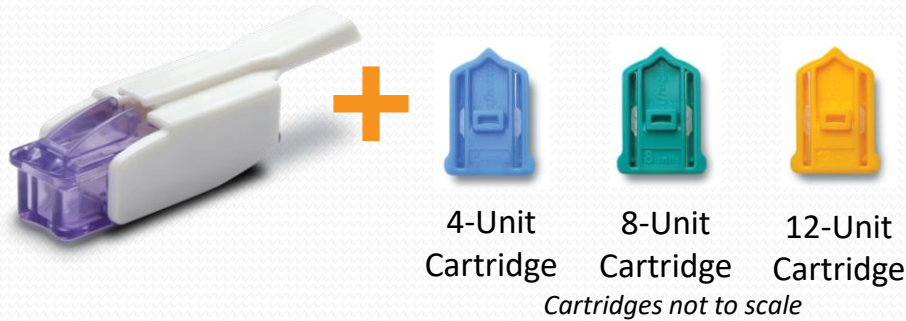
INHALE-3 Protocol

- 17-wk randomized controlled trial with 1:1 random assignment to:
 - Degludec plus inhaled insulin
 - Usual care (AID, nonautomated pump, or MDI)
- Sample size: minimum of 120
- Key Inclusion Criteria
 - Age >18 years old
 - Type 1 diabetes for at least 6m
 - HbA1c <11.0%
 - Using CGM on regular basis
- Key Exclusion Criteria
 - Use of non-insulin glucose lowering medications in prior 3m
 - Asthma treatment in prior year
 - Smoking in prior 3m
 - History of lung cancer

Meal Challenge

- Fasting (unless hypo Rx needed) and no bolus insulin for 4 hrs
- Glucose 91-219 mg/dL 15min prior to start
- Ingestion of bottle of Boost (240 calories, 37g carbs, 10g protein, 4g fat)
- Inhaled insulin at start of meal or RAA 5-15min prior to meal
- Pump users continued to receive basal insulin through pump
 - *Inhaled insulin group: CIQ put into sleep mode (to avoid auto-boluses)*
- Glucose measurements
 - Glucose monitored with BGM at 15-30min intervals through 2hrs
 - Blinded Dexcom G6 Pro used for analyses

Technosphere Insulin Dosing



Drug/Device Combination Product

- Compact inhaler
- Pre-filled single-use insulin cartridges
- Breath-powered delivery

Converting from RAA units to “Afrezza Units”

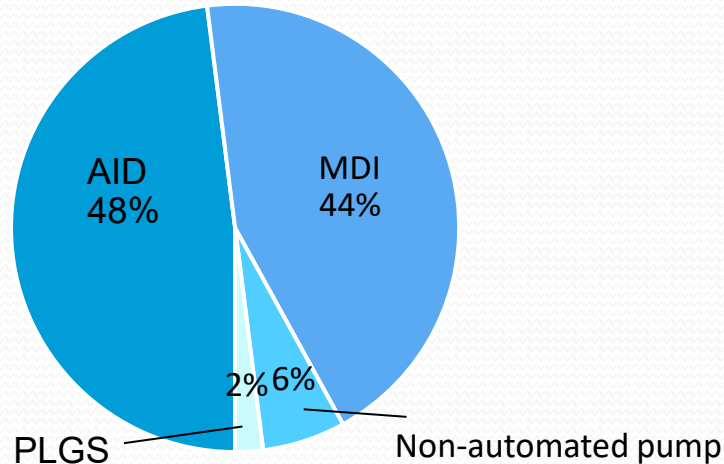
- Round # of RAA units to nearest whole number
- Multiply by 2
- Round down to nearest 4-unit cartridge

RAA Dose	Inhaled Insulin Dose (“Afrezza Units”)
≤3	4
4-5	8
6-7	12
8-9	16
10-11	20
12	24

Baseline Characteristics (N=122)

Mean Age	45 yrs (range 18-77)
Female	54%
Mean HbA1c	7.6% (range 5.4-10.5)

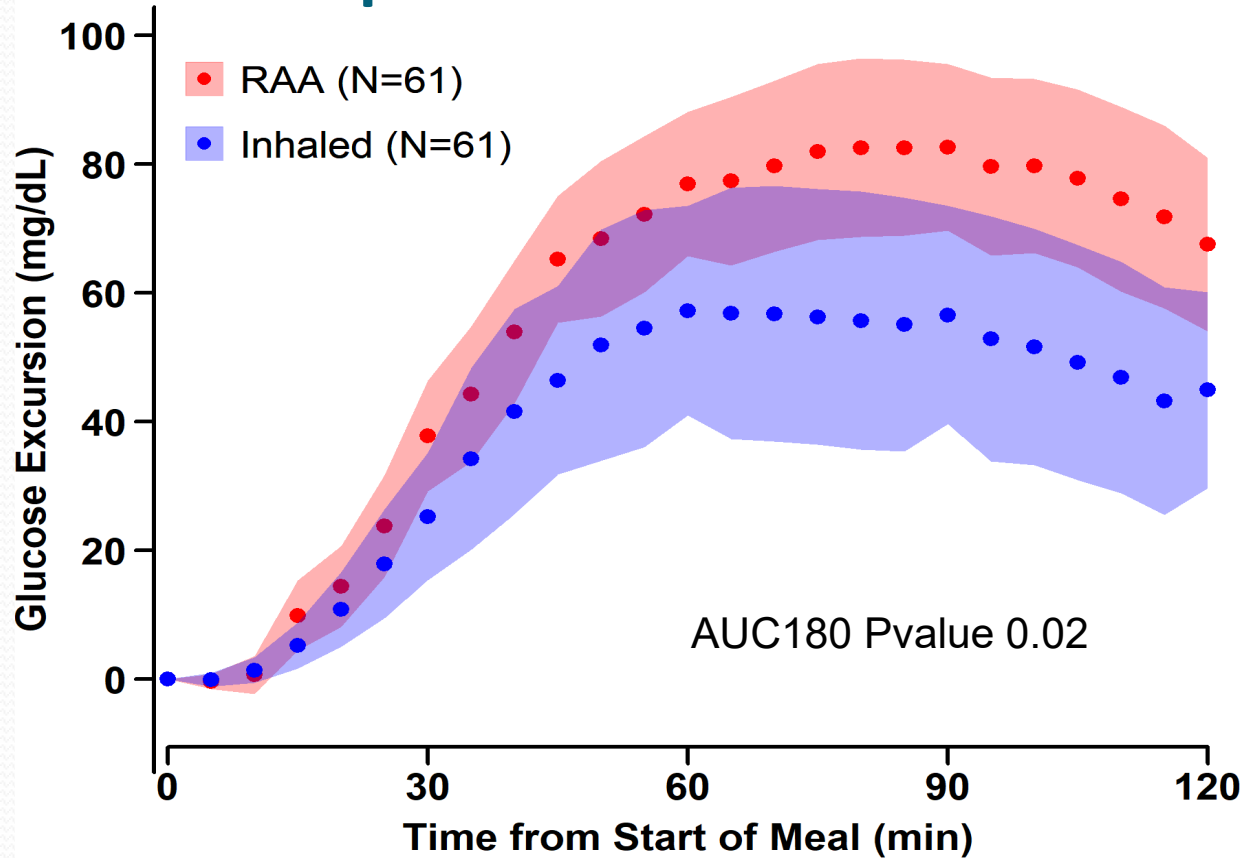
Insulin Delivery Modality



AID Systems (N=59)

Control-IQ	39
Omnipod 5	17
780G	3

Postprandial Glucose Excursion

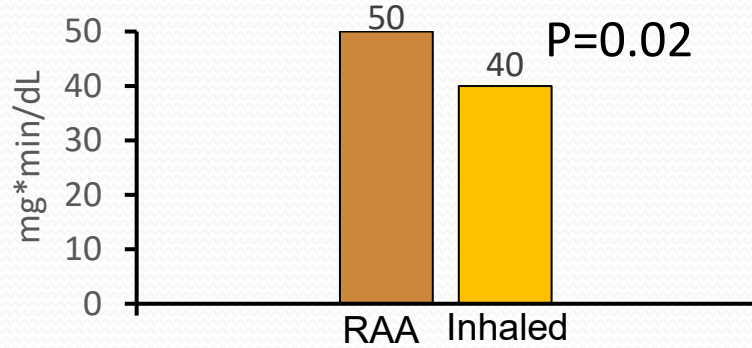


Control Group	
<i>Insulin Delivery</i>	
• AID	48%
• Non-automated pump	5%
• PLGS pump	5%
• MDI	43%
<i>Type of RAA Insulin</i>	
• lispro	32
• aspart	23
• fast-acting aspart	3
• glulisine	1
• ultra-rapid lispro	1
• regular insulin	1

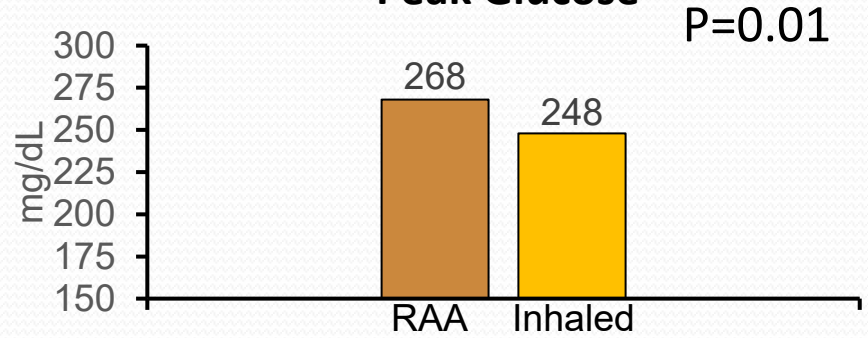
*Dots- mean excursion
Shaded region- 95% CI*

Glucose Outcomes During First 2 Hours

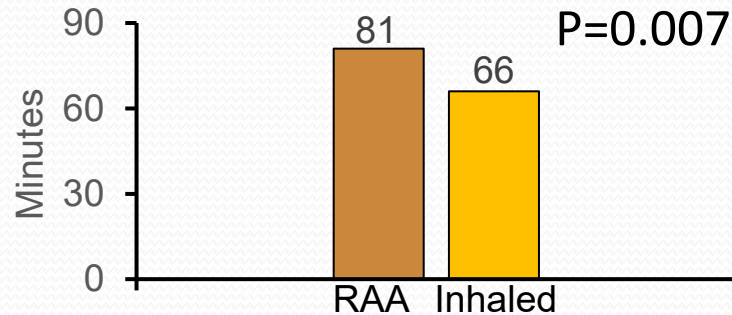
AUC 180 mg/dL



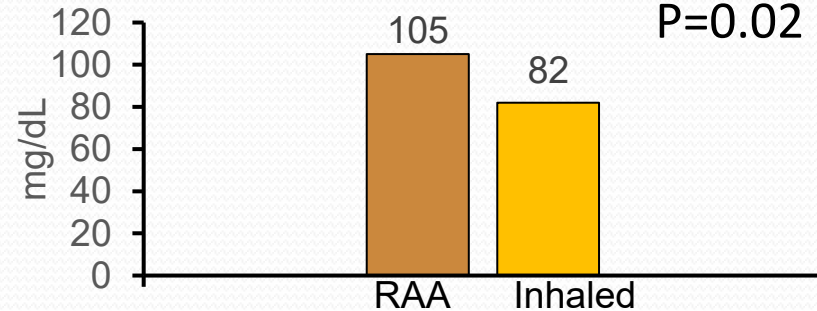
Peak Glucose



Time to Peak Glucose

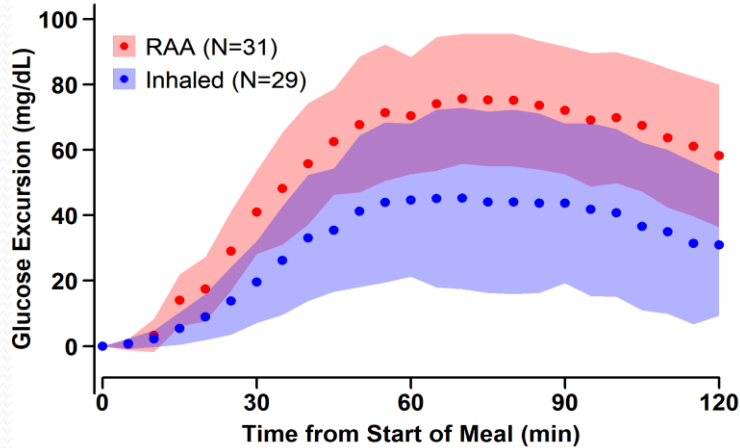


Excursion



Glucose Excursion by Insulin Delivery Method

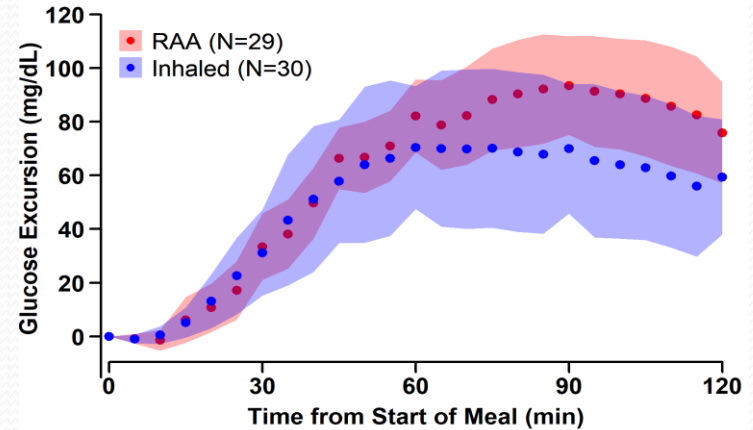
MDI/Non-Automated Pump



	RAA	Inhaled
AUC 180 mg/dL	65 mg/dL	46 mg/dL
Peak Glucose	284 mg/dL	251 mg/dL
Time to Peak Glucose	75 min	60 min
Excursion	97 mg/dL	70 mg/dL

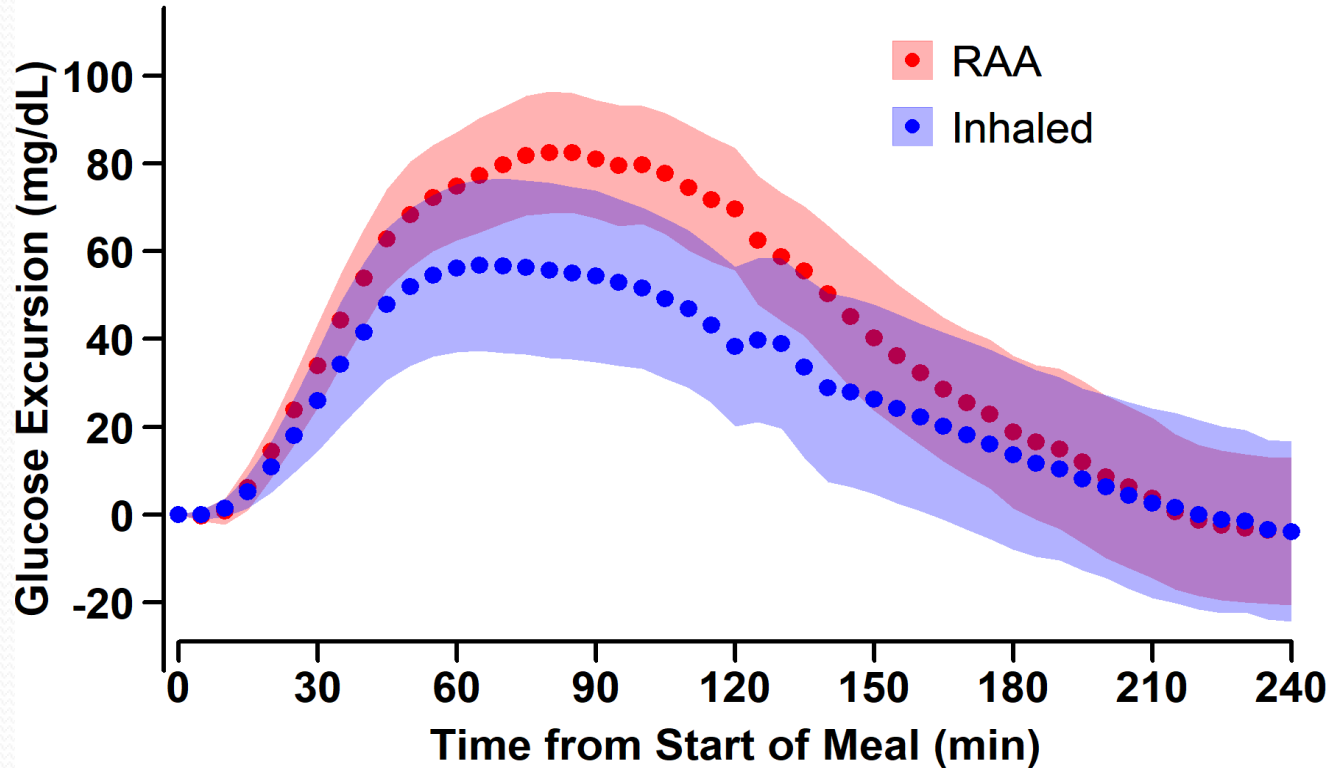
Dots- mean excursion Shaded region- 95% CI

Automated Insulin Delivery



	RAA	Inhaled
AUC 180-mg/dL	36 mg/dL	33 mg/dL
Peak Glucose	253 mg/dL	244 mg/dL
Time to Peak Glucose	87 min	73 min
Excursion	111 mg/dL	94 mg/dL

Glucose Excursion Over 4 Hours



*Limited to participants with
blinded CGM data*

*Dots- mean excursion
Shaded region- 95% CI*

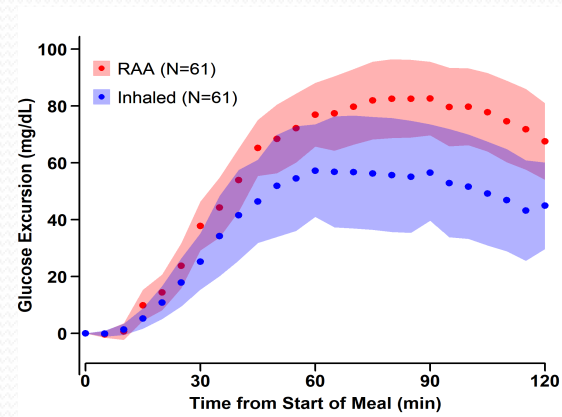
Treatment of Hypoglycemia and Hyperglycemia During 2-hour Meal Challenge

- Protocol:
 - BG <70 mg/dL: provide oral carbohydrate
 - BG >400 mg/dL or >300 mg/dL for 1 hr: administer RAA or inhaled insulin

	RAA (N=61)	Inhaled (N=61)
Treated for Hypoglycemia	1	1
Additional Insulin Given due to Hyperglycemia	1	0

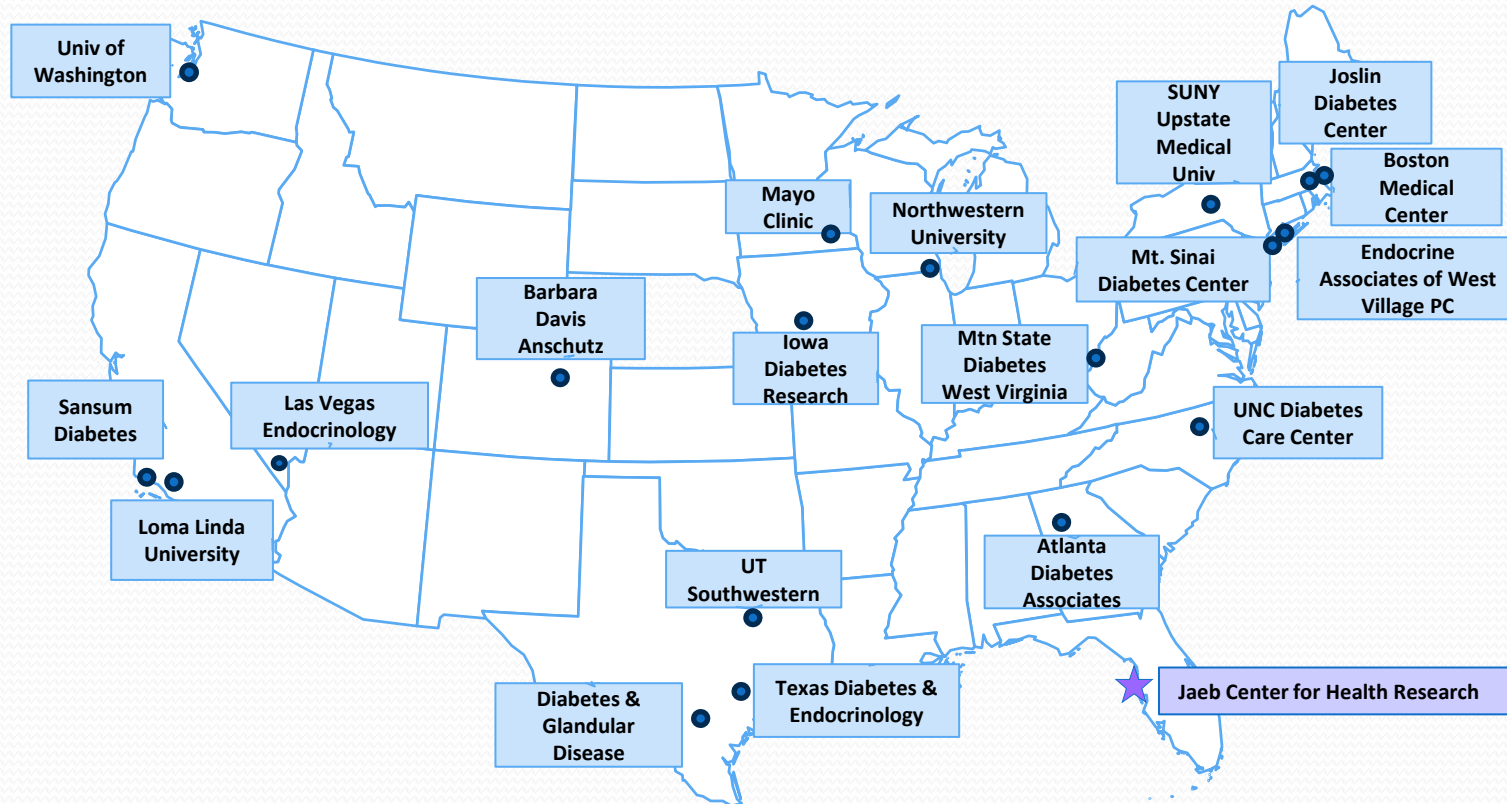
Summary

- Post-meal hyperglycemia was significantly reduced with inhaled insulin compared with subcutaneous RAA
 - Area under the curve reduced by 20%
 - Peak glucose reduced by 22 mg/dL
- Reduction in post-meal hyperglycemia with inhaled insulin greater for MDI users than AID users
- Post-meal hypoglycemia infrequent with both insulins



Results of the 17-week RCT including meal challenge with optimized inhaled insulin/degludec dosing will be presented at ADA meeting in June 2024

Participating Clinical Sites (19)



Clinical Trial Sites and Principal Investigators

Jaeb Center for Health Research- **Coordinating Center**

Univ of Washington- **Hirsch** (Protocol Chair)

Atlanta Diabetes Associates- **Bode**

Barbara Davis Anschutz- **Akturk**

Boston Medical Center-**Steenkamp**

Diabetes & Glandular Disease- **Kipnes**

Endocrine Associates of West Village PC- **Manassis**

Iowa Diabetes Research- **Bhargava**

Joslin Diabetes Center- **Hamdy**

Las Vegas Endocrinology- **Nguyen**

Loma Linda University- **Codorniz**

Mayo Clinic- **Kudva**

Mountain State Diabetes West Virginia- **Pickering**

Mt. Sinai Diabetes Center- **Levy**

Northwestern University- **Aleppo**

Sansum Diabetes- **Castorino**

SUNY Upstate Medical University- **Weinstock**

Texas Diabetes & Endocrinology- **Blevins**

UNC Diabetes Care Center- **Diner and Buse**

UT Southwestern- **Raskin**