Inhaled Insulin in Pediatric Diabetes Results of the INHALE-1 Trial

Michael Haller, MD

Professor and Chief

Pediatric Endocrinology

University of Florida

American Diabetes Association®

85TH SCIENTIFIC SESSIONS

#ADASciSessions

Disclosures

- Photography is allowed / @HallerMichael
- Mannkind – Consultant, Advisory Board, Grantee
- Sanofi – Consultant, Grantee

INHALE-1

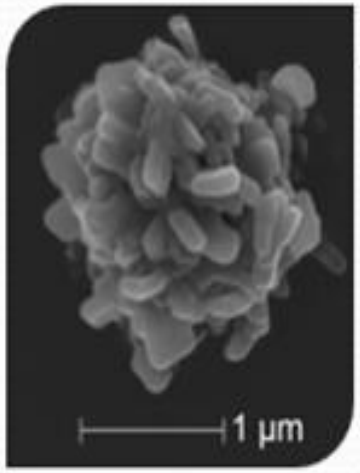
American Diabetes Association.

85TH SCIENTIFIC SESSIONS

#ADASciSessions

Inhaled Technosphere Insulin (TI) / Afrezza

Technosphere
Microparticles (FDKP)



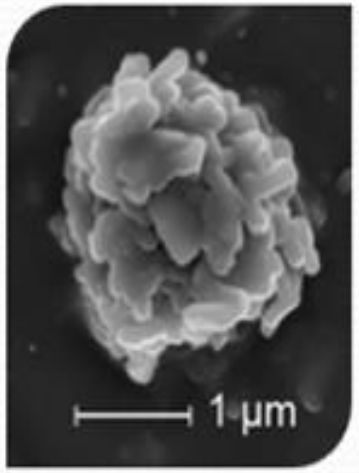
Water

+

Human Regular Insulin

=

Technosphere Insulin (TI)



→

pH <6

Technosphere Insulin:

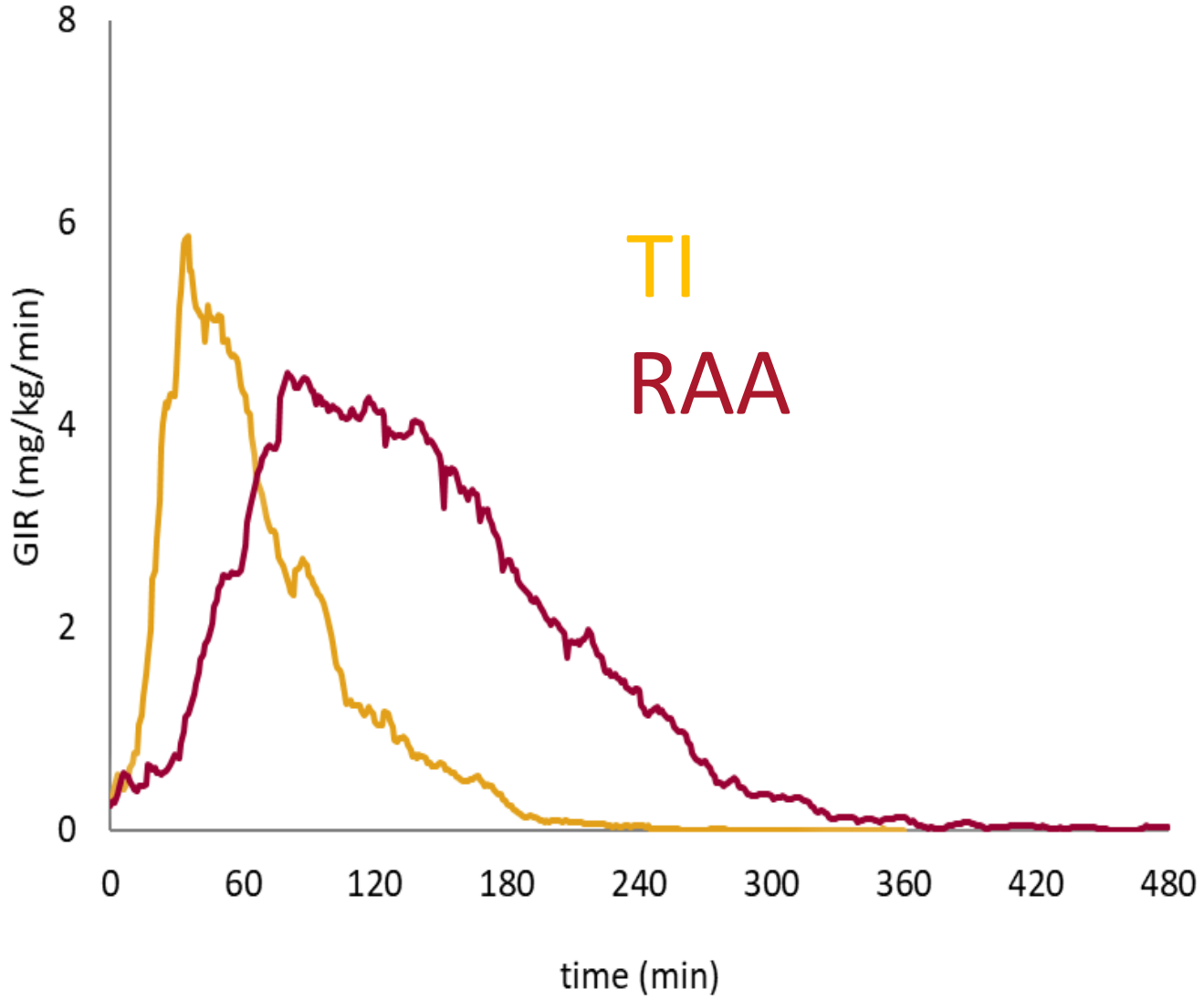
Insulin adsorption onto FDKP particle

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

INHALE-1

Inhaled Technosphere Insulin (TI) / Afrezza

- TI - max serum insulin concentration in 12-15m
- Rapid Acting Analog (RAA) max serum in 45-60m
- TI effect dissipates faster than RAA
- Potentially improving meal excursions and reducing post-meal hypoglycemia



INHALE-1

TI / Afrezza – Inhaler and Cartridges

Drug/Device Combination Product

Compact inhaler

Pre-filled single-use insulin cartridges

Breath-powered delivery

4-Unit Cartridge

8-Unit Cartridge

12-Unit Cartridge

Cartridges not to scale

Inhaled Insulin (TI) in Adults

- FDA approved in 2014
- Adult Phase 4 Study – INHALE-3
- Higher Dose TI than Label
- Confirmed Safety/Non-Inferiority

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

Irl B. Hirsch, Roy W. Beck, Martin C. Marak, Yogish Kudva, Halis K. Akturk, Anuj Bhargava, Kevin Codorniz, Jamie Diner, Grazia Aleppo, Thomas Blevins, Carol J. Levy, Philip Raskin, Kristin Castorino, Anastasios Manessis, David Pickering, Devin W. Steenkamp, Ruth S. Weinstock, Bruce W. Bode, Osama Hamdy, Quang T. Nguyen, Mark Kipnes, Katrina J. Ruedy, Donna Desjardins, Zehra Haider, Christopher Jacobson, Scott Lee, John B. Buse, Klara Rachel Klein, Grenye O'Malley, Mei Mei Church, Adham Mottalib, Jesica D. Baran, Corey Kurek, Shafaq Rizvi, Cassandra Donahue, Denisa Tamarez, Astrid Atakov Castillo, Sarah Borgman, Sarah Frey, and Peter Calhoun, on behalf of the INHALE-3 Study Group

Diabetes Care 2025;48(3):353–360 | https://doi.org/10.2337/dc24-1832

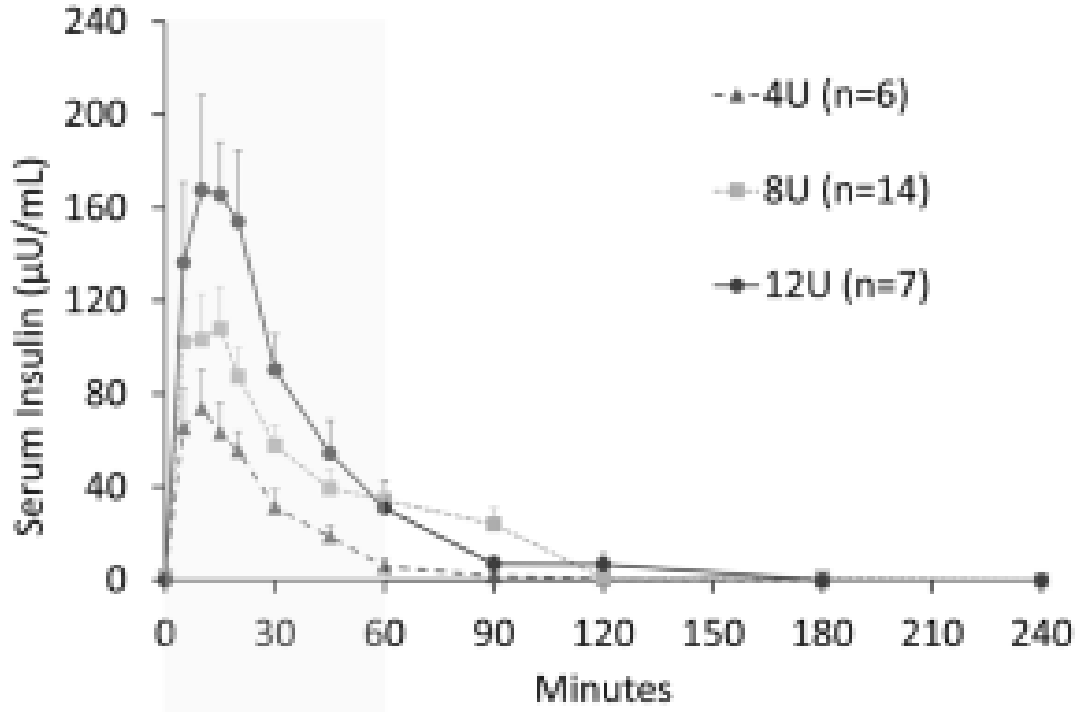
Inhaled Insulin in Pediatrics – PK/PD

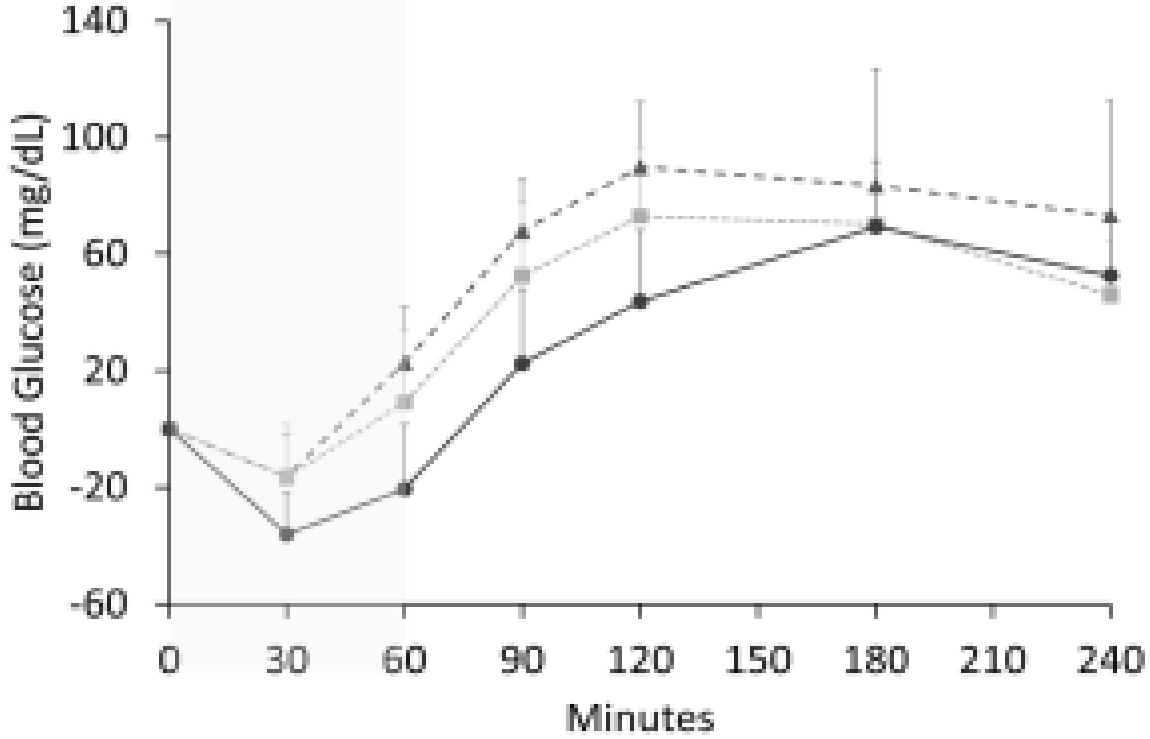
Diabetes Ther (2023) 14:611–617
https://doi.org/10.1007/s13300-023-01368-7

BRIEF REPORT

Time–Action Profile of Technosphere Insulin in Children with Type 1 Diabetes

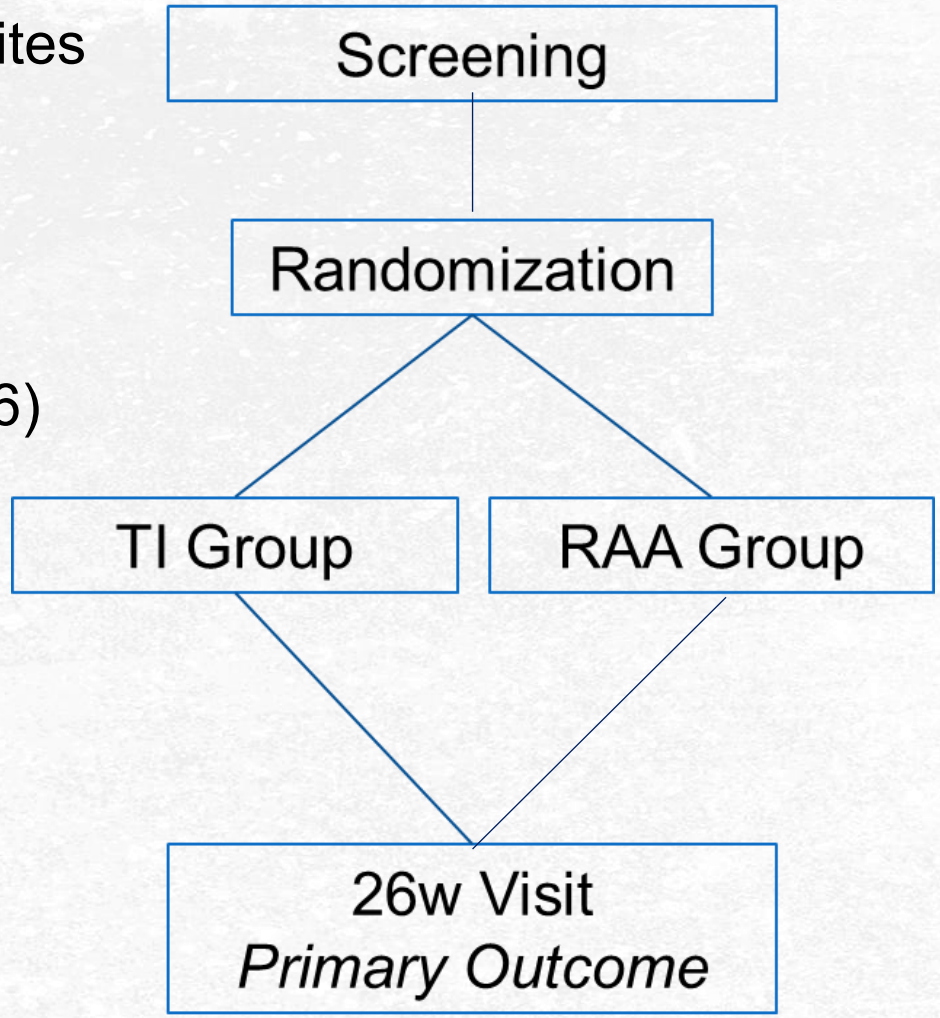
Michael J. Haller · Marisa C. Jones · Sunil Bhavsar · Kevin B. Kaiserman





INHALE-1 - Protocol Summary

- Youth with T1D or T2D randomized at 38 U.S. sites
- Planned sample size = 200 completing 26 wks
- 1:1 Randomization
  - TI + basal insulin or RAA + basal insulin
  - Both groups used real-time CGM (Dexcom G6)
- Primary outcome
  - HbA1c (non-inferiority) at 26 weeks
- Secondary outcomes
  - CGM metrics, insulin dose, weight, DTSQ
- Safety outcomes
  - Severe hypoglycemia/DKA
  - Pulmonary and other adverse events
  - FEV1



INHALE-1

Key Eligibility Criteria

INHALE-1

Inclusion

- Age 4 to <18 years old
- T1D for ≥ 6m or
- T2D for ≥ 3m
- MDI treatment (allowed to come off pump)
- HbA1c 7.0% to 11.0%
- Average Prandial >2 units

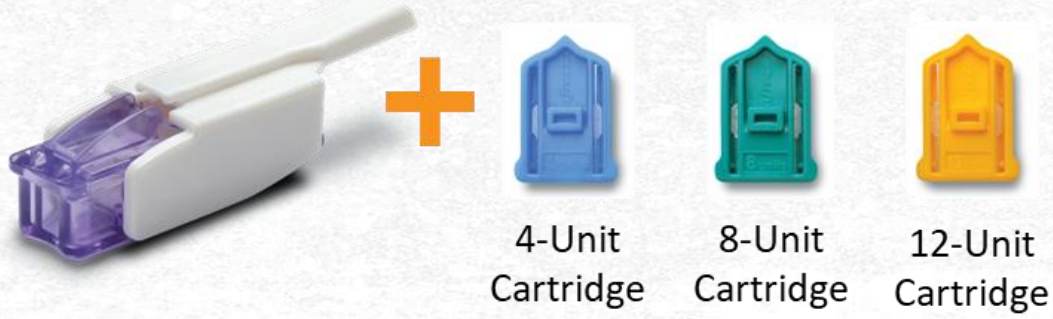
Exclusion

- Asthma tx in prior 12m
- Smoking in prior 6m
- FEV1 <80% Predicted
- History of lung cancer
- Pregnant or breastfeeding
- DKA/severe hypo prior 3m

Inhaled Insulin Dosing Regimen

- Starting dose – double the RAA dose and rounding down to nearest multiple of 4
- First dose - in clinic with a standardized meal (max of 16 “Afrezza units”)
- Subsequent doses increased without limit
- Inhale at start of meal and no later than 20 min after start of meal
- Titrate to 60-90 min post prandial 70-160 mg/dl
- 4 unit corrections if > 160 at 1 hour
- Bed time corrections
- Blinded insulin titration committee

RAA Dose (Units)	Starting TI Dose* (“Afrezza Units”)
≤3	4
4-5	8
6-7	12
8-9	16
≥10	16



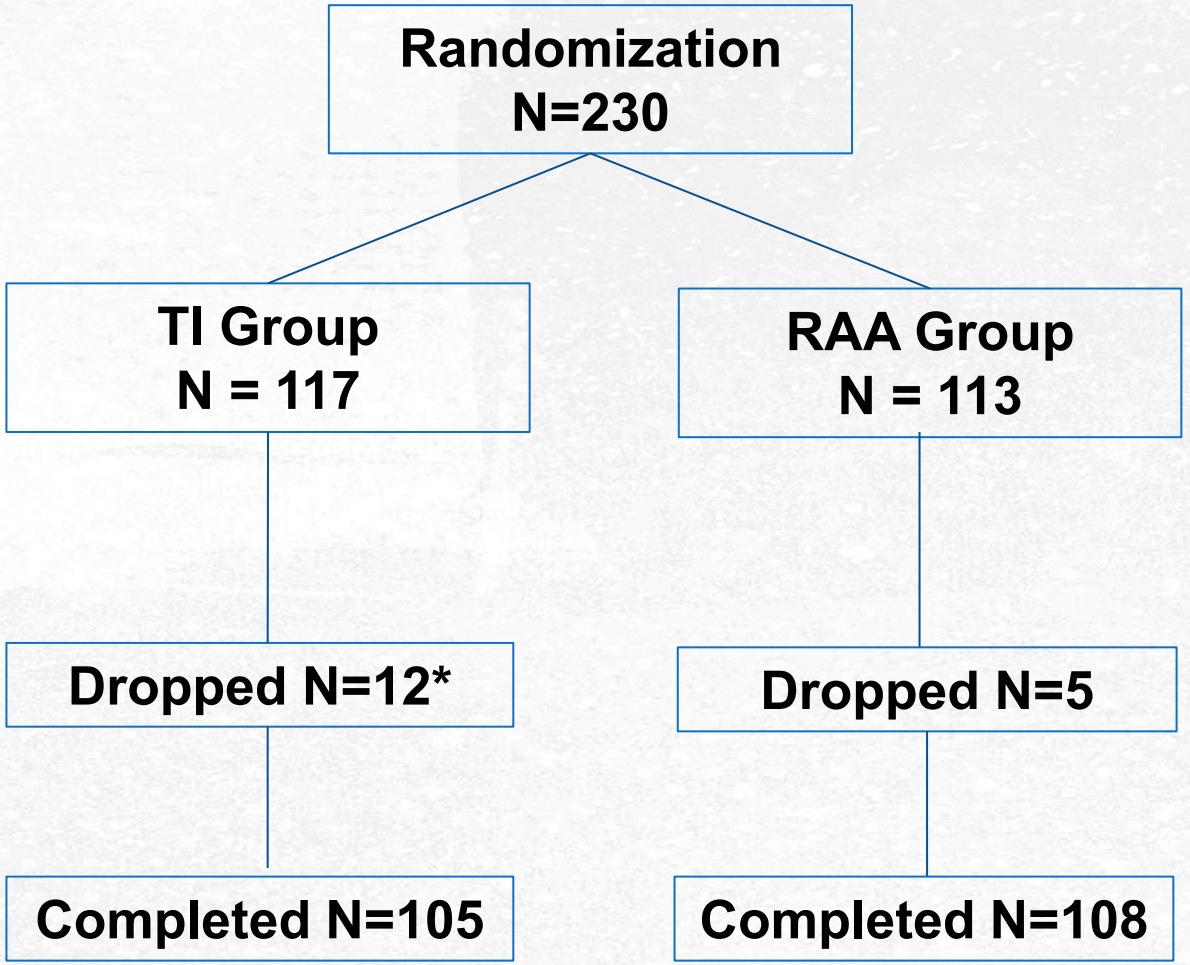
Rapid Acting Analog (RAA) Injection Group

- Instructed to give RAA bolus ~15min prior to meal
- RAA dose adjustments for breakfast based on the lowest pre-lunch glucose level over a 3-day period, for lunch based on lowest pre-dinner glucose, and for dinner based on lowest pre-bedtime glucose
- Basal insulin dose adjusted with goal of fasting glucose 70-120 mg/dL without hypo for both groups

INHALE-1

RESULTS

INHALE-1



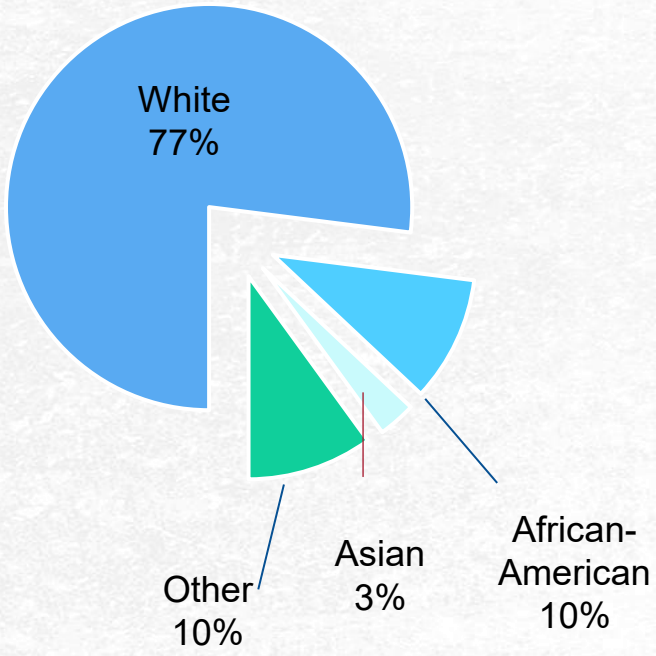
*15 additional participants stopped TI but completed the trial

INHALE-1

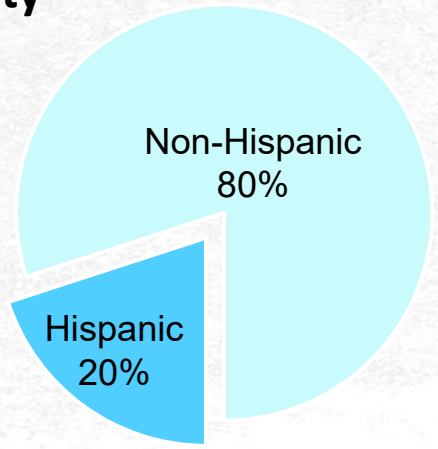
Baseline Characteristics (N=230)

Age mean	12.6 yrs (range 4-17)
Female	38%
T1D/T2D	225 (98%) / 5 (2%)
Mean Diabetes Duration	4.4 yrs (range 0.5-15yrs)
Parent Education < Bachelors Degree	45%
Annual Household Income <100K	44%
Private Insurance	67%
BMI mean percentile / $\geq 95^{th}$%	74 / 23%

Race

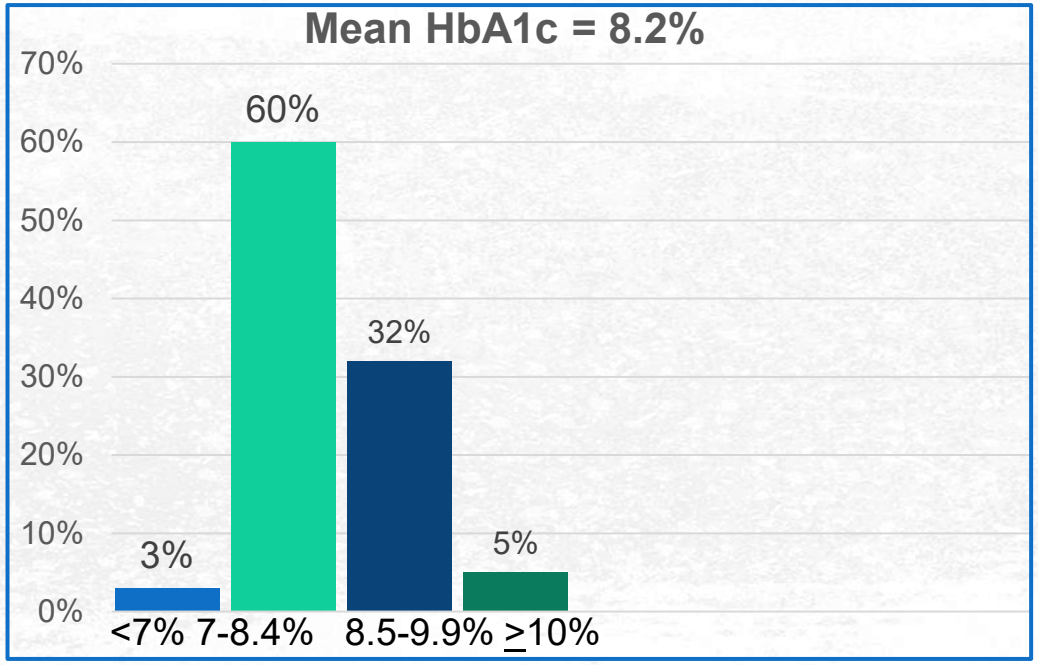


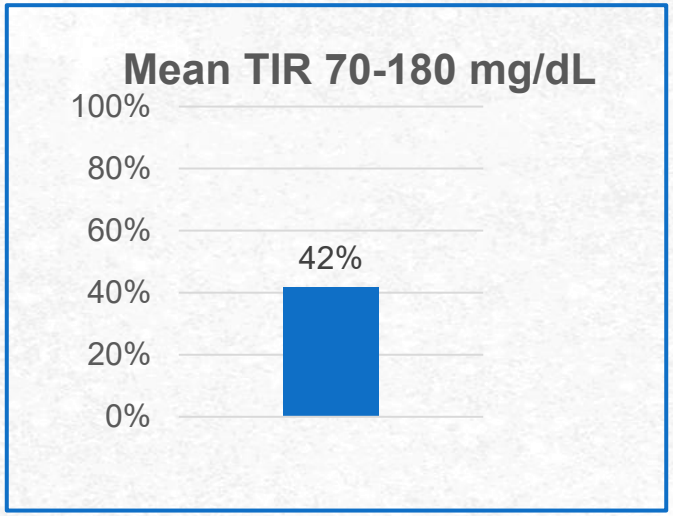
Ethnicity

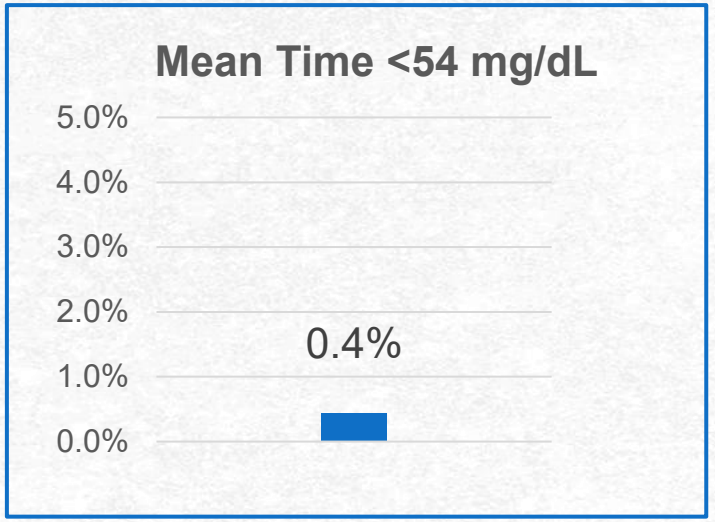


Other Baseline Characteristics (N=230)

Total Daily Insulin mean	1.02 units/kg/day
Prior Asthma Dx	2%
DKA in Prior 12m	9%
Severe Hypo in Prior 12m	4%





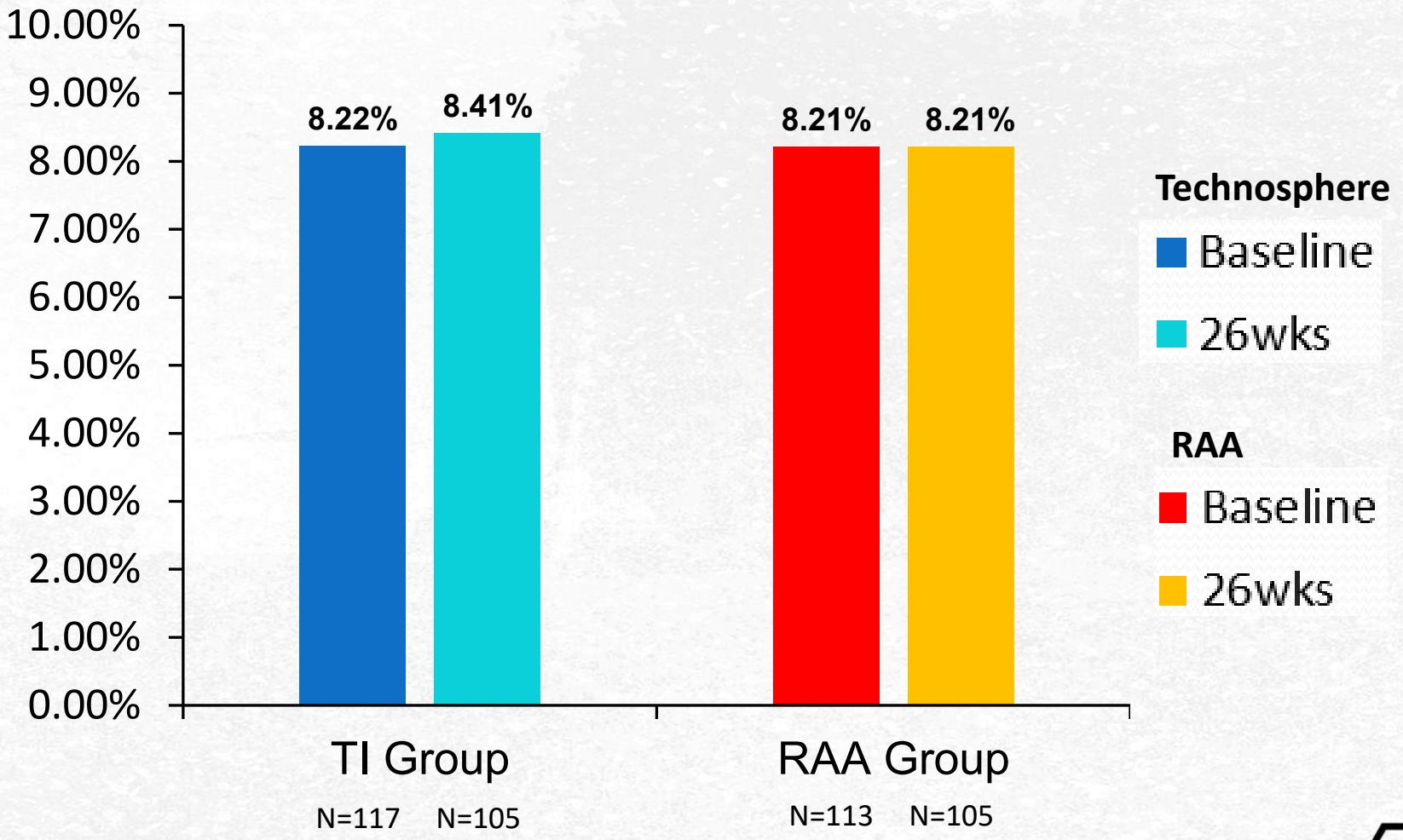


INHALE-1

INHALE-1

Primary Endpoint

Primary Endpoint: HbA1c at 26 weeks



Difference 0.18% (95% CI -0.07 to 0.43)

P=0.091 for non-inferiority*

*non-inferiority margin 0.4%

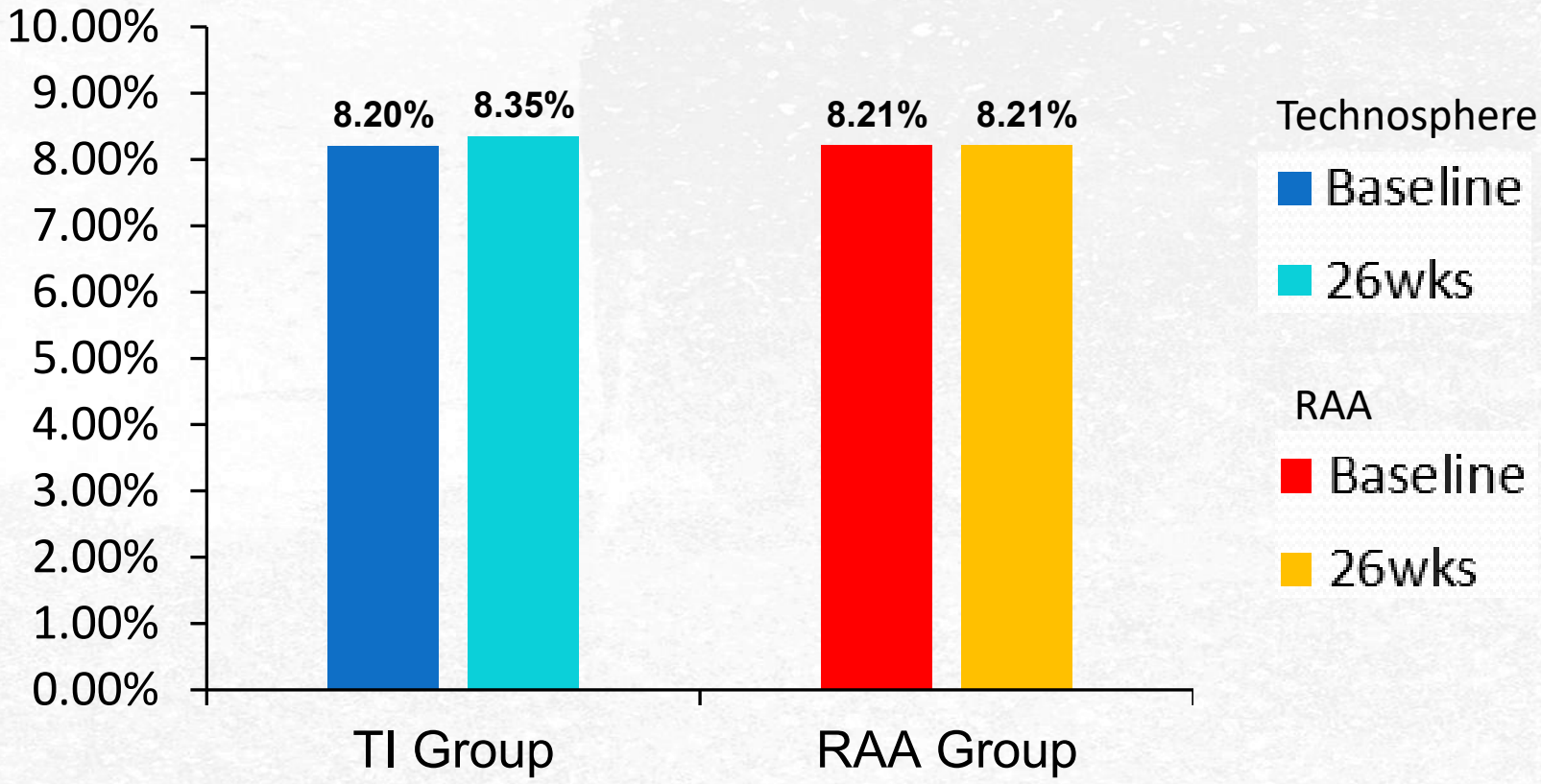
INHALE-1

American Diabetes Association.

85TH SCIENTIFIC SESSIONS

#ADASciSessions

Sensitivity Analysis*



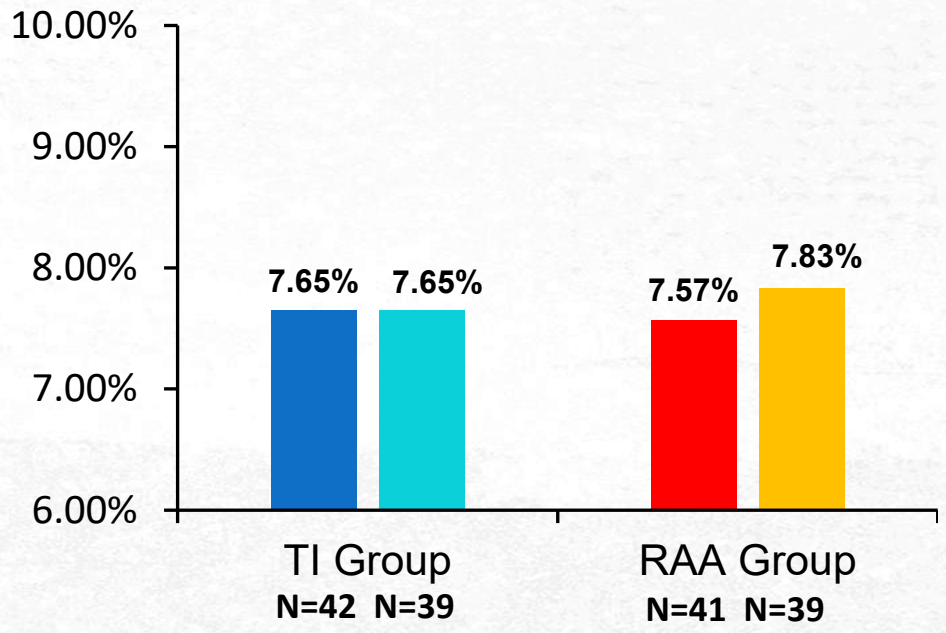
Difference 0.14% (95% CI -0.10 to 0.37)

P=0.026 for non-inferiority*

INHALE-1

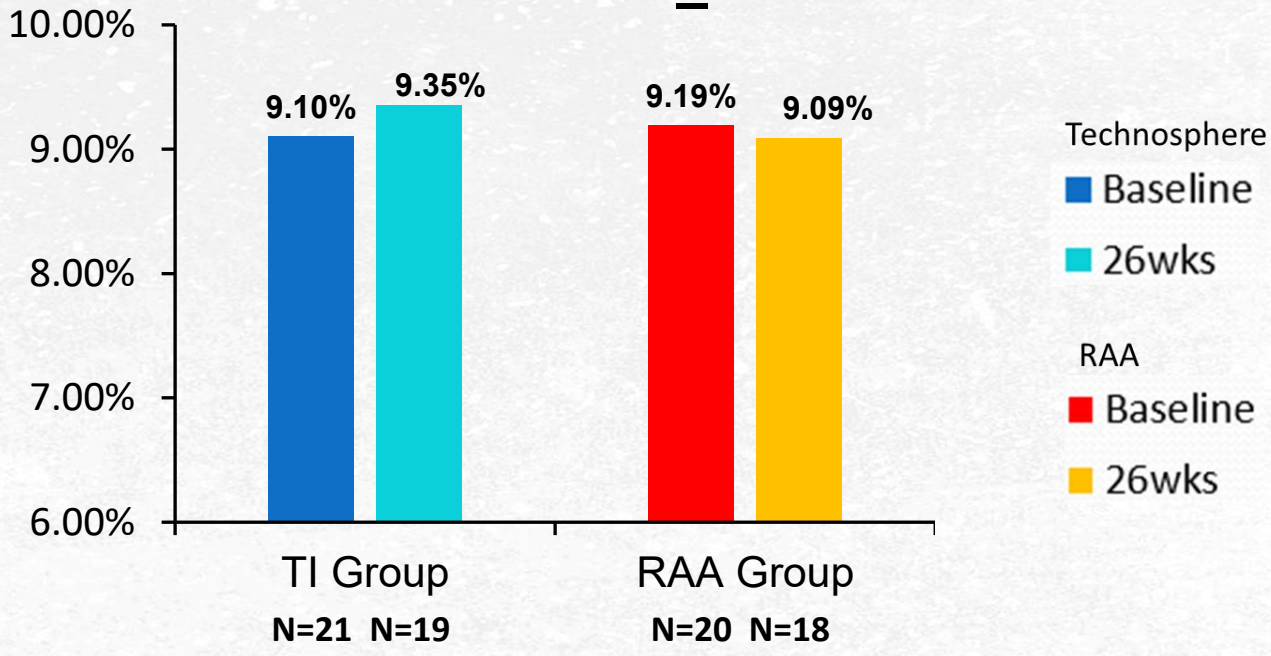
HbA1c by Age ≥ 13 years and Baseline A1c < or > 8.5%

Baseline A1C <8.5%



Trt grp diff = -0.17
(95% CI -0.56 to 0.22)

Baseline A1c ≥8.5%



Trt grp diff = 0.17
(95% CI -0.61 to 0.94)

INHALE-1

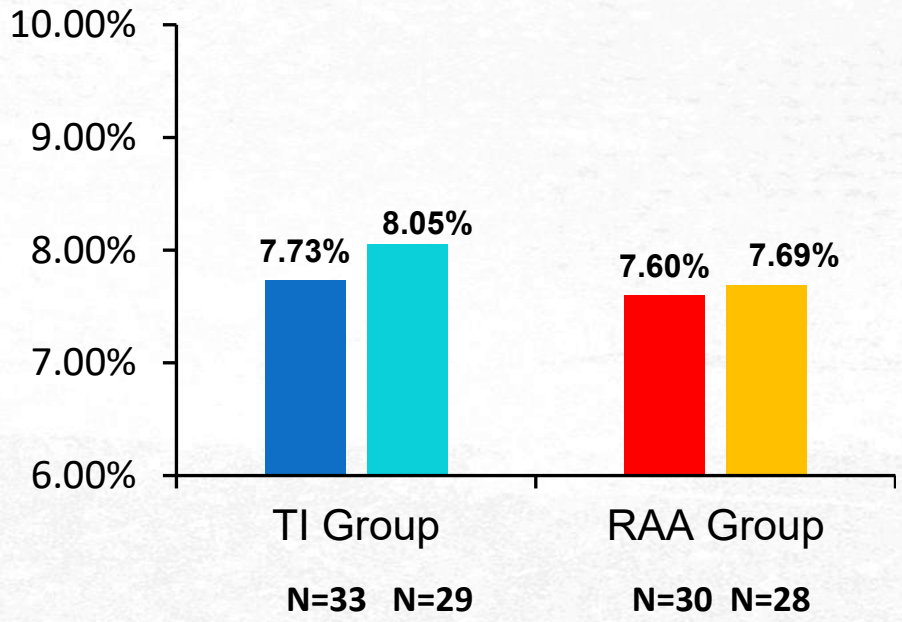
American Diabetes Association.

85TH SCIENTIFIC SESSIONS

#ADASciSessions

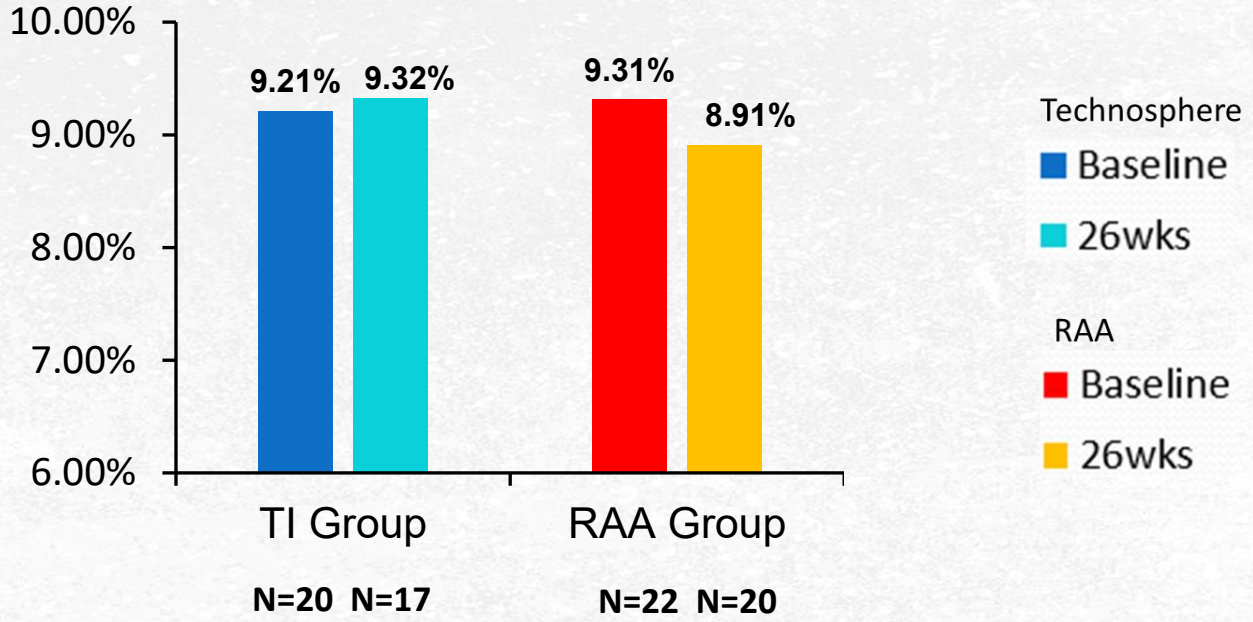
HbA1c by Age < 13 and Baseline A1c < or > 8.5%

A1C <8.5%



Trt grp diff = 0.23
(95% CI -0.36 to 0.82)

A1C ≥8.5%



Trt grp diff = 0.58
(95% CI -0.10 to 1.25)

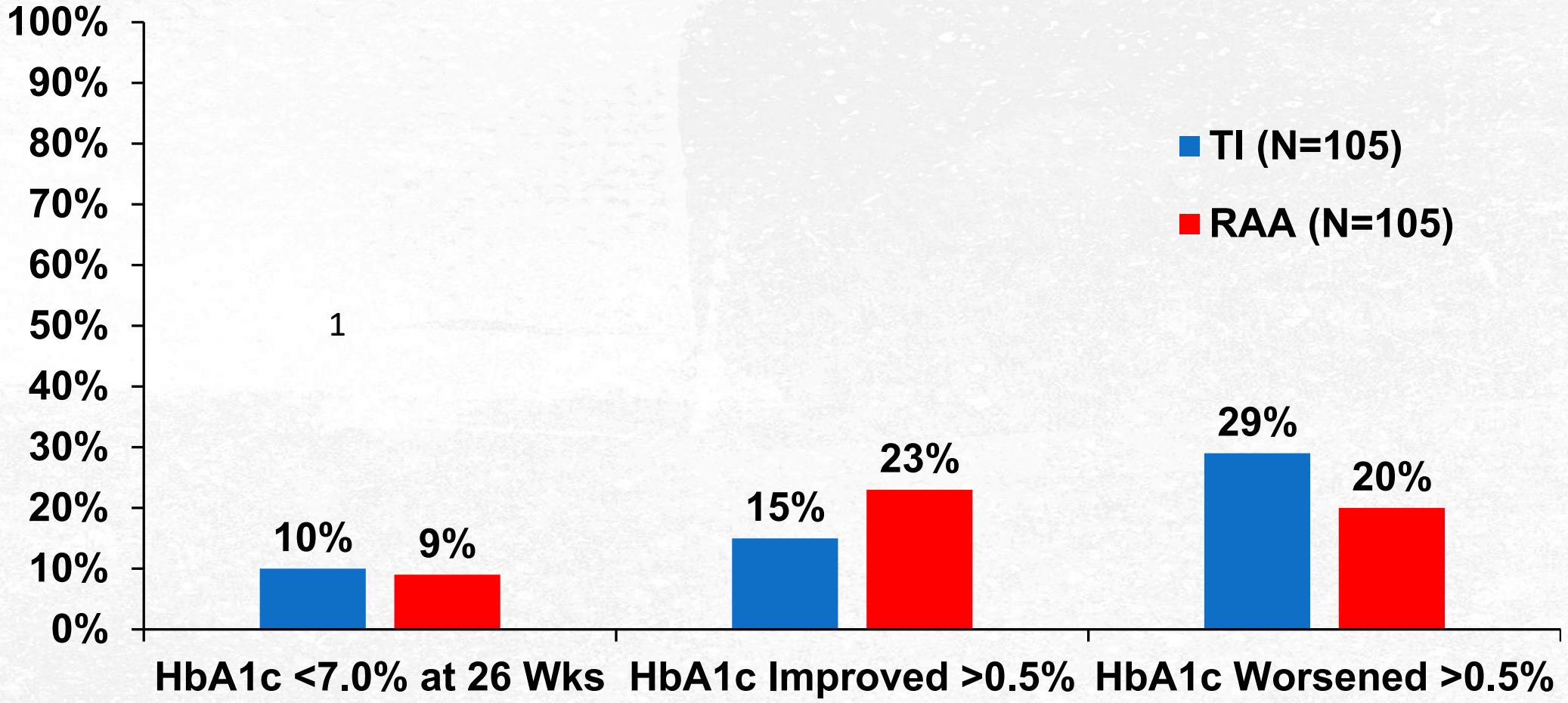
INHALE-1

American Diabetes Association.

85TH SCIENTIFIC SESSIONS

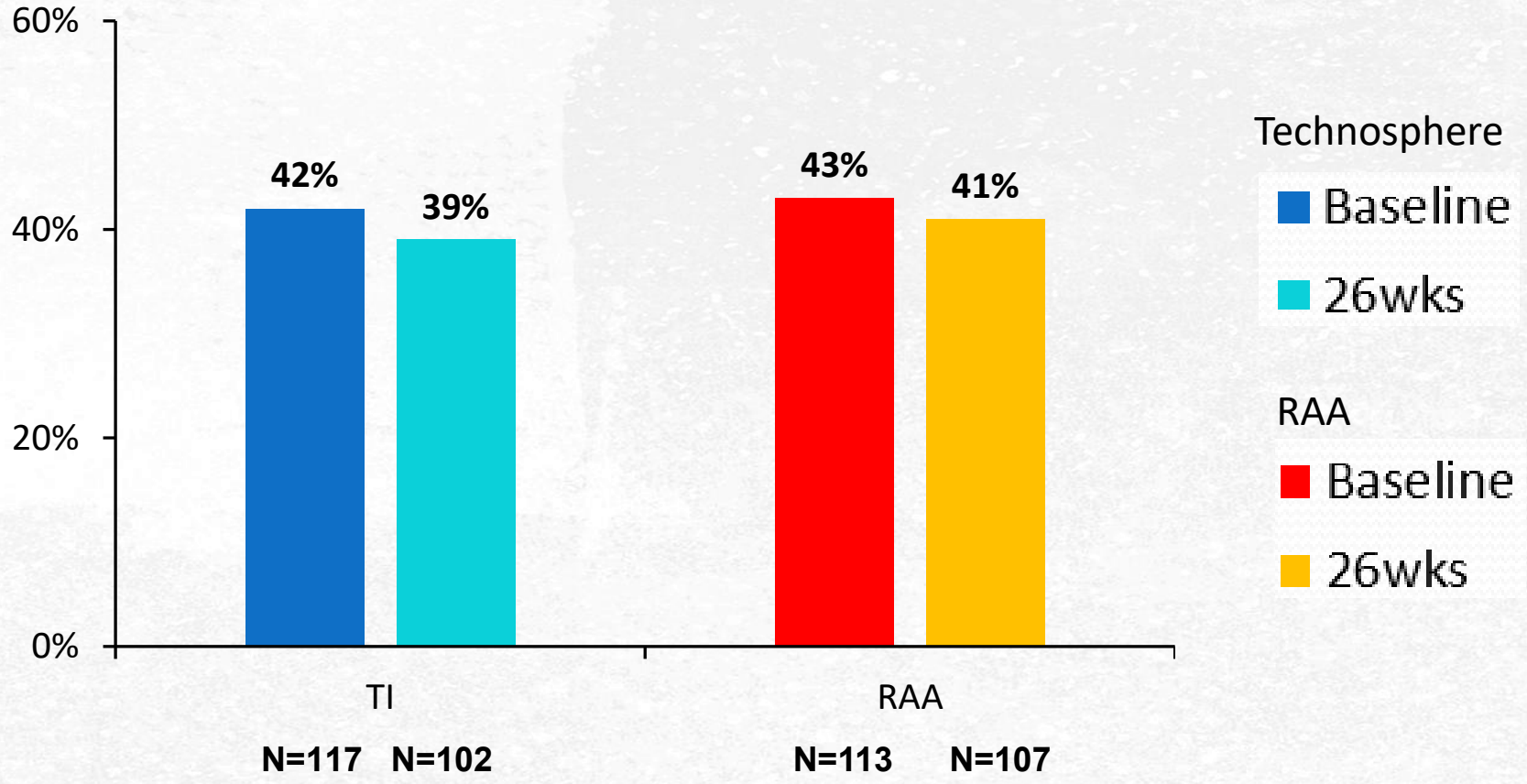
#ADASciSessions

HbA1c Secondary Endpoints



INHALE-1

CGM Time-in-Range 70-180 mg/dL



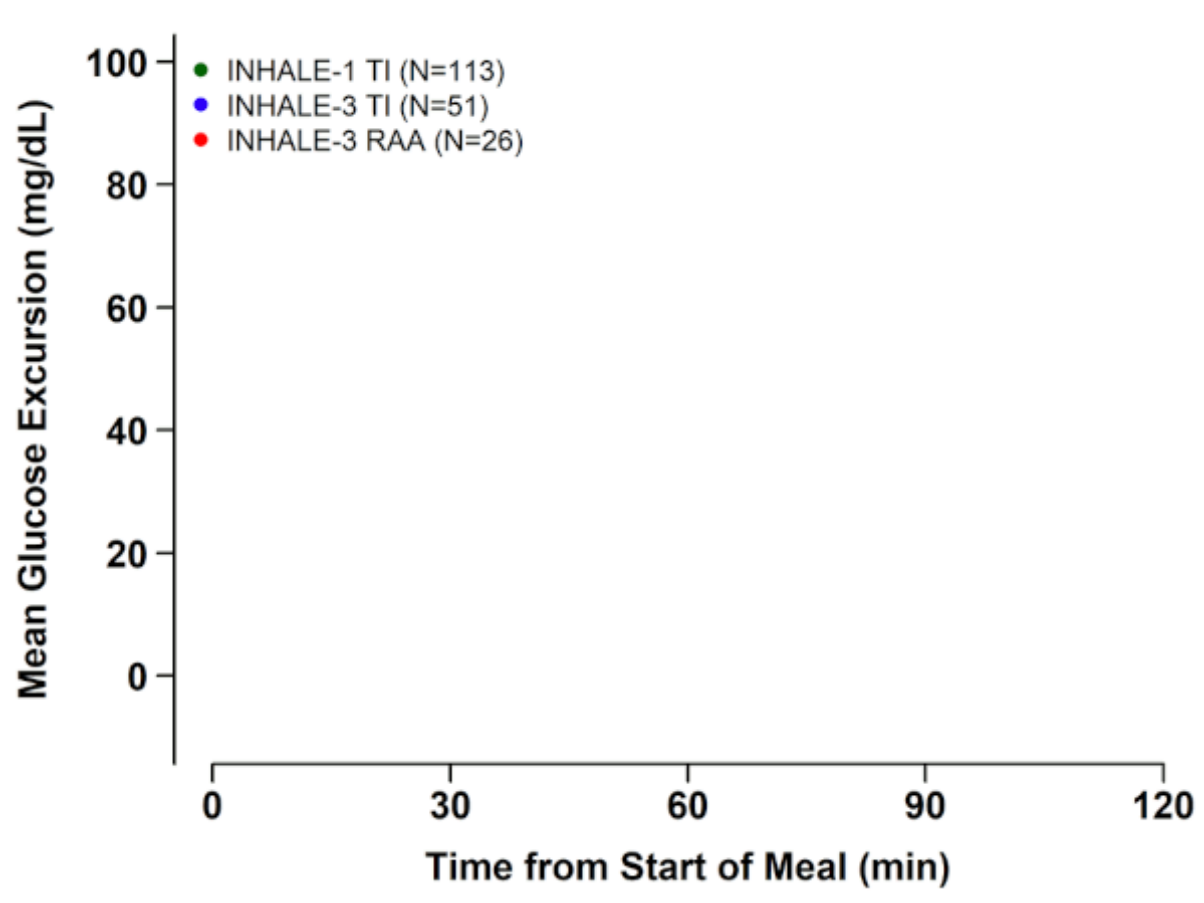
Trt grp difference = -2.2%
95% CI -7.0% to 2.7%
P = 0.38

INHALE-1

Observed Meal Challenge at TI Initiation

INHALE -3 (Adults) RAA
INHALE -3 (Adults) – TI
INHALE -1 (Peds) - TI

- Mean (±SD) glucose excursion less with TI
  - 101±45 mg/dL in adults with RAA
  - 73±50 mg/dL adults with TI
  - 69±56 mg/dL in Peds with TI
- Time to peak glucose shorter with TI:
  - 78±31 min in adults with RAA
  - 71±36 min in adults with TI
  - 69±34 min in Peds with TI

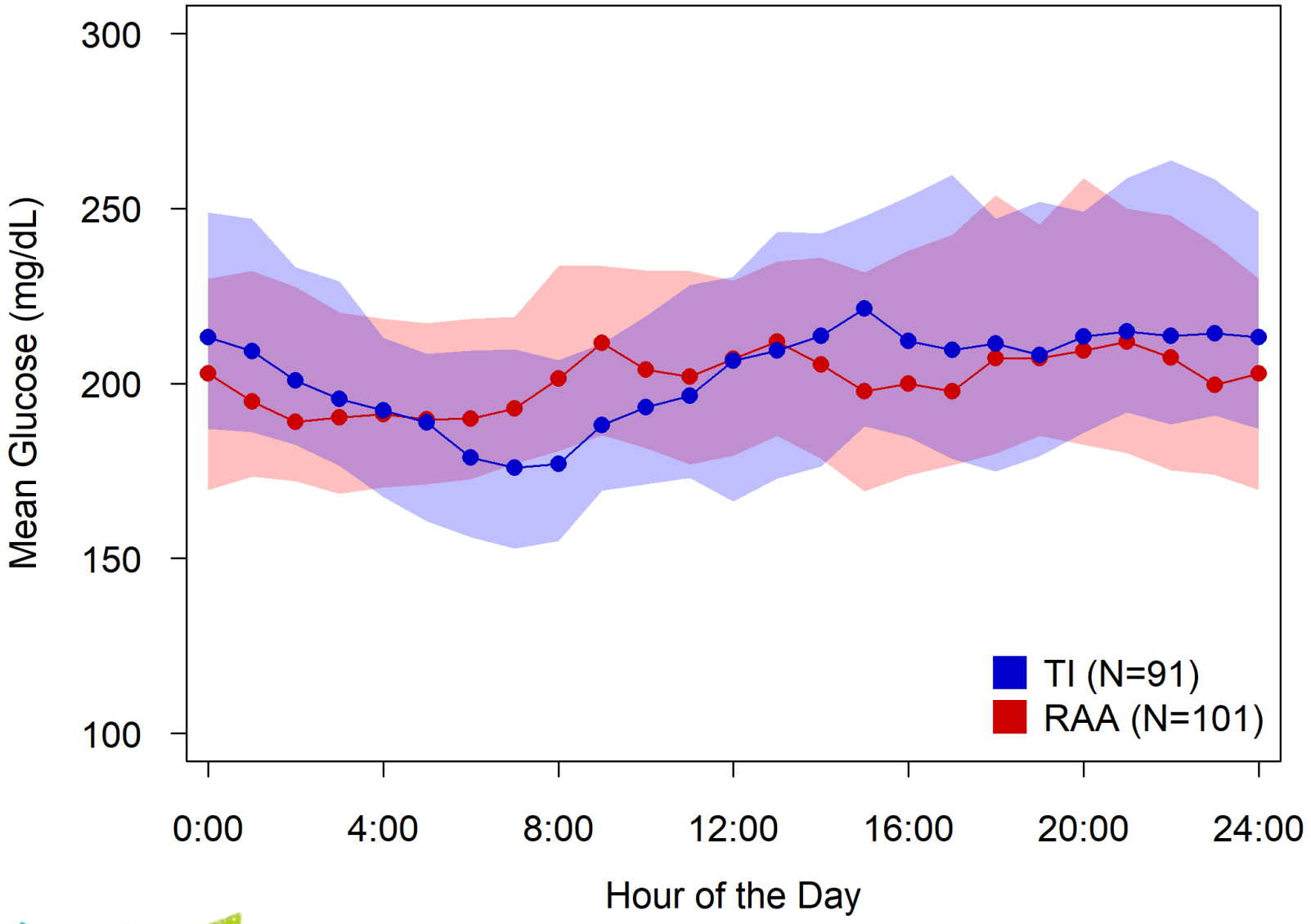


INHALE-1

American Diabetes Association.

85TH SCIENTIFIC SESSIONS
#ADASciSessions

Mean Glucose By Time of Day - 26 weeks



INHALE-1

American Diabetes Association.

85TH SCIENTIFIC SESSIONS

#ADASciSessions

Insulin Use – Baseline to 26 Weeks

TI

	units/kg/day
Baseline	
Total Daily Insulin	1.06
Basal Insulin	0.46
RAA Insulin	0.60
26 Weeks	
Total Basal Insulin	0.50
Total TI Insulin	1.45
Ratio of 26w TI to Baseline RAA*	2.96

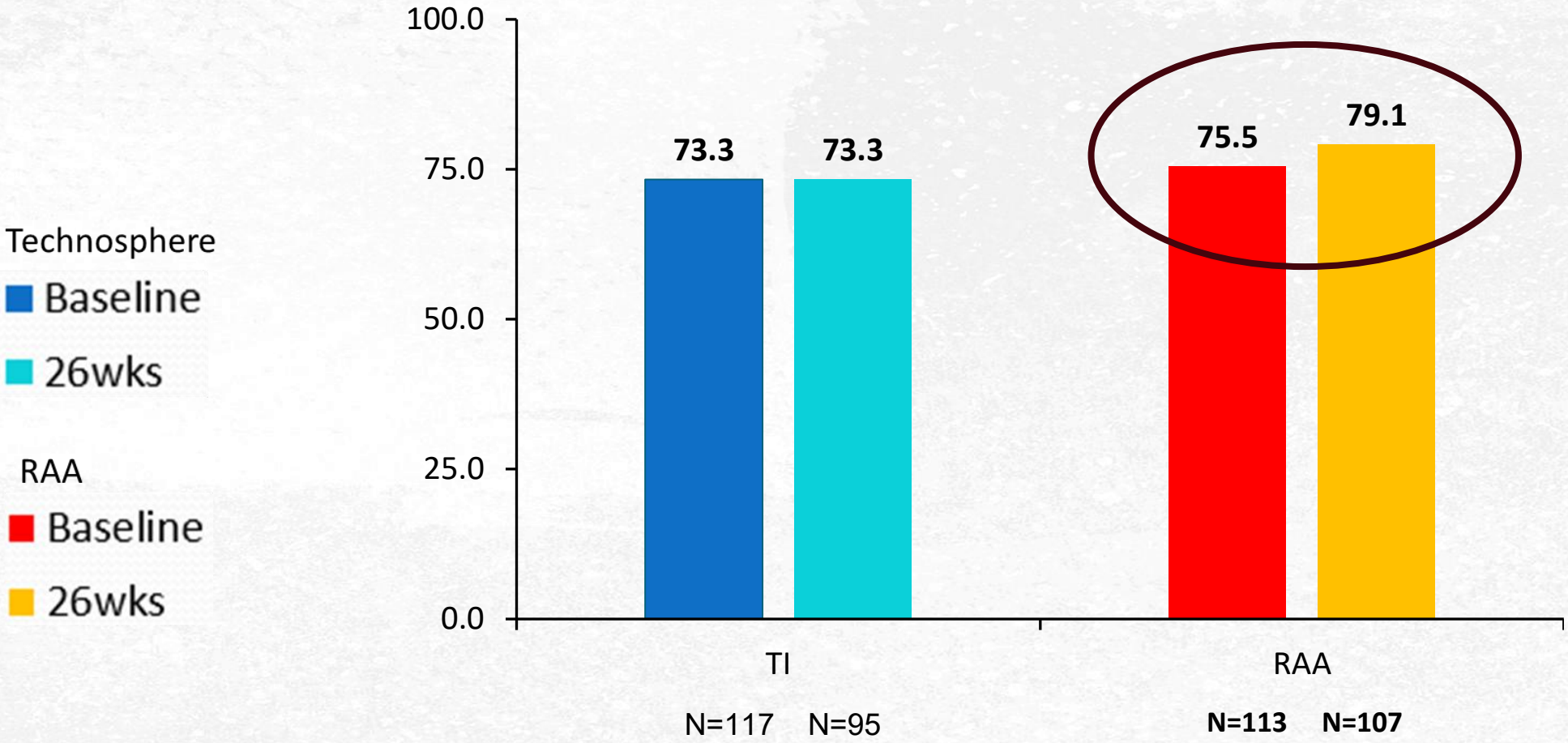
RAA

	units/kg/day
Baseline	
Total Daily Insulin	0.98
Basal Insulin	0.41
RAA Insulin	0.56
26 Weeks	
Total Daily Insulin	1.06
Basal Insulin	0.45
RAA Insulin	0.61

*Afrezza Units are note the same as RAA units

INHALE-1

BMI Increases with RAA but not TI



Trt grp difference -4.2

95% CI -7.4 to -0.9

P = 0.009

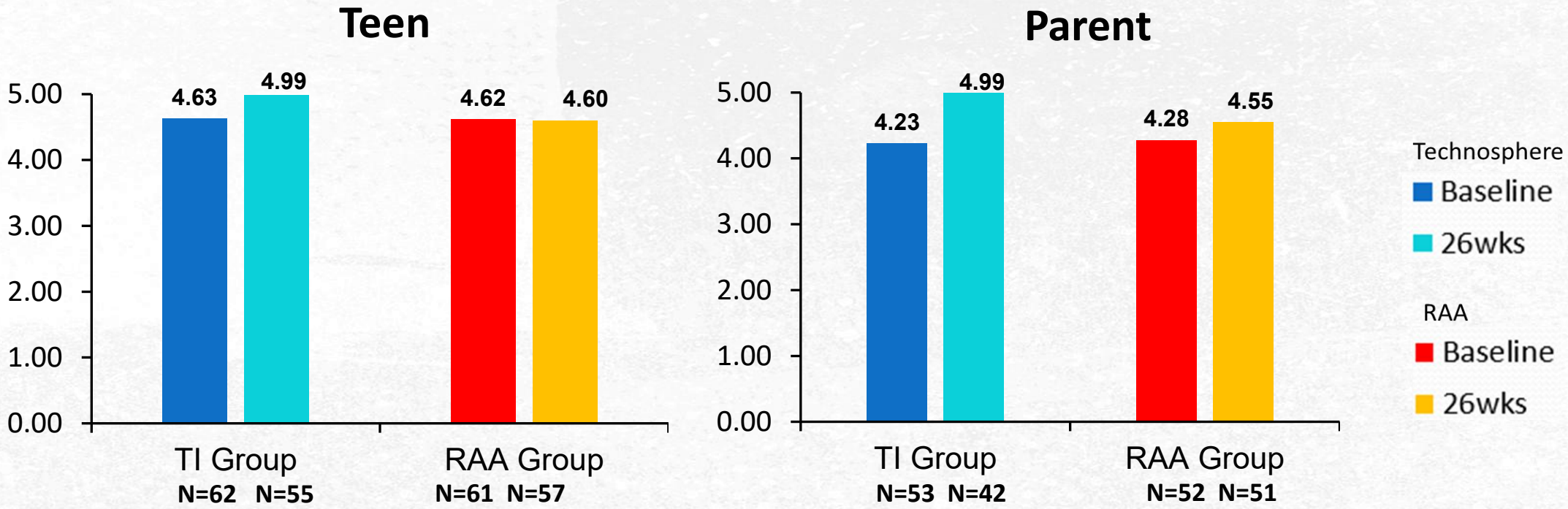
INHALE-1

American Diabetes Association.

85TH SCIENTIFIC SESSIONS

#ADASciSessions

Diabetes Treatment Satisfaction Questionnaire (DTSQ)



TI group vs. RAA group
Pooled for teens and parents
P = 0.004

INHALE-1

SAFETY OUTCOMES

Summary of Adverse Outcomes

	TI (n=117)	RAA (n=113)
All Adverse Events (AEs) N Events	240	195
# of Participants with ≥ 1 AE	88 (75%)	75 (66%)
Severe Hypoglycemia Events	2	1
Diabetic Ketoacidosis Events	0	1
Other Serious Adverse Events	1[a]	2[b]

[a]Spinal surgery

[b]Osteomyelitis and suicide attempt in one participant

INHALE-1

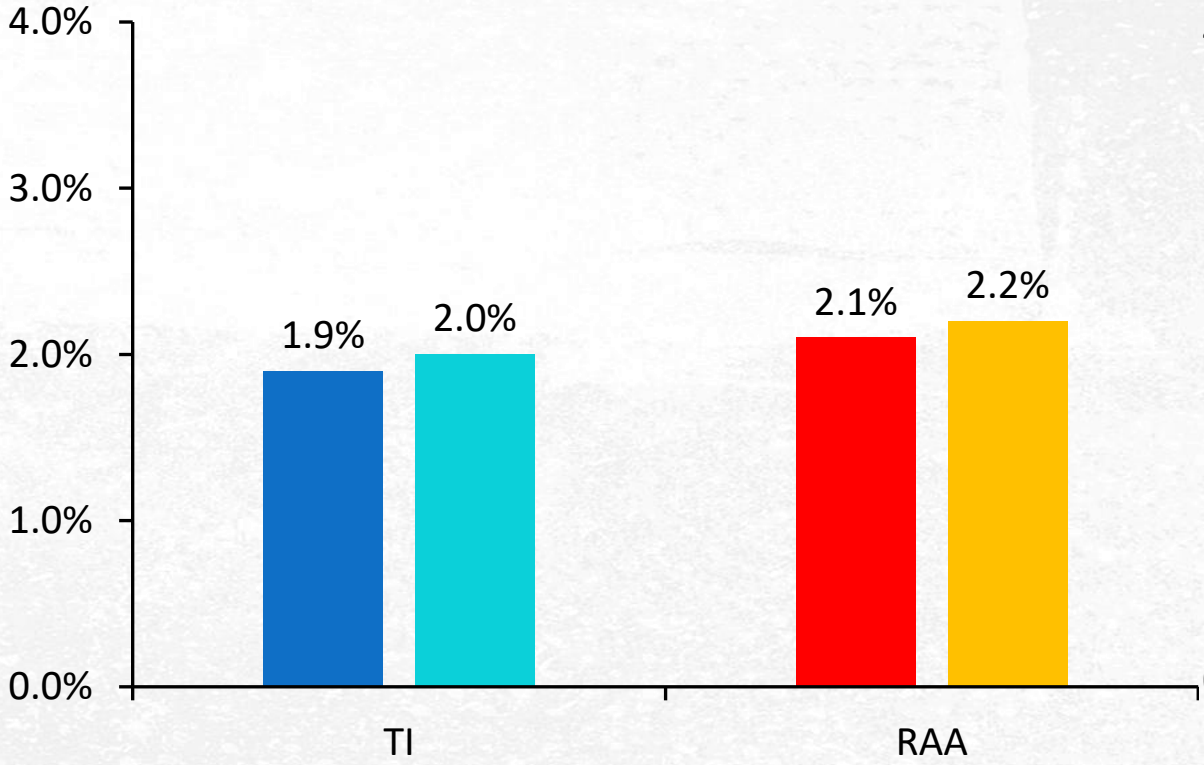
Respiratory/Pulmonary Adverse Events Considered Possibly Related to TI Inhalation

	N of participants
Cough	20
Oropharyngeal pain	9
Pulmonary function test abnormal*	5
Dysgeusia	2
Dyspnea	1
Chest discomfort	1
Anxiety	1
Bronchospasm	1
Ketosis	1
Hypoglycemia	1
Fatigue	1
Headache	1
Nausea	1
Pain	1
Wheezing	1
Chest Pain	1

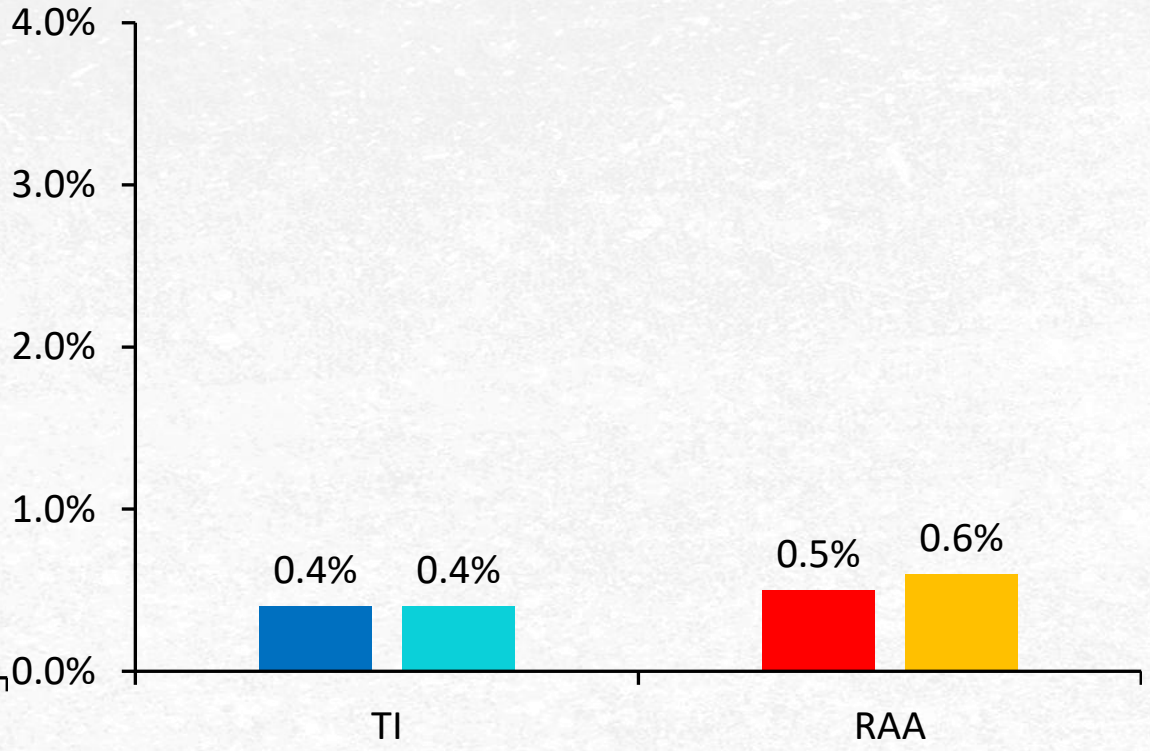
- Cough with inhalation - Only 20/117 (17%)
- Typically mild at time of inhalation (sip of water prior mitigates)
- Frequency consistent with adult studies

CGM Metrics: Hypoglycemia

Percent Time <70 mg/dL

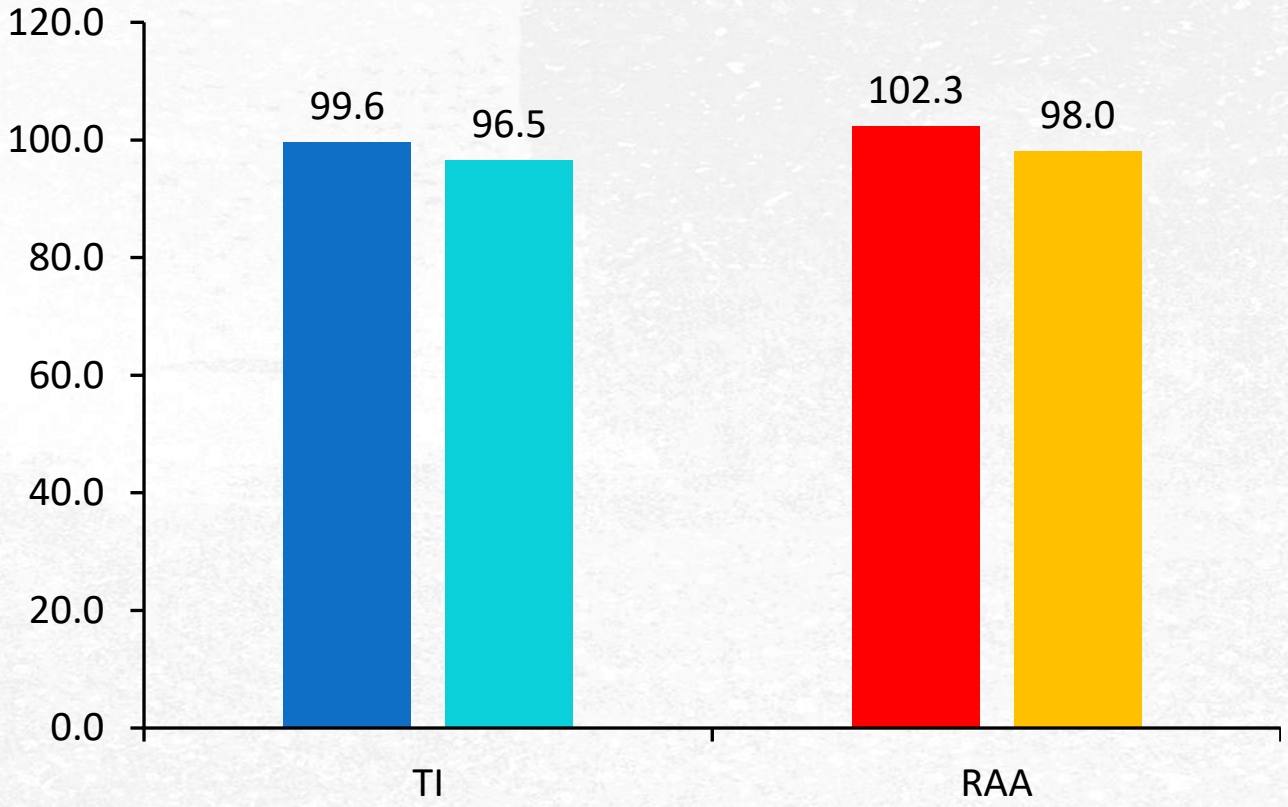


Percent Time <54 mg/dL



INHALE-1

Percent Predicted Forced Expiratory Volume in 1 Second (FEV_1)Results



26w adjusted trt grp difference = +0.7
95% CI -1.5 to +2.8)
P = 0.53

INHALE-1

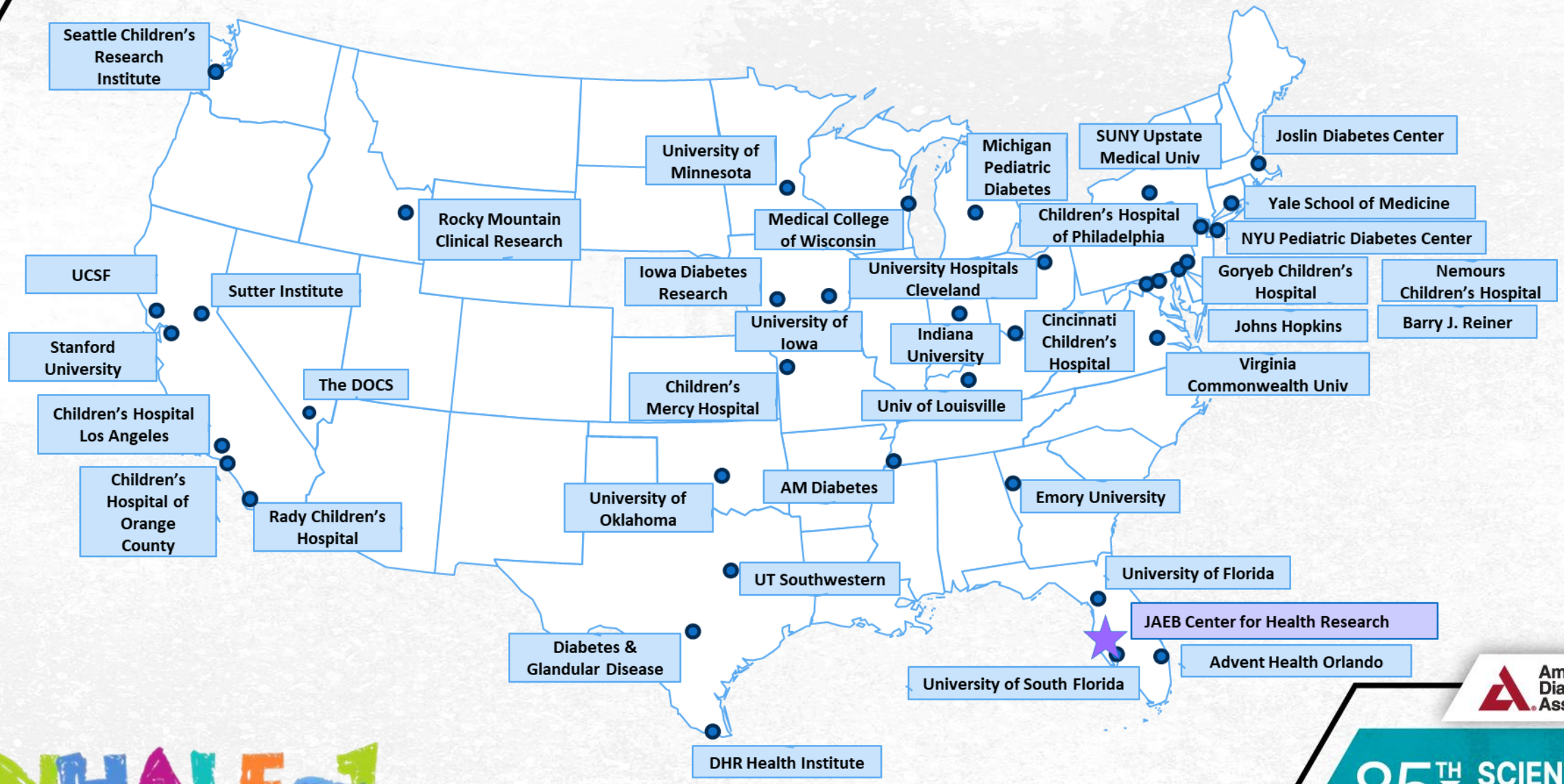
Summary

- Multi-center (38 U.S sites) 26w RCT
- 230 youth age 4-17 years with diabetes (98% T1D), using MDI
- Primary analysis did not meet pre-specified criteria for non-inferiority
- Sensitivity analysis met non-inferiority excluding one outlier
- More weight gain with RAA than TI
- Greater treatment satisfaction with TI than RAA
- No safety signals: FEV_1 at 26w
- Standardized meal challenge shows reduced post-meal excursion with TI

Conclusions

1. INHALE-1 supports the safety and efficacy of TI (Afrezza) in youth with diabetes
2. Inhaled insulin is associated with less weight gain and increased patient and parent satisfaction
3. Inhaled Insulin is an important alternative to injected RAA for youth with diabetes

INHALE-1 Participants, Clinical Sites, Staff



INHALE-1

American Diabetes Association.

85TH SCIENTIFIC SESSIONS

#ADASciSessions

Principal Investigators / Sites

- Joslin Diabetes Center, Boston MA: Lori Laffel
- Stanford University, Palo Alto, CA: David Maahs
- Yale School of Medicine, New Haven, CT: Michelle Van Name
- Children's Hospital of Orange County, Orange, CA: Himala Kashmiri
- UT Southwestern, Dallas, TX: Perrin White
- Rady Children's Hospital, San Diego, CA: Anna Cymbaluk
- Emory University, Atlanta, GA: Kristina Cossen
- University of Florida, Gainesville, FL: Michael Haller
- Iowa Diabetes & Endocrinology Research, West Des Moines, IA: Anuj Bhargava
- Advent Health Orlando, Orlando, FL: Konda Reddy
- Rocky Mountain Clinical Research, Idaho Falls, ID: Joshua Smith
- Children's Hospital Los Angeles, Los Angeles, CA: Roshanak Monzavi
- Children's Hospital of Philadelphia, Philadelphia, PA: Steven Willi
- Children's Mercy Hospital, Kansas City, MO: Mark Clements
- University of Louisville, Louisville, KY: Kupper Wintergerst
- University of California, San Francisco, CA: Laya Ekhlaspour
- University Hospitals Cleveland, Cleveland, OH: Jamie Wood
- Seattle Children's Research Institute, Seattle, WA: Faisal Malik
- SUNY Buffalo, Buffalo, NY: Kathleen Bethin
- Indiana University, Indianapolis, IN: Linda DiMeglio
- University of Minnesota, Minneapolis, MN: Shannon Beasley & Dr. Toni Moran
- University of South Florida, Tampa, FL: Henry Rodriguez
- University of Iowa, Iowa City, IA: Michael Tansey
- Michigan Pediatric Endocrine & Diabetes Services: Michael Wood
- Diabetes & Glandular Disease Clinic, San Antonio, TX: Mark Kipnes
- AM Diabetes & Endocrinology Center, Bartlett, TN: Kashif Latif
- Goryeb Children's Hospital, Morristown, NJ: Kanika Shanker
- The DOCS, Las Vegas, NV: Asheesh Dewan
- Sutter Institute for Medical Research, Sacramento, CA: Gnanagurudasan Prakasam
- Barry J. Reiner, MD, LLC, Baltimore, MD: Barry J. Reiner
- Medical College of Wisconsin, Milwaukee, WI: Rosanna Fiallo-Scharer
- NYU Pediatric Diabetes Center, New York, NY: Mary Pat Gallagher
- University of Oklahoma Health Sciences Center, Oklahoma City, OK: David Sparling
- Virginia Commonwealth University, Richmond, VA: Bryce Nelson
- Johns Hopkins, Baltimore, MD: Scott Blackman
- DHR Health Institute for Research & Development , Edinburg, TX: Surya Narayan Mulukutla
- Cincinnati Children's Hospital, Cincinnati, OH: Nicole Sheanon
- Nemours Children's Hospital, Wilmington, DE: Patrick Hanley