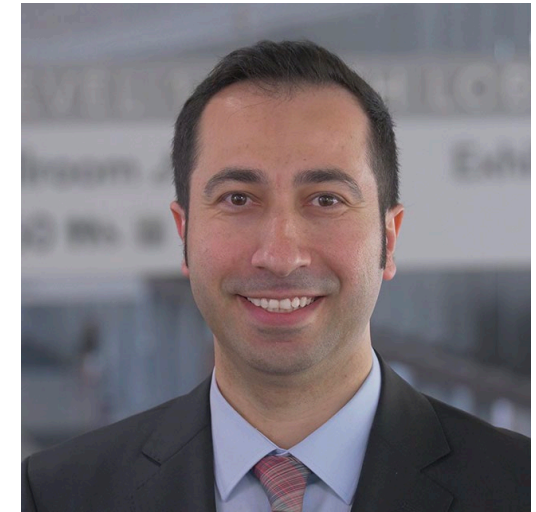


SESSION 4 ADULT SESSION

NOVEL AND UPCOMING INSULINS: FASTER INSULINS, INHALED INSULIN, AND WEEKLY BASAL INSULINS



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JUNE 1, 2024 CU ANSCHUTZ MEDICAL CAMPUS

EMPOWERING PATIENTS
FOR
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COI- DR. POLSKY

- Contributing Writer: diaTribe.
- Medical Advisory Board: Medtronic MiniMed, Inc (2020).
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COI-DR.AKTURK

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Beatson Foundation**

Consultant: Dexcom, Tandem Diabetes, Medtronic

OVERVIEW OF BASAL INSULINS

How the body secretes insulin:

Basal • Continuous insulin: constant regulation of glucose production from the liver and of fat breakdown **in between meals or while fasting**

Bolus • Pulsatile insulin: pulses of higher insulin secretion **after meals** which stimulate glucose uptake in body tissues and inhibit glucose production in the liver

Retnakaran and Zinman. *Diab Obes Metab.* 2022; 24 Suppl 1: 17-26.



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OVERVIEW OF BASAL INSULINS

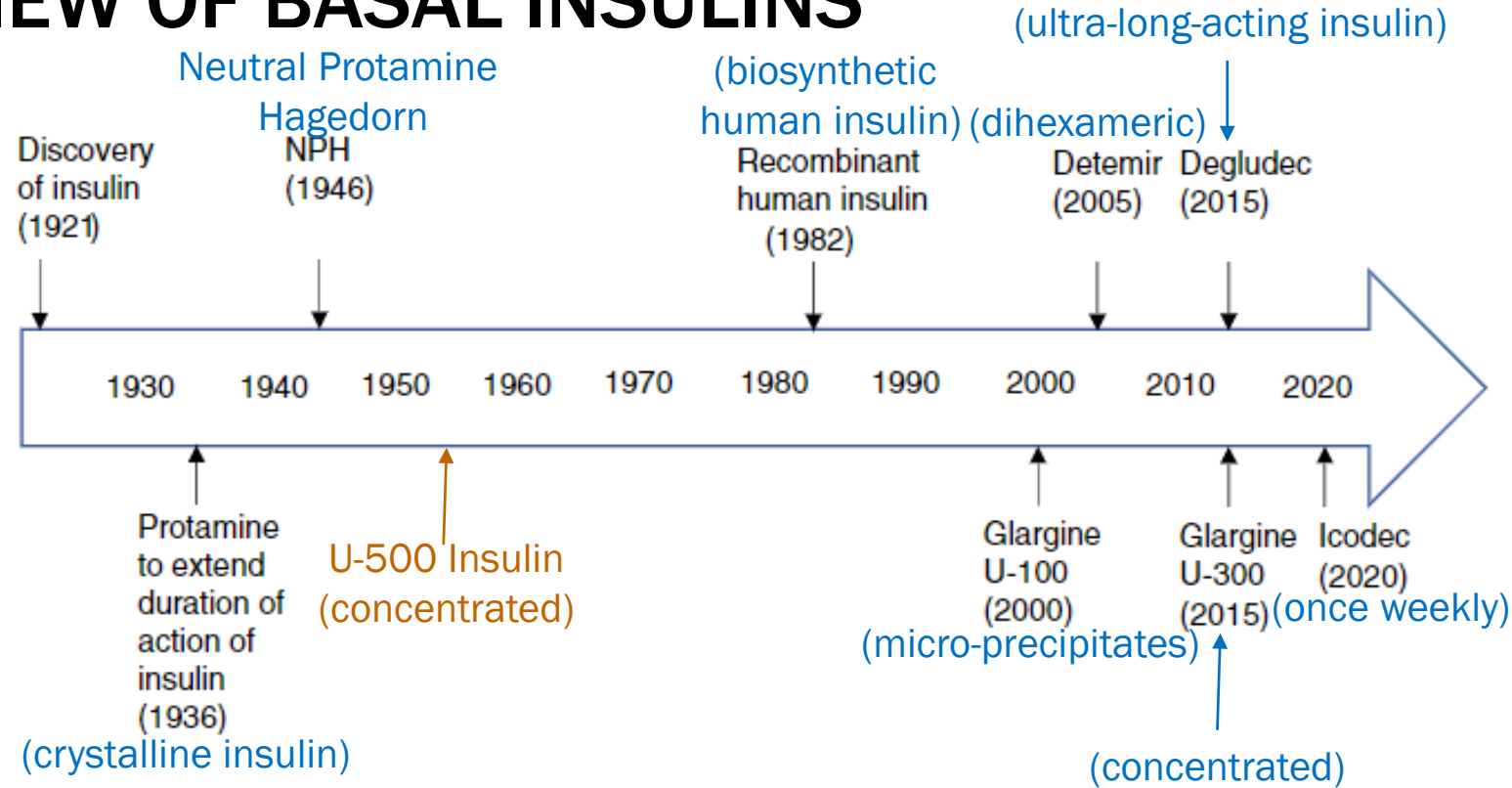


FIGURE 1 Milestones in the evolution of basal insulin formulations

Adapted from Retnakaran and Zinman. *Diab Obes Metab.* 2022; 24 Suppl 1: 17-26.



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OVERVIEW OF BASAL INSULINS

| Type of Insulin (Year) | Generic Name | Brand Name | Onset of Action (minutes) | Peak Time (hours) | Duration of Action (hours) |
|------------------------|--------------------|---------------------------------------------|---------------------------|-------------------|----------------------------|
| Intermediate-Acting | NPH | Humulin [®] , Novolin [®] | 2-4 | 4-10 | 13-18 |
| Long-Acting | Glargine-100 | Lantus [®] | N/A | -- | 24 |
| Long-Acting | Determir | Levemir [®] | N/A | -- | 14-24 |
| Long-Acting | Glargine-300 | Toujeo [®] | N/A | -- | Up to 36 |
| Long-Acting | Degludec | Tresiba [®] | N/A | -- | >40 |
| Long-Acting | (not yet approved) | Icodec [®] | N/A | 16 | >168 |

Emad-Eldin M, et al. *World J Diab.* 2024; 15(5): 828-852. Nishimura E, et al. *BMJ Open Diabetes Res Care.* 2021; 9(1): e002301.

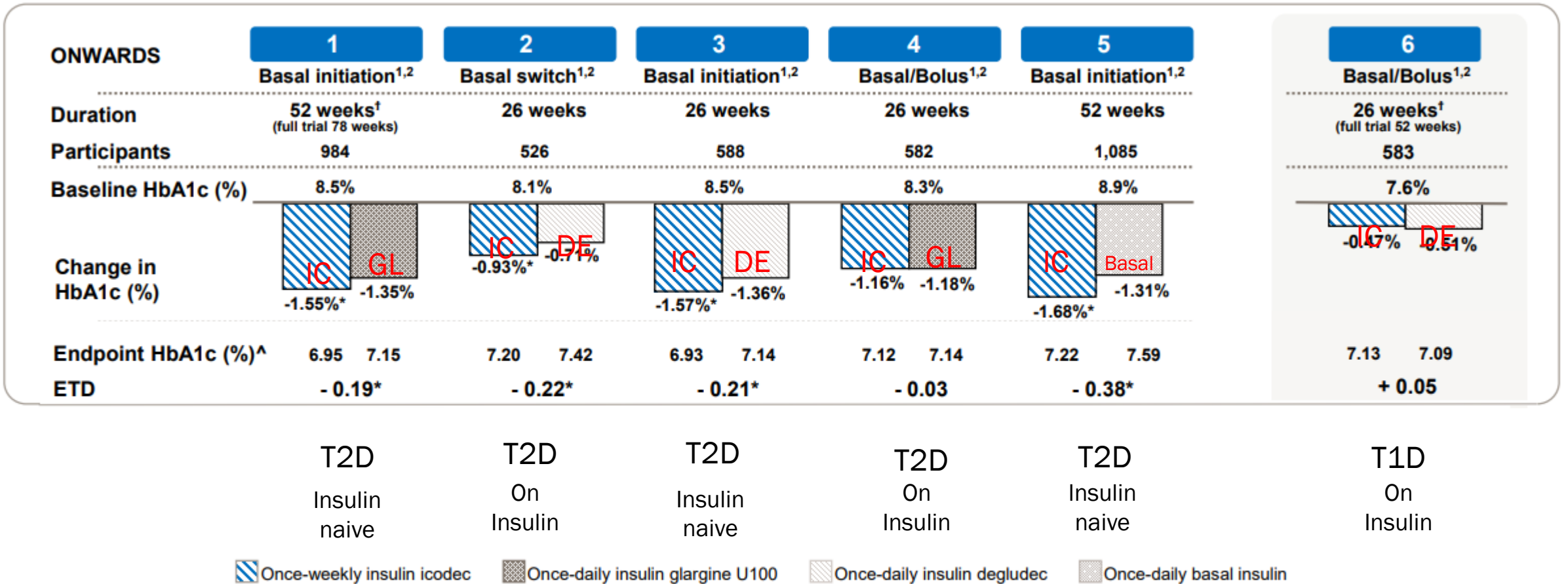


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INSULIN ICODEC STUDIES



- All studies achieved NI for HbA1c change from baseline, NI margin 0.3%
- * ONWARDS 1,2,3,5 achieved statistically significant superiority in HbA1c reduction
- Onwards 1 demonstrated statistically significant improvement in TIR₇₀₋₁₈₀ mg/dL

FUTURE BASAL INSULIN: ICODEC (META-ANALYSIS)

3.1 Mean HbA1c Changes

| Study or Subgroup | Icodec | | | Non Icodec | | | Weight | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|---------------------------------------------------------------------------------------------------------------|--------|------|-------------|------------|------|-------------|---------------|---------------------------------------|---------------------------------------|
| | Mean | SD | Total | Mean | SD | Total | | | |
| 3.1.1 Vs Glargine 100 | | | | | | | | | |
| Bajaj et al. | -0.8 | 0.98 | 54 | -0.5 | 0.98 | 50 | 7.0% | -0.30 [-0.68, 0.08] | |
| Onwards 1 | -1.55 | 0.04 | 492 | -1.44 | 0.04 | 492 | 18.7% | -0.11 [-0.11, -0.11] | |
| Onwards 4 | -1.16 | 1.21 | 291 | -1.18 | 1.27 | 291 | 12.6% | 0.02 [-0.18, 0.22] | |
| Rosenstock 2020 et al | -1.4 | 0.07 | 125 | -1.09 | 0.07 | 122 | 18.7% | -0.31 [-0.33, -0.29] | |
| Titration C Lingvay et al | -1.38 | 0.08 | 51 | -1.02 | 0.08 | 51 | 18.5% | -0.36 [-0.39, -0.33] | |
| Subtotal (95% CI) | | | 1013 | | | 1006 | 75.6% | -0.22 [-0.36, -0.07] | |
| Heterogeneity: Tau ² = 0.02; Chi ² = 683.37, df = 4 (P < 0.00001); I ² = 99% | | | | | | | | | |
| Test for overall effect: Z = 2.93 (P = 0.003) | | | | | | | | | |
| 3.1.2 Vs Degludec | | | | | | | | | |
| Degludec Onwards 2 | -0.97 | 1.08 | 263 | -0.68 | 1.08 | 263 | 13.3% | -0.29 [-0.47, -0.11] | |
| Degludec Onwards 3 | -1.6 | 1.56 | 294 | -1.4 | 1.42 | 294 | 11.1% | -0.20 [-0.44, 0.04] | |
| Subtotal (95% CI) | | | 557 | | | 557 | 24.4% | -0.26 [-0.40, -0.11] | |
| Heterogeneity: Tau ² = 0.00; Chi ² = 0.34, df = 1 (P = 0.56); I ² = 0% | | | | | | | | | |
| Test for overall effect: Z = 3.43 (P = 0.0006) | | | | | | | | | |
| Total (95% CI) | | | 1570 | | | 1563 | 100.0% | -0.22 [-0.35, -0.10] | |
| Heterogeneity: Tau ² = 0.02; Chi ² = 686.55, df = 6 (P < 0.00001); I ² = 99% | | | | | | | | | |
| Test for overall effect: Z = 3.50 (P = 0.0005) | | | | | | | | | |
| Test for subgroup differences: Chi ² = 0.15, df = 1 (P = 0.70), I ² = 0% | | | | | | | | | |

- HbA1C: -0.22% (favors Icodec)
- Fasting glucose: -1.59 mg% (favors Icodec)
- TIR: 4.24% (favors Icodec)
- Overall hypoglycemia: risk ratio 1.24 (favors other insulins)
- Severe hypoglycemia: risk ratio 0.81 (not a significant difference)
- Weight gain: 0.64 kg (favors other insulins)

Mukhopadhyay P, et al. *Endocr Pract.* 2024; 30(2): 128-134.



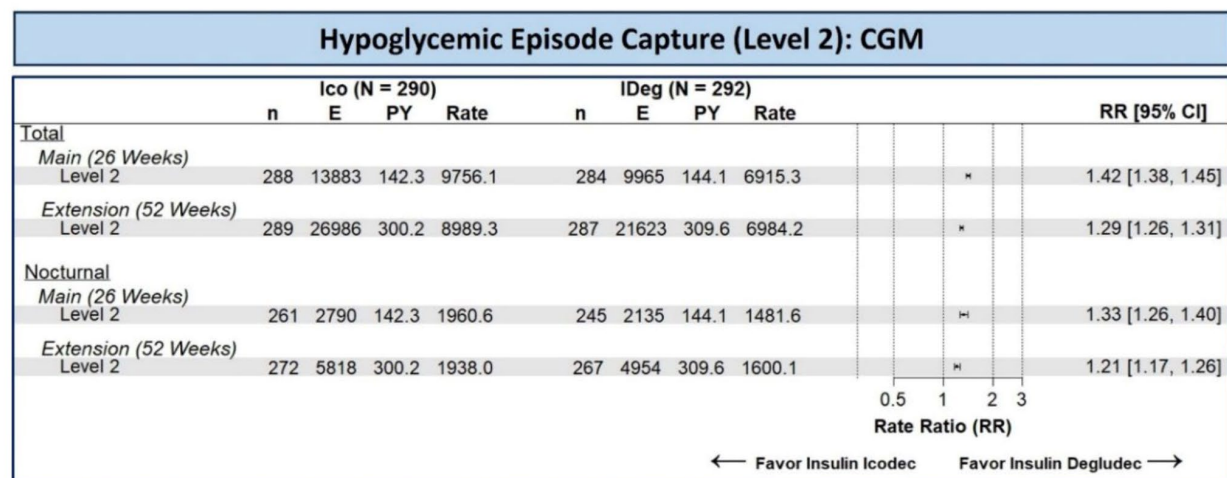
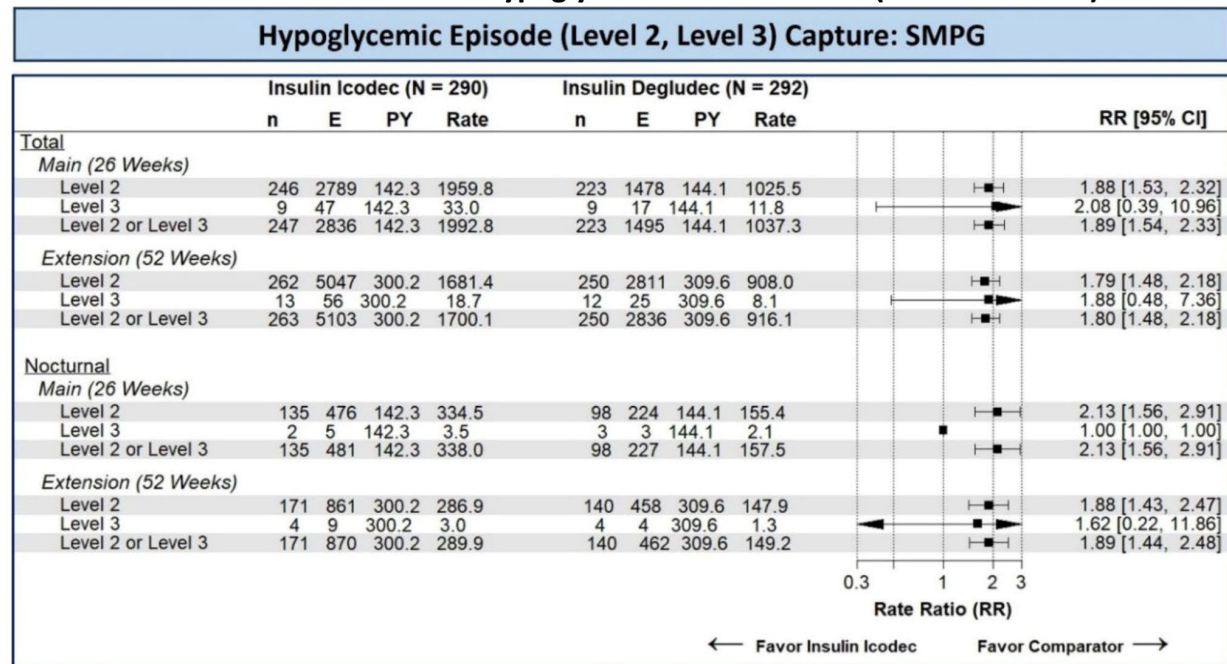
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ICODEC SUMMARY

Table 8. Event Rates of Level 2 or 3 Hypoglycemia—ONWARDS 6 (On-Treatment*)



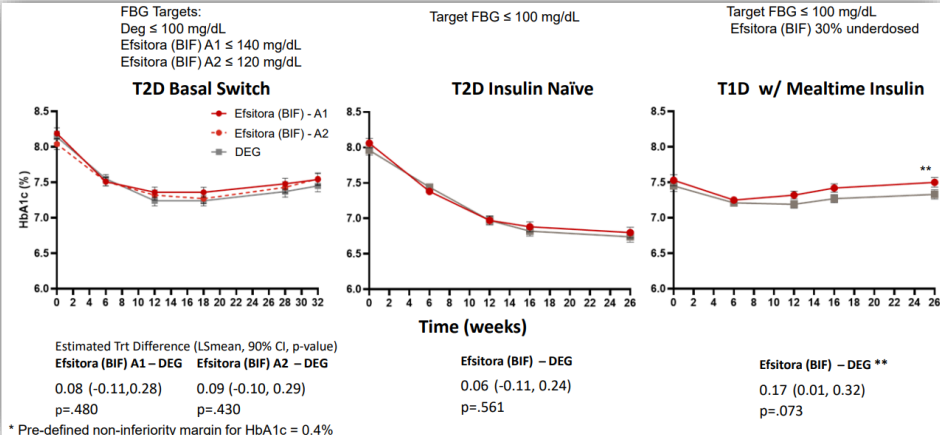
24% increase in hypoglycemia with icodec
 Last week FDA committee voted for
 rejection 7-4 of approval

| | Week 26 | Week 52 |
|---------------------------------------------------------------------------|----------------------------------------|--------------------------|
| Baseline Mean (SD) [N] | | |
| Insulin icodec | | 7.59 (0.96) [290] |
| Insulin degludec | | 7.63 (0.93) [292] |
| LS Mean change from baseline (SE) | | |
| Insulin icodec | -0.47 (0.04) | -0.38 (0.04) |
| Insulin degludec | -0.52 (0.04) | -0.52 (0.04) |
| Treatment difference (Ico – IDeg) (SE) (95% CI) | 0.06 (0.05) (-0.05, 0.16) ^a | 0.14 (0.06) (0.02, 0.25) |
| Average number of subjects with A1C <7.0% / N (%)^{b,c} | | |
| Insulin icodec | 121 / 290 (42%) | 116 / 290 (40%) |
| Insulin degludec | 132 / 292 (45%) | 118 / 292 (40%) |

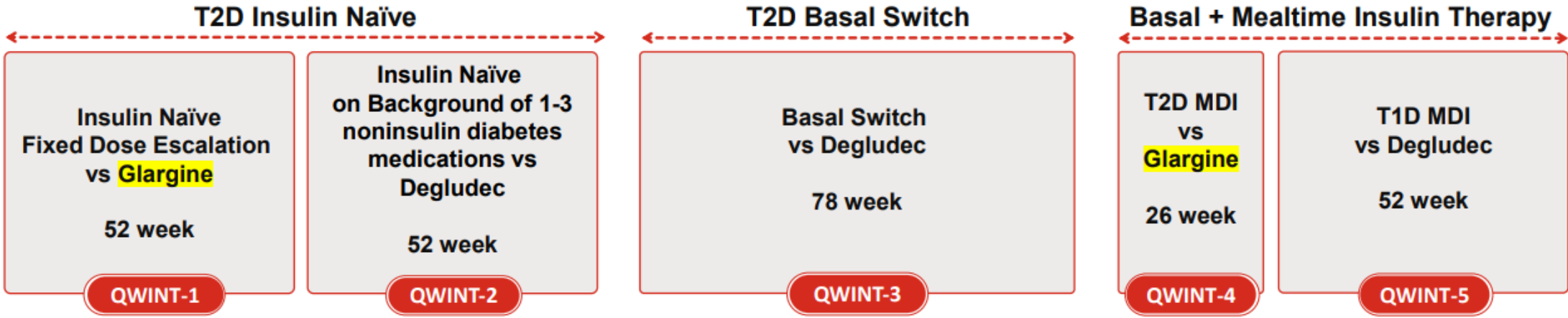
INSULIN EFSITORA STUDIES

Phase 2 studies are ongoing

| Study Description | T2D Basal Switch | T2D Insulin Naive | T1D w/ Mealtime Insulin |
|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------|
| Population | Previously treated with daily basal insulin analog ± up to 3 Oral medications (metformin, DPP-4, SGLT-2 inhibitors, sulfonylureas, alpha-glucosidase inhibitors) | Previously treated with orals: Metformin ± DPP4 and/or SGLT2 Inhibitors | Multiple Daily Injections rapid analog insulin |
| Fasting Glucose Target Efsitora Degludec | ≤140 mg/dL; adjusted every 2 wks ≤120 mg/dL; adjusted every 4 wks ≤100 mg/dL; adjusted weekly | ≤100 mg/dL adjusted weekly | ≤100 mg/dL adjusted weekly |
| Treatment Duration | 32 Weeks | 26 Weeks | 26 Weeks |
| CGM Assessment | Real-time Throughout | Blinded, 14 days prior to Baseline, 12, 26 Wks | Real-time Throughout |



Phase 3 studies are ongoing



Frias J, et al. Lancet Diabetes Endocrinol. 2023 Mar;11(3):158-168.
 Bue-Valleskey JM et al. Diabetes Care. 2023 Mar 21.
 Kazda CM et al. Diabetes Care. 2023 Mar 15.

BASAL INSULIN: FUTURE DIRECTIONS

- **Glucose-responsive insulin = “smart insulin”**

- A glucose-responsive sensor releases insulin when blood glucose concentrations are outside the target range
- Theoretically lowers the risk of hypoglycemia
- Ongoing interest in this but concept has not materialized yet

Retnakaran and Zinman. *Diab Obes Metab.* 2022; 24 Suppl 1: 17-26.



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RAPID INSULINS

RAPID INSULIN ANALOGS

Insulin Lispro (Humalog®)

Insulin Aspart (Novolog®)

Insulin Glulisine (Apidra®)

ULTRA RAPID INSULIN

Insulin Lispro-aabc
(Lyumjev®)

Fast Acting Insulin Aspart
(Fiasp®)

Technosphere Insulin
(Afrezza®)

FAST ACTING INSULIN ASPART



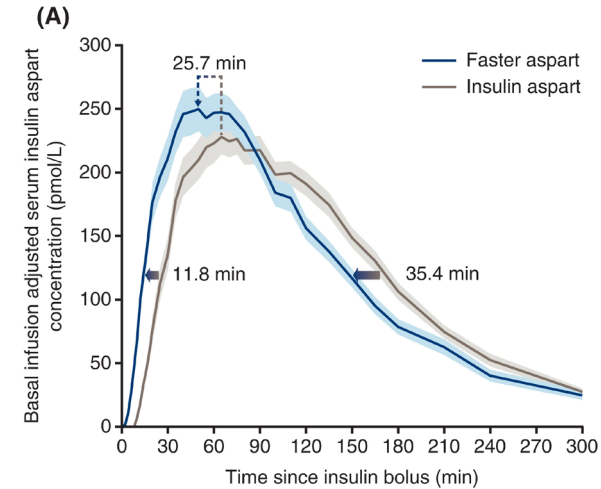
Insulin aspart + Vitamin B3 + L-arginine



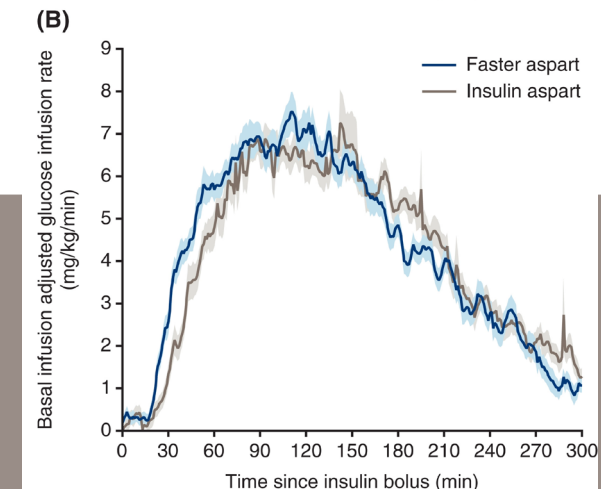
Vitamin B3
(Niacinamide) → Increase
absorption



L-arginine → Stabilizer



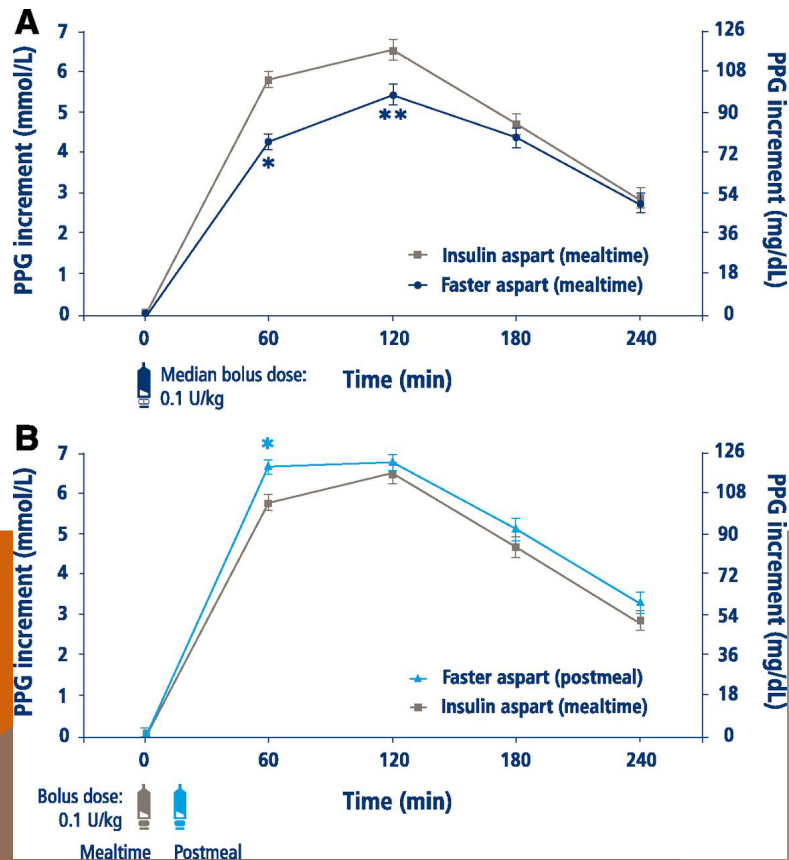
Pharmacokinetics



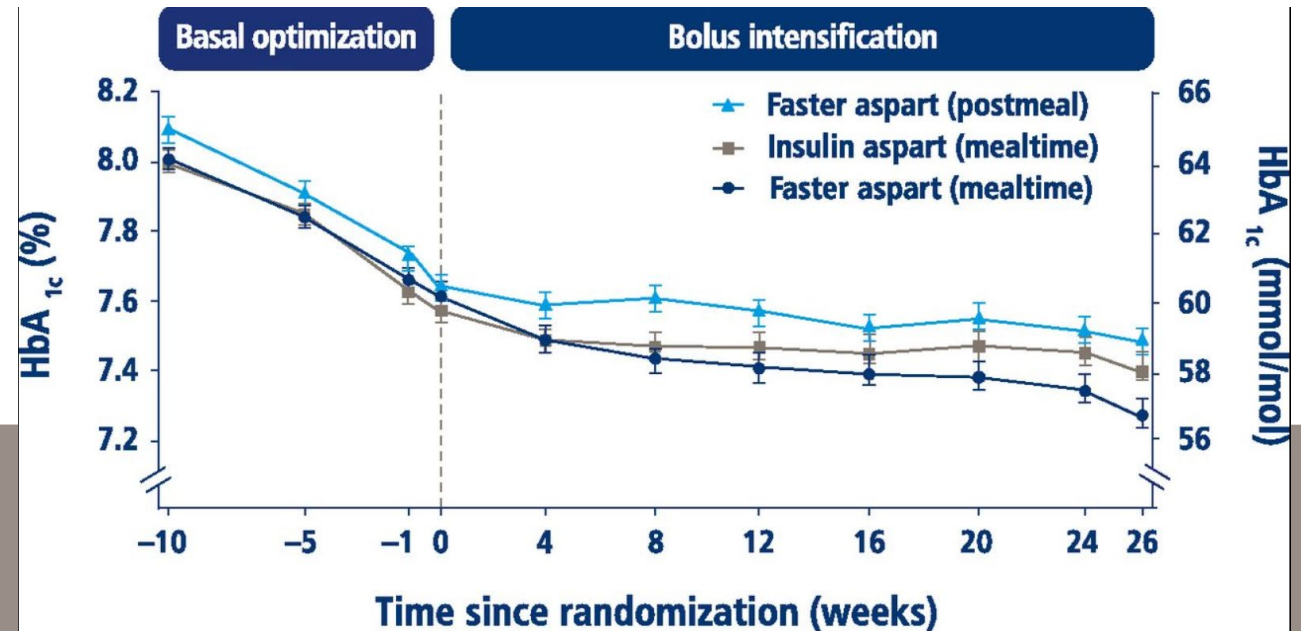
Pharmacodynamics

FAST ACTING INSULIN ASPART- ONSET-1 STUDY

Better PPGE in 1 and 2-hours



Similar A1c (non-inferiority met but not superior)

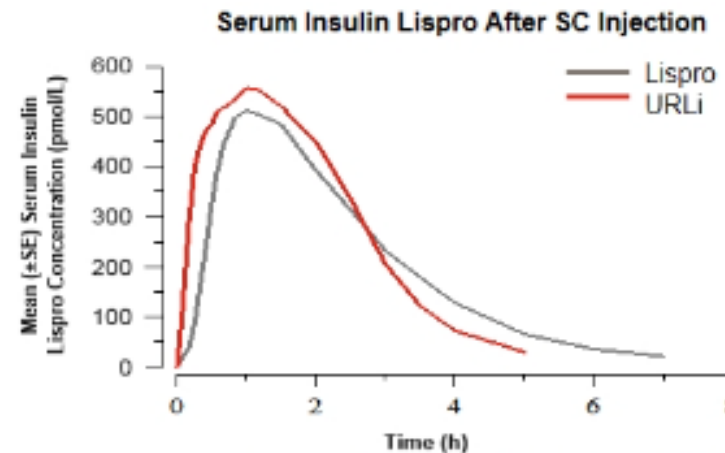


INSULIN LISPRO-AABC

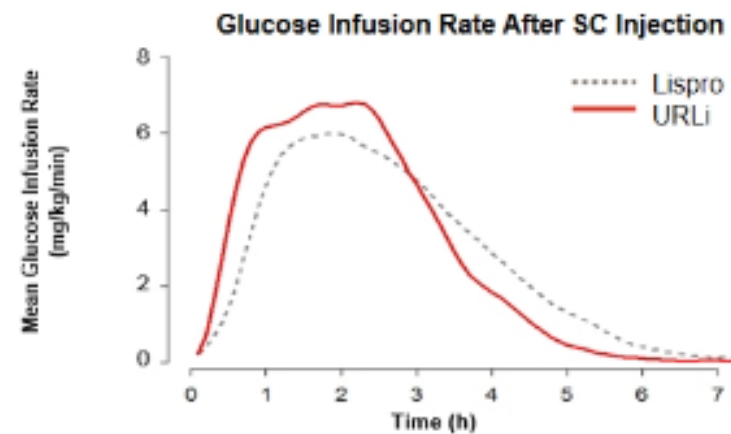
Insulin lispro
+Trephestinil
+Citrate

Citrate →
Enhancing
vascular
permeability

Trephestinil →
Prostacyclin
analog → Local
vasodilatation



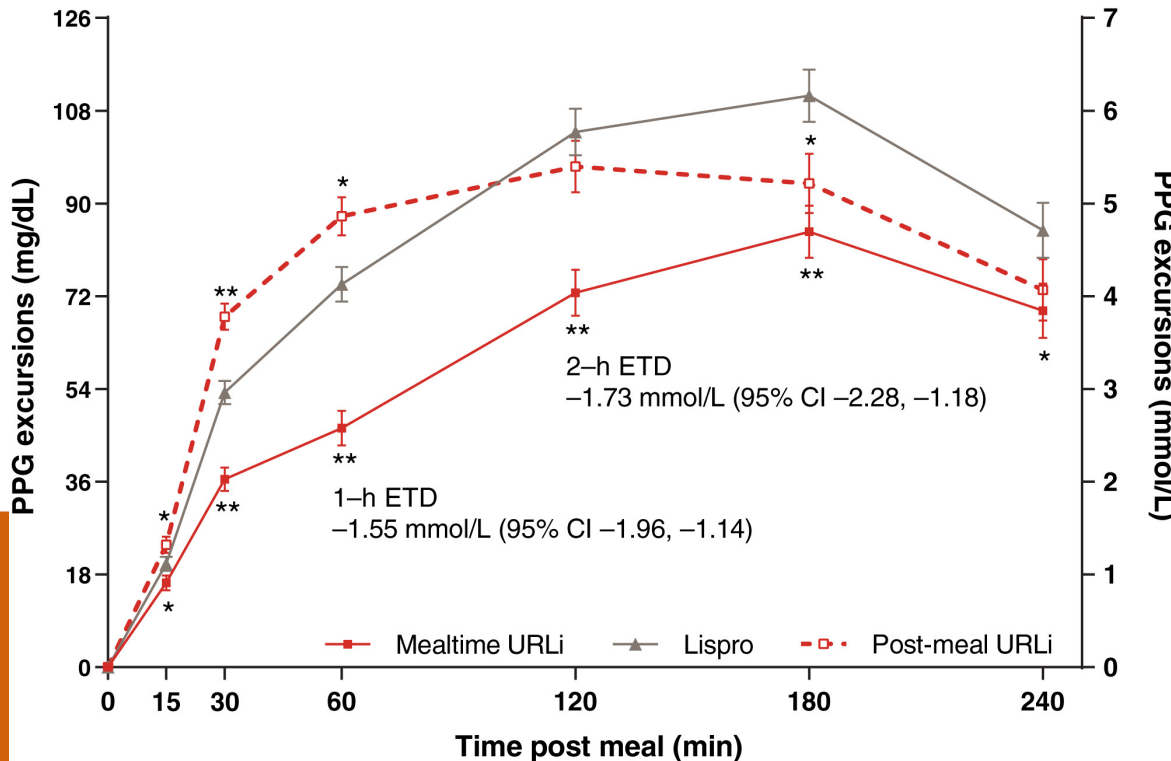
Pharmacokinetics



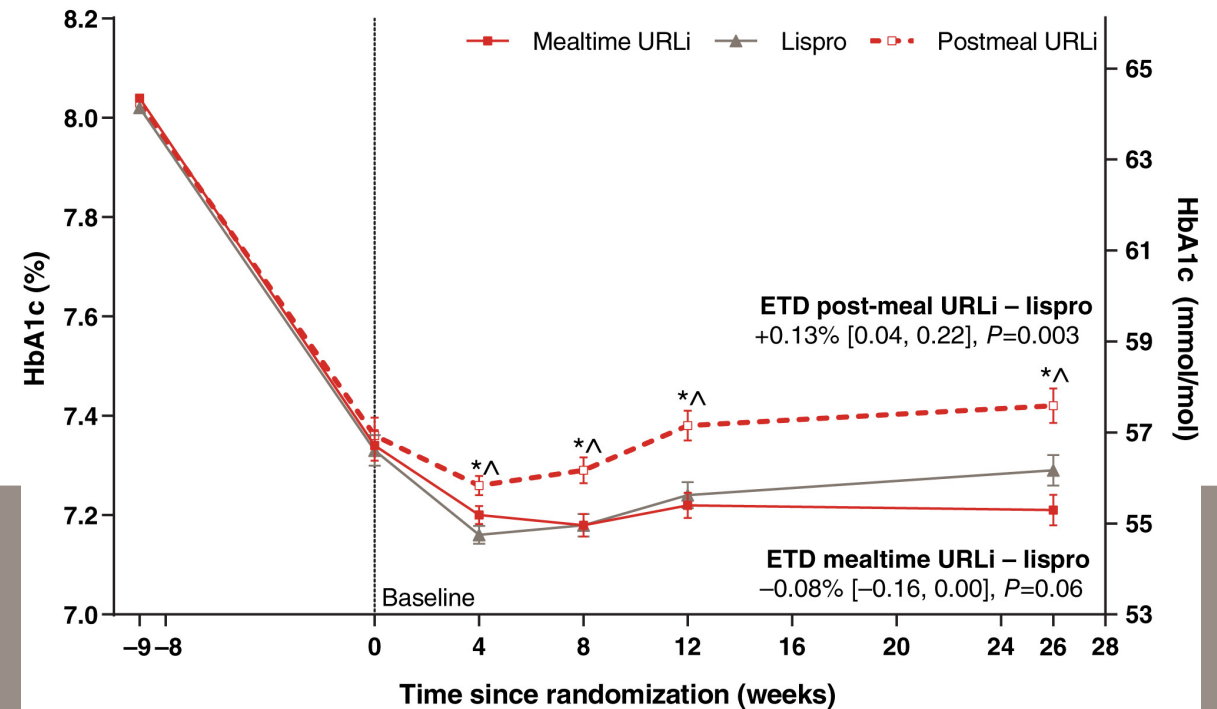
Pharmacodynamics

INSULIN LISPRO-AABC-PRONTO-T1D STUDY

Better PPGE in 1 and 2-hours



Similar A1c (non-inferiority met but not superior)



STARTING INHALED INSULIN

ANTICIPATED INHALED INSULIN DOSE

Inhaler can be used for up to 15 days



4-Unit Cartridges
8-Unit Cartridges
12-Unit Cartridges



Inhaler

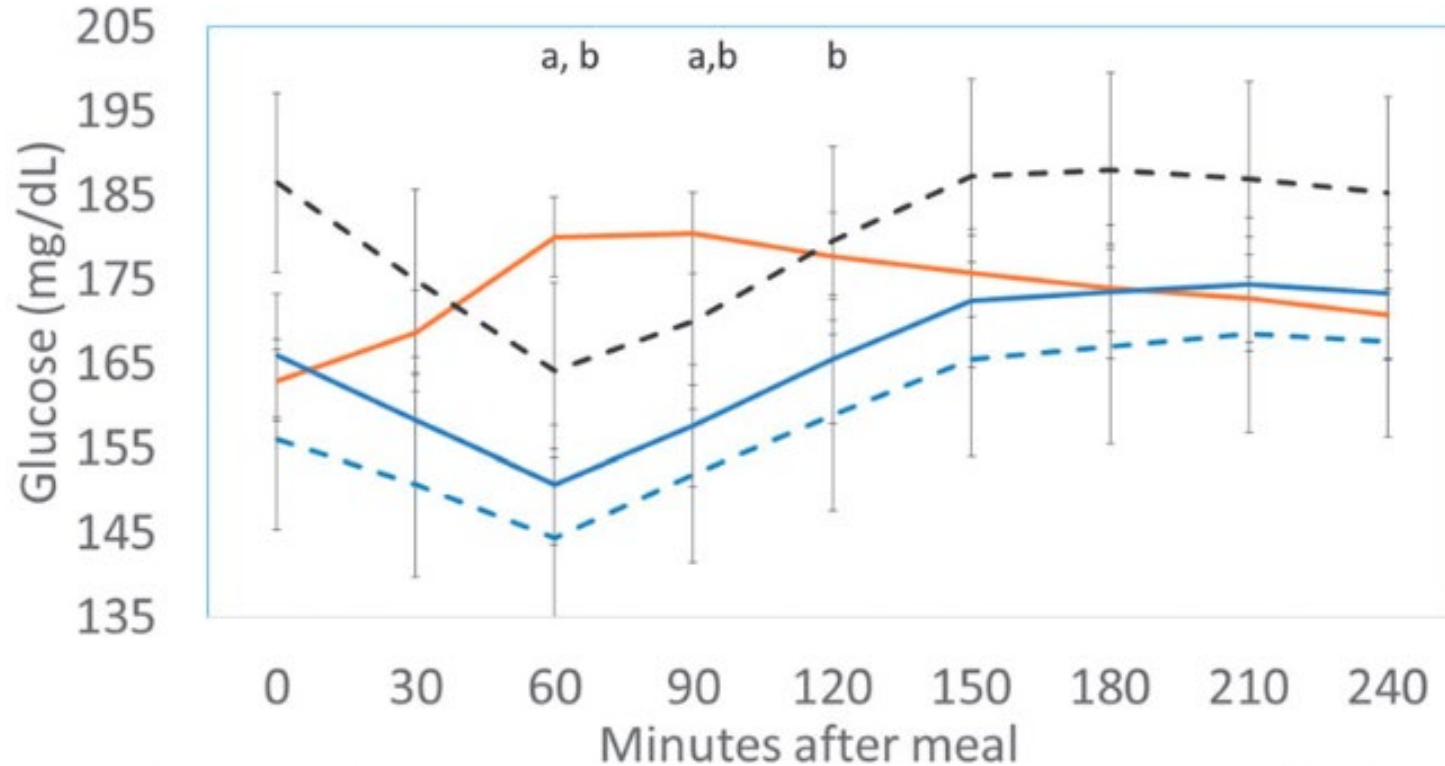
| Injection bolus dose | Inhaled Insulin dose | Anticipated titration dose inhaled insulin |
|----------------------|----------------------|--------------------------------------------|
| Up to 4 | 4 | 4-8 |
| 5-8 | 8 | 8-12 |
| 9-12 | 12 | 12-20 |
| 13-16 | 16 | 16-24 |
| 17-20 | 20 | 20-32 |
| 21-24 | 24 | 24-36 |

FDA approved label

1.5X dosing based on studies

Label information

STAT STUDY- INHALED INSULIN IN T1D



Orange Line: Insulin Aspart

Blue Line: Inhaled Insulin (All)

Dotted Black Line: Underdosed inhaled insulin (less corrections than the protocol)

Dotted Blue Line: Inhaled insulin taking according to the correction protocol

a, $p < 0.05$ for inhaled insulin (all) vs. insulin aspart

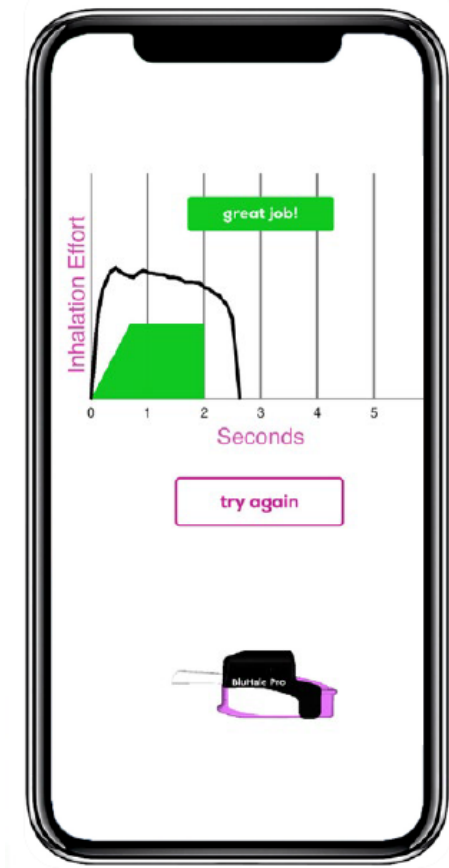
b, $p < 0.05$ for taking inhaled insulin according to the correction protocol vs insulin aspart

IMPROVING ABSORPTION OF INHALED INSULIN- BLUEHALE® TECHNOLOGY

Bluetooth enabled accessory device that mounts onto the inhaler

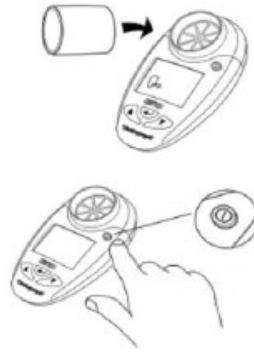
Educates patients on the correct inhalation technique and handling of the inhaler

Provides patients with a visual display of their inhalation length and effort in a smart phone app



CLINIC MEASUREMENT OF FEV₁

1 | INSERT MOUTHPIECE
& SWITCH DEVICE ON



2 | INSTRUCT PATIENT
TO EXHALE 3 TIMES



3 | RECORD BEST
FEV₁ RESULT



Contraindicated in: COPD, Asthma

Medical history, physical exam, spirometry (FEV₁) before initiation

FEV₁ measurements: After 6 months of initiation then annual

Consider discontinuation if >20% decline in FEV₁ measurements

SAFETY PRECAUTIONS WITH INHALED INSULIN

SUMMARY OF INHALED INSULIN

ADVANTAGES

- Ultra rapid acting, in and out, faster than any insulin in the market
- Better postprandial blood glucose
- Less risk of hypoglycemia
- No needles, easy to carry and use
- Good for snacks coverage (touch on)
- Good for young adults and busy professionals
- Ideal for patients can't wait 10-15 mins to eat after injections

DISADVANTAGES

- Requirement of FEV₁ testing
- High fat/protein meals may need additional dosing
- People tend to under-dose (1.5-2X dose needed)
- Confusion with dosing units
- Only available in 4-, 8-, and 12-unit cartridges
- No pediatric indication yet
- Insurance coverage

THANK YOU



Barbara Davis
Center for Diabetes

UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS