Hepatocyte-Directed Insulin Lispro (HDV-L) Reduces Hypoglycemia Risk in Adults with Type 1 Diabetes Compared with Insulin Lispro (OPTI-2 Study)

Klara Klein, MD, PhD
Assistant Professor, Division of Endocrinology and Metabolism
Director, Endocrine, Diabetes, and Obesity Clinical Research Unit

On behalf of L. Billings, J. Buse, S. Garg, D. Larsen, R. Weinstock, W. Geho, H. Plotkin, D. Muchmore, C. El Sanadi, L. Chapin, J. Ilgenfritz, R. Geho, P. Strumph and the OPTI-2 research group | Trial ID: NCT06238778

School of Medicine

Disclosures

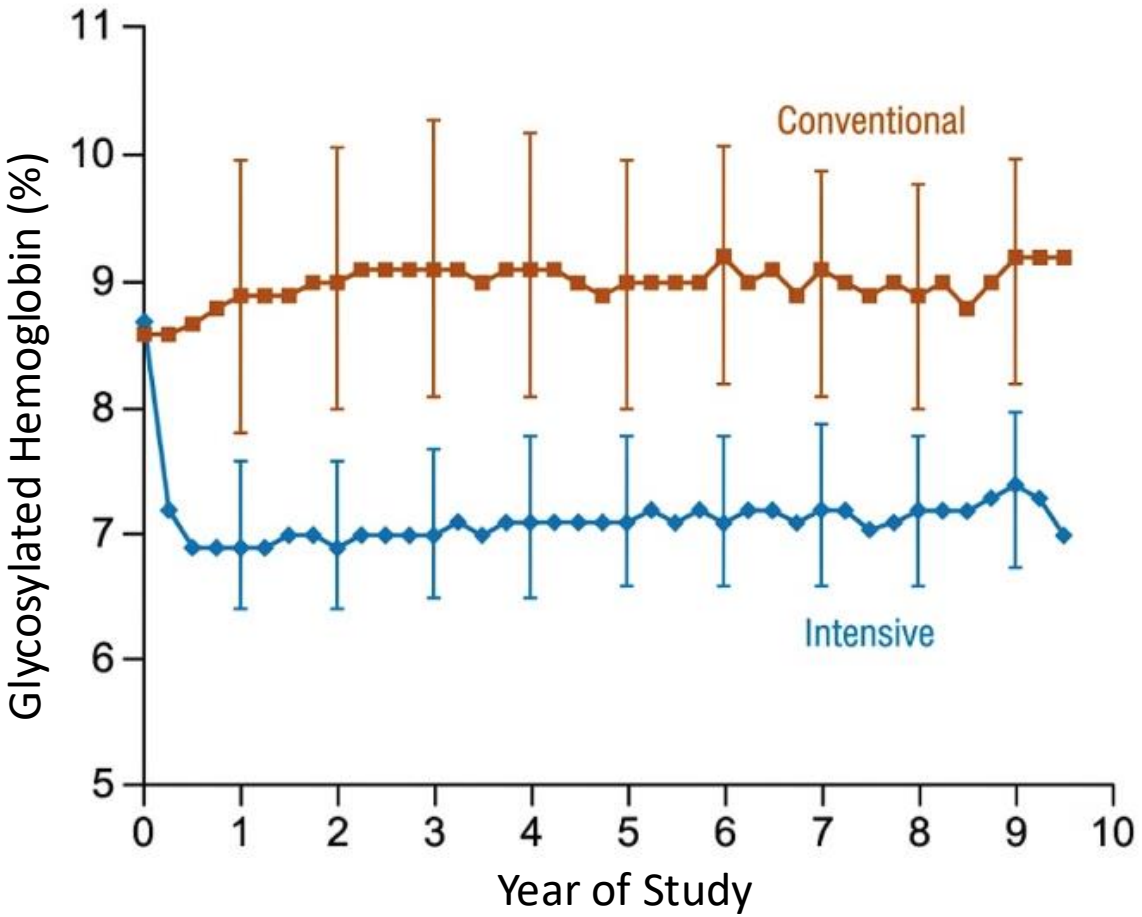
- KRK has consulted for Antag Therapeutics, Metsera, Novo Nordisk, Roche Pharmaceuticals, and vTv Therapeutics and has received research related contracts (paid to the institution) from Bayer, Boehringer-Ingelheim, Carmot, Diasome, Eli Lilly, GentiBio, Novo Nordisk, Rhythm Pharmaceuticals, Roche Pharmaceuticals, and vTv Therapeutics.

- Diasome co-authors disclose employment with Diasome Pharmaceuticals

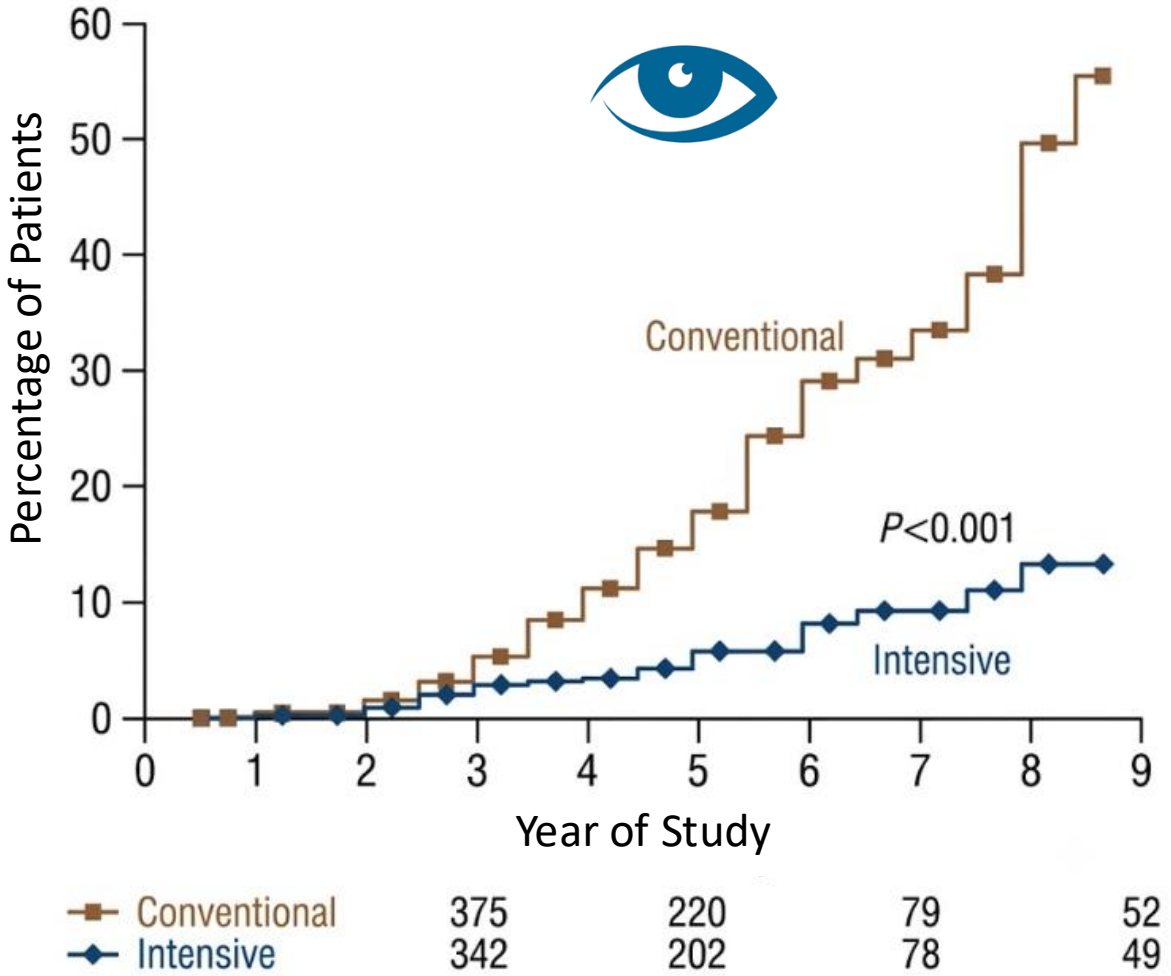
- *All other co-author disclosures available upon request*

Tight glycemic control is essential — but comes at a price

Change in A1C



Incidence of Retinopathy



DCCT Research Group. *N Engl J Med*. 1993;329:977

DCCT Research Group. *Diabetes*. 1997;46:271

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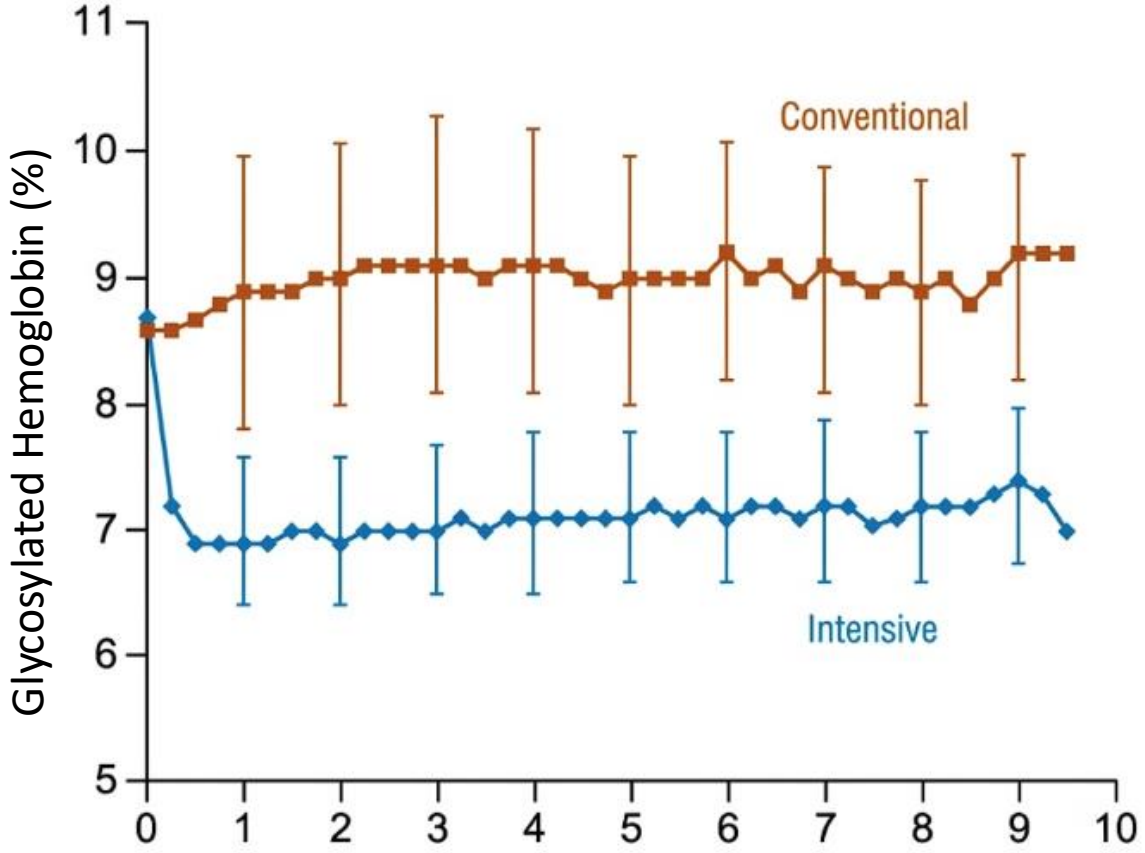
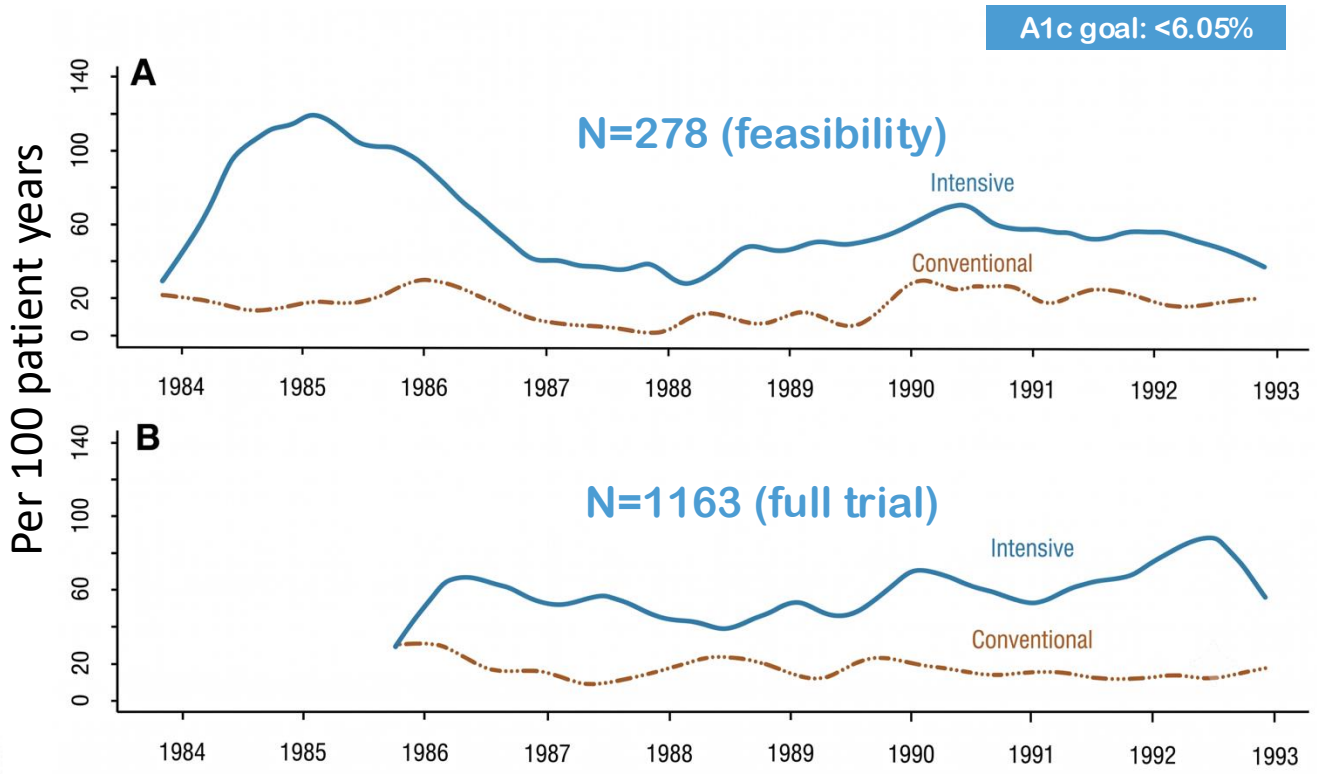
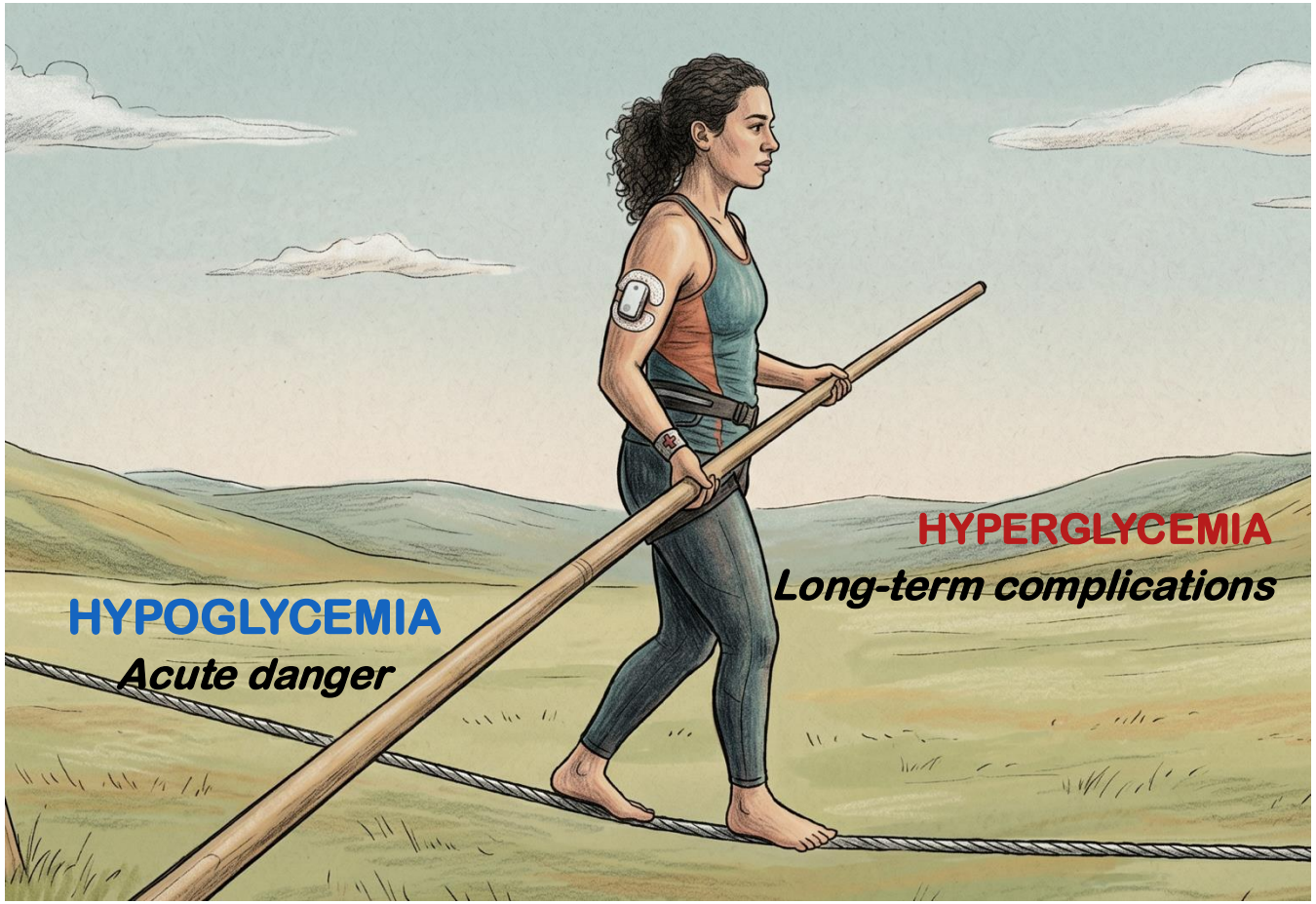


Rate of Severe Hypoglycemic Events



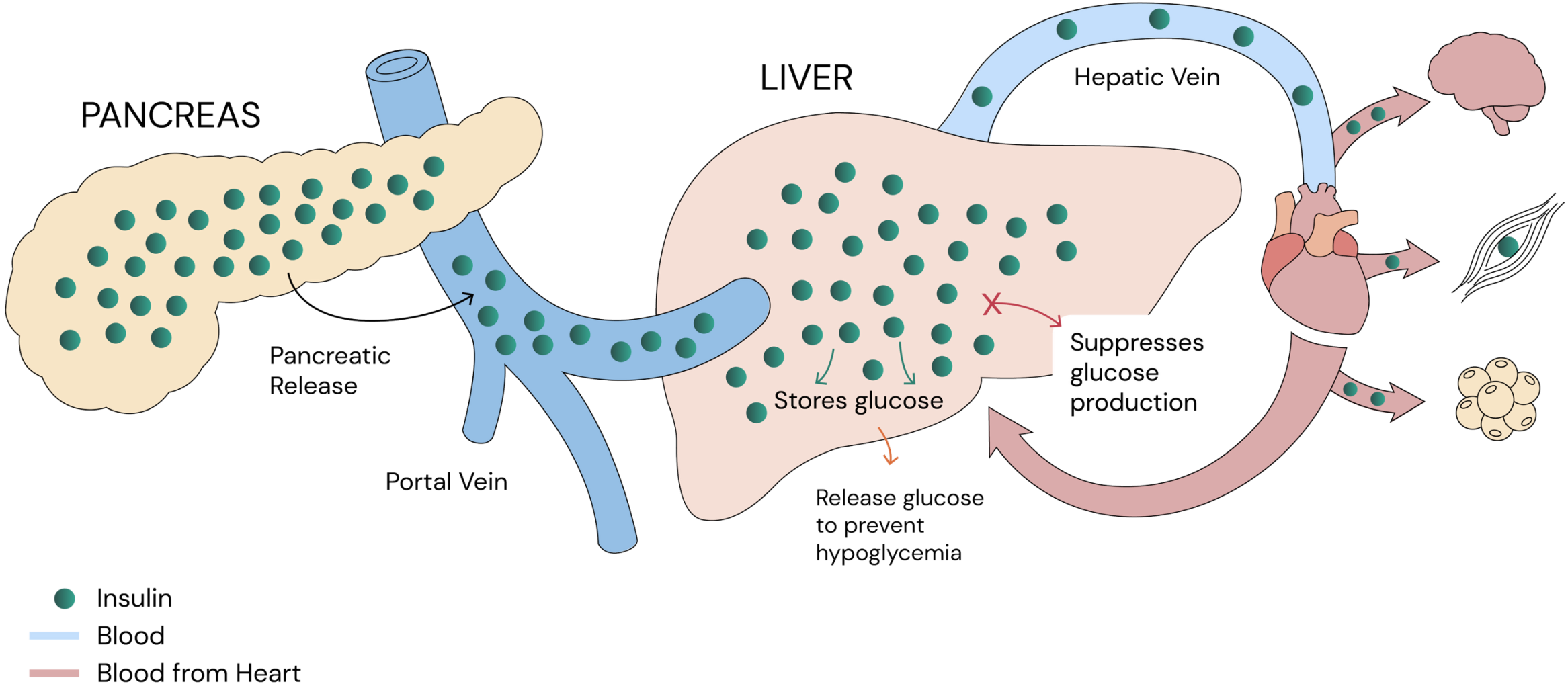
Intensive insulin treatment couples with an increased risk of hypoglycemia

Type 1 diabetes management is like walking a tightrope



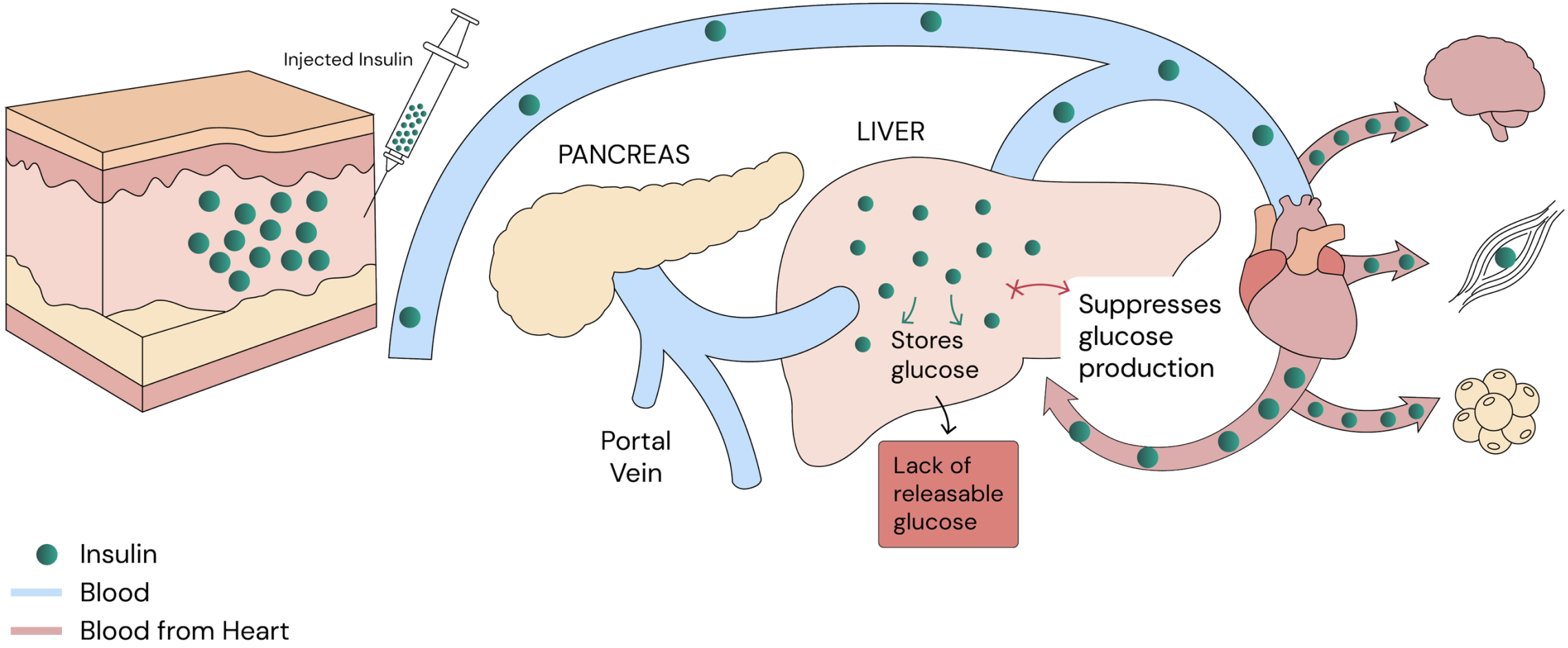
Uncoupling intensive insulin therapy from hypoglycemia risk could offer people living with T1D greater safety and better outcomes

Endogenous insulin reaches the liver through portal vein



Adapted from Meier et al., Diabetes (2005) and Duckworth et al., Endocrine Reviews (1998).
Graphic: Original illustration synthesized from physiologic data via AI (Google Gemini).

In type 1 diabetes, subcutaneous insulin bypasses the liver leading to reduced hepatic glucose storage



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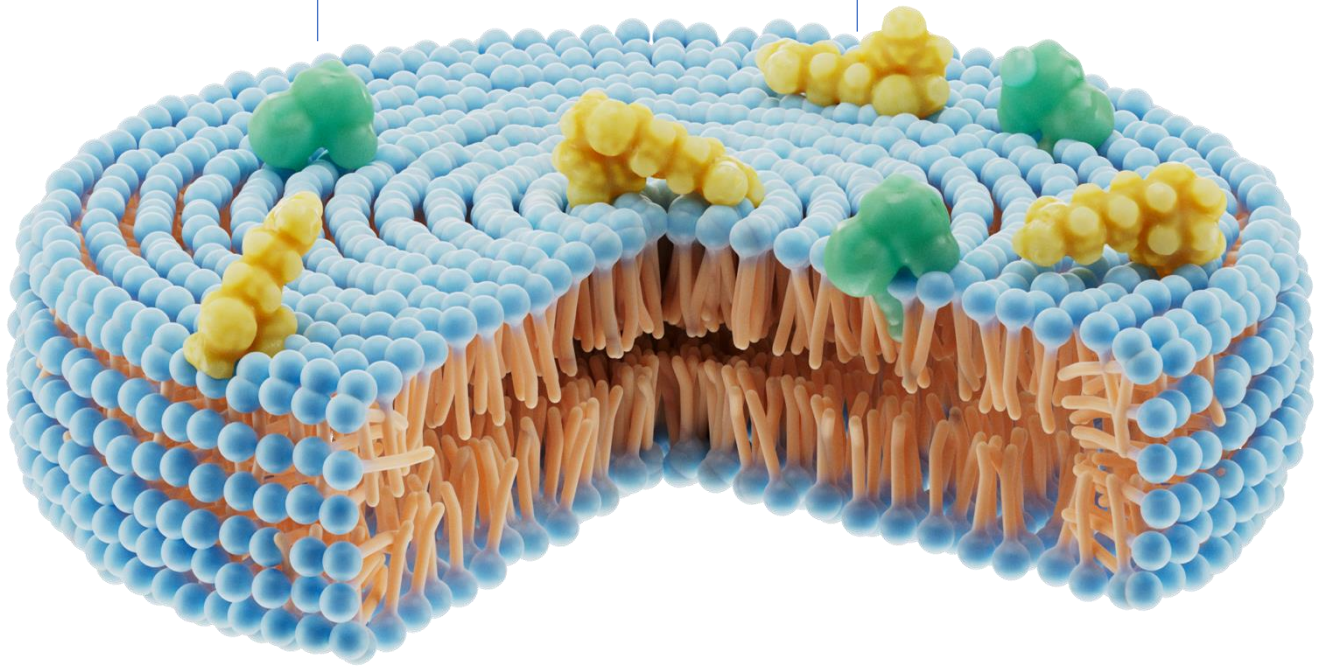
Hepatocyte-directed vesicles (HDV) target insulin to the liver

INSULIN
Prefentially delivered to the liver

BIOTIN
Binds to receptors on hepatocytes



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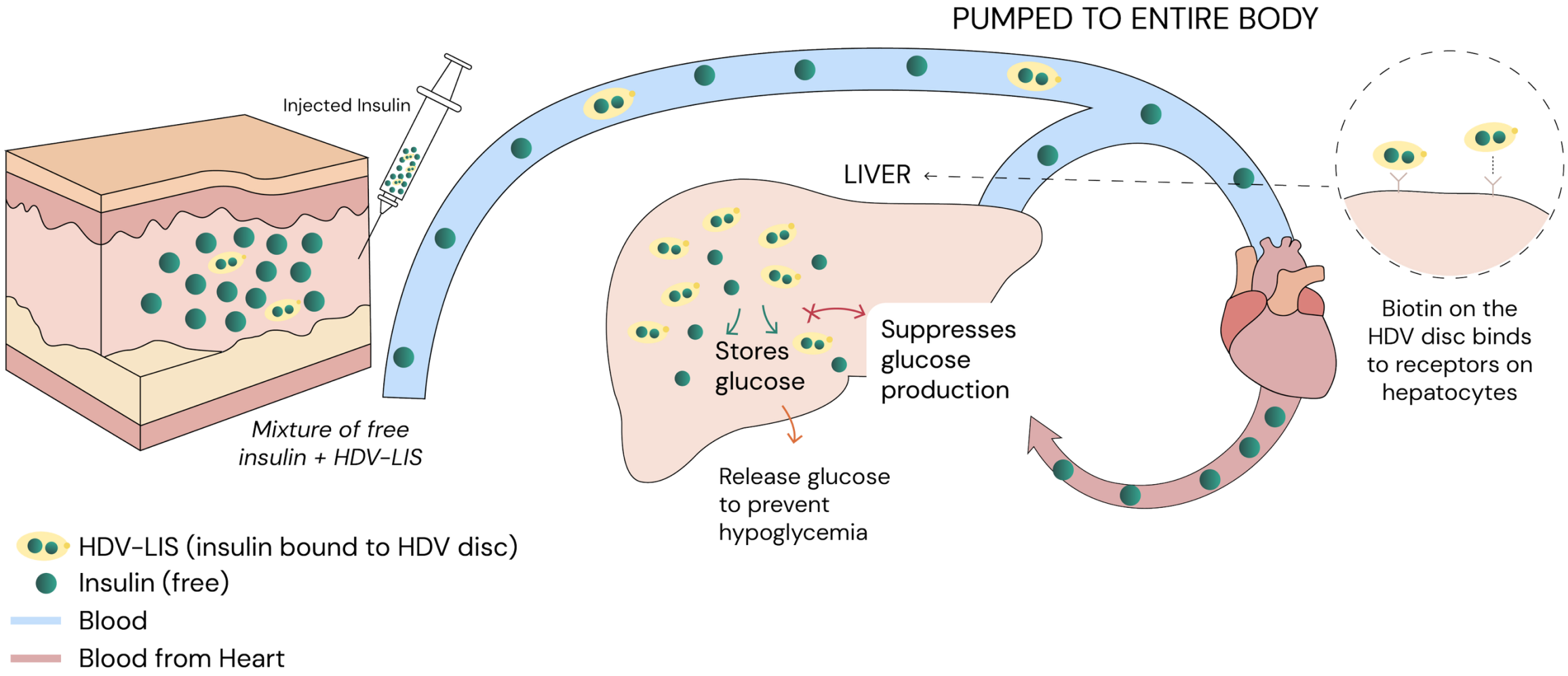
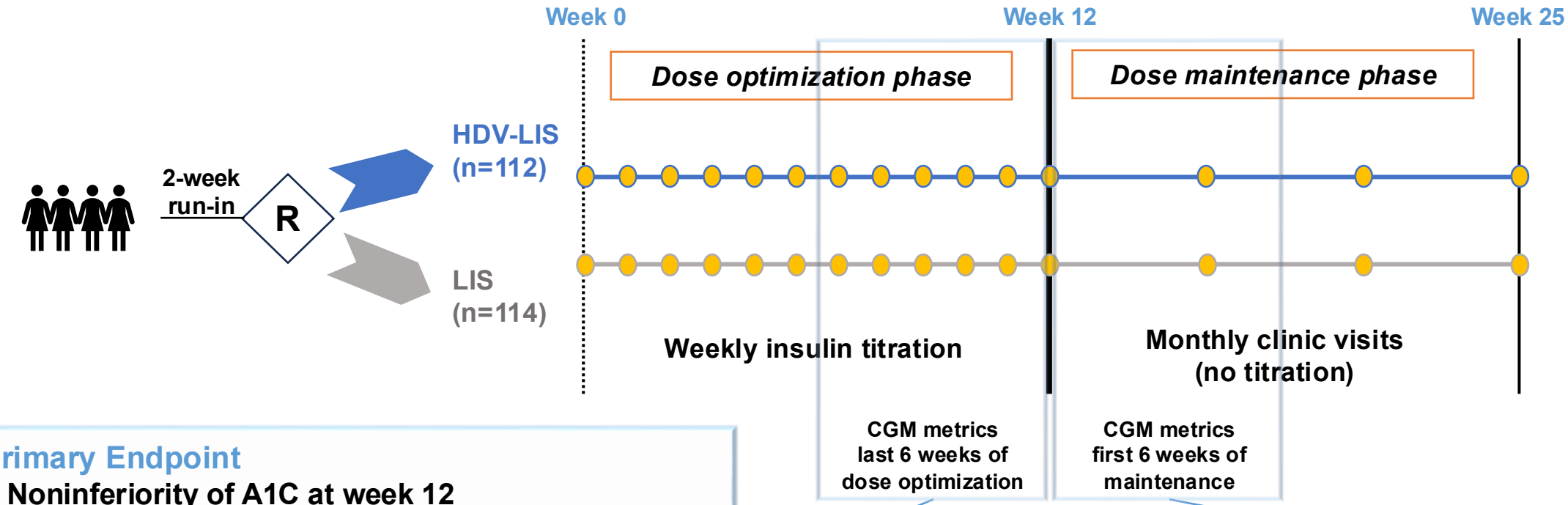


OPTI-2: A double-blind, randomized controlled trial to evaluate HDV-LIS in adults with type 1 diabetes



Primary Endpoint

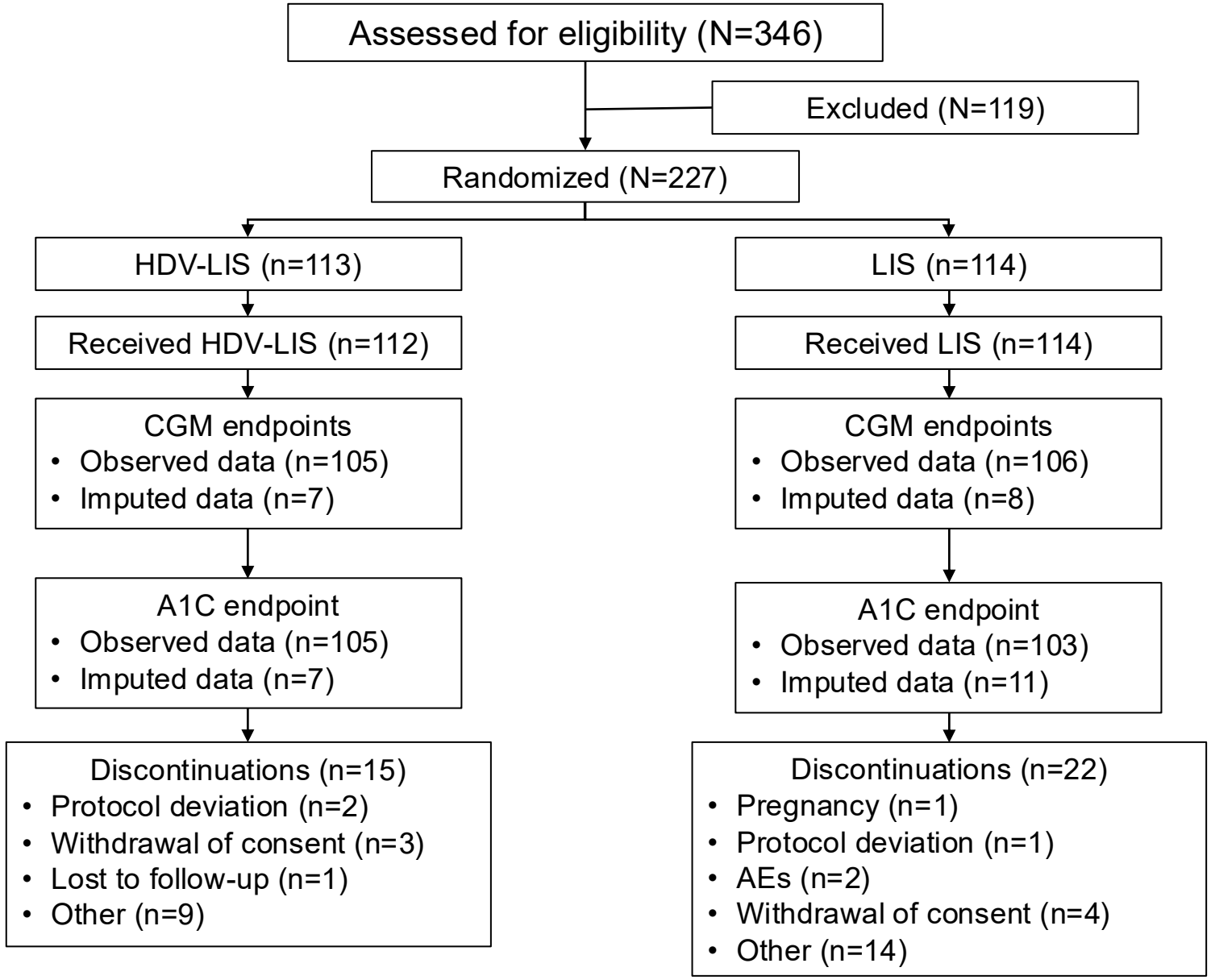
- **Noninferiority of A1C at week 12**
  AND
- **Superiority of prespecified CGM metrics during last 6 weeks of dose optimization**
  - **Rate of nocturnal level 2 hypoglycemia**
  - **Nocturnal % time <54 mg/dL**
  - **Proportion with <1% of 24-h day <54 mg/dL**

Key Secondary Endpoints

- A1C at week 12
- CGM metrics during first 6 weeks of dose maintenance

= clinic/virtual visit; CGM = continuous glucose monitor; HDV-LIS = hepatocyte-directed insulin lispro; L2 = level 2; LIS = insulin lispro; R = randomization

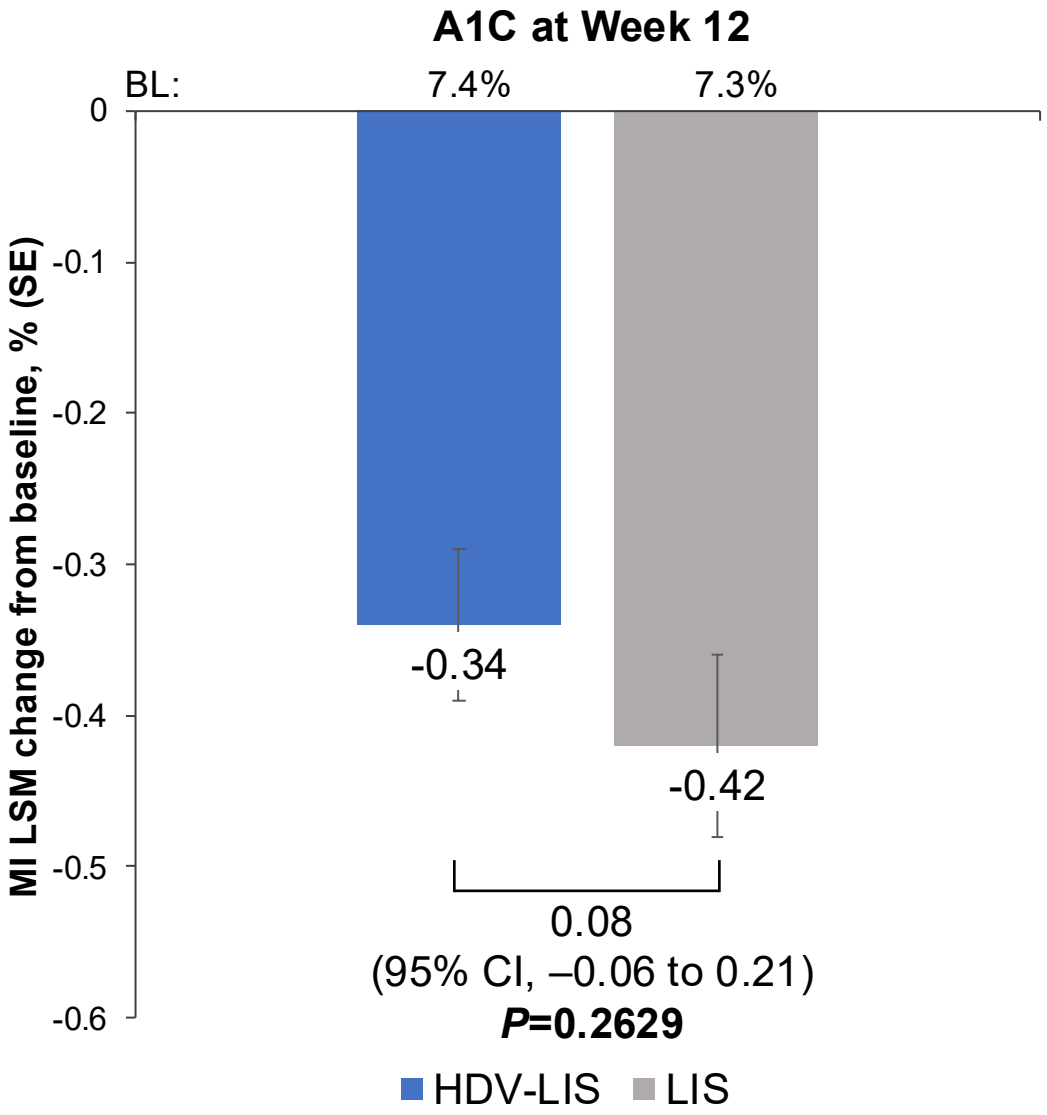
Participant disposition



Baseline characteristics were well balanced between groups

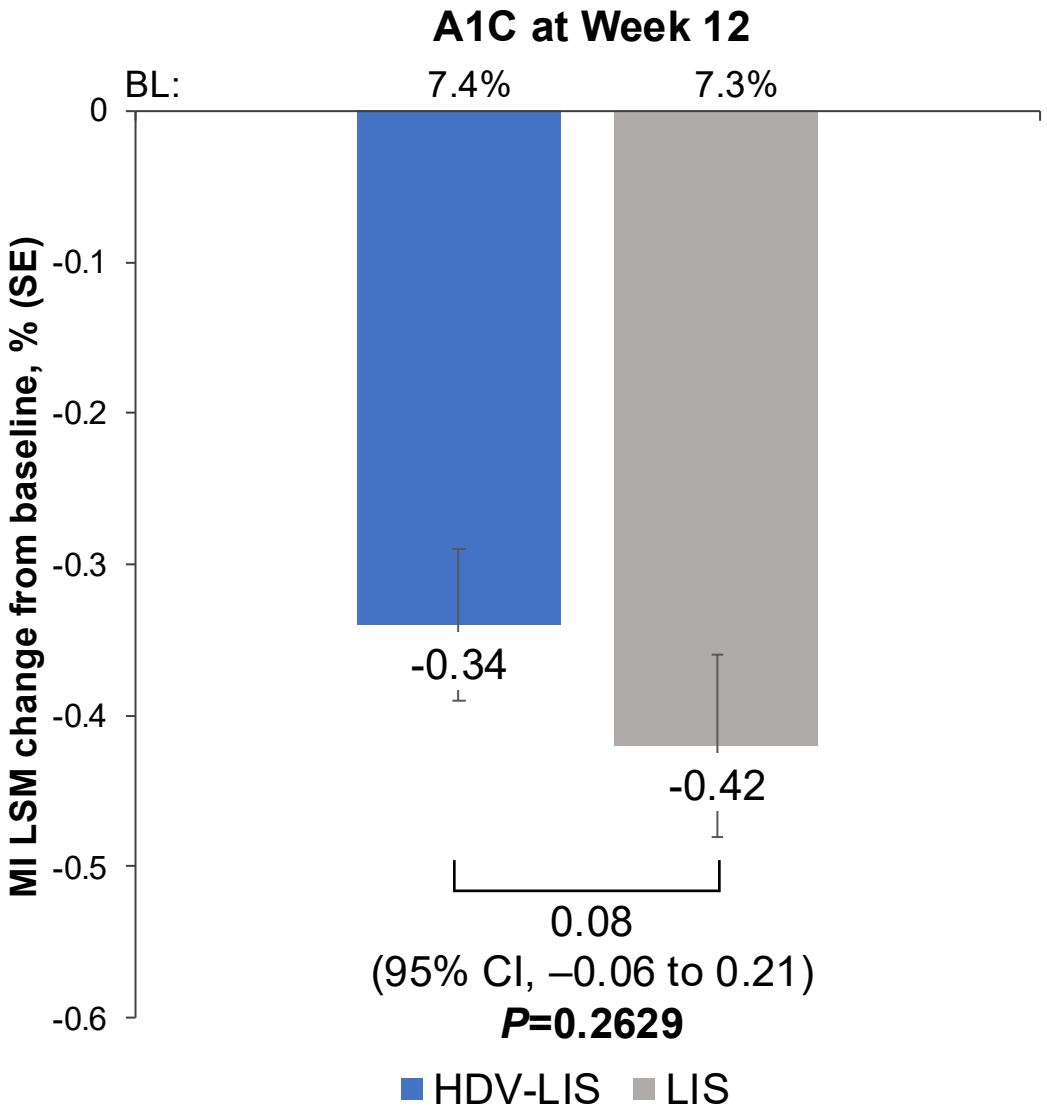
Outcome	HDV-LIS (n=112)	LIS (n=114)
Age, years, mean (range)	46.5 (19–76)	43.9 (19–76)
Female sex, n (%)	50 (44.6)	54 (47.4)
Race and ethnicity, n (%)		
Asian	3 (2.7)	3 (2.6)
Black	7 (6.3)	6 (5.3)
White	101 (90.2)	103 (90.4)
Hispanic or Latino	16 (14.3)	13 (11.4)
BMI, kg/m^2, mean (SD)	27.4 (4.5)	27.1 (3.8)
Time since diagnosis, years, mean (SD)	22.7 (14.1)	21.0 (15.3)
A1C, %, mean (SD)	7.40 (0.82)	7.30 (0.88)
Daily insulin dose, U/kg, mean (SD)		
Total	0.53 (0.21)	0.50 (0.19)
Bolus:basal insulin ratio	0.88 (0.57)	0.87 (0.66)
CGM 24-h average glucose reading, mg/dL, mean (SD)	168.1 (27.0)	165.6 (27.7)
CGM percent time (per 24 h)		
TIR (70-180 mg/dL), mean (SD)	59.27 (15.16)	60.97 (15.17)
<70 mg/dL, mean (SD)	3.23 (3.27)	3.39 (3.42)
<54 mg/dL, mean (SD)	0.79 (1.42)	0.93 (1.48)

Dose Optimization: Noninferiority in A1C was demonstrated

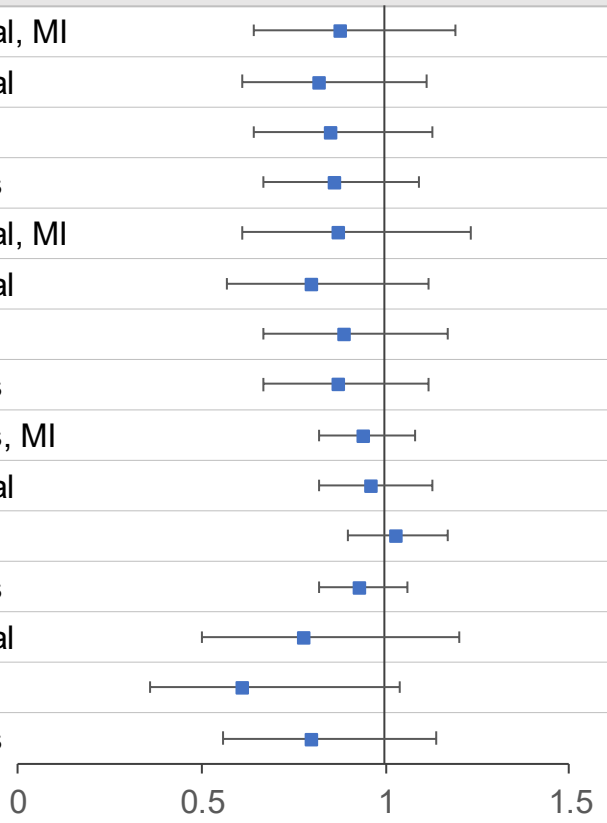


LSM= least squares mean; MI = calculated using multiple imputation

Dose Optimization: 14/15 hypoglycemia endpoints trended lower, but superiority was not reached



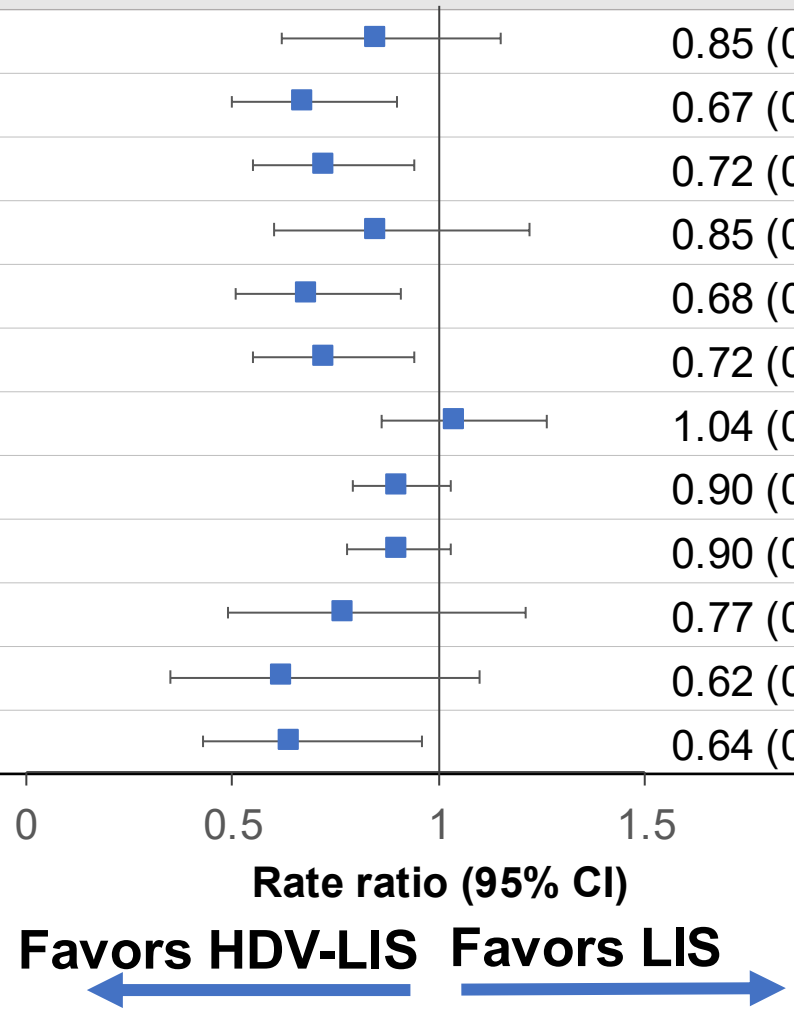
CGM Metric		Rate Ratio (95% CI)
Last 6 weeks of dose optimization		
Level 2 hypoglycemia	Nocturnal, MI	0.88 (0.64–1.19)
	Nocturnal	0.82 (0.61–1.11)
	Daytime	0.85 (0.64–1.13)
	24 hours	0.86 (0.67–1.09)
% Time <54 mg/dL	Nocturnal, MI	0.87 (0.61–1.23)
	Nocturnal	0.80 (0.57–1.12)
	Daytime	0.89 (0.67–1.17)
	24 hours	0.87 (0.67–1.12)
<1% Time <54 mg/dL	24 hours, MI	0.94 (0.82–1.08)
	Nocturnal	0.96 (0.82–1.13)
	Daytime	1.03 (0.90–1.17)
	24 hours	0.93 (0.82–1.06)
Extended hypoglycemia (≥120 min)	Nocturnal	0.78 (0.50–1.20)
	Daytime	0.61 (0.36–1.04)
	24 hours	0.80 (0.56–1.14)



LSM= least squares mean; MI = calculated using multiple imputation

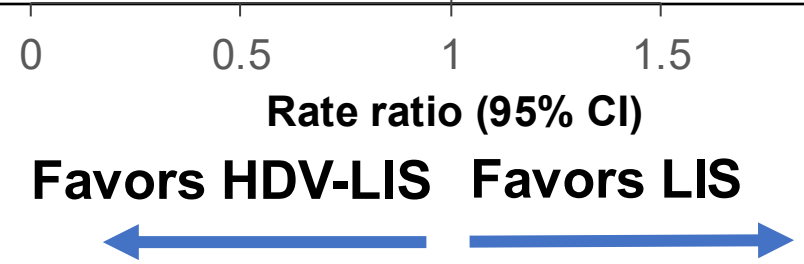
First 6 weeks of maintenance: Significant reductions in Level 2 and extended hypoglycemia

CGM Metric		Rate Ratio (95% CI)
First 6 weeks of maintenance		
Level 2 hypoglycemia	Nocturnal	0.85 (0.62–1.15)
	Daytime	0.67 (0.50–0.90)
	24 hours	0.72 (0.55–0.94)
% Time <3.0 mmol/L (<54 mg/dL)	Nocturnal	0.85 (0.60–1.22)
	Daytime	0.68 (0.51–0.91)
	24 hours	0.72 (0.55–0.94)
<1%Time <3.0 mmol/L (<54 mg/dL)	Nocturnal	1.04 (0.86–1.26)
	Daytime	0.90 (0.79–1.03)
	24 hours	0.90 (0.78–1.03)
Extended hypoglycemia (≥120 min)	Nocturnal	0.77 (0.49–1.21)
	Daytime	0.62 (0.35–1.10)
	24 hours	0.64 (0.43–0.96)

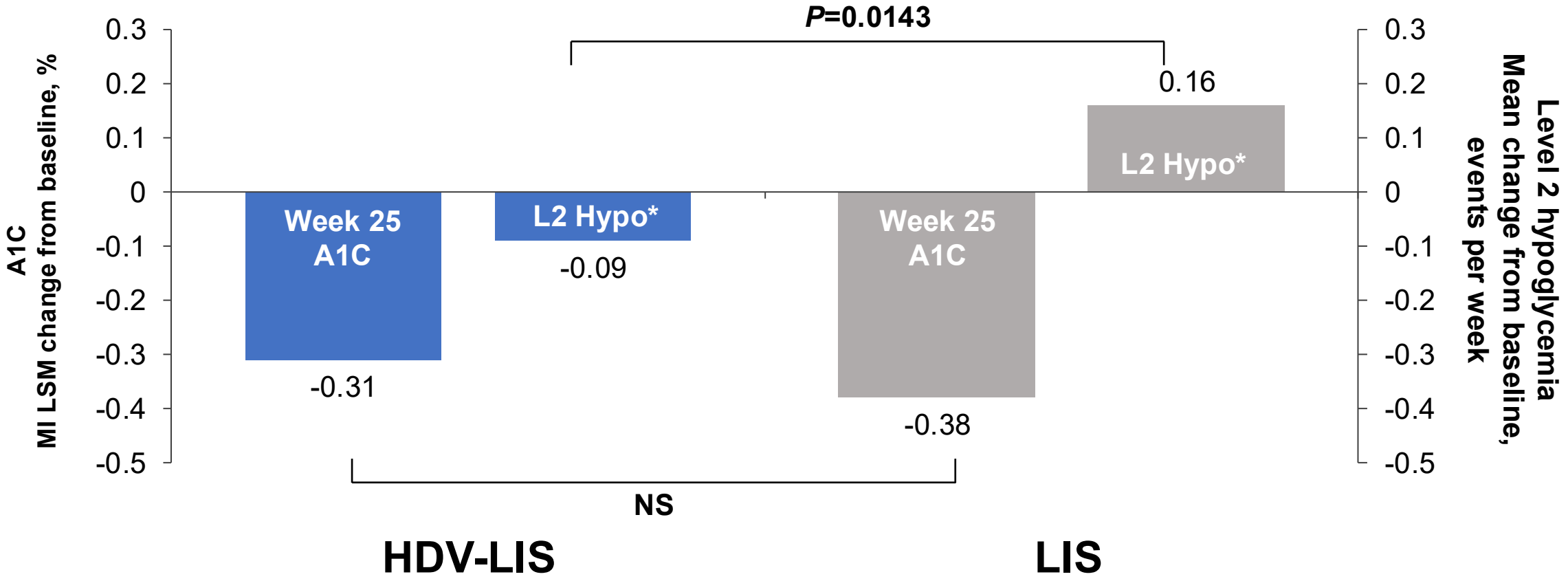


Entirety of maintenance: 12 out of 12 rate ratios favor HDV-LIS

CGM Metric		Rate Ratio (95% CI)
Entirety of maintenance		
Level 2 hypoglycemia	Nocturnal	0.92 (0.70–1.20)
	Daytime	0.74 (0.56–0.98)
	24 hours	0.80 (0.63–1.02)
% Time <3.0 mmol/L (<54 mg/dL)	Nocturnal	0.96 (0.71–1.30)
	Daytime	0.80 (0.61–1.04)
	24 hours	0.84 (0.66–1.07)
<1%Time <3.0 mmol/L (<54 mg/dL)	Nocturnal	0.96 (0.79–1.17)
	Daytime	0.92 (0.81–1.04)
	24 hours	0.96 (0.84–1.10)
Extended hypoglycemia (≥120 min)	Nocturnal	0.83 (0.56–1.22)
	Daytime	0.78 (0.49–1.24)
	24 hours	0.77 (0.55–1.08)

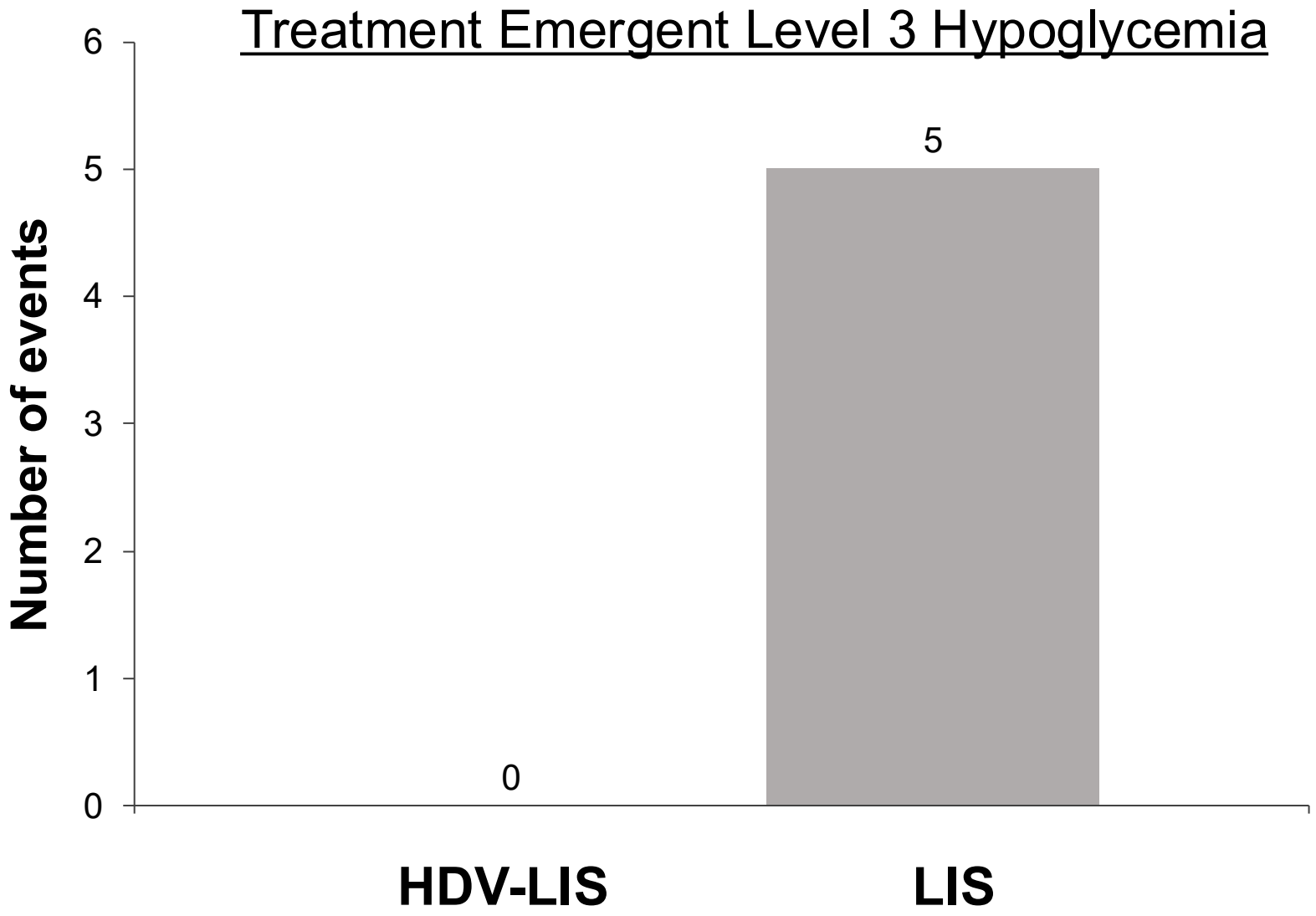


HDV-LIS decoupled glycemic control from hypoglycemia risk during the first 6 weeks of maintenance



CI = confidence interval; HDV-LIS = hepatocyte-directed insulin lispro; LIS = insulin lispro; LSM = least squares mean; MI = calculated using multiple imputation; NS = not significant.

No participants in the HDV-LIS group had severe hypoglycemia



The safety profile of HDV-LIS was favorable

Outcome	HDV-LIS (n=112)	LIS (n=114)
Total number of AEs	139	126
Participants reporting one or more AE, n (%)		
AE	60 (53.6)	57 (50.0)
Study drug-related AE	2 (1.8)	8 (7.0)
AE leading to study drug discontinuation	0	2 (1.8)
Level 3 hypoglycemia event	0	5 (4.4)
DKA event	0	0
SAE	1 (0.9)	8 (7.0)
Study drug-related SAE	0	5 (4.4)
AE resulting in death	0	0
Laboratory results of interest		
Liver function tests	0	0

Conclusions

- HDV-LIS was non-inferior to LIS in A1C reduction at both week 12 and week 25.
- Trends toward hypoglycemia reduction were seen in the dose optimization period.
- As dosing stabilized, HDV-LIS associated with significant reductions in hypoglycemia.
- No severe hypoglycemia events seen in HDV-LIS treated participants, compared with FIVE in LIS-treated participants.
- OPTI-2 study suggests that HDV-LIS can decouple glycemic control from hypoglycemia risk.

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If confirmed in Phase 3, HDV-LIS has the potential to help people living with type 1 diabetes walk the tightrope between hyperglycemia and hypoglycemia.

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27 U.S. clinical sites contributing to OPTI-2

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