# Pharmacodynamics, Pharmacokinetics, Safety, and Tolerability of INS068 vs Insulin Degludec in Type 1 Diabetes at Steady State: a Phase I, Randomised, Double-blind, Cross-over Trial

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OP 36 Optimising Insulin Therapy

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# Disclosure

- Dr. Marcus Hompesch is the Chief Executive Officer and Chairman of the Board of ProSciento.
- No other interests to report.

# Background

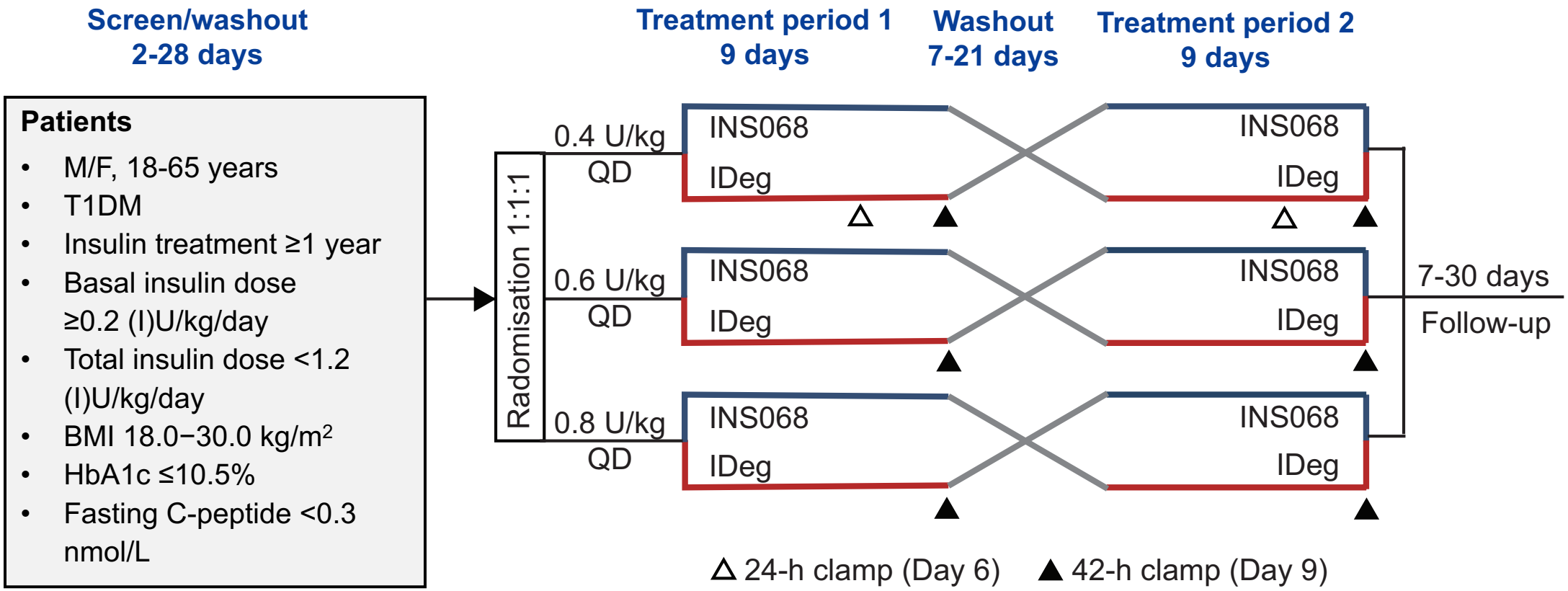
- Long-acting insulins, represented by insulin degludec (IDeg), have been shown to provide sustained insulin coverage (>24 h) with lower peak action and lower hypoglycaemic risk compared with other basal insulins [1]
- INS068 is a novel soluble long-acting insulin analog which has been demonstrated good tolerability in healthy men following a single administration at doses of 1.8-7.2 nmol/kg
- This was a randomised, cross-over phase 1 study to characterize the steady-state pharmacodynamic (PD) and pharmacokinetic (PK) properties as well as safety of INS068 vs IDeg in type 1 diabetes

1. Misra S, et al. Diabet Med. 2020;37(4):522-531.

# Study Design

**Objectives:**

To compare INS068 vs IDeg in potency (primary), PD, PK and safety (secondary)




**A single-center, randomised, double-blind, cross-over phase 1 study**

# Study Endpoints

**Primary endpoint**

- Molar dose ratio between INS068 and IDeg based on $AUC_{GIR,tau,ss}$

**Key secondary PD endpoints**

- End of action, completed clamps
- Within-subject variance of natural log-transformed $AUC_{GIR,tau,ss}$ at 0.4 U/kg
- Fluctuation as measured by $PTF_{GIR,tau,SS}$ and $AUCF_{GIR,tau,SS}$
- $AUC_{GIR,12\text{-}24h,SS}/AUC_{GIR,tau,SS}$
- $GIR_{max,SS}$
- $t_{GIRmax,SS}$

**Key secondary PK endpoints**

- Accumulation ratio, as measured by $AUC_{tau,SS/AUC0\text{-}24h,SD}$
- $t_{½,SS}$
- $AUC_{tau,SS}$
- $C_{max,SS}$
- $T_{max,SS}$

**Secondary safety endpoints**

- Adverse events
- Hypoglycemic episodes

tau=24 h. $AUC_{GIR,12\text{-}24h,SS}$, area under the GIR curve from 12-24 h at SS; $AUC_{GIR,tau,SS}$, area under the GIR curve during a dosing interval of 24 h at SS; $AUCF_{GIR,tau,SS}$, fluctuation of the GIR curve during one dosing interval of 24 h at SS; $AUC_{tau,SS}$, area under the concentration curve during one dosing interval at SS; $AUC_{tau,SS}/AUC_{0\text{-}24h,SD}$, accumulation ratio between $AUC_{tau}$ at SS and $AUC_{0\text{-}24h}$ after a single dose; $C_{max,SS}$, maximum serum concentration at SS; $C_{max,SS}/C_{max,SD}$, accumulation ratio between $C_{max,ins}$ at SS and $C_{max,ins}$ after a single dose; GIR, glucose infusion rate; $GIR_{max,SS}$, maximum GIR at SS; PTF, peak-to-trough fluctuation; SS, steady state; $t_{GIRmax,SS}$, time to maximum GIR at SS; $T_{max,SS}$, time to maximum concentration.

# Methods

## PD assessment：euglycemic clamp

- PD profile of INS068/IDeg at steady state was assessed using 42-hour euglycemic clamp with a target blood glucose level of 5.5 mmol/L (100 mg/dL).
- Within-subject variability of insulin actions was assessed using an additional 24-hour euglycemic clamp in subjects at the low dose level.

## PK assessment：

- Dense PK sampling will be performed on Day 1 and Day 9 for all subjects.
- Serum samples for INS068/IDeg were assayed using validated high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) methods.

## Safety assessment:

- Adverse events, hypoglycemia, injection site reactions, safety laboratory tests, ECGs, vital signs, physical examination and immunogenicity will be evaluated.

# Baseline Characteristics

| | 0.4 U/kg (n=31) | 0.6 U/kg (n=33) | 0.8 U/kg (n=34) | Total* (n=98) |
|---|---|---|---|---|
| Age (year) | 32.0 ± 9.9 | 35.5 ± 12.6 | 36.6 ± 12.3 | 34.8 ± 11.7 |
| Gender male, n (%) | 18 (58.1%) | 22 (66.7%) | 16 (47.1%) | 56 (57.1%) |
| Race white, n (%) | 26 (83.9%) | 32 (97.0%) | 30 (88.2%) | 88 (89.8%) |
| BMI (kg/m²) | 24.9 ± 3.2 | 25.1 ± 2.8 | 25.7 ± 2.6 | 25.3 ± 2.9 |
| Duration of T1DM (year) | 20.3 ± 10.8 | 19.9 ± 11.0 | 22.3 ± 11.8 | 20.9 ± 11.1 |
| HbA1c (%) | 7.53 ± 1.31 | 7.84 ± 1.24 | 7.33 ± 1.08 | 7.60 ± 1.18 |
| Fasting C-peptide (ng/mL) | 0.14 ± 0.19 | 0.10 ± 0.16 | 0.08 ± 0.07 | 0.10 ± 0.15 |
| Insulin dose (U/kg/day) | | | | |
| Basal insulin dose - Low | 0.34 ± 0.11 | 0.36 ± 0.12 | 0.34 ± 0.09 | 0.34 ± 0.11 |
| Basal insulin dose - High | 0.34 ± 0.11 | 0.36 ± 0.12 | 0.34 ± 0.09 | 0.34 ± 0.10 |
| Total insulin dose - Low | 0.62 ± 0.18 | 0.67 ± 0.18 | 0.61 ± 0.18 | 0.63 ± 0.18 |
| Total insulin dose - High | 0.65 ± 0.19 | 0.67 ± 0.18 | 0.64 ± 0.19 | 0.66 ± 0.19 |

Data are mean ± SD unless otherwise indicated. * 98 of 99 randomised patients received treatment and were included in analysis.

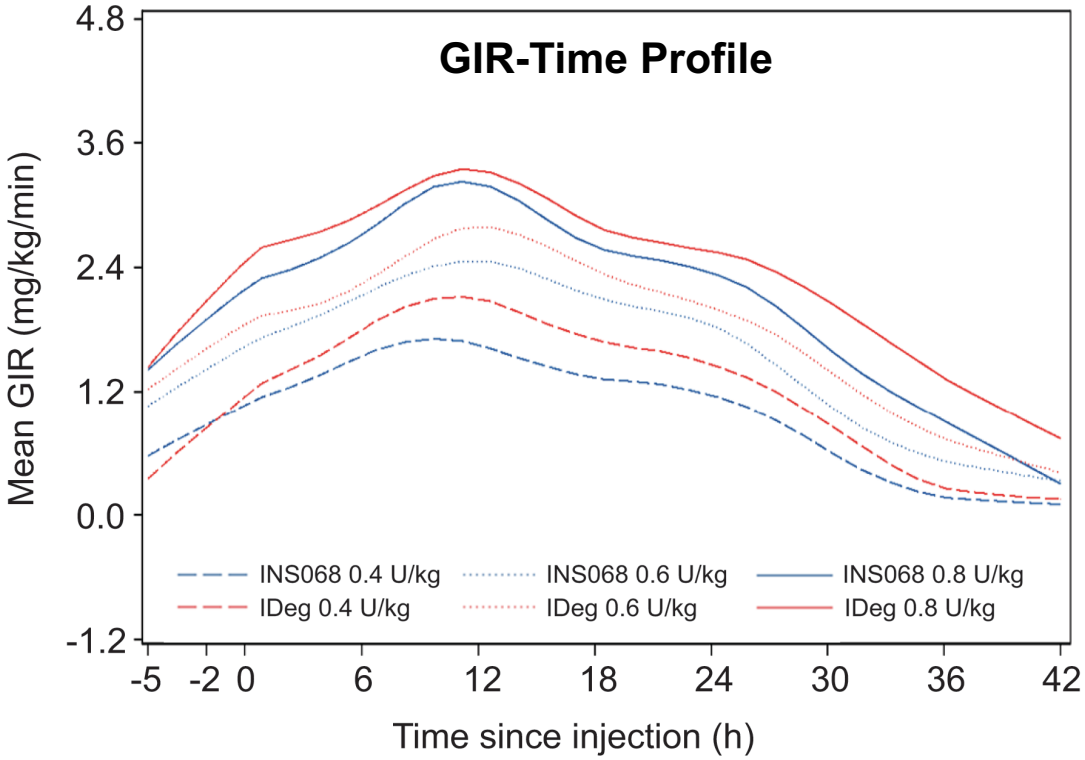
# Quality of 42-hour Clamps

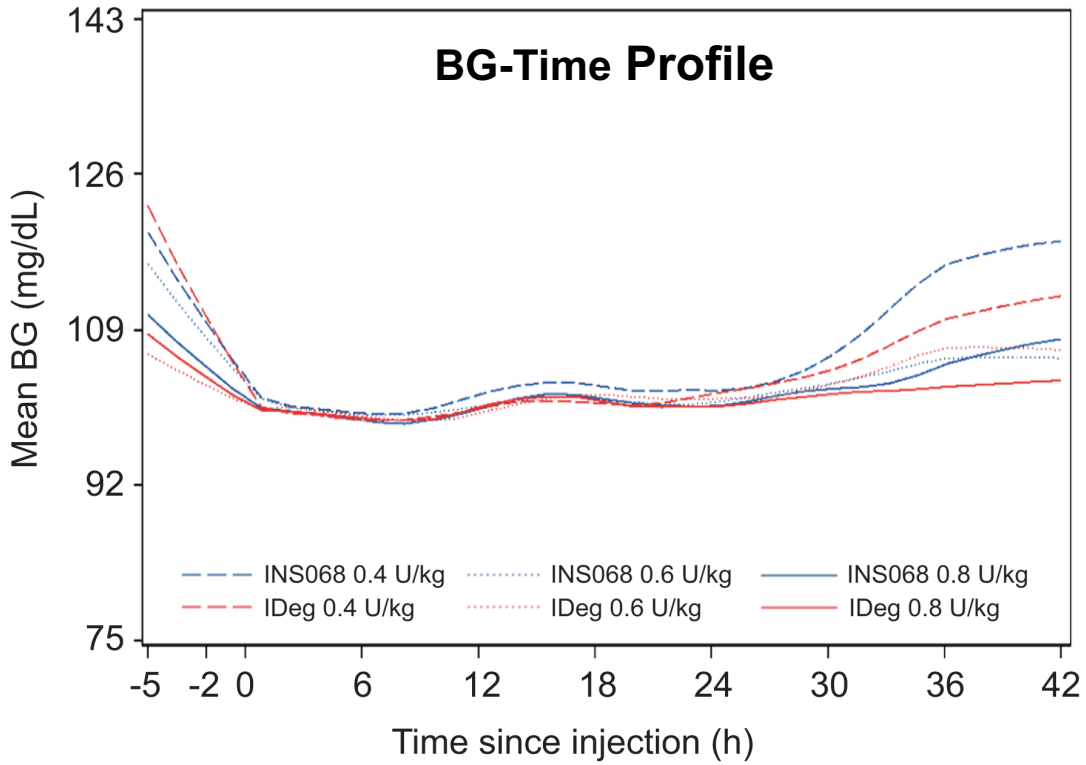
The quality of clamps as measured by coefficient of variation (CV) and deviation from target (DFT) were 6-7% and 5-6% respectively.

| | 0.4 U/kg | | 0.6 U/kg | | 0.8 U/kg | |
|---|---|---|---|---|---|---|
| | INS068 (n=25) | IDeg (n=30) | INS068 (n=28) | IDeg (n=28) | INS068 (n=28) | IDeg (n=29) |
| **CV (%)** | | | | | | |
| n | 25 | 27 | 28 | 28 | 28 | 29 |
| Mean ± SD | 7.0 ± 1.7 | 6.4 ± 1.3 | 6.1 ± 1.2 | 6.6 ± 1.6 | 7.1 ± 1.7 | 6.9 ± 1.2 |
| Median | 6.7 | 6.2 | 5.7 | 6.3 | 6.9 | 7.0 |
| Range | 4.6-11.7 | 4.1-9.7 | 4.5-9.2 | 3.2-9.7 | 4.3-12.0 | 3.7-8.9 |
| **DFT (%)** | | | | | | |
| n | 25 | 27 | 28 | 28 | 28 | 29 |
| Mean ± SD | 5.8 ± 1.4 | 5.2 ± 1.0 | 5.0 ± 1.0 | 5.4 ± 1.3 | 5.7 ± 1.3 | 5.5 ± 0.9 |
| Median | 5.5 | 4.9 | 4.7 | 5.2 | 5.6 | 5.7 |
| Range | 3.8-9.5 | 3.4-7.6 | 3.7-7.5 | 2.9-8.3 | 3.7-9.2 | 3.0-7.5 |

CV of one clamp was 12% and therefore excluded from the analysis of molar dose ratio.

# Pharmacodynamic Profile at Steady State
## (42-h clamp starting on Day 9)




- GIR-time profiles of INS068 were generally similar to IDeg, though slightly lower at all dose levels

- In all groups, BG was maintained at the target level (100 mg/dL) until >30 h; mean BG was <150 mg/dL at 42 h

BG, blood glucose; GIR, glucose infusion rate

# Primary Endpoint

Molar dose ratio (MDR) of INS068 vs IDeg

| | No. of patients | No. of observations | MDR (95% CI) * |
|---|---|---|---|
| $AUC_{GIR,tau,SS}$ (mg/kg) | 88 | 164 | 0.85 (0.75-0.93) |

- Based on $AUC_{GIR,tau,ss}$ from 42-h clamp starting on Day 9
- Included patients who completed the initial 24 h of at least one 42-h clamp which met the quality requirement †

* MDR and a 95% CI using Fieller's method was provided by adopting the estimated parameters and covariance matrix from a mixed effect model. † Defined as both CV and DFT <12%. $AUC_{GIR,tau,ss}$, area under the GIR curve during a dosing interval of 24 h at steady state.

# Pharmacodynamic Parameters at Steady State

| | 0.4 U/kg | | 0.6 U/kg | | 0.8 U/kg | |
|---|---|---|---|---|---|---|
| | INS068 (n=25) | IDeg (n=30) | INS068 (n=28) | IDeg (n=28) | INS068 (n=27) | IDeg (n=29) |
| Completion of 42-h clamp, n (%) | 24 (96.0%) | 26 (86.7%) | 28 (100.0%) | 28 (100.0%) | 27 (100.0%) | 29 (100.0%) |
| End of action* (h) | 40.8 | 41.5 | 42.0 | 42.0 | 42.0 | 42.0 |
| $AUC_{GIR,tau,SS}$ (mg/kg) | 1555 | 2177 | 2725 | 3079 | 3728 | 3987 |
| $GIR_{max,SS}$ (mg/kg/min) | 1.48 | 1.99 | 2.39 | 2.67 | 3.22 | 3.33 |
| $t_{GIRmax,SS}$† (h) | 12.0 | 13.3 | 12.4 | 13.3 | 11.9 | 12.9 |
| $PTF_{GIR,tau,SS}$ | 0.73 | 0.71 | 0.54 | 0.52 | 0.47 | 0.41 |
| $AUCF_{GIR,tau,SS}$ | 0.12 | 0.12 | 0.10 | 0.10 | 0.10 | 0.08 |
| $AUC_{GIR,12\text{-}24h,SS}/AUC_{GIR,tau,SS}$ | 0.46 | 0.50 | 0.50 | 0.50 | 0.49 | 0.49 |

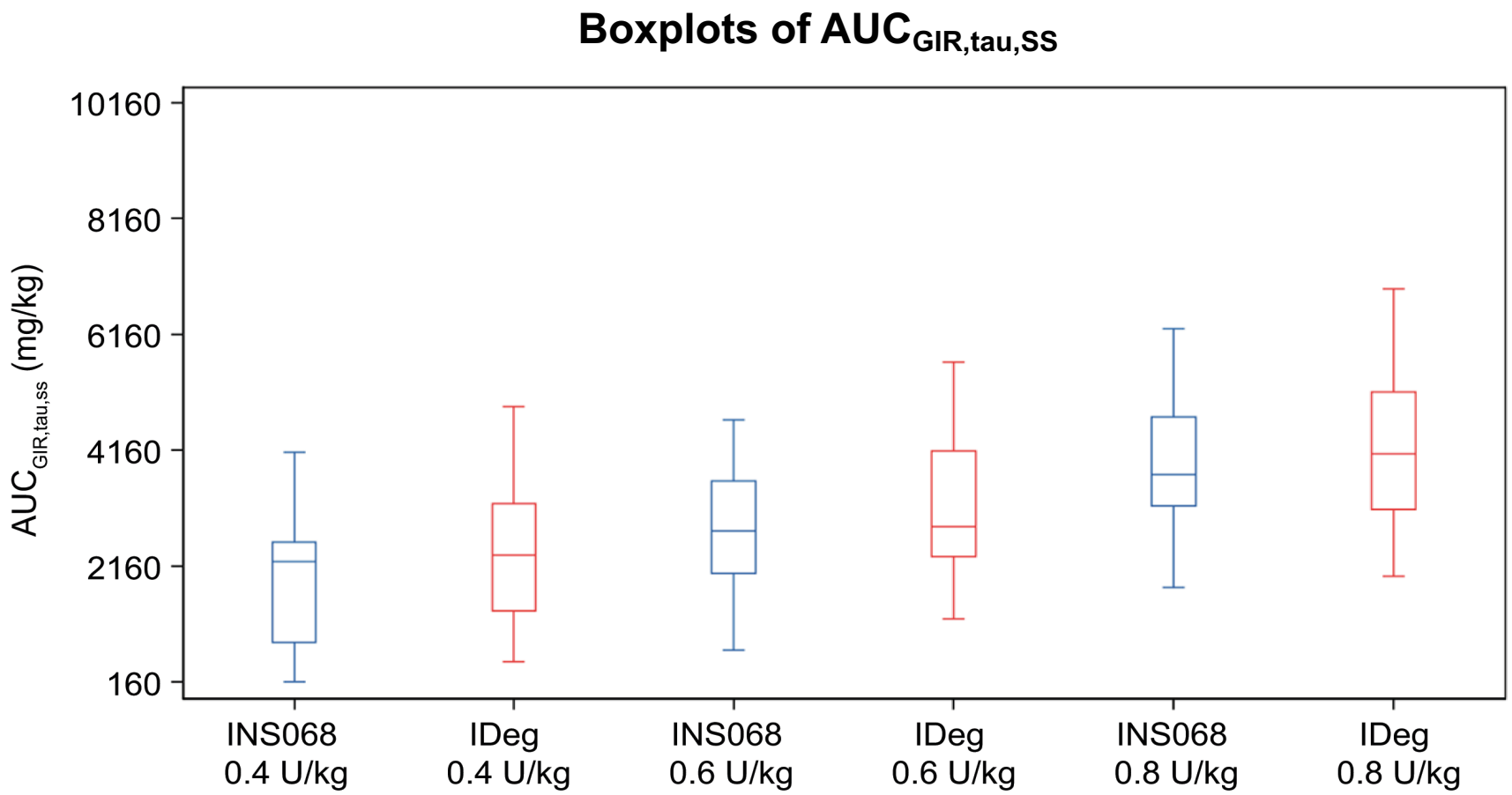
Continuous variables are presented in mean (†) or geometric mean. * Defined as time from administration of the last dose until the last time when blood glucose was ≤8.3 mmol/L (150 mg/dL). $AUC_{GIR,12\text{-}24h,SS}$, area under the GIR curve from 12-24 h at SS; $AUC_{GIR,tau,SS}$, area under the GIR curve during a dosing interval of 24 h at SS; $AUCF_{GIR,tau,SS}$, fluctuation of the GIR curve during one dosing interval of 24 h at SS; $GIR_{max,SS}$, maximum GIR at SS; PTF, peak-to-trough fluctuation; SS, steady state; $t_{GIRmax,SS}$, time to maximum GIR at SS.

# Within-Subject Variability in $AUC_{GIR,tau,SS}$

| $AUC_{GIR,tau,SS}$ (mg/kg) | n | Estimate | 95% CI |
|---|---|---|---|
| Within-subject variance of log transformed parameter | | | |
| INS068 | 28 | 0.016 | 0.005-0.049 |
| IDeg | 28 | 0.020 | 0.007-0.059 |
| Ratio: INS068/IDeg | 28 | 0.813 | 0.198-3.335 |
| CV% of parameter | | | |
| INS068 | 28 | 12.8 | |
| IDeg | 28 | 14.2 | |

The model included data from Day 6 and Day 9. A linear mixed model was applied to log-transformed variance of log-transformed $AUC_{GIR,tau,SS}$ with insulin type and period as fixed effect and subject as random effect.

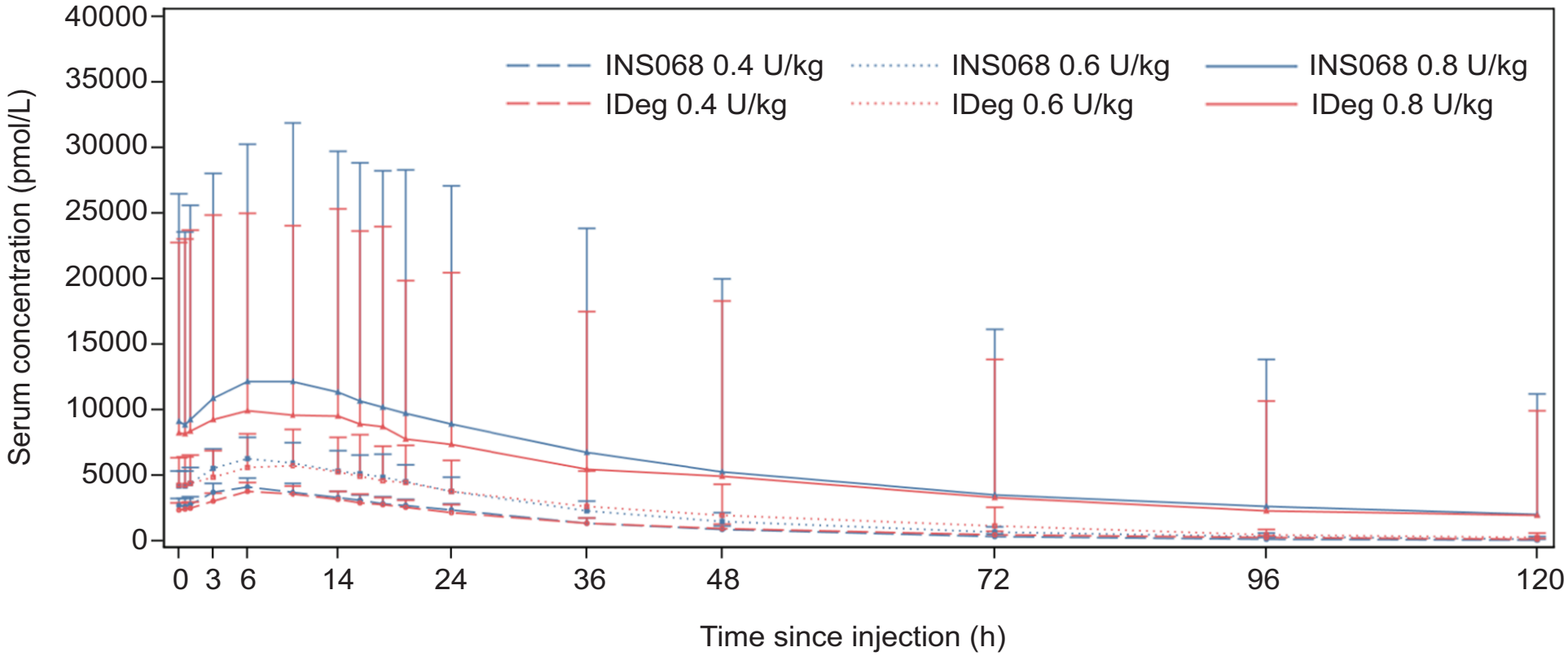
# Dose Proportionality in Pharmacodynamic Response




$AUC_{GIR,tau,SS}$ for INS068 increased approximately proportional to dose (power model: β = 0.74, 90% CI 0.33-1.16).

Data from Day 9 during 42-h clamp.

# Pharmacokinetic Profile at Steady State
## (0-120 h starting on Day 9)




- PK concentration-time profiles of INS068 and IDeg were generally similar.
- PK profiles appeared to be slightly higher with INS068 vs IDeg at 0.8 U/kg.
- Mean terminal half-life ($t_{1/2}$) was 21 h with INS068 vs 26 h with IDeg across all doses.

Data are mean ± SD.

# Pharmacokinetic Parameters at Steady State

| | 0.4 U/kg | | 0.6 U/kg | | 0.8 U/kg | |
|---|---|---|---|---|---|---|
| | INS068 (n=27) | IDeg (n=30) | INS068 (n=30) | IDeg (n=30) | INS068 (n=30) | IDeg (n=30) |
| $AUC_{tau,SS}$ (h*pmol/L) | 77676 | 72337 | 121546 | 111489 | 186112 | 159017 |
| $C_{max,SS}$ (pmol/L) | 4131 | 3788 | 6225 | 5672 | 9517 | 7954 |
| $T_{max,SS}$*(h) | 6.0 | 6.0 | 6.0 | 8.0 | 8.0 | 6.0 |
| $C_{max,SS}/C_{max,SD}$† | 1.5 | 1.4 | 1.5 | 1.3 | 1.8 | 1.6 |
| $AUC_{tau,SS}$/ $AUC_{0\text{-}24h,SD}$† | 1.6 | 1.6 | 1.6 | 1.5 | 2.0 | 1.8 |

Data are from Day 9 and presented as median (* ) or geometric mean. † Overall accumulation ratio for INS068 vs IDeg was 1.7 vs 1.6 for AUC and 1.6 vs 1.4 for $C_{max}$ based on a mix effects model. $AUC_{tau,SS}$, area under the concentration curve during one dosing interval at SS; $AUC_{tau,SS}/AUC_{0\text{-}24h,SD}$, accumulation ratio between $AUC_{tau}$ at SS and $AUC_{0\text{-}24h}$ after a single dose; $C_{max,SS}$, maximum serum concentration at SS; $C_{max,SS}/C_{max,SD}$, accumulation ratio between $C_{max,ins}$ at SS and $C_{max,ins}$ after a single dose; SS, steady state; $T_{max,SS}$, time to maximum concentration.

# Safety Profile

| | INS068 (n=87) | IDeg (n=90) |
|---|---|---|
| TEAE | 47 (54.0%) | 58 (64.4%) |
| TRAE | 15 (17.2%) | 12 (13.3%) |
| Severe AE* | 0 | 1 (1.1%) |
| Serious AE* | 0 | 1 (1.1%) |
| Death | 0 | 0 |
| TRAE occurring in ≥2% of patients in either group | | |
| Hyperglycaemia | 6 (6.9%) | 2 (2.2%) |
| Injection site pain | 3 (3.4%) | 4 (4.4%) |
| Headache | 3 (3.4%) | 4 (4.4%) |
| Hypoglycaemic episode† | 74 (85.1%) | 78 (86.7%) |

Data are n (%). * One patient had hypoglycaemia after withdrawal from study. † No Level 3 episode (per 2017 ADA/EASD classification) was reported. AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

# Conclusions

- At doses of 0.4-0.8 U/kg, INS068 demonstrated generally similar PD and PK profiles to IDeg at steady state
- The glucose-lowering effect and exposure of INS068 were dose proportional
- INS068 was well-tolerated, with a similar safety profile to IDeg

# Acknowledgements

We would like to thank:

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- All research personnel and staff at ProSciento Inc who conducted this trial
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- 2021 EASD Meeting Organization Committee