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Variability of 501 Inhaled Insulin Absorption and Action

AN UNRIVALLED COMBINATION OF SCIENCE AND PROFESSIONAL CLINICAL CONDUCT.

WE DELIVER SOLUTIONS.

WE ARE UNIQUE.

1019-P

American Diabetes Association
80th Scientific Sessions

Financial disclosures

- Dr. Zijlstra is an employee of Profil
- Dr. Zijlstra has received speaker honoraria and travel grants from Eli Lilly, Novo Nordisk and Roche Diabetes Care

- Aerami Therapeutics is the company developing 501 inhaled insulin
- Aerami Therapeutics sponsored this research

Introduction

501 inhaled insulin

- Inhaled insulin: A convenient and favorable alternative to injections[1]
- 501: A novel liquid formulation of human insulin

Enables easy and accurate dose-loading of the device

Variability of drop weight approximately 3-4%

Strong, sterile microbial barrier

Stability for >4 years at 2-8°C and >1 month at 25°C

501 biologic drop dispenser

Breath-activated

Transforms liquid insulin into a gentle mist upon inhalation

Afina smart inhaler

[1]Testa MA and Simonson DC, *Diabetes Care* 30:1399–1405, 2007

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501 inhaled human insulin

Clinical pharmacology

- Previous findings[1,2]:
  - Fast absorption and fast onset of action vs. lispro injection
  - Duration of action similar to lispro
  - Linear dose response
  - Delivery efficiency around 13%
  - Well-tolerated, no cough upon inhalation

- Current study objective
  - Investigate dosing variability of 501 inhaled insulin

[1]Zijlstra E et al., *Diabetes* 2019 Jun; 68 (Supplement 1): 1085-P.
[2]Zijlstra E et al., *Diabetes Technology Meeting* 2019 Nov; Bethesda MD: Dance 501 Inhaled Human Insulin: Linear Dose Response in Patients with Type 1 Diabetes

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Methods

Trial Design

- Randomized, crossover, replicated dose (2x2), open-label, active comparator controlled, glucose clamp trial

501 inhaled human insulin (INH)

- Administered INH dose: 92.2 IU*
- The inhalations were done by the subjects after a brief training on the correct inhalation technique

Insulin lispro (100 U/mL) for s.c. injection (LIS)

- Administered LIS dose: 12 U
- The injections were given by a small group of trained staff

*Assumption on delivery efficiency: 13% for INH vs. LIS. Zijlstra E et al., *Diabetes,* 64 (Suppl. 1): 978-P, 2015
s.c. subcutaneous

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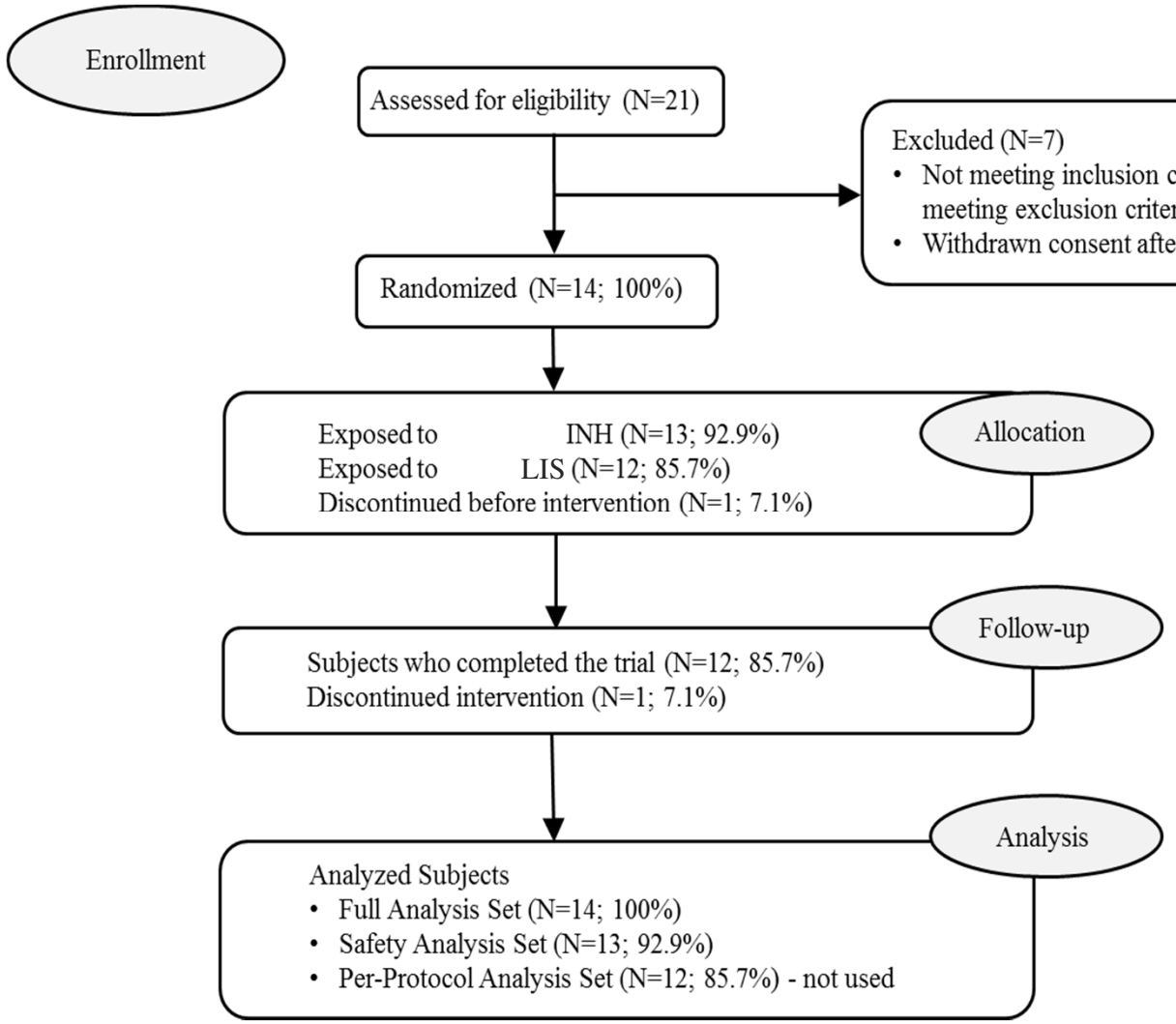
Trial subjects

Subject flow, baseline characteristics and safety



	N = 13*
Diabetes type	Type 1
Age [years]	32.5 ± 7.9
Gender, female / male [n]	4 / 9
BMI [kg/m2]	26.5 ± 2.1
HbA1c [%]	7.5 ± 0.8
C-peptide [nmol/L]	0.07 ± 0.06
Diabetes duration [years]	13.1 ± 8.2
FVC [L]	5.1 ± 0.7

Safety and tolerability

- 21 AEs (8 INH vs. 13 LIS) were observed
  All mild or moderate in intensity, no SAE
- No cough was observed after INH dosing
- No acute changes in lung function were observed

*Safety Analysis Set (subjects exposed to trial product)
AE adverse event; BMI body mass index; FVC forced vital capacity; SAE serious adverse event

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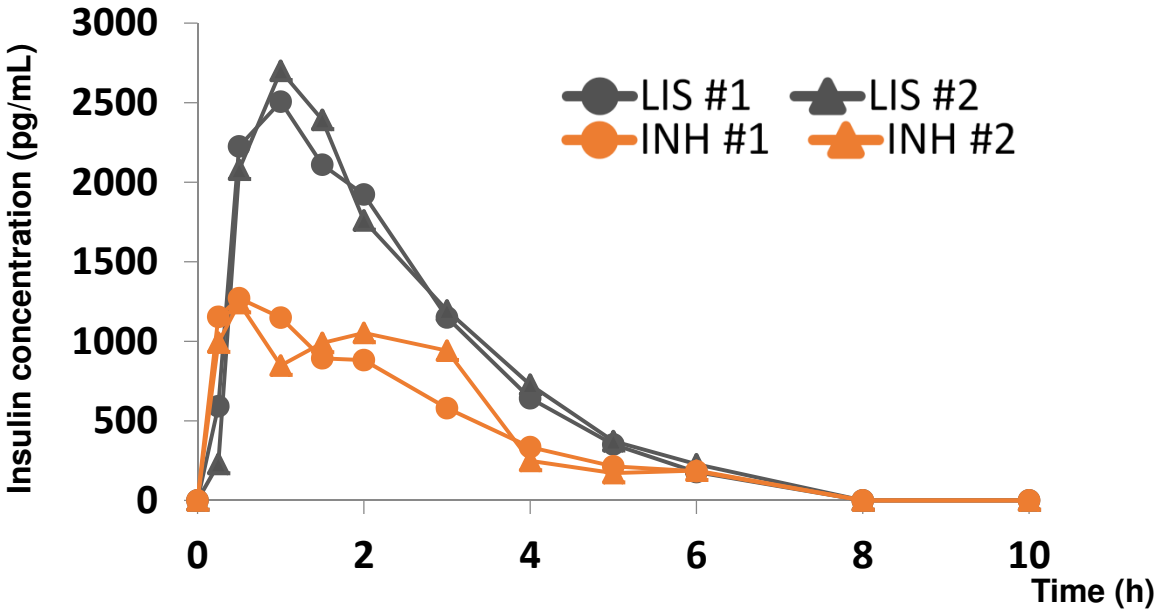
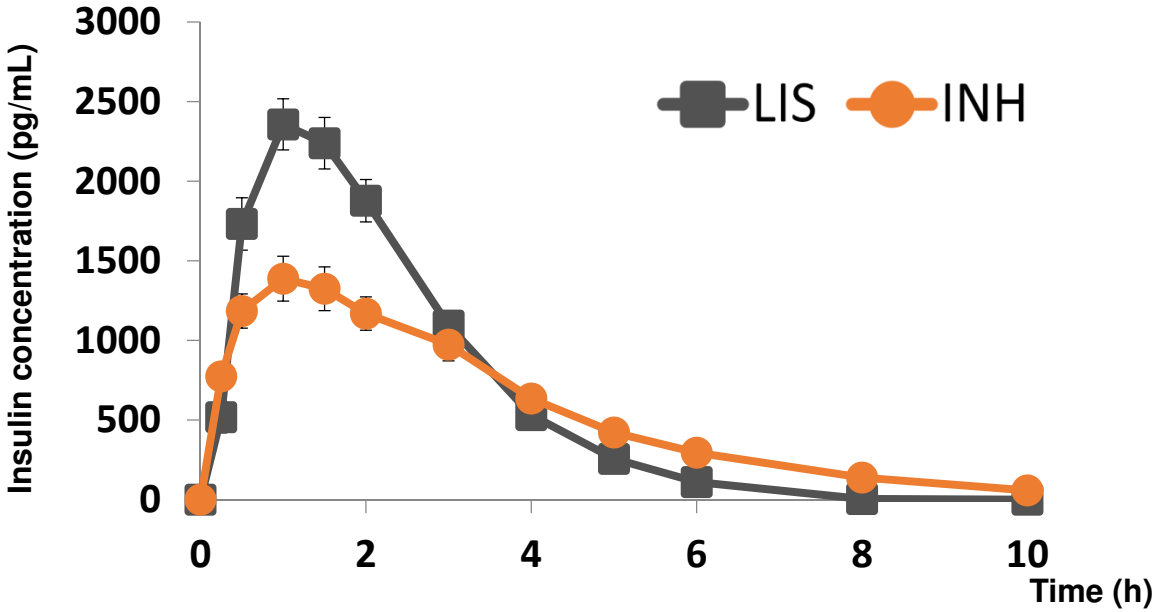
Results

Individual and mean pharmacokinetic response

Example individual subject PK response (N=1)



Mean PK response (N=13)



- INH is absorbed equally fast as LIS
- Maximum exposure is lower with INH
- Delivery efficiency around 13%

Parameter	Treatment	Mean ± SD
AUC (0-10h) [pg*h/mL]	INH LIS	6049 ± 2454 6834 ± 2001
Cmax [pg/mL]	INH LIS	1646 ± 778 2341 ± 827
Tmax [h]	INH LIS	1.22 ± 0.63 1.26 ± 0.63
Delivery efficiency [%]	INH	12.6 ± 6.0

AUC area under the curve; Cmax maximum insulin concentration; PK pharmacokinetic; Tmax; time to maximum insulin concentration

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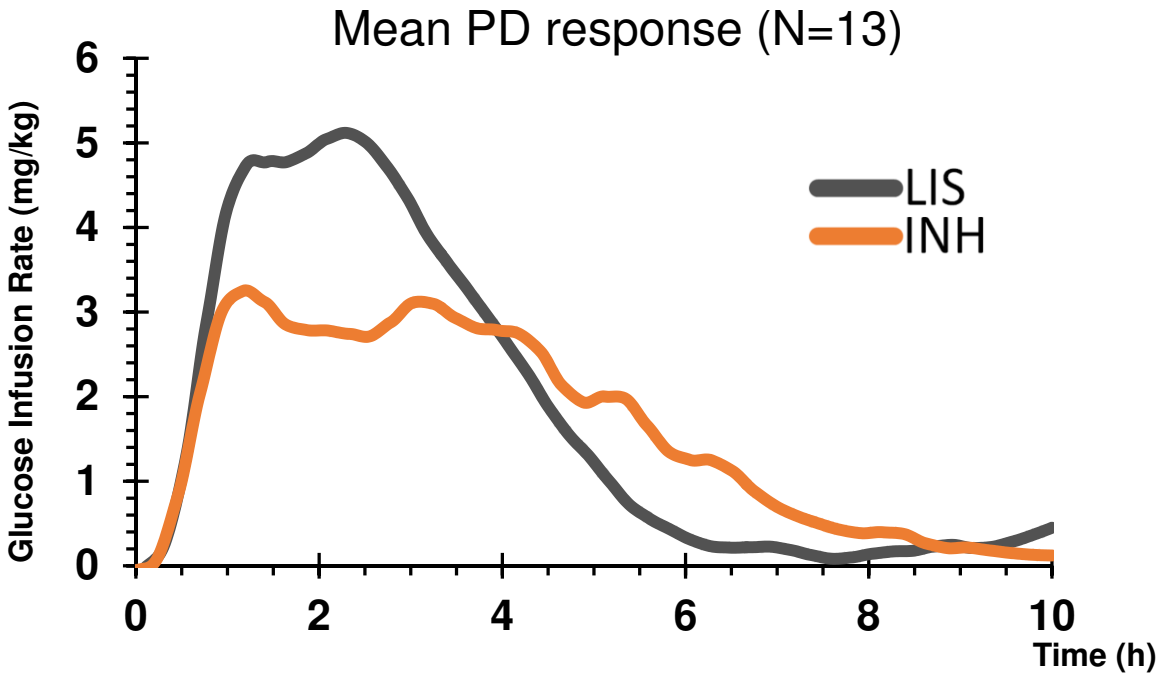
Results

Mean pharmacodynamic response



- Automated glucose clamp (ClampArt®)
- Clamp BG target: 100 mg/dL
- 10 hour assessment

- INH has fast onset of insulin action
- Duration of action long enough to cover postprandial period
- Total insulin action comparable to LIS

Parameter	Treatment	Mean ± SD
AUC GIR (0-10h) [mg/kg]	INH LIS	970 ± 601 1062 ± 429
GIRmax [mg/kg]	INH LIS	4.38 ± 2.25 5.66 ± 2.28
Onset of action [min]	INH LIS	31.8 ± 11.2 36.0 ± 13.1
TGIRmax [h]	INH LIS	2.48 ± 1.28 1.85 ± 0.77

AUC area under the curve; GIR glucose infusion rate; PD pharmacodynamic; TGIRmax; time to maximum glucose infusion rate

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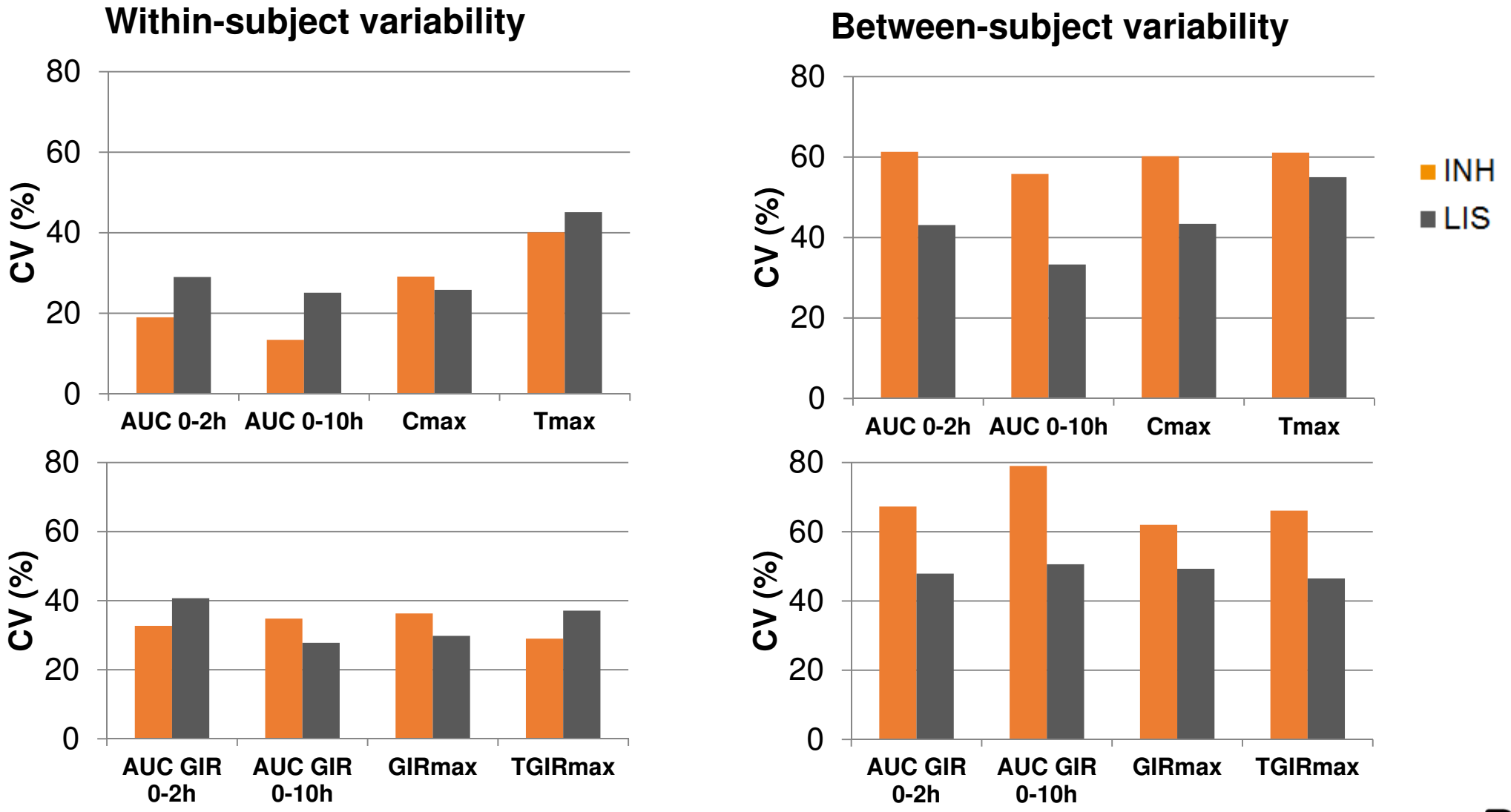
Results

PK / PD variability

PK

PD



AUC area under the curve; CV coefficient of variability; GIR glucose infusion rate; PD pharmacodynamics; PK pharmacokinetics

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Main conclusion

- The intra-individual response to self-administration of 501 inhaled insulin is as reproducible as that of s.c. insulin lispro injected by experienced staff
- This is a clinically meaningful outcome and enables individual dose titration of 501 insulin in future treatment

Thank you very much !

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