Faster Absorption and Greater Earlier Insulin Action of 501 Inhaled Human Insulin vs. s.c. Insulin Lispro in Patients with Type 2 Diabetes

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STUDY OBJECTIVES

- To investigate the pharmacokinetic (PK) and glucodynamic (PD) response after 3 doses of 501 inhaled human insulin (INH) in patients with type 2 diabetes
- To compare the PK/PD responses of INH with those of 3 equivalent subcutaneous (s.c.) doses of insulin lispro (LIS)

CONCLUSIONS

- **501 showed faster insulin absorption, more rapid onset of action and greater early insulin action vs. LIS**
- **From 1 hour post-dosing, insulin exposure and action were comparable between treatments**
- **Inhalations were without cough**
- **501 may become a valuable and clinically meaningful option for insulin treatment in type 2 diabetes**

INTRODUCTION

- Inhalation of insulin provides a convenient alternative to insulin injections [1]
- 501 is a novel liquid formulation of human insulin for inhalation (INH)
- 501 is inhaled with a smart inhaler: a small, silent handheld electronic aerosol device with vibrating mesh micro-pump technology. The inhaler is breath-activated and transforms the liquid insulin formulation into a mist upon patient inhalation (Fig. 1)
- An individualized prandial dose of insulin can be delivered in a single or multiple breaths (Fig. 2)

METHODS

- Randomized, crossover, open label and active comparator-controlled trial
- 8 Visits: A screening examination, 6 dosing visits separated by a 3-17 day washout period and a follow-up examination
- Eligible subjects (Table 2) had normal lung function with a forced vital capacity (FVC) > 75% relative to reference values

Figure 2 –
Person using the 501 inhaler. All subjects performed their own inhalations under medical supervision; s.c. injections were performed by a trial physician

TRIAL PRODUCTS

- 501 human insulin for inhalation
- Insulin lispro (100 U/mL) for s.c. injection

Table 1 – Dose levels

	Administered INH dose (IU)	Assumed efficacious* INH dose (IU)	LIS dose (U)
LOW	92.2	12	12
MED	184.4	24	24
HI	368.8	48	48

*INH administration assumes a 13% delivery efficiency compared to LIS [2]

- Insulin action after dosing was measured using the automated glucose clamp method (ClampArt, Profil, Germany)
  - Duration: 10 hours
  - Target BG level: 100 mg/dL

RESULTS

Table 2 – Subject baseline characteristics

	N = 24
Age [years]	61.8 ± 7.9
Gender, female / male [n]	5 / 19
BMI [kg/m^2]	30.4 ± 2.6
HbA1c [%]	7.4 ± 0.7
Fasting C-peptide [nmol/L]	0.52 ± 0.27
Diabetes duration [years]	10.4 ± 4.8
FVC [L]	4.2 ± 1.0

Mean ±SD

- 24 subjects with T2D on insulin therapy and/or metformin were enrolled (Table 2), 22 completed the trial
- Key PK/PD responses and results are shown on the right (Fig. 3,4 and Table 3,4)

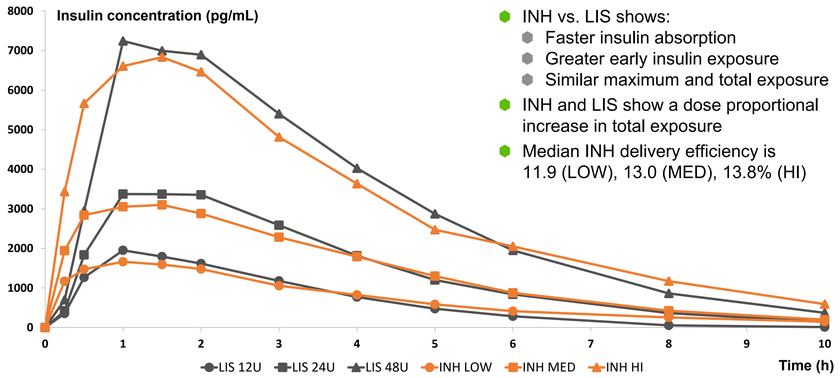
SAFETY

- 13 adverse events (AEs) were observed with INH vs. 18 with LIS. 30 out of 31 AEs were rated mild to moderate in intensity
- 1 SAE after a LIS 24U dose; A causal relationship with trial product was unlikely
- No cough was observed after INH dosing
- No changes in lung function were observed

Figure 1 –
The inhaler produces a soft mist of human insulin upon inhalation

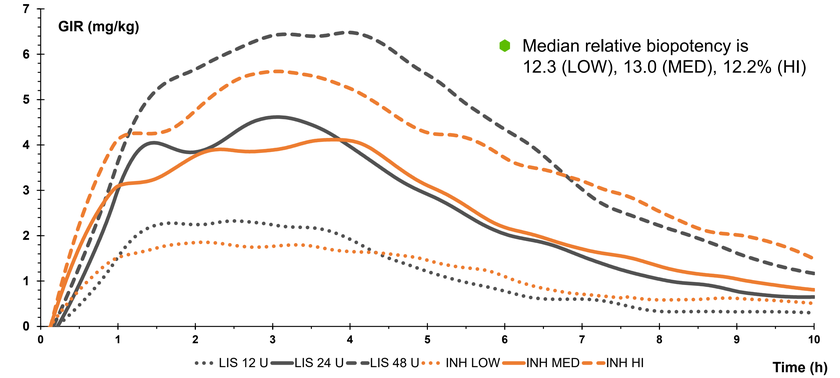
PK/PD RESPONSE PROFILES

Figure 3 – Mean time-concentration profiles for 501 inhaled insulin (INH) and insulin lispro (LIS)



- INH vs. LIS shows:
  - Faster insulin absorption
  - Greater early insulin exposure
  - Similar maximum and total exposure
- INH and LIS show a dose proportional increase in total exposure
- Median INH delivery efficiency is 11.9 (LOW), 13.0 (MED), 13.8% (HI)

Figure 4 – Mean time-action profiles for 501 inhaled insulin (INH) and insulin lispro (LIS)



- Median relative biopotency is 12.3 (LOW), 13.0 (MED), 12.2% (HI)

Table 3 – Key PK results (INH/LIS)

Endpoint	Dose	Treatment ratio (95% CI)
$AUC_{INS.0\text{-}1h}$	LOW	1.28 (0.99; 1.66)
	MED	1.50 (1.16; 1.95)*
	HI	1.43 (1.11; 1.85)*
$AUC_{INS.0\text{-}10h}$	LOW	1.07 (0.90; 1.27)
	MED	0.94 (0.79; 1.11)
	HI	0.93 (0.79; 1.10)
$C_{INS.max}$	LOW	0.90 (0.71; 1.13)
	MED	0.91 (0.72; 1.15)
	HI	0.90 (0.71; 1.13)

*p<0.01; AUC = area under the curve

Table 4 – Key PD results medium dose

Endpoint	Treatment	Result	Difference (95% CI)
Onset of action [min]	INH	24.3 ± 8.2	-16.5
	LIS	39.5 ± 13.6	(-24.0; -10.0)*
AUC GIR (0-1h) [mg/kg]	INH	94.0 ± 43.6	35.7
	LIS	52.9 ± 36.3	(7.5; 60.3)*
AUC GIR (0-10h) [mg/kg]	INH	1479 ± 709	42
	LIS	1436 ± 523	(-203; 287)
GIR max [mg/kg/min]	INH	4.9 ± 2.4	-0.5
	LIS	5.4 ± 2.1	(-1.3; 0.3)
T GIR max [h]	INH	3.2 ± 0.9	-0.0
	LIS	3.2 ± 1.5	(-0.9; 0.6)

Mean ± SD; *p<0.01; AUC = area under the curve

- Faster onset of action for INH vs. LIS (median 20.0, 16.5 and 6.5 min faster for LOW, MED and HI doses, p<0.02)
- Greater action in the first hour after administration with INH vs. LIS for all dose levels (median relative differences 107%, 57% and 45%, p<0.05)
- Comparable time to maximum insulin action at each dose level (p>0.7)
- Reduced maximum action with INH vs. LIS at the highest dose level (mean difference -0.9 mg/kg/min, p<0.05)
- Comparable total glucose lowering action (p>0.2 for AUC GIR (0-10h) comparison at each dose level)

References: 1. Testa MA and Simonson DC, *Diabetes Care* 30:1399–1405, 2007; 2. Zijlstra E et al., Diabetes. 2015; 64 (Suppl. 1): 978-P

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