501 Inhaled Human Insulin: Linear Dose Response in Patients with Type 1 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 1 diabetes
- To compare the PK/PD responses of INH with those of 3 equivalent subcutaneous (s.c.) doses of insulin lispro (LIS)

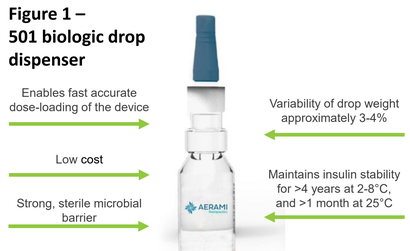
CONCLUSIONS

- **501 showed linear dose proportional increases in total exposure and total and maximum insulin action**
- **501 showed rapid onset of action**
- **Inhalations were well tolerated and without cough**

INTRODUCTION

- 501 is a novel liquid formulation of human insulin for inhalation (INH), contained in a biologic drop dispenser (Fig. 1)
- Each drop contains a fixed amount of insulin. Multiple drops can be loaded into a smart inhaler (Fig. 2) for insulin dosing

Figure 1 – 501 biologic drop dispenser



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 – 501 smart inhaler. The inhaler is breath-activated and transforms the liquid insulin formulation into a gentle mist upon patient inhalation

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	61.5	8	8
MED	123	16	16
HI	245.9	32	32

*INH administration assumes a 13% delivery efficiency compared to LIS [1]

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

RESULTS

Table 2 – Subject baseline characteristics

	N = 24
Age [years]	44.8 ± 10.2
Gender, female / male [n]	9 / 15
BMI [kg/m^2]	25.4 ± 2.6
HbA1c [%]	7.5 ± 0.7
Fasting C-peptide [nmol/L]	≤ 0.3 nmol/L
Diabetes duration [years]	23.7 ± 10.7
FVC [L]	4.9 ± 1.0

Mean ±SD

- 24 subjects with type 1 diabetes were enrolled (Table 2), all completed the trial

KEY RESULTS

- Dance 501 showed a dose proportional increase for total exposure and a linear dose response for total and maximum insulin action (Fig. 3 and 4, Table 5)
- The median INH delivery efficiency and median relative biopotency (Table 3) was ~9-12%, lower than the 13% seen in studies in patients with T2D [1]

Table 3 – INH bioavailability and biopotency

Endpoint	Dose	Median	Min	Max
Delivery efficiency [%]	LOW	8.9	4.0	26.6
	MED	10.8	4.8	27.5
	HI	10.1	2.6	32.7
Relative biopotency [%]	LOW	9.0	0.0	18.4
	MED	10.7	3.2	23.0
	HI	12.1	2.4	20.1

- Insulin exposure and insulin action were significantly lower for INH vs. LIS, at all dose levels, due to the lower than assumed delivery efficiency and relative biopotency
- Speed of absorption and action were comparable between the two routes of administration (Table 6)

PK RESPONSE PROFILES (INH)

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

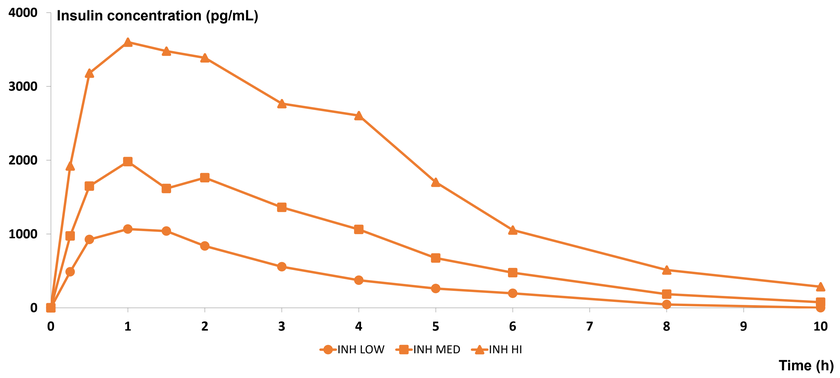


Figure 4 – Linear dose responses for inhaled insulin (INH) and insulin lispro (LIS)

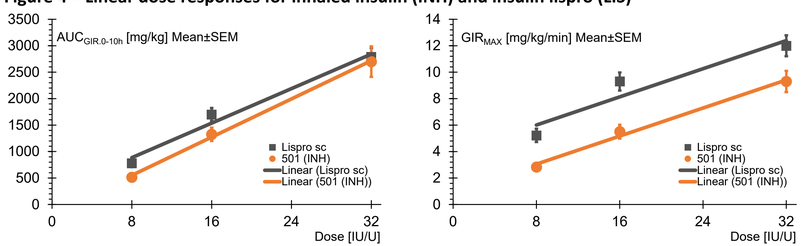


Table 4 – Number of breaths needed to complete dose inhalation

Endpoint	Dose	Median	Min	Max
No. of breaths	LOW	3	1	5
	MED	4	2	9
	HI	6.5	2	14

- All subjects performed their own insulin inhalations
- The LOW dose could be administered in a single inhalation, the HI dose in two inhalations (Table 4)
- The number of breaths needed for full dose inhalation varied among subjects and is expected to be lower after subjects have accustomed to the optimal inhalation speed

Table 5 – Key PK and PD results (INH)

Endpoint	Dose	Result
AUC$_{INS.0-1h}$ [pg*h/mL]	LOW	762.5 ± 612.3
	MED	1386.4 ± 1067.4
	HI	2599.1 ± 2040.7
AUC$_{INS.0-10h}$ [pg*h/mL]	LOW	4027.4 ± 4436.2
	MED	8769.7 ± 7830.4
	HI	18060 ± 18901
C$_{INS.max}$ [pg/mL]	LOW	1210.3 ± 1096.1
	MED	2294.7 ± 1934.9
	HI	4048.6 ± 3308.4
AUC GIR (0-1h) [mg/kg]	LOW	72.0 ± 42.9
	MED	103.1 ± 48.4
	HI	174.2 ± 96.0
AUC GIR (0-10h) [mg/kg]	LOW	515.3 ± 318.1
	MED	1326.0 ± 612.8
	HI	2699.4 ± 1413.3
GIR max [mg/kg/min]	LOW	2.8 ± 1.3
	MED	5.5 ± 2.6
	HI	9.3 ± 3.9

Mean ± SD; AUC = area under the curve

Table 6 – Onset of exposure and action INH vs. LIS

Endpoint	Dose	INH vs. LIS
Onset of appearance [min]	LOW	15.7 vs. 17.0
	MED	15.6 vs. 18.1
	HI	15.1. vs. 15.1
Onset of action [min]	LOW	32.9 vs. 32.5
	MED	30.5 vs. 27.7
	HI	23.7 vs. 26.9

Mean values

SAFETY

- 14 adverse events (AEs) were observed with INH vs. 17 with LIS. All AEs were rated mild to moderate in intensity
- No coughing occurred after dosing with INH. No injection site reactions were reported after dosing with LIS
- No changes in lung function were observed

References: 1. Zijlstra E et al., Diabetes. 2015; 64 (Suppl. 1): 978-P

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