Dance 501 Inhaled Human Insulin: Linear Dose Response, Earlier Onset of Action and Higher Early Effect than s.c. Insulin Lispro

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STUDY OBJECTIVES

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

INTRODUCTION

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

Figure 1 –
The Dance-501 inhaler device produces a fine mist of human insulin upon inhalation

METHODS

- Randomized, crossover, open label and active comparator-controlled trial
- 8 Visits: A screening examination, 6 dosing visits seperated 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 Dance-501 inhaler. All subjects performed their own inhalations under medical supervision; s.c. injections were performed by a trial physician

- Trial products
  - Dance 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
Diabetes type	Type 2
BMI [kg/m^2]	30.4 ± 2.6
HbA1c [%]	7.4 ± 0.7
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 type 2 diabetes on insulin therapy and/or metformin were randomized (Table 2)
  - 22 completed the trial
  - 1 withdrawal due to a severe case of urinary retention after 1 dose (INH LOW)
  - 1 withdrawal due to inability to perform the last clamp experiment

Table 3 – primary PD results

Parameter	Treatment	N	
AUC GIR (0-10h) [mg/kg]	INH LOW INH MED INH HI	23 23 22	693 ± 384 1479 ± 709 2181 ± 932
GIR max [mg/kg/min]	INH LOW INH MED INH HI	24 23 22	2.4 ± 1.1 4.9 ± 2.4 6.3 ± 2.4

- Primary PD endpoints show a dose-dependent increase for INH in total and maximum glucose lowering effect (Table 3)
  - Dose-response linearity of INH and LIS was demonstrated for AUC GIR (0-10h) (Figure 4)
- The mean relative biopotency was 16.0%, 13.7% and 12.3% for the INH LOW, MED and HI dose levels. This confirms previous findings [2]

RESULTS

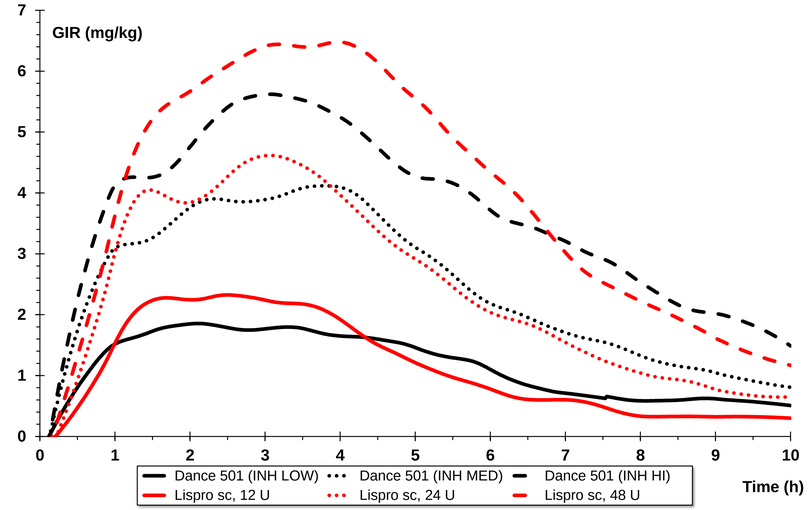
- Time-action profiles from Figure 3 show:
  - Faster onset of action for INH vs. LIS (median 20.0, 16.5 and 6.5 min faster for LOW, MED and HI doses, p<0.02)
  - Greater action in the first hour of administration with INH vs. LIS for all dose levels (median relative differences 107%, 57% and 45%, p<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)
- 31 adverse events (AEs) were observed, 13 with INH vs. 18 with LIS. 30 out of 31 AEs were rated mild to moderate in intensity
- 1 SAE, hospitalization with increased myocardial necrosis marker, occurred after last dose (LIS MED). A causal relationship with trial product was unlikely
- No cough was observed after INH dosing
- No changes in lung function were observed

Table 4 – Comparison medium dose INH vs LIS

Parameter	Treatment	N	
Onset of action [min]	INH MED LIS MED	23 22	24.3 ± 8.2 39.5 ± 13.6
AUC GIR (0-1h) [mg/kg]	INH MED LIS MED	23 22	94.0 ± 43.6 52.9 ± 36.3
AUC GIR (0-10h) [mg/kg]	INH MED LIS MED	23 22	1479 ± 709 1436 ± 523
GIR max [mg/kg/min]	INH MED LIS MED	23 22	4.9 ± 2.4 5.4 ± 2.1
T GIR max [h]	INH MED LIS MED	23 22	3.2 ± 0.9 3.2 ± 1.5

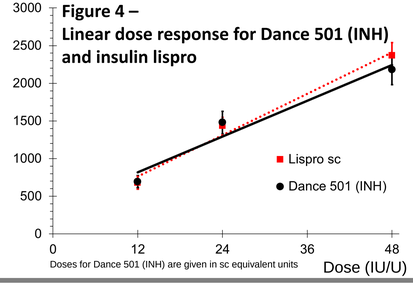
TIME-ACTION PROFILES

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



AUC GIR (0-10h) [mg/kg] Mean±SEM

Figure 4 –
Linear dose response for Dance 501 (INH) and insulin lispro



Doses for Dance 501 (INH) are given in sc equivalent units

CONCLUSIONS

- Dance 501 showed comparable pharmacodynamic properties and more rapid onset of action vs. Insulin lispro
- Dance 501 showed good tolerabilty, no changes in lung function and no cough after insulin inhalation
- Dance 501 may become a clinically meaningful alternative to rapid-acting insulin injections

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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