Technosphere® Insulin Inhalation Powder (TI) Displays Earlier Onset and Shorter Duration than Insulin Lispro (Lispro)

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Abstract

The dose-response curve of TI (4, 12, and 48 U doses) was compared to that of Lispro (8, 30, and 90 U doses) in a cross-over hyperinsulinemic, euglycemic clamp with 30 T1DM patients.

Key parameters: PD – onset, time to 50% max GIR ($T_{50\%}$-GIR_{max}), max effect (GIR_{max}), duration ($T_{100\%}$-GIR-$AUC_{0\text{-}end}$), total effect (GIR-$AUC_{0\text{-}end}$). PK – max insulin conc (INS-C_{max}), time of max conc (T_{max}) and exposure (INS-AUC_{last}).

Pharmacodynamic Response: [mean (SD)]				
Insulin - Dose	"Onset" $T_{50\%}$-GIR_{max} (min)	GIR_{max} (mg/min)	"Duration" $T_{100\%}$ of GIR-AUC_{end} (hr)	GIR-$AUC_{0\text{-}end}$ (g)
TI- 4 U	15.6 (10.2)	182 (84.9)	1.83 (1.03)	8.8 (5.7)
TI – 12 U	21.4 (7.10)	491 (218)	3.13 (1.30)	32.1 (14.9)
TI – 48 U	18.9 (3.32)	905 (236)	6.43 (2.23)	131.2 (37.5)
Lispro – 8 U	52.4 (16.6)	423 (198)	5.03 (1.30)	59.7 (29.7)
Lispro – 30 U	51.3 (17.1)	898 (243)	7.24 (1.39)	191.9 (55.6)
Lispro – 90 U	44.5 (11.2)	1194 (273)	9.78 (1.98)	372.7 (85.5)

Key Pharmacokinetics Parameters			
Insulin - Dose	C_{max} (µU/mL) [mean (SD)]	T_{max} (min) (median)	AUC_{last} (µU·hr/mL) [mean (SD)]
TI – 4 U	43.9 (21.2)	10	59.5 (66.2)
TI – 12 U	123 (67.2)	15	150 (124)
TI – 48 U	597 (259)	20	673 (340)
Lispro – 8 U	62.9 (19.1)	68	210 (65.2)
Lispro – 30 U	167 (48.3)	75	543 (158)
Lispro – 90 U	551 (251)	90	1760 (515)

C_{max} and AUC were dose proportional for TI but slightly sublinear for Lispro; saturable GIR_{max} was obtained over the dose range for both insulins. Onset of activity for TI occurred ca. 25-35 minutes earlier than for Lispro. TI duration of action is about 2 hours shorter than an equivalent dose of Lispro. Dose-response was almost linear up to 48U TI and 30 U Lispro.

Background & Objective

Technosphere® insulin (TI), an inhaled insulin with a fast onset of action, provides a novel option for the control of prandial glucose [1]. A euglycemic clamp study comparing 4 doses of Afrezza to a single dose of regular human insulin suggested the relationship between Afrezza dose and GIR $AUC_{0\text{-}240min}$ was less than dose-proportional. The US FDA requested a post-marketing PK/PD euglycemic clamp study in Type 1 patients to compare the dose-response of Afrezza with a SC rapid-acting analog (SC RAA).

Specifically, the study was to identify the doses of Afrezza and RAA where the PD response becomes non-linear.

Clinical Study

Study Design

A randomized, controlled, 6-treatment, 6-sequence, 6-period crossover dose-response study of 3 single doses of Afrezza® (Technosphere® Insulin) inhalation powder and 3 single doses of subcutaneous (SC) insulin lispro in patients with diabetes mellitus type 1 using the euglycemic clamp technique (NCT02470637).

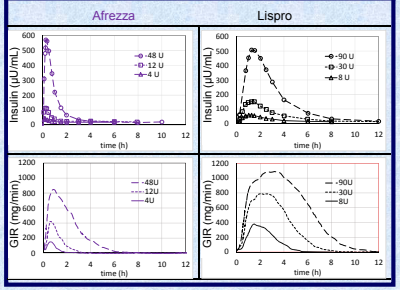
Thirty patients enrolled; all completed the study.

Demographics (N = 30)				
Characteristic	Mean±SD	Characteristic	N (%)	
Age (yr)	42.4±11.5	Sex	Male: 29	(96.7%)
			Female: 1	(3.3%)
Height (cm)	180.13±6.52	Race	Caucasian: 29	(96.7%)
			Black: 1	(3.3%)
Weight (kg)	83.1±8.73	BMI ≤ 29 m²/kg	30	(100.0%)
BSA (m²)	2.03±0.13			

Glucose Clamp Summary

- Clamp system: ClampArt®
- Clamp level: 5.5 mmol/L (100 mg/dL) ±10%
- Duration: up to 20 h or until BG > 11.1 mmol/L (200 mg/dL) for 30 minutes with no glucose infusion
- GIR smoothing: LOESS, smoothing factor 0.06
- Clamp performance:
  - RSD < 6.3%
  - Utility: >85% in 171 out of 176 profiles (97%)

PK/PD Profiles

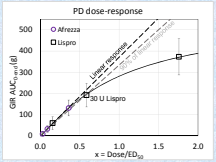


Pharmacodynamic Dose-Response

GIR AUC

- Mean GIR $AUC_{0\text{-}end}$ for both treatments was fit to a model with common E_{max} and Hill coefficient (γ) but with separate ED_{50}
- The PD response of 4 U Afrezza and 1.6 U Lispro are equivalent (e.g., 20 units Afrezza produces the same GIR AUC as 8 U Lispro)

$$GIR\ AUC_{0\text{-}end} = E_{max}\frac{(Dose/ED_{50})^{\gamma}}{1+(Dose/ED_{50})^{\gamma}}$$

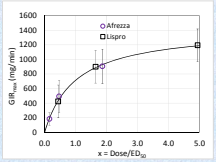


	Afrezza	Lispro
ED_{50}	133 U	51 U
E_{max}	562 g	
γ	1.17	

GIR_{max}

- Mean GIR_{max} for both treatments was fit to a model with common E_{max} but separate ED_{50}
- To elicit the same GIR_{max}, ~40% more Afrezza is required (e.g., a 4 unit cartridge of Afrezza and 2.8 U Lispro produce the same GIR_{max})

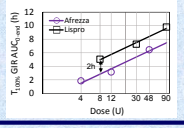
$$GIR_{max} = E_{max}\frac{(Dose/ED_{50})}{1+(Dose/ED_{50})}$$



	Afrezza	Lispro
ED_{50}	25.7 U	18.2 U
E_{max}	1427 mg/min	

End of effect

- On a dose basis, the effect of Afrezza ends 2 h before Lispro

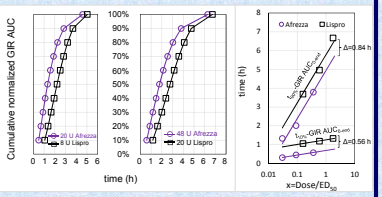


Onset and Duration

- No criteria have been established to define onset and duration of insulin action, so both GIR AUC and GIR/GIR_{max} were examined.
- For comparison, two dose pairs in the therapeutic range were chosen to give the same GIR $AUC_{0\text{-}end}$ (20 U Afrezza, 8 U Lispro) and (48 U Afrezza, 20 U Lispro)

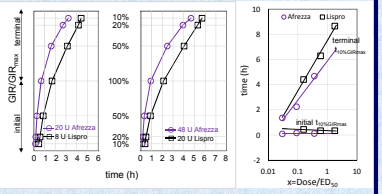
GIR AUC

- Cumulative GIR AUC curves for Afrezza are left-shifted from Lispro curves.
  - Afrezza's action begins ($t_{10\%GIR\ AUC}$) ~ 0.6 h before Lispro's
  - Afrezza's action ends ($t_{90\%GIR\ AUC}$) ~ 0.8 h before Lispro's



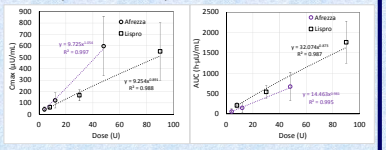
GIR_{max}

- GIR_{max} occurs an hour earlier than Lispro.
- Afrezza's onset (initial $t_{10\%GIRmax}$) occurs at ~ 7 min vs. ~25 min for Lispro
- Afrezza reaches terminal $t_{10\%GIRmax}$ faster than Lispro and the difference increases with increasing dose



Pharmacokinetics

- C_{max} and AUC for Afrezza and Lispro were approximately dose-proportional over the dose range studied
- Each 4 unit Afrezza cartridge provides approximately the same insulin exposure as 3.1 U Lispro



Conclusions

- Lispro doses up to 30 U produce approximately linear GIR AUC response (within 10% of linear response)
- From the E_{max} model for dose-GIR $AUC_{0\text{-}end}$, the corresponding dose for Afrezza is ~ 80 units
- Nonlinearity in GIR AUC occurs above these doses

- For matched doses providing the same GIR AUC:
  - Every quantile of Afrezza's GIR and GIR AUC curves occurs before the corresponding point on the Lispro curves
  - Afrezza's onset of action is faster than Lispro's
  - Afrezza's duration is shorter than Lispro's

- Afrezza's labeled dose over-estimates its effect
  - A single conversion factor does not fully describe Afrezza's effect relative to SC insulin
  - For safety, initial conversion to Afrezza tends to under-estimate dose
  - Titration to appropriate dose is essential

References & Disclosures

[1] Boss AH, Petrucci R, Lorber D. Coverage of prandial insulin requirements by means of an ultra-rapid-acting inhaled insulin. J Diabetes Sci Technol. 2012;6(4):773-9.

Disclosures

- *Clinical study was performed and funded by Sanofi.*
- *MG and RB are employees of Mannkind.*
- *PG, LP, YH, BG and RD are employees of Sanofi.*
- *TH is an employee of Profil, Germany and is a member of advisory panels for Novo Nordisk; received travel funds and honoraria from Eli Lilly, Mylan, and Novo Nordisk; conducted research sponsored by Adocia, Astra Zeneca, Becton Dickinson, Biocon, Boehringer Ingelheim, Dance Pharmaceuticals, Eli Lilly, Grünenthal, Gulf Pharmaceuticals, Johnson&Johnson, Marvel, Medimmune, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi, Senseonics, Zealand Pharma*