Within-Subject Variability of Insulin Exposure and Metabolic Activity Following Replicate Doses of Technosphere® Insulin Inhalation Powder (TI) in Patients with T1DM

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Abstract

Point estimates and 95% CIs for the variance components of key PK and PD parameters were estimated using a linear mixed-effect model with period (fixed) and subject (random) effects. In hyperinsulinemic, euglycemic clamp studies, single doses of TI were administered on 2 occasions to 22 T1DM subjects to assess within-subject variability in PK and PD.

Key parameters: PD - glucose infusion rate (GIR-$AUC_{0\text{-end}}$) and maximum GIR (GIR_{max}); PK - maximum observed serum insulin concentration (C_{max}) and insulin exposure (AUC_{last}).

Pharmacodynamic Response: [mean (SD)]		
Insulin - Dose	Glucose disposition GIR $AUC_{0\text{-end}}$ (mg)	Maximum GIR GIR_{max} (mg/min)
TI – 16 U (Period 1)	48,151 (16,732)	642 (231)
TI – 16 U (Period 2)	52,377 (20,061)	596 (206)
Pharmacokinetic Parameters : [mean (SD)]		
	C_{max} (µU/mL)	AUC_{last} (h·µU/mL)
TI – 16 U (Period 1)	279 (133)	262 (91.9)
TI – 16 U (Period 2)	286 (146)	265 (120)

Statistical analysis (Point estimate and 95% CI):				
	Within-subject SD		Total SD	
PD Parameter	Estimate	95% CI	Estimate	95% CI
Log(GIR-$AUC_{0\text{-end}}$)	0.283	(0.214 to 0.418)	0.433	(0.352 to 0.591)
Log(GIR_{max})	0.271	(0.204 to 0.400)	0.418	(0.340 to 0.572)
PK Parameter	Estimate	95% CI	Estimate	95% CI
Log(C_{max})	0.209	(0.161 to 0.299)	0.446	(0.355 to 0.621)
Log(AUC_{last})	0.162	(0.124 to 0.231)	0.412	(0.325 to 0.578)

In T1DM subjects receiving replicate single 16 U TI doses, the within-subject SD was less than 21% for PK parameters and less than 28% for PD parameters.

Clinical Study

Study Design

An open-label, 2 replicate single dose euglycemic glucose-clamp trial to characterize PK and PD within-subject variability of a single dose of Afrezza inhaled insulin in patients with diabetes mellitus type 1 (T1DM) [1].

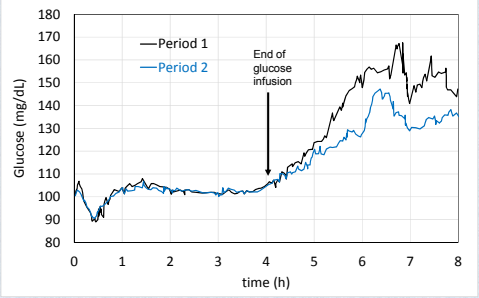
Each patient received 16 U Afrezza ® (labeled dose) on 2 occasions.

Inclusion criteria

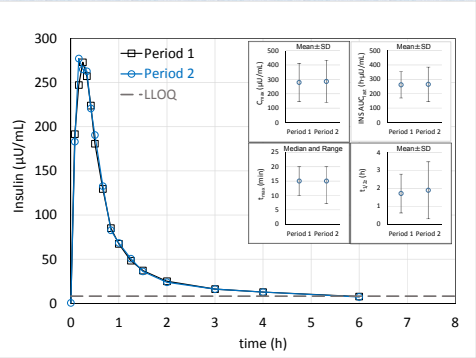
- Male or female patients, between 18 and 65 years of age, inclusive
- Type 1 diabetes for more than 1 year, as defined by the American Diabetes Association
- Stable insulin regimen for at least 2 months prior to study and a total insulin dose of <1.2 U/kg/day
- Body weight between 50 and 95 kg, inclusive, and body mass index (BMI) between 18.5 and 29 kg/m², inclusive.
- Glycohemoglobin ≤9%
- Fasting serum C-peptide <0.3 nmol/L

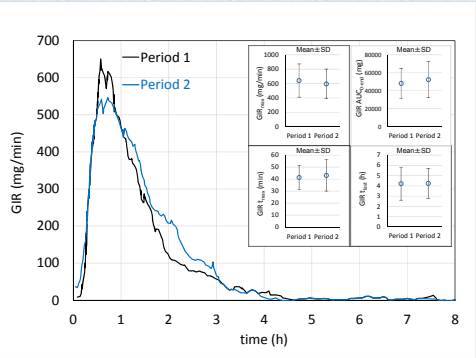
Demographics (N = 22)			
Characteristic			
Age (yr)	mean±std. dev:36.1±14.9	median:31.0	range: 19-65
Weight (kg)	mean±std. dev:77.50±10.48	median:77.75	range: 57.8-92.8
Duration of T1D (yr)	mean±std. dev:18.71±14.25	median:13.22	range: 2.8-51.6
Sex	male:14 (63.6%)	female:8 (36.4%)	
Race	Caucasian:22 (100%)		

Median Glucose Profiles



PK/PD Profiles





Results/Conclusions

Pharmacokinetics

- Within-subject variability for C_{max} (20.9%) and AUC_{last} (16.2%) in T1DM agrees with previously published results for Afrezza in T2DM (20.4% and 15.9%, respectively) [2]
  - Previous studies have with Afrezza in healthy volunteers, T1DM, and T2DM have not shown variability in absorption across these groups
- Mean PK profiles are essentially superimposable
- Insulin concentration peaks at t_{max} ~ 15 min and returns to near-baseline by 180 min after dosing
- Terminal half-life is $t_{1/2z}$ ~ 1.8 h

Pharmacodynamics

- Within-subject variability for GIR_{max} (27.1%) and GIR AUC_{last} (28.3%) in T1DM patients is comparable to previously published results for Afrezza in T2DM patients (22.0% and 25.7%, respectively) [2]
- GIR_{max} occurs at GIR t_{max} ~ 40-45 min
- Onset of action (GIR = 50% GIR_{max}) occurs at GIR $t_{50\%\text{-}max}$ ~ 18-20 min
- Glucose infusion ends at GIR t_{last} ~ 4 h after dosing

References & Disclosures

[1] Plum-Mörschel L. An open-label, 2 replicate single dose euglycemic glucose-clamp trial to characterize PK and PD within-subject variability of a single dose of Afrezza inhaled Technosphere® Insulin in patients with diabetes mellitus type 1 (T1DM) Sanofi; 2016

[2] Rave K, Heise T, Heinemann L and Boss AH. Inhaled Technosphere® Insulin in Comparison to Subcutaneous Regular Human Insulin: Time Action Profile and Variability in Subjects with Type 2 Diabetes. J Diabetes Sci Technol. 2008;2(2):205-212.

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