

Online Resources

Comparison of Pharmacokinetics and Pharmacodynamics of Inhaled Technosphere Insulin and Subcutaneous Insulin Lispro in Treatment of Type 1 Diabetes Mellitus; *Clinical Pharmacokinetics*; Marshall Grant, Tim Heise, Robert Baughman; corresponding author: Marshall Grant, mgrant@mannkindcorp.com (MannKind Corporation, Westlake Village, CA, USA)

**Each Online Resource is shown chronologically (1-5) on separate pages of this document.*

Online Resource 1. Doses Administered and Planned Clamp Durations

Dose level	Labeled dose (U)	TI		LIS	
		Insulin content (U)	Clamp duration	Dose (U)	Clamp duration
Dose 1	4	10	8 h	8	8 h
Dose 2	12	30	10 h	30	12 h
Dose 3	48	120	16 h	90	20 h

LIS, insulin lispro; TI, Technosphere Insulin.

Online Resource 2. Experimental Design

Screening	Arm	n	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Follow-up
Screening visit 3 to 28 days before first treatment	1	5	TI dose 1	TI dose 2	TI dose 3	LIS dose 1	LIS dose 2	LIS dose 3	End-of-study visit 7 to 14 days after last treatment
	2	5	TI dose 2	LIS dose 1	TI dose 1	LIS dose 3	TI dose 3	LIS dose 2	
	3	5	TI dose 3	TI dose 1	LIS dose 2	TI dose 2	LIS dose 3	LIS dose 1	
	4	5	LIS dose 1	LIS dose 3	TI dose 2	LIS dose 2	TI dose 1	TI dose 3	
	5	5	LIS dose 2	TI dose 3	LIS dose 3	TI dose 1	LIS dose 1	TI dose 2	
	6	5	LIS dose 3	LIS dose 2	LIS dose 1	TI dose 3	TI dose 2	TI dose 1	

There was a 7- to 28-day washout period between treatments. LIS, insulin lispro; TI, Technosphere Insulin.

Online Resource 3. Demographic and Patient Characteristics at Baseline—Safety Population (N=30)

Parameter	Value
Age, years	
Mean (SD)	42.4 (11.5)
Median	44.0
Min, max	22.0, 61.0
Sex, n (%)	
Male	29 (96.7)
Female	1 (3.3)
Race, n (%)	
Caucasian/White	29 (96.7)
Black	1 (3.3)
Height, cm	
Mean (SD)	180.1 (6.5)
Median	181.0
Min, max	160.0, 194.0
Weight, kg	
Mean (SD)	83.1 (8.7)
Median	85.5
Min, max	63.3, 94.9
BMI, kg/m ²	
Mean (SD)	25.6 (1.9)
Median	25.4
Min, max	21.1, 29.0
BSA, m ²	
Mean (SD)	2.0 (0.1)
Median	2.1
Min, max	1.7, 2.3
Duration of diabetes, years	
Mean (SD)	22.5 (9.9)
Median	22.9
Min, max	3.5, 46.5
HbA1c, %	
Mean (SD)	7.4 (1.0)
Median	7.7
Min, max	5.3, 9.0

BMI, body mass index; BSA, body surface area; HbA1c, glycated hemoglobin; max, maximum; min, minimum.

Online Resource 4. Coefficients From Regression in Log-Transformed Variables

Independent variables	Terms	Dependent variables							
		ln(AUC _{last})		ln(GIR AUC)		ln(MRT)		ln(t _{GIRend})	
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Treatment and dose	Intercept	6.533	0.1682	3.636	0.6279	4.463	0.1062	5.096	0.137
	TI	-2.666	0.2419	-3.438	0.3271	-1.457	0.1527	-1.856	0.197
	ln(Dose)	1.076	0.0486	1.613	0.4035	0.1373	0.0307	0.2816	0.0396
	TI × ln(Dose)	0.2789	0.0682	0.4641	0.093	0.0871	0.043	0.2781	0.0555
	ln ² (Dose)	—	—	-0.1233	0.061	—	—	—	—
	TI × ln ² (Dose)	—	—	—	—	—	—	—	—
	AIC	224.7	—	305.0	—	62.77	—	152.5	—
Treatment and AUC _{last}	Intercept	—	—	-8.067	1.030	2.074	0.6165	—	—
	TI	—	—	—	—	-0.8907	0.047	—	—
	ln(AUC _{last})	—	—	2.413	0.2304	0.4429	0.1354	—	—
	TI × ln(AUC _{last})	—	—	—	—	—	—	—	—
	ln ² (AUC _{last})	—	—	-0.0852	0.0126	-0.0158	0.0074	—	—
	TI × ln ² (AUC _{last})	—	—	-0.0049	0.0008	—	—	—	—
	AIC	—	—	230.1	—	43.36	—	—	—
AUC _{last} and MRT	Intercept	—	—	-4.466	1.459	—	—	—	—
	ln(AUC _{last})	—	—	2.511	0.2749	—	—	—	—
	ln ² (AUC _{last})	—	—	-0.0926	0.0147	—	—	—	—
	ln(MRT)	—	—	-2.192	0.7618	—	—	—	—
	ln ² (MRT)	—	—	0.284	0.088	—	—	—	—
	AIC	—	—	243.3	—	—	—	—	—

AIC, Akaike information criterion; AUC, area under the concentration-time curve; AUC_{last}, AUC from time 0 to the last measurable concentration; GIR, glucose infusion rate; MRT, mean residence time; t_{GIRend}, time to end of insulin effect (taken to be the end of glucose infusion).

Online Resource 5. Comparison of PK and PD profiles at comparable insulin exposure plotted at full scale. **(a)** Mean PK profiles ($n = 5$) with $AUC_{last} = 6537 \pm 638 \text{ min} \cdot \mu\text{U/mL}$ (TI) and $6538 \pm 65 \text{ min} \cdot \mu\text{U/mL}$ (LIS), **(b)** mean PK profiles ($n = 5$) with $AUC_{last} = 61,489 \pm 7327 \text{ min} \cdot \mu\text{U/mL}$ (TI) and $61,371 \pm 9082 \text{ min} \cdot \mu\text{U/mL}$ (LIS), **(c)** mean GIR profiles corresponding to the mean PK profiles in Online Resource 5a, **(d)** mean GIR profiles corresponding to the mean PK profiles in Online Resource 5b. AUC_{last} , area under the concentration-time curve from time 0 to the last measurable concentration; GIR, glucose infusion rate; PD, pharmacodynamic; PK, pharmacokinetic.

