



Presentation 929-P / 929 Faster Onset and Greater Early Exposure and Glucose-Lowering Effect with Faster-Acting Insulin Aspart vs. Insulin Aspart: A Pooled Analysis in Subjects with Type 1 Diabetes

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Abstract:

Faster-acting insulin aspart (faster aspart) is insulin aspart (IAsp) set in a new formulation with added excipients and faster initial absorption after subcutaneous (s.c.) injection. This pooled analysis of PK/PD properties of faster aspart vs. IAsp included 218 adult subjects with type 1 diabetes from 6 phase 1 randomized, double-blind, crossover trials. Subjects received single s.c. doses (0.2 U/kg) of faster aspart and IAsp. In 3 trials, a 12-hour automated euglycemic clamp was performed (target 100 mg/dL). Onset of appearance was twice as fast (~5 min earlier; Table) and $t_{50\%C_{max}}$ was 9.5 min earlier with faster aspart than IAsp, resulting in two-fold higher insulin exposure during the first 30 min and higher insulin exposure up to 2 hrs after injection with faster aspart than IAsp. The higher early exposure of faster aspart translated into a left shift of the glucose-lowering effect profile. Onset of action was 23% faster, $t_{50\%GIR_{max}}$ was 21% earlier and the glucose-lowering effect during the first 30 min was 74% greater with faster aspart than IAsp. Total exposure, maximum concentration and total and maximum glucose-lowering effect were similar between treatments. In conclusion, in a pooled analysis faster aspart demonstrated faster onset and higher early insulin exposure that led to greater early glucose-lowering effect vs. IAsp.



Table: Pharmacokinetic and pharmacodynamic results for faster aspart vs IAsp.

PK endpoints (insulin exposure ^a)	N=261/256 ^b	PD endpoints (glucose-lowering effect)	N=163/160 ^b
Onset	Treatment difference Faster aspart-IAsp [95% CI] (minutes)	Onset	Treatment difference Faster aspart-IAsp [95% CI] (minutes)
Onset of appearance t50%C _{max}	-4.9 [-5.3;-4.4] -9.5 [-10.7;-8.3]	Onset of action t50%GIR _{max}	-4.9 [-6.9;-3.0] -9.5 [-12.5;-6.4]
Early exposure	Treatment ratio Faster aspart/IAsp [95% CI]	Early effect	Treatment ratio Faster aspart/IAsp [95% CI]
AUC _{0-15min}	3.83 [3.41;4.29]	-	-
AUC _{0-30min}	2.01 [1.87;2.17]	AUC _{GIR,0-30min}	1.74 [1.47;2.10] ^c
AUC _{0-1h}	1.32 [1.26;1.39]	AUC _{GIR,0-1h}	1.34 [1.25;1.43]
AUC _{0-2h}	1.10 [1.06;1.14]	AUC _{GIR,0-2h}	1.13 [1.07;1.19]
Total exposure	Treatment ratio Faster aspart/IAsp [95% CI]	Total effect	Treatment ratio Faster aspart/IAsp [95% CI]
AUC _{0-12h}	1.01 [0.98;1.04]	AUC _{GIR,0-12h}	0.98 [0.94;1.03]
C _{max}	1.04 [1.00;1.08]	GIR _{max}	1.01 [0.96;1.05]

^aBased on free serum insulin aspart; ^b N is number of profiles contributing to the analysis for faster aspart/IAsp; ^c Treatment ratio and 95% CI estimated using Fieller's method. AUC, area under the curve; CI, confidence interval; C_{max}, maximum observed concentration; Faster aspart, faster-acting insulin aspart; GIR_{max}, maximum glucose infusion rate; IAsp, insulin aspart; Onset of appearance, time from dosing until the first time serum IAsp concentration \geq lower limit of quantification; PK, pharmacokinetic; PD, pharmacodynamic; t50%C_{max}, time to 50% of maximum serum insulin aspart concentration; t50%GIR_{max}, time to 50% of maximum glucose infusion rate.

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