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Sponsor: Sanofi Drug substance(s): INSULIN GLULISINE	Study Identifiers: U1111-1183-8636, NCT02910518, 2016-001498-34 Study code: BEQ13941
Title of the study: A randomized, double-blind, single-dose, 2-treatment, 2-period, 2-sequence crossover bioequivalence study comparing 2 formulations of insulin glulisine (insulin glulisine 300 U/mL versus insulin glulisine 100 U/mL marketed as Apidra® 100 U/mL) using the euglycemic clamp technique, in patients with type 1 diabetes mellitus (BEQ13941)	
Study center(s): 1 center in Germany.	
Study period: Date first subject/patient enrolled: 29/Sep/2016 Date last subject/patient completed: 03/May/2017	
Phase of development: Phase 1	
Objectives: Primary: • To demonstrate bioequivalence (expressed in terms of rate and extent of absorption) between insulin glulisine given as 300 U/mL test formulation (T) and insulin glulisine 100 U/mL reference formulation (R) after a single subcutaneous (SC) dose. Secondary: • To assess the pharmacodynamic (PD) profiles and further pharmacokinetic (PK) characteristics of the insulin glulisine (T) in comparison to the insulin glulisine (R) after a single SC dose. • To assess safety and tolerability of the test and reference formulations of insulin glulisine.	
Methodology: This was a single-center, randomized, double-blind, single-dose, 2-treatment, 2-period, 2-sequence crossover euglycemic clamp study in patients with type 1 diabetes mellitus (T1DM). There was a washout of 5 to 18 days (preferred 7 days) between dosing occasions.	
Number of patients:	Planned: 44 (22 in each sequence) Randomized: 44 Treated: 44
Evaluated:	Pharmacodynamics: 44 (43 patients for Apidra® [100 U/mL; R] and 44 patients for insulin glulisine [300 U/mL; T]) Safety: 44 (43 patients for Apidra [100 U/mL; R] and 44 patients for insulin glulisine [300 U/mL; T]) Pharmacokinetics: Pharmacokinetics: 44 (43 patients for Apidra [100 U/mL; R] and 44 patients for insulin glulisine [300 U/mL; T])

Diagnosis and criteria for inclusion:

Male or female patients between 18 and 64 years of age, inclusive; body weight between 50 and 95 kg, inclusive; body mass index between 18 and 30.0 kg/m^2, inclusive; and with T1DM 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. Fasting serum C-peptide <0.30 nmol/L, glycohemoglobin (HbA1c) ≤75 mmol/mol (≤9%), and anti-insulin antibody titer at screening ≤30.0 kU/L.

Study treatments:

Investigational medicinal product: Insulin glulisine (300 U/mL) – test (T)

Formulation: Solution for injection with a concentration of 300 U/mL insulin glulisine.

Route of administration: SC injection.

Dose regimen: Single dose of 0.3 U/kg on Day 1 of either period under fasted conditions.

Investigational medicinal product: Apidra (100 U/mL) – reference (R)

Formulation: Solution for injection with a concentration of 100 U/mL of Apidra.

Route of administration: SC injection.

Dose regimen: Single dose of 0.3 U/kg on Day 1 of either period under fasted conditions.

Other products:

Products used for euglycemic clamp, and rescue medication for cases of uncontrolled high or low blood glucose.

Duration of treatment: Two treatment periods of 1 single dose of insulin glulisine (300 U/mL; T) or Apidra (100 U/mL; R) administered in a crossover design.

Duration of observation: Up to 62 days (maximum), including screening (Day -28 to Day -4), insulin regimen change (Day -3 to Day -1 of each period), 2 treatment periods of 4 days duration overall (in-patient stay of 2 days, including 1 day of dosing each), washout period of minimum 5 days and up to 18 days between dosing occasions, and end-of-study visit (Day 5 to Day 12 after last treatment period).

Criteria for evaluation:

Pharmacokinetics:

Primary PK variables:

- Maximum observed serum insulin concentration (INS-Cmax).
- Area under the serum insulin concentration-time curve from time zero to time of last measurable concentration (INS-AUC_{last}).
- Area under the serum insulin concentration-time curve extrapolated to infinity (INS-AUC).

Secondary PK variables:

- Time to reach INS-C_{max} (INS-t_{max}).
- Insulin terminal elimination half-life (INS-$t_{1/2z}$).

Pharmacodynamics:

- The area under the body weight standardized glucose infusion rate (GIR) versus time curve from 0 to 10 hours post administration (GIR-AUC_{0-10}).
- Time to GIR_{max} (GIR-t_{max}).
- Duration of blood glucose control under clamp conditions with smoothed blood glucose ≤105 mg/dL, 110 mg/dL, 130 mg/dL, and 150 mg/dL.

Safety and tolerability:

Safety was assessed by: Adverse events (AEs), electrocardiograms (ECGs), vital sign parameters, clinical laboratory tests, injection site reactions (ISRs), aural temperature, and incidence of hypoglycemia.

Pharmacokinetic/Pharmacodynamic sampling times and bioanalytical methods:

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples for the determination of serum concentrations of insulin glulisine were collected on Day 1 of each treatment period at the following time points: 0 (predose) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 8, 9, and 10 hours after dose.

Serum concentrations of insulin glulisine were determined using a validated radioimmunoassay method with a lower limit of quantification (LLOQ) of 5 µU/mL (0.2 ng/mL).

Pharmacodynamic sampling times and bioanalytical methods:

Arterialized venous blood was continuously drawn at a rate of 2 mL/hr for determination of arterial blood glucose concentration from about 2.5 to 6.5 hours prior to IMP until end of clamp up to 10 hours after IMP dosing.

In addition, arterialized venous blood samples (approximately 0.2 mL) for concurrent clamp device adjustment, were collected at approximately 30-minute intervals (more often if required) after connection to the clamp device until end of the clamp.

Statistical methods:

Primary analysis:

Pharmacokinetic parameters of insulin glulisine were summarized by treatment using descriptive statistics.

For log-transformed INS-Cmax, INS-AUClast, and INS-AUC, the bioequivalence between the 2 formulations was assessed using a linear mixed effects model with fixed terms for sequence, period, and treatment (Test, Reference), and random term for patient-within-sequence, with treatment-specific between-patient and within-patient variances. Estimates with 90% confidence intervals (CI) for the geometric mean ratios between the 2 formulations (T/R) were computed.

Bioequivalence was to be concluded if the 90% CI for the formulation ratios of the geometric means (T/R) of INS-Cmax, INS-AUClast, and INS-AUC were entirely contained within (0.8-1.25).

Secondary analysis:

Pharmacodynamic parameters of insulin glulisine were summarized by treatment using descriptive statistics.

For log-transformed GIR-AUC0-10 and GIRmax, estimates and 90% CI for the geometric means ratio of treatments (T/R) were obtained using the same model as for primary analysis.

Glucose infusion rate and blood glucose parameters obtained during clamp procedure were summarized graphically using overlay figures.

The safety evaluation was based upon the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables, graphics). All safety analyses were performed using the safety population. Adverse events were coded according the Medical Dictionary for Regulatory Activities (MedDRA, v20.0), and the number of patients with treatment-emergent adverse events (TEAEs) was summarized by treatment. For vital sign parameters and ECGs the number of patients with abnormalities and/or potentially clinically significant abnormalities (PCSAs) was summarized in frequency tables by treatment, where appropriate.

Documented symptomatic hypoglycemia and severe hypoglycemic episodes were collected as AEs.

Summary

Population characteristics:

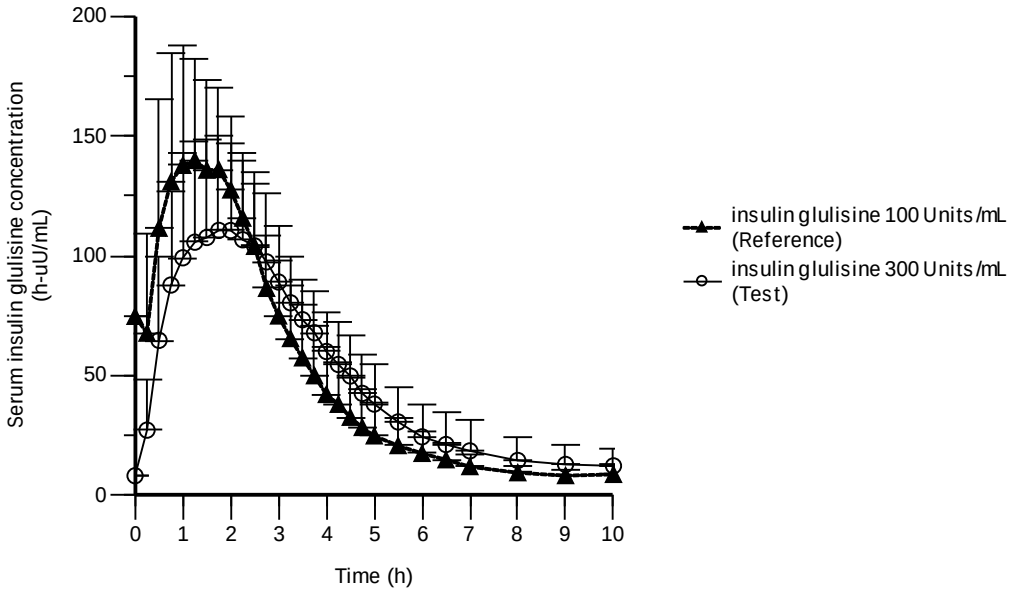
Forty-four patients (26 males and 18 females) were randomized and were exposed to the IMP. Forty-three patients completed both treatment periods. One patient prematurely discontinued the study after Treatment Period 1; the patient had an increased creatine phosphokinase (CPK) value at baseline in Treatment Period 1 that remained above the upper limit of normal 4 days later. The patient was not able to attend the rescheduled dosing for the second clamp (Treatment Period 2) after the normalization of the CPK value due to personal reasons.

Pharmacokinetic results:

All patients were evaluable for PK in all periods in which they received treatments.

Mean (standard deviation [SD]) serum insulin glulisine concentration-time profiles following single SC doses of 0.3 U/kg insulin glulisine in T1DM patients are shown in the following figure:

Mean (± SD) serum insulin glulisine concentration-time profiles after administration of a single dose of 0.3 U/kg bodyweight insulin glulisine 100 U/mL (R) or insulin glulisine 300 U/mL (T) in T1DM patients



Source = PKS Study : BEQ13941-EDv2; Scenario: BEQ13941 _ BEQ13941_ED (1), Version 2

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Pharmacokinetic parameters of insulin glulisine are summarized in the table below:

Mean ± SD (Geometric Mean) [CV%] PK parameters of insulin glulisine after a single subcutaneous dose of insulin glulisine 300 U/mL (T) and insulin glulisine 100 U/mL (R) marketed as Apidra

Parameter	Insulin glulisine 100 U/mL (R)	Insulin glulisine 300 U/mL (T)
N	43[a]	44
INS-C_{max}	154 ± 47.7	120 ± 42.6
(µU/mL)	(146) [31.1]	(113) [35.6]
INS-t_{max}[b]	1.50	2.00
(hr)	(0.25 - 2.50)	(0.75 - 3.50)
-		-
-	-	-
INS-$t_{1/2z}$	0.978 ± 0.425	1.12 ± 0.627
(hr)	(0.902) [43.5]	(1.02) [55.8]
INS-AUC_{last}	452 ± 67.5	452 ± 83.6
(hr•µU/mL)	(447) [15.0]	(445) [18.5]
INS-AUC	462 ± 66.3	468 ± 86.4
(hr•µU/mL)	(458) [14.3]	(460) [18.5]

[a] One patient discontinued the study after completing one treatment period
b Median
(Min - Max)

Source = PKS Study : BEQ13941-EDv2; Scenario: BEQ13941 _ BEQ13941_ED (1) Version 5
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The point estimate of formulation ratio [90% CI] of T versus R was 1.0 [0.97 - 1.03] for INS-AUClast, 1.01 [0.98 - 1.03] for INS-AUC, and 0.77 [0.71 - 0.84] for INS-Cmax. For both INS-AUClast and INS-AUC, the 90% CI were within the accepted bioequivalence range of 0.80 – 1.25, however for INS-Cmax the 90% CI were not contained within the accepted bioequivalence range, therefore bioequivalence cannot be concluded for all primary PK parameters (see table below).

Estimates of formulation ratio with 90% confidence interval (CI) for insulin glulisine

Formulation ratio	Parameter	Estimate	90% CI
Test vs Reference	INS-AUC	1.01	(0.98 to 1.03)
	INS-AUClast	1.00	(0.97 to 1.03)
	INS-Cmax	0.77	(0.71 to 0.84)

Test = Test Formulation Insulin Glulisine (300 U/mL), Reference = Reference Formulation Apidra (100 U/mL)
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Pharmacodynamic results:

All treated patients were evaluable for PD in both treatment periods.

The area under the GIR versus time curve from 0 to 10 hours (GIR-AUC0-10) and GIRmax were not strictly equal between insulin glulisine 300 U/mL (T) and insulin glulisine 100 U/mL (R), however, the 90% CI of formulation ratios of PD parameters (GIR-AUC0-10 and GIRmax) were within the 0.80 – 1.25 range as shown in the table below.

Statistical analyses of pharmacodynamic variables $GIR\text{-}AUC_{0\text{-}10}$ and GIR_{max}
Point estimates of formulation ratio with 90% confidence intervals

Treatment ratio	Parameter	Estimate	90% CI
T (300 U/mL)[b]/R (100 U/mL)[a]	$GIR\text{-}AUC_{0\text{-}10}$	1.07	(1.01 to 1.14)
	GIR_{max}	0.89	(0.83 to 0.96)

[a] R: Reference formulation Apidra® (100 U/mL)

[b] T: Test formulation Insulin glulisine (300 U/mL)

$GIR\text{-}AUC_{0\text{-}10}$ = Area under the body weight standardized glucose infusion rate time curve

GIR_{max} = Maximum smoothed body weight standardized glucose infusion rate

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The mean values of GIR-AUC_{0-10}, GIR_{max}, and GIR-T_{max} were not equal between both formulations as presented in the table below.

Glucose infusion rate (GIR) - Descriptive statistics
GIR-AUC_{0-10} (mg/kg), smoothed GIR_{max} (mg/min/kg), GIR-t_{max} (h)

	R (100 U/mL) [a] (N=43)	**T (300 U/mL) [b] (N=44)**
GIR-AUC_{0-10} (mg/kg)		
Number	43	44
Mean (SD)	1990.01 (487.73)	2114.60 (534.00)
Geometric Mean (CV%)	1927.91 (24.509)	2044.40 (25.253)
Median	2002.61	2137.93
Min : Max	1072.6 : 3273.4	972.9 : 3242.9
Q1 : Q3	1698.96 : 2326.44	1682.89 : 2460.64
GIR_{max} (mg/min/kg)		
Number	43	44
Mean (SD)	9.56 (2.81)	8.44 (2.44)
Geometric Mean (CV%)	9.15 (29.427)	8.12 (28.909)
Median	9.03	8.17
Min : Max	4.2 : 15.8	4.3 : 15.2
Q1 : Q3	8.00 : 11.31	6.80 : 9.89
GIR-t_{max} (h)		
Number	43	44
Mean (SD)	2.30 (0.87)	3.26 (1.01)
Median	2.22	3.11
Min : Max	0.9 : 4.3	1.0 : 6.5
Q1 : Q3	1.73 : 2.75	2.60 : 3.92

[a] R: Reference formulation Apidra® (100 U/mL)

[b] T: Test formulation Insulin glulisine (300 U/mL)

GIR-AUC_{0-10} = Area under the body weight standardized glucose infusion rate time curve

GIR_{max} = Maximum smoothed body weight standardized glucose infusion rate

GIR-t_{max} = Time to GIR_{max}

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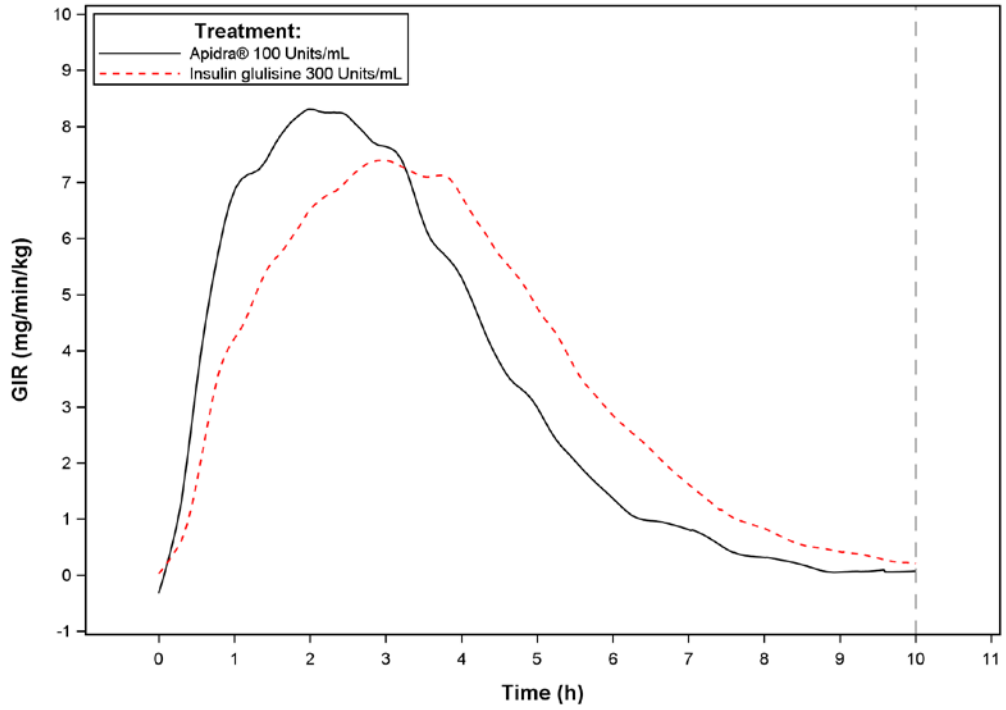
Mean smoothed GIR profiles for insulin glulisine 100 U/mL (R) and insulin glulisine 300 U/mL (T) are presented in the figure below. The GIR profiles were not equal between insulin glulisine 100 U/mL (R) and insulin glulisine 300 U/mL (T).

Overlay plots of mean smoothed GIR profiles up to 10h after dosing over time



GIR = Body weight standardized glucose infusion rate

Smoothing factor: 0.06

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Blood glucose (BG) during clamp procedure - Descriptive statistics -
Duration of smoothed blood glucose controlled (at or below 105/110/130/150 mg/dL)

	R (100 U/mL) [a] (N=43)	T (300 U/mL) [b] (N=44)
Duration (h) of controlled BG ≤ 105 mg/dL (5.8 mmol/L)		
Number	43	44
Mean (SD)	7.36 (1.50)	8.20 (1.33)
Median	7.28	8.23
Min : Max	4.5 : 10.0	5.4 : 10.0
Q1 : Q3	6.05 : 8.68	7.05 : 9.40
Duration (h) of controlled BG ≤ 110 mg/dL (6.1 mmol/L)		
Number	43	44
Mean (SD)	7.65 (1.50)	8.48 (1.25)
Median	7.40	8.47
Min : Max	4.7 : 10.0	5.7 : 10.0
Q1 : Q3	6.25 : 9.15	7.49 : 9.79
Duration (h) of controlled BG ≤ 130 mg/dL (7.2 mmol/L)		
Number	43	44
Mean (SD)	8.43 (1.41)	9.11 (0.99)
Median	8.68	9.23
Min : Max	5.2 : 10.0	6.0 : 10.0
Q1 : Q3	7.28 : 9.80	8.42 : 10.00
Duration (h) of controlled BG ≤ 150 mg/dL (8.3 mmol/L)		
Number	43	44
Mean (SD)	8.86 (1.30)	9.50 (0.84)
Median	9.37	9.91
Min : Max	5.6 : 10.0	6.2 : 10.0
Q1 : Q3	7.95 : 10.00	9.40 : 10.00

[a] R: Reference formulation Apidra® (100 U/mL)

[b] T: Test formulation Insulin glulisine (300 U/mL)

BG = Blood glucose (smoothed, LOESS factor 0.06)

Note: Calculated as the last timepoint at or below the respective threshold

Q1 and Q3 denote first and third quartiles

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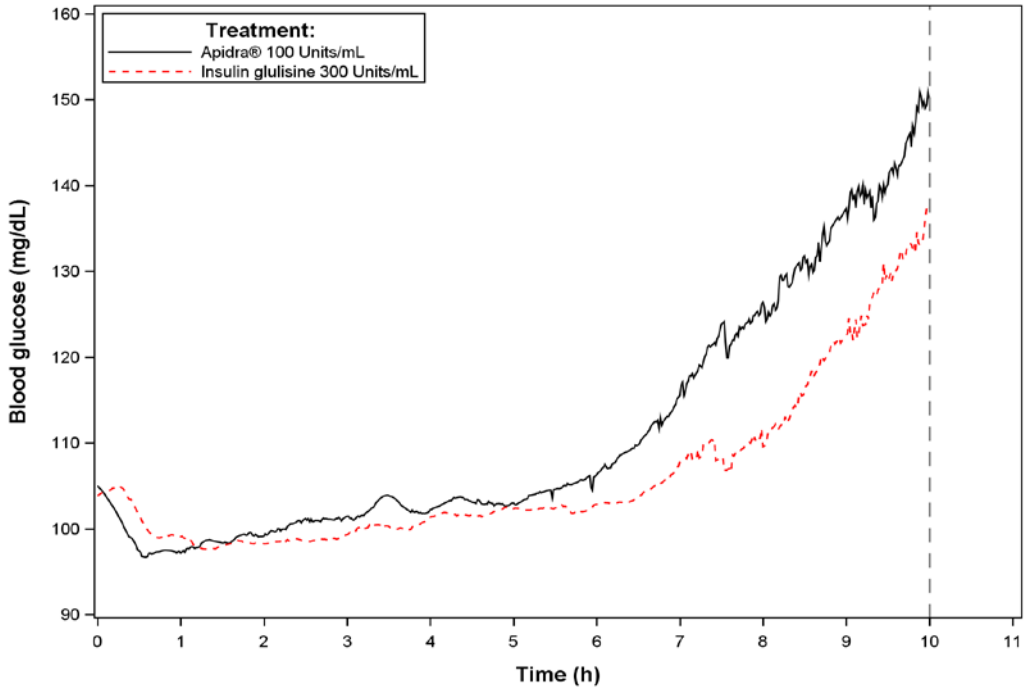
For the duration of BG control, as shown in the table above, both mean overall BG profiles over time are not comparable between treatments, as also presented in the figure below.

Overlay plots of mean smoothed BG profiles up to 10h after dosing over time



Smoothing factor: 0.06

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Safety results:

There were no deaths, SAEs, or severe TEAEs reported during the study. One patient withdrew after Treatment Period 1 due to personal reasons. Treatment-emergent AEs were reported in 6 out of 43 patients (14.0%) following administration of insulin glulisine 100 U/mL (R) and 6 out of 44 patients (13.6%) following administration of insulin glulisine 300 U/mL (T). The most common TEAE reported was headache which was reported in 3 out of 43 patients (7.0%) following administration of insulin glulisine 100 U/mL (R) and 3 out of 44 patients (6.8%) following administration of insulin glulisine 300 U/mL (T). Most of the headaches were mild in intensity and not related to the IMP. No AEs were reported consistent with local site reactions for either formulation.

There were no observed severe/serious hypoglycemic events during the conduct of the study. Documented symptomatic hypoglycemia was reported in 2 out of 43 patients following administration of insulin glulisine 100 U/mL (R) and 3 out of 44 patients following administration of insulin glulisine 300 U/mL (T). There were no abnormalities reported in vital signs except 1 patient with orthostatic diastolic blood pressure following administration of insulin glulisine 100 U/mL (R) and 1 patient with orthostatic systolic blood pressure following administration of insulin glulisine 300 U/mL (T) with no relation to the IMP in either case.

There were no clinically relevant abnormalities reported in laboratory parameters. For ECG evaluations, very few PCSAs were reported and all were considered not clinically significant. No patient had a QTc interval >480 ms or QTc interval change from baseline >60ms.

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