

A Novel pH-Neutral Formulation of the Monomeric Insulin VIAject® Has a Faster Onset of Action Than Insulin Lispro

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Introduction

- Rapid-acting insulin analogs were developed to reduce postprandial glucose excursions by providing an earlier onset and a shorter duration of action than regular human insulin
- However, even rapid-acting insulin analogs are not acting fast enough to replicate the natural first-phase insulin release observed in healthy subjects after meal intake
- VIAject® is a novel formulation of recombinant human insulin in development which is absorbed faster and has a faster onset of action than insulin lispro (Steiner S, et al. Diabetologia 2008; 51: 1602-1606)
- In previous studies VIAject® was used in a formulation with a pH of approximately 4 and a concentration of 25 U/ml
- In this study, we compared the pharmacodynamic (PD) and pharmacokinetic (PK) properties of a novel formulation of VIAject® with a concentration of 100 U/ml and a neutral pH with those of the previously used VIAject® formulation and insulin lispro in people with type 1 diabetes

VIAject®: Mechanism of Absorption

Human insulin forms hexamers around zinc ions, however only insulin monomers are efficiently absorbed into the circulation. After subcutaneous injection, the time required for dissociation of hexamers results in delay of insulin absorption.

In the VIAject® formulation EDTA is used to chelate zinc, destabilizing the insulin hexamers.

Citric acid is used to mask charges on the surface of the insulin molecule preventing re-association of insulin monomers and directly facilitating absorption into the circulation.

VIAject® promotes more rapid dissociation of insulin hexamers after subcutaneous injection resulting in more rapid absorption.

Ultra-fast absorption

Study Medication

- VJ7: VIAject® in a formulation with a concentration of 100 U/ml and a neutral pH of approximately 7
- VJ25: VIAject® in a formulation with a concentration of 25 U/ml and a pH of approximately 4
- LIS: Insulin lispro (Eli Lilly, Indianapolis, IN, USA) in its commercially available formulation with a concentration of 100 U/ml and a neutral pH

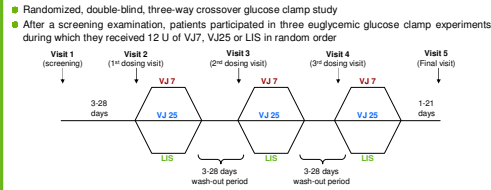
Study Objectives

- Primary objective: To demonstrate bioequivalence between VJ7 and VJ25
- Secondary objectives:
 - to compare the pharmacokinetic and pharmacodynamic characteristics of VJ7 and LIS
 - to evaluate the safety and tolerability of VJ7, VJ25 and LIS

Study Population: Inclusion/Exclusion criteria

- Key inclusion criteria
 - Type 1 diabetes mellitus for at least 1 year
 - Age 19-65 years, BMI 18-28 kg/m², non-smokers
 - Insulin antibody levels < 10 µU/ml
- Key exclusion criteria
 - HbA1c > 10%, C-peptide > 1 ng/ml
 - Changes in concomitant medication other than insulin in the last 3 weeks prior to randomization
 - Clinically significant abnormalities in laboratory parameters (e.g. liver enzymes >2 times the upper limit of normal, serum creatinine above the upper limit of normal)

Study Design



- Insulins were given subcutaneously into a lifted skin fold around the umbilicus with an insulin syringe
- Dosings were done by a competent unblinded person not otherwise involved in the study conduct

Glucose clamp technique

- Patients came to the investigational site after an overnight fast (only water from 22:00 hours onwards)
- Last intermediate-acting insulin was given no later than at 20:00 hours, last dose of insulin glargine or insulin detemir no later than at 08:00 hours of the day before the visit. Last injection of short-acting insulin no later than 03:00 hours in the morning of the visit. Patients on insulin pumps stopped insulin infusion immediately after arrival at the clinic
- Patients were connected to a Biostat (mbi Medizintechnik, Amstetten, Germany), and a variable intravenous infusion of insulin aspart was started to reach a target blood glucose level of 100 mg/dl
- Insulin aspart infusion was decreased as much as possible to consistently stabilize blood glucose concentration at the target level with as little glucose infusion as possible 3 hours before dosing. Fifteen minutes before insulin injection the insulin aspart infusion was stopped completely
- The Biostat calculated and administered the glucose infusion rate (GIR) necessary to maintain blood glucose close to the target level for 8 hours post-dosing. The clamp experiment was stopped earlier if blood glucose levels increased to >200 mg/dl without any GIR in the last 30 min
- Blood samples for determination of pharmacokinetics were drawn at -30, -10, 0, 3, 7, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, 360, 420 and 480 minutes (with dosing at t=0 min)
- Serum human insulin concentrations were determined with an immunoluminometric sandwich assay (LIAISON® Insulin assay, DiaSorin, Saluggia, Italy). Insulin lispro concentrations were determined with a radio-immunoassay specific for insulin lispro (Millipore, St. Charles, MO, USA)

Statistical methods

- Glucose infusion rate profiles were smoothed using a local weighted regression technique. Time-related parameters were derived from the smoothed curves, AUCs from the raw (unsmoothed) data.
- Primary endpoints were the maximum serum insulin concentrations (C_{NSmax}) and the area under the serum insulin concentration curves for 0-480 min (AUC₀₋₄₈₀)
- Efficacy parameters were analyzed after log-transformation with an analysis of variance (ANOVA, mixed effects model fitting fixed effect terms of sequence, period, and treatment, and fitting subject within sequence as a random effect).
- In accordance with regulatory guidelines, the 90% confidence interval for the ratio of VJ7 and VJ25 for both C_{NSmax} and AUC₀₋₄₈₀ had to be contained within the acceptance interval of 80-125% to demonstrate bioequivalence.

Table 1: Demographics (N=43*)

Parameter	Mean (SD)	Min	Max
Gender		22 male, 21 female	
Age (years)	42.5 (10.6)	21	65
Height (m)	1.74 (0.08)	1.60	1.92
Weight (kg)	73.4 (10.5)	52.7	97.0
BMI (kg/m ²)	24.1 (2.3)	20.0	28.0
Diabetes duration (years)	21.8 (10.9)	4.5	45.5
HbA1c (%)	7.5 (1.0)	5.7	9.5

*3 subjects without consent after the first dosing. All completed clamps (40 with VJ25, 41 with VJ7 and 42 with LIS) were included in the safety, pharmacokinetic and pharmacodynamic analysis

Figure 1: Insulin/insulin lispro concentrations

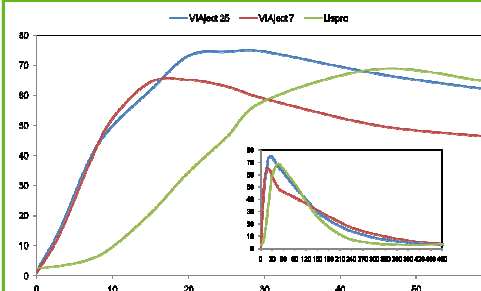


Figure shows pharmacokinetic profiles in the first 60 min (large panel) and over 480 min (inset) post-dosing. Human insulin concentrations were determined after injection of VIAject® 7 and VIAject® 25, whereas insulin lispro concentrations were measured after dosing with insulin lispro. All pharmacokinetic concentrations are given in mU/L

Table 2: PK/PD Parameters

	VJ7	VJ25	LIS	Ratio/Difference VJ7 vs. VJ25 [90% CI]	Ratio/Difference VJ7 vs. LIS [90% CI]
Pharmacokinetic (PK) Parameters, based on insulin (INS) concentrations					
C _{NSmax} [mU/L]	66	74	65	0.89 [0.82; 0.96]	-
AUC ₀₋₄₈₀ [mU·min]	10,221	10,408	7438	0.98 [0.95; 1.01]	-
t _{NSmax} [min]	23*	28	60	-5 [-10; -2.5]	-30 [-35; -22.5]
t _{NS 50%max} [min]	7.8*	9.7	21.9	-1.9 [-3.1; -0.8]	-15.5 [-17.3; -13.8]
t _{NS 90%max} [min]	136	131	129	8 [-5; 23]	7 [-15; 27]
t _{NS 50% AUC} [min]	28*	30	45	0.0 [-2.5; 2.5]	-12.5 [-15.0; -10.0]
Pharmacodynamic (PD) Parameters, based on glucose infusion rates (GIR)					
GIR _{max} [mg/kg/min]	6.1	6.3	6.6	0.97 [0.90; 1.06]	0.93 [0.85; 1.01]
AUC _{GIR 0-480} [mg/kg]	1263*	1186	1095	1.07 [0.98; 1.16]	1.15 [1.06; 1.26]
AUC _{GIR 0-60} [mg/kg]	176*	192	107	0.92 [0.71; 1.19]	1.65 [1.27; 2.14]
t _{GIR max} [min]	129	75	114	36 [13; 60]	20 [-3; 43]
t _{GIR 50%max} [min]	24.5*	23.5	44.3	-0.4 [-7.0; 5.9]	-17.9 [-25.6; -10.4]
t _{GIR 90%max} [min]	274*	252	228	31 [13; 55]	50 [25; 73]
t _{GIR 50% AUC} [min]	46.8	42.2	52.5	2.4 [-2.7; 7.0]	-5.3 [-10.5; -0.8]

Table shows geometric means and ratios with 90% confidence intervals (90% CI) for C_{NSmax}, GIR_{max} and AUCs. Time-related parameters (i.e. time to maximum concentration GIR and time to half-maximal concentration GIR before t_{NSmax} and after t_{NSmax}) the maximum are expressed as medians and differences with 90% confidence intervals. As two different assays were used for the determination of VIAject® and insulin lispro concentrations, no comparisons were done for C_{NSmax} and AUC₀₋₄₈₀ between VIAject® preparations and insulin lispro. *p<0.05 vs insulin lispro

Efficacy Results: Summary

- VJ7 was bioequivalent to VJ25 as the 90% confidence intervals for the ratios for C_{NSmax} and AUC₀₋₄₈₀ were completely within the required limits of 0.8-1.25
- In comparison to LIS, VJ7 was absorbed faster as indicated by lower values for the time to reach 10% of the total area under the insulin concentration curve (t_{NS 10%max}) and the time to reach maximum concentrations (t_{NSmax}) and early half-maximal concentrations (t_{NS 50%max})
- The faster absorption led to an earlier onset of action as indicated by higher values for the area under the glucose infusion rate curve in the first 60 min post-dosing (AUC_{GIR 0-60}) and by reaching early half-maximal activity (t_{GIR 50%max}) earlier

Figure 2: Mean glucose infusion rate (GIR) profiles

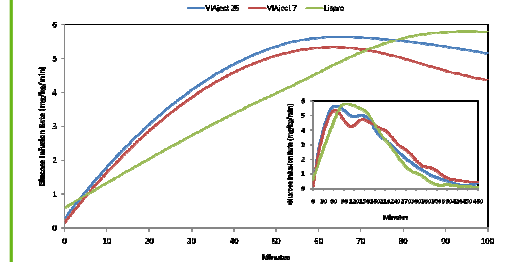
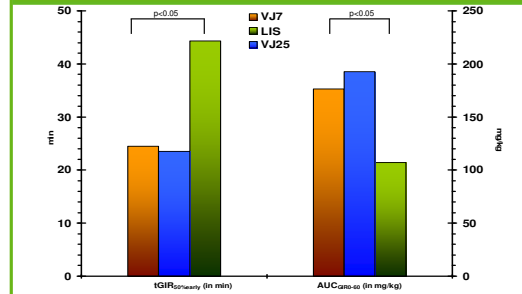


Figure 3: PD-parameters for Onset of Action



Safety

- All study insulins were well tolerated. Adverse Events occurred in about a quarter (11 out of 43) of study participants with headache (a known side effect of glucose clamp experiments) being the most frequent adverse event (occurring in 8 patients).
- Adverse events were considered to be mild (90% of cases) or moderate (10%)
- There was no difference in the rate of treatment-emergent adverse events between VJ7 and LIS (6 events, respectively)
- No serious adverse events occurred in this trial

Conclusions

- The new, pH-neutral formulation of VIAject® is bio-equivalent to the formulation used in previous studies
- The pH-neutral formulation of VIAject® shows a faster absorption and a faster onset of action than insulin lispro
- All study insulins were well tolerated. The rate of adverse events was low and similar between the pH-neutral formulation of VIAject® and insulin lispro