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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**NA**
		Study Code:	**HMR1964A_3505**
Generic drug name:	**Insulin Glulisine**	**Date:**	**February 5th, 2007**

Name of the Study: Multi-center, international, open-label, phase IIIb non-randomized clinical study to evaluate efficacy and safety of insulin glulisine (HMR 1964) administrated subcutaneously in patients with type 1 diabetes mellitus, who also use insulin glargin during 26 weeks of therapy.

Investigators:

Department of Endocrine Diseases Pharmacotherapy, Department of Clinical Pharmacology – PhD Skybun V.M., Dr. Kushnaryova N.M., Dr. Korpacheva-Zinych L.V.
City Endocrinology Center – professor Bodnar P.M., PhD Mikhalchyshyn G.P., PhD Peshko AV.
Ukraine Scientific Center of Endocrine Surgery – PhD Larin O.S., PhD Savran O.V., Dr. Kidalova G.A., Dr. Bertayeva L.V.

Investigational Sites:

Academy of Medical Sciences of Ukraine, Komisarenko V. P. Institute of Endocrinology and Metabolism
City Endocrinology Center, Kyiv
Ukraine Scientific Center of Endocrine Surgery

Publications (references)

Study Timelines (years):	
The date of the first inclusion	22.09.2004
The date of the full completion	08.06.2005

Rationale:

the aim of this study was to evaluate the efficacy and safety of the insulin glulisine (sc) during 26 weeks therapy in patients with type 1 DM treated by insulin glargin as basal insulin

Methodology:

the clinical and laboratory examination was performed in the patients, who were administered insulin glulisine in combination with Lantus (insulin glargin): before treatment with the mentioned drug (1 week screening phase), run-in phase – therapy with Lantus as basal insulin and short-acting insulin used previously (4 weeks), treatment phase – treatment with ultra short-acting insulin analogue Apidra® (insulin glulisine) in combination with Lantus (8 weeks) with the following statistical processing of the data obtained.

Number of Patients (planned and analyzed): 60 subject with type 1 diabetes mellitus, who were treated by Apidra® (insulin glulisine) produced by *"Aventis Pharma Deutchland GmbH", Germany*

Diagnosis and the Main Criteria of Inclusion:

- Type 1 diabetes mellitus with HBA1c from 6,5 to 11%,
- Written Informed Consent for the participation in the study.

The Investigational Product, its Dosage, Rout of Administration, Lot Number:
Apidra® (insulin glulisine), solution for injections, 3 ml in a cartridge, 100 IU/ml, lot number 1630. Administration 3-6 times daily, subcutaneously.

Treatment Phase Duration with the Investigational Product: 26 weeks.

Description of the Therapy, Dosage and Route of Administration: insulin glulisine was administrated 0-15 min. before food intake subcutaneously, if necessary, patient was administered the corrective dose of the drug under the control of glycemia. Insulin dose was depended from the individual patient's requests. Insulin glargin was administered once a day in the evening, between 21 and 23 hours.

Criteria for evaluation:
Clinical study data, patient's status of health, laboratory tests dynamics.

Efficacy:
Criteria: daily glycemia rate dynamics, rate of glycated hemoglobin, main biochemical blood rates, general state of organism during study period, diabetes mellitus compensation degree.

Safety:
Tolerance and adverse events evaluation of the investigational product.

Methods of Statistics: Data statistical processing with the use of t-criterion and with the assistance of Origin 7.0 software and determination of the p-value.

Summary

Study population

- A total of 60 patients with T1DM participated in this study; baseline characteristics and demographics are summarized in Table 1

Table 1. Baseline characteristics

Variable	
Patients, n	60
Male, n (%)	27 (45)
Female, n (%)	33 (55)
Age (years)*	34.7 ± 1.4
BMI (kg/m^2)*	23.8 ± 0.4
Duration of diabetes (years)*	12.7 ± 1.2

Efficacy

Fasting blood glucose

- Mean FBG decreased significantly from baseline (8.57 ± 0.28 mM [154.3 ± 0.5 mg/dL; mean ± SEM]) to endpoint (6.88 ± 0.39 mM [123.8 ± 7.0 mg/dL]; $p<0.001$) (Table 2, Figure 1)

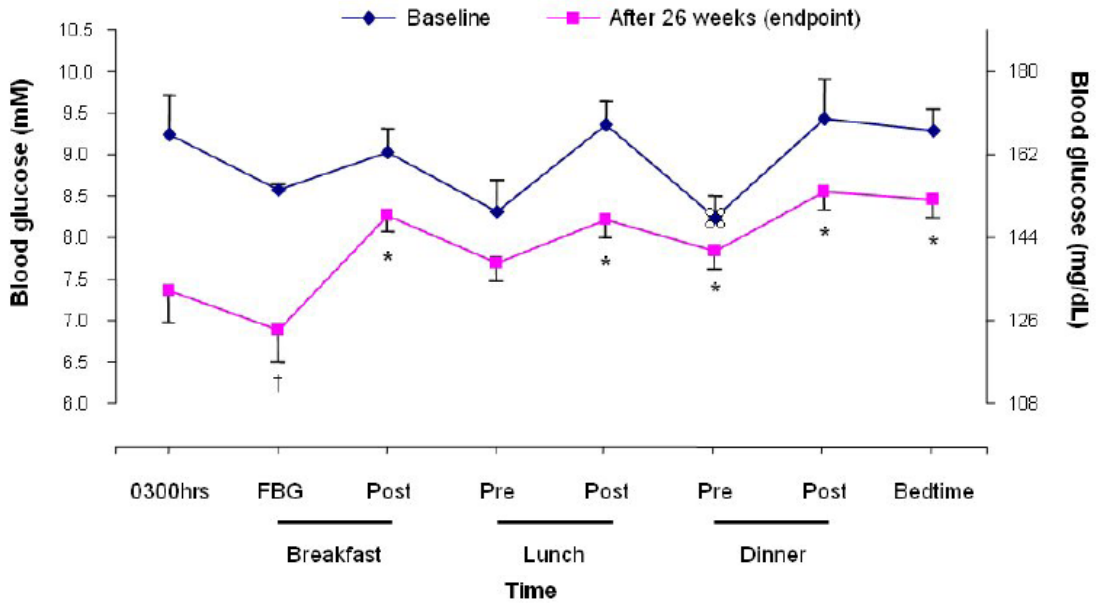
Blood glucose profiles

- For all three main meals, 2-hour postprandial BG levels at endpoint decreased significantly from baseline ($p<0.05$) (Table 2, Figure 1).
- The reduction in 2-hour postprandial BG levels reached significance after 12 weeks of glargine–glulisine treatment

Table 2. Changes of blood glucose values

Glycemia values (mmol/l)	Statistical values	After insulin Apidra® administration						
		Before prescription	In 4 weeks	In 8 weeks	In 12 weeks	In 16 weeks	In 20 weeks	In 26 weeks
At 3 a.m.	M±m P	9,23±0,48	9,09±0,48 >0,05	8,18±0,44 >0,05	7,64±0,37 <0,05	8,4±0.41 >0,05	7,72±0,36 <0,05	7,36±0,38 >0,05
Fasting	M±m P	8,57±0.0,28	8,55±0,49 >0,05	7,62±0.38 <0,05	7,44±0,37 <0,05	7,76±0,22 <0,05	7,21±0,35 <0,05	6,88±0,39 <0,001
In 2 hours after the breakfast	M±m P	9,03±0.27	8,38±0,48 >0,05	7,32±0,4 <0,05	7,72±0,39 <0,05	8,06±0,21 <0,05	8,94±0,4 >0,05	8,27±0,21 <0,05
Before lunch	M±m P	8,3±0,39	7,33±0.43 >0,05	8,27±0,51 >0,05	8,77±0.47 >0,05	7,96±00,22 >0,05	8,34±0,4 >0,05	7,68±0,21 >0,05
In 2 hours after the lunch	M±m P	9,36±0.29	8,93±0,46 >0,05	9,0±0,49 >0,05	8,85±0,45 <0,05	8,12±0,23 <0,001	8.15±0,41 <0,05	8,21±0,21 <0,05
Before dinner	M±m P	8,25±0,25	9,08±0,49 >0,05	8,39±0,51 >0,05	8,46±0,4 >0,05	8,16±0,21 <0,001	8.08±0,41 <0,05	7,84±0,22 <0,05
In 2 hours after the dinner	M±m P	9,42±0,49	9,06±0,46 >0,05	9,24±0.5 >0,05	8,59±0,42 <0,05	8,6±0,24 <0,05	8,58±0,39 <0,05	8,55±0,22 <0,05
Before going to bed	M±m P	9,29±0,25	8,93±0,43 >0,05	8,78±0.47 <0,05	9,53±0,82 >0,05	8,64±0,21 >0,05	8,51±0,39 >0,05	8,46±0,21 <0,05

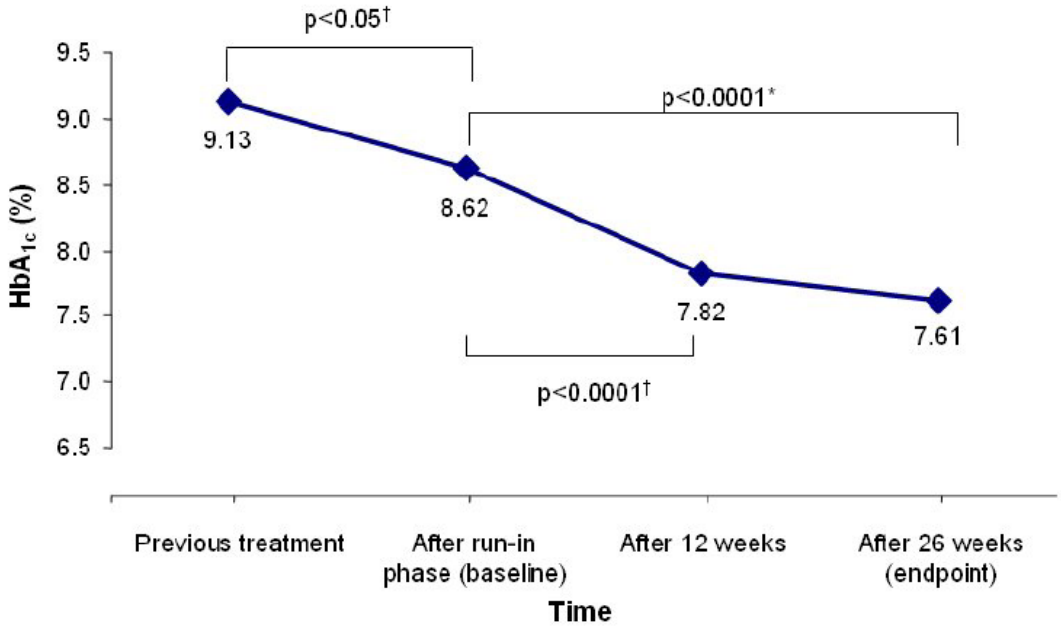
Figure 1. Blood glucose values at baseline and at endpoint



Changes in HbA1c levels

- There was a significant decrease in HbA1c after 12 and 26 weeks (endpoint) following initiation of the glargine–glulisine regimen (both $p<0.0001$) (Figure 2)
- A significant reduction in HbA1c was also initially observed during the run-in phase, following the replacement of previous basal insulin with glargine ($p<0.05$) (Figure 2); this reduction continued with the initiation of the glargine–glulisine combination
- Overall, 20 patients (33.3%) achieved HbA1c ≤7% at endpoint

Figure 2. HbA1c values with previous insulin therapy, after run-in, during treatment and at endpoint



Insulin dose

- The mean glargine dose remained almost unchanged throughout the study; 19.3 ± 0.6 U/day (mean ± SEM) at baseline and 20.9 ± 0.7 U/day at endpoint
- The mean glulisine dose also remained largely unchanged; 24.2 ± 0.7 U/day at baseline and 25.1 ± 0.4 U/day at endpoint

Safety

- A total of 50 patients (83%) reported mild hypoglycemic events (BG levels between 1.4–3.9 mM [25.2–70.2 mg/dL]); one patient reported a single case of severe hypoglycemia
- Overall, there was a reduction in hypoglycemic events from 2.16 episodes/month/patient during the first 6 weeks with glargine–glulisine treatment to 1.23 episodes/month/patient for the subsequent 20 weeks
- Episodes of nocturnal hypoglycemia decreased from 18.1% at baseline to 8.8% at endpoint
- A total of four non-serious adverse events were reported during the study

Date of Report: 10, January, 2006