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Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glulisine (HMR1964) Insulin Glargine (HOE901)	**Study Identifiers:** NCT01202474, U1111-1116-8645 **Study code:** APIDR_L_04884
Title of the study: A study of effectiveness and safety of Apidra in combination with Lantus therapy in basal-bolus insulin regimen in inadequately controlled children and adolescents with Type 1 diabetes in the Russian Federation.	
Study center(s): 8 centers (Russia): Moscow, St.Petersburg, Ufa, Samara, Krasnoyarsk, Ivanovo, Izhevsk, Novosibirsk	
Study period: Date first patient enrolled: 17 May 2011 Date last patient completed: 18 October 2012	
Phase of development: 4	
Objectives: Primary objective: To evaluate the percentage of patients who achieved HbA1c level < 8% (in patients 6-12 years old) and HbA1c level < 7.5 % (in patients 13-17 years old)* at 6 and 12 months of treatment **ADA recommendations age-specific HbA1c target* Secondary objectives: •To evaluate the change in HbA1c level at 6 and 12 months of treatment; •To evaluate the change in daily dose of glargine and glulisine at 6 and 12 months of treatment; •To evaluate the monthly rate of hypoglycemia per patient from the baseline to the end of the study;	
Methodology: Multicenter, local, non-randomized, open-label prospective phase 4 study	
Number of patients**:** Planned: initially 210 patients, modified to 100 (adjustment approved by independent National Ethical Committee) Treated: 90 **Evaluated:** Safety: 90 Efficacy: 90	
Diagnosis and criteria for inclusion: 1. Children and adolescents with Type 1 diabetes; 2. Duration of diabetes more than 1 year; 3. Age 6 -17 years old; 4. 8%≤HbA1c ≤10%; 5. Patients treated with insulin glargine and any short acting insulin in basal-bolus regimen; 6. Ability of patients to perform a Self Blood-Glucose Monitoring; 7. Signed Informed consent form.	

Study treatments

Investigational medicinal product(s):

Insulin glulisine: Apidra (100 U/ml) in a cartridge containing 3 ml for the reusable insulin pen OptiClick

Insulin glargine: Lantus (100 U/ml) in a cartridge containing 3 ml in the pre-filled insulin pen SoloStar

Route(s) of administration: subcutaneous injection

Dose regimen: Patients were treated with insulin glargine and insulin glulisine in basal-bolus regimen.

Insulin glargine: continued titration according to recommendations of treatment children and adolescents. The administration of insulin glargine was done once daily through a subcutaneous injection. The dose of insulin glargine was individually adjusted.

Insulin glulisine: the initial dose of insulin glulisine was selected individually. Physicians were advised to use the calculation based on carbohydrate counting. The administration of insulin glargine was done before meal (0-15) minutes, or within 20 minutes after a meal start. Dose was titrated in accordance with the algorithm to achieve the following targets:

1) plasma glucose levels before meals:

Children 6-12 years including 5-10 mmol/L;

Children 13-17 years old 5-7,3 mmol/L;

2) plasma glucose levels at bedtime / night:

Children 6-12 years including 5,6-10 mmol/L;

Children 13-17 years old 5-8,4 mmol/L;

Duration of treatment: 12 months

Duration of observation: 1-2 weeks of screening followed by treatment/observation period of 12 months

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the percentage of patients who achieved HbA1c level < 8% (in patients 6-12 years old) and HbA1c level < 7.5 % (in patients 13-17 years old) at 6 and 12 months of treatment.

Secondary endpoints: change in HbA1c at 6 and 12 months of treatment; change in daily dose of glargine and glulisine at 6 and 12 months of treatment.

Safety:

Safety was assessed through recording the monthly rate of hypoglycemia per patient from the baseline to the end of the study; all the adverse events (AEs) including serious adverse events (SAE) at each visit.

Safety evaluation criteria included frequency of all adverse events, serious and non-serious during the study time, and frequency of hypoglycemic episodes.

Statistical methods:

All studied populations were analyzed using descriptive statistics. Maximum, minimum, mean, standard deviation (SD) and median, (first and third quartile) were provided for quantitative variables. Frequency ratio and percentage were used for qualitative variables.

All statistical tests were two-sided at significance level of 0.05.

Efficacy population was defined as population of patients, who received at least one dose of insulin glargine and glulisine, signed an informed consent, had no inclusion/exclusion criteria violations (Intent To Treat population).

Safety population was defined as population of patients who received at least one dose of insulin glargine according to Case Report Form records.

Summary:

Population characteristics: 100 patients were enrolled in the study. 90 patients were treated and evaluable (10 patients were excluded due to protocol noncompliance linked to the Investigational product insulin glargine - the investigator in 1 center did not provide to his patients investigational samples of insulin but insulin through federal reimbursement program i.e. like in real practice. This issue was detected during the monitor's call).

1 patient (age group from 6 to 12 years old) was lost to follow-up (he refused to take part to Visit 13). A total of 89 patients completed the study.

The efficacy analysis population included 44/90 (48.9%) female and 46/90 (51.1%) male patients

The median age of patients was 12.5 years: 45 patients were in range 6 - 12 years old (50%) and 45 patients were in range 13 -17 years old (50%).

Mean ±SD patient's weight was 48.9±16.6 kg; mean ±SD body mass index (BMI) was 19.5±3.2 kg/m_2.

Efficacy results:

Primary efficacy analysis:

Patients 6-12 years old

In this subgroup, 22/45 (48.9%) of patients and 23/45 (51.1%) of patients achieved HbA1c < 8% at 6 and 12 months of treatment, respectively. 14/45 patients (31.1%) achieved HbA1c < 8% at 12 months of treatment without symptomatic hypoglycemia episodes.

Patients 3-17 years old

In this subgroup, 10/45 (22.2%) of patients and 14/45 (31.1%) of patients achieved HbA1c < 7.5% at 6 and 12 months of treatment respectively. 6/45 patients (13.3%) achieved HbA1c < 7.5% at 12 months of treatment without symptomatic hypoglycemia episodes.

Secondary efficacy analysis:

Common analysis:

At baseline, mean ±SD HbA1c level was 8.8±0.6%. At 6 months of the therapy, the mean ±SD HbA1c value was 8.3±1, 2%. At 12 months of the therapy, mean ±SD HbA1c value was 8.0±1.1% (p<0.001 comparison to baseline)

At baseline, mean ±SD insulin glargine dose was 17.0±8.2 IU (median= 15.5 IU) or 0.3 IU/kg. After 6 months of the therapy, mean ±SD insulin glargine dose was 17.9±8.1 IU (median = 17 IU). At 12 months, mean ±SD insulin glargine dose was 18.4±8.2 IU (median =18IU) or 0.4 IU/kg (p=0.80). Most of all patients used insulin glargine at bedtime (median time = 9:37 p.m.)

At baseline, mean ±SD insulin glulisine dose was 23.8 ± 10.3 IU (median= 22 IU) or 0. 5 IU/kg. After 6 months of the therapy mean ±SD insulin glulisine dose was 24.5 ± 11.4 IU, (median = 22 IU). At 12 months, mean ±SD insulin glulisine dose was 25.9±11.6 IU (median =24.0 IU) or 0.6 IU/kg. Dose change from baseline was not statistically significant (p=0. 65)

Patients 6-12 years old

At baseline mean ±SD HbA1c level in this subgroup was 8.6±0.6%. At 12 months of the therapy, mean ±SD HbA1c value was 8.1±1.1%, (p=0.04).

Patients 3-17 years old

At baseline mean ±SD HbA1c level in this subgroup was 8.8±0.6%. At 12 months of the therapy, mean ±SD HbA1c value was 7.9±1.1% (p=0.02).

Safety results: Hypoglycemic episodes were collected during the study treatment. Doctors collected information recorded in patient's "Self-control diary" and reported it in the case report forms (CRF).

Symptomatic episodes (events with typical symptoms of hypoglycemia following Blood Glucose change ≤3.9 mmol/L);

Nocturnal episodes were defined as events which happened during the sleep time (after falling asleep or before wakeup);

Severe hypoglycemia was defined as an event with clinical symptoms that are considered to result from hypoglycemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure because the patient could not treat her/himself.

Overall 1866 episodes of hypoglycemia were recorded in 77/90 (85.6%) patients. Hypoglycemia difference by group was not planned in this analysis.

The biggest numbers of the hypoglycemia episodes refer to symptomatic hypoglycemia-1844 episodes (98.8%). Asymptomatic hypoglycemia was registered 22 times (1.2%).

The analysis of hypoglycemia based on the time of day showed that 1672 (90.7%) episodes of symptomatic hypoglycemia refer to daytime hypoglycemia and 172 (9.3%) refer to night hypoglycemia. All 22 episodes of asymptomatic hypoglycemia refer to daytime hypoglycemia.

A total of 53 episodes of severe hypoglycemia were registered.

Thirteen 13 (14.4%) patients didn't have any episode of hypoglycemia during the study.

Overall 20.7 episodes per patient per year were registered during the study. Hospitalization was necessary in 5 (0.3%) of hypoglycemia episodes.

Adverse events

During the study, the following serious adverse events were reported in 5 patients:

- diabetic ketoacidosis. The investigator didn't associate the SAE with the investigational product

- serious hypoglycemia. The investigator associated the SAE with the investigational product (insulin glargine). Patient continued to receive insulin glargine

- chronic inflammatory demyelinating polyradiculopathy. The investigator didn't associate the SAE with the investigational product

- epileptic seizure. The investigator didn't associate the SAE with the investigational product

- serious hypoglycemia. The investigator didn't associate the SAE with the investigational product.

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