These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor/Company : sanofi-aventis **Generic drug name :** Insulin Glulisine	**Clinicaltrials.gov Identifier** : NCT00964574 **Study Code** : APIDR_L_02483		
Title of the study:	**Multicenter, open, non-randomised controlled phase IV clinical trial of efficacy and safety for insulin glulisine injected subcutaneously in patients with type 1 diabetes mellitus using also insulin glargine**		
Study center(s):	Minsk City Hospital # 1, Belarus Minsk City Hospital # 10, Belarus		
Study period: Date first patient enrolled: 31-JUL-2009 Date last patient completed: 26-JUL-2010			**Phase of development:** IV
Objectives:	*Primary objectives* To evaluate the efficacy and the safety (in terms of hypoglycemia and other adverse events) of insulin glulisine in type I Diabetes Mellitus (DM) patients *Secondary objectives* To evaluate insulin glulisine doses		
Methodology:	Multicenter, open, non-randomised clinical trial was required by local legislation.		
Number of patients:	**Planned:** 60	**Randomized:** 68	**Treated:** 64 out of 68 treated as 4 drop outs during of the Initiation phase of the study (duration of 4-6 weeks) with no intake of IP
Evaluated:	**Efficacy:** -Mean change in HbA1c -Mean HbA1c, -Mean Fasting Blood Glucose (FBG), - Mean Post Prandial Glycemia (PPG) and changes from baseline	**Safety:** - Description of adverse events and serious adverse events: type and frequency -Number of documented symptomatic hypoglycemic episodes	**Pharmacokinetics**: NA

Diagnosis and criteria for inclusion:	**Diabetes Mellitus, Type 1** - Adult patients > 18 years old with type 1 diabetes - Patients who need insulin basal + bolus regimen - 6.5 <=HbA1c <= 11% at visit 1 - Body Mass Index <35 kg/m²
Investigational product:	Insulin Glulisine
Dose:	Individual titration
Administration:	3-4 subcutaneous injections per day
Duration of treatment: 12 weeks	**Duration of observation:** 12 weeks (treatment) + 1 day (follow up)
Reference therapy:	NA
Criteria for evaluation:	
Efficacy:	-Mean change in HbA1c -Mean HbA1c, -Mean Fasting Blood Glucose, Mean Post Prandial Glycemia and changes from baseline
Safety:	-Description of adverse events and serious adverse events: type and frequency -Number of documented symptomatic hypoglycemic episodes
Statistical methods:	Investigated populations. Population of "all-included patients" (AIP) includes all patients who received therapy. Population "on the protocol" (OP) – is a part of the AIP population that involves all the patients who achieved the treatment and towards whom there wasn't any serious protocol infringements revealed and who achieved therapy not less than 20 weeks – in the frames of the following study in was a cohort of 62 patients. For analysis of all efficacy parameters population OP was used as well as AIP population. Population of AIP was used for examinations of results uniformity analysis in the population OP and for analysis of the initial demographic data and safety parameters (in the cases of quantity distinction of the AIP population and population OP) was used for examinations in the frames of the following study the present population capacity for safety analysis is 64 patients.
Summary:	Clinical trial proved efficacy and safety of Insulin Glulisine

Efficacy results:

Demographic characteristics (based on the per protocol analysis ie. Patients who completed the study)

Out of 62 patients who completed the study, 20 were female (32.3%) and 42 male (67.7%).
Mean age ±SD was 33,8±9,7 years (median=31).
Duration of diabetes mellitus and duration of insulin therapy was 108±70 months in a group (median of duration of 99 months, interquartile range 51-146 months).
One patient (1.6% of population) had 3 affections of target organs as a result of diabetes mellitus related complication, 13 patients (21%) had 2 complications, and 4 patients (22.6%) had only 1.
Concomitant disease: 6/62 (9.7%) had a thyroid disease gland and 2 (3.2%) suffered from HBP, and 2 other patients (3.2%) had a diagnosis of Gilbert's syndrome.

Administration of insulin glargin and insulin glulisine

- Insulin glargine must be injected subcutaneously once a day always at the same time of the day.
- Insulin glulisine must be injected subcutaneously 0-15 minutes before meals

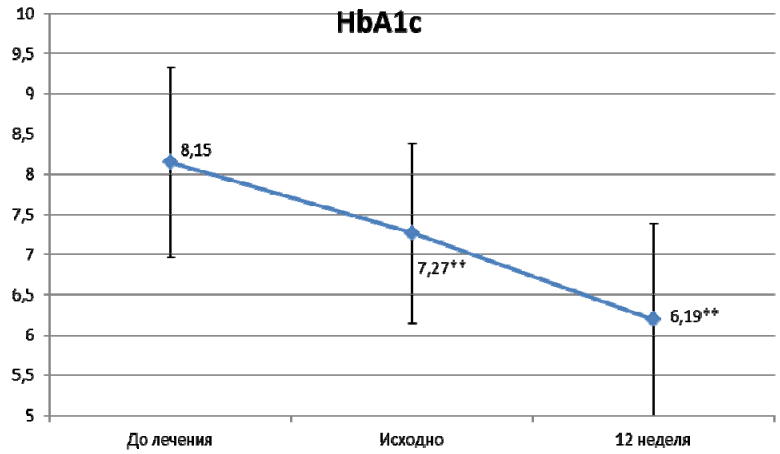
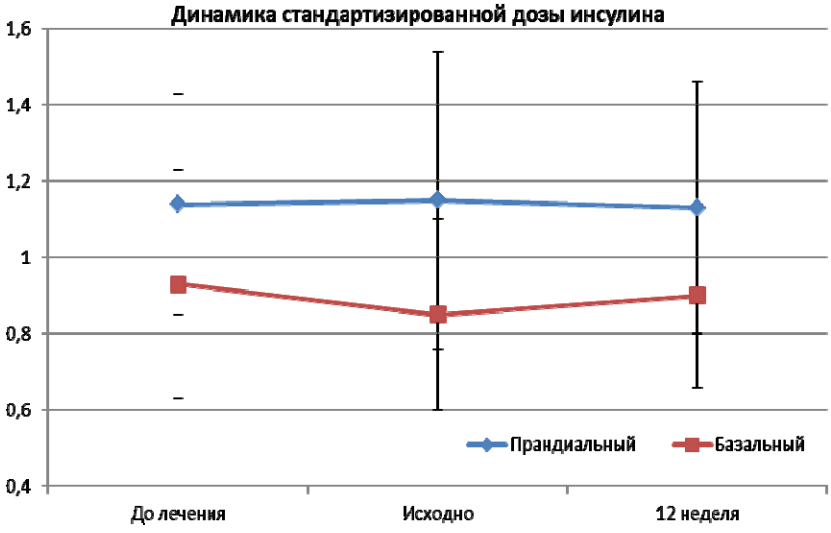
Titration schemes of insulin glargine and insulin glulisine

- Insulin glargine was titrated according Fasting Blood Glucose (FBG) and modalities of changing the dose left to the judgement of the investigator. Targeted FBG was 90-120 mg/dl (5.0-6.7 mmol/l) while avoiding hypoglycemia.

- Insulin glulisine dose was titrated according Postprandial Plasma Glucose (PPG) (2 hours after meal) and modalities of changing the dose left to the judgement of the investigator. Targeted PPG was 120 -160 mg/dl (6.7-8.9 mmol/l) while avoiding hypoglycemia.

Change in HbA1c from baseline to end of therapy

Variable	Descriptive Statistics (Apidra)							
	Valid N	Mean	Median	Minimum	Maximum	Lower Quartile	Upper Quartile	Std.Dev.
HbA1c 1	62	8,146129	7,815000	5,740000	10,86000	7,200000	9,100000	1,178624
HbA1c 2	62	7,273226	7,195000	4,800000	10,16000	6,690000	7,870000	1,122474
HbA1c 3	62	6,185000	5,965000	4,400000	10,60000	5,400000	7,020000	1,200117

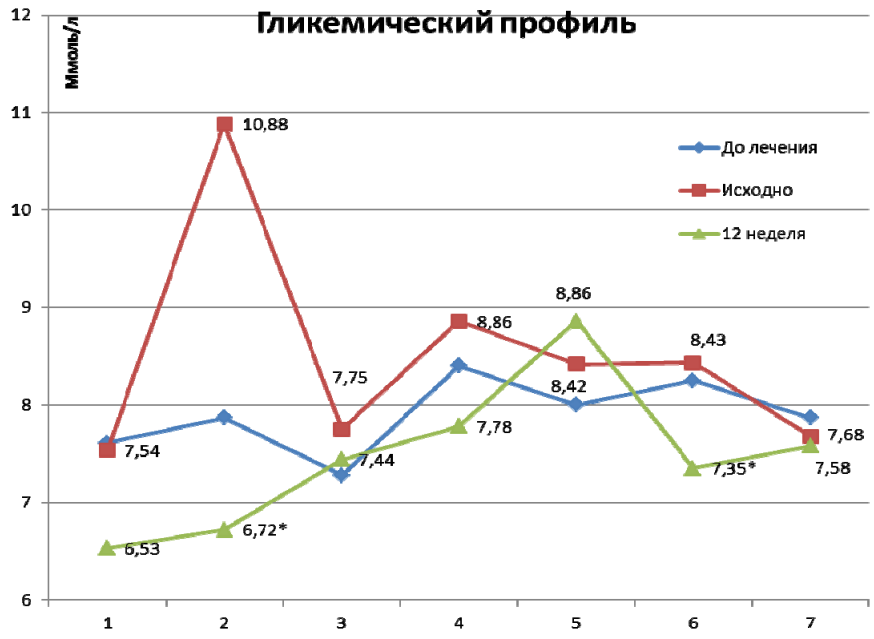
Efficacy results:	 Before treatment Initially 12th week ** p<0,001 **Change in dose (UI/kg) of insulin glargine + insulin glulisine**  Blue line=insulin glulisine, red line=insulin glargine

Efficacy results:

Change in dosing of insulin glargine and insulin glulisine over the 12 week study duration

	Prandial Insulin		Basal Insulin	
	Dose, IU/day	p	Dose, IU/day	p
Before trial	27,3±7,1	0,79	22,5±8,3	0,54
Screening	27,4±9,3	0,79	20,1±6,5	0,54
Initial point	28,9±11,4	0,79	20,8±6,7	0,54
2nd week	27,1±8,9	0,79	20,4±6,8	0,54
4th week	28,9±12,7	0,79	21,4±7,0	0,54
8th week	26,8±8,5	0,79	21,5±6,8	0,54
12th week	27,0±8,7	0,79	21,6±6,8	0,54

Glycemic Profile



Red line = at screening , Blue line = before treatment, Green line = 12th week

Points 1.3.5 are related to glycemia before breakfast, lunch and dinner

Points 2.4.6 are related to post prandial glycemia

Point 7 = night glycemia.

* p<0,05

Safety results:	**Adverse Events:** During the course of 12 weeks therapy with insulin glulisine no patients had no symptomatic hypoglycemic episodes. **Hypoglycemia will be classified as follows:** - Symptomatic hypoglycemia is defined as a condition with clinical symptoms that are estimated as symptoms of hypoglycemia. - Severe hypoglycemia is defined as a condition with clinical symptoms that are estimated as symptoms of hypoglycemia and when patient needs help from outside persons. And one of the following signs: • condition with glycemia level less that 50 mg/dl=2.8 mmol/l, • **or** condition quickly released after peroral take of carbohydrates, intravenous injection of glucose or glucagon administration Further clarification: severe hypoglycemia definition includes all episodes under which neurological impairments were marked enough so that patient couldn't help himself and which therefore endangered patient make harm to himself or others. "Needs help" means that patient couldn't help himself. -Night hypoglycemia is defined as a condition with clinical symptoms that are estimated as symptoms of hypoglycemia and develops when patient sleeps in period between going to sleep and waking up. In all cases suspicious to symptoms of hypoglycemia patients will be asked to measure blood glucose level before taking carbohydrates, if only safety considerations don't dictate the need of urgent glucose intake or glucose intake without making analysis. These results of glycemia measurement help to analyze hypoglycemia cases better. **Death, other serious adverse events and serious adverse reactions:** During the treatment there wasn't any death case and serious adverse events needed to be reported to the Ministry of Health of Republic of Belarus. **Clinical and laboratory characteristics assessment:** In the tables 1 and 2 is dynamic of hematological and biochemical patients characteristics during 12-weeks therapy with Insulin Glulisine.

Table 1 Dynamic of hematological characteristics (n=64).

Parameter	Initially	At the end point	p
Red blood cells, l^{-1}	4,90±0,47	4,86±0,46	>0,05
Hemoglobin, g/l	144,2±14,5	144,2±13,7	>0,05
Hematocrit, %	42,0±5,5	43,3±4,6	>0,05
White blood cells, l^{-1}	6,10±1,47	6,10±1,23	>0,05
Neutrophils, %	54,6±16,7	53,8±14,5	>0,05
Lymphocytes, %	32,3±7,1	33,5±8,5	>0,05
Monocytes, %	6,4±5,2	6,9±3,8	>0,05
Eosinophils, %	2,9±2,9	3,2±2,8	>0,05*
Basophils, %	0,5±0,8	0,5±0,6	>0,05*
Plateles, $л^{-1}$	219,1±56,2	204,4±44,5	>0,05
BSR, mm/h	6,9±5,5	6,9±4,5	>0,05*

Note: positions marked with (*) had allocation different from normal, when comparing groups of characteristics U-criterion Mana-Whitney was used.

Table 2 Dynamic of biochemical characteristics (n=64).

Parameter	Initially	At the end point	p
Common biochemical profile			
Creatinine mmol/l	78,5±19,8	79,8±16,7	>0,05
Urea, mmol/l	5,41±1,28	5,45±1,19	>0,05
Total protein, g/l	70,0±6,5	72,9±4,7	>0,05
Total billirubin, мМ/л	17,0±10,1	16,2±9,0	>0,05
Direct billirubin, mol/l	5,0±2,3	4,7±2,0	>0,05
Electrolites profiles			
Potassium, mol/l	5,25±5,23	4,57±0,41	>0,05
Sodium, mol/l	141,15±4,89	141,64±4,43	>0,05
Enzyme profiles			
Alkaline phosphatase	168,4±54,6	158,4±43,6	>0,05
AST,	28,3±9,1	24,0±8,9	>0,05
ALT,	28,3±14,8	24,1±10,9	>0,05*
Lipid profile			
Total cholesterol, mol/l	5,24±0,86	5,32±1,00	>0,05
Triglycerides, mol/l	1,26±0,88	1,11±0,41	>0,05

Note: positions marked with (*) had allocation different from normal, when comparing groups of characteristics U-criterion Mana-Whitney was used.

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