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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** Insuman Basal, Insuman Comb 25, Insuman Rapid	**Study Identifiers:** NCT01630369, UTN U1111-1128-8605 **Study code:** HUBIN_L_05574
Title of the study: Multicenter, open, non-randomized 6 months study to evaluate efficacy and safety Insuman® Basal, Insuman® Comb 25, Insuman® Rapid in insulin-naïve patients with T2DM who received baseline education course in the diabetes school	
Study center(s): 11 investigational sites in Ukraine	
Study period: Date first patient enrolled: 07/Feb/2012 Date last patient completed: 17/May/2013	
Phase of development: Phase 4 study with 6 months treatment duration	
Objectives: **Primary**: Evaluating the effectiveness of Insuman Basal, Insuman Comb 25, Insuman Rapid in patients with type 2 diabetes mellitus (T2DM) who were not compensated by oral therapy on the basis of glycated hemoglobin (HbA1c) reduction level after 6 months of treatment **Secondary**: • Evaluating the safety and tolerability of Insuman Basal, Insuman Comb 25, Insuman Rapid • Evaluating the effectiveness of diabetes education in schools • Evaluation of the average dose of insulin at the end of the treatment period	
Methodology: Open, non-randomized, non-comparative clinical phase 4 study	

Number of patients**:**	Planned: 550
	Randomized: 552
	Treated: 552
Evaluated:	
	Efficacy: 550
	Safety: 550

Data from 2 patients were lost and they were excluded from the study and hence 550 patients were included in data analysis. The distribution of patients among the treatment groups were as follows:

Insuman Basal – 341 patients.

Insuman Comb 25 – 173 patients.

Insuman Rapid – 36 patients.

Diagnosis and criteria for inclusion: T2DM patients treated with maximum tolerated dose (MTD) of 1-2 oral antidiabetics (OADs); males and females >18 years; time from diagnosis of diabetes to insulin initiation >1 year; patients with abilities of self-monitoring of diabetes, managing of patient's diary, ability to obtain education in Diabetes School, completion of Questionnaire; informed consent must be obtain in writing.

Study treatments

Investigational medicinal product(s): Insuman Basal, Insuman Comb 25, and Insuman Rapid

Formulation: Insuman SoloStar 100 IU/ml, suspension or solution in a pre-filled pen

Route of administration: Subcutaneous

Dose regimen: According to individual prescription by investigator

Duration of treatment: 6 months

Duration of observation: 6 months

Criteria for evaluation:

Efficacy:

Primary endpoint: Evaluating the effectiveness of Insuman Basal, Insuman Comb 25, Insuman Rapid in patients with T2DM who were not compensated by oral therapy on the basis of HbA1c reduction level after 6 months of treatment.

Secondary endpoints:

- Evaluating the safety and tolerability of Insuman Basal, Insuman Comb 25, Insuman Rapid
- Evaluating the effectiveness of diabetes education in schools
- Evaluation of the average dose of insulin at the end of the treatment period

Safety: Adverse events (AE) reported by the patient or noted by the Investigator

Statistical methods: Peculiarity of this trial was that data analysis was only descriptive (due to observational design of the study).So that the tests results are only exploratory.

Summary:

Population characteristics:

The demographic and baseline characteristics are summarized in the table below.

Parameter	Insuman Basal (N=341)	Insuman Comb 25 (N=173)	Insuman Rapid (N=36)	p
Age, mean±SD (years)	58.18±9.51	60.10±9.71	60.44±9.38	0.063*
Male, n (%) Female, n (%)	144 (42.23) 197 (57.77)	71 (41.04) 102 (58.96)	16 (44.44) 20 (55.56)	0.923**
BMI, mean±SD kg/m2	31.41±4.71	29.69±4.77	30.84±4.47	
Duration of diabetes, mean±SD (years)	8.76±5.05	7.78±5.52	9.92±6.81	0.0499*
HbA1c (%)	10.46±1.93	11.01±1.96	10.17±1.54	0.004*
FBG (min) mean±SD, mmol/L	10.74±2.24	11,31±2.77	10.40±2.68	0.022*
FBG (max) mean±SD, mmol/L	13.08±2.88	14.30±3.25	13.09±2.61	0.0001*
FBG_mean (Visit 1) mean±SD, mmol/L	11.92+2.24	12.74+2.46	11.70+2.19	0.0004*
No. (%) of patients with macrovasc. Complications	255 (74.78)	138 (79.77)	26 (72.22)	0.385**
No. (%) of patients with microvasc. Complications	328 (96.21)	161 (93.06)	36 (100.0)	0.110**
Previous OAD (n, %)	335 (98.24)	166 (95.95)	35 (97.22)	0.548**

Efficacy results:

Effectiveness by evaluation of HbA1c dynamic in groups (achievement of target level of HbA1c <7,5%).

Groups	n / N	%	p ($\chi 2$)
Basal	169 / 339	49.85	$\chi 2 = 12,88$ p=0.0016
Comb 25	57 / 166	33.34	
Rapid	11 / 34	32.35	
All groups	237 / 539	43.97	-

The difference between the groups in the target level of HbA1C <7,5% was statistically significant (p = 0.0016). The maximum efficacy for a given parameter was detected in patients receiving Insuman Basal - 49,85%. There was a statistically significant difference in reduction of HbA1c from baseline and after 6 months of treatment (p <0,05). Differences at baseline stratification groups was carried out taking into account the severity and duration of diabetes and the individual selection of the drug and dosage. The difference between groups due to the peculiarities of formation of groups. The difference between groups was decreased towards the end of the study. The maximum reduction of HbA1c was observed in groups of patients treated by Basal (Δ = -2,61) and Comb 25 (Δ = -2,81). The overall evaluation of effectiveness in groups (No. of patients with reduction of HbA1c >1%, n/N (%)) was 430/539 (79.78%). Differences between groups in frequency of reduction A1c >1% are not statistically significant.

Effectiveness of diabetes school: The data shows statistically significant increase of total amount of correct answers given by patients upon completion of education course in diabetes school in all groups. Maximal efficacy of diabetes school (following increase of % of correct answers) was observed in the group of patients treated by Insuman Rapid - 86,11%.The minimal was observed in the group of Comb 25 with 64,16% of patients.

Changes in insulin doses during study:

Insulin dose for patients who reached and did not reach reduction of HbA1c >1%

Period	Insuman Basal (mean±SD)	Insuman Comb 25 (mean±SD)	Insuman Rapid (mean±SD)
Mean daily dose of insulin (UI) in patients who did not reach a reduction of HbA1c >1% Visit 1	29.29±15.16	32.06±12.60	30.91±9.31
Mean daily dose of insulin (UI) in patients who reached reduction of HbA1c >1% Visit 1	35.23±16.39	36.73±13.88	26.4±13.91
P (t-test)	0.0070	0.086	0.335
Mean daily dose of insulin (UI) in patients who did not reach reduction of HbA1c >1% Visit 4	34.58±14.07	38.19±10.74	31.45±8.94
Mean daily dose of insulin (UI) in patients who reached reduction of HbA1c >1% Visit 4	38.78±15.98	44.25±15.00	32.82±13.03
P (t-test)	0.049	0.035	0.755

There was statistically significant difference in doses of insulin between patients who reached and those who did not reach a reduction of HbA1c >1%.

Safety results: During the treatment period, among all of 550 included patients the number of all types of symptomatic hypoglycemia was 91 episodes, with 56 documented hypoglycemia and 19 nocturnal hypoglycemia. No cases of severe hypoglycemia were reported.

One serious adverse event (SAE) resulted in the death of the patient. The follow up of the case showed that cause of fatal accident was hypertensive encephalopathy which was assessed by company and by the investigator as SAEs without relationship to the investigational product. On the basis of evaluation criteria there was no link between AE and the investigational product given. No other SAEs in this study were recorded.

Overall, 8 AEs were reported by investigators within the study period (weight gain, itching at the injection site, induration at the injection site, temperature increases due to viral infection, muscle tremors, dizziness, hyperhidrosis, and hyperglycemia owing to missed injection). All of them were considered by investigators as non-serious and not requiring specific measurements.

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