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

Sponsor: Sanofi **Drug substance(s):** Insulin glargine (HOE901)	**Study Identifiers:** NCT02954692, U1111-1183-8755 **Study code:** GLARGL07921
Title of the study: A national, multicenter, prospective, interventional, open-label, single-arm, 24-week phase IV study to evaluate the Effectiveness and sAfety of initiation and titration of InSulin GlarginE 300 U/mL in insulin-naïve patients with T2DM inadequately controlled on OAD treatment in Turkey	
Study center(s): 20 study centers participated from 10 different cities in Turkey.	
Study period: Date first patient enrolled: 30/Nov/2016 Date last patient completed: 22/Dec/2017	
Phase of development: 4	
Objectives: Primary objective: To assess mean change in HbA1c from baseline to week 24. Secondary objectives: To evaluate the efficacy and safety of the titration of insulin glargine 300 U/mL in terms of: • Target HbA1c • Target fasting self- measured blood glucose (SMBG) • Hypoglycemic events • Adverse events • Quality of life (QoL) assessment by Diabetes Treatment Satisfaction Questionnaire – status version (DTSQs) and Diabetes Treatment Satisfaction Questionnaire – change version (DTSQc). • Blood glucose fluctuation by using continuous glucose monitoring system (CGMS) in a subgroup of patients	
Methodology: National, Multicenter, Prospective, Interventional, Open-label, Single-arm	
Number of patients: Planned: 110 Randomized:112 Treated: 108 **Evaluated:** Efficacy: 108 Safety: 108	
Diagnosis and criteria for inclusion: • Insulin-naïve patients diagnosed with type 2 diabetes mellitus who were 18 years or older at the time of enrollment • Duration of diabetes from first diagnosis must have been at least one year.	

- Patients pre-treated with one or more oral antidiabetic drugs for at least 6 months
- HbA1c between 8.0% and 11% at inclusion

Study treatments

Investigational medicinal product(s): Insulin glargine 300 U/mL (Gla-300)

Formulation: Gla-300 was a sterile, non-pyrogenic, clear, colorless solution provided in a prefilled disposable SoloSTAR® pen).

Route(s) of administration: Gla-300 was administered subcutaneously.

Dose regimen: Starting from day 1, insulin glargine 300 U/mL solution (Gla-300) was self-administered subcutaneously once daily in the evening.

Duration of treatment: 24 weeks

Duration of observation: 27 weeks

Criteria for evaluation:

Efficacy: Primary efficacy endpoint was the mean change in HbA1c from baseline to Week 24. Secondary endpoints were listed below;

- Percentage of patients achieving target fasting SMBG (80-130 mg/dL) at Week 12 and 24 without experiencing severe and/or confirmed hypoglycemia ≤ 70 mg/dL and <54 mg/dL
- Number and percentage of patients experiencing hypoglycemia and number of hypoglycemic events per patient-year during the study treatment period:
  - According to definitions (severe, confirmed and/or severe ≤ 70 and <54 mg/dL, documented symptomatic hypoglycemia ≤ 70 and <54 mg/dL)
  - And according to the time (nocturnal i.e. 00:00 to 05:59 am, at any time of the day)
- Percentage of patients reaching target fasting SMBG (80-130 mg/dL) at Week 12 and Week 24.
- Time (weeks) from baseline to reach target pre-breakfast SMBG
- Mean change in HbA1c from baseline to Week 12
- Mean of 7-point SMBG profile at baseline, Week 12 and Week 24 along with mean change from baseline to Week 12 and Week 24 by each SMBG time point
- Mean change in fasting plasma glucose (FPG) from baseline to Week 12 and Week 24
- Percentage of patients achieved target HbA1c ≤ 7% at Week 12 and 24
- Percentage of patients achieved target HbA1c ≤ 7% at Week12 and 24 without experiencing severe and/or confirmed hypoglycemia ≤ 70 mg/dL and <54 mg/dL
- Mean change in Gla-300 dose from baseline to Week 12 and Week 24
- Glycaemic variability change from baseline to 24th week measured with CGMS
- Adverse events (AEs)/Serious AEs (SAEs)/Product Technical Complaints (PTCs)
- Mean change in body weight from baseline to week 12 and 24
- DTSQs assessment at baseline and Week 24 and mean change in score from baseline to Week 24.

Safety: The safety endpoints were assessed by hypoglycemic events, AEs/SAEs and adverse event of special interest (AESI). Adverse events and SAEs were reported by the Investigator. The standard hematology and blood chemistry tests were performed at baseline visit.

Statistical methods:

The primary efficacy variable (mean change in HbA1c from baseline to Week 24 in %) were analyzed in the ITT population using post-baseline HbA1c data available on the 24-week on-treatment period.

Mean change in HbA1c from baseline to Week 24 were evaluated with measurements of HbA1c levels obtained at baseline and V4 End of Treatment by using paired sample t-test (if continuous data is normally distributed), Wilcoxon Signed Rank test (if continuous data is non-normally distributed).

Summary:

Population characteristics: Overall, 108 patients were enrolled in the study, of which 51.9% of the patients (n=56) were female and the mean age was 55.9 (±8.1) years, ranging from 36 to 72 years. Majority of the participants were not following a diet regimen (n=83, 76.9%). At the beginning of the study, the mean body weight was 83.5 (±15.9) kg. Mean height and body mass index of the patients were 162.4 (±10.5) cm and 31.8 (±6.0) kg/m^2, respectively.

Table 1 – Age/Weight/Height/BMI

	N	Mean	Median	Std. Dev.	Min.	Max.
Age	108	55.9	56.5	8.1	36.0	72.0
Weight (kg)	108	83.5	81.3	15.9	57	154.3
Height (cm)	108	162.4	162.5	10.5	126	186
BMI (kg/m^2)	108	31.8	30.8	6.0	21.1	59.5

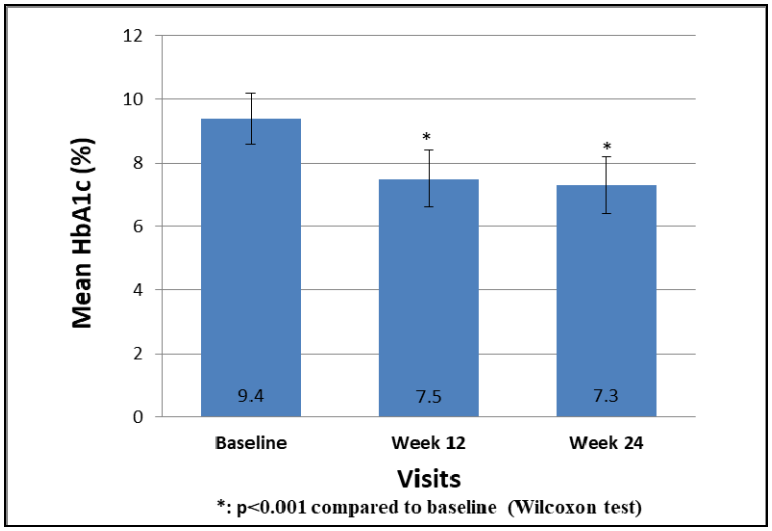
Efficacy results: According to the primary objective of the study, mean HbA1c values at Week 24 and 12 were compared to baseline HbA1c values. Mean HbA1c decreased significantly at 12 and 24 weeks. Descriptive analysis of HbA1c levels are presented in Table 2 and Figure 1.

Table 2 – Comparison of mean HbA1c (%) levels at baseline vs. Week 12 and Week 24

							Percentiles			p
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	
Baseline	108	9.4	9.3	0.8	7.5	11.0	8.7	9.3	10.0	
Week 12	108	7.5	7.4	0.9	6.0	10.5	6.8	7.4	8.0	**<0.001**[1]
Week 24	108	7.3	7.2	0.9	5.8	10.2	6.5	7.2	7.8	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

Figure 1 – Mean HbA1c Levels (%)



Since hypoglycemic events were not assigned to the study visits and event data were collected sporadically, hypoglycemic events were not evaluated by visits. In this study, 28.4% of patients reached target SMBG levels 80-130 mg/dL without experiencing any hypoglycemia. Detailed results regarding SMBG levels and hypoglycemia are summarized in Table 3.

Table 3 – Number and Percentage of Patients Reaching Target SMBG Levels (80-130 mg/dL) at Week 24

	Patients with hypoglycemia		Patients with no hypoglycemic event		Total	
	N	Percent	N	Percent	N	Percent
Achieved target (80-130 mg/dL)	34	33.3%	29	28.4%	63	61.7
Above target (>130 mg/dL)	13	12.7%	24	23.5%	37	36.2
Below target (<80 mg/dL)	1	1.0%	1	1.0%	2	2.0
Total	48	47.0%	54	52.9	102	100.0

During the study 48 patients (44.4%) experienced 193 hypoglycemic event. If the patient required assistance of another person, this event was considered as a severe hypoglycemia. Hypoglycemic events that were associated with clinical symptoms were considered as confirmed events. Summaries of hypoglycemic events are shown through Table 4a to Table 4c.

Table 4a – Number and Proportion of Patients Experiencing Hypoglycemia According to Time and Severity

	Daytime*		Nocturnal*		Total	
	N	Percent**	N	Percent**	N	Percent**
Non-severe hypoglycemia	1	2.1%	44	91.7%	45	93.8%
Severe hypoglycemia (requiring 3rd party assistance)	0	0.0%	3	6.3%	3	6.3%
Total	1	2.1%	47	97.9%	48	100.0%

*Nocturnal: 00:00-05:59, Daytime: 06:00-23:59, **Percentage according to total number of patients (n=108).

Table 4b – Number of Documented Hypoglycemic Events per Patient Year

	Daytime*			Nocturnal*			Total		
	N	Percent**	PPY***	N	Percent**	PPY***	N	Percent**	PPY***
Hypoglycemia (<54 mg/dL)	8	4.1	6.2	NA	NA	NA	8	4.1	6.2
Hypoglycemia (≤70 mg/dL)	76	39.4	0.7	13	6.7	3.8	89	46.1	0.6
Hypoglycemia (>70 mg/dL)	86	44.6	0.6	1	0.5	49.8	87	45.1	0.6
Hypoglycemia (unknown)	7	3.6	7.1	2	1.0	24.9	9	4.7	5.5
Total	177	91.7	0.3	16	8.3	3.1	193	100.0	0.3

*Nocturnal: 00:00-05:59, Daytime: 06:00-23:59, **Percentage according to total number of events (n=193), *** Per patient-years.

Table 4c – Number of Confirmed Hypoglycemic Events per Patient Year

	Daytime*			Nocturnal*			Total		
	N	Percent**	PPY***	N	Percent**	PPY***	N	Percent**	PPY***
Hypoglycemia (<54 mg/dL)	3	1.6	16.6	NA	NA	NA	3	1.6	16.6
Hypoglycemia (≤70 mg/dL)	35	18.1	1.4	10	5.2	5.0	45	23.3	1.1
Hypoglycemia (>70 mg/dL)	28	14.5	1.8	NA	NA	NA	28	14.5	1.8
Hypoglycemia (unknown)	7	3.6	7.1	2	1.0	24.9	9	4.7	5.5
Total	73	37.8	0.7	14	6.2	4.2	85	44.0	0.6

*Nocturnal: 00:00-05:59, Daytime: 06:00-23:59, **Percentage according to total number of events (n=193), *** Per patient-years.

Almost half of the patients (n=45, 41.7%) had reached target pre-breakfast SMBG levels 4 weeks after the initiation of insulin treatment, while 18.5% of the patients (n=20) were not successful in reaching the target pre-breakfast SMBG levels during the entire study period.

Table 5 – Time to Reach Target Pre-Breakfast SMBG (80-130 mg/dL) Levels

	Target Pre-breakfast SMBG (80-130 mg/dL)	
	N	Percent
4 Weeks	45	41.7%
12 Weeks	28	25.9%
24 Weeks	15	13.9%
Not reached to the target level	20	18.5%
Total	108	100%

In this study, 7-point SMBG values were measured at pre-breakfast, post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner and bedtime time-point at baseline, Week 12 and Week 24 visits. Each SMBG time-point (pre-breakfast, post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner and bedtime) were compared to baseline measurements. For each time-point, significant improvements (p<0.001) were observed when compared to baseline. Comparisons for each SMBG time-point are presented through Table 6 to Table 12.

Table 6 – Comparison of Mean Pre-Breakfast SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			p
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	
Baseline	103	183.3	172.0	46.9	106.0	333.0	154.0	172.0	210.0	
Week 12	94	126.9	123.5	26.5	77.0	220.0	109.8	123.5	135.0	**<0.001[1]**
Week 24	94	126.1	124.5	30.0	84.0	276.0	107.8	124.5	135.5	**<0.001[1]**

1: Compared to baseline (Wilcoxon test)

Table 7 – Comparison of Mean Post-Breakfast SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	102	234.9	230.0	69.5	75.0	406.0	189.0	230.0	276.3	
Week 12	93	169.8	153.0	54.4	94.0	386.0	131.5	153.0	194.0	**<0.001**[1]
Week 24	90	178.1	165.5	60.7	73.0	361.0	135.0	165.5	219.3	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

Table 8 – Comparison of Mean Pre-Lunch SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	99	178.5	165.0	68.1	40.0	413.0	138.0	165.0	219.0	
Week 12	93	134.1	124.0	48.2	35.0	362.0	106.5	124.0	143.0	**<0.001**[1]
Week 24	92	136.5	131.0	42.4	63.0	267.0	109.0	131.0	158.8	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

Table 9 – Comparison of Mean Post-Lunch SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	96	225.1	211.0	76.8	105.0	520.0	174.5	211.0	262.5	
Week 12	89	165.2	158.0	43.1	82.0	312.0	139.0	158.0	185.0	**<0.001**[1]
Week 24	91	175.7	162.0	58.1	72.0	511.0	137.0	162.0	209.0	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

Table 10 – Comparison of Mean Pre-Dinner SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	97	195.2	177.0	75.5	76	521	147.0	177.0	236.5	
Week 12	92	148.1	137.0	46.8	66.0	284.0	120.3	137.0	170.0	**<0.001**[1]
Week 24	91	140.8	132.0	41.6	68.0	288.0	115.0	132.0	168.0	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

Table 11 – Comparison of Mean Post-Dinner SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	100	229.8	218.5	70.4	61.0	472.0	184.0	218.5	282.0	
Week 12	89	179.2	165.0	51.7	107.0	377.0	140.5	165.0	211.5	**<0.001**[1]
Week 24	89	178.6	179.0	52.8	77.0	320.0	137.5	179.0	218.0	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

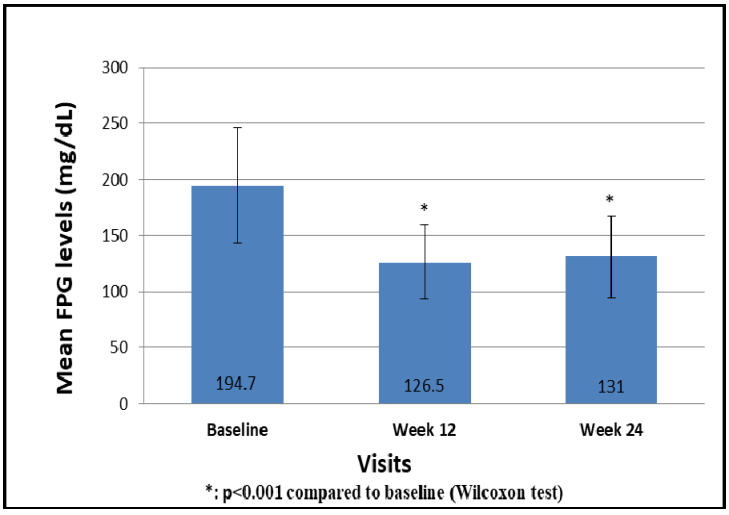
Table 12 – Comparison of Mean Bedtime SMBG (mg/dL) Values at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	95	221.6	207.0	69.7	97.0	420.0	168.0	207.0	258.0	
Week 12	84	158.7	149.5	45.5	52.0	346.0	129.3	149.5	181.8	**<0.001**[1]
Week 24	82	163.1	150.0	49.8	65.0	307.0	127.0	150.0	195.5	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

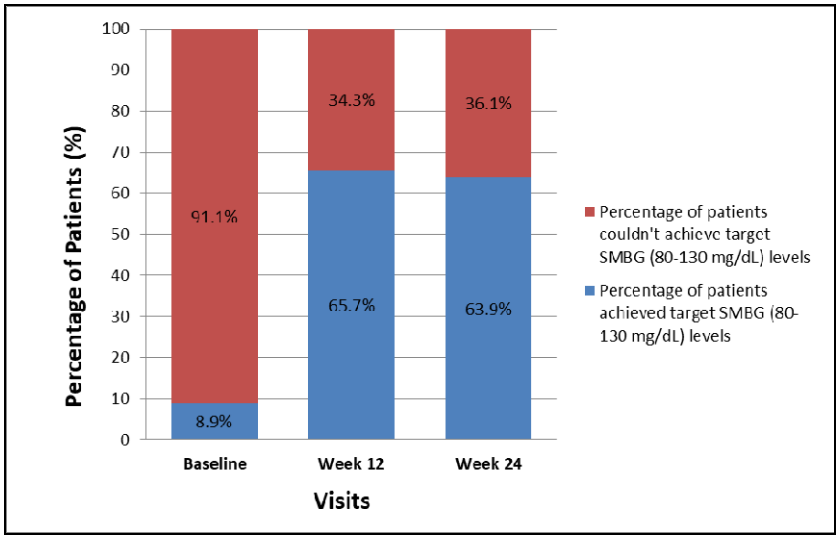
In addition to the reduction in HbA1c levels, mean fasting plasma glucose levels were decreased both at week 12 and week 24, as compared with baseline (Figure 2).

Figure 2 – Mean FPG Levels (mg/dL)



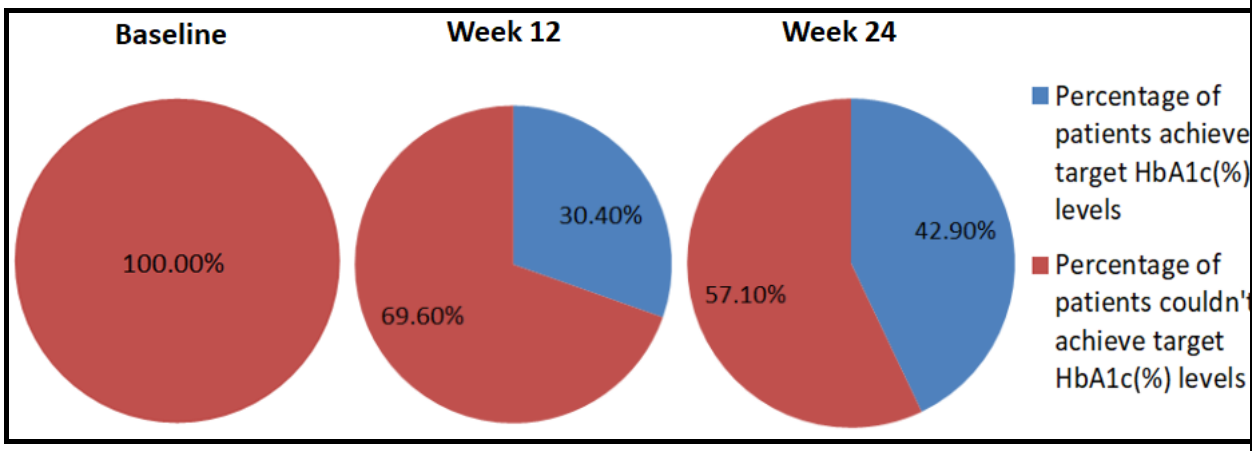
More patients achieved their target SMBG levels (80-130 mg/dL) at week 12 and 24 compared to baseline with no difference between week 12 and week 24 to 12 weeks (Figure 3).

Figure 3 – Percentage of Patients Achieved and Couldn't Achieve Target SMBG Levels (80-130mg/dL)



The percentage of patients who achieved target HbA1c level ≤7.0% was significantly increased from baseline to week 12 (30.4%) and further increased at week 24 (42.9%) (Figure 4).

Figure 4 – Percentage of Patients Achieved and Couldn't Achieve the Target HbA1c Levels (≤7%)



Number and percentage of patients who reached target HbA1c level ≤7% with and without experiencing any hypoglycemic event at the end of the study is presented in Table 13. Study results revealed that 21 patients (19.4%) reached target HbA1c levels without experiencing any hypoglycemic event.

Table 13 – Hypoglycemia Experience of Patients with Target HbA1c Levels

	HbA1c			
	Out of Target Range (>7%)		Within Target Range (≤7%)	
	N*	Percent*	N*	Percent*
No hypoglycemic event	34	31.5%	21	19.4%
Hypoglycemic event experienced	21	19.4%	27	25.0%
Assistance not required	20	18.5%	25	23.1%
Assistance required (severe hypoglycemia)	1	0.9%	2	1.9%

*Some patients experienced both severe and not severe hypoglycemia. Number of patients that experienced at least one event was provided. Percentage within all patients (n=108) is provided.

Mean body weight did not change significantly at week 12 when compared to baseline (+0.5 kg; p=0.30). However, a slight but significant increase was observed in mean body weight at week 24 when compared to baseline (+0.9 kg; p=0.042). Mean body weight values at each visit are presented in Table 14.

Table 14 – Comparison of Mean Body Weight (kg) at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	108	83.1	80.3	15.9	56.0	152.0	71.3	80.3	90.9	
Week 12	103	83.6	80.4	16.1	56.0	147.6	72.5	80.4	92.0	**0.300**[1]
Week 24	103	84.0	82.0	15.5	55.0	144.0	72.4	82.0	93.0	**0.042**[1]

1: Compared to baseline (Wilcoxon test)

A statistically significant increase in mean daily Gla-300 dose was observed both at week 12 and week 24 when compared to baseline (p<0.001). Mean dose levels with descriptive statistics are provided in Table 15 (in units/day) and in Table 16 (in units/kg).

Table 15 – Comparison of Mean Gla-300 Dose (units/day) Levels at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	108	18.7	18.0	4.2	8.0	33.0	16.0	18.0	21.0	
Week 12	103	28.4	27.0	12.5	7.0	65.0	20.0	27.0	35.0	**<0.001**[1]
Week 24	104	30.3	29.0	13.6	7.0	68.0	20.0	29.0	38.0	**<0.001**[1]

1:Compared to baseline (Wilcoxon test)

Table 16 – Comparison of Mean Gla-300 Dose (units/kg) Levels at Baseline vs. Week 12 and Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	108	0 20	0.20	0.11	0.11	0.25	0.20	0.20	0.20	
Week 12	103	0.33	0.33	0.10	0.10	0.77	0.23	0.33	0.39	**<0.001**[1]
Week 24	104	0.36	0.34	0.11	0.11	0.82	0.24	0.34	0.44	**<0.001**[1]

1:Compared to baseline (Wilcoxon test)

Patient satisfaction was evaluated using the DTSQ questionnaire. Statistically significant improvements (p<0.001) were observed in treatment satisfaction scores of patients at week 24 as compared to baseline scores. Perceived frequency of hyperglycemia scores were improved significantly (p<0.001) at week 24 as compared with baseline. There was no statistically significant (p=0.681) difference in perceived frequency of hypoglycemia scores at week 24 as compared with baseline. Details of DTSQ evaluations are given in Tables 17, 18 and 19.

Table 17 – Comparison of Mean Treatment Satisfaction Scores (Item: 1, 4, 5, 6, 7, 8) at Baseline vs. Week 24

							Percentiles			
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	103	24.76	25.0	6.81	4.0	36.0	21.0	25.0	30.0	
Week 24	102	30.08	30.0	5.41	9.0	36.0	29.0	30.0	34.0	**<0.001**[1]

1: Compared to baseline (Wilcoxon test)

Table 18 – Comparison of Mean Perceived Frequency of Hyperglycemia Scores (Item: 2) at Baseline vs. Week 24

							Percentiles		
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	103	4.6	5.0	1.4	0.0	6.0	4.0	5.0	6.0	
Week 24	102	2.3	2.0	1.9	0.0	6.0	1.0	2.0	4.0	**<0.001[1]**

1: Compared to baseline (Wilcoxon test)

Table 19 – Comparison of Mean Perceived Frequency of Hypoglycemia Scores (Item: 3) at Baseline vs. Week 24

							Percentiles		
	N	Mean	Median	Std. Dev.	Minimum	Maximum	25	50	75	p
Baseline	103	1.6	1.0	1.7	0.0	6.0	0.0	1.0	2.0	
Week 24	102	1.7	1.0	1.6	0.0	6.0	0.0	1.0	3.0	**0.681[1]**

1: Compared to baseline (Wilcoxon test)

A subgroup of 15 patients performing CGM measurements was planned in two centers of the study. Finally, CGM data were available for 12 patients with only one data point. According to CGM data, percentage (%) of time where glucose concentrations were within the target range of 80-130 mg/dL for each visit Increased to 35 % after 4 visits, as compared to 11.7% at baseline (Table 20).

Table – 20 Percentage (%) of Time Glucose Concentrations within the Target Range of 80-130 mg/dL – Analyses on All-time (24h) CGM Data

	Screening Visit		Visit 4	
	Time*	Percent (%)	Time*	Percent (%)
In target range	202	11.7	591	35.0
Out of target range	1526	88.3	1099	65.0
Total	1728	100.0	1690**	100.0

*: Number of measurements. Measurements were performed in every 5 minutes. **: One patient's (1-10) visit 4 measurements were not done, therefore last measurements data were missing.

Safety results: In this study, 42 (38.8%) of the 108 enrolled patients experienced 83 cases of adverse events. There were 69 non-serious adverse events (AEs), 13 serious adverse events (SAEs) and 1 adverse event of special interest (AESI) recorded. The most frequent non-serious adverse event was influenza, and the most frequent serious adverse event was hypoglycemia. One case of overdose was reported as an adverse event of special interest. There were no deaths. There were no product technical complaints reported during the study. Details of adverse events are presented in the tables below (Table 21, Table 22 and Table 23).

Table 21 – Adverse Events

MedDRA System Organ Class MedDRA Preferred Term [n (%)]	N=108	Percent (%)
Any class	**67**	**62.0**
Infections and infestations	**16**	**14.8**
Influenza	5	4.6
Abscess	1	0.9
Bacterial infection	1	0.9
Cystitis	1	0.9
Furuncle	1	0.9
Gastroenteritis	1	0.9
Nasopharyngitis	1	0.9
Pharyngitis	1	0.9
Pneumonia	1	0.9
Tooth abscess	1	0.9
Upper respiratory tract infection	1	0.9
Urinary tract infection	1	0.9
General disorders and administration site conditions	**6**	**5.6**
Injection site haemorrhage	2	1.9
Injection site paraesthesia	1	0.9
Injection site pain	1	0.9
Asthenia	1	0.9
Fatigue	1	0.9
Gastrointestinal disorders	**6**	**5.6**
Diarrhoea	2	1.9
Abdominal pain upper	1	0.9
Dyspepsia	1	0.9
Nausea	1	0.9
Toothache	1	0.9
Injury, poisoning and procedural complications	**6**	**5.6**
Overdose	2	1.9
Humerus fracture	1	0.9
Limb injury	1	0.9
Tendon injury	1	0.9
Wrist fracture	1	0.9

MedDRA System Organ Class MedDRA Preferred Term [n (%)]	N=108	Percent (%)
Musculoskeletal and connective tissue disorders	**5**	**4.6**
Back pain	2	1.9
Bone pain	1	0.9
Myalgia	1	0.9
Pain in extremity	1	0.9
Nervous system disorders	**5**	**4.6**
Headache	2	1.9
Dizziness	1	0.9
Hypoaesthesia	1	0.9
Vertebrobasilar insufficiency	1	0.9
Surgical and medical procedures	**3**	**2.8**
Tooth extraction	2	1.9
Cataract operation	1	0.9
Skin and subcutaneous tissue disorders	**3**	**2.8**
Contusion	1	0.9
Pruritus	1	0.9
Urticaria	1	0.9
Blood and lymphatic system disorders	**2**	**1.9**
Anemia	2	1.9
Ear and labyrinth disorders	**2**	**1.9**
Deafness neurosensory	1	0.9
Vertigo	1	0.9
Immune system disorders	**2**	**1.9**
Hypersensitivity	2	1.9
Psychiatric disorders	**2**	**1.9**
Anxiety disorder	1	0.9
Sleep disorder	1	0.9
Respiratory, thoracic and mediastinal disorders	**2**	**1.9**
Chronic obstructive pulmonary disease	1	0.9
Cough	1	0.9
Vascular disorders	**2**	**1.9**
Hypertension	2	1.9
Eye disorders	**1**	**0.9**
Eye haemorrhage	1	0.9
Hepatobiliary disorders	**1**	**0.9**
Hepatic steatosis	1	0.9
Investigations	**1**	**0.9**
Blood creatinine increased	1	0.9
Metabolism and nutrition disorders	**1**	**0.9**
Vitamin B12 deficiency	1	0.9

Reproductive system and breast disorders	**1**	**0.9**
Postmenopausal haemorrhage	1	0.9

N= Number of patients included in the safety analysis, n (%)= number and % of subjects with at least one AE.

Table 22 – Serious Adverse Events

MedDRA System Organ Class MedDRA Preferred Term [n (%)]	**N=108**	**Percent (%)**
Any class	**13**	**12.0**
Metabolism and nutrition disorders	**2**	**1.9**
Hypoglycaemia	2	1.9
Cardiac disorders	**2**	**1.9**
Angina pectoris	1	0.9
Myocardial infarction	1	0.9
Infections and infestations	**2**	**1.9**
Gastroenteritis	1	0.9
Pneumonia	1	0.9
Endocrine disorders	**1**	**0.9**
Thyroid cyst	1	0.9
Injury, poisoning and procedural complications	**1**	**0.9**
Subdural haematoma	1	0.9
Neoplasms benign, malignant and unspecified (inc. cysts and polyps)	**1**	**0.9**
Invasive ductal breast carcinoma	1	0.9
Nervous system disorders	**1**	**0.9**
Transient ischaemic attack	1	0.9
Reproductive system and breast disorders	**1**	**0.9**
Uterine polyp	1	0.9
Surgical and medical procedures	**1**	**0.9**
Breast conserving surgery	1	0.9
Vascular disorders	**1**	**0.9**
Peripheral artery stenosis	1	0.9

N= Number of patients included in the safety analysis, n (%)= number and % of subjects with at least one AE.

Table 23 – Adverse Event of Special Interest

MedDRA System Organ Class MedDRA Preferred Term [n (%)]	**N=108**	**Percent (%)**
Injury, poisoning and procedural complications	**1**	**0.9**
Overdose	1	0.9

N= Number of patients included in the safety analysis, n (%)= number and % of subjects with at least one AE

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