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Six Months Comparative Evaluation of Efficacy and Safety of Wockhardt's Biosimilar Insulin Glargine (Glaritus®) with Reference Insulin Glargine (Lantus®) in Type 2 Diabetes Mellitus in India: Results of Interim Analysis

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Abstract **Objective:** To compare the change in immunogenic response, safety and efficacy of insulin glargine in Glaritus® and Lantus® treatment arms from baseline to six months in patients with type 2 diabetes mellitus (T2DM) uncontrolled on oral antidiabetic drugs (OADs). **Material and methods:** In an ongoing prospective, open-label, randomized, parallel-group, comparative, multicenter, phase IV study, adult patients with uncontrolled T2DM are treated with either Glaritus® once daily or Lantus® once daily for six months, both given subcutaneously. Glaritus® treatment arm is to be continued for another six months. The primary endpoint for the study was the percentage change in anti-insulin antibodies (AIA) titer to glargine in both treatment arms from baseline to six months. **Results:** Ninety patients were randomized to each group. Baseline characteristics were comparable between the groups (p>0.05). There was no significant difference in percent change in the AIA titer between the two treatment arms at the end of six months in ITT (intent-to-treat) and mITT(modified intent to treat) population (LS mean diff [95% CI]: 2.2% (-15.1%, 19.6%), p=0.7987 and 3.4% (-15.1%, 21.9%), p=0.7181, respectively). No significant between-group difference was seen in change in the HbA1c level at the end of six months in ITT and mITT population [LS mean diff (95% CI): -0.2 (-0.4, 0.0), p=0.1072 for ITT population; and -0.1 (-0.3, 0.1), p=0.2283, for mITT population]. There was also no significant difference between two groups for the incidence of adverse events [Glaritus® 17 (18.9%) and Lantus® 20 (22.2%) p=0.5800]. **Conclusion:** Glaritus® was found to be non-inferior to Lantus® in glycaemic control and comparable in immunogenic response and safety at the end of six months in patients with T2DM uncontrolled on OADs.

Keywords Immunogenicity, Insulin Glargine, Glaritus®, Lantus®, Type 2 Diabetes Mellitus

1. Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia with metabolic disturbances occurring due to defects in insulin secretion and/or action. Poor glycemic control may result in chronic complications, dysfunction or failure of different body organs. A recently published four year retrospective study showed prevalence of macrovascular and microvascular complications in

31.8% and 35.3% type 2 diabetes mellitus (T2DM) patients respectively. The prevalence of neuropathy, nephropathy and retinopathy, was 20.8%, 12.5% and 6.5% espectively [1]. An optimal glucose regulation in patients with diabetes mellitus reduces the risk of complications. The UK Prospective Diabetes Study (UKPDS), a landmark clinical trial showed that improvement in glycemic control reduced diabetes related complications. The study also demonstrated that intensive glucose control can significantly reduce microvascular complications [2].

The onset of T2DM is earlier in Indians. Moreover, glycaemic control in patients with T2DM is often not optimal [3]. Because of these reasons, early and effective treatment is essential for these patients. Insulin is an attractive option for the treatment of T2DM. Insulin decreases blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and adipose tissues, and by suppressing glucose production by the liver. Insulin also inhibits lipolysis and proteolysis [4].

Different types of insulin preparations including insulin glargine, NPH (Neutral Protamine Hagedorn) insulin, and insulin ultralente are available in the market [5]. Long-acting basal insulins are commonly prescribed in patients with T2DM. Insulin glargine is a well established long-acting basal insulin commonly used worldwide [6]. A study reported that insulin glargine has high and similar reproducibility of total absorption and glucodynamic effect like NPH (Neutral Protamine Hagedorn) insulin [5].

As the cost of the treatment is important for the management of T2DM considering long-term requirement, biosimilars represent alternative options for the innovator's insulin product. Glaritus® is a biosimilar of insulin glargine developed by Wockhardt. It is an r-DNA derived insulin glargine injection 100 IU/mL.

Glaritus® has been compared with innovator Lantus® in healthy volunteers [6] and patients with type 1 diabetes [7] as well as T2DM [8]. A study in healthy volunteers has shown that Glaritus is bioequivalent with Lantus [6]. A 12-week study in adult patients with type 1 diabetes mellitus showed that biosimilar insulin glargine, Glaritus®, is comparable to Lantus® for glycemic control [7].

Immunogenicity is one of the concerns with the use of insulin regardless of their source and purity [9]. Insulin glargine is known to be antigenic and associated with the development of antibodies [10]. Although the occurrence of severe immunological complications is rare, [9] immunogenic potential of insulin carries the risk of severe antibody-mediated insulin resistance [11,12]. Presence of insulin antibodies may hamper the glucose control [13] resulting in hyperglycemia as well as hypoglycemia [14-16]. Exact prevalence and comparison of immunogenicity of biosimilar glargine with innovator's product are not known.

Considering the low incidence of adverse events (AEs) due to immunogenicity, post-marketing studies play an important role in detecting such events. Secondly, evidence for glycemic control from head to head clinical trials will help clinicians to select proper drug for their patients.

1.1. Objective

The primary objective of this study was to evaluate the change in immunogenic response (measured as percentage change in anti-insulin antibody [AIA]) to glargine in Glaritus® and Lantus® treatment arms from baseline to 6 months in Indian patients with T2DM.

Secondary objectives were an evaluation of change in immunogenic response to glargine in Glaritus® treatment arm from baseline to 12 months and comparison of efficacy and safety in both treatment arms at 6 months. The exploratory objective was to assess efficacy in Glaritus® treatment arm from baseline to 12 months.

2. Material and Methods

In this prospective, open-label, randomized, parallel-group, multicenter, phase IV study, adult patients (age ≥18 and ≤55 years) with uncontrolled T2DM (HbA1c ≥8.0% and ≤10.0% and inadequately controlled by one or more OADs) with body mass index (BMI) ≥18.0 and ≤38.0 kg/m^2 who were either insulin-naïve or had received insulin for short term (≤2 weeks) only and ≥6 months prior to enrolment and according to investigator needed glargine treatment as standard-of-care were enrolled in the study. Enrolled patients are planned to receive Glaritus® once daily or Lantus® once daily for six months, both given subcutaneously. Glaritus® treatment arm is to be continued for another six months. Other details of study design are described in the protocol and first interim analysis published recently [8].

The primary endpoint was the percentage change in anti-insulin antibodies (AIA) titer to glargine in Glaritus® and Lantus® treatment arms from baseline to six months. The secondary endpoints were the change in HbA1c (%) from baseline to six months, safety assessment at six months in both treatment arms and change in AIA titer to glargine in Glaritus® treatment arm from baseline to 12 months. The study was approved by ethics committee at respective center and written informed consent was obtained from the patients before entering the study. The study is planned with two interim analyses. The first interim analysis planned after 100 subjects who completed their Visit 8 (6 months) assessments is published recently. This is a second interim analysis which was planned after at least 144 randomized subjects from all study sites had completed their Visit 8 (6 months) assessments.

2.1. Statistical Analysis

Descriptive statistics, namely, number of subjects (n), arithmetic mean, SD, median, interquartile range (IQR)

were presented for continuous data variables and for the baseline (Visit 2) and end of 6 months (Visit 8) and for the percentage change in AIA titer from baseline (Visit 2) to end of 6 months (Visit 8). The two-sided 95% confidence interval (CI) and p-value for the difference between treatments was calculated. The statistical significance of any treatment group difference in the distribution of continuous variables, such as AIA and HbA1c was analyzed using an analysis of covariance (ANCOVA) with treatment as main factor and baseline values as covariate. If the p-value was less than 0.05 then null hypothesis was rejected and inequality was concluded. Categorical data variables were summarized using the frequency count (n) and percentage (%) for each possible value.

The statistical significance of any treatment group difference in the distribution of variables, such as age, height, weight, BMI was analyzed using an independent t test.

The mITT population was used in the interim analysis to assess the efficacy and immunogenicity measurements for the first 144 subjects who have completed Visit 8 assessments. The safety population consisted of all subjects that received at least one dose of the study drug. The intent-to-treat (ITT) population consisted of all subjects included into the safety population and had at least one post-randomization assessment. The modified ITT (mITT) population is a subset of the ITT population and consisted of subjects who completed Visit 8 (six months of comparative phase) and had performed the AIA titer and HbA1c assessment.

3. Results

A total of 335 subjects were screened across 10 centers in India. Of these, 180 subjects who satisfied the study inclusion and exclusion criteria were enrolled in the study (90 subjects in each Glaritus® and Lantus® group). All randomized subjects received at least 1 dose of the assigned study treatment.

Eighty-four (93.3%) subjects in the Glaritus® group and 85 (94.4%) subjects in the Lantus® group had at least one post-randomization assessment and were included in the ITT population. While seventy-six (84.4%) subjects in the Glaritus® group and 68 (75.6%) subjects in the Lantus® group completed 6 months of study treatment (Visit 8) and were included in mITT population.

Twenty-eight of 180 randomized subjects discontinued the study within six months (i.e. before study Visit 8): 15(16.7%) in the Glaritus® group and 13(14.4%) in the Lantus® group. Study disposition is given in Figure 1.

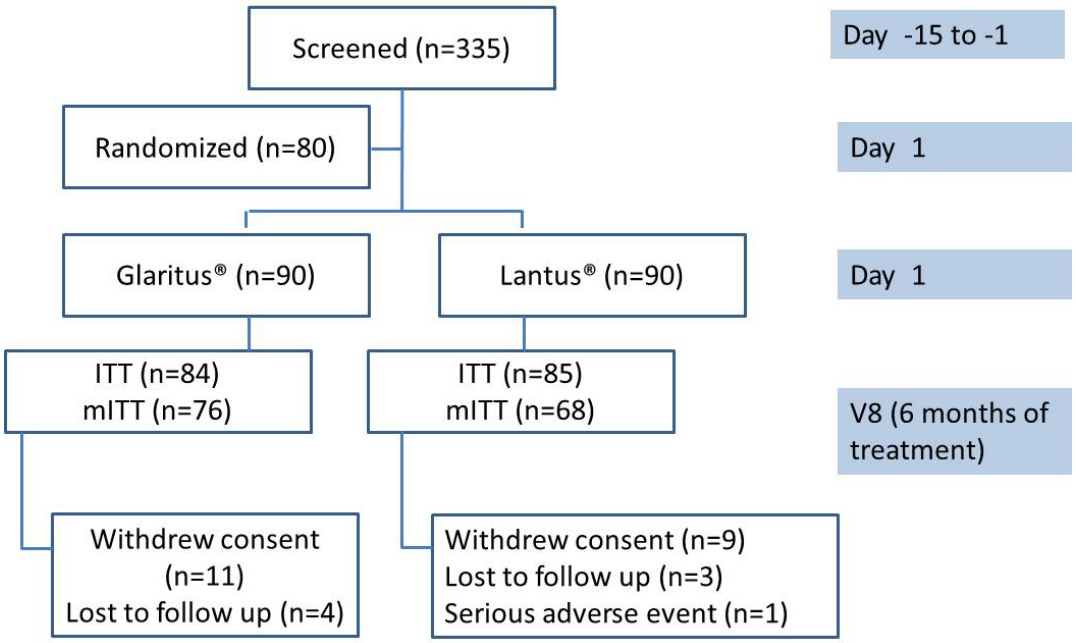


Figure 1. All subject disposition

3.1. Baseline Characteristics

Glaritus® treatment group was comparable to the Lantus® group in terms of age (p=0.4516; Table 1) and gender (p=0.5408; Table 1). Glaritus® treatment group was also comparable to Lantus® group in terms of height (p=1.0000), weight (p=0.9441) and body mass index (p=0.7163).

Overall, 37 (20.6%) subjects were receiving at least one medication within 15 days before first study treatment. The most common prior medications received by the subjects were oral antidiabetic agents [30 (16.7%) overall). Metformin [18 (10.0%)], glimepiride [14 (7.8%)], and glibenclamide [5 (2.8%)] were the most frequently used oral antidiabetic agents.

3.2. Efficacy Results

Immunogenicity analysis

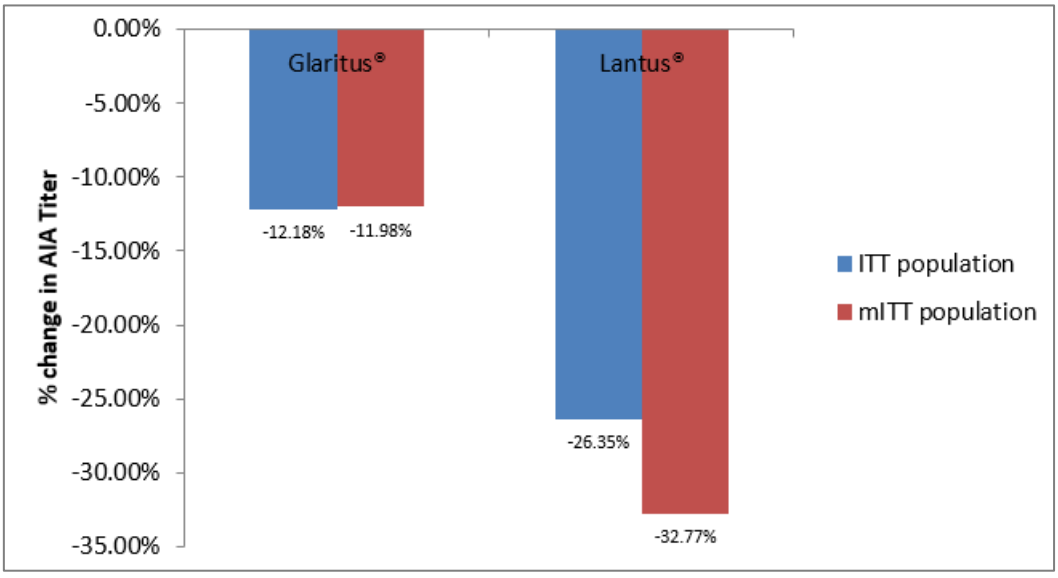
In the ITT population, the median (IQR) decrease in the AIA titer from baseline to six months was greater in Lantus® group [-13.95 (54.8)%] as compared to the Glaritus® group [-7.59 (42.9)%]. In the mITT population, the median (IQR) decrease in AIA titer was greater in Lantus® [-14.12 (45.9)%] as compared to the Glaritus® group [-7.13 (44.9)%].

Mean percentage change in AIA titer from baseline to visit 08 in ITT population and mITT population is shown in figure 2. There was no significant difference in percent change in the AIA titer between the two treatment groups at the end of six months in ITT and mITT population (LS mean diff [95% CI]: 2.2% (-15.1%, 19.6%), p=0.7987 and 3.4% (-15.1%, 21.9%), p=0.7181, respectively) (Figure 2 and Table 2: Percentage change in AIA titer -ITT population Table 3: Percentage change in AIA titer -mITT population).

Table 1. Demographic characteristics

Characteristic (Unit)	Statistics	Glaritus® (N = 90)	Lantus® (N = 90)	Total (N = 180)	P-value
Age (Years)	n	90	90	180	0.4516
	Mean (SD)	46.8 (7.13)	46.8 (5.88)	46.8 (6.52)	
	Median	48.0	47.5	48.0	
	Min, Max	24.0, 55.0	27.0, 55.0	24.0, 55.0	
Gender	n (%)				0.5408
Male		53 (58.9)	57 (63.3)	110 (61.1)	
Female		37 (41.1)	33 (36.7)	70 (38.9)	

N=number of subjects in randomized population in the respective treatment groups; n=number of subjects in the respective treatment groups in safety population



AIA= anti-insulin antibodies; ITT=intent to treat mITT=modified intent to treat

Figure 2. Percentage change in AIA titer from baseline to 6 months

Table 2. Percentage change in AIA titer (ITT population)

Parameter	Visit	Statistics	Glaritus® (N = 84)	Lantus® (N = 85)	Total (N = 169)
AIA Titer	Visit 01: Screening	N	84	85	169
		Mean (SD)	2.91 (3.012)	2.81 (2.922)	2.86 (2.959)
		Median	3.05	3.20	3.10
		IQR	2.0	1.5	1.6
	Visit 05: End of Month 3	N	72	76	148
		Mean (SD)	2.95 (3.124)	2.27 (3.042)	2.60 (3.090)
		Median	2.80	2.90	2.90
		IQR	1.5	1.2	1.3
	Visit 08: End of Month 6	N	77	71	148
		Mean (SD)	2.94 (3.573)	2.81 (3.871)	2.88 (3.707)
		Median	2.80	2.80	2.80
		IQR	1.6	1.4	1.5

AIA= anti-insulin antibodies, IQR=interquartile range, ITT=intent to treat, N = number of subjects in randomized population in respective treatment group; n=number of subjects in respective treatment group in ITT population with AIA titer, SD=standard deviation

Table 3. Percentage change in AIA titer (mITT population)

Parameter	Visit	Statistics	Glaritus® (N = 76)	Lantus® (N = 68)	Total (N = 144)
AIA Titer	Visit 01: Screening	N	76	68	144
		Mean (SD)	2.75 (3.061)	2.67 (2.948)	2.71 (2.998)
		Median	3.00	3.20	3.05
		IQR	1.8	1.5	1.5
	Visit 05: End of Month 3	N	68	66	134
		Mean (SD)	2.76 (2.942)	2.00 (3.071)	2.38 (3.019)
		Median	2.70	2.80	2.75
		IQR	1.5	1.2	1.3
	Visit 08: End of Month 6	N	76	68	144
		Mean (SD)	2.95 (3.596)	2.71 (3.872)	2.84 (3.718)
		Median	2.80	2.80	2.80
		IQR	1.8	1.5	1.6

AIA= anti-insulin antibodies, IQR=interquartile range, mITT= modified intent to treat, N = number of subjects in randomized population in respective treatment group; n=number of subjects in respective treatment group in mITT population with AIA titer, SD=standard deviation

Percentage decrease in HbA1c

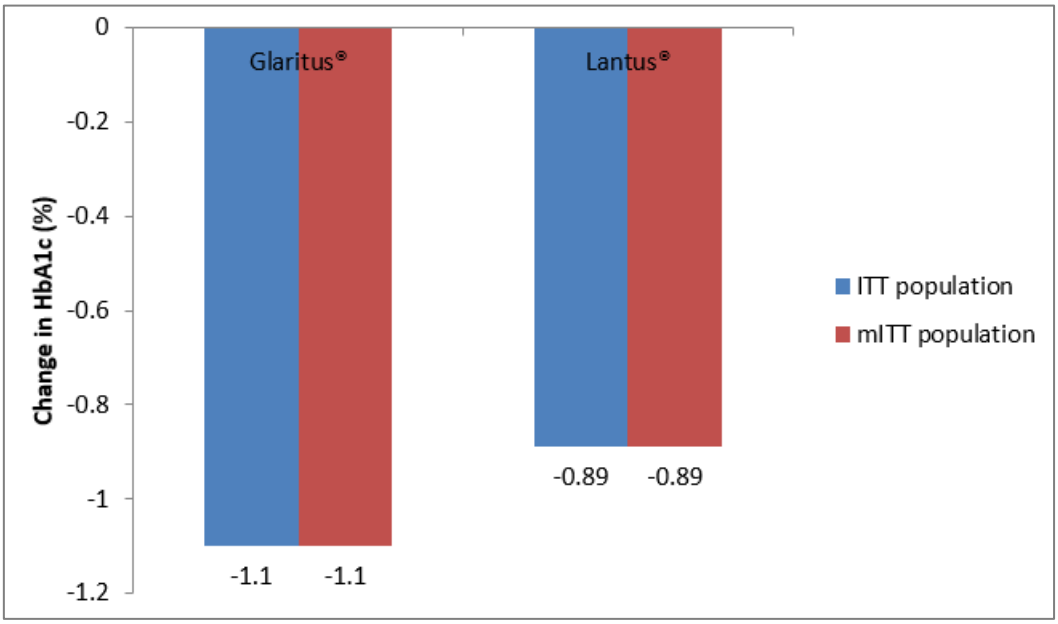
The overall mean (SD) HbA1c at the screening was 9.06 (0.574) %. It decreased over six months by a mean (SD) of 1.00 (1.283) %.

In the ITT population, the overall median (IQR) HbA1c decreased by 1.00% from baseline to six months. The median (IQR) decrease was greater in Glaritus® group [-1.20 (1.5)%] as compared to the Lantus® group [-1.00 (1.6)%].

In the mITT population also, the overall median (IQR) HbA1c decreased by 1.00% from baseline to six months. The median (IQR) decrease was greater in Glaritus® group [-1.20 (1.5)%] as compared to the Lantus® group

[-1.00 (1.6)%]. Change in HbA1c in ITT population and mITT population from baseline to visit 8 is shown in figure 3.

There was no significant difference in change in the HbA1c level at the end of six months, between the two treatment groups in ITT and mITT population [LS mean diff (95% CI): -0.2 (-0.4, 0.0), p=0.1072 for ITT population; and -0.1 (-0.3, 0.1), p=0.2283, for mITT population; Table 4 and 5]. Further, in line with the assumption of the non-inferiority margin in sample size calculation, upper margin of the 95% CI for both ITT and mITT populations is lower than 0.4% establishing non-inferiority of Glaritus® with Lantus® in terms of efficacy.



ITT=intent to treat mITT=modified intent to treat

Figure 3. Change in HbA1c in ITT population and mITT population from baseline to 6 months

Table 4. Change in HbA1c (ITT population)

Parameter	Visit	Statistics	Glaritus® (N = 84)	Lantus® (N = 85)	Total (N = 169)
HbA1c	Visit 01: Screening	N	84	85	169
		Mean (SD)	9.04 (0.604)	9.05 (0.534)	9.05 (0.569)
		Median	8.95	9.10	9.10
		IQR	1.1	0.9	0.9
	Visit 05: End of Month 3	N	72	76	148
		Mean (SD)	8.00 (1.205)	8.26 (1.118)	8.13 (1.165)
		Median	7.75	8.15	8.00
		IQR	1.3	1.6	1.5
	Visit 08: End of Month 6	N	76	68	144
		Mean (SD)	7.93 (1.283)	8.15 (1.140)	8.03 (1.219)
		Median	7.70	8.10	8.00
		IQR	1.6	1.2	1.2

HbA1c= glycated hemoglobin; ITT=intent to treat; IQR=interquartile range; N = number of subjects in randomized population in the respective treatment group; n=number of subjects in the respective treatment group in ITT population with HbA1c level; SD=standard deviation

Table 5. Change in HbA1c (mITT population)

Parameter	Visit	Statistics	Glaritus® (N = 76)	Lantus® (N = 68)	Total (N = 144)
HbA1c	Visit 01: Screening	N	76	68	144
		Mean (SD)	9.03 (0.624)	9.04 (0.519)	9.03 (0.575)
		Median	8.90	9.10	9.10
		IQR	1.2	0.8	0.9
	Visit 05: End of Month 3	N	68	66	134
		Mean (SD)	7.95 (1.134)	8.13 (0.972)	8.04 (1.057)
		Median	7.70	8.05	7.90
		IQR	1.3	1.3	1.4
	Visit 08: End of Month 6	N	76	68	144
		Mean (SD)	7.93 (1.283)	8.15 (1.140)	8.03 (1.219)
		Median	7.70	8.10	8.00
		IQR	1.6	1.2	1.2

HbA1c= glycated hemoglobin; IQR=interquartile range; mITT=modified intent to treat; N = number of subjects in randomized population in the respective treatment group; n=number of subjects in the respective treatment group in mITT population with HbA1c level; SD=standard deviation

The overall mean (SD) of estimated average glucose at the screening was 213.18 (16.481) mg/dL. It decreased over six months by a mean (SD) of 28.56 (36.821) mg/dL. The mean (SD) decrease was numerically greater in the Glaritus® group [31.68 (37.937) mg/dL] as compared to the Lantus® group [25.17 (35.529) mg/dL].

Overall, 171 (95.0%) subjects received at least one concomitant medication during the six months of the study. The most frequently used concomitant medications were oral antidiabetic agents [167 (92.8%)], Metformin [87 (48.3%)], glimepiride [68 (37.8%)], glimepiride/metformin [28 (15.6%)], pioglitazone [27 (15%)] and teneligliptin [23 (12.8%)]. Lipid-modifying agents were used concomitant to study treatment in 63 (35.0%) patients and agents acting on renin-angiotensin system were prescribed to 45 (25.0%) patients.

3.3. Safety Analysis

A total of 37 (20.6%) subjects experienced at least one AE through six months of treatment without any significant difference between the two treatment groups [Glaritus® group 17 (18.9%) and Lantus® group 20 (22.2%) p=0.5800]. AEs in two patients (one each in Glaritus® group and in Lantus® group) were moderate in severity. No deaths were reported in the study.

Two serious AEs (myocardial ischemia and renal colic, respectively) were reported in 2 subjects of the Lantus® group. None of the SAEs (Spontaneous adverse events) were related to study treatment and both were resolved. The SAE (Spontaneous adverse events) of renal colic was mild in intensity and unlikely to be related to the study treatment. However, the study drug and the subject was withdrawn due to this event. The SAE (Spontaneous adverse events) of myocardial ischemia was severe in intensity and unlikely to be related to the study treatment. No action was taken with study treatment due to this event.

Adverse events in two (2.2%) patients in Glaritus® group were considered probably related and none of the AEs in Lantus® group were considered related to study treatment. Adverse events in most of the subjects (32/37) were resolved.

A total of six hypoglycemic episodes were reported in 5 (2.8%) patients without any significant difference between the two treatment groups (1.1% in the Glaritus® group vs 4.4% subjects in the Lantus® group; p=0.3680; p=0.3680). The mean number of hypoglycemia events per subject was 0.01 in the Glaritus® group and 0.06 in the Lantus® group. None of the hypoglycemic events met the SAE (Spontaneous adverse events) criteria and all of them recovered with intake of food or drink.

There was no clinically significant difference in clinical and other laboratory parameters. Clinically significant rise in blood pressure was observed in one patient in each group.

4. Discussion

Insulin glargine is a long-acting, human insulin analogue administered once daily that results in relatively constant basal level of circulating insulin. It is useful to achieve target blood glucose levels more effectively compared with NPH (Neutral Protamine Hagedorn) insulin with lesser risk of hypoglycaemia [17]. Several studies [18-21] have evaluated efficacy and safety of insulin

glargine in patients with diabetes. The GALAPAGOS study compared insulin glargine versus premixed insulin in insulin-naïve T2DM patients uncontrolled on oral antidiabetic drugs [18]. In this study, both groups showed similar rates of well-controlled patients without hypoglycemia. The rate of overall symptomatic hypoglycemia was lesser with glargine. Another 24-week, international, multicenter randomized study [19] among insulin-naive patients with poor glycemic control with sulfonylurea plus metformin compared once-daily insulin glargine plus glimepiride and metformin versus 30% regular/ 70% human NPH (Neutral Protamine Hagedorn) insulin twice daily without oral agent. Basal insulin glargine group was more effective than twice-daily NPH (Neutral Protamine Hagedorn) insulin without oral agent [19]. In a study from India [20], insulin glargine has been shown to be effective in reducing glycaemia in patients with uncontrolled T2DM on one or two- oral antihyperglycemic agents. Cost of insulin therapy is one of the important concerns in the management of diabetes. Strategies to lower the treatment costs are welcomed by everyone. In this regards, biosimilars can play a signigicant role for reducing cost of insulin therapy [22]. However, differences in the manufacturing process of biosimilar insulin may result in insulin slightly different than that of originator insulin. An important question may arise in such cases if such small changes in the structure and purity are relevant in clinical practice [23]. The answer for this question can only be answered by conducting well designed clinical trials. Glaritus® has been shown to be bioequivalent with Lantus® in healthy subjects [7]. Similarly, in adult patients with type 1 diabetes mellitus, it was found to be comparable to Lantus® for glycemic control [6]. An ongoing prospective study compares Glaritus® with Lantus® in patients with type 2 diabetes mellitus. Results of the first interim analysis of the same have recently been published [8].

In this article, we presented the results of second interim analysis. A total of 180 patients were randomized of which 152 completed the study till the time of second interim analysis.

In the mITT population of first interim analysis, AIA was reduced by 10.52% in the Glaritus® group and increased by 0.48% in the Lantus® group [8]. In the current analysis, in the mITT population, the median (IQR) and mean decrease in AIA titer was greater in Lantus® than in the Glaritus® group, without significant difference in percent change in the AIA titer between the two treatment groups. Similar results were observed in ITT population. Overall, Glaritus® similar immunogenicity as that of Lantus®.

In the first interim analysis, in the mITT population, HbA1c reduction was 1.09% in the Glaritus® group as compared to 0.63% in the Lantus® group [8]. In this second interim analysis, the median (IQR) as well as decrease in HbA1c was greater in Glaritus®group. Howeer, the difference was not statistically significant. The results suggests Glaritus® provides similar efficacy as that of Lantus®.

At the time of the second interim analysis, one subjects in the Glaritus® group and four in the Lantus® group were reported to have hypoglycemic events. Overall incidence of adverse events were 18.9% and 22.2% respectively. The difference between two groups was not significant, indicating similar tolerability profile of both insulin formulation.

This study had significant insights about the immunogenicity, tolerability and efficacy of Glaritus®, a biosimilar of insulin glargine in patients with T2DM. Overall results suggest no significant difference in terms of immunogenicity, reduction in HbA1c and tolerability profile of Glaritus® and Lantus® groups.

4.1. Clinical Implications

There is steady increase in the number of patients on insulin.[22]However, despite the known efficacy, insulin usage is associated with poor adherence. One of the reasons for missing doses or poor adherence to insulin is cost. High cost of insulin is a concern for people with diabetes not only in India but in the USA [24-26] and Europe [22]. More than 25% people compromise their insulin therapy because of cost related concerns [25]. Poor compliance to insulin therapy can result in poor glycemic control and diabetes related complications. In such a scenario, biosimilars can reduce the cost of insulin therapy. Biosimilar insulin glargine can be a cost effective option to the the innovator insulin analogues when there are rising conserns about the cost of the insulin not only in developing countries like India but also globally.

4.2. Limitations and Future Scope

The study was open-label in design and the patients also received oral hypoglycemic agents in addition to their insulin regimen which might interfere with the study results. Contribution of these agents in the efficacy i.e. reduction in HbA1c of both insulin regimens should also be considered. The long-term immunogenicity, efficacy, and safety of Glaritus® for up to 12 months in T2DM patients will be available at the end of the trial which will provide much awaited essential data of the biosimilar Glaritus® to further support its clinical interchangeability.

5. Conclusions

Glaritus® and Lantus® both reduced HbA1c and AIA levels with a low incidence of hypoglycemic events and other AEs over six months treatment. Glaritus® was non-inferior to Lantus® in terms of HbA1c reduction and comparable in terms of immunogenic response, hypoglycemic events, and other AEs over six months of

treatment in patients with T2DM uncontrolled on OADs.

Conflict of Interest

None

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