

# Immunogenicity, Safety and Efficacy Comparison of Wockhardt's Biosimilar Insulin Glargine—Glaritus® with Reference Product—Lantus®: Study Protocol & Early Data Trends

S. K. Sharma<sup>1</sup>, A. K. Ajmani<sup>2</sup>, P. Khosla<sup>3</sup>, P. Mukhopadhyay<sup>4</sup>, G. Bhatia<sup>5</sup>, K. G. Prakash<sup>6</sup>, G. Chhaya<sup>7</sup>, P. D. Supe<sup>8</sup>, V. Pavithran<sup>9</sup>, H. Bora<sup>10</sup>, R. Jain<sup>11</sup>, S. Ingole<sup>11</sup>, A. Shah<sup>11</sup>

<sup>1</sup>Diabetes, Thyroid and Endocrine Centre, Jaipur, India

<sup>2</sup>BL Kapoor Hospital, Delhi, India

<sup>3</sup>Sir Ganga Ram Hospital, Delhi, India

<sup>4</sup>Institute of Post Graduate Medical Education and Research, Kolkata, India

<sup>5</sup>Medipoint Hospitals Pvt. Ltd., Pune, India

<sup>6</sup>Bangalore Medical College and Research Institute, Bangalore, India

<sup>7</sup>Sanjivani Supers PECIALITY Hospital, Ahmedabad, India

<sup>8</sup>Supe Heart and Diabetes Hospital and Research Centre, Nashik, India

<sup>9</sup>KVM Hospital, Kerala, India

<sup>10</sup>Downtown Hospital, Guwahati, India

<sup>11</sup>Wockhardt Ltd., Mumbai, India

Email: [singole@wockhardt.com](mailto:singole@wockhardt.com)

**How to cite this paper:** Sharma, S.K., Ajmani, A.K., Khosla, P., Mukhopadhyay, P., Bhatia, G., Prakash, K.G., Chhaya, G., Supe, P.D., Pavithran, V., Bora, H., Jain, R., Ingole, S. and Shah, A. (2018) Immunogenicity, Safety and Efficacy Comparison of Wockhardt's Biosimilar Insulin Glargine—Glaritus® with Reference Product—Lantus®: Study Protocol & Early Data Trends. *Open Journal of Endocrine and Metabolic Diseases*, 8, 157-166.

<https://doi.org/10.4236/ojemd.2018.88016>

**Received:** July 15, 2018

**Accepted:** August 27, 2018

**Published:** August 30, 2018

## Abstract

**Objective:** Present Phase IV Trial is aimed at evaluating the immunogenicity, safety, and efficacy of Wockhardt's insulin glargine, Glaritus® in comparison with reference insulin glargine, Lantus® in subjects with type 2 diabetes mellitus (T2DM), inadequately controlled on oral hypoglycaemics. **Setting:** A head-to-head, prospective, open-label, parallel group, randomized, Phase IV, non-inferiority study over 6 months treatment conducted in 10 centres in India. **Participants:** Considering 20% drop-out rate, 180 subjects of either sex, age 18 - 55 years, diagnosed with T2DM with body mass index (BMI) 18 - 38 kg/m<sup>2</sup> and HbA1c levels 8.0% - 10.0% inadequately controlled by 1 or more oral hypoglycaemics and according to investigator needed glargine treatment were enrolled in the study. **Interventions:** Subjects self-administered insulin glargine (Glaritus® or Lantus®) subcutaneously once daily for 6 months. Treatment in Glaritus® arm was continued till 12 months. Percentage change in anti-insulin antibody (AIA) titre and HbA1C was ascertained at every 3 months interval. The tests were performed at accredited central laboratory.

Copyright © 2018 by authors and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0). <http://creativecommons.org/licenses/by/4.0/>



Open Access

**Treat-to-target dose titration:** Starting doses of Glaritus® and Lantus® was 10 units (or 0.2 units/kg) once daily. The target fasting blood glucose was 70 to 130 mg/dL. Daily glargine dose was titrated by  $\pm 10\%$  based on average of last 3 FBG values being out of target range and presence of nocturnal hypoglycemia. **Early data trends:** First interim analysis was planned once 100 subjects complete visit 8 (6 months treatment). By then, 119 subjects (78 males and 41 females) with mean age 46.3 years were enrolled, of which 90 (75.6%) subjects had evaluable data. The results of analysis indicated trend of comparability between Glaritus® and Lantus® at the end of 6 months in terms of immunogenicity (% change in AIA titre from baseline,  $-10.52 \pm 23.06$  vs.  $0.48 \pm 63.95$ ), glycemic control (change in HbA1c from baseline,  $-1.09\% \pm 1.29\%$  vs.  $0.63\% \pm 1.19\%$ ) and hypoglycemic events (reported by 1 vs. 2 patients), respectively. **Conclusion:** The present study represents a robust design in line with international guidelines on biosimilar insulin development and the early data trends presents expected similarity of Glaritus® in immunogenicity, efficacy and safety to that of Lantus® in treatment of T2DM.

## Keywords

Insulin Antibodies, Immunogenicity, Insulin Glargine, Biosimilar, HbA1c

## 1. Introduction

The diabetic population of India increased from 26 million in 1990 to 65 million in 2016 with increase of age-standardised disability adjusted life years rate for diabetes by 39.6% over the same period [1]. There were 1.2 million deaths (14.2% of all adult deaths) reported attributed to complications of diabetes from India during the year 2013 [2]. Recently updated WHO guidelines suggest that human insulin treatment shall be introduced in patients with type 2 diabetes mellitus (T2DM), who do not achieve glycemic control with metformin and/or sulfonylurea [2]. The DiabCare 2011 Study reported that 35.2% patients of T2DM in India are being managed with insulin with or without oral antidiabetics [2]. The “treat-to-target” (TTT) clinical trials established that the addition of basal insulin to existing oral glucose-lowering therapy achieves good glycaemic control in T2DM patients [3] [4] [5].

Unfortunately, many patients with T2DM are unable to achieve the American Diabetes Association guideline-recommended glycosylated hemoglobin (HbA1c) level of  $<7\%$  [6] [7]. Stringent glycemic control is typically associated with an increased risk of hypoglycaemia [8] in patients with T2DM [9] [10]. Basal insulins provide constant insulin activity over 24 h with only a single injection thereby improving fasting glycemic control, without an increased risk of hypoglycemia. The published literature supports early and timely basal insulin initiation as it improves FPG control and beta-cell function when compared to prolonged continuation of Oral Antidiabetic Drugs (OADs) [11]. Further, in T2DM, insu-

lin glargine provides comparable glycemic control to that with neutral protamine Hagedorn (NPH) insulin with fewer severe hypoglycemic events (odds ratio 0.65, 95% CI 0.49 to 0.88) [3].

Lantus® was the first long acting basal insulin analogue, insulin glargine manufactured by recombinant DNA technology. It was approved by the US FDA and European EMA in 2000 for use in type 1 and type 2 diabetes mellitus [12] [13]. Glaritus® is a biosimilar insulin glargine manufactured by Wockhardt with an identical primary amino acid sequence as Lantus®. Glaritus® is registered and marketed in India since August 2007, in Nepal, Peru, and Vietnam since August 2010, and in Myanmar since November 2011 for the same indications as that of Lantus® [14].

As a part of physico-chemical-biological comparability exercise, Glaritus® was found comparable to Lantus® in *in-vitro* pharmacodynamics studies (receptor binding, receptor autophosphorylation and metabolic assays like glucose uptake and inhibition of lipolysis), *in-vivo* pharmacodynamics studies (hypoglycaemic potency studies in rodents and dogs) and sub chronic toxicity studies (in rodents including toxicokinetics and immunogenicity) [15]. In terms of human pharmacokinetics and pharmacodynamics, Glaritus® was found bioequivalent to Lantus® in 40 healthy volunteers [16] and 111 type 1 diabetics [17] under 24 hours euglycemic clamp settings glucose lowering effect and insulin glargine exposure.

The present study is the first Indian Phase IV Trial on biosimilar insulin glargine that is designed considering international guidelines such as from EMA [18] & USFDA [19] with “treat to target” strategy for study treatment.

## 2. Background and Rationale

Anti-insulin antibody (AIAs) can potentially alter insulin pharmacokinetics and pharmacodynamics in patients treated with modern, genetically engineered insulin analogues [20]. Such patients may present with insulin resistance, because AIAs not only bind to and sequester acutely administered insulin, but are also a source of long-acting bioavailable insulin, since insulin dissociates from these complexes in the fasting state [21]. Recently, the prevalence and levels of AIAs have remarkably decreased because of the purity of insulin preparations and the use of recombinant human insulin preparations [22], but it has not been completely eliminated. Multiple sporadic case reports have been published reporting high titre serum AIAs while being treated with recombinant human insulin or human insulin analogues, especially in Asian populations [23]-[30].

In phase IV study in 161 type 1 diabetics, Glaritus® was found comparable to Lantus® in terms of glycemic control (mean reduction in HbA1c from baseline  $0.69\% \pm 1.81\%$  vs.  $0.53\% \pm 1.94\%$ , respectively;  $P = 0.454$ ), incidence of hypoglycaemia (27.2% vs. 28.6%,  $P = 0.8432$ ) and immunogenicity (mean reduction in AIA from baseline  $0.25 \pm 0.97$  vs.  $0.02 \pm 0.68$ , respectively;  $P = 0.306$ ) over 12 weeks of treatment [31].

The proposed protocol was developed in line with following international guidelines:

EMA guidance [20] states that immunogenicity study duration should be at least 12 months, including a comparative phase of at least 6 months, but there is no need to power the study to formally demonstrate non-inferiority regarding immunogenicity.

USFDA guidance [32] states that assessment of the immunogenic potential of insulins and insulin analogues should be performed over a period of at least 6 to 12 months. Further, it states that reduction in HbA1c should be considered for demonstration of efficacy with non-inferiority design and non-inferiority margin of 0.3 or 0.4 HbA1c percentage units.

### 3. Objectives

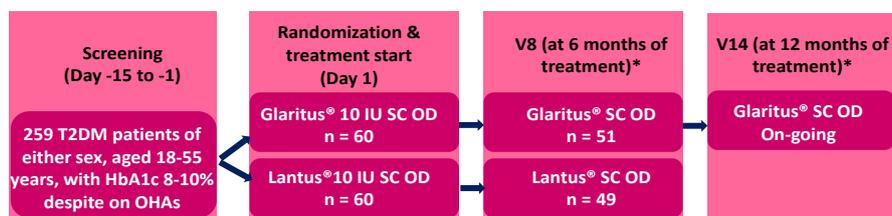
Primary objective of this study is to evaluate the change in immunogenic response (measured as percentage change in AIA using a quantitative ELISA test) to glargine in Glaritus® and Lantus® treatment arms from baseline to 6 months. The secondary objectives are to 1) evaluate the change in immunogenic response to glargine in Glaritus® treatment arm from baseline to 12 months; 2) assess and compare efficacy in both treatment arms at 6 months in terms of change in HbA1c from baseline; and 3) assess and compare subjects' safety in both treatment arms in terms of adverse events (including hypoglycaemia events). Further, an exploratory endpoint of assessing efficacy in Glaritus® treatment arm at 12 months in terms of change in HbA1c from baseline has also been included to judge sustenance or further improvement of glycaemic control obtained at 6 months.

## 4. Material and Method

### 4.1. Study Design

This is a prospective, open-label, randomized, active-controlled, non-inferiority, parallel-group, multi-centre, Phase IV study conducted in 180 subjects who had inadequately controlled T2DM with use of oral hypoglycaemic agents (OHAs). The study design is shown in **Figure 1**.

The study included a screening phase (maximum 2 weeks), treatment phase (12 months for Glaritus® arm and 6 months for Lantus® arm) and a follow-up phase (1 month for both arms as consensual supply). After providing a written informed consent for participation in the study, subjects underwent screening phase, which included recording of subject's demographic characteristics and medical history, assessment of vital signs, physical examination, laboratory tests, including urine pregnancy test, and 12-lead electrocardiogram (ECG). The treatment phase started at 10 units (or 0.2 units/kg) once daily on Day 1 (Visit 2) immediately following randomization of subjects to 2 treatment arms in a 1:1 ratio by an interactive web response system. After Visit 8, in the Lantus® arm 1-month supply of the same is being provided for compassionate use followed by



**Figure 1.** Study design. \*Dose was subsequently titrated based on the subject's FBG.

Visit 9, which will constitute the end-of-study. After Visit 14, 1-month supply of the same is being provided for compassionate use followed by Visit 15, which will constitute the end-of-study.

The laboratory tests were performed by the central laboratory (Metropolis Healthcare Ltd., Mumbai). The trial was registered at Clinical Trial Registry of India before enrolment of first subject with no. CTRI/2015/05/005808 on 25/05/2015. Study was initiated on each site only after approval of institutional ethics committee and approval of Drug Controller General (India). Written informed consent was obtained from each study subject before starting any study related activities with them.

#### 4.2. Duration of Treatment

In line with the EMA and USFDA guidance, comparative phase consisting of parallel treatment arms were considered for 6 months followed by continuation of only Glartitus® arm further till 12 months. Considering 1 additional month of consensual supply, the total duration of the study was expected to be approximately 410 days for subjects in the Glartitus® arm and approximately 225 days for subjects in the Lantus® arm.

#### 4.3. Dosing

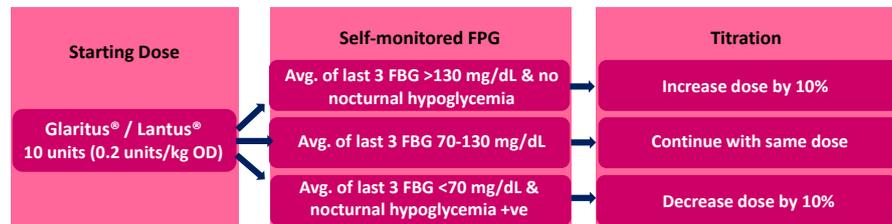
The study utilizes treat-to-target (TTT) strategy for insulin dose titration endorsed by the FDA as a means of evaluating the different insulins' therapeutic potential. The starting doses of Glartitus® and Lantus® were recommended to be 10 units (or 0.2 units/kg) once daily, which had to be subsequently titrated based on the subject's FBG (target FBG 70 to 130 mg/dL). Dose was titrated based on the average 3 FBG levels recorded by the subject using a glucometer and history of nocturnal hypoglycaemia. The dose titration algorithm is shown in **Figure 2**.

#### 4.4. Concomitant Antidiabetics

Investigators are permitted to use any medication concomitantly as per their discretion and as per standard of medical care. However, details of all such concomitant drugs were recorded in CRF from 15 days prior to first dose of study treatment till end of the same.

#### 4.5. Patients

Male or female subjects,  $\geq 18$  and  $\leq 55$  years of age, with uncontrolled T2DM were enrolled in the study. Additionally, subjects were to have the body mass



**Figure 2.** Dose titration.

index (BMI)  $\geq 18.0$  and  $\leq 38.0$  kg/m<sup>2</sup> and HbA1c levels  $\geq 8.0\%$  and  $\leq 10.0\%$ . Subjects had to be insulin-naïve or had received insulin for short term ( $\leq 2$  weeks) only and  $\geq 6$  months prior to enrolment. Subjects had to be inadequately controlled by 1 or more OHAs and according to investigator needed glargine treatment as standard-of-care. Subjects had to be able to use the self-glucose-monitoring device and to self-administer insulin and willing to record the daily FBG values and the insulin dose in a subject diary. Schematic representation of the patient flow is given in **Figure 3**.

#### 4.6. Data Analysis and Statistical Considerations

Considering the estimated difference in mean changes in HbA1c for Glaritus® versus Lantus® as 0 and a non-inferiority margin fixed at 0.4, at level of significance alpha at 0.025 with power of 80%, 72 completers are required in each treatment arm. Considering drop-out rate of 10%, initial sample size was calculated at 160, which was subsequently revised based on high drop-out rate of 20% to 180.

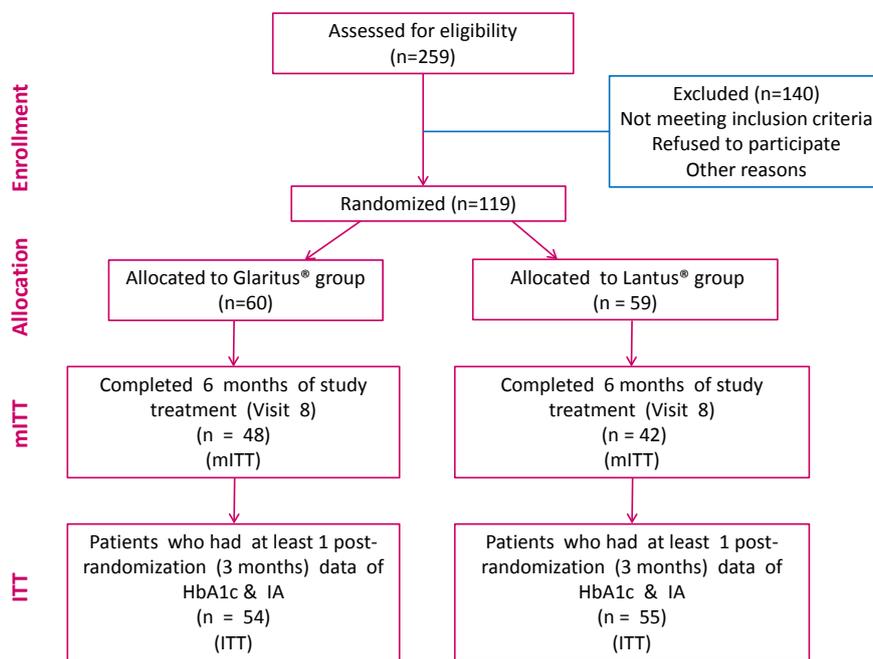
This interim analysis was undertaken after 100 subjects have completed their visit 8 (6 months treatment) needed for assessment of primary objective across 10 centres. Further, second interim analysis was added once the required number of completers (144) completed their visit 8 to analyse the comparative phase data. Final analysis would be done once Glaritus® arm also completes their study treatment.

The statistical evaluations will be performed using SAS®, version 9.2 or later. For change in AIA and HbA1c at 6 months from baseline, two-sided 95% confidence interval (CI) and p-value for the difference between treatments will be calculated using an analysis of covariance (ANCOVA) with treatment as main factor and baseline values as covariate. The Cochran-Mantel-Haenzel test stratified by (pooled) center will be used to test for differences in the overall incidence of hypoglycaemia.

For the interim analysis, the results for the immunogenicity, efficacy, and safety are presented by descriptive statistics.

### 5. Early Data Trends

From July 2015 to November 2017, 180 patients have been enrolled in the study. Last (100<sup>th</sup>) subject completed visit 8 in March 2017 and interim analysis of the data was completed in July 2017. Both treatment groups were comparable in



**Figure 3.** Patient flow.

demographic characteristics and baseline parameters. Trend of similarity was observed between Glaritus® and Lantus® in the data analysed as follows:

- For mITT population, AIA decreased in the Glaritus® group by  $10.52\% \pm 23.06\%$ , whereas, it increased by  $0.48\% \pm 63.95\%$  in the Lantus® group
- For mITT population, HbA1c reduction was  $1.09\% \pm 1.29\%$  in the Glaritus® group as compared to  $0.63\% \pm 1.19\%$  in the Lantus® group
- Hypoglycaemic episodes were reported in 1 subject in the Glaritus® group and 2 subjects in the Lantus® group
- Adverse events were observed in 8/60 subjects (13.3%) in the Glaritus® group and 9/59 subjects (15.3%) in the Lantus® group

## 6. Conclusion

Glaritus® has shown comparable efficacy and safety to Lantus® in the pre-clinical as well as clinical studies conducted so far. The present study represents a randomised, controlled design in line with international guidelines on biosimilar insulin glargine development with assessment of immunogenicity, glycaemic control, hypoglycaemic events and other adverse events in a comparative phase for 6 months and in a single arm phase for another 6 months thereafter. Further, the early data trends from first interim analysis presents expected similarity of Glaritus® in immunogenicity, efficacy and safety to that of Lantus® in treatment of T2DM.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

- [1] India State-Level Disease Burden Initiative Diabetes Collaborators (2018) The Increasing Burden of Diabetes and Variations among the States of India: the Global Burden of Disease Study 1990-2016. *The Lancet Global Health*, **6**, PE1352-E1362. [https://doi.org/10.1016/S2214-109X\(18\)30387-5](https://doi.org/10.1016/S2214-109X(18)30387-5)
- [2] Mohan, V., Shah, S.N., Joshi, S.R., Seshiah, V., Sahay, B.K., Banerjee, S., *et al.* (2014) Current Status of Management, Control, Complications and Psychosocial Aspects of Patients with Diabetes in India: Results from the Diabcare India 2011 Study. *Indian Journal of Endocrinology and Metabolism*, **18**, 370-378. <https://doi.org/10.4103/2230-8210.129715>
- [3] Riddle, M.C., Rosenstock, J. and Gerich, J. (2003) The Treat-to-Target Trial: Randomized Addition of Glargine or Human NPH Insulin to Oral Therapy of Type 2 Diabetic Patients. *Diabetes Care*, **26**, 3080-3086. <https://doi.org/10.2337/diacare.26.11.3080>
- [4] Hermansen, K., Davies, M., Derezinski, T., Martinez Ravn, G., Clauson, P. and Home, P. (2006) On Behalf of the Levemir Treat-to-Target Study Group. A 26-Week, Randomized, Parallel, Treat-to-Target Trial Comparing Insulin Detemir with NPH Insulin as Add-On Therapy to Oral Glucose-Lowering Drugs in Insulin-Naive People with Type 2 Diabetes. *Diabetes Care*, **29**, 1269-1274. <https://doi.org/10.2337/dc05-1365>
- [5] Rosenstock, J., Davies, M., Home, P., Larsen, J., Koenen, C. and Schernthaner, G. (2008) A Randomised, 52-Week, Treat-to-Target Trial Comparing Insulin Detemir with Insulin Glargine when Administered as Add-On to Glucose-Lowering Drugs in Insulin-Naive People with Type 2 Diabetes. *Diabetologia*, **51**, 408-416. <https://doi.org/10.1007/s00125-007-0911-x>
- [6] Nathan, D.M., Cleary, P.A., Backlund, J.Y., Genuth, S.M., Lachin, J.M., Orchard, T.J., *et al.* (2005) Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *The New England Journal of Medicine*, **353**, 2643-2453. <https://doi.org/10.1056/NEJMoa052187>
- [7] Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group (2002) Effect of Intensive Therapy on the Microvascular Complications of Type 1 Diabetes Mellitus. *JAMA*, **287**, 2563-2569. <https://doi.org/10.1001/jama.287.19.2563>
- [8] Mattila, T.K. and de Boer, A. (2010) Influence of Intensive Versus Conventional Glucose Control on Microvascular and Macrovascular Complications in Type 1 and 2 Diabetes Mellitus. *Drugs*, **70**, 2229-2245. <https://doi.org/10.2165/11585220-000000000-00000>
- [9] Zoungas, S., Patel, A., Chalmers, J., de Galan, B.E., Li, Q., Billot, L., *et al.* (2010) Severe Hypoglycemia and Risks of Vascular Events and Death. *The New England Journal of Medicine*, **363**, 1410-1418. <https://doi.org/10.1056/NEJMoa1003795>
- [10] Hsu, P.F., Sung, S.H., Cheng, H.M., Yeh, J.S., Liu, W.L., Chan, W.L., *et al.* (2013) Association of Clinical Symptomatic Hypoglycemia with Cardiovascular Events and Total Mortality in Type 2 Diabetes: A Nationwide Population-Based Study. *Diabetes Care*, **36**, 894-900. <https://doi.org/10.2337/dc12-0916>
- [11] Pistrosch, F., Köhler, C., Schaper, F., Landgraf, W., Forst, T. and Hanefeld, M. (2013) Effects of Insulin Glargine Versus Metformin on Glycemic Variability, Microvascular and Beta-Cell Function in Early Type 2 Diabetes. *Acta Diabetologica*, **50**, 587-595. <https://doi.org/10.1007/s00592-012-0451-9>
- [12] Lepore, M., Pampanelli, S., Fanelli, C., Porcellati, F., Bartocci, L., Di Vincenzo, A., *et*

- al.* (2000) Pharmacokinetics and Pharmacodynamics of Subcutaneous Injection of Long-Acting Human Insulin Analog Glargine, NPH Insulin, and Ultralente Human Insulin and Continuous Subcutaneous Infusion of Insulin Lispro. *Diabetes*, **49**, 2142-2148. <https://doi.org/10.2337/diabetes.49.12.2142>
- [13] Scholtz, H.E., Pretorius, S.G., Wessels, D.H. and Becker, R.H.A. (2005) Pharmacokinetic and Glucodynamic Variability: Assessment of Insulin Glargine, NPH Insulin and Insulin Ultralente in Healthy Volunteers Using a Euglycaemic Clamp Technique. *Diabetologia*, **48**, 1988-1995. <https://doi.org/10.1007/s00125-005-1916-y>
- [14] Wockhardt Limited (2013) Glaritus® (Package Insert) Waluj, Aurangabad, Maharashtra, India. Wockhardt Limited, Mumbai.
- [15] Wockhardt Ltd. Data on File. Unpublished Pre-Clinical Study Reports.
- [16] Bhatia, A., Tawade, S., Mastim, M., Kitabi, E.N., Gopalakrishnan, M., Shah, M., *et al.* (2018) Comparative Evaluation of Pharmacokinetics and Pharmacodynamics of Insulin Glargine (Glaritus®) and Lantus® in Healthy Subjects: A Double-Blind, Randomized Clamp Study. *Acta Diabetologica*, **55**, 461-468. <https://doi.org/10.1007/s00592-018-1113-3>
- [17] Wockhardt Ltd. Data on File. Unpublished PK-PD Data in Type 1 Diabetes Patients Dated 2011.
- [18] European Medicines Evaluation Agency (EMA) (2012) Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Recombinant Human Insulin and Insulin Analogues. EMA/CHMP/BMWP/32775/2005.
- [19] Center for Drug Evaluation and Research (CDER) (2008) Draft Guidance for Industry—Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.
- [20] Segal, T., Webb, E.A., Viner, R., Pusey, C., Wild, G. and Allgrove, J. (2008) Severe Insulin Resistance Secondary to Insulin Antibodies: Successful Treatment with the Immunosuppressant MMF. *Pediatric Diabetes*, **9**, 250-254. <https://doi.org/10.1111/j.1399-5448.2008.00408.x>
- [21] Berson, S.E. and Yalow, R.S. (1957) Kinetics of Reaction between Insulin and Insulin-Binding Antibody (Abstract) in Proceedings of the Forty-Ninth Annual Meeting of the American Society for Clinical Investigation Held in Atlantic City, New Jersey. *The Journal of Clinical Investigation*, **36**, 873-874.
- [22] Lahtela, J.T., Knip, M., Paul, R., Anttonen, J. and Salmi, J. (1997) Severe Antibody-Mediated Human Insulin Resistance: Successful Treatment with the Insulin Analog Lispro. A Case Report. *Diabetes Care*, **20**, 71-73. <https://doi.org/10.2337/diacare.20.1.71>
- [23] Fineberg, S.E., Kawabata, T.T., Finco-Kent, D., Fountaine, R.J., Finch, G.L. and Krasner, A.S. (2007) Immunological Responses to Exogenous Insulin. *Endocrine Reviews*, **28**, 625-652. <https://doi.org/10.1210/er.2007-0002>
- [24] Ishizuka, T., Ogawa, S., Mori, T., Nako, K., Nakamichi, T., Oka, Y., *et al.* (2009) Characteristics of the Antibodies of Two Patients who Developed Daytime Hyperglycemia and Morning Hypoglycemia because of Insulin Antibodies. *Diabetes Research and Clinical Practice*, **84**, 21-23. <https://doi.org/10.1016/j.diabres.2009.02.007>
- [25] Zhao, T.Y., Li, F. and Xiong, Z.Y. (2010) Frequent Reoccurrence of Hypoglycemia in a Type 2 Diabetic Patient with Insulin Antibodies. *Molecular Diagnosis and Therapy*, **14**, 237-241. <https://doi.org/10.1007/BF03256379>
- [26] Itoh, A., Saisho, Y., Mitsuishi, M., Oikawa, Y., Kawai, T., Tanaka, M., *et al.* (2011) Insulin Glulisine May Ameliorate Nocturnal Hypoglycemia Related to Insulin An-

- tibody—A Case Report. *Diabetes Research and Clinical Practice*, **94**, 53-54.  
<https://doi.org/10.1016/j.diabres.2011.04.001>
- [27] Hattori, N., Duhita, M.R., Mukai, A., Matsueda, M. and Shimatsu, A. (2014) Development of Insulin Antibodies and Changes in Titres over a Long-term Period in Patients with Type 2 Diabetes. *Clinica Chimica Acta*, **433**, 135-138.  
<https://doi.org/10.1016/j.cca.2014.03.008>
- [28] Hu, X., Ma, X., Wang, X., Zhao, X., Xu, X., Gong, H., Chen, F., et al. (2015) Insulin Antibodies in Patients with Type 2 Diabetic Receiving Recombinant Human Insulin Injection: A Report of 12 Cases. *Annales d'Endocrinologie*, **76**, 694-697.  
<https://doi.org/10.1016/j.ando.2015.10.004>
- [29] Li, R., Mao, J., Yu, K., Wang, L., Hu, M. and Xu, L. (2016) Medical Nutrition Therapy is Effective in the Management of Hypoglycemia Caused by Insulin Antibodies: A Case Report and Literature Review. *Journal of the American College of Nutrition*, **35**, 86-90. <https://doi.org/10.1080/07315724.2014.976673>
- [30] Quan, H., Tan, H., Li, Q., Li, J. and Li, S. (2015) Immunological Hypoglycemia Associated with Insulin Antibodies Induced by Exogenous Insulin in 11 Chinese Patients with Diabetes. *Journal of Diabetes Research*, **2015**, 74627.  
<https://doi.org/10.1155/2015/746271>
- [31] Puppalwar, G., Sawant, S., Silgiri, B., Shukla, K. and Barkate, H. (2017) Evaluation of Safety and Efficacy of Glaritus<sup>®</sup> Versus Lantus<sup>®</sup> in Combination with Insulin Lispro among Adults with Type 1 Diabetes Mellitus-Phase IV Study. *Open Journal of Endocrine and Metabolic Diseases*, **7**, 111-125.  
<https://doi.org/10.4236/ojemd.2017.74011>
- [32] US Food and Drug Administration (2008) Center for Drug Evaluation and Research. Guidance for Industry. Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.  
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf>