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ORIGINAL ARTICLE

Comparative evaluation of pharmacokinetics and pharmacodynamics of insulin glargine (Glaritus®) and Lantus® in healthy subjects: a double-blind, randomized clamp study

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Abstract

Aims The objective of the study was to compare the pharmacokinetic (PK) and pharmacodynamic (PD) properties of an insulin glargine formulation, Glaritus® (test) with the innovator's formulation Lantus® (reference) using the euglycemic clamp technique in a single-dose, double-blind, randomized, two sequences, four-period replicate crossover study in healthy volunteers ($n = 40$).

Methods Subjects received subcutaneous administration of the insulin glargine (0.4 IU/kg) formulation at two occasions for test and reference and a 20% glucose solution was infused at variable rate to maintain euglycemia for 24 h.

Results Both PK [area under the plasma concentration time curve ($AUC_{0–24\,h}$) and maximum insulin concentration (C_{max})] and PD endpoints [area under glucose infusion rate time curve ($_{AUCGIR0–24}$) and maximum glucose infusion rate (GIR_{max})] demonstrated bioequivalence of Glaritus to Lantus with the 90% confidence interval of geometric mean ratio of test to reference entirely contained within 0.80–1.25. Both formulations showed equivalent geometric least-square mean LSM value (0.08 nmol/L) for C_{max}. The geometric LSM $AUC_{0–24\,h}$ value for Glaritus® (1.09 h nmol/L) was comparable to Lantus (1.05 h nmol/L). Median T_{max} values were also identical (12 h for both), and median t1/2 values were also equal (18 h for both). For GIR_{Tmax}, the difference between the means for the two was not statistically significant. No AEs related to study formulations were reported, and both products were well tolerated.

Conclusions The test product (Glaritus) was found to be bioequivalent to the reference product (Lantus).

Clinical trial registration number CTRI/2015/06/005890; http://www.ctri.nic.in/.

Keywords Insulin glargine · Pharmacokinetics · Pharmacodynamics · Bioequivalence · Diabetes mellitus

Introduction

Insulin analogs, that closely mimic the normal insulin profile through improved pharmacokinetic (PK) and pharmacodynamic (PD) effects, have gained greater importance in the anti-diabetes treatment options in recent years [1, 2]. Insulin glargine (Lantus®: a registered trademark of Sanofi), a long-acting basal insulin analog, manufactured by recombinant DNA technology was approved by the US FDA and European EMA in 2000 for use in type 1 and type 2 diabetes mellitus [2, 3]. Upon subcutaneous administration, insulin glargine provides a release profile that resembles a physiological endogenous insulin secretion and therefore a convenient method of basal insulin replacement [4] with low risk of nocturnal hypoglycemia [5, 6]. The PK and PD studies of insulin glargine show that a single injection leads to

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a smooth 24-h time action profile with no undesirable pronounced peaks of activity [7]. Consequently, compared with protamine insulin (NPH) or premixed insulins (NPH + regular) or human insulin treatment (NPH before dinner and regular insulin before meals), insulin glargine has higher probability of reaching target HbA1c level without hypoglycemic events and with less glycemic variability [8, 9]. In prospective observational studies, insulin glargine provided significant reduction in HbA1c in patients failing premixed insulin treatment [10]. Allergic reaction to insulin analogs is rare but may occur in some individuals and can be managed through insulin desensitization immunotherapies [11–13].

Glaritus® is a non-innovator recombinant insulin glargine formulation developed by Wockhardt Ltd., which has successfully been in clinical use in several Asian and African countries since 2009. Clinical and non-clinical evaluations of Glaritus to meet the official requirements for biosimilar and 'follow on' status in European countries and USA, respectively, are currently underway. Comparable safety, immunogenicity, and efficacy outcomes of Glaritus compared to Lantus have been demonstrated in an open label, randomized clinical trial [14]. There are no evidence of safety or efficacy concerns in countries where Glaritus is approved indicating that it meets the expected outcomes.

This article presents the results from a PK/PD study that was designed to evaluate the similarity of the pharmacokinetic and pharmacodynamic properties of Glaritus and Lantus by means of a euglycemic glucose clamp over 24 h in healthy volunteers. The main objectives of the study were to: (1) compare mean and variability of the PK and PD parameters between Glaritus and Lantus; (2) demonstrate average bioequivalence (BE) in the PK endpoints between Glaritus and Lantus; and (3) assess safety and local tolerability of the two insulin preparations.

Materials and methods

Study design

The PK/PD comparative study was designed as a double-blind, randomized, single-center, two-treatment, two-sequence, four-period replicate crossover euglycemic glucose clamp study conducted in healthy subjects between September 2015 and January 2016 at the Veeda Clinical Research Clamp facility, Ahmedabad-India. Subjects were randomly allocated to two sequences in which they received 0.4 IU/kg subcutaneous doses of the two insulin formulations (Glaritus/Lantus) on two occasions each. The study comprised of a screening visit (− 28 to − 1 days) followed by four dosing visits separated by 10–28 days and a final follow-up within 10 days after Visit 5. The study design is depicted in Fig. 1.

Study subjects

The study enrolled healthy, male subjects, non-smokers aged between 18 and 45 years with BMI of 18–27 kg/m^2 and normal ECG, X-ray and 2-h glucose tolerance test results. The study excluded subjects participated in other clinical trials

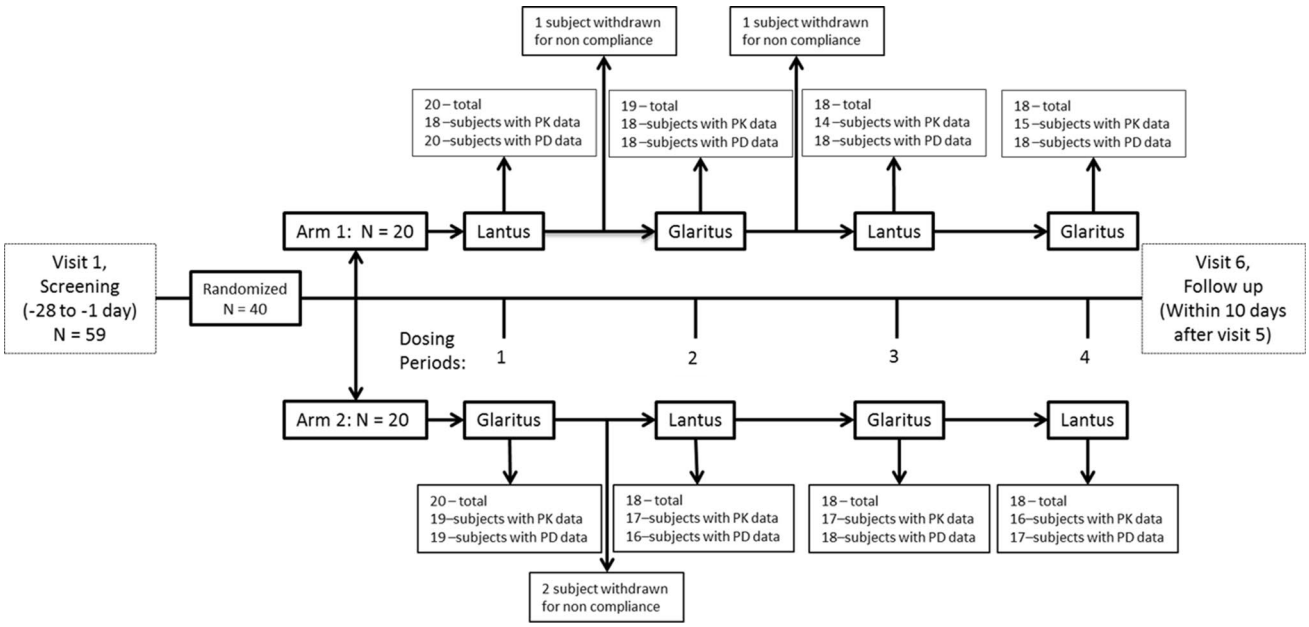

Fig. 1 Study design and subject disposition

in the last 90 days and subjects with abnormal hematology results, elevated liver enzymes (AST or ALT > 2 times the upper limit of normal) or impaired renal function (serum creatinine > upper limit of normal) or having a significant disease or history of infection. The study was conducted in accordance with the declaration of Helsinki and as per the guidelines formulated by the ICH GCP and the Indian Council of Medical Research (ICMR) for biomedical research on human subjects [15, 16]. The study protocols, informed consent forms (ICFS), audio–video consent was reviewed by the ethics committee prior to the enrollment of subjects in the study. All participants have provided their written informed consent to participate in the study. The study also received approval from Central Drugs Standard Control Organization (CDSCO). This study is registered in the Clinical Trial Registry of India (CTRI).

Quantification of insulin and C-peptide

Serial blood samples for quantification of insulin and C-peptide were drawn at 30 and 15 min prior to drug administration and then at 0, 30, 60 min, 2, 3, 4, 6, 9, 12, 15, 18, 21 and 24 h after drug administration. The blood samples were centrifuged at 3000 rpm for 10 min at 4 °C to obtain plasma which was stored at − 20 °C or below until bioanalysis.

Insulin glargine and its metabolites (M1 and M2) were quantified by a validated Liquid Chromatography–Mass Spectrometry (LC–MS) method. During analysis, insulin glargine, M1, M2, B-32 insulin (internal standard) and B-29 insulin (internal standard) were extracted from plasma by solid phase extraction and immediately injected into the LCMS for quantification. The linearity ranges were 0.202–12.076, 0.198–11.836, 0.205–12.303 ng/mL for insulin glargine, M1, and M2, respectively.

The plasma concentration of C-peptide was measured using a validated electrochemiluminescent immunoassay method (ECLIA) method. The linearity ranges were 0.245–19.600 ng/mL for two subjects and 0.245–9.776 ng/mL for the remaining subjects.

Euglycemic clamp procedure

For each subject, the 24-h euglycemic clamp procedure aimed to maintain the clamp value at 9 mg/dL below the subject's mean fasting glucose level at each visit. After a single subcutaneous injection of insulin glargine, a glucose analyzer was used to measure blood glucose level every 5 min for the first 8 h and every 10 min for remaining 16 h. Blood for glucose concentration measurement was collected from a wrist vein or hand vein of the left arm which was cannulated for insertion of the 18 gauge IV cannula. The hand was maintained under the heating pad to allow for arterialization of the venous blood and hence accurate measurement of the insulin activity. After each glucose measurement, glucose infusion rate (GIR) was adjusted (and recorded) to maintain the glucose level at the predefined clamp value. Glucose (dextrose 20%) was infused via an infusion pump through an 18-gauge cannula inserted into a cubital vein of the right forearm and performed by an experienced clinician. Glucose infusion rate was adjusted if blood glucose deviated by more than ± 3 mg/dL from the clamp value.

Safety assessments

Local tolerability at the injection site was evaluated at 3, 12 and 24 h post-dose by assessing spontaneous pain, pain on palpation, itching, erythema, edema and induration on a scale of 0 (none) to 3 (severe). If an injection site reaction was observed, it was reported as an adverse event (AE).

Blood glucose concentrations after termination of the clamp were measured at the investigator's discretion. Blood pressure monitoring, cholesterol tests, hematological and urine analysis tests and other biochemical tests including liver function tests (bilirubin, ALT, AST), renal tests (blood urea nitrogen, creatinine, calcium and sodium potassium chloride) were assessed by the standard laboratory procedures. The adverse events were classified under system organ class (SOC) and preferred term (PT) for severity, action taken, relationship and outcome.

Pharmacokinetic analysis

Insulin glargine is rapidly metabolized to its active metabolites M1 and M2 after subcutaneous injection. Therefore, the sum of the molar concentrations of glargine and its metabolites represented total glargine concentration and was used for pharmacokinetic analysis. C-peptide concentration was quantified to monitor differences in endogenous insulin production between Glaritus and Lantus during the euglycemic clamp procedure. According to the study protocol, total glargine concentration was to be adjusted for endogenous insulin production if differences in C-peptide profiles were observed between the two formulations. Pharmacokinetic parameter estimates were computed by non-compartmental analysis (NCA) of the total insulin glargine concentration–time profiles. The primary PK parameters for statistical analysis were area under the glargine concentration versus time curve ($AUC_{0-24\,h}$) and peak glargine concentration (C_{max}). Other computed PK parameters were time to C_{max} (T_{max}) and terminal elimination half-life ($t_{1/2}$). Phoenix®6.4 (Certara, Cary, NC) was used for the NCA analysis.

Pharmacodynamic analysis

Raw GIR profiles were smoothed before calculation of PD parameters. Smoothing of the GIR profiles was achieved by

locally weighted least-square regression technique (LOESS procedure) using the SAS software. A local regression smoothing factor of 0.25 was used. The primary PD parameters were area under the smoothed glucose infusion rate versus time curve ($AUC_{GIR(0–24\ h)}$) and peak of smoothed glucose infusion rate (GIR_{max}). Time to GIR_{max} (GIR_{Tmax}) was also calculated.

Statistical analysis

Considering a 35% within-subject variability in $AUC_{0–24\ h}$ and C_{max} of serum insulin concentrations following insulin glargine administration [3] and assuming a difference of 5% between test and reference and a type-I error rate of 5%, a sample size of 40 subjects was planned (after considering 5% dropout rate) for the replicate crossover study to have 90% power to reject the null hypothesis that Glaritus PK is not bioequivalent to Lantus. Log-transformed insulin glargine $AUC_{0–24\ h}$ and C_{max} were assessed by a linear mixed effects model with treatment, period, and sequence as fixed effects, while subject within sequence and treatment was treated as a random effect. Compound symmetry heterogeneous (CSH) covariance structure was used for the random between-subject effects. For each endpoint, geometric mean ratios (Glaritus to Lantus) and 90% confidence interval (CI) were obtained by taking the anti-logarithm of the least-squares mean (LSM) and the 90% CI for the adjusted differences. In addition, T_{max} of the two formulations were compared by the nonparametric Wilcoxon rank-sum test. Average BE was demonstrated if the 90% CI geometric mean ratio of both the PK endpoints was contained within 80 and 125% interval. A similar analysis was performed on the log-transformed $AUC_{GIR\ (0–24\ h)}$ and GIR_{max}.

Results

Subjects disposition, demographic and baseline characteristics

In total, 59 subjects were enrolled for eligibility evaluation; of these, 40 subjects were randomized in 1:1 ratio to the two treatment arms (sequences). Table 1 shows the demographic profile and baseline clinical characteristics of the randomized subjects. Figure 1 shows subject disposition and subjects with analyzable PK and PD data in all periods of the trial. Ten subjects did not have detectable concentration of insulin glargine or its metabolites (M1 and M2) in all or some of the dosing periods. These data were considered missing and therefore, only 65 subject-period data for Lantus and 69 subject-period data for Glaritus were available for pharmacokinetic analysis. Some subjects had zero glucose infusion rates throughout some of the dosing periods. The data for these subjects in these instances were considered missing. Therefore, only 71 subject-period data for Lantus and 73 subject-period data for Glaritus were available for pharmacodynamic analysis.

Pharmacokinetics

The mean C-peptide concentration profiles after Glaritus and Lantus subcutaneous injection were similar, indicating comparable (Fig. 2) endogenous insulin production between the two treatments. For this reason, the measured insulin

Table 1 Demographic profile and baseline clinical characteristics (visit 1) of subjects

Parameters	Arm 1 (ABAB)	Arm 2 (BABA)	*p* value
Age (years) (mean ± SD)	31.65 ± 7.42	31.1 ± 7.2	0.63
Height (cm) (mean ± SD)	168.63 ± 6.98	166.48 ± 5.79	0.29
Body weight (kg) (mean ± SD)	64.10 ± 7.54	60.10 ± 7.56	0.10
BMI (kg/m2) (mean ± SD)	22.54 ± 2.21	21.67 ± 2.45	0.25
Diastolic blood pressure (mmHg) (mean ± SD)	78.6 ± 3.79	77.3 ± 4.41	0.32
Systolic blood pressure (mmHg) (mean ± SD)	120.2 ± 6.19	120 ± 4.86	0.91
Albumin (g/mL)	4.81 ± 0.32	4.63 ± 0.34	0.1
Globulin (g/mL)	3.00 ± 0.19	3.04 ± 0.22	0.54
Albumin/globulin (A/G) ratio (mean ± SD)	1.6 ± 0.13	1.5 ± 0.14	0.03
Alkaline phosphatase (IU/L) (mean ± SD)	85.2 ± 23.67	77.7 ± 17.18	0.26
Alanine aminotransferase (U/L) (mean ± SD)	23 ± 10.84	22.3 ± 9.75	0.83
Aspartate aminotransferase (U/L) (mean ± SD)	23.8 ± 8.38	21.3 ± 4.95	0.26
Bilirubin total (mg/dL) (mean ± SD)	0.6 ± 0.35	0.7 ± 0.33	0.34
Blood urea nitrogen (mg/dL) (BUN) (mean ± SD)	8.5 ± 2.79	7.4 ± 1.88	0.15

B = Insulin glargine (Wockhardt's Glaritus; 100 U/mL), Glaritus vials, 10.0 mL, A = Insulin glargine (Lantus; 100 U/mL), Lantus vials, 10.0 mL, *SD* Standard deviation

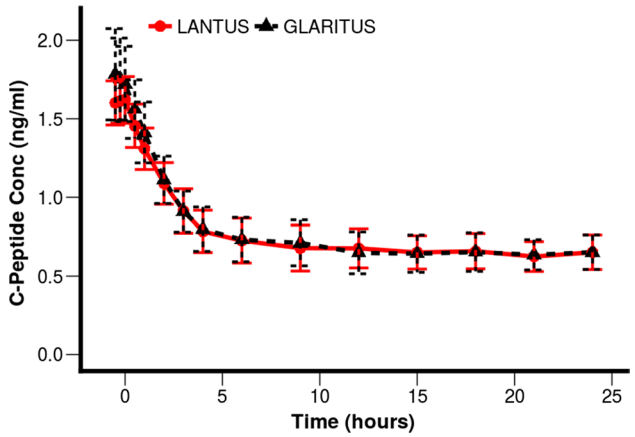

Fig. 2 Mean C-peptide concentration–time profiles after treatment with Glaritus or Lantus. The error bars represent the 95% confidence intervals

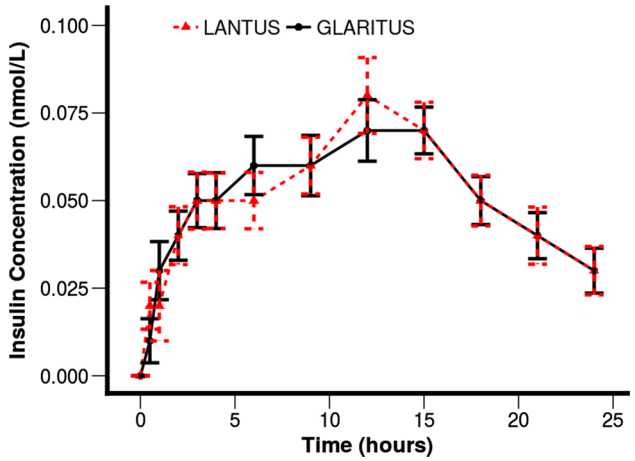

Fig. 3 Mean insulin glargine concentration–time profiles for Glaritus and Lantus. The error bars represent the 95% confidence intervals

glargine concentrations were not adjusted for endogenous insulin. The mean insulin glargine profiles after injection of 0.4 IU/kg were also similar between Glaritus and Lantus (Fig. 3) with median time to reach maximum concentration at 12 h.

The mean and variability in PK parameters were comparable between Glaritus and Lantus, with Glaritus having lower within-subject variability. The geometric LSM and between- and within-subject variability of $AUC_{0–24\ h}$ for Glaritus were 1.09 h × nmol/L, 50 and 38%, respectively, and were 1.05 h × nmol/L, 53 and 46% for Lantus, respectively. Both formulations were found to have the same geometric LSM value (0.08 nmol/L) for C_{max}, with between- and within-subject variability of 31 and 25%, respectively, for Glaritus and 31 and 48%, respectively, for Lantus.

The similarity in PK profiles was confirmed by bioequivalence results in $AUC_{0–24\ h}$ and C_{max} (Table 2). The geometric mean ratio and 90% confidence interval for $AUC_{0–24\ h}$ and C_{max} were 1.04 (0.91–1.18) and 0.96 (0.86–1.08), respectively, demonstrating average bioequivalence between Glaritus and Lantus in PK parameters. The difference in T_{max} between the two insulin formulations was not statistically significant ($p = 0.564$). Similarly, median terminal elimination half-lives (t1/2) were the same (18 h) between Glaritus and Lantus.

Pharmacodynamics

The GIR profiles (median and inter-quartile range) after 0.4 IU/kg insulin glargine injection were comparable between Glaritus and Lantus (Fig. 4). Time to maximum infusion rate for each of the dosing periods ranged between 8 and 13 h, with no pronounced peak infusion rate. Reflecting the PK, the PD parameters were also comparable between the two formulations but had high between- and

Table 2 Comparison of pharmacokinetic and pharmacodynamic parameters between Glaritus and Lantus

	Geometric least-square mean					BSV (%)		WSV (%)	
	Lantus $n = 69$	Glaritus $n = 65$	Ratio	90% CI of the ratio		Glaritus	Lantus	Glaritus	Lantus
Primary PK parameters									
$AUC_{0–24}$ (h nmol/L)	1.09	1.05	1.04	0.91	1.18	50%	53%	38%	46%
C_{max} (nmol/L)	0.078	0.081	0.96	0.86	1.08	31%	31%	25%	48%
Primary PD parameters									
$AUC_{GIR(0–24h)}$ (h•mg/kg/min)	20.99	21.63	0.97	0.83	1.14	68%	58%	56%	57%
GIR_{max}(mg/kg/min)	1.82	1.85	0.98	0.87	1.11	48%	40%	44%	42%
	Median (IQR)		p value						
T_{max} (h)	12 (9–15)		0.564						
GIR_{Tmax} (h)	12.83 (10.83–14.50)		0.74						

BSV between-subject variability, *WSV* within-subject variability, *IQR* inter-quartile range

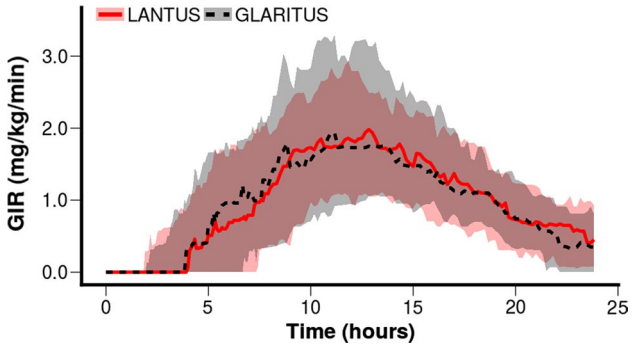

Fig. 4 Raw glucose infusion rate (GIR)-time profiles for Glaritus and Lantus. The lines and shaded area represent median and inter-quartile range, respectively

within-subject variability for both formulations. The geometric LSM and between- and within-subject variability of $AUC_{GIR(0–24\ h)}$ for Glaritus were 20.99 h × mg/kg/min, 68 and 56% and were 21.63 h × mg/kg/min, 58 and 57% for Lantus, respectively. For GIR_{max}, geometric LSM and between- and within-subject variability values were 1.82 mg/kg/min, 48 and 44% for Glaritus and 1.85 mg/kg/min, 40 and 42% for Lantus, respectively. The 90% CI of the geometric mean ratios for $AUC_{GIR(0–24\ h)}$ and GIR_{max} was also entirely contained within the BE interval of 80–125% (Table 2). The median GIR_{Tmax} for Glaritus was comparable to that of Lantus (p value = 0.74)**.**

Safety evaluation

No notable differences in the AE profiles were observed between Lantus and Glaritus, and no clinically significant alterations of laboratory, urinalysis, or vital signs values were identified. Of the eight AEs observed in six subjects (*Online Resource Table S1*), three AEs were from the Glaritus arm and five from the Lantus arm. Cellulitis and thrombophlebitis (1 in Lantus and 1 in Glaritus) at the injection site were of mild-to-moderate intensity and required drug treatment for both cases. Mild hypoglycemic episodes were observed in the Lantus ($n = 2$) and the Glaritus ($n = 1$) with no action required. The mean blood glucose concentration after the clamp procedure for the two treatment arms in all dosing periods are presented in *Online Resource table S2*.

Discussion

The present study provides assessment of PK and PD similarity between Glaritus and Lantus after a single 0.4 IU/Kg subcutaneous injection in healthy subjects. The results show similarity in rate and extent of absorption of the two formulations as depicted by comparable 24-h exposure ($AUC_{0–24\ h}$), maximum exposure (C_{max}) and time to reach maximum exposure since injection (T_{max}). The magnitude of the between- and within-subject variability reported in this study is consistent with the values reported in previous studies [17, 18]. In addition, the results also demonstrated similar glucose lowering activity of the two formulations as indicated by comparable amount of glucose administered in the 24-h duration ($AUC_{GIR\ (0–24\ h)}$) and maximum glucose infusion rate (GIR_{max}), and time to GIR_{max} (GIR_{Tmax}).

In accordance with the regulatory requirement to show average BE in PK/PD endpoints, the 90% CI of geometric mean ratio of test to reference product was contained within 80–125% limits for both PK ($AUC_{0–24\ h}$ and C_{max}) and PD ($AUC_{GIR(0–24\ h)}$ and GIR_{max}) endpoints.

The observed concentration and glucose infusion rate profiles and the estimated PK and PD parameters are comparable to those reported previously for insulin glargine [3, 17, 19]. In the present study, consistency of insulin glargine exposure and its activity between Lantus and Glaritus is demonstrated in the four dosing periods (*Online Resource figures S1 and S2*).

The evaluation of safety of the two formulations in this study indicated no safety concerns, and adverse events profiles were comparable. No clinically significant alterations in the vital signs or laboratory results were reported. A different safety profile for biosimilar insulin may arise if its manufacturing process results into a different molecular entity and/or a change in folded final structure. The manufacturing process may also introduce different impurity profiles or result into a product with different shelf-life stability. The comparable safety profile between Glaritus and Lantus in this study and the previous efficacy and safety study provides confidence in the manufacturing process of Glaritus.

This study was designed as per the industry guidelines of BE and recommendations as per schedule Y [20]. A replicate crossover study design was chosen as the within-subject variability in PK parameters from prior studies of Lantus were at least 35%, thus also leading to increased precision of the estimated parameters. The replicate crossover design typically leads to a reduced sample size relative to a 2 × 2 crossover, and estimation of within-subject variability for both the test and the reference is possible.

The EMA guidance on clinical development of biosimilar insulins recommend using either healthy subjects or type 1 diabetes patients to evaluate PK/PD bioequivalence of two formulations [21]. This study was designed in healthy subjects as they represent a homogeneous and sensitive population to detect functional differences between the two insulin formulations. Endogenous insulin secretion was suppressed by using the hyperinsulinemic-euglycemic glucose clamp procedure. As a result, the observed variation in insulin activity over the 24-h fasting was mainly due to administered insulin glargine.

Frequently used insulin doses in clamp studies for long-acting insulin are 0.4–0.6 IU/kg. The dose of 0.4 IU/kg was selected as it results in measurable plasma concentration and provides a concentration–response relationship in the healthy subjects. Adequate washout of at least 10 days was chosen to avoid any carryover effect.

C-peptide concentrations were measured to detect potential changes in endogenous insulin secretion and to enable a correction for endogenous insulin secretion, if necessary. In this study, C-peptide concentrations were comparable between the two formulations in all four periods and therefore adjusting for endogenous insulin production was not considered necessary.

The euglycemic glucose clamp technique is a requirement of EMA for PK/PD studies aiming to demonstrate of similarity of insulin formulations [21, 22]. The technique was considered in this study to assess PD effects and, for the safety reasons, to avoid hypoglycemia. The 24-h clamp duration was chosen based on the known glargine duration of activity, to avoid prolonged fasting of the healthy volunteers and to mimic the dosing interval.

In summary, the study demonstrated similarity in PK ($AUC_{0–24\ h}$ and C_{max}) and PD ($GIR_{AUC\ (0–24\ h)}$ and GIR_{max}) characteristics of Glaritus and Lantus upon single subcutaneous dose of 0.4 IU/Kg in healthy subjects with comparable safety profiles.

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Authors' contribution Eliford Ngaimisi contributed to data analysis and manuscript writing. Mathangi Gopalakrishnan contributed to data analysis and manuscript writing. Joga Gobburu contributed to manuscript writing. Prasanna Kumar analyzed and interpreted the data. Ashima Bhatia contributed to the study methodology and procedures and data interpretation, Shraddha Tawade, Mushtaque Mastim, Sridhar Yeshamaina and Manish Shah were involved in study design, data collection, data analysis and interpretation. Maharaja Sahib and Dipak Thakur contributed to the development of bioanalysis method of Glargine. All the authors approved the final draft of the manuscript after critical review and revision.

Compliance with ethical standards

Conflict of interest Prasanna Kumar K M is an advisory board member of Wockhardt, Sanofi, Biocon, Novo- Nordisk and Eli Lilly and has conducted clinical research as PI for the insulin analogs for these companies. Shraddha Tawade, Mushtaque Mastim, Manish Shah, Sridhar Yeshamaina, Maharaja Sahib, Dipak Thakur and Ashima Bhatia are employees of Wockhardt Ltd. Eliford Ngaimisi, Mathangi Gopalakrishnan and Joga Gobburu have no conflict of interest to declare.

Ethical approval The study was conducted in accordance with the declaration of Helsinki and as per the guidelines formulated by the ICH GCP and the Indian Council of Medical Research (ICMR) for biomedical research on human subjects.

Informed consent Informed consent was obtained from all individual participants included in the study.

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