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SHORT REPORT

Preserved pharmacokinetics and pharmacodynamics of insulin degludec and liraglutide when administered as insulin degludec/liraglutide in a Chinese population

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ABSTRACT

We report the findings of a single-dose, randomized, three-period cross-over, clinical trial in healthy Chinese individuals (n = 24) comparing the pharmacokinetics of insulin degludec/liraglutide (IDegLira) with its individual components. Furthermore, we report a population pharmacokinetic analysis of a 26-week, phase III, treat-to-target, randomized trial of 720 Chinese individuals with type 2 diabetes. Participants were randomized to IDegLira, degludec or liraglutide, all once daily with metformin. The pharmacokinetic profiles of IDegLira were similar to its individual components. Dose proportionality was indicated for both IDegLira components. Although there were no relevant covariate effects on degludec exposure, liraglutide exposure was inversely correlated with bodyweight. In conclusion, for the Chinese population, the pharmacokinetics of the fixed-ratio combination IDegLira is similar to that of its individual components.

INTRODUCTION

Insulin degludec/liraglutide (IDegLira) is a fixed-ratio combination of basal insulin degludec (degludec) and liraglutide (100 units [U]/3.6 mg/mL). The global, phase III, DUAL clinical trial program showed improved glycemic control with IDegLira, lower hypoglycemia risk (versus basal insulin) and a neutral effect on bodyweight[1–10].

A pharmacokinetic (PK) trial in a healthy European population, and a population PK evaluation of individuals with type 2 diabetes, showed general preservation of PK properties for degludec and liraglutide with IDegLira[11]. There were no relevant deviations from dose proportionality for either IDegLira component, and the glycemic response to IDegLira was larger than either component alone[11].

The present analyses assessed whether the PK and exposure–response of degludec and liraglutide are similar when administered as IDegLira or separately in a Chinese population.

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MATERIALS AND METHODS

Ethical consideration

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration[12], and the International Conference on Harmonization Good Clinical Practice[13].

Single-dose pharmacokinetics

The China PK trial (NCT03292185) was a randomized, double-blind, single-dose trial investigating the pharmacokinetics of degludec and liraglutide when administered as IDegLira, or as separate administrations, in healthy Chinese individuals (Methods S1). Participants received the following single-dose treatments subcutaneously in randomized order on separate visits: IDegLira 17 dose steps (17 U degludec/0.6 mg liraglutide); degludec 17 U; and liraglutide 0.6 mg.

Bioanalysis of degludec and liraglutide was carried out using validated enzyme-linked immunosorbent assays. The primary end-point was exposure for each component of IDegLira, and for degludec and liraglutide given alone (Methods S1).

Population pharmacokinetic and exposure-response analyses (DUAL I China)

DUAL I China (NCT03172494) was a 26-week, phase III, parallel, three-arm, open-label, multicenter, treat-to-target trial in Chinese individuals with type 2 diabetes[14] (Methods S1). Participants were randomized 2:1:1 to receive IDegLira (maximum 50 dose steps), degludec (no maximum) or liraglutide (1.8 mg) once daily, each in combination with metformin.

The population PK analysis assessed dose proportionality of degludec and liraglutide exposures after doses of IDegLira and investigated the effects of pre-specified covariates on exposure to both components during 26 weeks of treatment. The exposure–response analysis was used to show the contribution from each component of IDegLira to the overall glycemic response across the exposure range (Methods S1).

RESULTS

Baseline demographics

In total, 24 healthy male (62.5%) and female participants were randomized and completed the China PK trial. Mean (standard deviation [SD]) age was 31.4 years (6.2 years), bodyweight was 63.4 kg (7.2 kg) and body mass index (BMI) was 22.4 kg/m^2 (1.4 kg/m^2). DUAL I China included 720 participants (59.3% male) with type 2 diabetes; 713 participants were exposed to trial products: 358 to IDegLira, 175 to degludec and 180 to liraglutide. The mean (SD) age was 54.7 years (10.3 years), bodyweight was 74.1 kg (13.8 kg) and BMI was 26.7 kg/m^2 (3.7 kg/m^2).

The final data retained 507 and 504 participants for PK analysis of degludec and liraglutide, respectively (Table S1). For the degludec PK analysis, the mean (SD) age was 54.8 years (10.2 years), bodyweight was 74.3 kg (13.9 kg) and BMI was 26.8 kg/m^2 (3.8 kg/m^2). For the liraglutide PK analysis, the mean (SD) age was 54.2 years (10.2 years), bodyweight was 74.6 kg (14 kg) and BMI was 26.8 kg/m^2 (3.8 kg/m^2).

Single-dose pharmacokinetics

General PK patterns were similar, but with a maximum concentration (C_{max}) appearing slightly lower for degludec and liraglutide when administered as IDegLira compared with their administration alone (Figure 1a,b). The estimated relative bioavailability of degludec (treatment ratio of the area under the curve from 0 to last quantifiable observation [$AUC_{Degludec,\ 0\text{-}tz}$]) when administered as IDegLira versus degludec alone was 1.00 (90% confidence interval [CI] 0.96;1.04), meeting the equivalence criterion (90% CI 0.80;1.25)[15] (Table 1). The treatment ratio of $AUC_{Liraglutide,\ 0\text{-}tz}$ when administered as IDegLira versus liraglutide alone was 0.88 (90% CI 0.83;0.94), meeting the equivalence criterion[15] (Table 1). The corresponding analysis for the estimated treatment ratio of $AUC_{0\text{-}\infty}$ was in accordance with the $AUC_{0\text{-}tz}$ for degludec and for liraglutide. The lower limit of the 90% CI for $C_{max,\ degludec}$ and $C_{max,\ liraglutide}$ was below the lower limit for equivalence (Table 1). The median time to C_{max} for degludec and liraglutide was comparable when administered as IDegLira (degludec: 12.0 h; liraglutide: 12.0 h) or separately (degludec: 11.0 h; liraglutide: 11.0 h).

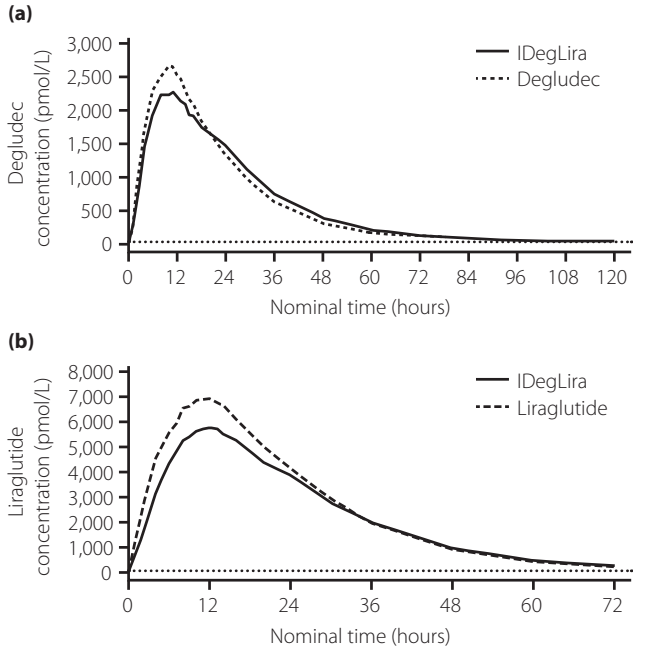

Figure 1 | Concentration-time profiles for (a) degludec and (b) liraglutide by treatment in healthy Chinese participants (China PK trial). For (a), the horizontal dotted line at 20 pmol/L indicates the lower limit of quantification; for (b), the horizontal dotted line at 30 pmol/L indicates the lower limit of quantification. Degludec, insulin degludec; IDegLira, insulin degludec/liraglutide.

Table 1 | Analysis of the $AUC_{0\text{-}tz}$ and C_{max} treatment ratios for degludec and liraglutide exposure from a single-dose trial in healthy Chinese participants

Treatment/comparison	Estimate	90% CI
$AUC_{0\text{-}tz,\ degludec}$; treatment ratio IDegLira/degludec	1.00	0.96;1.04
$C_{max,\ degludec}$; treatment ratio IDegLira/degludec	0.90	0.78;1.04
$AUC_{0\text{-}tz,\ liraglutide}$; treatment ratio IDegLira/liraglutide	0.88	0.83;0.94
$C_{max,\ liraglutide}$; treatment ratio IDegLira/liraglutide	0.83	0.75;0.92

The end-point was log-transformed and analyzed using a linear mixed model with treatment, period and participant as fixed effects. $AUC_{0\text{-}tz}$, area under the curve from 0 to last quantifiable observation; CI, confidence interval; C_{max}, maximum concentration; degludec, insulin degludec; IDegLira, insulin degludec/liraglutide.

Population pharmacokinetic analysis

Dose-proportionality expressed as $AUC_{0-24\ h}$ at steady state versus dose is shown in Figure S1. The 90% CIs for both the degludec and liraglutide models with dose effects were within the 80–125% CI of the reference dose-proportional model for each component indicating dose proportionality.

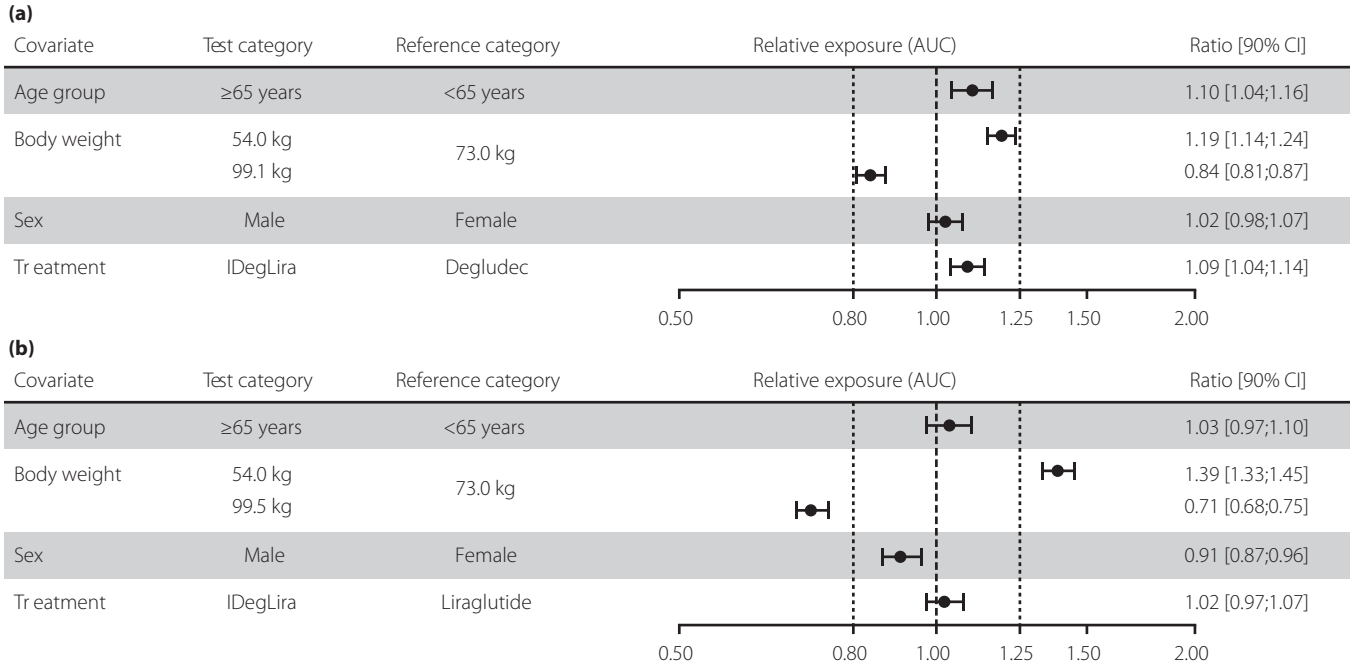

Figure 2 | Forest plot of covariate analysis for (a) degludec and (b) liraglutide in Chinese participants with type 2 diabetes (DUAL I China). Data points and 90% CIs are expressed as dose-normalized steady-state exposure (area under the curve from 0 to 24 h [$AUC_{0–24\ h}$]) relative to a median bodyweight (73.0 kg), female participants aged <65 years dosed with degludec or liraglutide, respectively. Bodyweight test categories represent the 5th and 95th percentiles, respectively, in the dataset. Dotted lines show the acceptance interval used for bioequivalence testing, for comparison. The column to the right provides the geometric mean relative exposures with 90% CIs obtained by likelihood profiling. AUC, area under the curve; CI, confidence interval; degludec, insulin degludec; IDegLira, insulin degludec/liraglutide.

For DUAL I China, the covariate analysis for degludec showed no relevant effects for any of the investigated covariates (Figure 2). The covariate with the most influence on exposure was bodyweight, as degludec exposure decreased with increasing bodyweight, although this effect was within the equivalence range. There was no difference in degludec exposure when dosed as IDegLira or degludec alone (estimated mean ratio 1.09, 90% CI 1.04;1.14). The covariate analysis for liraglutide showed a lower exposure with increasing bodyweight. There was no difference in liraglutide exposure when dosed as IDegLira or liraglutide alone (estimated mean ratio 1.02, 90% CI 0.97; 1.07).

Exposure–response analysis

The exposure–response relationships were relatively flat due to dose titrations to specified fasting glucose levels for IDegLira and degludec, and due to the pharmacodynamic properties of liraglutide, acting only when glucose levels are elevated above normal (Figure S2). The effect of IDegLira was larger than the effect of degludec or liraglutide alone at all exposure levels, confirming that both components contributed to the glycemic effects of IDegLira.

DISCUSSION

The single-dose PK analysis showed similar PK for degludec and liraglutide when administered as IDegLira or separately in Chinese participants. This was supported by the similar $AUC_{0-\infty}$ of degludec and liraglutide obtained when administered as IDegLira or separately. Treatment ratios showed that $C_{max,\ degludec}$ was 10% lower with IDegLira than with degludec alone; and $C_{max,\ liraglutide}$ was 17% lower with IDegLira than with liraglutide alone. As IDegLira is intended to be titrated based on individuals' plasma glucose levels, these differences in C_{max} are not expected to affect clinical use.

The population PK analysis showed dose proportionality across the IDegLira dose range for degludec and liraglutide, as previously shown for the individual components[16,17], which is consistent with the global PK evaluation[11]. There were no relevant covariate effects on degludec exposure; bodyweight showed the most effect, but within the equivalence criterion[15] for the range tested (54.0–99.1 kg). However, liraglutide exposure was inversely correlated with bodyweight for the investigated range (54.0–99.5 kg). There was no difference in degludec or liraglutide exposure when dosed as IDegLira or individually, conforming with the China PK trial. The AUC ratio of IDegLira/degludec was similar in the DUAL I China and China PK trials, consistent with the global PK data[11]. However, the AUC ratio of IDegLira/liraglutide was not in the same direction in the two trials, although the equivalence criterion[15] was met. The exposure–response analysis showed that both IDegLira components contributed to glycemic control aligning with the global phase III trial[11].

In conclusion, the general PK pattern of degludec and liraglutide are similar, when administered as IDegLira, or separately, in both healthy Chinese individuals and in those with type 2 diabetes. Overall, the present findings in a Chinese population align with those previously published for a global population.

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DISCLOSURE

Bin Luo is an employee of Novo Nordisk China Pharmaceuticals Co. Ltd. and holds shares/stock in the company. Ting Jia and Lisbeth Vestergård Jacobsen are employees of Novo Nordisk A/S and hold shares/stock in the company. Steen Hvass Ingwersen is a former employee of Novo Nordisk A/S and holds shares/stock in the company. Hongzhong Liu, Xia Chen and Pei Hu have no conflicts of interest to disclose.

Approval of the research protocol: The study was conducted in accordance with the provisions of the Declaration of Helsinki. The China PK study protocol was approved by the ethics committee of Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing City, China (approval number: KS2017031; approval date: 21 Mar 2017). The DUAL I China trial protocol was approved by the ethics committee of Rui Jin Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China (approval number: 2016-64-2; approval date 24 Jan 2017), and by the appropriate independent ethics boards/institutional review boards at each site.

Informed consent: All informed consent was obtained from the patients.

Registry and the registration no. of the study/trial: The China PK and DUAL I China trials are registered at clinicaltrials.gov (NCT03292185 and NCT03172494, respectively).

Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed for this article are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Method S1 | Additional methodology.

Table S1 | Baseline characteristics of participants in the final dataset for pharmacokinetic analysis of degludec and liraglutide.

Figure S1 | Dose-proportionality analysis for (a) degludec and (b) liraglutide after steady-state doses of insulin degludec/liraglutide in Chinese participants with type 2 diabetes (DUAL I China).

Figure S2 | Exposure–response for change in glycated hemoglobin from baseline to Week 26 in Chinese participants with type 2 diabetes (DUAL I China).