SUPPLEMENTARY INFORMATION FOR:

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

Hongzhong Liu¹,², Bin Luo³, Xia Chen¹,⁴, Steen H. Ingwersen⁵, Ting Jia⁵, Lisbeth Vestergård Jacobsen⁵ and Pei Hu¹,²

1. Clinical Pharmacology Research Center, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College
2. Beijing Key Laboratory of Clinical Pharmacokinetics & Pharmacodynamics Investigation for Innovative Drugs, Beijing, China
3. Novo Nordisk China Pharmaceuticals Co. Ltd, Beijing, China
4. National Clinical Research Center for Neurological Diseases, Clinical Trial Center, Beijing Tiantan Hospital
5. Novo Nordisk, Copenhagen, Denmark
Supplementary Methods 1. Additional methodology

China PK trial – additional methodological details

The trial period consisted of five visits, of which three were in-house dosing visits. There was a 7–15-day washout period between each dosing visit. Eligible participants were Chinese males and females aged 18–45 years, considered generally healthy by the investigator, with body mass index (BMI) 19.0–24.0 kg/m$^2$, body weight $\geq$50.0 kg, and fasting plasma glucose $<6.1$ mmol/L (110 mg/dL). Concomitant medications were not permitted, except for paracetamol, acetylsalicylic acid, contraceptives, and vitamins.

Sampling and endpoints for single-dose pharmacokinetics

Sampling 0–120 hours for degludec and 0–72 hours for liraglutide, after which the concentrations were likely to be near the lower limit of quantification (LLOQ) of 20 pmol/L for insulin degludec (degludec) and 30 pmol/L for liraglutide. For degludec, blood samples were obtained 1, 2, 4, 6, and 8 hours post-dosing, hourly between 10 and 16 hours, every 2 hours between 18 and 24 hours, at the 30-hour point, every 12 hours between 36 and 72 hours, and at the 96-hour point post-dosing. For liraglutide, blood samples were obtained at 2 and 4 hours, hourly between 6 and 14 hours, and 16, 20, 24, 30, 36, 48, 60, and 72 hours post-dosing.

Endpoints were defined as: $\text{AUC}_{\text{Degludec}, \ 0-\text{tz}}$, area under the serum degludec concentration time curve from 0 to last quantifiable observation after single dose of insulin degludec/liraglutide (IDegLira) and degludec; $\text{AUC}_{\text{Liragludte}, \ 0-\text{tz}}$, area under the plasma liraglutide concentration-time curve from 0 to last quantifiable observation after single dose of IDegLira and liraglutide; $C_{\text{max}}$, maximum concentration; $t_{\text{max}}$, time to $C_{\text{max}}$.

DUAL I China – additional methodological details

Eligible participants were aged $\geq$18 years, with glycated hemoglobin (HbA$\text{\tiny 1c}$) 7.0–10.0 %, BMI $\leq$40 kg/m$^2$, and treated with metformin $\pm$ one other oral antidiabetic drug (α-glucosidase inhibitor, sulfonylurea, glinide, or thiazolidinedione) for $\geq$90 days prior to screening. Exclusion criteria included treatment with glucagon-like peptide-1 receptor agonists or dipeptidyl peptidase-4 inhibitors within 90 days prior to screening.
Sampling for population pharmacokinetic and exposure-response analysis

Single blood samples for PK analysis were drawn at weeks 0, 1, 2, 4, 8, 12, 16, 20, and 26. No pre-defined time of day was specified for the sampling, but the investigator recorded the date and exact clock time of sampling. Participants were instructed to write in a diary: the date, exact clock time, dose and injection site of the previous three days of dosing as well as the dose on the day of the visit, if taken before pharmacokinetic (PK) blood sampling.

Data cleaning for population PK analysis

For the population PK analysis of degludec and liraglutide, data were cleaned using pre-specified rules to secure data quality. The timing of the blood samples in relation to dosing was not pre-defined but the investigator recorded the actual clock time of sampling in the case report form (CRF). Furthermore, the actual clock time, date, dose level and injection site for the latest three drug administrations were transcribed into the CRF from participants’ diaries.

Structural models

The structural models and covariate relationships were predefined, and previously developed population PK models for degludec and liraglutide were used. Standard one-compartment models with first-order absorption and elimination were used to describe degludec and liraglutide PK. The structural models were parameterised in terms of an absorption rate constant (\( k_a \)), an apparent clearance (\( CL/F \)), and an apparent volume of distribution (\( V/F \)). To ensure identifiability of the models with the sparsely sampled data, the absorption rate constants were set to previously estimated values (0.0382 h\(^{-1}\) for insulin degludec and 0.0704 h\(^{-1}\) for liraglutide). For both PK models, the \( k_a \) was fixed and the \( CL/F \) and \( V/F \) were estimated. The covariates of interest were evaluated using pre-specified criteria. Covariates tested on \( CL/F \) included dose, treatment (IDegLira, degludec, liraglutide), body weight, age group (<65, ≥65 years), and sex.
Variability models

Between-participant variability (log-normal; without correlation between parameters) was estimated for CL/F and V/F. To ensure identifiability of the individual parameters, no between-participant variability was included for $k_a$. Proportional error models were used to describe the residual variability for the degludec and liraglutide concentrations.

Analysis of covariate effects

For the covariate analysis, the following equations were used for the covariates on CL/F:

\[
\frac{CL}{F_i} = TVCL \cdot E_{\text{treatment}} \cdot E_{\text{weight \_CL}} \cdot E_{\text{sex}} \cdot E_{\text{age group}} \cdot \exp(\eta_{CL,i})
\]

\[
E_{\text{treatment}} = (\theta_{\text{DegLira}})^{\text{DegLira}}
\]

\[
E_{\text{weight \_CL}} = \left(\frac{\text{weight}_i}{\text{median weight}}\right)^{\theta_{\text{weight \_CL}}}
\]

\[
E_{\text{sex}} = (\theta_{\text{male}})^{\text{male}}
\]

\[
E_{\text{age group}} = (\theta_{\geq 65y})^{\geq 65y}
\]

and the following equation was used for body weight on V/F:

\[
\frac{V}{F_i} = TVV \cdot E_{\text{weight \_V}} \cdot \exp(\eta_{V,i})
\]

\[
E_{\text{weight \_V}} = \left(\frac{\text{weight}_i}{\text{median weight}}\right)^{\theta_{\text{weight \_V}}}
\]

Here, TVCL and TVV are the typical values of apparent clearance and apparent volume of distribution, respectively, for a reference participant (a median-weight, Chinese female below 65 years of age, dosed with insulin degludec or liraglutide alone).

The results of the covariate analysis were presented as forest plots showing the mean and 90% confidence interval (CI) of the effects of each of the covariates relative to the reference
Exposure-response analysis

The exposure-response analysis was performed by relating the HbA₁c response across the exposure range for IDegLira to that obtained with each of its components dosed separately. Data sets used for the exposure-response analysis of HbA₁c were derived from the PK data set used for the population PK analysis. Participants without recorded values of HbA₁c at Week 26 were excluded to avoid bias originating from imputed values.

Supplementary Table 1: Baseline characteristics of participants in the final dataset for PK analysis of degludec and liraglutide

| Category                  | IDegLira/Degludec | IDegLira/Liraglutide |
|---------------------------|-------------------|-----------------------|
| Total number of participants, N | 507†             | 504‡                  |
| Age (years)               | 54.8 (10.2)       | 54.2 (10.2)           |
| BMI (kg/m²)               | 26.8 (3.8)        | 26.8 (3.8)            |
| Body weight (kg)          | 74.3 (13.9)       | 74.6 (14.0)           |

Data are mean ± SD or number of participants

†As a consequence of data cleaning, of 531 participants available for PK analysis of degludec, approximately 5.5% of the data points were excluded, retaining 507 participants (IDegLira: 339, degludec: 168) in the final dataset

‡For the PK analysis of liraglutide, of 534 participants available, approximately 7.5% of the data points were excluded, retaining 504 participants (IDegLira: 339, liraglutide: 165) in the final dataset

BMI, body mass index; IDegLira, insulin degludec/liraglutide; PK, pharmacokinetic; SD, standard deviation
**Supplementary Figure 1:** Dose-proportionality analysis for A) degludec and B) liraglutide following steady-state doses of IDegLira in Chinese participants with T2D (DUAL I China)

AUC, area under the curve; CI, confidence interval; degludec, insulin degludec; IDegLira, insulin degludec/liraglutide; SS, steady state; T2D, type 2 diabetes; U, unit
Supplementary Figure 2: Exposure-response for change in HbA\textsubscript{1c} from baseline to Week 26 in Chinese participants with T2D (DUAL I China)

IDegLira, degludec, and liraglutide are represented by blue squares, grey and green circles respectively. Data for HbA\textsubscript{1c} (%) are expressed as baseline-adjusted mean with 95% CI versus percentiles of exposure of degludec (A) or liraglutide (B)

AUC, area under the curve; HbA\textsubscript{1c}, glycated hemoglobin; CI, confidence interval; degludec, insulin degludec; IDegLira, insulin degludec/liraglutide; T2D, type 2 diabetes