A study investigating the pharmacokinetic properties of insulin degludec/insulin aspart in healthy Chinese subjects

Shi Aixin1, Li Yang1, Xie Panpan1, Qi Wenyuan1, Yang Lei1, Xu Hongfei1, Zhang Ran2, Hanne Haahr*3

ABSTRACT

Objective: This study aimed to characterize the pharmacokinetic (PK) properties of the insulin degludec (degludec)/insulin aspart (IAsp) co-formulation (IDegAsp) in healthy Chinese subjects, and compare these with previous findings in Caucasian and Japanese subjects. Methods: In this single-center, open-label study, 24 healthy Chinese adults received a single dose (SD) of IDegAsp (0.5 U/kg body weight). Regular blood sampling for serum IAsp and degludec measurements was performed for the first 20 hours, and less frequently up to 120 hours post-dose. Results: Total exposure of IAsp (AUCIAsp,total,SD) was estimated as 541 pmol·h/L (95% confidence interval [CI] 502;582), maximum concentration (Cmax,IAsp,SD) as 217 pmol/L (95%CI 193;244), time to maximum concentration (tmax,IAsp,SD) as 1 hour, and onset of appearance as 14 min. Total exposure of degludec (AUCdeglidec,total,SD) was estimated as 88,271 pmol·h/L (95%CI 83,615;93,187), maximum concentration (Cmax,deglidec,SD) as 3472 pmol/L (95%CI 3013;4002), and time to maximum degludec concentration (tmax,deglidec,SD) as 10.5 hours. Importantly it should be noted that serum concentrations of degludec and IAsp cannot be directly compared and are not additive, as concentrations differ by several orders of magnitude due to the reversible binding of degludec to serum albumin. Six treatment-emergent adverse events occurred in three subjects; none were serious. The PK properties of IAsp and degludec were consistent with those observed in previous trials in Japanese and Caucasian subjects. Conclusion: The rapid absorption of IAsp and the ultra-long PK profile of degludec were present in healthy Chinese subjects. The clinical benefits of IDegAsp observed in previous IDegAsp studies are expected in Chinese patients, and no specific IDegAsp dosing recommendations should be required. Clinicaltrials.gov identifier: NCT02844790

Highlights

- The distinct pharmacokinetic profiles of the IDegAsp component insulins are present in healthy Chinese adults, and are consistent with results from previous studies in Japanese and Caucasian populations.
- The clinical benefits of IDegAsp observed in other populations are also expected in Chinese patients.

Introduction

Chinese Diabetes Society (CDS) guidelines recommend the use of either once-daily basal insulin or once- or twice-daily premix insulin for insulin initiation in Chinese patients with type 2 diabetes (T2D), if adequate glycemic control (i.e. HbA1c <7%) cannot be achieved with lifestyle changes plus metformin and ≥1 oral antidiabetic drugs [1]. When further intensification is required, the CDS guidelines recommend multiple daily injections of insulin (basal-bolus regimen or 2-3 injections of premix insulin) or continuous subcutaneous insulin infusion [1]. Premix insulin, which covers both basal and prandial insulin needs in one injection, is a widely used treatment option in China [2,3].
However, overlap between the PK/PD profiles of current premix insulin components (biphasic suspensions with soluble insulin and protamine-crystallized insulin) results in a ‘shoulder effect’ (i.e. a prolonged post-meal glucose-lowering action with inadequate duration of basal action) [4]. The composition of premix insulin also necessitates resuspension prior to use, creating substantial variability in the pharmacological response, and an additional requirement for patient education [5]. IDegAsp (Ryzodeg 70/30, Novo Nordisk A/S, Seborg, Denmark) is a unique co-formulation of two insulin analogues: 70% ultra-long-acting insulin degludec (degludec) and 30% rapid-acting insulin aspart (IAsp), approved for the treatment of diabetes in adults in many countries [6,7]. Unlike premix insulin formulations, degludec and IAsp are present in IDegAsp as separate stable, soluble components; thus, IDegAsp is optimized for use without the need for resuspension. IDegAsp provides a superior glucose-lowering profile versus premix insulins, with fewer daily injections versus basal-bolus regimens [8]. The individual components of IDegAsp underpin the mode of action. After subcutaneous injection, IAsp hexamers immediately break down into rapidly absorbed monomers, providing a rapid onset of glucose-lowering effect. In contrast, upon injection, degludec di-hexamers form long chains of multi-hexamers in a subcutaneous depot [9]. Monomers are slowly and continuously released from the hexamers into the circulation, where they attach with high selectivity to circulating albumin, producing a flat, long-lasting glucose-lowering effect [6,8,10,11]. Race and ethnic background may influence the pharmacological properties of exogenous insulin and could potentially affect dosing recommendations [12,13]. To date, the pharmacological properties of IDegAsp have been described in Japanese and Caucasian subjects with type 1 diabetes (T1D) [11,14-17]. In addition, the PK properties of the IAsp component of IDegAsp have been described in Caucasian subjects with T1D [11,15], and the PK properties of degludec have been described in Japanese and Caucasian subjects with T1D [10,18,19]. Caucasian, African American and Hispanic/Latino subjects with T2D [20,21], as well as healthy Chinese adults [22]. The present study aimed to characterize the PK properties of IDegAsp in healthy Chinese adults, enabling comparison with IDegAsp data obtained from previous trials in other populations which used similar methodology.

Methods

■ Study design

This was a single-center (Clinical Trial Centre, Beijing Hospital), open-label, single-dose study investigating the PK properties of IDegAsp in healthy Chinese adults (ClinicalTrials.gov identifier: NCT02844790). The protocol was reviewed and approved according to local regulations by the appropriate health authorities, and the local Ethics Committee of Beijing Hospital (IRB approval number: 2015BJYYEC-094-02). The study was conducted in agreement with the Declaration of Helsinki (World Medical Association 2008). All subjects gave their informed consent prior to inclusion in the study.

■ Subjects

Subjects were healthy male or female Chinese adults aged 18-45 years (both inclusive), with body mass index 19–24 kg/m2 (both inclusive) and fasting plasma glucose ≤6.0 mmol/L. Exclusion criteria included abnormal hematology, biochemistry, lipid, or urinalysis screening test results; systolic blood pressure <90 or >140 mmHg; diastolic blood pressure <60 or >90 mmHg; any potentially confounding illness; pregnancy or intention of becoming pregnant; or use of non-herbal Chinese or local medicine with unknown/unspecified content within the 90 days prior to screening. No concomitant illnesses or medications were recorded in the included trial population at screening. One subject reported use of levofloxacin hydrochloride and sodium bicarbonate during the trial period.

■ Procedures

All subjects attended a screening visit, a dosing visit (2-14 days after screening), and a follow-up visit (7-21 days after dosing visit). Subjects were instructed to avoid smoking, strenuous exercise, consumption of alcohol, coffee, tea, or beverages containing methylxanthine for 24 hours prior to the dosing visit. At the dosing visit, all eligible subjects received a single dose of IDegAsp (0.5 U/kg body weight) via subcutaneous injection in the lower abdomen using a 3 mL pre-filled pen (PDS290 [FlexTouch®] 100 U/mL, Novo Nordisk A/S). Subjects were provided with standard meals (breakfast [served after dosing], lunch [-4 hours after breakfast], and dinner [-10 hours after breakfast]). Subjects were permitted water ad libitum throughout; however, tea and coffee were prohibited. If signs of hypoglycemia occurred, subjects were encouraged to have sweet
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**Outcomes**

The primary endpoint was to assess the total PK exposure after a single dose of IDegAsp in terms of degludec and IAsp, determined using area under the serum IAsp concentration–time curve from 0 to 12 hours (AUCIAsp,total,SD), and area under the serum degludec concentration–time curve from 0 to 120 hours (UAUCdeglatec,total,SD). Secondary endpoints included additional PK properties and assessment of the safety and tolerability of IDegAsp. Safety data included treatment-emergent adverse events (AEs), electrocardiogram, physical examination, vital signs, and laboratory assessments.

**Statistical analyses**

Endpoints were analyzed from data obtained from all subjects dosed with IDegAsp. Primary endpoints were derived from individual PK profiles using the linear trapezoidal technique based on observed values. Missing data were imputed using linear interpolation. Secondary PK endpoints were derived from insulin concentration–time curves. All PK endpoints and safety data were summarized using descriptive statistics. Statistical operations were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

**Results**

**Subjects**

Of the 65 subjects screened, 24 were eligible for the study. The majority of subjects (32) failed screening due to violation of inclusion or exclusion criteria. Nine subjects failed screening due to withdrawal of consent. All eligible subjects were exposed, completed the study, and contributed to the PK and safety analyses. There were no withdrawals due to safety concerns or protocol deviation. Baseline demographics are shown in Table 1.

**IAsp PK endpoints in healthy Chinese subjects following a single dose of IDegAsp**

The estimated mean total IAsp exposure following a single dose of IDegAsp (AUCIAsp,total,SD) was 541 pmol·h/L (95% confidence interval [CI] 502;582). The estimated mean maximum IAsp concentration (Cmax,IAsp,SD) was 217 pmol/L (95% CI 193;244). The estimated median onset of IAsp appearance (time from administration until concentration >30 pmol/L) was 14 min, and the median time to maximum IAsp concentration (tmax,IAsp,SD) was 1.0 hour.

**IAsp PK characteristics obtained in healthy Chinese subjects and other populations following a single dose of IDegAsp**

To facilitate comparison of IAsp PK characteristics following a single dose of IDegAsp in healthy Chinese subjects versus those in other populations, the IAsp PK profiles in healthy Chinese subjects, heathy Caucasian subjects, and Caucasian and Japanese subjects with T1D are shown in Figure 1 [17,23,24]. In addition, selected IAsp PK characteristics following single-dose IDegAsp derived from the present study and other PK trials with similar methodology are provided in Table 2 [17,23,24].

**Degludec PK endpoints in healthy Chinese subjects**

The estimated mean total degludec exposure following single-dose IDegAsp (AUCdeglatec,total,SD) was 88,271 pmol·h/L (95% CI 83,615;93,187). The estimated mean maximum degludec concentration (Cmax,deglatec,SD) was 3472 pmol/L (95% CI 3013;4002), and the median time to maximum degludec concentration (tmax,deglatec,SD) was 10.5 hours.

**Degludec PK characteristics in different populations following IDegAsp or degludec after a single dose, and degludec at steady state**

The degludec PK profile, observed following a...
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A single dose (0.4 U/kg) of degludec in healthy Chinese subjects, is displayed in Figure 2 alongside PK profiles derived from a population PK model (non-linear mixed-effects method) applied to simulate degludec at steady state in these subjects [22]. To facilitate comparisons across populations, overviews of selected PK properties are provided in Table 3 (single-dose IDegAsp or degludec) [17,22–24] and Table 4 (at degludec steady state) [10,19,22,25–28].

Safety

IDegAsp was well tolerated in all subjects. A total of six treatment-emergent AEs (otitis externa, mouth ulceration, chest discomfort, and diarrhea, dyspnea, and heart palpitations) were observed in three subjects; no AEs were serious and all were mild in severity. No AEs were assessed by the investigator as being probably related to the study drug. No safety concerns were raised following electrocardiogram, physical examination, or laboratory assessments.

Discussion

This is the first study to investigate the PK properties of IDegAsp in healthy Chinese adults. However, before the results are considered in detail, it is important to note that serum concentrations of degludec and IAsp are not additive and should not be directly compared. Serum concentrations of degludec and IAsp differ by several orders of magnitude due to the reversible binding of degludec to albumin in the circulation, thus the translation of PK data for the individual degludec and IAsp

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28.6 (5.2)</td>
<td>26.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.7 (6.0)</td>
<td>63.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.0 (1.3)</td>
<td>22.0</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>15 (62.5)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>9 (37.5)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Race, Asian non-Indian (Chinese)</td>
<td>24 (100)</td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation.

Table 2. PK properties of IAsp in different populations following a single dose of IDegAsp

<table>
<thead>
<tr>
<th>Population</th>
<th>AUC&lt;sub&gt;IAsp,total,SD&lt;/sub&gt; (pmol·h/L), mean (CV)</th>
<th>C&lt;sub&gt;max,IAsp,SD&lt;/sub&gt; (pmol/L), mean (CV)</th>
<th>t&lt;sub&gt;max,IAsp,SD&lt;/sub&gt; (hours), median (min;max)</th>
<th>Onset of appearance† (minutes), median (min;max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy, Chinese</td>
<td>541 (18)</td>
<td>217 (27)</td>
<td>1.0 (0.7;1.3)</td>
<td>14 (7;28)</td>
</tr>
<tr>
<td>(current study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy, predominantly Caucasian</td>
<td>645 (22)</td>
<td>218 (27)</td>
<td>1.3 (0.7;2.5)</td>
<td>20 (6;24)</td>
</tr>
<tr>
<td>(n = 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1D, Japanese</td>
<td>813 (53)</td>
<td>280 (49)</td>
<td>1.2 (0.5;2.8)</td>
<td>12 (2;23)</td>
</tr>
<tr>
<td>(n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1D, Caucasian</td>
<td>833 (33)</td>
<td>252 (30)</td>
<td>1.3 (0.5;2.8)</td>
<td>N/A</td>
</tr>
<tr>
<td>(n = 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IDegAsp dosed at 0.5 U/kg in all trials. Values for AUC<sub>IAsp,total,SD</sub> and C<sub>max,IAsp,SD</sub> are the geometric mean. †Time from administration until the first time concentration >30 pmol/L. AUC<sub>IAsp,total,SD</sub> total IAsp exposure (area under the serum aspart concentration–time curve) following an SD of IDegAsp. C<sub>max,IAsp,SD</sub> maximum IAsp concentration following an SD of IDegAsp. CV, coefficient of variation. IAsp, insulin aspart. IDegAsp, insulin degludec/insulin aspart co-formulation. N/A, not applicable. t<sub>max,IAsp,SD</sub> time to maximum IAsp concentration following IDegAsp SD. SD, single dose. T1D, type 1 diabetes.
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Table 3. PK properties of degludec in different populations following a single dose of IDegAsp or degludec

<table>
<thead>
<tr>
<th>Population</th>
<th>AUC&lt;sub&gt;degludec,total,SD&lt;/sub&gt; (pmol·h/L), mean (CV)</th>
<th>C&lt;sub&gt;max,degludec,SD&lt;/sub&gt; (pmol/L), mean (CV)</th>
<th>t&lt;sub&gt;max,degludec,SD&lt;/sub&gt; (hours), median (min; max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy, Chinese† (n = 24) (current study)</td>
<td>88,271 (13)</td>
<td>3472 (35)</td>
<td>10.5 (7.0; 20.0)</td>
</tr>
<tr>
<td>Healthy, Chinese‡ (n = 24)</td>
<td>78,192 (11)</td>
<td>3489 (26)</td>
<td>11.0 (4.0; 15.0)</td>
</tr>
<tr>
<td>Healthy, mainly Caucasian† (n = 26)</td>
<td>76,398 (15)</td>
<td>2400 (20)</td>
<td>13.0 (7.0; 19.0)</td>
</tr>
<tr>
<td>T1D, Japanese† (n = 21)</td>
<td>66,178 (45)</td>
<td>2068 (36)</td>
<td>12.0 (6.0; 24.0)</td>
</tr>
<tr>
<td>T1D, Caucasian† (n = 27)</td>
<td>81,363 (23)</td>
<td>2498 (22)</td>
<td>13.0 (8.0; 22.0)</td>
</tr>
</tbody>
</table>

†IDegAsp dosed at 0.5 U/kg (equal to 0.35 U/kg degludec); ‡degludec dosed at 0.4 U/kg. Values for AUC<sub>degludec,total,SD</sub> and C<sub>max,degludec,SD</sub> are the geometric mean. AUC<sub>degludec,total,SD</sub> is total degludec exposure (area under the serum degludec concentration–time curve) following IDegAsp or degludec SD; C<sub>max,degludec,SD</sub> is maximum degludec concentration following IDegAsp or degludec SD. CV, coefficient of variation. IAsp, insulin aspart. IDegAsp, insulin degludec/insulin aspart co-formulation. N/A, not applicable. t<sub>max,degludec,SD</sub> is time to maximum IAsp concentration following IDegAsp or degludec SD. SD, single dose. T1D, Type 1 diabetes.

Figure 2. Mean 24-hour PK profile after a single dose of degludec (observed and model-based) and at steady state after once-daily dosing of degludec (simulation-based) in healthy Chinese subjects [22].

Data are observed values and model-based estimates following a single dose of degludec (0.4 U/kg), and a simulation of degludec at steady state based on a population PK model. PK, pharmacokinetic. SD, single dose. SS, steady state.

Components into PD results for IDegAsp is complex [8]. The degludec component has a half-life of >25 hours, and clinically meaningful steady state serum concentrations are only achieved after 2-3 days of once-daily IDegAsp administration. Therefore, given the single-dose design, interpretation of the present study is necessarily focused on ascertaining whether the IDegAsp PK profile confirms separation of the basal and bolus glucose-lowering actions in a Chinese population (i.e., confirms the absence of the ‘shoulder effect’, reported with premix insulins [4]), rather than serving as a broader investigation into the clinical efficacy of IDegAsp. The shape of the mean IAsp PK profile following a single dose of IDegAsp in healthy Chinese adults was similar to that obtained in other populations (Table 1) [17,23,24]. In addition, the AUC<sub>IAsp,total,SD</sub> observed in healthy Chinese adults was comparable with the exposure levels in other populations, and appears to be lower in healthy individuals compared with people with T1D [17,23,24]. The C<sub>max,IAsp,SD</sub> and t<sub>max,IAsp,SD</sub> and time to onset of IAsp appearance in healthy Chinese adults were also comparable with the same endpoints in healthy Caucasian subjects, and Caucasian and Japanese subjects with T1D [17,23,24]. Taking normal inter-subject variation into consideration, these data suggest similar PK properties for IAsp when administered as IDegAsp in all populations investigated to date. For the degludec component of IDegAsp, the AUC<sub>degludec,total,SD</sub> in healthy Chinese subjects was comparable with that in other populations following single-dose IDegAsp or degludec (Table 3) [17,22-24]. The t<sub>max,degludec,SD</sub> however, was of marginally shorter duration in healthy Chinese subjects versus other populations [17,22-24]. The maximum concentration of degludec...
subjects, healthy Caucasian adults, and Caucasian and Japanese subjects with T1D (Figure 3) [10,19,22]. Across the wider literature, degludec PK endpoints reported in healthy Chinese subjects with steady state degludec (including the \(C_{\text{max,degludec,SS}}\) and \(t_{\text{max,degludec,SS}}\)) are comparable with the same endpoints reported in other populations (Table 4) [10,19,25-28]. Given that the PK properties of IAsp after a single dose of IDegAsp, and degludec at steady state in healthy Chinese subjects, were comparable with other populations, it is reasonable to infer that IDegAsp PD data from Caucasian and Japanese adults are applicable to Chinese adults (see Haahr et al. 2017 for an overview). The glucose-lowering profile of IDegAsp at steady state over 24 hours (administered once-daily in patients with T1D) shows a clear separation between the bolus and basal components; the rapid increase and distinct peak of IAsp, and the flat, consistent, ultra-long duration of degludec (Figure 4) [11].

For both IAsp and degludec, the between-subject variability in insulin absorption was low as the observed coefficient of variation in PK endpoints was small. Recent data confirmed the ability of a population PK model to accurately predict the degludec PK profile following a single dose of degludec in healthy Chinese subjects (note the similarity of the model-based and observed single-dose profiles, Figure 2) [22]. The model was subsequently employed to simulate a steady state degludec PK profile. Additional modelling data demonstrated the similarity of the degludec PK profiles that have been simulated with IDegAsp at steady state in healthy Chinese subjects, healthy Caucasian adults, and Caucasian and Japanese subjects with T1D (Figure 3) [10,19,22]. Across the wider literature, degludec PK endpoints reported in healthy Chinese subjects with steady state degludec (including the \(C_{\text{max,degludec,SS}}\) and \(t_{\text{max,degludec,SS}}\)) are comparable with the same endpoints reported in other populations (Table 4) [10,19,25-28]. Given that the PK properties of IAsp after a single dose of IDegAsp, and degludec at steady state in healthy Chinese subjects, were comparable with other populations, it is reasonable to infer that IDegAsp PD data from Caucasian and Japanese adults are applicable to Chinese adults (see Haahr et al. 2017 for an overview). The glucose-lowering profile of IDegAsp at steady state over 24 hours (administered once-daily in patients with T1D) shows a clear separation between the bolus and basal components; the rapid increase and distinct peak of IAsp, and the flat, consistent, ultra-long duration of degludec (Figure 4) [11].

### Table 4. PK properties of degludec at steady state in different populations

<table>
<thead>
<tr>
<th>Population</th>
<th>(\text{AUC}_{\text{degludec,SS}}) (pmol·h/L), mean</th>
<th>(\text{AUC}<em>{\text{degludec,total,SS}} / \text{AUC}</em>{\text{degludec,\tau,SS}}), mean</th>
<th>(C_{\text{max,degludec,SS}}) (pmol/L), mean</th>
<th>(t_{\text{max,degludec,SS}}) (hours), median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy, Chinese</td>
<td>76,609</td>
<td>0.53</td>
<td>3996</td>
<td>9.5</td>
</tr>
<tr>
<td>(n = 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy, Caucasian</td>
<td>74,353</td>
<td>0.51</td>
<td>3367</td>
<td>10.5</td>
</tr>
<tr>
<td>(n = 19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1D, Japanese</td>
<td>81,270</td>
<td>0.53</td>
<td>4311</td>
<td>8.0</td>
</tr>
<tr>
<td>(n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1D, Caucasian</td>
<td>82,612</td>
<td>0.53</td>
<td>4363</td>
<td>9.0</td>
</tr>
<tr>
<td>(n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values for \(\text{AUC}_{\text{degludec,SS}}, \text{AUC}_{\text{degludec,total,SS}} / \text{AUC}_{\text{degludec,\tau,SS}}\) and \(C_{\text{max,degludec,SS}}\) are the geometric mean. \(\text{AUC}_{\text{degludec,SS}}\) total degludec exposure (area under the serum degludec concentration-time curve) at steady state. \(\text{AUC}_{\text{degludec,total,SS}}\) 12-hour degludec exposure (area under the serum degludec concentration-time curve) at steady state. \(C_{\text{max,degludec,SS}}\) maximum steady state degludec concentration. \(t_{\text{max,degludec,SS}}\) time to maximum steady state degludec concentration. SS, steady state. T1D, type 1 diabetes. Adapted from Hu et al. Pharmacokinetic properties of insulin degludec in healthy Chinese subjects. Diabetes Manag 2019;9(1):20–27, under the terms of the Creative Commons Attribution (CC-BY) license.
The degludec basal component allows flexibility in the timing of IDegAsp administration [31]. It has also been argued that the ultra-long duration of action of the IDegAsp basal component may reduce the impact of missed injections in Japanese patients [19]. Given that we demonstrate the applicability of the Japanese and Caucasian PD data, this would also be expected for Chinese patients.

**Limitations**

The main limitations of the present study were the single-dose design (being representative of the first day of IDegAsp once-daily dosing only), and that no direct PD measurements were performed. However, the study fulfilled the intention of demonstrating that, following a single dose of IDegAsp, the PK properties of the component insulins in Chinese adults were comparable with those obtained in other populations.

**Conclusion**

This study demonstrates that the distinct PK profiles of the IDegAsp component insulins are present in healthy Chinese adults, and are consistent with similar observations in Japanese and Caucasian populations. Although insulin doses are adjusted on an individual basis, this study suggests that no specific IDegAsp dosing recommendations are required for Chinese patients. The clinical benefits of IDegAsp observed in other populations, including basal and prandial insulin coverage with one injection and low rates of hypoglycemia, are also expected in Chinese adults.

**Acknowledgements**

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**Data sharing**

The subject level analysis data sets presented in the publication are available from the corresponding author on reasonable request.

**Disclosures**

Shi Aixin, Li Yang, Xie Panpan, Qi Wenyuan and Yang Lei have no conflicts of interest to declare. Zhang Ran, Hanne Haahr and Hongfei Xu are employees of Novo Nordisk. Hanne Haahr and Hongfei Xu are also shareholders of Novo Nordisk.

**Contributions**

Shi Aixin contributed to the concept/design of the protocol, subject recruitment, data collection, data interpretation, and statistical analysis. Li Yang contributed to the concept/design of the protocol, subject recruitment, data collection, data interpretation, and statistical analysis. Xie Panpan contributed to subject recruitment, data collection, data interpretation, and statistical analysis. Qi Wenyuan contributed to subject recruitment, data collection, data collection, data interpretation, and statistical analysis.
interpretation, and statistical analysis. Yang Lei contributed to subject recruitment, data collection, data interpretation, and statistical analysis. Xu Hongfei contributed to the concept/design of the protocol, medical support to trial execution and data interpretation. Zhang Ran contributed to the statistical analysis. Hanne Haahr was responsible for trial design and data interpretation. All authors contributed to drafting and critical revision of the manuscript.

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