Population Pharmacokinetics of Survodutide in Subjects with Overweight or Obesity with and without Type 2 Diabetes Mellitus Based on Phase I and Phase II Data

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Objectives

To characterize the population PK of survodutide based on Phase I and Phase II data. Specific objectives were to describe survodutide absorption and disposition, quantify the associated inter-individual variability, and evaluate the impact of subjects' characteristics on survodutide exposure.

Introduction

- Agonists of incretin receptors are increasingly developed as novel treatment options in a range of metabolic diseases.
- Survodutide is a dual glucagon/GLP1 receptor agonist resulting in increased energy expenditure, reduced energy intake, and weight loss.[1].
- The aim of the present analysis was to characterize the population PK of survodutide in subjects with overweight or obesity with and without T2DM based on Phase I and Phase II data.

Data and Methods

- 3 Phase I studies (1404-0001, 1404-0003 and 1404-0021) and 2 Phase II studies in subjects with obesity with (1404-0002) and without (1404-0036) T2DM were included in the analysis. Survodutide was administered subcutaneously. Single doses from 0.3 to 1.2 mg, daily maintenance dose of 0.45 mg and weekly maintenance doses from 0.3 to 4.8 mg were evaluated in a total of 745 subjects. Different escalation schemes to the maintenance doses were evaluated. PK sampling was rich in Phase I and sparse in Phase II studies.
- Covariates tested using SCM with adaptive scope reduction and stage-wise filtering[2]: WT, BMI, percentage fat mass, eGFR, race, sex and dose.
- Covariates tested using a full-model approach, after model finalization: ADA both as subject-level and time-varying covariate.
- The population analysis was performed using NONMEM. Univariate covariate effects were visualized on $C_{max,ss}$ and $AUC_{\tau,ss}$. Parameters uncertainty was derived by drawing 250 samples from the variance-covariance matrix obtained from NONMEM.

Results

- A one-compartment model with linear absorption and elimination (Table 1) best described the data (Figures 1 and 2). Forest plots illustrating the covariates' effect on $C_{max,ss}$ and $AUC_{\tau,ss}$ are presented in Figures 3 and 4. The post hoc analysis based on the full-model approach suggested that ADA had no impact on survodutide PK (Figure 4).

Table 1. Parameter estimates of the final PK model for survodutide.

	Parameter (unit)	Estimate (RSE%)	Shrinkage
Structural parameters	CL/F (L/h)	0.0629 (1.08)	13.2 %
	V/F (L)	11.2 (2.02)	20.6 %
	K_a (h^{-1})	0.194 (9.65)	56.3 %
Covariate effects	Allometric exponent for WT on CL/F	1.10 (5.62)	
	Allometric exponent for WT on V/F	1.17 (9.28)	
	Fractional change in CL/F for study 1404-0036†	-0.143 (9.58)	
	Fractional change in CL/F for Black or African American	-0.122 (25.7)	
	F_{rel} for qd regimens	1.16 (3.93)	
	F_{rel} for SRD study	1.21 (2.30)	
	Dose effect on Ka	0.0675 (45.5)	
	WT effect on Ka	-0.0133 (51.8)	
Inter-individual variability	IIV on CL/F (CV)	0.145 (4.47)	13.2 %
	IIV on V/F (CV)	0.234 (11.5)	20.6 %
	Relative increase in IIV V/F for study 1404-0036	1.77 (18.0)	
	Correlation IIV CL/F and V/F	0.391 (14.4)	
	IIV on Ka (CV)	0.542 (11.8)	56.3 %
	IIV on proportional RUV for Phase I studies	0.411 (6.52)	10.5 %
	Relative increase in IIV RUV for Phase II studies	1.36 (9.29)	
Residual unexplained variability	Proportional RUV for Phase I studies (CV)	0.0992 (3.76)	0.0957 %
	Proportional RUV for Phase II studies (CV)	0.153 (2.78)	3.35 %
	Additive RUV (nM)	0.610 (8.94)	1.36 %

†Lower CL/F estimates in normoglycemic subjects with obesity compared to subjects with obesity and T2DM have consistently been reported for other mono or dual GLP1 receptor agonists.[3,4]

Results

Figure 1. Prediction-corrected visual predictive check of survodutide concentrations versus time after first dose, stratified by study.

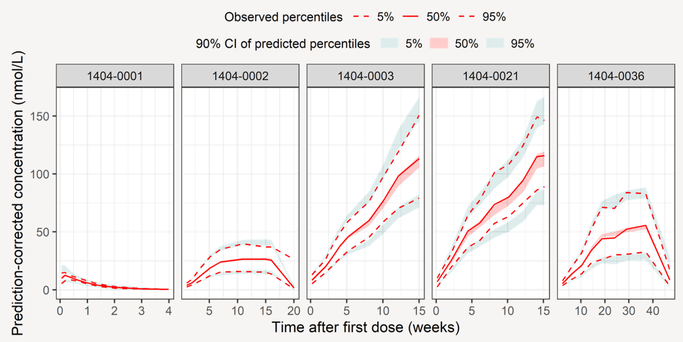


Figure 2. Prediction-corrected visual predictive check of survodutide concentrations versus time after first dose, stratified by BMI group.

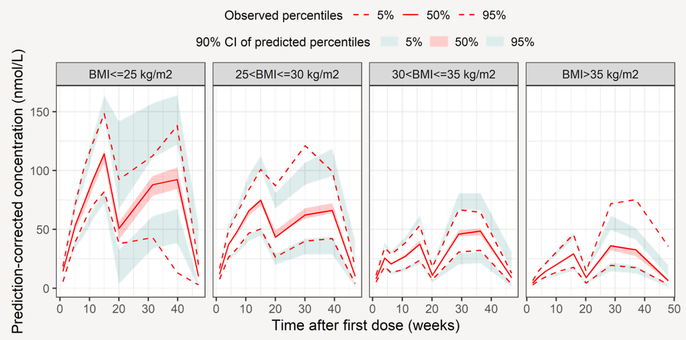


Figure 3. Forest plot illustrating the effects of covariates identified in the SCM analysis. Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CI.

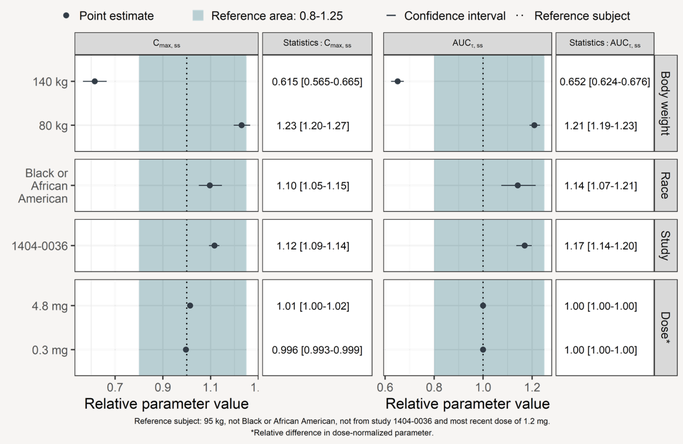
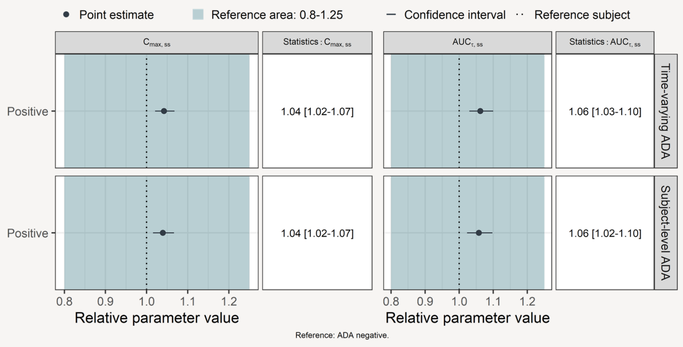


Figure 4. Forest plot illustrating the effect of ADA based on the full-model approach. Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CI.



Conclusions

The PK of survodutide was best described by one-compartment model with first-order absorption and elimination.

Among the different covariates that were evaluated, only WT had a relevant effect on the steady state exposure of survodutide, with heavier subjects being less exposed in terms of $AUC_{\tau,ss}$ and $C_{max,ss}$ compared to lighter subjects.

The observed magnitude of the covariate effects alongside the flexible dose escalation scheme suggests that no dose adjustments are warranted for survodutide.

Abbreviations
ADA, anti-drug antibody; $AUC_{\tau,ss}$, area under the concentration-time curve during a dosing interval at steady state; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; $C_{max,ss}$, maximum concentration during a dosing interval at steady state; CL/F, apparent clearance; eGFR, estimated glomerular filtration rate; F_{rel}, relative bioavailability; GLP1, glucagon-like-peptide 1; IIV, inter-individual variability; K_a, first-order absorption rate constant; PK, pharmacokinetic; qd, once daily; RSE, relative standard error; RUV, residual unexplained variability; SCM, stepwise covariate modeling; SRD, single rising dose; T2DM, Type II Diabetes Mellitus; V/F, apparent volume of distribution; WT, body weight.

References
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3.) Overgaard et al. Clin Pharmacokinet. 55(11):1413-22 (2016).
4.) URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/ 2022/215866Orig1s000ClinPharmR.pdf.

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