

Population pharmacokinetic/pharmacodynamic modeling to demonstrate comparability of exposure and activity of insulin aspart Sanofi

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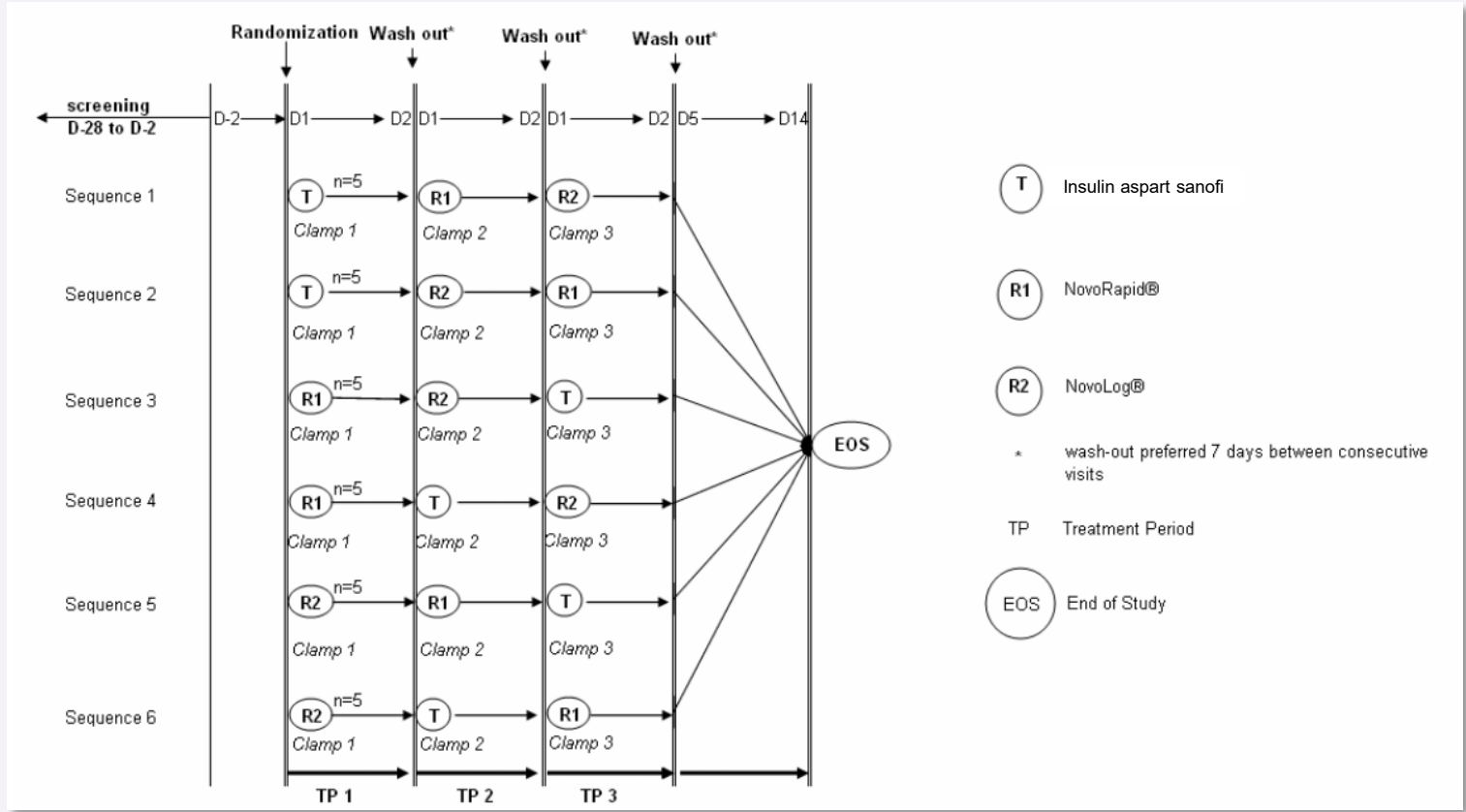
sanofi

Background and Objective

Insulin aspart Sanofi (IAS) is a biosimilar of Novo Nordisk's rapid acting insulin aspart, approved as NovoLog® in the US and NovoRapid® in the EU. In a phase 1 study (PDY12695, ClinicalTrials.gov Identifier: NCT03202875), the pharmacokinetic (PK) parameters $AUC_{0-\infty}$ and C_{max} demonstrated bioequivalence (confidence intervals in the range of 0.8 to 1.25 between IAS, NovoRapid, and NovoLog). Likewise, the pharmacodynamic (PD) variables $GIR-AUC_{0-12}$ and GIR_{max} (GIR = glucose infusion rate, AUC = area under the curve) were similar for all 3 insulin formulations. However, in the late phase (4 to 12 hours) of the PK and PD profiles, partial AUC 4-12 hours was significantly lower for IAS than for NovoRapid (**Tab. 1**). Differences in the late phase could indicate differences in the absorption process due to flip-flop kinetics (i.e., elimination rate is faster than absorption rate). A similar absorption rate is essential to demonstrate bioequivalence between products. The main objective of the analysis was to use modeling and simulation to get a better understanding of potential differences in the absorption rates between IAS (test product) and NovoRapid/NovoLog (reference products) and their impact on the GIR.

Study Design

PDY12695: A randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence crossover study to compare exposure and activity of IAS to NovoRapid and NovoLog using the euglycemic clamp technique. Male and female subjects, aged between 18 and 65 years, inclusive, with type 1 diabetes mellitus for more than 1 year. Single dose injections of 0.3 U/kg.



Tab.1 Statistical analysis of PK and PD variables in study PDY12695 – Point estimates of treatment ratios with 90% confidence intervals; AUC is the $AUC_{0-\infty}$ of insulin aspart, C_{max} is C_{max} of insulin aspart

Treatment ratio	GIR-AUC ₀₋₁₂	AUC	GIR-AUC ₄₋₁₂	AUC ₄₋₁₂
IAS vs. NovoRapid	0.96 (0.89, 1.04)	0.92 (0.88, 0.96)	0.71 (0.56, 0.91)	0.73 (0.61, 0.87)
IAS vs. NovoLog	0.99 (0.91, 1.07)	0.92 (0.88, 0.96)	0.83 (0.65, 1.06)	0.73 (0.60, 0.87)
NovoLog vs. NovoRapid	0.97 (0.90, 1.05)	1.00 (0.95, 1.04)	0.86 (0.67, 1.09)	1.00 (0.84, 1.20)

Treatment ratio	GIR-C _{max}	C _{max}
IAS vs. NovoRapid	1.02 (0.95, 1.09)	0.97 (0.90, 1.05)
IAS vs. NovoLog	1.03 (0.96, 1.10)	0.93 (0.87, 1.01)
NovoLog vs. NovoRapid	0.99 (0.92, 1.06)	1.04 (0.96, 1.12)

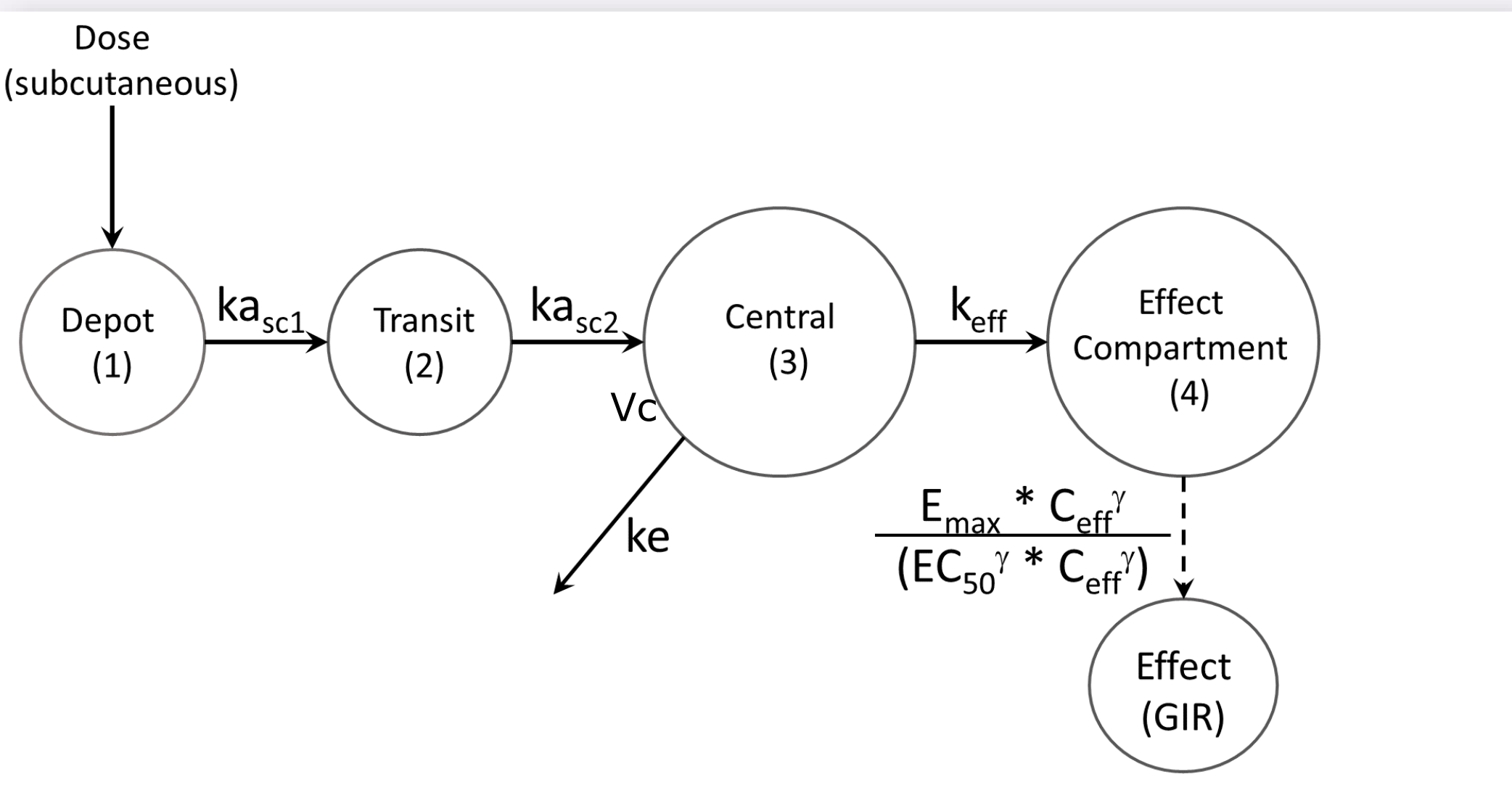
Methods

To describe the insulin aspart concentrations, two empirical PK/PD models with similar structure were developed, i.e., one for the test product (IAS) and one for the reference product. The two reference products (NovoRapid and NovoLog) were considered as one. The PK model that best described the time course of insulin aspart concentrations (**Tab. 2**) was a one-compartment model with first-order absorption and a transit compartment (**Fig. 1**). The "M3" method was used to maximize the likelihood for a measurement being below the quantifiable range. The PK/PD model consisted of an effect compartment model linked to the central compartment for insulin aspart disposition in plasma as previously reported [1, 2]. PK was modeled first, and PK parameters served as input for the PK/PD model (sequential approach). Simulations considering the uncertainty in the population parameter estimates (number of IDs = 30, number of trials = 100) were performed to evaluate potential differences in insulin aspart PK (AUC) and PD effect (GIR-AUC) between the products.

Tab. 2 Data included in the analysis

	N, subjects	N, PK samples	N (%), PK samples < LLOQ	N, GIR
IAS	29	789	187 (19.2)	19402
NovoLog / NovoRapid	30	1638	338 (17.1)	39862

Fig. 1 PK/PD model. GIR, glucose infusion rate; EC_{50} , concentration of half maximum effect in effect compartment; k_{eff} , transfer rate constant for effect compartment; C_{eff} , concentration in effect compartment; ka_{sc1} , absorption rate constant 1; ka_{sc2} , absorption rate constant 2; V_c , volume of distribution in central compartment; ke , elimination rate constant; γ , Hill factor



Results

The PK and PK/PD models adequately described the concentration versus time profiles of IAS and NovoRapid/NovoLog as well as the relationship between insulin aspart and GIR as evaluated by likelihood of data, accuracy of parameter estimates (standard error), goodness of fit plots, and visual predictive check (**Fig. 2**).

Partially, model parameters were different among the products (k_e , V_c , EC_{50}).

Simulations considering only population PK/PD parameter estimates and their uncertainties showed the insulin aspart and GIR time profiles to almost fully overlap (**Fig. 3**).

The simulations showed slight differences in the typical (median) values describing the late phases of the PK (AUC_{4-12}) and PD ($GIR-AUC_{4-12}$) profiles. However, the 90% confidence intervals formed by the uncertainty of the typical values were fully overlapping (**Tab. 3**).

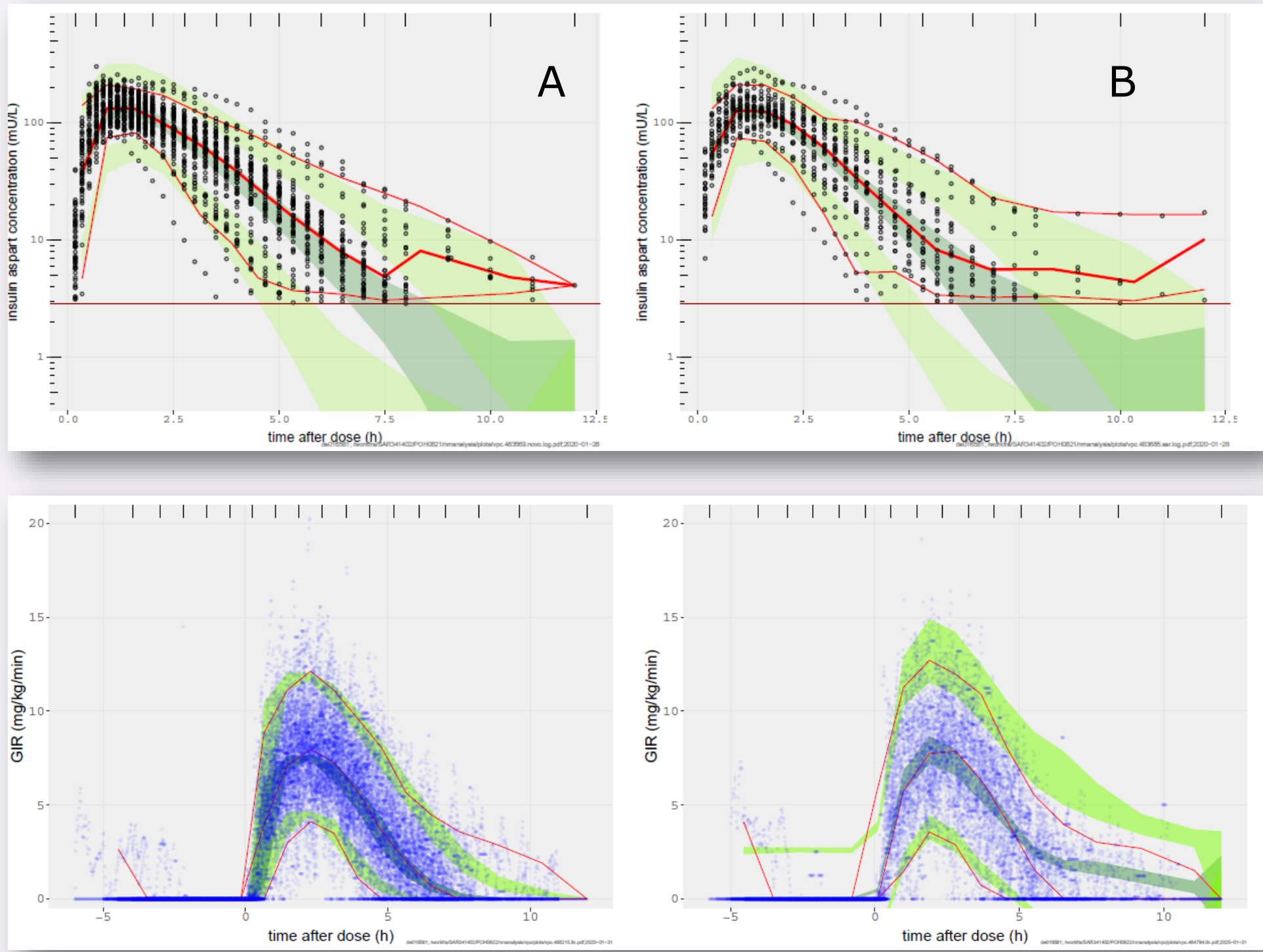
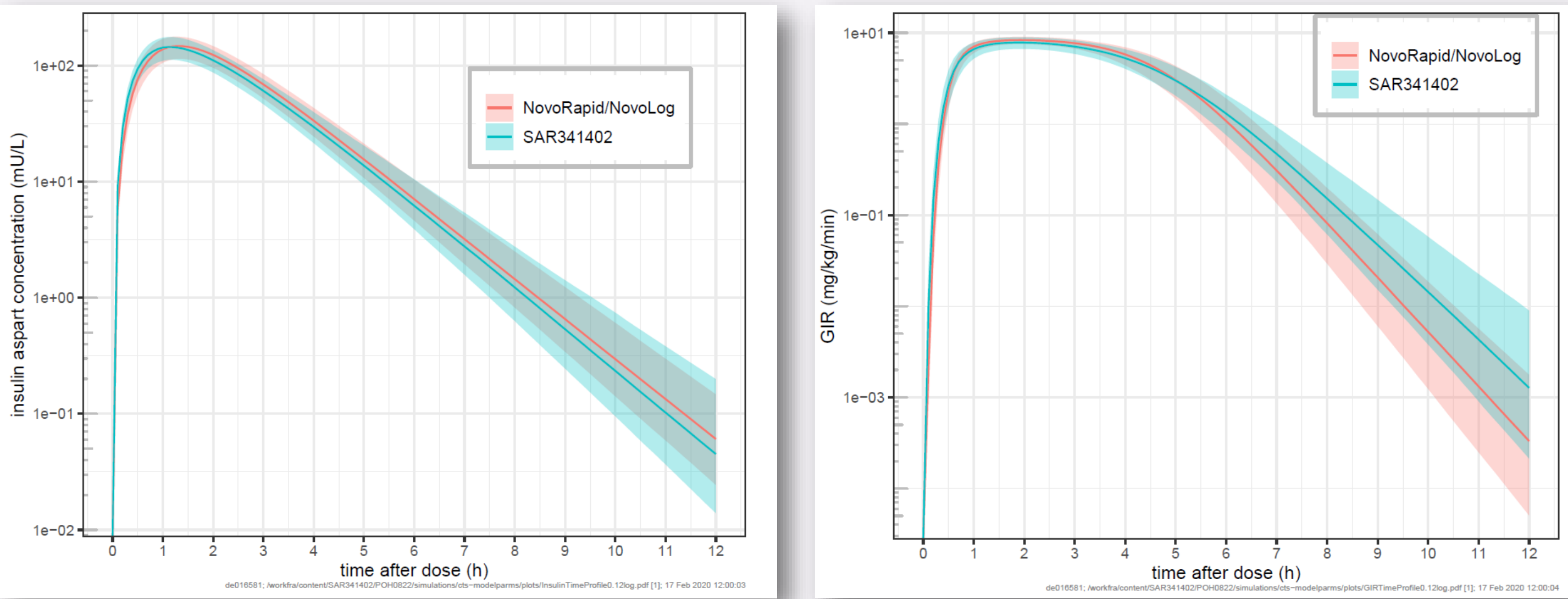


Fig. 2 Visual predictive check of insulin aspart (upper row) and GIR versus time after dose (lower row). A = NovoRapid/NovoLog, B = IAS. Dots represent observations. The solid red lines represent 5th, 50th (median) and 95th percentiles of observations. The green shaded areas represent the 90% confidence interval around the 5th, 50th (median) and 95th percentiles of the simulations (n = 200 subproblem simulations)

Tab. 3 Prediction of AUC_{4-12} of insulin aspart and GIR. Values are median (5th, 95th percentile) defined by the standard error of the estimated parameters

	GIR-AUC ₄₋₁₂ (mg/kg)	AUC ₄₋₁₂ (ng.h/L)
NovoRapid/NovoLog	433 (280, 619)	1511 (1037, 2107)
IAS	446 (305, 639)	1324 (897, 2061)

Fig. 3 Predicted insulin aspart concentration versus time profiles (left panel) and GIR versus time profiles (right panel). Shaded areas represent the 90% prediction intervals resulting from the uncertainty in the population parameter estimates estimated by NONMEM (SAR341402 = IAS)



Conclusions

Models were successfully developed to describe the PK of the insulins and their PK/PD (GIR) relationship. The simulations clearly illustrated that neither the profiles nor the derived AUCs allow to conclude that they are different. Therefore, the differences observed in the study are most likely due to chance. This evaluation was also accepted by the regulators.

References

- Landersdorfer CB, Jusko WJ. Pharmacokinetic/pharmacodynamic modeling of glucose clamp effects of inhaled and subcutaneous insulin in healthy volunteers and diabetic patients. Drug Metab. Pharmacokinet. 2010;25 (5):418–29.
- Rueppel D, Dahmen R, Boss A, et al. A Population Dose-Response Model for Inhaled Technosphere Insulin Administered to Healthy Subjects. CPT Pharmacometrics Syst Pharmacol 2017;6 (6):365–72.