

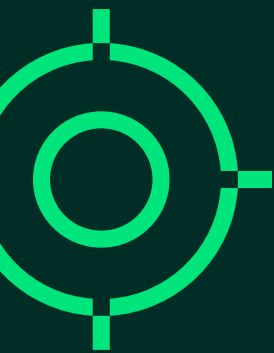
Deconvolution of gastric emptying based on interaction between paracetamol and liraglutide and its extrapolation to comedications using a PBPK modelling approach

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Objective

- To simulate the impact of delayed GE caused by the GLP-1RA liraglutide^{1,2} on the PK of various oral drugs (atorvastatin, digoxin, ethinylestradiol, griseofulvin, levonorgestrel, and lisinopril)^{3–6} using PBPK modelling for GE deconvolution

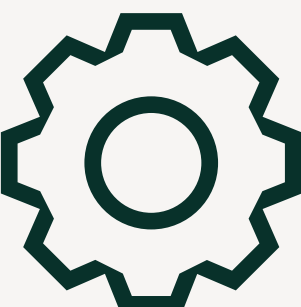


Introduction



- GLP-1RAs are a class of medications intended to manage T2D, obesity, and MASH
- A key effect of GLP-1RAs is delayed GE, which can impact the absorption and PK of other medications
- Therefore, pharmaceutical companies developing GLP-1RAs must conduct clinical DDI studies with potential comedications

Methods



- GastroPlus® version 9.8 (Simulations Plus, Inc.) was used to build PBPK models for paracetamol, atorvastatin, digoxin, ethinylestradiol, griseofulvin, levonorgestrel, and lisinopril to describe their in vivo absorption and PK
- Published physicochemical properties and PK of these compounds were used to develop and validate their PBPK models
- Simulations for paracetamol, given as a 1500 mg dose dissolved in a drink, were conducted to match the clinical study design,⁵ with ingestion during a fixed breakfast
- The PBPK model used in the simulations matched several characteristics of the study participants, including age, weight, sex, and disease state (healthy or living with obesity)
- A number of modelling assumptions were made, focusing on GE as the main factor affecting the PK of drugs administered with and without liraglutide, under consistent food conditions and meal timing for the deconvolved GET as in the source clinical study
- GE was manually deconvolved from paracetamol plasma concentration vs time profiles obtained under fed conditions in the absence/presence of liraglutide at steady state
- Two types of deconvolutions were used
 - During the simple deconvolution, one value of GET was fitted over the entire length of paracetamol absorption to approximately reproduce its observed plasma concentration vs time profiles
 - In complex deconvolution, multiple GETs were fitted over the time of paracetamol absorption to match its plasma concentration vs time profiles as closely as possible
- The deconvolved GET using the complex deconvolution was then applied to simulate the PK of the other comedications in the absence and presence of liraglutide
- The simulated impact of liraglutide-induced prolonged GE was then compared against the observed data

Results



- While complex deconvolution allowed a better reproduction of the plasma PK profile of co-administered drugs, simple deconvolution (not shown) still captured the impact of GE prolongation on their PK. It can serve as a good approximation for PK parameter estimation

Figure 1. Observed vs simulated plasma concentration vs time profiles for paracetamol dosed before (left) and after (right) administration of liraglutide 1.8 mg

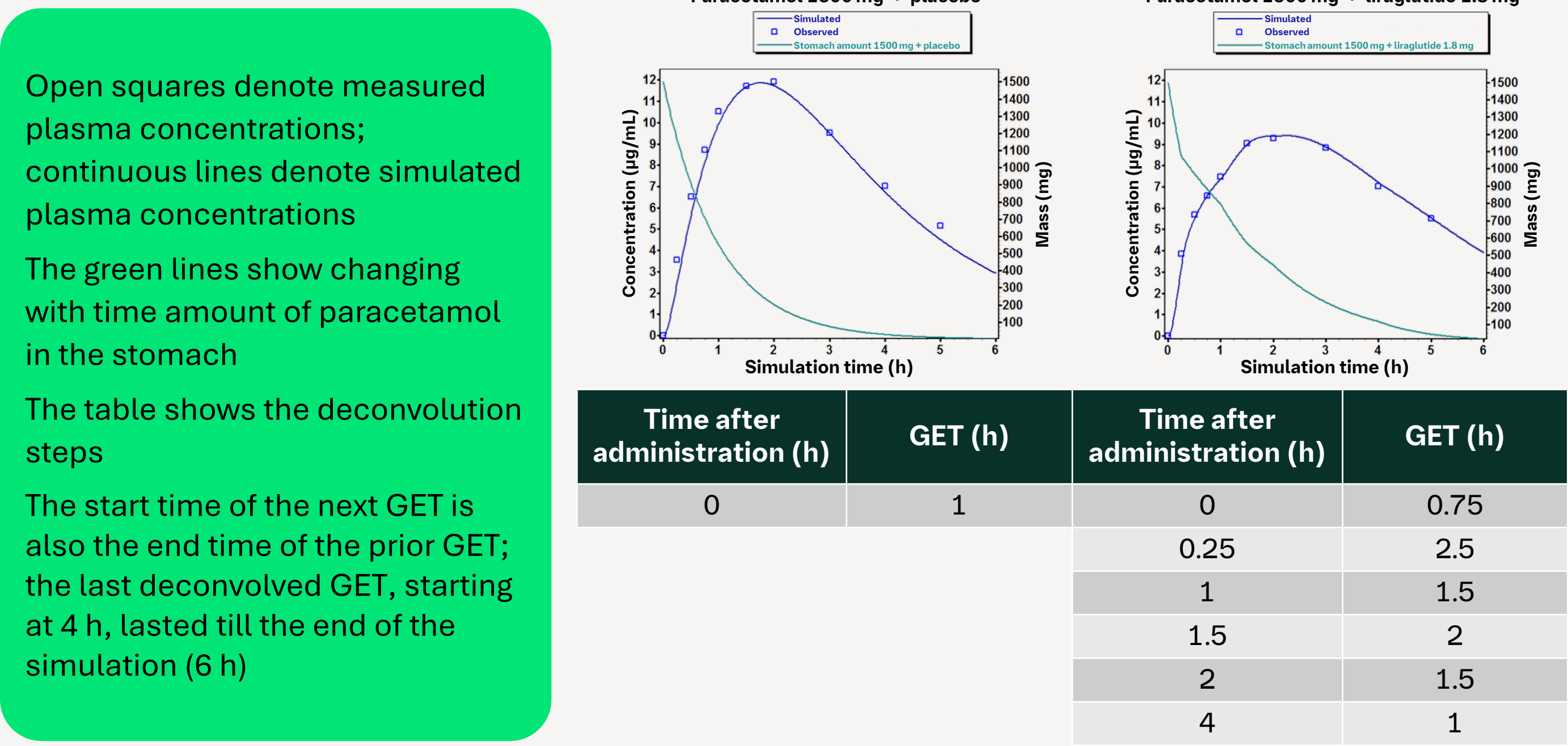


Table 1. Simulated vs observed PK parameters obtained for paracetamol 1500 mg administered prior to, and after administration of 1.8 mg of liraglutide to healthy-fed participants

Parameter	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-6h} (µg·h/mL)	Parameter	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-6h} (µg·h/mL)
Observed	11.92	2.00	42.58	Observed	9.27	2.00	36.95
Simulated	11.87	1.76	44.76	Simulated	9.4	2.25	37.22

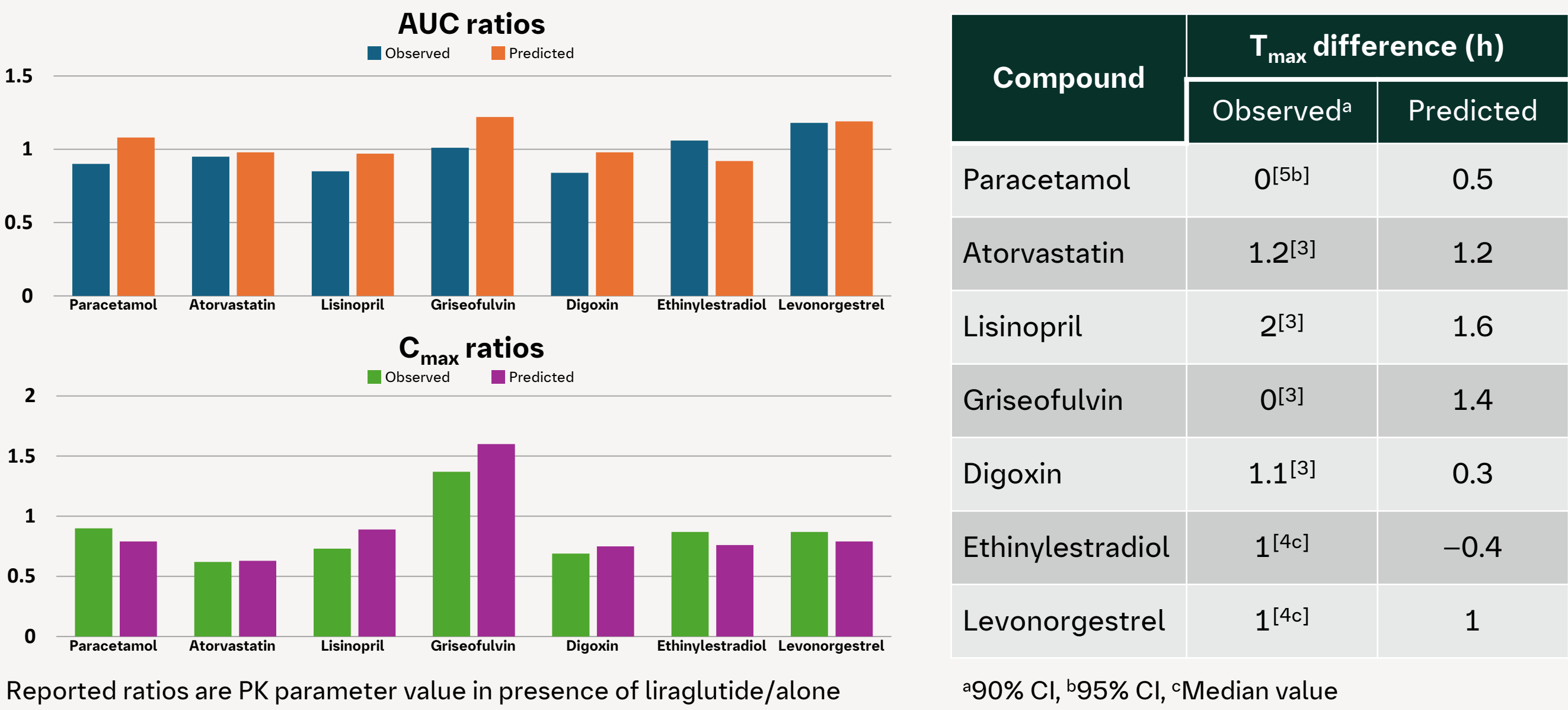
Paracetamol 1500 mg + placebo				Paracetamol 1500 mg + liraglutide 1.8 mg			
Rs _q	SSE	RMSE	MAE	Rs _q	SSE	RMSE	MAE
0.96	3.29	0.60	0.48	0.98	0.55	0.25	0.15
RC _{max}	RT _{max}	RAUC _{0-t}	RAUC _{0-inf}	RC _{max}	RT _{max}	RAUC _{0-t}	RAUC _{0-inf}
1.00	0.88	1.05	0.87	1.01	1.12	1.00	0.92

The upper tables show the observed vs. simulated values for C_{max}, T_{max} and AUC_{0-6h} for paracetamol administration as described above.

The lower tables show the prediction errors (Rs_q, SSE, RMSE and MAE) and the ratios of simulated to observed values for C_{max}, T_{max} and AUCs for the predictions of paracetamol administered with placebo (left panel) and paracetamol affected by liraglutide (right panel).

- Overall, the simulated results were in accordance with the observed values (**Figure 2**) and showed that while slower GE tends to prolong T_{max} and lower the C_{max} due to the slower absorption, the AUC was not substantially affected

Figure 2. Method qualification based on model prediction of liraglutide interaction studies



Discussion



- Most PK parameters were predicted within BE limits (not shown) except for ethinylestradiol AUCs, which were marginally below the BE limit of 0.8-fold, and digoxin C_{max} and AUC_{0-inf}, which marginally exceeded the upper BE limit of 1.25-fold
- Low-solubility drugs, and drugs that have a high first-pass extraction can be more affected than the other types of drugs by the GE prolongation
- Longer GE can enhance the absorption of the low solubility and high permeability drugs either by slowing down the intestinal precipitation process (weak bases) or by increasing intestinal dissolution by reaching solubility limits at later times (lipophilic and not ionizable drugs)
- Griseofulvin belongs to the latter class of drugs and displayed slightly higher absorption and exposure with longer GE; however, this effect was low (~20%)
- Ethinylestradiol (a low solubility and high permeability drug that is highly extracted pre-systemically) was affected to a low extent by longer GE time in terms of exposure, even though the model predicted a slightly higher gut extraction ratio for this compound under slower GE conditions
- Atorvastatin, which is highly metabolised and transported, was almost unaffected by the longer GE as well
- Model predictions were aligned with a very small exposure decrease observed for atorvastatin during liraglutide coadministration

Conclusions

- This analysis was intended as a proof-of-concept to show how PBPK models can reliably predict DDIs caused by prolonged GE utilising limited clinical studies with paracetamol and the perpetrator compound
- This model can be applied to characterise GE prolongation caused by other GLP-1RAs, including the GCGR/GLP-1R dual agonist, survodutide
- This approach can reduce the number of clinical studies with comedications

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Abbreviations
AUC, area under the concentration curve; AUC_{0-6h}, area under the concentration curve from time 0 to 6 hours; AUC_{0-inf}, area under the concentration curve from time 0 to infinity; BE, bioequivalence; C_{max}, maximum plasma concentration; DDI, drug–drug interaction; GCGR, glucagon receptor; GE, gastric emptying; GET, gastric emptying time; GLP-1R, glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MAE, mean absolute error; MASH: metabolic dysfunction–associated steatohepatitis; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetics; RAUC, AUC ratio; RC_{max}, C_{max} ratio; RMSE, root-mean-square error; Rs_q (r squared), coefficient of determination; RT_{max}, T_{max} ratio; SSE, error sum of squares; T2D, type 2 diabetes; T_{max}, time of maximum concentration.

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Disclosures

Survodutide is an investigational compound; **GF** and **RC** are employees of Simulations Plus, Inc. **AF** is an employee of Boehringer Ingelheim

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