

A PBPK based simulation study to predict potential gastric transit time and permeability driven drug – drug interactions caused by Rybelsus® (semaglutide + SNAC)

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PURPOSE

Rybelsus® (semaglutide) is an oral medication used to manage type 2 diabetes by reducing blood sugar levels. The drug product is an immediate release tablet formulated with sodium salcaprozate (SNAC). Semaglutide is a polypeptide that contains a linear sequence of 31 amino acids, and as a GLP-1 receptor agonist, one of its pharmacological effects is to slow gastric transit [1]. SNAC is a permeation enhancer which increases the absorption of poorly permeable compounds [2]. There are no CYP450 enzyme or transporter interactions reported for semaglutide [3]. SNAC has been found to inhibit OAT1 and OAT3 transporters, but these interactions have been reported as low risk [4]. Pre-treatment and repeated co-administration of Rybelsus® with metformin had no impact on metformin's Cmax (DDI ratio= 0.98, 90% confidence interval (90% CI) = 0.90 – 1.06) but led to an increase in AUC0-t (DDI ratio = 1.32, 90% CI = 1.23 – 1.43) [5]. In contrast, when co-dosed with furosemide, furosemide's Cmax decreased (DDI ratio = 0.66, 90% CI = 0.53 – 0.82) while AUC0-t increased (DDI ratio = 1.28, 90% CI = 1.16 – 1.42) [6]. This study uses Physiologically based pharmacokinetic (PBPK) modelling to evaluate the effect of increased gastric transit time and permeability, perpetrated by Rybelsus® on the Cmax and AUC of metformin and furosemide. After understanding the changes caused by Rybelsus®, PBPK modelling was used to predict the effect of co-administering Rybelsus® on dipyrindamole, phenytoin, ribociclib, atazanavir, dolugratevir, efavirenz, midazolam and warfarin.

METHODOLOGY

All the modelling and simulation work was performed using GastroPlus® X (v 10.1) (Simulations Plus, Research Triangle Park, NC, USA). Published metformin [7,8] and furosemide [9] models were used to simulate the clinically observed DDI with Rybelsus® by varying gastric transit time (GTT) and effective jejunal permeability (Peff). The impact of Rybelsus® on GTT and the fold increase in Peff was then fixed for subsequent DDI predictions with other compounds. These effects were evaluated using published models for dipyrindamole [10], phenytoin [11], ribociclib [12], and a subset of the models included in the GastroPlus® X DDI database (atazanavir, dolutegravir, efavirenz, midazolam and warfarin). Virtual populations of n = 50 subjects, were utilised for the DDI predictions, default parameter variability and distributions were applied throughout, except for GTT and Peff which were specified as following a log-normal distribution with a coefficient of variation (%CV) of 30%. 90% CIs were calculated in Phoenix WinNonLin v 8.3.4 (Certara, UK). R/Rstudio (version 4.4.2/2024.12.1) [13,14] and the “forestplot” package were used for data visualisation [15].

RESULTS

The published models of metformin and furosemide predicted the observed PK parameters from the DDI studies (when dosed alone) within ± 30% deviation (Cmax = –17%, AUC0-t = 0.1%, and Cmax = –20%, AUC0-t = 29%, respectively). The effect of increasing GTT resulted in a decrease in Cmax and no change in AUC0-t (Figure 1). In the simulations shown in Figure 1, %Fa was 33% and 54% for metformin and furosemide, respectively; with the extent of absorption limited by permeability.

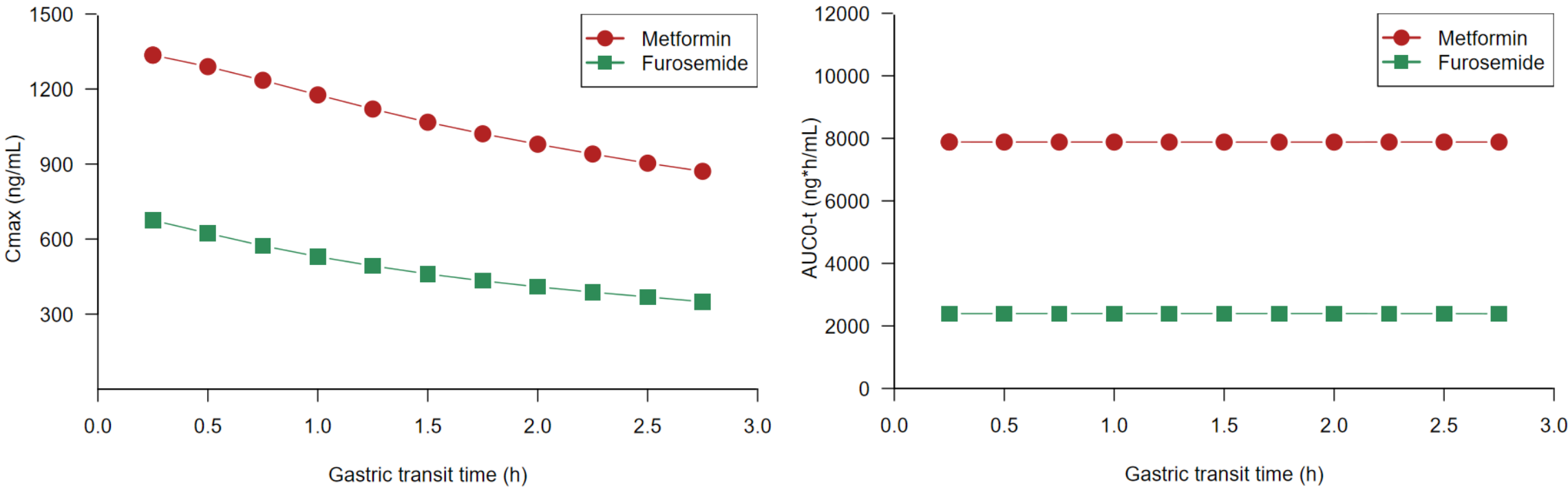


Figure 1. Effect of gastric transit time on Cmax and AUC0-t of metformin and furosemide

Increasing Peff in a 2-fold range, increased Cmax and AUC0-t (Figure 3). In the simulations shown in Figure 2, %Fa increased from from 33 to 54% for metformin and 54 to 75% for furosemide.

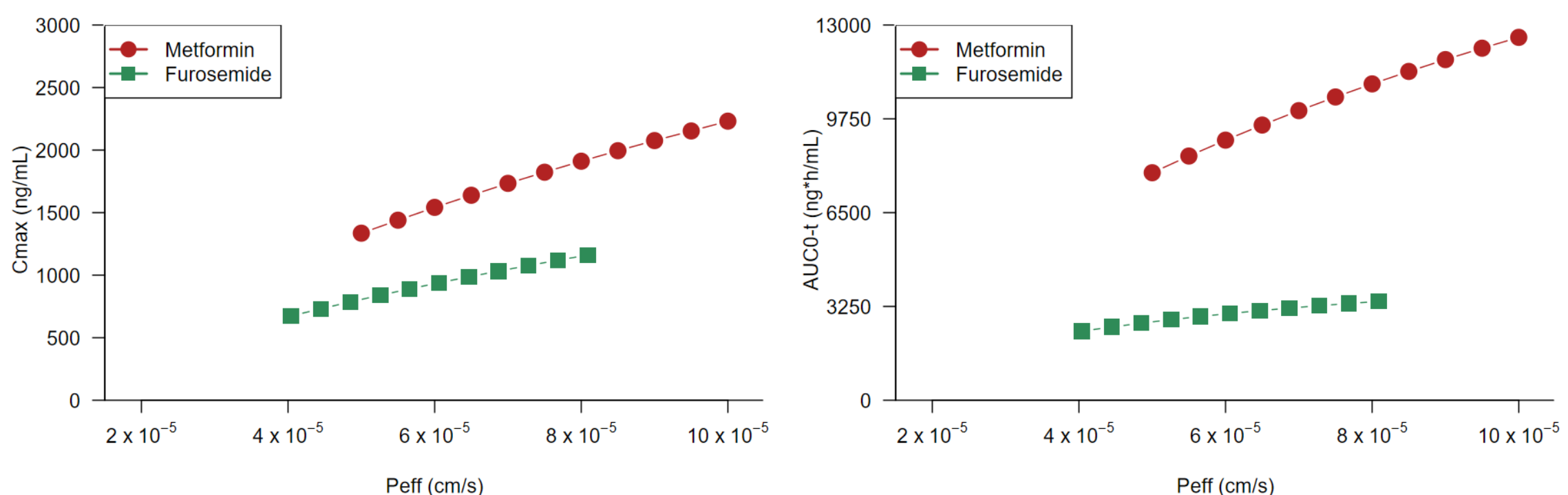


Figure 2. Effect of effective permeability on Cmax and AUC0-t of metformin and furosemide

Based on the parameter sensitivity analysis presented in Figures 1 and 2, the increase in Peff and GTT were fixed at 1.4x and 2 h, respectively, was used in the virtual populations to simulate the DDI observed between 20 mg Rybelsus® plus 800mg metformin (Figure 3, left), and 14 mg Rybelsus® plus 40mg furosemide (Figure 3, right). The observed versus model predicted geometric mean DDI ratios and associated 90% CIs are presented in Table 1.

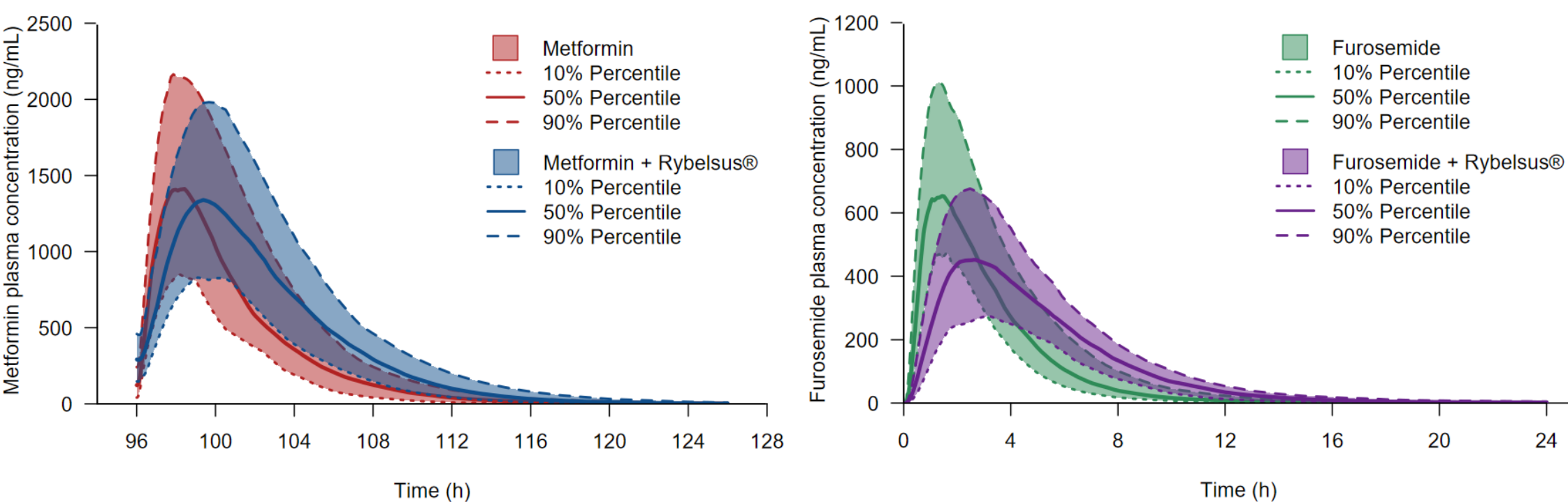


Figure 3. Population simulation of the administration of 800 mg metformin alone and in combination with 20 mg Rybelsus®, and 40 mg furosemide alone and in combination with 14 mg Rybelsus®

Table 1. Observed and model predicted geometric mean DDI ratios and associated 90% CIs of the administration of 800 mg metformin alone and co-administered with 20 mg Rybelsus®, and 40 mg furosemide alone and co-administered with 14 mg Rybelsus®

Metformin			Furosemide		
DDI ratio	Observed	Predicted	DDI ratio	Observed	Predicted
Cmax	0.98 (0.90 – 1.06)	0.95 (0.84 – 1.07)	Cmax	0.66 (0.53 – 0.82)	0.74 (0.68 – 0.81)
AUC	1.32 (1.23 – 1.43)	1.22 (1.08 – 1.38)	AUC	1.28 (1.16 – 1.42)	1.24 (1.13 – 1.35)

Figure 4 summarises the model predicted impact of co-dosing a range of drugs with Rybelsus® (GTT increased to 2 h + Peff increased 1.4x). The model predicts no interaction for phenytoin and warfarin. In terms of Cmax, the model predicts an interaction for dipyrindamole, atazanavir, and midazolam as the entire 90% CI is below 80%. For ribociclib and efavirenz an interaction cannot be ruled out due to one side of the predicted 90% CI breaking the 80% and 125% limits, respectively. Regarding AUC0-t, the model predicts an interaction for midazolam; the 90% CI is 43.4% – 64.1%, significantly below the 80% limit, while for atazanavir, and efavirenz and dolutegravir an interaction cannot be ruled out due to one side of the predicted 90% CI breaking the 80% and 125% limits, respectively.

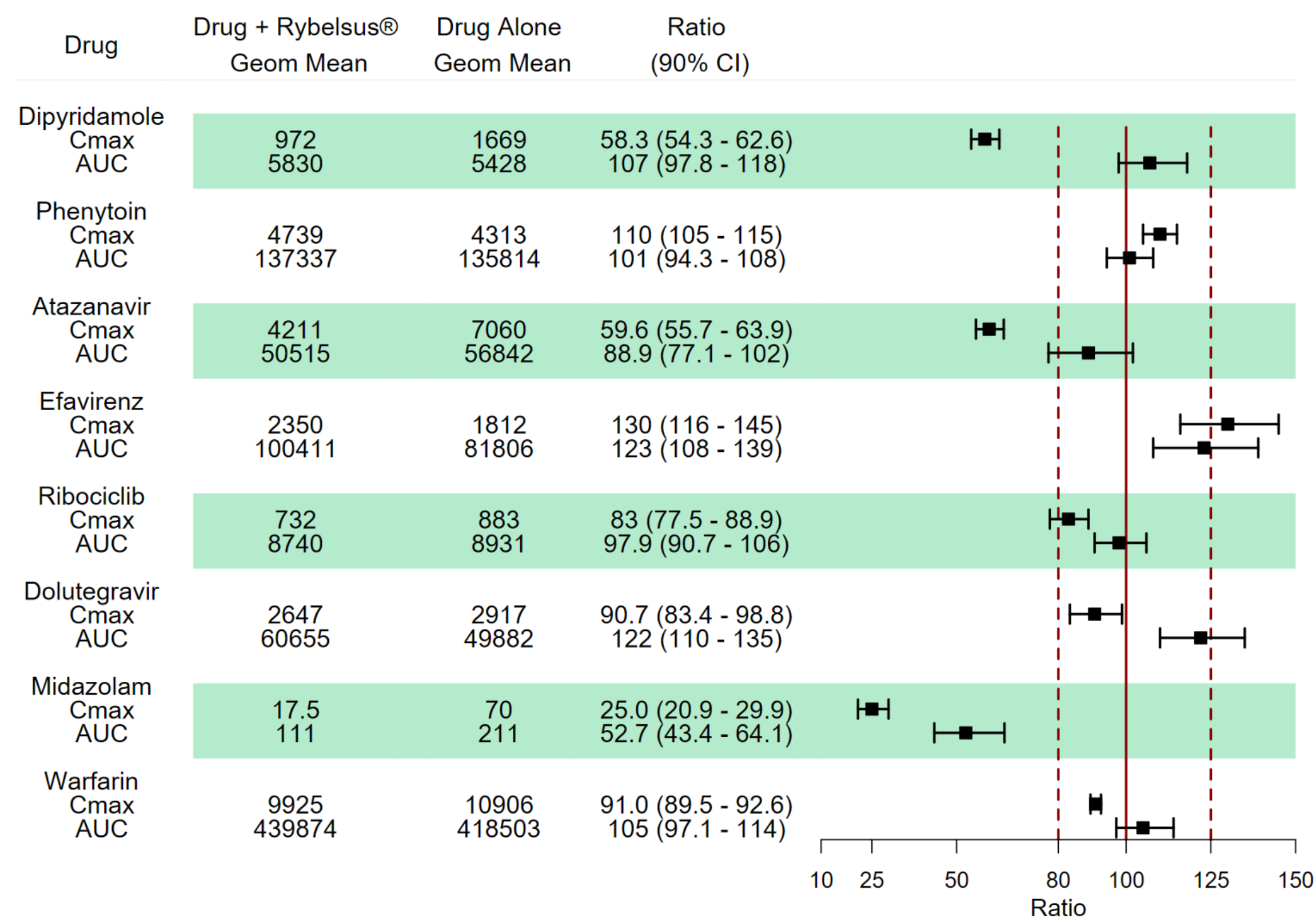


Figure 4. Predicted DDI ratios evaluating the effect of a longer GTT and an increased Peff on the Cmax and AUC0-t of the selected drugs for this study. Cmax in ng/mL and AUC in ng•h/mL

Table 2 shows the physicochemical properties and predicted fraction absorbed (%Fa), bioavailability (%F) and maximum % dissolved obtained from the simulations. The models predict that the most common effect of co-dosing with Rybelsus® is a reduction in the Cmax of victim drugs, which can be related to the longer GTT caused by semaglutide. However, drugs that show incomplete absorption when dosed alone (%Fa below 100%) are likely to also see an increase in %Fa due to the permeability increase resulting from the inclusion of SNAC in the Rybelsus® tablet.

In-vivo dissolution of efavirenz and dolutegravir, (both acidic drugs), benefit from a longer gastric transit time. While in the case of efavirenz, in addition to a higher amount absorbed, Cmax and AUC0-t may be further boosted through saturable metabolism. For midazolam, where solubility and permeability are already enabling complete absorption (even in the absence of Rybelsus®), slower gastric emptying results in less drug surviving gut wall metabolism. A similar effect is predicted for atazanavir due to active efflux and metabolism in the gastrointestinal tract.

Potential interactions with Rybelsus® depend on the victim's solubility, permeability, ionisation state, and whether there is any saturable metabolism and/or transport in the gut. PBPK modelling is a useful tool to evaluate these interactions as all these factors are considered dynamically.

Table 2. Physicochemical properties, %Fa, %F and maximum percent dissolved (Max % diss) of the drugs evaluated in this study

Drug	BCS Class	Acid/Base	Gut metabolism	Transporters	Drug alone			Drug + Rybelsus®		
					%Fa	%F	Max %Diss	%Fa	%F	Max %Diss
Metformin	III	base			33	33	100	43	43	100
Furosemide	IV	acid			52	49	100	63	59	100
Dipyrindamole	II	base			100	92	100	100	92	100
Phenytoin	II	acid			98	96	100	99	98	100
Atazanavir	II	base	CYP3A4	P-gp	96	87	100	98	85	100
Efavirenz	II	acid	CYP3A4		74	57	74	84	69	84
Ribociclib	IV	base			88	88	100	94	94	100
Dolutegravir	II	acid	CYP3A4, UGT1A1		72	52	72	81	56	81
Midazolam	I	base	CYP3A4		100	24	100	100	14	100
Warfarin	I	acid			100	100	100	100	100	100

BCS: biopharmaceutics classification system; Max %Diss: maximum percent dissolved throughout the simulation

CONCLUSIONS

PBPK modelling is a useful tool to risk assess DDIs caused by changes in GTT and permeability that result from repeated dosing of Rybelsus® (and other developmental drugs with similar pharmacodynamic effects), highlighting drug combinations that may benefit from clinical investigation. Further work is needed to establish the magnitude of changes in GTT and intestinal permeability caused by semaglutide and SNAC.

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