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ARTICLE

Pharmacokinetic/pharmacodynamic modeling of drug interactions at the $P2Y_{12}$ receptor between selatogrel and oral $P2Y_{12}$ antagonists

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Abstract

Selatogrel is a potent and reversible $P2Y_{12}$ receptor antagonist developed for subcutaneous self-administration by patients with suspected acute myocardial infarction. After single-dose emergency treatment with selatogrel, patients are switched to long-term treatment with oral $P2Y_{12}$ receptor antagonists. Selatogrel shows rapid onset and offset of inhibition of platelet aggregation (IPA) to overcome the critical initial time after acute myocardial infarction. Long-term benefit is provided by oral $P2Y_{12}$ receptor antagonists such as clopidogrel, prasugrel, and ticagrelor. A population pharmacokinetic (PK)/pharmacodynamic (PD) model based on data from 545 subjects in 4 phase I and 2 phase II studies well described the effect of selatogrel on IPA alone and in combination with clopidogrel, prasugrel, and ticagrelor. The PK of selatogrel were described by a three-compartment model. The PD model included a receptor-pool compartment to which all drugs can bind concurrently, reversibly or irreversibly, depending on their mode of action. Furthermore, ticagrelor and its active metabolite can bind to the selatogrel-receptor complex allosterically, releasing selatogrel from the binding site. The model provided a framework for predicting the effect on IPA of selatogrel followed by reversibly and irreversibly binding oral $P2Y_{12}$ receptor antagonists for sustained effects. Determining the timepoint for switching from emergency to maintenance treatment is critical to achieve sufficient IPA at all times. Simulations based on the interaction model showed that loading doses of clopidogrel and prasugrel administered 15 h and 4.5 h after selatogrel, respectively, provide sustained IPA with clinically negligible drug interaction.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Selatogrel is a potent reversible $P2Y_{12}$ receptor antagonist developed for subcutaneous self-administration by patients in case of suspected acute myocardial infarction. Transition to oral $P2Y_{12}$ receptor antagonists without drug interaction and sufficient inhibition of platelet aggregation must be assured at all times.

WHAT QUESTION DID THIS STUDY ADDRESS?
The pharmacokinetic/pharmacodynamic model semimechanistically describes the effect of selatogrel on platelet inhibition alone and in combination with the oral $P2Y_{12}$ receptor antagonists clopidogrel, prasugrel, and ticagrelor.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Model-based simulations showed that loading doses of clopidogrel and prasugrel can be administered from 15 h and 4.5 h after selatogrel, respectively.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
These results support guiding the clinical transition from selatogrel emergency treatment to oral maintenance therapy in a safe and efficacious way.

INTRODUCTION

Selatogrel is a potent reversible $P2Y_{12}$ receptor antagonist developed for subcutaneous (s.c.) self-administration by patients with suspected acute myocardial infarction (AMI). Selatogrel shows a fast onset of action,[1] an important characteristic to follow the "time is muscle" paradigm.[2]

Inhibition of platelet aggregation (IPA) via $P2Y_{12}$ receptor antagonists is key in the treatment of AMI and its secondary prevention.[3–5] Clopidogrel, prasugrel, and ticagrelor are available as oral $P2Y_{12}$ receptor antagonists. Although clopidogrel and prasugrel are prodrugs with their active metabolites binding irreversibly to the $P2Y_{12}$ receptor, ticagrelor and its active metabolite both bind reversibly.[6] Ticagrelor and its active metabolite bind noncompetitively, that is, exhibit allosteric binding at a binding site different from that of selatogrel, clopidogrel, prasugrel, and the natural ligand adenosine diphosphate (ADP).[6]

After emergency treatment with selatogrel, patients in phase III of clinical development and later in clinical practice will be switched to treatment with an oral $P2Y_{12}$ receptor antagonist. Transfer between $P2Y_{12}$ receptor antagonists was associated with the risk of pharmacodynamic (PD) drug interactions.[7] For cangrelor, an intravenously administered reversible $P2Y_{12}$ receptor antagonist, it is assumed that clopidogrel's and prasugrel's active metabolites are eliminated before cangrelor dissociates from the $P2Y_{12}$ receptor. Thus, clopidogrel and prasugrel cannot convey their sustained IPA if administered during cangrelor infusion.[8,9] Similarly, reduced IPA was apparent with clopidogrel and prasugrel if administered shortly after selatogrel.[10] No reduction in IPA was seen for ticagrelor administered after selatogrel.

The aim of this analysis was to develop a population pharmacokinetic (PK)/PD model to describe the effect of selatogrel on IPA alone and in combination with the three oral $P2Y_{12}$ receptor antagonists. This model can be used to determine the optimum time to transition from one $P2Y_{12}$ receptor antagonist to another to maintain sufficient IPA at all times, a critical component of AMI treatment.

METHODS

Data

The analysis comprised data from 4 phase I and 2 phase II studies.

- Two single-ascending dose (SAD) studies covering an s.c. dose range from 0.1 to 16 mg[1]
- A PD interaction study with the $P2Y_{12}$ receptor antagonists clopidogrel, prasugrel, and ticagrelor (the SWITCH study)[10]
- A study to investigate absorption, distribution, metabolism, and excretion of selatogrel using ^{14}C-radiolabeling (PK only)[11]
- A study to investigate PK and PD in subjects with stable coronary artery disease[12]
- A study to investigate PK and PD in subjects with AMI[13]

Table 1 provides details on study designs, populations, study treatments, and PK/PD assessments. The selatogrel plasma concentrations were determined using a validated liquid chromatography assay.[1] The PD variable was $P2Y_{12}$ reaction units (PRU) determined by VerifyNow®.[14–16] VerifyNow® is a point-of-care device measuring platelet aggregation turbidimetrically in whole blood after inducing platelet aggregation with the natural $P2Y_{12}$ receptor agonist ADP. IPA was calculated as relative change from baseline:

$$\%\,\mathrm{IPA} = (\mathrm{PRU}_0 - \mathrm{PRU})/\mathrm{PRU}_0 \cdot 100$$

PRU_0 was defined as the naïve baseline PRU, that is, the baseline PRU without influence of any $P2Y_{12}$ receptor antagonist. For subjects missing this information, for example,

TABLE 1 Study overview

Study	Study design	Study population	Study treatment	PK/PD assessment timepoints
AC−076–101 (NCT01954615)	Single-center, double-blind, placebo-controlled, randomized SAD study	Eight healthy male subjects per cohort (six on active, two on placebo) 22 subjects in total	Selatogrel/placebo s.c.: C1, 0.1 mg; C2, 0.4 mg; C3, 1.6 mg	Day −1[a] and 0 (predose); 5,[b] 10, 15, 20, 25,[b] and 30 min; and 1, 1.5,[b] 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 h
AC−076–102[1]	Single-center, double-blind, placebo-controlled, randomized SAD study	Eight healthy male subjects per cohort (six on active, two on placebo) 48 subjects in total	Selatogrel/placebo s.c.: C1, 1 mg; C2, 2 mg; C3, 4 mg; C4, 8 mg; C5, 16 mg; C6, 32 mg	Day −1[a] and 0 (predose); 5,[b] 10, 15, 20, 25,[b] and 30 min; and 1, 1.5,[b] 2, 3, 4, 5, 6, 8, 12, 24, 36, and 48 h
ID−076–103[10]	Single-center, double-blind (selatogrel), open-label (clopidogrel, prasugrel, and ticagrelor), placebo-controlled, randomized, two-way crossover study	12 healthy male and female subjects per cohort 77 subjects in total	16 mg selatogrel/placebo s.c. followed by: Part A: clopidogrel p.o. C1, 600 mg at 0.5 h; C2, 300 mg at 12 h; C3, 600 mg at 12 h Part B: prasugrel p.o. C4, 60 mg at 0.5 h; C5, 60 mg at 12 h Part C: ticagrelor p.o. C7, 180 mg at 0.5 h	Day −1[a] and 0 (predose); 15 and 30 min; and 1, 1.5, 2, 3, 4, 5, 6, 7,[a] 8, 9,[a] 10, 11,[a] 12, 24, and 36 h
ID−076–104[11]	Single-center, open-label study to investigate its mass balance, PK, and metabolism	Six healthy male subjects	16 mg ^{14}C-radiolabeled selatogrel s.c.	0[b] (predose); 5,[b] 10,[b] 15,[b] 30,[b] and 45[b] min; and 1,[b] 1.5,[b] 2,[b] 3,[b] 4,[b] 5,[b] 6,[b] 8,[b] 12,[b] 24,[b] 36,[b] 48,[b] and 72[b] h
ID−076A201[12]	Multicenter, double-blind, randomized, placebo-controlled study	345 male and female subjects with coronary artery syndrome	8 or 16 mg selatogrel/placebo s.c.	0 (predose); 15 and 30 min; and 1, 2, 4, 8, and 24 h
ID−076A202[13]	Multicenter, open-label, randomized study	47 male and female subjects with acute myocardial infarction	8 or 16 mg selatogrel s.c.	0[b] (predose), 15 and 30 min, and 1 and 8 h[c]

Abbreviations: C, Cohort; p.o., per oral; PD, pharmacodynamic(s); PK, pharmacokinetic(s); SAD, single-ascending dose; s.c., subcutaneous.

[a]PD sampling only.

[b]PK sampling only.

[c]The 8-h PK postdose timepoint was flexible. If the subject received an invasive procedure (percutaneous coronary intervention/angiography) within 8 h of study drug administration, the blood sample was to be collected at the end of the procedure. If no invasive procedure was performed within 8 h of study drug administration, the blood sample was to be collected approximately 8 h after study drug administration.

subjects in phase II studies on background medication of oral $P2Y_{12}$ receptor antagonists, a typical value close to the observed median, 200 PRU, was imputed. The mean of the baseline measurements of both periods was used for both treatment periods in the crossover study, SWITCH. Missing covariate values were imputed by the corresponding medians of the entire data set.

Selatogrel PK model development

Starting from a two-compartment model with linear absorption from the s.c. injection site, the model was enhanced by a further distribution compartment and a single transition compartment for absorption. Interindividual variability with log-normal distribution was included on all parameters. The residual error term was proportional to the selatogrel concentration. Concentration measurements below the lower limit of quantification (LLOQ) were treated as censored values and simulated from a truncated distribution restricted to the range (0, LLOQ).[17]

Covariate relationships for continuous covariates were implemented as power functions centered to a typical value. Covariate selection was performed using conditional sampling for stepwise approach based on correlation tests (COSSAC), an automated covariate model-building algorithm implemented in Monolix (Lixoft, Antony, France).[18] Body weight, age, sex, and race were assessed as covariates on all PK parameters. Injection site (thigh, abdomen) and AMI disease status were assessed on absorption parameters, and bilirubin and creatinine clearance on drug clearance.

After the automated COSSAC run, correlated covariates such as sex and body weight were reduced to the covariate with a stronger effect. Covariates with an estimated effect on the parameter below 20% for the extremes of the covariate in the data were considered not clinically relevant and removed from the model. Covariate effects estimated with low precision, that is, relative standard error (RSE) >50% were removed from the model stepwise (highest RSE first).

PK model development for other $P2Y_{12}$ antagonists

Structural PK models for clopidogrel, prasugrel, and ticagrelor were implemented from the literature.[19,20] Interindividual variability was not included in this part of the model because individual PK data of these compounds were not available. As a consequence, the variability of the PD parameter estimates describing the effect of those compounds increases. This higher variability in PD parameters reflects variability in PK and PD and therefore allows for reasonable prediction of the PD effect.

The clopidogrel literature model included dose as a categorical covariate (75 and 600 mg) on bioavailability and the formation rate constant of the inactive precursor (2-oxo-clopidogrel) of the active metabolite. Parameter estimates for 300-mg doses were derived from the 600-mg parameter values based on the assumption that dose-dependent processes are saturated at 300 mg since deviations from dose-proportionality in area under the concentration-time curve decrease for doses of 300 mg and higher.[21] For ticagrelor, identical activity was assumed for parent compound and active metabolite AR-C124910XX.[22]

PD model development

The subject-specific individual parameter estimates from the final PK model were used to predict the individual PK and relate it to the PD effect. In a first step, a PK/PD model for selatogrel was developed based on the SAD studies. Thereafter, clopidogrel, prasugrel, and ticagrelor were included sequentially based on PD data from the SWITCH study. Finally, phase II data were included, and parameters were re-estimated. Different structural models were investigated to describe the complex PD effect of selatogrel in combination with oral $P2Y_{12}$ receptor antagonists, for example, nonlinear binding kinetics.

Baseline PRU was described by the observed naïve baseline PRU (or imputed with 200 PRU if the observation was missing), allowing for an exponential error similar to the baseline method B3.[23,24] Interindividual variability was included on all parameters assuming a log-normal distribution. A combined (additive and proportional) residual error model was used.

Disease status AMI was assessed on parameters related to drug effect of any $P2Y_{12}$ receptor antagonist using COSSAC covariate selection. Subsequently, covariate relations estimated with low precision (RSE >50%) were removed from the model stepwise (highest RSE first). Other covariates such as age or use of opioids were highly correlated to disease status and therefore not considered.

Model selection and qualification

Model selection and qualification were based on goodness-of-fit plots (observed data vs. model predictions, residuals vs. time and population predictions), visual predictive checks (VPCs), objective function values (OFVs), and RSEs of parameter estimates. The corrected Bayesian information criterion[25,26] served as the model selection criterion in the COSSAC step. The default settings with p value thresholds of 0.5 for the addition and 0.01 for the removal of covariates were used.

Simulations to evaluate the influence of covariates

Simulations were used to evaluate the clinical relevance of covariates. The typical subject was defined with the reference covariate values body weight 70 kg, age 60 years, naïve baseline PRU 200, and disease status healthy/coronary artery disease. Naïve baseline PRU was not implemented as covariate; however, it was taken into account by the baseline method and is therefore regarded as covariate in the following. A total of 1000 subjects were simulated per covariate value, including interindividual variability and without residual variability and parameter uncertainty. The area under the concentration-time curve between 0 and 48 h ($AUC_{0–48\ h}$) and the proportion of responders as defined in the phase II studies,[12,13] that is, subjects with PRU <100 from 0.5 to 3 h after single-dose administration of selatogrel, were derived from the simulated data. A response definition based on PRU is preferable over IPA in a clinical setting in which concomitant medication prevents the measurement of a naïve baseline PRU that is required to derive IPA.

Model predictions of selatogrel in combination with clopidogrel and prasugrel

Model-based predictions for the reference subject were performed to investigate the effect of different time intervals between administration of selatogrel and clopidogrel/prasugrel.

In analogy to the SWITCH study, interaction was defined as the ≥20 percentage points decrease of arithmetic mean percent IPA at 24 and 36 h following administration of selatogrel or placebo.[10] The primary end point in the clinical study was the difference in mean IPA such that simulations were based on typical profiles. A selatogrel dose of 16 mg was administered at 0 h. A clopidogrel loading dose (600 mg) or a prasugrel loading dose (60 mg) was administered at different times after selatogrel. For comparison, clopidogrel or prasugrel alone were administered at different timepoints (mimicking placebo treatment of selatogrel). The SWITCH study showed PD interactions with clopidogrel 600 mg administered 0.5 and 12 h after selatogrel such that dosing times >12 h were investigated. For prasugrel, the SWITCH study showed no interaction for dosing at 12 h but at 0.5 h. Thus, dosing times between 0.5 and 12 h were investigated to estimate the dosing time after which no interaction can be expected.

Software

R version 3.6.1 (The R Project Foundation, Vienna, Austria) was used for data set preparation, exploratory analyses, and visualization of results. Population PK/PD modeling was performed using Monolix version 2019R2 (Lixoft). Parameters were estimated using the stochastic approximation of expectation maximization algorithm. The likelihood and the Fisher information matrix were estimated using importance sampling. Simulations were performed using Simulx version 2019R2 (Lixoft), and model predictions were generated with Berkeley Madonna version 8.3.18 (Macey and Oster, Berkeley, CA).

RESULTS

Data

The data set comprised 545 subjects (405 on active treatment and 140 on placebo, 434 males and 111 females) with 3924 PK and 7251 PD measurements, respectively (Table S1).

Missing data were imputed by the respective medians of all subjects for laboratory parameters at baseline (four subjects). Missing values for the covariate for race were imputed by race Other (two subjects), and missing height and body weight (the same two subjects in both) by the respective sex-adjusted medians.

The PK of selatogrel showed a fast absorption followed by an elimination with two or more phases depending on the data set. PRU measurements showed high variability within and between subjects. Doses of 8 mg achieved full IPA for most subjects. Higher doses prolonged the duration of the full inhibition.

The concentration-response relation (Figure S1) showed a dose-dependent effect with steeper relation for higher doses, for example, at a selatogrel concentration of approximately 20 ng/ml the 32-mg dose led to almost complete platelet inhibition (PRU close to 0) while PRU remained above 100 for doses of up to 1.6 mg (at the same concentration). Investigation of hysteresis, a time-delayed effect, was inconclusive due to the rapid absorption and therefore lack of information in the early phase.

Selatogrel PK model development

A linear three-compartment model with a transit compartment for absorption described the PK data best (Figure 1, Table 2). The distribution to the second peripheral compartment from the first peripheral compartment decreased the OFV by 161.71 points compared with a distribution from the central compartment, yielding a decrease in OFV of 100.63 points. An additional transit compartment for the absorption process decreased the OFV by 840.84 points without additional parameters.

Bilirubin on clearance as well as injection site and disease status on the absorption rate constant were statistically

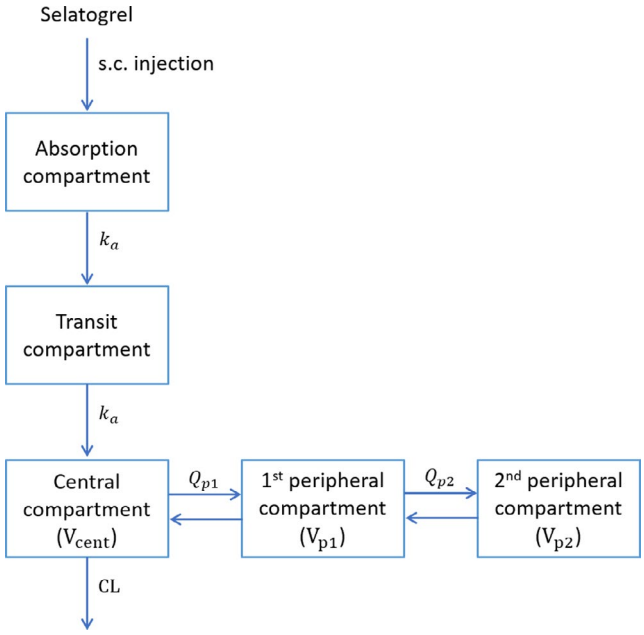

FIGURE 1 Pharmacokinetic model structure. CL, clearance; k_a, absorption rate constant; Q_{p1}, intercompartmental clearance for distribution between central and first peripheral compartment; Q_{p2}, intercompartmental clearance for distribution between first and second peripheral compartment; s.c., subcutaneous; V_{cent}, central volume of distribution; V_{p1}, volume of distribution of first peripheral compartment; V_{p2}, volume of distribution of second peripheral compartment

significant but did not meet the criteria for clinical relevance and were therefore not included in the final model. The final PK model included age and body weight on multiple PK parameters.

VPCs showed a good alignment of PK model predictions and observed selatogrel concentrations (Figures S2 and predictive checks for data below the LLOQ in Figure S3). Some very high concentrations after the administration of 32 mg of selatogrel were slightly overpredicted. Parameters were estimated with high precision (RSE ≤25.9%). The condition number for the PK model was 72, indicating that the model was well parameterized.[27]

PK/PD model development

The PK/PD base model structure is depicted in Figure 2, parameter estimates are provided in Table 2, and the differential equations are provided in the Supplementary Material. The free $P2Y_{12}$ receptors were modeled on an arbitrary scale with a baseline of 1 nmol/L. Free $P2Y_{12}$ receptors are generated with a zero-order formation rate constant, k_{in}, and eliminated with a first-order elimination rate constant, k_{out}. Selatogrel, ticagrelor, and its active metabolite as well as the active metabolites of clopidogrel and prasugrel can all bind to the free receptor. The relationship between receptor binding and PRU was modeled using a sigmoidal function. The condition number of the PK/PD model was 17, indicating that the model was well parameterized (VPCs in Figures S3-S5).[27]

A cumulative effect compartment integrating the fraction of bound receptors with the rate constant k_{Cum} is cleared with the same rate constant. A factor modifying the binding activity of the selatogrel and prasugrel active metabolite was derived based on the cumulative effect compartment value: a high fraction of bound receptors increases the value of the cumulative effect compartment, ultimately leading to increased binding rates for selatogrel and prasugrel. Implementation of this effect for clopidogrel and ticagrelor led to an increase in the OFV for both and was thus not used.

Ticagrelor and its active metabolite can bind allosterically to the selatogrel–receptor complex, releasing selatogrel from its binding site. Adding this (un)binding mechanism decreased the OFV by 46.83 points without additional parameters. However, fitting ticagrelor with all PD data from phase I and phase II resulted in an underprediction of PRU between 24 and 36 h for the corresponding Cohort 7 of the SWITCH study. Therefore, ticagrelor parameters including interindividual variability were estimated with phase I data only and fixed to those values in the final model. This step increased the OFV by 5.12 points, indicating that the overall goodness of fit was similar. The phase II data with sparse PD sampling can possibly be described by more than one parameter set, whereas the dense sampling in phase 1 with fewer subjects provided a solid basis for structural model identification. For the purpose of the simulations, the phase I data, including the SWITCH interaction study, were considered to be more relevant to describe the ticagrelor effect.

Similarly, the binding rate constant for clopidogrel was estimated with phase I data only and fixed to this estimate in the final model. This step was necessary to adequately describe the effect of clopidogrel alone (i.e., selatogrel-matching placebo in the SWITCH study Cohorts 1–3). The OFV increased by 17.46 points by fixing this parameter and its interindividual variability.

Influence of covariates

Low body weight and high age led to higher exposure ($AUC_{0–48\ h}$), with body weight having the larger influence (Figure 3). Despite the relevance for PK, the effect on PD and the proportion of responders was limited for both body weight and age. Nevertheless, a higher exposure led to a prolonged PD effect: subjects with low body weight (50 kg) had returned to 100 PRU after 14.4 h, whereas subjects with high body weight (150 kg) returned to 100 PRU after 9.3 h. Although naïve baseline PRU influenced the shape of the PRU profile, IPA was not affected. As responders were

TABLE 2 PK/PD parameter estimates

		Fixed effects parameters			Interindividual variability (random effects)		
Parameter	**Description**	**Estimate**	**%RSE**	***P* value (covariates)**	**Estimate**	**%RSE**	**%CV**
k_a (1/h)	Absorption rate constant	5.95	2.11	-	0.362	4.35	37.4
β_{ka_age} (-)	Effect of age on k_a	−0.280	19.9	$4.98 * 10^{-7}$	-	-	-
CL (L/h)	Clearance	8.51	2.15	-	0.297	3.85	30.4
β_{CL_age} (-)	Effect of age on clearance	−0.437	10.1	$<2.2 * 10^{-16}$	-	-	-
β_{CL_WT} (-)	Effect of body weight on CL	0.678	12.1	$2.22 * 10^{-16}$	-	-	-
V_{cent} (L)	Central volume of distribution	17.0	2.33	-	0.307	4.19	31.4
β_{Vcent_age} (-)	Effect of age on V_{cent}	−0.293	16.1	$5.67 * 10^{-10}$	-	-	-
β_{Vcent_WT} (-)	Effect of body weight on V_{cent}	0.990	8.84	$<2.2 * 10^{-16}$	-	-	-
Q_{p1} (L/h)	Intercompartmental clearance between central and first peripheral compartment	3.19	2.92	-	0.329	6.13	33.8
β_{Qp1_age} (-)	Effect of age on Q_{p1}	−0.137	42.0	$1.72 * 10^{-2}$	-	-	-
β_{Qp1_WT} (-)	Effect of body weight on Q_{p1}	1.00	11.1	$<2.2 * 10^{-16}$	-	-	-
$corr_{CL\_Qp1}$	Correlation between CL and Q_{p1}	-	-	-	0.702	6.27	-
$corr_{CL\_Vcent}$	Correlation between CL and V_{cent}	-	-	-	0.724	3.69	-
$corr_{Vcent\_Qp1}$	Correlation between Q_{p1} and V_{cent}	-	-	-	0.349	18.8	-
V_{p1} (L)	Volume of distribution of first peripheral compartment	51.4	2.28	-	0.181	8.94	18.2
β_{Vp1_WT} (-)	Effect of body weight on V_{p1}	1.58	6.39	$<2.2 * 10^{-16}$	-	-	-
Q_{p2} (L/h)	Intercompartmental clearance between first and second peripheral compartment	4.18	1.87	-	-	-	-
β_{Qp2_WT} (-)	Effect of body weight on Q_{p2}	1.43	5.65	$<2.2 * 10^{-16}$	-	-	-
V_{p2} (L)	Volume of distribution of second peripheral compartment	448	25.9	-	1.18	12.3	174
β_{Vp2_age} (-)	Effect of age on V_{p2}	1.95	23.8	$2.69 * 10^{-5}$	-	-	-
PRU_0 (PRU)	Variability in baseline PRU	0	Fix	-	0.0694	7.15	6.95
PD_{50} (-)	Half-maximum PRU signal	0.278	1.44	-	0.05	fix	-
γ (-)	Hill coefficient for PRU signal	2.49	3.89	-	0.641	4.89	71.3
R_0 (-)	Baseline receptor	1	Fix	-	-	-	-
k_{out} (1/h)	Receptor elimination rate constant	0.00641	7.94	-	0.755	10.6	87.7
E_{50} (-)	Half-maximum cumulative effect	0.0473	1.90	-	0.05	fix	5.00
γ_c (-)	Hill coefficient cumulative effect	3.63	2.19	-	0.05	fix	5.00
k_{Cum} (1/h)	Rate constant cumulative effect	0.00820	1.70	-	0.05	fix	5.00
k_{Sel} (L/nmol/h)	Selatogrel binding rate constant to receptor	6.57	3.49	-	0.05	fix	5.00
K_{dSel} (nmol/L)	Selatogrel dissociation constant	11.0	4.10	-	0.542	6.20	58.4
β_{KdSel_AMI} (-)	AMI on K_{dSel}	1.60	10.7	$<2.2 * 10^{-16}$	-	-	-
M_{kSel} (-)	Selatogrel maximum cumulative effect	2.22	1.81	-	0.05	fix	5.00

(Continues)

TABLE 2 (Continued)

Parameter	Description	Fixed effects parameters			Interindividual variability (random effects)		
		Estimate	%RSE	*P* value (covariates)	Estimate	%RSE	%CV
k_{Pr} (L/nmol/h)	Prasugrel binding rate constant to receptor	0.0071	12.6	-	0.724	18.6	83.0
M_{kPr} (-)	Prasugrel maximum cumulative effect	1.32	1.92	-	0.05	fix	5.00
k_{Clo} (L/nmol/h)	Clopidogrel binding rate constant to receptor	0.00773	Fix	-	0.492	fix	52.3
k_{Ti} (L/nmol/h)	Ticagrelor allosteric binding rate constant to receptor	2.21	Fix	-	0.05	fix	5.00
K_{dTi} (nmol/L)	Ticagrelor dissociation constant	193	Fix	-	0.489	fix	52.0
Residual error term							
b1	Proportional error for PK	0.140	1.72				
a2	Additive error for PD	3.65	2.90				
b2	Proportional error for PD	0.170	2.07				

$CV(\%) = 100 \cdot \sqrt{e^{\omega^2} - 1}$ with ω the standard deviation of the associated random effect. P values derived from the Wald test.

Abbreviations: %CV, coefficient of variation; %RSE, relative standard error; AMI, acute myocardial infarction; PD, pharmacodynamics; PK, pharmacokinetics; PRU, $P2Y_{12}$ reaction units.

defined based on PRU, lower naïve baseline PRU resulted in a higher proportion of responders. Presence of AMI led to a shorter PD effect (PRU returned to 100 after 4.1 h compared with 13 h) with a lower proportion of responders (76.3% compared with 99.7%).

A sensitivity analysis to assess the influence of imputing missing naïve baseline PRU (PRU_0) due to concomitant $P2Y_{12}$ background therapy showed that model parameter estimates remained stable with PRU imputations of 150, 180, 200, 220, and 250. Comparing parameter estimates for these imputations, only k_{out} and its interindividual variability as well as interindividual variability of PRU_0 and k_{Pr} changed by more than 10% (Table S2).

Model predictions of selatogrel in combination with clopidogrel and prasugrel

Based on the model predictions of different dosing times of clopidogrel after selatogrel, a clopidogrel loading dose (600 mg) administered ≥15 h after selatogrel did not lead to an interaction of >20 percentage points IPA at times 24 and 36 h (Figure 4). A prasugrel loading dose (60 mg) could be administered ≥4.5 h after selatogrel without a clinically relevant interaction.

To address interindividual variability, an extended simulation was conducted that included the estimated random effects of the PD model parameters. The simulations are limited in that no individual PK data were available for clopidogrel and prasugrel such that all estimated variability had to be attributed to the PD parameters. The simulations confirmed the known large interindividual variability for clopidogrel and showed a shift in prediction intervals similar to the shift in median PD effects (Figure S6).

DISCUSSION

To our knowledge, this work is the first semimechanistic PK/PD model describing the effect of multiple concurrent $P2Y_{12}$ inhibitors with receptor-level interactions, including the investigational drug selatogrel. The model was used to evaluate clinically relevant scenarios of combined uses of selatogrel and other $P2Y_{12}$ inhibitors and to determine the time to safely and efficaciously transition to oral $P2Y_{12}$ inhibitors after s.c. emergency administration of selatogrel in suspected cases of AMI.

The PK/PD model included a nonlinear relation between receptor occupancy and PRU as described in the literature.[16,28] The estimated elimination rate constant of the $P2Y_{12}$ receptor (k_{out}) corresponds to an average life span of 6.5 days, approximately in line with the physiological life span of platelets of 7.1 to 9.5 days.[29,30]

The PK/PD model included an adjustment, that is, the cumulative effect compartment, for nonlinearity in the binding of selatogrel alone and in combination with oral $P2Y_{12}$ receptor antagonists to the $P2Y_{12}$ receptor. Different physiological hypotheses could explain the empirical implementation of the observed nonlinearity. Platelet aggregation is a complex process with many factors involved. Synergistic

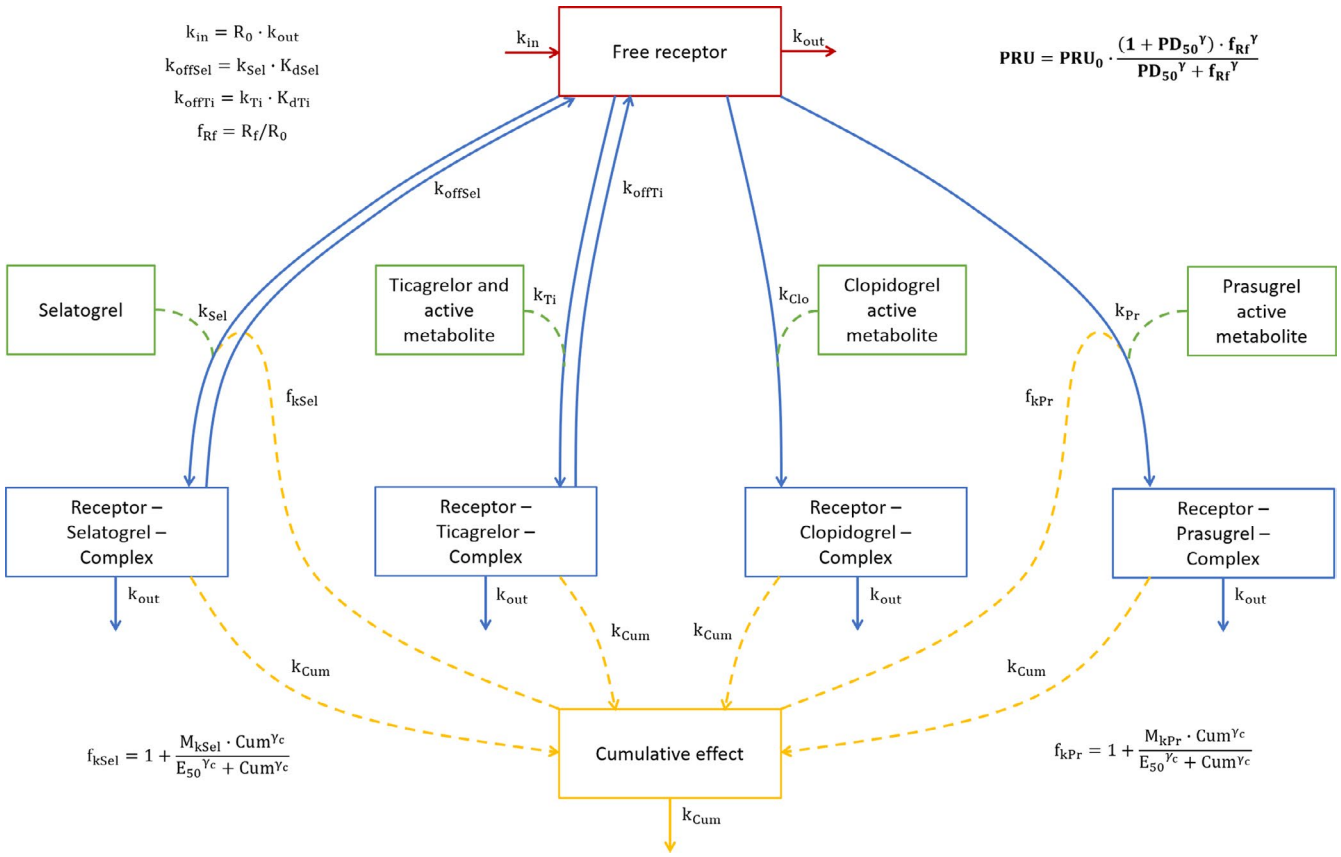

FIGURE 2 Pharmacokinetic/pharmacodynamic model structure. Solid lines, mass transfers; dashed lines, no mass transfer. Cum, cumulative effect; E_{50}, half-maximum for cumulative effect; f_{kPr}, factor resulting from cumulative effect modulating prasugrel binding; f_{kSel}, factor resulting from cumulative effect modulating selatogrel binding; f_{Rf}, fraction of free receptor; k_{Clo}, clopidogrel binding rate constant to receptor; k_{Cum}, rate constant for cumulative effect; K_{dSel}, selatogrel dissociation constant; K_{dTi}, ticagrelor dissociation constant; k_{in}, formation rate constant of receptor; k_{offSel}, dissociation rate constant of receptor complex with selatogrel; k_{offTi}, dissociation rate constant of receptor complex with ticagrelor; k_{out}, receptor elimination rate constant; k_{Pr}, prasugrel binding rate constant to receptor; k_{Sel}, selatogrel binding rate constant to receptor; k_{Ti}, ticagrelor allosteric binding rate constant to receptor; M_{kPr}, prasugrel maximum cooperativity effect; M_{kSel}, selatogrel maximum cooperativity effect; PD_{50}, half-maximum for PRU signal; PRU, $P2Y_{12}$ receptor units; PRU0, baseline $P2Y_{12}$ receptor units; R_0, baseline receptor; R_f, free receptor; γ, Hill coefficient for PRU signal; γ_c, Hill coefficient for cumulative effect

effects between ADP and nitric oxide,[31,32] prostacyclin,[33] and prostaglandin E_1[34] were postulated. Another hypothesis is the occurrence of positive cooperativity, that is, the binding of a molecule to a receptor resulting in an increase of binding affinity of the binding sites. Such positive cooperativity can occur for the binding of molecules with multiple binding sites,[35] as suggested for the $P2Y_{12}$ receptor.[36] This phenomenon is consistent with the observations in the present data analysis.

Finally, $P2Y_{12}$ receptors desensitize *in vitro* to ADP rapidly upon receptor occupation.[37] Although the prolonged binding to the receptor is caused by an antagonist in this case, it is possible that a similar desensitization of binding to ADP after selatogrel dissociation occurs. This would result in an apparent stronger IPA for higher doses due to prolonged binding to the receptor.

The selatogrel dissociation constant K_{dSel} was estimated to be 11.0 nmol/L, approximately seven times the observed *in vitro* value (1.5 nmol/L, data on file). Similarly, the dissociation constant of ticagrelor was estimated substantially higher than described in literature (193 nmol/L compared with 10.5 nmol/L).[38] The differences in binding kinetics between *in vitro* experiments and this analysis probably result from the different model structure that includes the cumulative effect.

The model included the ability of ticagrelor to bind to the allosteric binding site of the $P2Y_{12}$ receptor, making it an allosteric antagonist.[39,40] This binding can occur even if a reversible $P2Y_{12}$ receptor antagonist such as selatogrel is bound to the ADP binding site. The allosteric binding of ticagrelor will cause selatogrel to dissociate from the receptor. This mechanistic element in the model reflecting the actual receptor-antagonist interactions was found to provide the best description of the observed joint effect of ticagrelor and selatogrel, strengthening confidence in the predictive performance of the model.

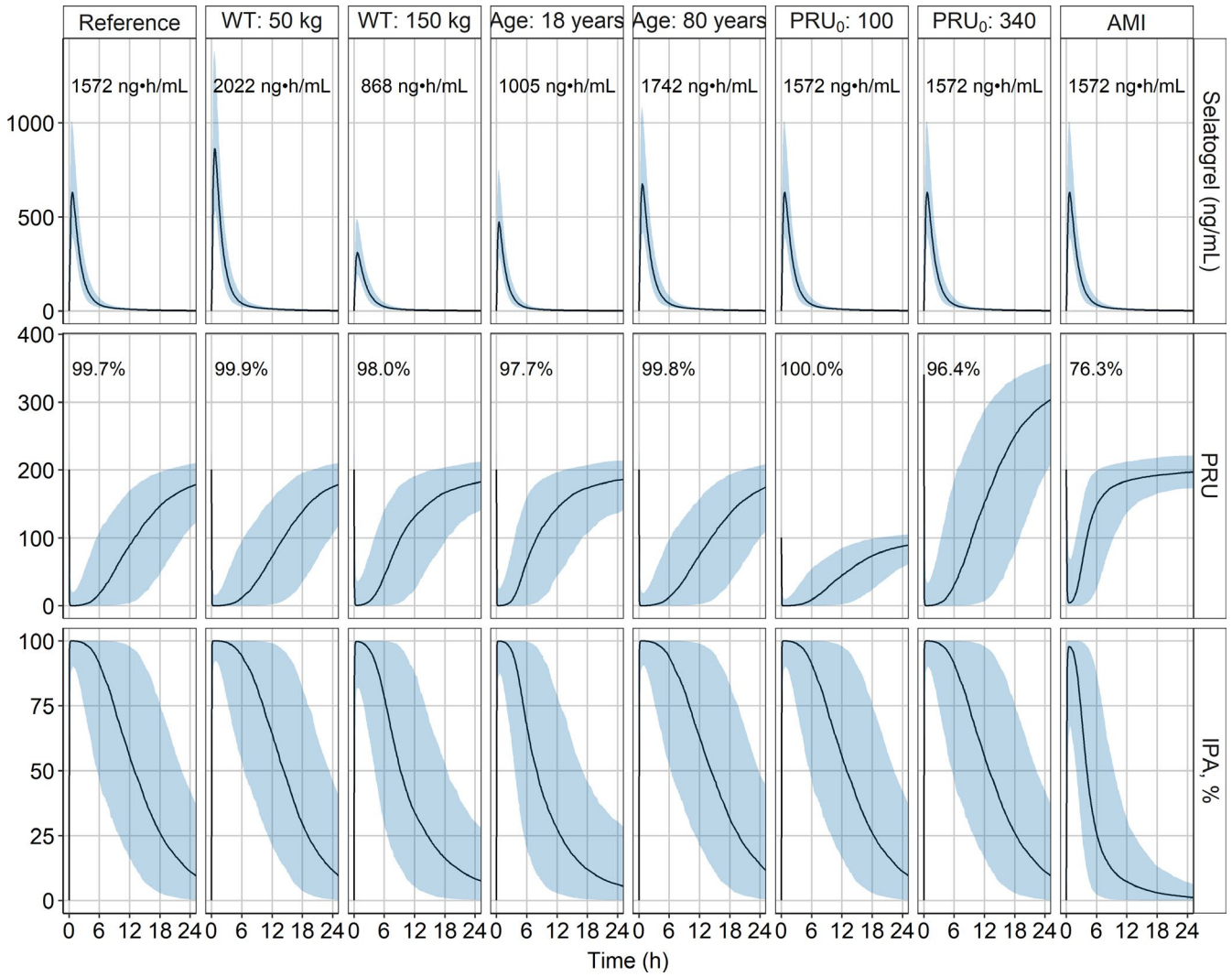

FIGURE 3 Covariate effects on pharmacokinetic and pharmacodynamic after 16 mg selatogrel administration. Lines, median shaded areas, 90% prediction interval (including 90% of simulated subjects with interindividual variability), values in the top row panels, area under the concentration-time curve between 0 and 48 h after selatogrel administration; values in the middle row panels, proportion of responders, that is, subjects with PRU <100 from 0.5 to 3 h after selatogrel administration. Reference subject: body weight 70 kg, age 60 years, naïve baseline PRU 200, and disease status healthy/CAD. AMI, acute myocardial infarction; IPA, inhibition of platelet aggregation; PRU, $P2Y_{12}$ reaction units; PRU_0, naïve PRU measured at baseline; WT, body weight

The PK model included body weight and age as covariates on multiple PK parameters influencing absorption, distribution, and elimination. Older subjects showed a slower absorption, lower clearance, and smaller volume of distribution, possibly explained by reduced skin perfusion[41] and liver function. Reduced volume of distribution is typical for polar drugs[42] such as selatogrel. Despite significant effects of body weight and age on PK, the effect on onset and maximum platelet inhibition was limited. Nevertheless, higher exposure led to a prolonged effect on IPA. The proportion of responders was not influenced to a relevant extent since also with low exposure, for example, due to high body weight of 150 kg, median PRU remained below 100 for 9.3 h after selatogrel dosing.

With respect to PK/PD, the presence of AMI (i.e., patients vs. healthy subjects) was statistically significant on the selatogrel dissociation constant leading to shorter IPA. The reduced effect of selatogrel might result from increased platelet reactivity during AMI.[43,44] PD measurements in patients in the phase II study were only performed up to 1 h after selatogrel dosing.[13] Therefore, the effect of AMI requires further investigation to validate the model prediction beyond 1 h for patients with AMI. Observed naïve baseline PRU influenced the PRU profile since it is contained in the baseline model. Plausibly, subjects with lower naïve baseline PRU are more likely to remain below the 100 PRU threshold while this is more difficult to achieve for subjects with higher naïve baseline PRU. Correction for baseline, that is, using percent IPA, eliminates these differences.

All PK and PK/PD model parameters were estimated with high precision. The PK model described the selatogrel

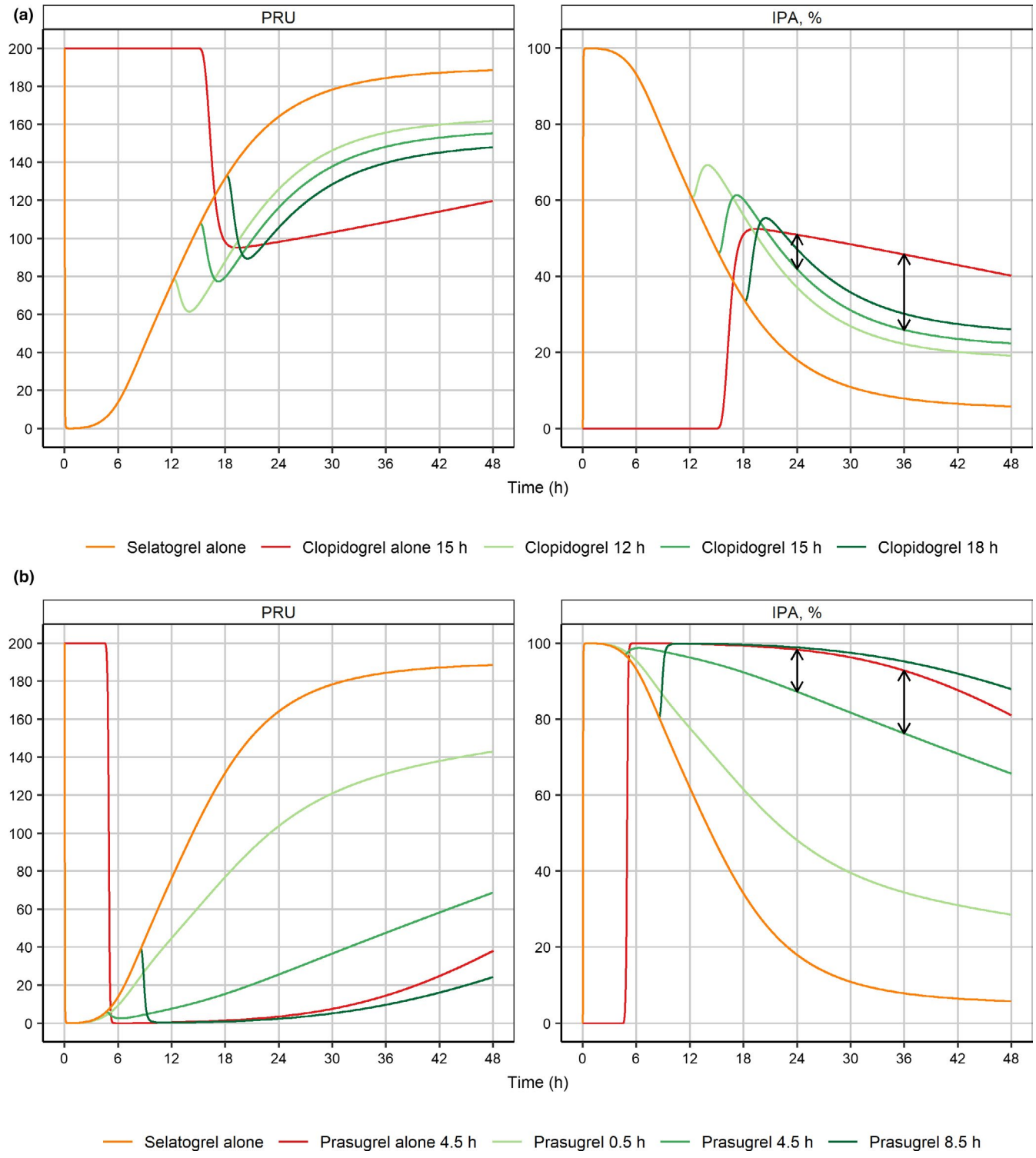

FIGURE 4 Joint effects of selatogrel, clopidogrel, and prasugrel on platelet aggregation for selected transition regimens. Model predictions of a reference subject with dosing of selatogrel (16 mg at time 0 h) and/or clopidogrel (600 mg; a) and prasugrel (60 mg; b) at different timepoints relative to selatogrel. Vertical arrows visualize the decision criterion for administration of clopidogrel 15 h after selatogrel/placebo and prasugrel 4.5 h after selatogrel/placebo. IPA, inhibition of platelet aggregation; PRU, $P2Y_{12}$ reaction units

concentration data well for all studies and doses. The additional absorption and distribution compartments particularly improved the fit of low selatogrel concentrations. These are important for the PD effect since the half-maximum inhibitory concentration is low (41.9 pmol/L = 25.9 ng/ml)[45] compared with the concentrations reached (435 ng/ml geometric mean maximum concentration after 16 mg of selatogrel).[1] VPCs showed a good fit for the mean selatogrel PD effect and its variability. Median PRU

effects for prasugrel and ticagrelor alone were well described, whereas PRU was slightly overestimated for clopidogrel alone for one of the 600-mg cohorts and the 300-mg cohort in the SWITCH study. The model adequately characterized the median PRU profiles of the combinations of selatogrel with all three oral $P2Y_{12}$ receptor antagonists. The variability in PD of the oral $P2Y_{12}$ receptor antagonists and their combination with selatogrel was generally overestimated, possibly inflated in the PK/PD model as only population-average PK data of the oral $P2Y_{12}$ inhibitors without variability were available. Particularly clopidogrel is known to have a high variability in the PK of the active metabolite due to genetic polymorphisms and environmental factors.[6] This variability was reflected in the variability of the effect parameters of these compounds when administered alone with interindividual variability of up to 83%. Further individual data including PK of the oral $P2Y_{12}$ receptor antagonists are needed to differentiate between interindividual variability in PK and PD to reduce model uncertainty and overestimation of variability.

Model predictions were used to interpolate and extrapolate different dosing intervals between selatogrel and clopidogrel/prasugrel administration. Extrapolation (for clopidogrel administration with data at 12 h and extrapolation to 15 h after selatogrel administration) requires more caution than interpolation (for prasugrel); however, the extrapolation in time is not very large.

These simulations showed that loading doses of clopidogrel and prasugrel can be administered from 15 h and 4.5 h after selatogrel, respectively, without clinically relevant PD drug interactions.

The PK/PD model developed here describes the effect of s.c. selatogrel on platelet inhibition alone and in combination with the oral $P2Y_{12}$ receptor antagonists clopidogrel, prasugrel, and ticagrelor in a semimechanistic manner. It was used to evaluate the interactions of multiple antagonists at the $P2Y_{12}$ receptor and its effect on PRU/IPA. These results are helpful to guide the transition from emergency treatment with selatogrel to oral maintenance therapy safely and effectively.

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CONFLICT OF INTEREST

A.H., J.D., and A.K. were employees of Idorsia at the timing of writing the manuscript. C.H.C. worked as a consultant for Idorsia on this project.

AUTHOR CONTRIBUTIONS

A.H., C.H.C., J.D., and A.K. wrote the manuscript, designed the research, performed the research, and analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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