ORIGINAL ARTICLE

Population Modeling of Selexipag Pharmacokinetics and Clinical Response Parameters in Patients With Pulmonary Arterial Hypertension

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Selexipag (Uptravi) is an oral selective IP prostacyclin receptor agonist approved for the treatment of pulmonary arterial hypertension (PAH). The pivotal GRIPHON study was the largest clinical study ever conducted in PAH patients, providing long-term data from 1,156 patients. PAH comedication did not affect exposure to selexipag, while exposure to its active metabolite ACT-333679 was reduced by 30% when taken in combination, clinically not relevant in the context of individual dose up-titration. Using log-linear regression models linking model-predicted steady-state exposure to pharmacodynamics (PD), exposure to selexipag and ACT-333679 showed some statistically significant, albeit not clinically relevant, effects on exercise capacity, laboratory values, and the occurrence of prostacyclin-related adverse events, but not on vital signs or adverse events denoting hemorrhage. Using suitable modeling techniques, the GRIPHON study yielded clinically relevant data with limited burden of pharmacokinetics (PK) blood sampling, demonstrating that PK/PD modeling enables firm conclusions even with sparse PK and PD sampling.
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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Intravenous prostacyclin therapy is effective in PAH patients.
WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Quantitative assessment of PK and clinical responses of the oral prostacyclin receptor agonist selexipag based on the largest study ever conducted in PAH patients.
WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ PAH comedication did not affect exposure to selexipag, while exposure to its active metabolite ACT-333679 was reduced by 30% when taken in combination, clinically not relevant in the context of individual dose

up-titration. Exposure to selexipag and ACT-333679 showed some statistically significant, albeit not clinically relevant, effects on exercise capacity, laboratory values, and the occurrence of prostacyclin-related adverse events but not on vital signs or adverse events denoting hemorrhage.
HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ The novel concept of individual up-titration of the selexipag dose to the maximum tolerated dose is confirmed. PK/PD modeling enables robust results from phase III studies with sparse sampling and limited burden of PK sampling on patients and staff.

Selexipag (Uptravi™) is an oral selective IP prostacyclin receptor agonist that is structurally distinct from prostacyclin. It is rapidly absorbed after oral administration and hydrolyzed to the active metabolite ACT-333679.[1]

In vitro experiments measuring cellular shape change using human pulmonary arterial smooth muscle cells showed that ACT-333679 is 37-fold more potent than selexipag in activating the human IP receptor.[2] Therefore, ACT-333679 is considered the major contributor to the efficacy of selexipag in man.

Selexipag was approved for the treatment of pulmonary arterial hypertension (PAH) in the United States in December 2015[3] and in the European Union in May 2016. Selexipag is a promising and novel treatment option for PAH patients due to its high selectivity for the human IP receptor.

PAH is a life-threatening disease characterized by progressive increase in pulmonary artery pressure and pulmonary vascular resistance.[4] The pathogenesis of PAH is thought to result from an imbalance in the level and ratio of vasoactive substances including prostacyclin, nitric oxide, and endothelin-1. The corresponding pathways are targeted by currently available PAH therapies.[5]

The GRIPHON study ("Prostacyclin (PGI2) Receptor agonist In Pulmonary arterial HypertensiON") was the largest clinical study ever conducted in PAH patients and provided a wealth of data on a diverse population of 1,156 patients with different disease status and demographics.[6]

A particular feature of the GRIPHON study was that patients were allowed to use concomitant PAH medication, an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE5) inhibitor, in combination with

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selexipag if they were on a stable dose of these concomitant medications.[6] This design allowed for assessment of selexipag pharmacokinetics (PK) and pharmacodynamics (PD) in a standard-of-care situation with patients on multiple PAH medications when starting selexipag treatment.

The study showed that the hazard ratio for a primary endpoint event (time-to-event analysis of death or a complication associated with underlying PAH) in the selexipag group compared to placebo was 0.6 (99% confidence interval 0.46–0.78, $P < 0.001$).[6]

The analyses presented here quantify exposure to selexipag and ACT-333679 and identify covariates influencing the exposure to a statistically significant extent. Subsequently, the exposure relation to exercise capacity, laboratory values, vital signs, and the occurrence of adverse events (AEs) is evaluated.

Orphan diseases such as PAH pose particular challenges due to the large number of sites, typically small numbers of patients per site, and complex logistics.[7] While such complexity contributes to variability in the data, the population modeling approach allows robust identification of effects on PK and PK/PD in patients differing by demographics, organ function, disease status, and concomitant medication.

METHODS
Study design
The GRIPHON study was a multicenter, double-blind, placebo-controlled phase III study conducted between 2009 and 2014 in 181 centers.[6] The primary study objective was to assess the effect of selexipag on time to death (from any cause) or a complication related to PAH.[6] During the 12-week dose adjustment phase, selexipag was initiated at a dose of 200 μg twice daily (b.i.d.) and increased weekly in increments of 200 μg b.i.d. until unmanageable AEs associated with prostacyclin use, such as headache or jaw pain, developed. The dose was then decreased by 200 μg in both daily doses, and this reduced dose was considered the maximum tolerated dose (MTD) for that patient. The maximum dose allowed was 1,600 μg b.i.d. After 12 weeks, patients entered the maintenance phase of the study. Starting at week 26, doses could be increased at scheduled visits; dose reductions were allowed at any time. Dose changes of more than 200 μg were rare. The individual maintenance dose (IMD) was defined as the dose a patient received for the longest duration, i.e., the steady-state dose corresponding to the MTD for most patients.

PK sampling
Blood samples were to be drawn before the morning dose to obtain trough plasma concentrations of selexipag and ACT-333679 at baseline, at weeks 4, 8, 16, 26, and 52 and at the end of study. An additional steady-state window sample was to be drawn at week 16 to allow for the characterization of the concentration–time course. The window sample was to be drawn during a specified time interval to which patients were randomized, either 0.5–1 h, 1–2 h, 2–4 h, 4–6 h, 6–8 h, or 8–12 h after the morning dose (due to b.i.d. dosing).

Clinical data collection
Efficacy parameters such as exercise capacity assessments (6-min walk distance, 6-MWD), plasma N-terminal probrain natriuretic peptide (NT pro-BNP), and the laboratory safety parameters leukocytes and bilirubin were chosen for PK/PD modeling to further explore the small changes found in the safety analysis. The effect of selexipag exposure on erythrocytes and hemoglobin was investigated since PAH patients frequently encounter anemia.[8] Vital signs (blood pressure, heart rate), occurrence of prostacyclin-related and hemorrhage AEs were investigated since prostacyclin analogs are known to have vasodilatory and platelet aggregation inhibitory effects.

Efficacy and safety parameter assessments were performed at baseline, weeks 4 (except 6-MWD), 8, 16, 26, every 6 months thereafter, at the end of study, and also if there was a suspected primary endpoint event. Treatment-emergent AEs were assessed up to 7 days after study drug discontinuation.

Population PK
Use of a population PK model in healthy subjects. It was anticipated that a population PK model in PAH patients with sparse sampling (trough samples and one window post-dose sample) might not be able to estimate the absorption phase in a robust fashion. A population PK model for healthy subjects was developed for this purpose and for comparison of PAH patients to healthy subjects. The data originated from a thorough QT (TQT) study with dense PK sampling.[9]

Handling of missing and BLQ data. Data with missing values for drug concentration, sampling time, dosing time, or dose administered were excluded (2,034/7,102 concentration records). Concentrations below the lower limit of quantification (351 for selexipag, 58 for ACT-333679) were imputed by sampling from the conditional distribution.[10,11]

Model development. The model building process followed a three-step approach: identification of the base model, forward selection of covariates, and successive elimination of the least statistically significant covariate until all remaining terms were significant. A covariate effect was declared statistically significant if the *P*-value associated with the covariate effect was <1% (0.01) for forward selection and covariate elimination.

The absorption lag time, t_{lag}, could not be estimated properly due to the sparseness of PK sampling. The population average was therefore fixed to the estimate from the healthy subject model, 0.668 h. Individual estimates were allowed to vary between 0–2 h (corresponding to the gastrointestinal passage time).

Covariate selection (PK). Physiologically meaningful relations between patient characteristics and model parameters were tested for statistical significance. To avoid analysis of small subgroups, only covariates present in more than 5% of the analyzed study population were formally tested.

The covariates tested (defined prior to database closure) were body weight, sex, age, race/ethnicity, organ function parameters aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and creatinine clearance

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(CLcr) as well as CYP3A4/2C8 inhibitors that could influence the exposure to selexipag or ACT-333679, frequently used comedications in PAH such as ERAs and PDE5 inhibitors as well as digoxin, and disease status (NYHA/WHO functional class (FC)).

Categorical (grouped) covariates were modeled as differences to a reference group. The reference group was female for sex, Asian for race/ethnicity, naïve for PAH-specific comedication, class II for NYHA/WHO FC at baseline, no use of CYP inhibitors, and digoxin comedication.

Covariates were modeled as a power relationship. For a continuous covariate, the parameter value for the i-th subject, for example, drug clearance (CL), was defined as:

$$CL_{pop,i} = CL_{pop} * (covariate/(typical covariate value))^{\Theta}$$

For categorical covariates, the parameter estimate for a category was estimated as the product of the reference category and the category-specific difference β, e.g.,

$$CL_{male} = CL_{female} * exp(\beta_{male})$$

The typical covariate values were derived from the data using a round value close to mean and median (40 years of age, 70 kg body weight, 100 mL/min/1.73 m^2 CLcr, 20 U/L AST, 20 U/L ALT, and 10 μmol/L total bilirubin).

Parameter estimation. Population PK parameters were estimated using the Stochastic Approximation of Expectation Maximization (SAEM) algorithm in Monolix with diagonal covariance matrix and option "auto" for the number of iterations. The residual error terms for parent and metabolite were proportional, an extra additive error term did not provide relevant improvement.

The long dosing history (multiple years for many patients) determined the computing time. Adding five doses prior to each PK sample (to reach steady state) proved to be substantially faster than adding all doses.

Clinical response modeling
Use of PK data. The model-estimated individual steady-state exposure at the IMD over one dosing interval (12 h) was defined as the combined AUC of selexipag and ACT-333679 with weights according to their potencies, ACT-333679 being 37-fold more potent than selexipag.[2] The individual steady-state combined exposure (AUC$_{combined}$) at the IMD over a 12-h dosing interval was derived as:

$$AUC_{combined} = 1/38 * AUC_{selexipag} + 37/38 * AUC_{ACT-333679}$$

Placebo subjects were assigned an IMD and AUC$_{combined}$ equal to 0.

Use of PD data. Vital signs (systolic, diastolic, and mean arterial blood pressure, heart rate), laboratory values (hemoglobin, red blood cell count, NT pro-BNP, total bilirubin, white blood cell count), and exercise capacity (6-MWD) were averaged per subject over the steady-state period from week 8 to week 52 (based on observed data only, missing data were not imputed). While this approach precludes detection of trends over time during the steady-state

period, it allows for a more robust analysis in the presence of random fluctuation and equal contribution of all patients with different numbers of assessments per patient.

Occurrence of prostacyclin-associated AEs and treatment-emergent AEs of hemorrhage and gastrointestinal hemorrhage were defined as occurrence of the AE at least once during the study (coded as 1 and 0 otherwise).

Nine patients had to be excluded from the PK/PD analysis due to not having PK or PD data at week 16 or later.

PK/PD relationships. AUC$_{combined}$ was calculated using the *individual* model-predicted AUCss on the IMD. Dose changes during the maintenance phase were observed in a limited number of patients (data on file). PK/PD modeling related AUC$_{combined}$ to PD. Technically, a model with the full individual dosing histories and longitudinal PK/PD modeling was impossible to fit due to computer run times.

Model development
PK/PD models for continuous PD parameters. The log-linear model was chosen to link PD response (effect) to exposure. The model was given as:

$$E = a * baseline + intercept + b * exposure + \varepsilon$$

with E denoting the PD observation at steady state, baseline the PD observation at baseline, exposure the logarithm base 10 of AUC$_{combined}$, and ε the residual error following a normal distribution. The parameters to be estimated were a (the relation of the effect at steady state to the baseline of the patient), b (the steepness of the relationship between exposure and PD change from baseline), and the intercept (shift in the effect from baseline to steady state without exposure to drug).

The log-linear model was chosen over the linear model to reduce the effect of few extreme exposures and over an E$_{max}$ model due to occasional convergence problems. Covariates were added as additive effect on the intercept and as multiplicative effect on the slope.

Because of the logarithmic scale, exposure of placebo patients was set to a value near the lowest observed exposure, 2.5 ng/mL.

PK/PD models for binary PD parameters. The logistic regression model was used for binary PD parameters such as the occurrence of AEs. The logistic regression model was given as:

$$\mu = intercept + b * exposure + \varepsilon$$
$$E = inverse\ logit(\mu) = exp(\mu)/(1+exp(\mu))$$

with the intercept denoting the effect in the absence of exposure (placebo group), b the slope parameter on exposure, ε the residual variability following a normal distribution, E the PD effect, and μ the expected value on the linear scale. A baseline effect is not given for AEs since the AE status at baseline is 0 – no AE. Covariates were added as additive effect (on the intercept) and as multiplicative effect (on the slope) of the linear term. Further details are given in the online supplement.
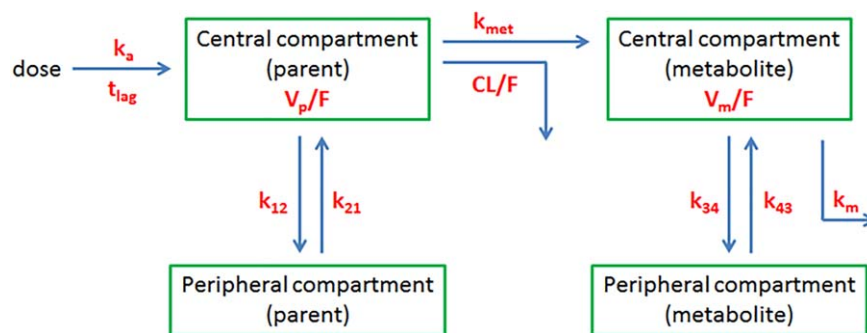
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Figure 1 PK model: compartments (boxes), drug flow (arrows), and model parameters. Absorption, drug flow between central and peripheral compartments, metabolism, and elimination of selexipag and ACT-333679 are first-order processes.

Covariate selection (PK/PD). If the base PK/PD model showed a significant relationship between PD and exposure, i.e., the slope being significantly different from 0 at the 1% level ($P < 0.01$), covariate effects were tested on the PK/PD relationship (intercept and slope). Covariates included baseline disease status (NYHA/WHO FC), PAH etiology, PAH comedication at baseline, and total bilirubin at baseline.

For categorical covariates, statistical significance was tested for the difference to the reference category, NYHA/WHO FC II, iPAH for PAH etiology, and naïve for PAH comedication. Only categories containing at least 5% of patients were considered for determination of statistical significance.

Covariate selection followed forward selection-backward elimination as for the PK model.

RESULTS

The following section focuses on the PK model. Details on data preprocessing, study population, distribution of PK sampling times, and distribution of IMD and AUC$_{combined}$ are provided in the online supplement.

Population PK

The PK of selexipag had been shown to be dose-proportional in the range 100–1,800 μg.[1] The population PK of selexipag and its metabolite ACT-333679 in PAH patients ($n = 512$) can be adequately described by a two-compartment model for parent compound and metabolite with first-order absorption with lag time, first-order transfers between compartments, first-order metabolism from parent to metabolite, and first-order elimination of parent and metabolite (**Figure 1**).

Table 1 gives the final population PK model parameter estimates. The parameters were estimated reasonably well, as evidenced by a low relative standard error (RSE). Population parameters were estimated with RSE between 10 and 20%. Interindividual variability (IIV) showed higher RSEs for the metabolic rate constant, k_{met}, and the metabolite volume of distribution, V_m/F, likely due to small IIV (below 0.1). These could be set to 0 but were estimated to support SAEM convergence.

The estimates for the proportional error term, 0.75 and 0.49 for parent and metabolite (i.e., 75% and 49% residual variability, respectively), suggest a relatively large variability that is not unexpected for phase III data compared to better-controlled phase I studies.

The covariates body weight, sex, total bilirubin, and PAH comedication were identified as statistically significant towards the PK of selexipag and ACT-333679 (**Table 2**). The difference in AUCss varies between -30 and $+30\%$ compared to the reference patient (**Table 3**). The IIV in concentration (**Figure 2**) exceeds the variability of all covariates (**Table 3**), such that the clinical relevance of the variability related to the statistically significant covariates is considered negligible.

Model qualification. Observed vs. model-predicted concentrations (population and individual predictions) for selexipag and ACT-333679 were in good agreement except for a small bias at very low selexipag concentrations (**Figure S3**).

Residuals showed an underprediction of selexipag and ACT-333679 of less than 0.5 ng/mL (**Figure S4**). Individual clearance estimates did not show any relation to time on study such that a change in drug clearance over time was not indicated.

Visual predictive checks (VPCs) comparing observed data to data simulated from the model show agreement between observed and simulated concentrations comparing the 10, 50, and 90% quantiles (**Figure S5**).

IIV terms were kept on all population parameters to stabilize the SAEM algorithm. Further goodness-of-fit assessments (online supplement) indicate an adequate characterization of the data by the model.

Model illustration. The population-typical concentration–time profile for the reference subject at steady state on a dose of 1,600 μg b.i.d. is shown in **Figure 2.** The effects of body weight, sex, concomitant PAH medication, and total bilirubin at baseline are illustrated in **Figure 3**.

Comparison to the healthy subject population PK model. **Figure 4** shows a comparison of model-predicted steady-state concentration–time profiles of selexipag and ACT-333679 between the population PK models for healthy subjects and PAH patients.

Table 1 Final population PK model parameter estimates

Parameter	Description	Population parameters				Interindividual variation (std. dev.)		
		Estimate	Std. error	Rel. std. error (%)	P-value	Estimate	Std. error	Rel. std. error (%)
t_{lag} (h)	Absorption lag time	0.67	-	-		1.92	0.20	10
k_a (1/h)	Absorption rate constant	0.71	0.04	5		0.39	0.05	12
V_p/F (L)	Apparent volume of distribution, central compartment selexipag	12.90	2.00	16		0.31	0.12	38
Body weight on V_p/F	Covariate effect	1.20	0.30	25	<0.001			
CL/F (L/h)	Apparent selexipag clearance	19.10	1.60	8		0.73	0.03	4
Body weight on CL/F	Covariate effect	0.61	0.15	25	<0.001			
Total bilirubin on CL/F	Covariate effect	−0.40	0.07	18	<0.001			
k_{12} (1/h)	Transfer rate constant central to peripheral compartment selexipag	0.09	0.02	18		0.25	0.18	73
k_{21} (1/h)	Transfer rate constant peripheral to central compartment selexipag	0.06	0.01	17		1.06	0.13	12
V_m/F (L)	Apparent volume of distribution, central compartment ACT-333679	4.65	0.80	17		0.10	0.25	241
Body weight on V_m/F	Covariate effect	0.88	0.18	21	<0.001			
k_{met} (1/h)	Metabolism rate constant selexipag to ACT-333679	0.67	0.12	18		0.05	0.42	788
k_{34} (1/h)	Transfer rate constant central to peripheral compartment ACT-333679	1.04	0.23	22		0.47	0.18	39
k_{43} (1/h)	Transfer rate constant peripheral to central compartment ACT-333679	0.18	0.03	14		0.89	0.14	16
k_m (1/h)	Elimination rate constant ACT-333679	0.49	0.08	16		0.27	0.06	20
Sex on k_m	Covariate effect	0.15	0.05	31	0.001			
PAH comedication on k_m (ERA)	Covariate effect	0.15	0.06	38	0.008			
PAH comedication on k_m (PDE5 inh.)	Covariate effect	0.07	0.05	77	0.190			
PAH comedication on k_m (ERA and PDE5 inh.)	Covariate effect	0.37	0.05	14	<0.001			
Residual error terms								
b_1	Proportional error selexipag	0.75	0.01	2				
b_2	Proportional error ACT-333679	0.49	0.01	2				

The figure shows that the concentration–time profiles of selexipag and ACT-333679 from the healthy and the patient model largely overlap. The AUC over a dosing interval at steady state was estimated to be 30% (selexipag) and 20% (ACT-333679) higher in PAH patients than in healthy subjects.

Population PK/PD
The PD analyses related the PD parameters to steady-state exposure ($AUC_{combined}$). Of the 559 patients on selexipag, 68 (12%) had an IMD of 200 μg, while 163 (29%) had the highest possible IMD, 1,600 μg (**Table S2**). The population PK/PD analysis included only patients with at least one steady-state assessment. Depending on the PD parameter, the number of patients available for the PD analyses ranged from 502 to 511 (patients on selexipag) and from 549 to 577 (patients on placebo).

Exercise capacity. The 6-MWD at steady state showed a change from 369 m on placebo to 392 m at the highest predicted steady-state exposure ($P < 0.001$). Disease status (NYHA/WHO FC) and total bilirubin at baseline showed

statistically significant effects on the intercept, reflecting a lower 6-MWD for patients who are sicker (**Table S2**).

Laboratory values. Plasma NT pro-BNP levels showed a statistically significant decrease with higher exposure, from 667 with no exposure (placebo patients) to 475 ng/mL at the highest exposure. The decrease was steeper in patients on concomitant PAH medication than in naïve patients (**Table S4**).

Total bilirubin levels showed a statistically significant decrease with higher exposure, from 12.03 μmol/L with placebo to 10.58 μmol/L at the highest exposure.

Erythrocyte count showed a small but statistically significant decrease with higher exposure, from $4.66*10^{12}$/L with placebo to $4.58*10^{12}$/L at the highest exposure. Similarly, hemoglobin showed a statistically significant decrease with higher exposure, from 138.84 G/L with placebo to 134.58 G/L at the highest exposure.

Leukocyte count showed a statistically significant decrease with higher exposure, from 6.82 G/L with placebo to 6.26 G/L at the highest exposure. Baseline levels and

Table 2 Covariate effects in the final model

Parameter	Covariate	Coefficient	Notes
V_p	Body weight	1.2	Volume increases with higher body weight: $V_p = V_{p, pop} (bw/70)^{1.2}$
V_m	Body weight	0.88	$V_m = V_{m, pop} (bw/70)^{0.88}$
CL	Total bilirubin at baseline	−0.40	Clearance decreases with higher bilirubin $CL = CL_{pop} (bilirubin/10)^{-0.4}$
CL	Body weight	0.61	Clearance increases with higher body weight: $CL = CL_{pop} (bw/70)^{0.61}$
k_m	PAH comedication	Naïve: $k_m = 0.49/h$ ERA: $k_m = 0.57/h$ PDE5: $k_m = 0.52/h$ Both: $k_m = 0.71/h$	k_m (metabolite elimination rate constant) is larger on PAH comedication ERA, PDE5 inhibitors, and both (compared to naïve)
k_m	Sex	Female: $k_m = 0.49/h$ Male: $k_m = 0.57/h$	Male patients have a larger k_m (faster metabolite elimination) than female patients.

steepness of change in laboratory parameters were statistically significantly different between PAH etiologies. PAH etiology associated with CHD or drug- or toxin-induced PAH showed higher baseline levels and smaller decreases with increasing exposure than etiologies associated with CTD (**Table S4**).

Vital signs. The PD parameters systolic, diastolic, and mean arterial blood pressure as well as heart rate did not show a statistically significant relationship to exposure (**Table S4**).

Adverse events. The occurrence of at least one prostacyclin-associated AE showed a statistically significant relationship to exposure, influenced by PAH etiology and PAH comedication (**Table S4**), although the probability only increased to a moderate extent (from 50–80% to 90–95%, depending on PAH etiology and concomitant PAH medication). Patients with PAH etiology CTD are predicted to have a statistically significantly higher probability of the occurrence of the AE than patients with iPAH and CHD etiologies. Patients randomized to placebo experienced fewer of these AEs than patients randomized to selexipag. However, no difference could be determined between low and high doses (exposures) of selexipag.

The probability of a treatment-emergent AE of hemorrhage and gastrointestinal hemorrhage showed no statistically significant relationship to exposure (**Table S4**).

DISCUSSION

GRIPHON was the largest clinical phase III study ever conducted in PAH patients. It allowed the participating patients to be on concomitant PAH medication (ERA and/ or PDE5 inhibitor), reflecting standard of care of PAH patients.

Collecting trough blood samples and a single sample per patient after dosing randomized into time windows proved sufficient to derive robust results with the use of an appropriate modeling methodology. A combined PK/PD modeling approach, starting from a population PK model in healthy subjects and extending it to PAH patients, allowed a good characterization of the PK of selexipag and its metabolite, ACT-333679, in PAH patients while minimizing the burden of blood sample collection.

Exposure was linked to PD effects (exercise capacity, laboratory values, vital signs, and occurrence of AEs) by relating model-predicted individual steady-state exposure (PK) to average steady-state observations (PD). This allowed condensation of the multiple-year long time axis into average observations per patient that are more robust than individual observations. Averaging precludes detection of trends over time or IIV in favor of reducing random fluctuation and allowing patients with different numbers of assessments to contribute equally.

The population PK model identified differences in body weight, sex, total bilirubin, and PAH comedication as

Table 3 Covariate effects: summary of effects on exposure over a steady-state dosing interval (AUCss)

Covariate	Covariate on parameter	Reference patient	Comparison patient	AUCss selexipag	AUCss ACT-333679
Body weight	Apparent volumes of distribution	70 kg	51 kg	+30%	−20%
			96 kg	−20%	−10%
Total bilirubin	Selexipag clearance	10 μmol/L	5 μmol/L	−20%	−20%
		10 μmol/L	25 μmol/L	+30%	+30%
PAH comedication	Elimination rate constant ACT-333679	PAH comedication naïve	PAH comedication ERA and PDE5 inhibitor combined	No change	−30%
Sex	Elimination rate constant ACT-333679	Female	Male	No change	−13%

Covariates tested and determined to be not statistically significant: age, race/ethnicity, CLcr, AST, ALT, PAH comedications strong CYP inhibitor and digoxin, baseline disease status NYHA/WHO.
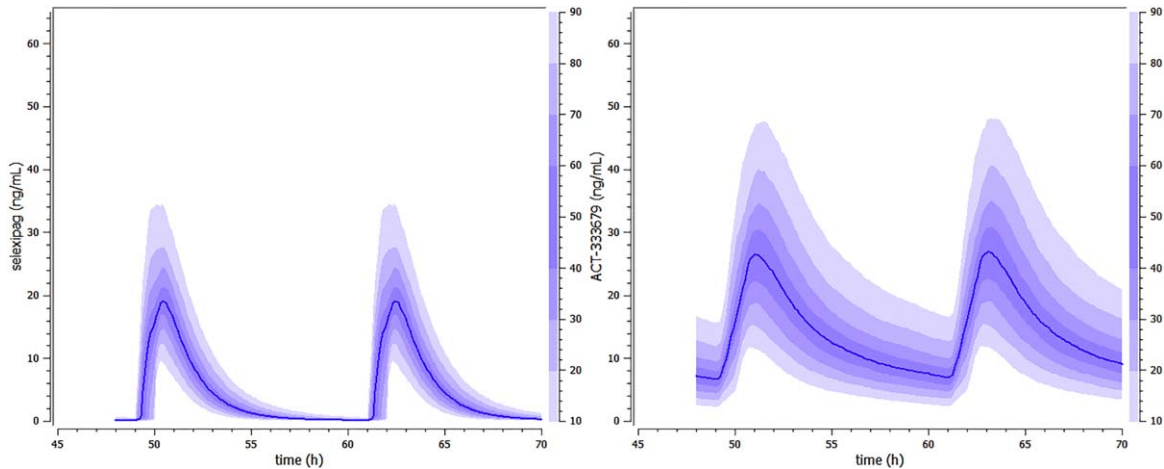
Figure 2 Population-typical concentration–time profile of selexipag (left) and ACT-333679 (right) at steady-state doses of 1,600 μg b.i.d. with interindividual variation. Colored areas indicate ranges of simulated concentration–time profiles (10th to 20th, ..., 80th to 90th percentile as indicated by the color legend on the right-hand side).

statistically significant factors towards differences in exposure to selexipag and ACT-333679 (**Table 3**). Similar effects have been observed for bosentan and macitentan.[12] Such effects could be due to reduced liver function in the severely sick PAH patients.[13]

Exposure to ACT-333679 was reduced by 30% in patients with two PAH-specific therapies (ERA and PDE5 inhibitor) compared to naïve patients, exposure to selexipag remained unchanged. Whether this is caused by a particular drug or disease state of the patients is unknown but
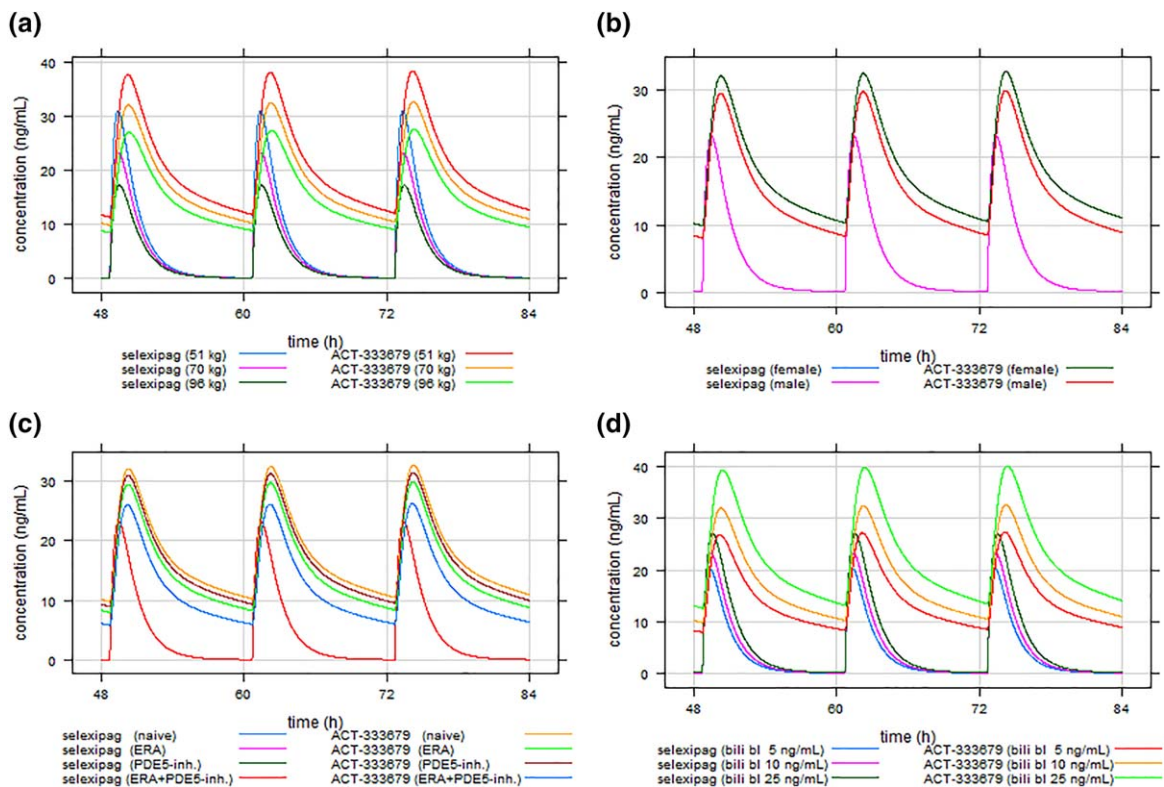
Figure 3 Covariate effects: Concentration–time profiles at steady state for selexipag and ACT-333679 for (**a**) body weights of 51, 70, and 96 kg, (**b**) male and female, (**c**) concomitant PAH medication, and (**d**) total bilirubin at baseline at steady-state doses of 1,600 μg b.i.d. Time denotes time after first dose. Some lines overlay since there was no effect of sex and PAH comedication on selexipag. The typical (reference) patient had 70 kg body weight, was female with total bilirubin at baseline of 10 μmol/L, and PAH comedication-naïve.

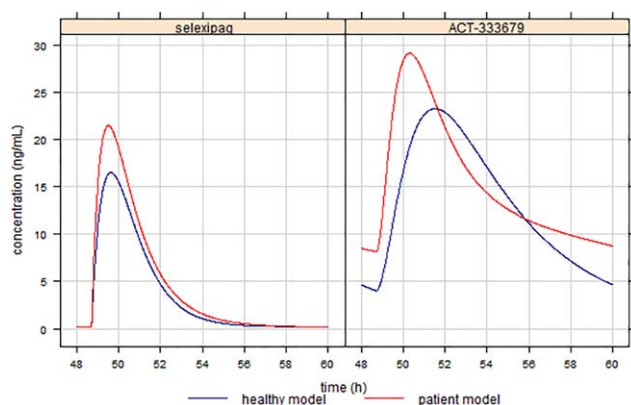**Population PK/PD Modeling of Selexipag in PAH Patients**
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Figure 4 Comparison of PK models for PAH patients and healthy subjects: Model-predicted concentration–time profiles of selexipag and ACT-333679 for a male subject with 80 kg body weight, total bilirubin 13 μmol/L, and no PAH comedication (healthy model) or naïve (patient model) at a steady-state dose of 1,600 μg b.i.d.

unlikely due to CYP2C8 inductive properties of bosentan. Fewer than half of the patients with high doses of selexipag (1,200, 1,400, or 1,600 μg) concomitantly received PDE5 inhibitor and ERA therapy (data on file).

Differences in exposure are mitigated on a patient level: the dose in patients experiencing lower exposure due to concomitant PAH drug use can be up-titrated to higher IMDs (up to 1,600 μg) if tolerated. The efficacy data from the GRIPHON study showed that a consistent treatment effect was observed both in patients without and with PAH-specific therapies.[6] In conclusion, a 30% lower exposure to ACT-333679 is unlikely to have a relevant impact on the efficacy or safety of selexipag.

In line with previous studies,[14] age, race/ethnicity, CLcr, AST, ALT, other comedication (strong CYP inhibitors, digoxin), baseline disease status (NYHA/WHO FC), and baseline CLcr did not show a significant effect on the PK of selexipag and ACT-333679. This is in line with previous results showing no clinically relevant change in the PK in patients with severe renal impairment compared to healthy subjects.[15]

The estimated steady-state exposure to selexipag and ACT-333679 was 30% and 20% higher, respectively, in PAH patients compared to healthy subjects, possibly due to reduced liver function in PAH patients or data sources (full PK profiles vs. mostly trough samples).

The population PK model in healthy subjects as a starting point for the population PK model in PAH patients proved very helpful, confirming the value of PK studies in healthy subjects for PAH patients.[6]

The main analysis showed that the magnitude of improvement in the 6-MWD (10 to 36 m, 12 m difference between placebo and selexipag at week 26 across doses[6]) was in the lower range of 6-MWD observed in other randomized, controlled trials. The PK/PD modeling yielded consistent results: a reference patient was predicted to have a 6-MWD of 369 m with no exposure (placebo) and 392 m at the highest exposure.

NT pro-BNP levels were significantly lower in the presence of selexipag,[6] in line with the PK/PD modeling results predicting 667 ng/mL with no exposure to 475 ng/mL at the highest exposure.

Consistent with the main analysis, no signal for a relationship between exposure to selexipag/ACT-333679 and hypotension or inhibition of platelet aggregation was detected. Laboratory values showed statistically significant but clinically not relevant changes with exposure to selexipag/ACT-333679.

The occurrence of at least one prostacyclin-associated AE was identified to increase with exposure to selexipag compared to placebo, a phenomenon commonly seen with prostacyclin and its analogs.[16,17] Statistical analysis showed no differences between dose groups, however.[6]

Vital signs and the occurrence of hemorrhage AEs (including gastrointestinal hemorrhage) showed neither differences between selexipag and placebo nor statistically significant relationships with increasing exposure to selexipag. Similarly, clinically relevant concentrations of selexipag and ACT-333679 in healthy subjects exert no effect on platelet aggregation.[1]

Covariate analyses showed that disease status (NYHA/WHO FC) correlates with baseline 6-MWD, the standard for noninvasive disease progression monitoring in PAH.[12] Different PAH etiologies were identified to correlate with baseline laboratory parameters (leukocytes, erythrocytes, hemoglobin) and changes in laboratory parameters (total bilirubin), reflecting reduced organ function with differences between PAH etiologies.[13]

No further covariates were found to be statistically significant towards exercise capacity, laboratory parameters, or AEs, suggesting homogeneous effects on PAH patients with individually up-titrated doses.

In conclusion, the model-based evaluation allowed for limited burden on patients and clinical staff by reducing the number of PK samples to be taken to a single postdose blood sample combined with predose samples. The robust estimation of exposure in turn enabled insight into the relationships between exposure and exercise capacity, laboratory values, vital signs, and the occurrence of AEs, supporting the concept of individual up-titration to achieve consistent clinical effects.

The results of the GRIPHON study presented here serve as a showcase for the contributions of PK/PD modeling in a severe orphan disease.

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