CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207947Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	207947
Submission Date	December 22, 2014
Submission Type	Original, NME – Standard Review
Brand Name	UPTRAVI®
Generic Name	Selexipag
Sponsor	Actelion Pharmaceuticals, Inc.
Therapeutic Class	Prostacyclin IP receptor agonist
Formulation	Oral immediate release tablet
[Strengths]	[8 strengths: 200 to 1600 µg in increments of 200 µg]
Dosing Regimen	Starting dose of 200 µg twice-daily titrated based on tolerability in increments of 200 µg up to 1600 µg twice-daily
Proposed Indication	Treatment of pulmonary arterial hypertension (PAH) to delay disease progression
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
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TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Actelion Pharmaceuticals, Inc. is seeking approval of selexipag for the treatment of pulmonary arterial hypertension [PAH] to delay disease progression. Selexipag is an agonist of the prostacyclin IP receptor. Unlike other prostacyclin analogs such as treprostinil and iloprost, selexipag is structurally distinct from prostacyclin. Selexipag is essentially a pro-drug as it is hydrolyzed by carboxylesterase-1 [CES-1] to an active metabolite, ACT-333679, which is 37-fold more potent than selexipag towards prostacyclin IP receptor. Selexipag, if approved, will be the third drug improving clinical worsening of the disease, next to riociguat and macitentan.

The efficacy and safety claims is based on GRIPHON, a placebo-controlled, event-driven trial where selexipag was initiated at 200 µg twice-daily and up-titrated based on tolerability in increments of 200 µg, up to a maximum dose of 1600 µg twice-daily. The submission also includes three phase II studies in PAH and chronic thromboembolic pulmonary hypertension [CTEPH] patients. The clinical pharmacology program for selexipag comprised of 11 *in vivo* studies conducted in healthy volunteers and special populations. The submission was further supported by *in vitro* studies which evaluated plasma protein binding, blood to plasma partitioning, isozyme characterization, metabolic enzyme and transporter interaction of selexipag and ACT-333679.

1.1. Recommendations

The New Drug Application [NDA 207947] for selexipag can be approved from a clinical pharmacology perspective.

We have the following recommendations to be included in the product insert:

- Once-a-day regimen in patients with moderate hepatic impairment
- Avoid use in severe hepatic impairment
- Avoid use in patients with concomitant use of strong CYP2C8 inhibitor

The applicant is in agreement with these recommendations.

1.2. Phase 4 Commitments

No specific post-marketing commitments or requirements are proposed at this point of time.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings are listed below.

Pharmacokinetics:

- Following oral administration, selexipag is absorbed with a median T_{max} of 1 h and a mean terminal elimination half-life of 0.8 to 2.5 h across studies. The oral bioavailability of selexipag is not known.

- Selexipag is hydrolyzed by CES-1 to a pharmacologically active metabolite, ACT-333679. Peak plasma concentration of ACT-333679 is achieved by 3 to 4 h [median] with a terminal elimination half-life of 6 to 13 h [mean] across studies. The systemic exposure to ACT-333679 at steady state is 3- to 4-fold higher than that of selexipag. In addition, ACT-333679 is 37-fold more potent than selexipag towards prostacyclin IP receptor.

- There is no significant accumulation of selexipag or ACT-333679 upon twice-daily dosing. The steady state exposures of selexipag and ACT-333679 are achieved within 3 days following repeat administration.

- The PK measures of selexipag are dose-proportional in the range of 100 µg to 1800 µg. For ACT-333679, the increase in PK measures is slightly less than dose-proportional in this range. For every 2-fold increase in dose, there is approximately 85% increase in exposure.

- Selexipag is eliminated mainly by metabolism followed by biliary excretion of the metabolites predominantly in the feces. No unchanged selexipag or ACT-333679 is excreted in the urine.

Pharmacodynamics:

- Selexipag, when titrated individually up to 800 µg twice-daily, caused a reduction in mean percent change from baseline in pulmonary vascular resistance [PVR] and cardiac index relative to placebo.

- At clinically relevant exposures following administration of selexipag up to 1600 µg twice-daily, no significant inhibition of platelet aggregation [measured *ex vivo* with ADP as agonist] was observed.

Exposure-response:

- There was a shallow but significant relationship between $\log_{10}$ $AUC_{combined}$ and 6-minute walk distance [6MWD] observed in GRIPHON. The 6MWD for the placebo group [assigned $AUC_{combined}$ of 2.5 ng x h/mL to facilitate analysis] was predicted to be 369 m at steady state. At the highest exposure, an $AUC_{combined}$ of 647.1 ng x h/mL, the predicted 6MWD is 392 m.

Impact of intrinsic factors:

- Subjects with hepatic impairment have higher exposures to selexipag and ACT-333679 due to reduced clearance. Due to the relative higher potency of ACT-333679 compared to selexipag, dosing recommendations are made based on the exposure to the metabolite. No dose-adjustments are required in mild hepatic impaired group as exposure to ACT-333679 is similar to that observed in subjects without liver impairment. The exposure to ACT-333679 was 2-fold higher in patients with moderate hepatic impaired group following twice-daily administration. Based on pharmacokinetic modeling and simulation, once-daily regimen is expected to result in similar exposure to ACT-333679 when compared to healthy subjects. Therefore, a once-daily dosing regimen without changes in starting dose or dosing increments is recommended in moderate hepatic impaired group. There is not enough data in severe hepatic impaired group (N=2); hence, it is not possible to derive alternate dosing recommendations. The two subjects with severe hepatic impairment exhibit a 3-fold increase in exposure to selexipag and ACT-333679 compared to subjects with normal hepatic function. Further, the intrinsic variability in subjects with severe impairment of hepatic function is expected to be high and as such the maximum increase in exposure cannot be projected from the available data. Therefore, the recommendation is to avoid dosing of selexipag in patients with severe hepatic impairment.

- Subjects with impaired renal function [eGFR: 15-29 mL/min/1.73 m^2; not on dialysis] showed an increase in the range of 1.4- to 1.7-fold in $AUC_{0\text{-}inf}$ as well as C_{max} of selexipag and ACT-333679, but not $t_{1/2}$, suggesting that impaired renal function did not affect the elimination of selexipag or ACT-333679. Given the modest increase in exposure and the fact that selexipag will be titrated to tolerability, no dose-adjustment is required in patients with renal impairment.

- Of the factors explored, body weight was found to be a covariate affecting selexipag and ACT-333679 plasma exposures [30% increase in a 50 kg subject compared to a subject weighing 75 kg]. Other covariates such as age, gender and ethnicity does not significantly impact the PK of selexipag or ACT-333679. No dose-adjustments are required based on these intrinsic factors.

Impact of extrinsic factors:

- Selexipag is hydrolyzed to ACT-333679 by CES-1. Potential for CES-1 inhibition *in vivo* is minimal because of its ubiquitous expression in many tissues. CYP3A4 and CYP2C8 are other CYP isoforms involved in the metabolism of selexipag to minor metabolites. Importantly, metabolism of ACT-333679 to P10, one of the major metabolite in feces is mediated by CYP2C8. Therefore, inhibition of CYP2C8 is expected to impact the systemic exposures to ACT-333679.

- *In vitro* experiments show selexipag and ACT-333679 to be substrates of OATP1B1/1B3 uptake transporters. Further, selexipag is also found to be a modest substrate of P-gp and ACT-333679 to be a substrate of BCRP.

- Co-administration of Kaletra® [CYP3A, P-gp and OATP1B1/1B3 inhibitor] with selexipag resulted in approx. 2-fold increase in the exposure to selexipag, but not ACT-333679. The nature

of increase in selexipag exposure with Kaletra® i.e., increase in C_{max} and AUC with no significant change in elimination half-life suggests that the interaction is a result of inhibition of OATP1B1/1B3 and/or P-gp, but not CYP3A. Moreover, as there was no change in exposure to ACT-333679 which is 37-fold more potent than selexipag (b) (4)

- The potential for selexipag or ACT-333679 to act as perpetrators of metabolizing enzymes or transporters at clinically relevant doses is low.

- Co-administration with a high fat meal prolonged the absorption of selexipag resulting in a delayed T_{max} and approx. 30% lower C_{max}. The AUC did not change or decreased modestly for selexipag or ACT-333679. In the food effect studies, there was a general trend towards better tolerability when selexipag was administered in a fed state; hence, the applicant performed GRIPHON by administering selexipag with a meal. Therefore, selexipag should be administered with a meal in an attempt to improve tolerability.

Biopharmaceutics:

- Final to-be-marketed formulation was used in GRIPHON. Therefore, no pivotal bioequivalence study was conducted. A strength bioequivalence study conducted showed that selexipag and ACT-333679 PK measures from 1 x 1600 µg tablet and 8 x 200 µg tablet are bioequivalent [reviewed by Office of Product Quality].

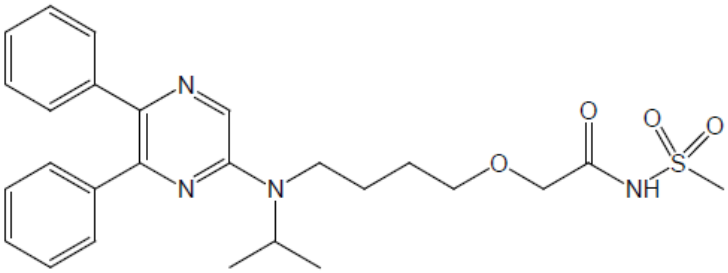
2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product?

Drug substance: The physicochemical characteristics of selexipag are summarized in Table 1.

Table 1: Physicochemical properties of selexipag

Appearance	Pale yellow crystalline powder
Chemical name	2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-methylsulfonyl)acetamide
Molecular formula	$C_{26}H_{32}N_4O_4S$
Molecular weight	496.62
Structural formula	 Molecule is achiral *Source*: Quality overall summary - Drug substance, Section 1.2
Solubility	(b) (4)
Partition coefficient	(b) (4)
Stability	
Hygroscopicity	Not hygroscopic
(b) (4)	

Drug product: Selexipag is formulated as an immediate release, film-coated tablets for oral administration in 8 different strengths [differentiated by debossing and color]. The excipients included D-mannitol, corn starch, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate, hypromellose, propylenglycol, titanium dioxide, iron oxides and carnauba wax.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Selexipag is a prostacyclin IP receptor agonist and is structurally distinct from prostacyclin and its analogs. Selexipag is hydrolyzed by CES-1 to an active metabolite, ACT-333679, which is 37-fold more potent than selexipag in inducing relaxation of the primary human pulmonary

arterial smooth muscle cells [hPASMCs; EC_{50}: 157 nM (selexipag) and 4.3 nM (ACT-333679)]. As the relative affinity towards IP receptor is higher for the hydroxyl metabolite than selexipag, any dose adjustments made are based on the plasma exposures of ACT-333679. Stimulation of IP receptor leads to vasodilation of pulmonary and systemic arterial vascular beds.

The proposed indication for selexipag is for the treatment of PAH [WHO Group I (b) (4) (b) (4) to delay disease progression.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosage form is an immediate release tablet for oral use available is 8 strengths – 200, 400, 600, 800, 1000, 1200, 1400 and 1600 µg. The recommended starting dose is 200 µg to be administered twice-daily. To achieve optimal clinical response, the dose is increased in increments of 200 µg twice-daily, usually at weekly intervals, until adverse pharmacological effects that cannot be tolerated or medically managed are experienced. The maximum dose evaluated for efficacy was 1600 µg twice-daily. Tolerability may be improved when taken with food.

2.1.4. What are the current treatments available for the proposed indications?

Drugs available for the treatment of PAH fall into the following classes – prostacyclin analogs [epoprostenol, treprostinil], phosphodiesterase type 5 (PDE-5) inhibitors [sildenafil, tadalafil], endothelin receptor antagonists (ERA) [ambrisentan, bosentan, macitentan], and soluble guanylate cyclase (sGC) stimulator [riociguat].

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The efficacy and safety claims for selexipag is based on the pivotal phase III trial, GRIPHON. GRIPHON was a multicenter, randomized, double-blind, placebo-controlled, parallel group event-driven trial. A total of 1156 patients were randomized 1:1 to either to selexipag or placebo. Selexipag was initiated at a dose of 200 µg twice-daily, up-titrated at weekly increments of 200 µg to a maximum dose of 1600 µg twice-daily based on tolerability. The primary endpoint was time to first morbidity or mortality event [further described in Q 2.2.2].

Three proof-of-concept/phase II studies were conducted in PAH [Caucasian and Japanese origin] and CTEPH [Japanese origin] patients. As with typical prostacyclin analog development programs, these studies were initiated at a dose where the prostacyclin mediated adverse events could be tolerated, and gradually up-titrated in an individual based on tolerability. The

efficacy/pharmacodynamic endpoints evaluated in these studies comprised of 6MWD and other cardio-pulmonary hemodynamic variables.

The clinical pharmacology program for selexipag comprised of 11 *in vivo* studies conducted in healthy volunteers and special populations. The submission was further supported by *in vitro* studies which evaluated plasma protein binding, blood to plasma partitioning, isozyme characterization, metabolic enzyme and transporter interaction of selexipag and ACT-333679.

2.2.2. What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Most of the drugs approved to-date are based on improvement in exercise ability as measured by 6MWD. The recently approved drugs, e.g., riociguat and macitentan, have shown improvement in clinical worsening of the disease. GRIPHON, the phase III trial for selexipag was also designed to demonstrate improvement in clinical worsening. The primary efficacy endpoint of selexipag was time from randomization to first morbidity or mortality event up to 7 days after the last study drug intake. The following morbidity and mortality events were considered –

- Death [all cause]
OR
- Hospitalization for worsening of PAH
OR
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
OR
- Initiation of parenteral prostanoid therapy or chronic oxygen therapy due to worsening of PAH
OR
- Disease progression

Disease progression in patients with WHO functional class II or III at baseline was defined by decrease in 6MWD from baseline ≥15% [confirmed by 2 tests on different days within 2 weeks] *and* worsening of NYHA/WHO functional class.

Disease progression in patients with WHO functional class III or IV at baseline was defined by decrease in 6MWD from baseline ≥15% *and* need for additional PAH-specific therapy.

Pulmonary hemodynamics and exercise capacity [as measured by 6MWD] were the response measures in proof-of-concept and phase II studies which are standard response metrics in the evaluation of an investigational drug for the treatment of PAH.

2.2.3. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Selexipag [parent] and ACT-333679 [metabolite] are the active moieties in plasma. They were appropriately identified and quantified in various biological matrices using validated LC-MS/MS methods [see Q 2.9] across clinical studies.

2.3. Exposure-Response

2.3.1. What was the basis of dose selection for phase 3 trial and is the rationale acceptable?

There were no dedicated studies conducted that characterized dose/concentration-effect relationship to guide dosing for phase III trial. Dosing is primarily based on tolerability and the basis comes from initial phase I/II studies in healthy subjects and PAH patients. In these studies, selexipag was well tolerated when initiated at 200 or 400 µg twice-daily with up-titration at increments of 200 µg every 3 days to achieve a maximum tolerated dose of 1600 µg twice-daily. The dosing regimen evaluated in GRIPHON is consistent with the established concept that starting at lower doses and up-titrating improves tolerability and allows attainment of higher doses of prostacyclin analogs.

2.3.2. What are the characteristics of the exposure-response relationship for efficacy?

The exposure-response relationship for efficacy was evaluated between combined AUC of selexipag and its metabolite, ACT-333679 at steady state [$AUC_{combined}$] and the endpoint 6-minute walk distance. Blood samples for the determination of trough concentration of selexipag and ACT-333679 [at weeks 4, 8, 16, 26, 52 and at the end of study] and one additional sample from a pre-specified time window post-dose at week 16 was collected in GRIPHON for the purpose of population PK analysis. The exposure metric, $AUC_{combined,}$ was calculated based on post-hoc AUC estimates weighted according to potency [e.g., ACT-333679 was estimated to have 37 times the potency of selexipag]. 6MWD was collected at multiple visits and values were averaged per subject over the steady-state period from week 8 to week 52 to obtain one steady state 6-minute walk distance [$6\text{-}MWD_{SS}$] value per patient.

A typical baseline 6MWD is 375 m. A significant slope was identified between exposure and 6MWD ($p<0.001$). An exposure of 2.5 h x ng/mL, which corresponds to the patients on placebo or with drug values below the limit of quantification, is predicted to result in a 6MWD of 369 m at steady state. The highest exposure, an $AUC_{combined}$ of 647.1 h x ng/mL, is predicted to result in a 6MWD of 392 m at steady state.

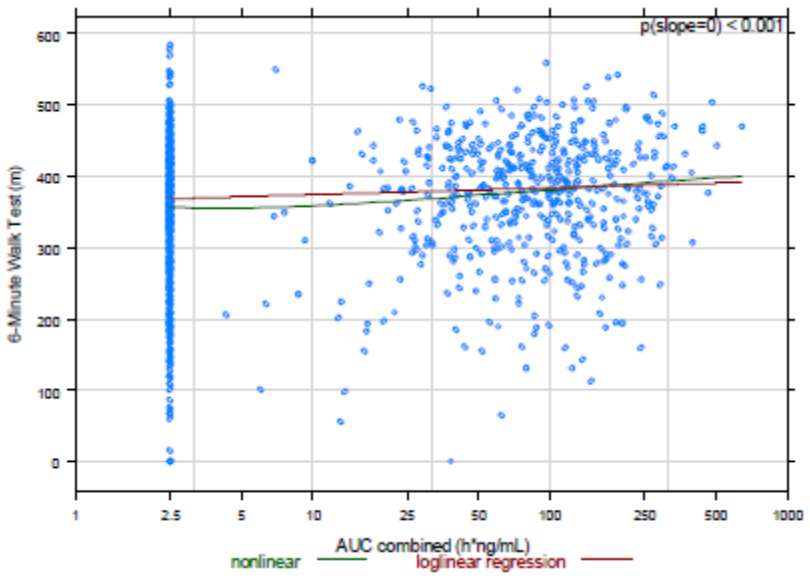


Figure 1: 6MWD vs individual model-predicted steady-state $AUC_{combined}$

[Source: Figure 33 of applicant's modeling and simulation report]

The 6MWD showed a significant relationship between baseline 6MWD and log-transformed drug exposure. Baseline disease status [NYHA/WHO functional class] and total bilirubin at baseline were also identified as significant covariates on the intercept, suggesting that the relationship between 6MWD and exposure shifts with baseline disease status [lower 6MWD for higher NYHA/WHO class] and total bilirubin level [lower 6-MWD for higher bilirubin levels].

Table 2: Full PD model: 6MWD

	Estimate	*Std. Error*	*t-statistic*	*p-value*	*p-value for comp.*	*Max(p) indicator*
(Intercept)	26.393	9.975	2.646	0.008	0.008	max(p)
log10.AUC.comb	9.304	2.188	4.252	0.000	0.000	
BASE	0.951	0.024	40.136	0.000	0.000	
NYHAWHO1	3.169	19.927	0.159	0.874	(ignored)	
NYHAWHO3	-18.858	3.678	-5.127	0.000	0.000	
NYHAWHO4	-28.798	18.115	-1.590	0.112	(ignored)	
BILIBL	-0.582	0.181	-3.216	0.001	0.001	

[Source: Table 52 of applicant's modeling and simulation report]

While the analysis provided above shows a significant exposure-response relationship when compared to placebo, the relationship between 6MWD and $AUC_{combined}$ when excluding placebo data may be shallower or flat. This may be in part to the phase III study design where subjects were titrated based on tolerability. However, all of the available results suggest that administration of selexipag 200 µg twice daily with an option to up-titrate offers improvement in 6MWD compared to placebo.

2.3.3. Does this drug prolong the QT or QTc interval?

Selexipag does not significantly prolong QTc interval up to the maximum tolerated dose of 1600 µg twice-daily. Moreover, there was no selexipag or ACT333679 concentration-ΔΔQTcI relationship over the dose range [800 to 1600 µg] achieved in the thorough QT study. Please refer to the QT-IRT review more information [DARRTS date: 03/25/2015].

2.4. Pharmacokinetics

2.4.1. What are the single- and multiple-dose PK parameters?

Pharmacokinetics of selexipag and ACT-333679 were characterized in single- and multiple-ascending dose studies [400 to 1600 µg twice-daily]. Following oral administration, selexipag is absorbed with a median T_{max} of 1 h and a mean terminal elimination half-life of 0.8 to 2.5 h across studies. ACT-333679, the primary active metabolite of selexipag, is formed with a median T_{max} of 3 to 4 h and a mean terminal elimination half-life of 6 to 13 h across studies.
Upon repeat dose administration, steady state exposures of selexipag and ACT-333679 are achieved within 3 days following twice-daily dosing. There is no significant accumulation of selexipag or ACT-333679 upon twice-daily dosing which suggests that the effective half-life is much shorter [approx. 3 h]. The systemic exposure to ACT-333679 at steady state is 3- to 4-fold higher than that of selexipag. PK dose-proportionality is discussed in response to Q 2.4.8.

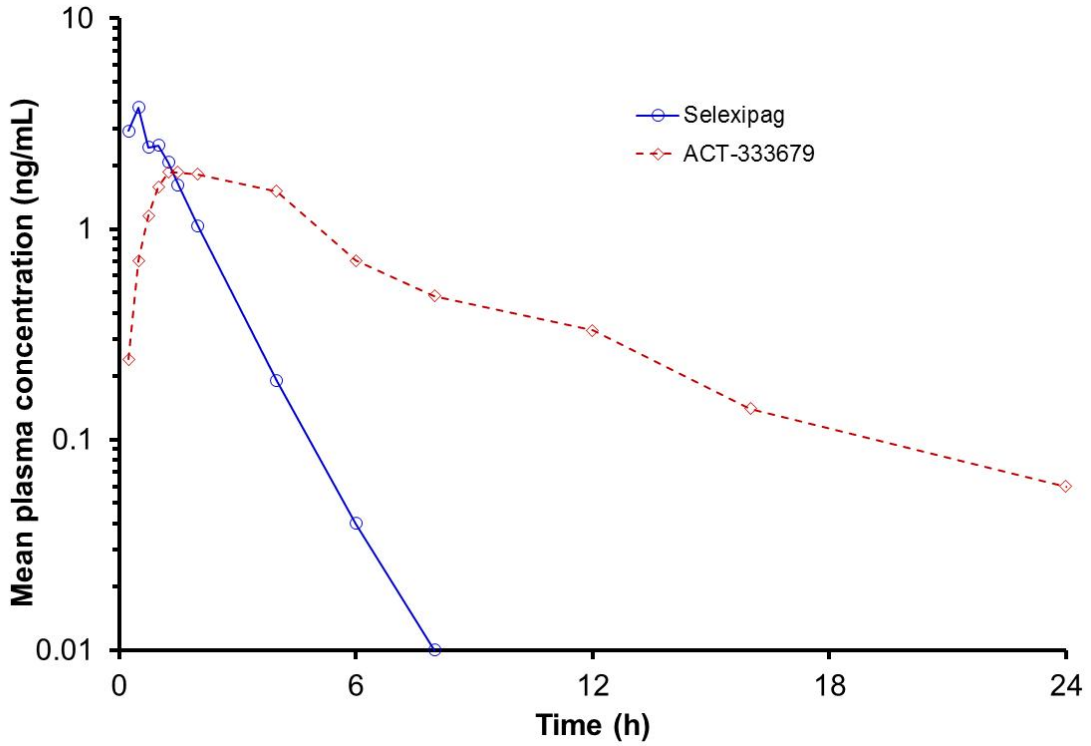


Figure 2: Mean plasma concentration of selexipag and ACT-333679 in healthy subjects following administration of single oral dose of selexipag 100 µg

2.4.2. How does the PK in healthy volunteers compare to that in patients?

Comparison of predicted selexipag and ACT-333679 plasma exposures from corresponding population PK models of healthy subjects and PAH patients, show a 20% to 30% increase in $C_{max,ss}$ and $AUC_{\tau,ss}$ for patients compared to healthy subjects [Table 3]. In general, there is a large overlap in the plasma concentration time-course observed in healthy subjects and PAH patients.

Table 3: Predicted PK exposures of selexipag and ACT-333679 between healthy subjects and PAH patients

	Selexipag		ACT-333679	
	$C_{max,ss}$	$AUC_{\tau,ss}$	$C_{max,ss}$	$AUC_{\tau,ss}$
Healthy subject*	15.7	42.4	22.5	153
PAH patient†	21.5	55.6	29.1	183
Fold-change in patients	1.3x ↑	1.3x ↑	1.3x ↑	1.2x ↑

Predicted PK measures for reference subject: body weight 80 kg, male, bilirubin 13 µM, naïve to PAH co-medications

* AC-065-106: Thorough QT study

† AC-065-A302: GRIPHON

2.4.3. What are the characteristics of drug absorption?

(b) (4) Therefore, the absolute bioavailability of selexipag is not known. A high fat meal has modest impact on the rate and extent of absorption of selexipag [see Q 2.8.3], but is not clinically significant.

2.4.4. What are the characteristics of drug distribution?

Volume of distribution at steady state [V_{ss}] cannot be determined due to lack of absolute bioavailability. Selexipag and ACT-333679 is highly bound to plasma proteins [>99%, equilibrium dialysis method]. Further characterization showed that selexipag and ACT-333679 bound to both albumin as well as α1-acid glycoprotein. Protein binding was not concentration dependent in the range studied [0.1 to 50 µg/mL]. Blood to plasma ratio was 0.57 and 0.58 for selexipag and ACT-333679, respectively, indicating limited partitioning into red blood cells.

2.4.5. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Selexipag is primarily metabolized followed by excretion of the metabolites predominantly in feces. Following oral administration of 400 µg ^{14}C-selexipag suspension, 92.7% of the administered dose was recovered in feces and 11.9% in urine within 7 days. Metabolite profiling in plasma was not possible due to levels of selexipag and metabolites below the limit of detection in the mass balance study. However, from a multiple ascending dose study [AC-065-101] it is known that selexipag and ACT-333679 are the major circulating moieties in plasma [selexipag: 14%, ACT-333679: 78%]. No unchanged selexipag or ACT-333679 was detected in urine

suggesting that the renal elimination pathway for selexipag or its metabolites is minimal. Metabolite profiling in feces found ACT-333679 in the range of 9-23%, but no unchanged selexipag was detected. Other major metabolites found in feces were P10 [hydroxylated at phenyl moiety] and P18 [hydroxylated at phenyl and isopropyl moiety] present in the range of 28-31% and 15-26%, respectively. Rest of the radioactivity was constituted by other hydrophilic metabolites [see Q 2.4.6] which were present in low levels.

2.4.6. What are the characteristics of drug metabolism?

Selexipag undergoes extensive metabolism. A total of nine metabolites were identified and quantified in human plasma. The major metabolite, ACT-333679, which is also pharmacologically active is formed by the hydrolysis of sulfonamide group of selexipag by CES-1. Only selexipag and ACT-333679 are present in plasma at concentrations greater than 10% of total drug related moieties. Most of the minor metabolites are formed by hydroxylation at one or more sites, dealkylation and pyrazine to imidazole ring contraction. Metabolite P11 is a result of glucuronidation of ACT-333679. Hydroxylated metabolite at phenyl ring [P10] which is further hydroxylated in the isopropyl group [P18, not shown in the figure] are major metabolites found in human feces in addition to ACT-333679.

The role of various cytochrome [CYP] P450 enzymes in the biotransformation of selexipag and its metabolites was studied *in vitro* using human liver microsomes and recombinant human CYP enzymes. Formation of most of the metabolites is mediated by CYP3A4 and CYP2C8. Importantly, metabolism of ACT-333679 to P10, the major metabolite in feces, is mediated by CYP2C8.

Figure 3: Proposed biotransformation pathway for selexipag. Moieties marked by asterisk (*) are possible intermediates which were observed in *in vitro* incubations

[Source: Figure 24 of applicant's Summary of Clinical Pharmacology Studies]

2.4.7. What are the characteristics of drug elimination?

Selexipag is primarily metabolized followed by excretion of the metabolites predominantly in feces. No unchanged selexipag or ACT-333679 is excreted in the urine. There is no significant enterohepatic recirculation of selexipag or ACT333679 based on the absence of secondary peaks in the concentration-time profile.

2.4.8. Based on PK parameters, what is the degree of linearity in dose-concentration relationship?

The PK measures of selexipag are dose-proportional in the range of 100 µg to 1800 µg. For ACT-333679, the increase in PK measures is slightly less than dose-proportional in this range. For every 2-fold increase in dose, there is approximately 85% increase in exposure.

2.4.9. What is the inter- and intra-subject variability of PK parameters in healthy volunteers and patients, and what are the major causes of variability?

The between subject variability in the PK measures i.e., $C_{max,ss}$ and $AUC_{0-\tau}$ as observed generally across phase 1 studies is in the range of 40% to 50% for selexipag and ACT-333679, expressed as percent coefficient of variation. Based on the results of a bioequivalence study which employed a crossover design, the within subject variability [residual variance] of selexipag and ACT-333679 is estimated to be 24.1% and 19%, respectively for $AUC_{0-\tau}$ and 31.7% and 22.9%, respectively for $C_{max,ss}$.

2.5. Pharmacodynamics

2.5.1. What are the PD characteristics of the drug?

Cardio-pulmonary hemodynamics

The effect of selexipag on pulmonary hemodynamic variables was assessed in phase II studies. PAH patients [WHO Functional Class II-III on a background of ERA and/or PDE5i] up-titrated to an individually tolerated dose of 800 µg twice-daily achieved a 33% [95% CI: -47% to -15.2%] reduction in mean percent change from baseline pulmonary vascular resistance [PVR] at week 17 when compared to placebo [mean percent baseline: 125.5% (placebo) *vs* 84.1% (selexipag)]. There was an increase in cardiac index [median treatment effect: 0.41 L/min/m^2 (95% CI: 0.10, 0.71)] and decrease in systemic vascular resistance [median treatment effect: -427 dyn∗sec/cm^5 (95% CI: -668, -135)] from baseline following treatment with selexipag compared to placebo. Trends for a decrease in systolic, diastolic, and mean PAP [pulmonary arterial pressure] and an increase in PCWP [pulmonary capillary wedge pressure] were also observed following treatment with selexipag relative to placebo, with no difference between treatments in mixed venous or arterial oxygen saturations.

NT pro-BNP

In GRIPHON, there was a decrease in NT pro-BNP from baseline [approx. 3%] in patients as early as week 4 [first post-baseline visit] in the selexipag group when compared to placebo where values remained near baseline. However, this effect was not sustained and the values reached baseline by the end of study. At the same time, NT pro-BNP values for patients in the placebo group increased during the study [approx. 7%] by the end of study visit. The clinical relevance of the marginal effect on NT pro BNP is not clear.

Inhibition of platelet aggregation

Selexipag and ACT-333679 were evaluated for its potential to inhibit platelet aggregation, as prostacyclins are known to be modulators of platelet aggregation. When platelet aggregation was measured *in vitro* in response to 10 µM adenosine diphosphate [ADP], selexipag and ACT-333679 inhibited platelet aggregation in a concentration dependent manner with an IC_{50} of 5.5

μM and 0.21 μM, respectively. A lower IC_{50} to inhibit platelet aggregation for ACT-333679 relative to selexipag is probably reflective of the relative potencies of the two moieties towards prostacyclin IP receptor. When investigated in an *ex vivo* setting where selexipag was administered up to 1600 μg twice-daily in healthy volunteers, no significant platelet aggregation inhibition was observed in response to ADP as agonist. This may be reflective of the fact that the maximum attained peak plasma concentration of selexipag and ACT-333679 following 1600 μg is 0.04 μM and 0.07 μM, respectively.

2.6. Intrinsic Factors

2.6.1. What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Selexipag and ACT-333679 is extensively metabolized, thus suggesting that impairment in hepatic function might impact the pharmacokinetics of selexipag and ACT-333679.

Hepatic impairment: The effect of hepatic impairment on the PK of selexipag and ACT-333679 was assessed following administration of a single dose of 400 μg [Child-Pugh A and B] or 200 μg [Child-Pugh C] selexipag in subjects with hepatic impairment versus matched healthy volunteers. Compared to healthy subjects, the plasma exposures to selexipag increased by approx. 2- and 4-fold in mild and moderate hepatic impaired groups, respectively. The increase in exposure was driven by a decrease in clearance of selexipag, as characterized by a longer $t_{1/2}$. The systemic exposure to ACT-333679 was similar in mild hepatic impaired group, but increased approx. 2-fold in moderate hepatic impaired group. The dose-normalized increase in exposure in severe hepatic impaired group [N=2] was 3-fold higher compared to subjects with normal hepatic function.

The relative potency of ACT-333679 is 37-fold higher than selexipag. Therefore, any dosing recommendation is made based on the plasma exposures to ACT-333679. As the ACT-333679 exposure in mild hepatic impaired group is similar to that observed in healthy subjects, no dose-adjustments are required. For moderate hepatic impaired group, as the increase in exposure was primarily driven by changes in clearance, modeling and simulation exercise was performed to explore a once-daily dosing regimen in this subgroup. The results show that a once-daily regimen in moderate hepatic impaired groups would result in similar exposure to ACT-333679 and 2-fold higher exposure to selexipag when compared to exposures observed in healthy subjects following twice-daily dosing [Table 4]. A 2-fold higher selexipag exposure is not of clinical significance due to a titration design and a relative lower potency for selexipag compared to the metabolite. Therefore, a once-daily regimen of selexipag is recommended in moderate hepatic impaired patients.

No alternative dosing regimen can be derived in severe hepatic impaired group, due to inadequate PK data. Further, the intrinsic variability in subjects with severe impairment of hepatic function is expected to be high and as such the maximum increase in exposure cannot be projected from the available data. In the hepatic impairment study, dosing in severe hepatic impaired group was terminated at N=2, due to the occurrence of hepatic encephalopathy [serious

adverse event] in one subject. Therefore, the recommendation is to avoid dosing of selexipag in patients with severe hepatic impairment.

Table 4: Predicted $C_{max,ss}$ and AUC_{τ} of selexipag and ACT-333679 following 400 µg twice-daily in healthy subjects and 400 µg once-daily in moderate hepatic impaired group

	Predicted exposures [geometric mean]	Subjects without hepatic impairment on selexipag 400 µg twice-daily	Moderate hepatic impaired subjects on selexipag 400 µg once-daily
Selexipag	C_{max}	1.74	4.87
	AUCτ	9.81	20.80
ACT-333679	C_{max}	3.10	3.84
	AUCτ	48.31	53.69

Renal impairment: As the expectation for renal impairment to have a significant impact on the pharmacokinetics of selexipag or ACT-333679 was minimal, the applicant conducted a reduced design study in subjects with end stage renal disease [ESRD, eGFR: 15-29 mL/min/1.73 m^2] not requiring hemodialysis versus matched normal renal function subjects [eGFR: 90-141 mL/min/1.73 m^2]. The results show an increase in the range of 1.4- to 1.7-fold in $AUC_{0\text{-}inf}$ as well as C_{max}, but not $t_{1/2}$, suggesting that impaired renal function did not affect the elimination of selexipag or ACT-333679. There was no difference in the extent of plasma protein binding of selexipag or ACT-333679 [as shown by % unbound drug] between healthy and ESRD groups. Comparison of the concentration-time curves between the two groups suggests an increase in bioavailability (F) in the ESRD group, however, the reason for such an observation is not clear. Population PK analyses from the data collected in GRIPHON did not show renal function as a significant covariate of selexipag or ACT-333679 PK. No unexpected adverse events were observed in ESRD group of the renal impairment study. Integrating these findings, an increase in exposure of ACT-333679 or selexipag in the range of 50% to 70% is not considered clinically relevant to warrant a dose adjustment in starting dose or dose escalation increments. The maximum dose attained in a patient with impaired renal function will be driven by tolerability.

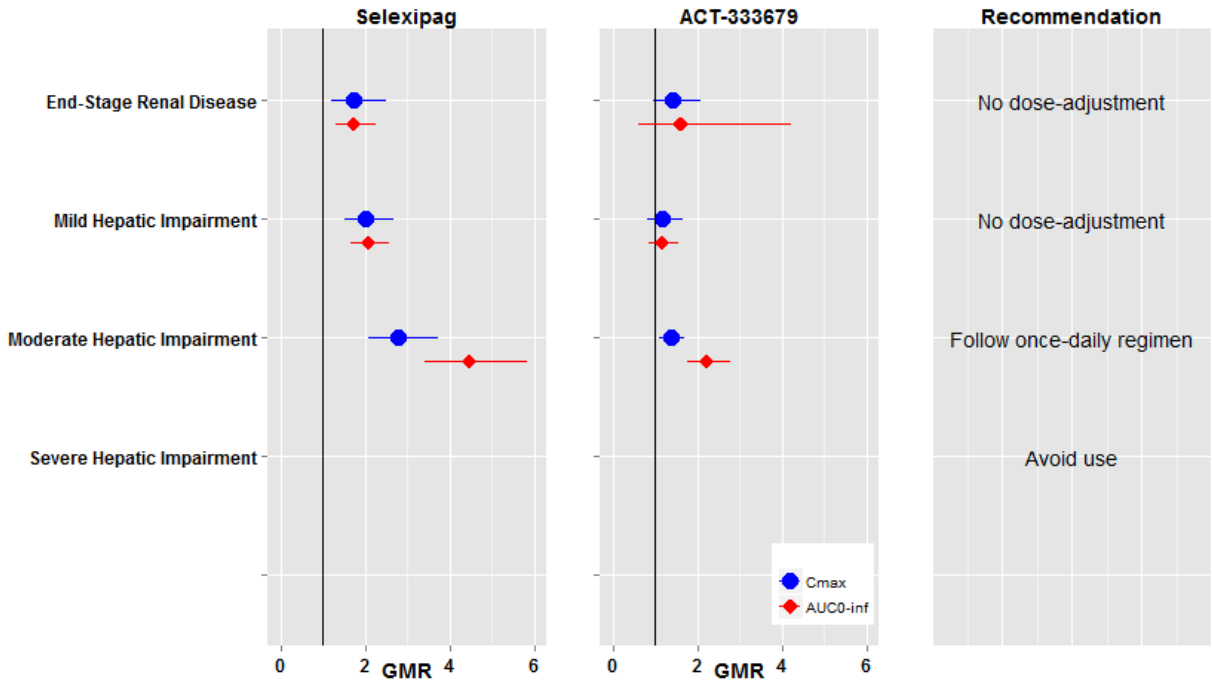


Figure 4: Impact of renal and hepatic impairment on the PK measures of selexipag and ACT-333679

Age, Gender, Body Weight, Race:

The impact of intrinsic factors such as age, gender, body weight and ethnicity can be inferred from early phase I studies as well from population PK analysis. Of the factors explored, only body weight was identified as a significant covariate on central apparent volumes of distribution of both selexipag and ACT-333679. Compared to a subject weighing 75 kg, the plasma concentration of selexipag and ACT-333679 were 22% and 27% higher in a 50 kg subject and 17% and 15% lower in a 100 kg subject. There was also a modest increase in the exposure to ACT-333679 in females [30%↑ *vs* males] and subjects of Japanese origin [50%↑ *vs* Caucasian subjects]. However, when corrected for body weight the changes in exposure were further modest in these subgroups. As the drug is titrated in increments of 200 µg twice-daily based on tolerability and efficacy, these differences in exposure are not considered clinically relevant. No adjustments based on body weight, age, gender or race is needed.

2.7. Extrinsic Factors

2.7.1. Is there an in vitro basis to suspect in vivo drug-drug interactions?

Metabolizing Enzymes

Selexipag is hydrolyzed to ACT-333679, the pharmacologically active metabolite, by CES-1. Potential for CES-1 inhibition *in vivo* is minimal because of its ubiquitous expression in many

tissues. No medicinal product has yet been known to act as an inhibitor of CES-1 *in vivo*. CYP3A4 and CYP2C8 are other CYP isoforms involved in the metabolism of selexipag to minor metabolites [refer Q 2.4.6]. Importantly, metabolism of ACT-333679 to P10, one of the major metabolite in feces is mediated by CYP2C8. Therefore, inhibition of CYP3A or CYP2C8 may impact the pharmacokinetics of selexipag and/or ACT-333679.

Selexipag and ACT-333679 inhibited CYP2C8 [IC_{50}=3.6 and 15 μM, respectively] and 2C9 [IC_{50}=8.3 and 32 μM, respectively] following incubations in human liver microsomes. However, the potential these CYP isoforms *in vivo* should be minimal at clinically relevant concentration. The average C_{max} following selexipag 1600 μg twice-daily is 0.04 and 0.07 μM for selexipag and ACT-333679, respectively. The inhibition potential towards other CYP isoforms [1A2, 2A6, 2B6, 2C19, 2D6, 2E1 and 3A4] is negligible as shown by IC_{50} values ≥ 50 μM. Selexipag and ACT-333679 did not demonstrate time-dependent inhibition of CYP enzymes [2C8, 2C9, 2D6 and 3A4]. Selexipag and ACT-333679 caused induction of CYP3A4 at 10 μM in human hepatocytes, where the effects represented 38% and 26%, respectively, of that of rifampin [positive control]. Again, at clinically relevant concentration, the induction potential of selexipag and ACT-333679 should be minimal.

Drug Transporters

P-gp: Bi-direction transport experiments performed in Madin-Darby canine kidney tubular epithelium type II [MDCKII] cells overexpressing MDR1, suggests that selexipag may be a modest substrate of P-glycoprotein [P-gp], but not ACT-333679. Both, selexipag and ACT-333679 did not inhibit the transport of digoxin or rhodamine 123, suggesting that the potential for selexipag and ACT-333679 to act as modulators of P-gp is minimal.

BCRP: Bi-directional transport experiments in breast cancer resistant protein [BCRP] overexpressing cells suggest that ACT-333679, but not selexipag, is a substrate of BCRP. The potential for BCRP modulators e.g., cyclosporine, to inhibit BCRP in the liver appears to be minimal. Selexipag and ACT-333679 showed potential to inhibit BCRP with an IC_{50} of 1.9 μM and 5.6 μM, respectively.

OATP: Based on uptake ratios in organic anion transporting protein [OATP] B1 and B3 overexpressing cells, selexipag and ACT-333679 are modest substrates of OATP1B1 and OATP1B3. Selexipag and ACT-333679 showed potential to inhibit OATP1B1 and 1B3 with IC_{50} in the range of 1.7 - 4.1 μM.

BSEP, MRP-2 and MATE-1: Based on uptake ratios in bile salt excretion protein [BSEP], multidrug resistant protein-2 [MRP-2] and multidrug and toxin extrusion protein 1 [MATE-1], ACT-333679 is not a substrate of BSEP, MRP-2 and MATE-1. The potential for selexipag or ACT-333679 to inhibit BSEP, MRP-2, MATE-1 and MATE-2K at clinically relevant concentration appears to be minimal based on the IC_{50} values shown in Table 5.

OAT1, OAT3, OCT1 and OCT2: Selexipag inhibited OAT1 and OAT3 with an IC_{50} value of 1.4 and 1.7 μM, respectively. Neither selexipag or ACT-333679 have the potential to inhibit OCT1 and OCT3 at clinically relevant concentration based on the IC_{50} values shown in Table 5.

In general, the interaction liability of selexipag or ACT-333679 to modulate any of the transporters at clinically relevant concentration is minimal based on the IC_{50} values shown in Table 5.

Table 5: *In vitro* inhibition potential of selexipag and ACT-333679 towards drug transporters

Transporter	Model substrate	Selexipag (IC_{50} in µM)	ACT-333679 (IC_{50} in µM)
OATP1B1	atorvastatin	2.4	3.5
OATP1B3	taurocholic acid	1.7	4.1
BCRP	methotrexate	1.9	5.6
OAT1	p-aminohippuric acid	1.4	25
OAT3	furosemide	1.7	2.1
OCT1	MPP^+	~ 100	> 100 [c]
OCT2	MPP^+	> 100[b]	> 100[d]
MATE1	metformin	22	30
MATE2K	ASP	> 100[a]	> 100[b]
MRP2	estradiol-17-β-glucuronide	~ 100	37
BSEP	taurocholic acid	11	20

IC_{50} = concentration that induces 50% of the maximal response. [a] 18 % inhibition at 100 µM; [b] no inhibition up to 100 µM; [c] 34 % inhibition at 100 µM; [d] 24 % inhibition at 100 µM. ASP: 4-(4-(dimethylamino)-styryl)-N-methyl-pyridinium. MPP: 1-methyl-4- phenylpyridinium iodide.

[Source: Table 35 from applicant's Summary of Clinical Pharmacology Studies]

2.7.2. What is the drug-drug interaction liability for selexipag?

The applicant conducted two *in vivo* drug interaction studies – (i) with warfarin, and (ii) with Kaletra® [lopinavir + ritonavir]. The drug interaction study with warfarin was performed as selexipag showed modest potential to inhibit CYP2C9 *in vitro*. The study with Kaletra® was performed to evaluate the impact of ritonavir, a CYP3A, P-gp and OATP inhibitor, on selexipag and ACT-333679 pharmacokinetics. (b) (4)

The results of the dedicated drug interaction study with warfarin showed that selexipag at 400 µg twice-daily did not impact the pharmacokinetics or pharmacodynamics of warfarin. Based on *in vitro* findings, the interaction potential at higher selexipag doses is also expected to be minimal [$R_1 = 1 + [I]/K_i < 1.1$].

Co-administration of Kaletra® with selexipag resulted in approx. 2-fold increase in C_{max} and AUC of selexipag, but not ACT-333679. The concentration-time profile for selexipag when co-administered with Kaletra® run parallel but at levels almost twice that of when selexipag is administered alone. This suggests an increase in the fraction of selexipag that is bioavailable

probably as a result of inhibition of hepatic uptake transporters [OATP1B1/B3] and/or P-gp. The slope of the elimination phase until inter-dosing interval is not significantly different between the two treatments suggesting that clearance of selexipag is not altered. The pharmacokinetics of ACT-333679 was not different between the two treatments. Though there is a 2-fold increase in the systemic exposure to selexipag with Kaletra®, there was no change in the pharmacokinetics of ACT-333679, which is 37-fold more potent than selexipag (b) (4)

(b) (4)

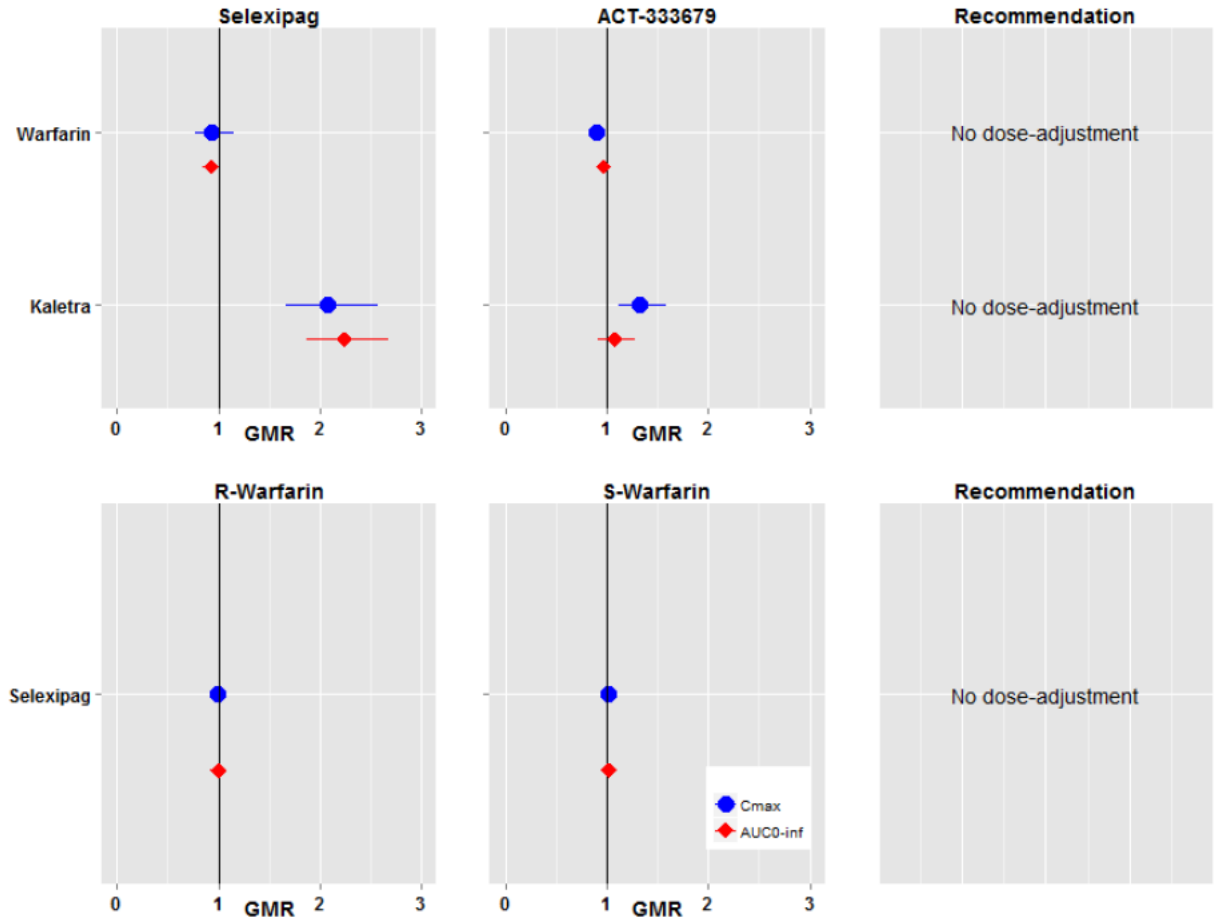


Figure 5: Impact of drug interactions on selexipag and ACT-333679 PK

2.7.3. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Other extrinsic factor that may affect the systemic exposure to selexipag or ACT-333679 is food, which is addressed in response to Q. 2.8.3.

2.8. General Biopharmaceutics

2.8.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

In the absence of an estimate of oral bioavailability or apparent permeability across Caco-2 cell monolayers, BCS classification for selexipag cannot be made. (b) (4) (b) (4) (b) (4)

2.8.2. What is the relative bioavailability of the to-be-marketed formulation with Phase 3 trial formulation?

The final to-be-marketed formulation was used in the registration trial, GRIPHON. Therefore, no pivotal bioequivalence study was required in this development program.

A strength bioequivalence study between 1 x 1600 µg and 8 x 200 µg showed bioequivalence in the PK measures of selexipag and ACT-333679 [reviewed by OPQ], suggesting that the available strengths can be used interchangeably for selexipag dosing.

2.8.3. What is the effect of food on the bioavailability of the drug from the dosage form?

The effect of food on the pharmacokinetics of selexipag and ACT-333679 was evaluated in Caucasians and Japanese healthy volunteers following a single oral dose of 400 µg selexipag. In both the studies, absorption of selexipag was prolonged resulting in a delayed T_{max} and lower C_{max} [Table 6]. The changes were more prominent for selexipag than ACT-333679. The AUC did not change or modestly decreased for selexipag or ACT-333679 across both the studies [Table 6]. These changes are not considered clinically significant to warrant any dose-adjustment. However, these studies showed a general trend for better tolerability while administering selexipag in the fed state. Hence, the applicant performed GRIPHON by administering selexipag with food. Therefore, it is recommended that selexipag be administered following a meal in an effort to improve tolerability.

Table 6: Impact of a high fat meal on selexipag and ACT-333679 PK

		Selexipag			ACT-333679		
		Fasted	Fed	Ratio Fed/Fasted	Fasted	Fed	Ratio Fed/Fasted
Study 1 Caucasians	**C_{max}** [ng/mL]	7.67	4.91	0.65	8.40	4.28	0.52
	$AUC_{0\text{-}inf}$ [ng*h/mL]	14.7	16.2	1.10	50.8	36.8	0.73
Study 2 Japanese	**C_{max}** [ng/mL]	10.9	7.34	0.68	10.2	9.52	0.93
	$AUC_{0\text{-}inf}$ [ng*h/mL]	19.8	16.8	0.85	65.3	57.4	0.88

Values represent geometric mean

2.9. Bioanalytical Method

Five bioanalytical methods were used to quantify the concentration of selexipag and ACT-333679 in biological matrices across the clinical development program [Table 7]. All bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is therefore acceptable.

Table 7: Summary of bioanalytical methods used in the clinical development program

Report	Assay Method	Matrix	Range [ng/mL]	Inter-batch Accuracy	Inter-batch Precision
	Selexipag				
PBC38-23	LC-MS/MS	Plasma	0.01 to 10	-14.6 to 15%	2.8 to 9.7%
PBC119-001	LC-MS/MS	Plasma	0.01 to 10	-2.5 to 7.9%	3.7 to 12.2%
BP-304-001	LC-MS/MS	Plasma	0.01 to 10	3.5 to 5.3%	5.5 to 7.2%
SBQ-09003	LC-MS/MS	Plasma	0.01 to 10	-4.8 to 6.3%	4.7 to 11.4%
BA-12.396	LC-MS/MS	Plasma	0.01 to 20	-4.5 to 6.0%	5.4 to 12.9%
	ACT-333679				
PBC38-23	LC-MS/MS	Plasma	0.01 to 10	-10.6 to 11%	3.6 to 10.1%
PBC119-001	LC-MS/MS	Plasma	0.01 to 10	-4.8 to 2.0%	3.9 to 10.6%
BP-304-001	LC-MS/MS	Plasma	0.01 to 10	5.4 to 9.0%	3.8 to 4.1%
SBQ-09003	LC-MS/MS	Plasma	0.01 to 10	-3.3 to 7.7%	2.0 to 13.2%
BA-12.396	LC-MS/MS	Plasma	0.01 to 20	2.8 to 16.1†%	4.0 to 8.5%

†LLOQ sample

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/s/

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CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	207947	**NDA Submission Type**	505(b)(1)
OCP Division	I	**Brand Name**	Uptravi®
Medical Division	DCRP	**Generic Name**	Selexipag
OCP Reviewers	Sudharshan Hariharan Luning Zhuang	**Drug Class**	Prostacyclin IP receptor agonist
OCP Team Leaders	Rajanikanth Madabushi Jeffry Florian	**Indication(s)**	Treatment of pulmonary hypertension
		Dosage Form/Strength	IR tablet 200, 400, 600, 800, 1000, 1200, 1400, 1600 µg
Date of Submission	12/22/2014	**Dosing Regimen**	Twice daily
OCP Review Due	10/22/2015	**Route of Administration**	Oral
AC Meeting	TBD	**Sponsor**	Actelion
PDUFA Due Date	12/22/2015	**Priority Classification**	Standard

Clinical Pharmacology Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**5**	**5**	PBC119-001, PBC38-23, BP-304-001, SBQ-09003, and BA-12.396
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	186933
Isozyme characterization:	**X**	**4**	**4**	(b)(4) 09.156, (b)(4) 09.316, (b)(4) 9.671, (b)(4) 3.107
Blood/plasma ratio:	**X**	**1**	**1**	09.319
Plasma protein binding:	**X**	**1**	**1**	08.308
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**3**	**3**	PS003: Single-dose QGUY/2006/NS304/-01 (Part A): SAD NS304/P1/01: SAD and food effect in Japanese adult and elderly subjects
multiple dose:	**X**	**2**	**2**	QGUY/2006/NS304/-01 (Part C): MAD AC-065-101: MAD
Patients-				
single dose:				
multiple dose:	**X**	**1**	**1**	AC-065-A201: Japanese patients
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**	**2**	QGUY/2006/NS304/-01 (Part D): Drug interaction with warfarin AC-065-106: Drug interaction with lopinavir/ritonavir

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In-vivo effects of primary drug:				(b) (4) (b) (4) (b) (4) (b) (4)
In-vitro:	**X**	**9**	**9**	09.029 -09.030, 09.319, 09.670, 11.386 -13.028, 14.028, 14.007, 14.022
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**	**1**	AC-065-105 (reduced design)
hepatic impairment:	**X**	**1**	**1**	AC-065-104
PD -				
Phase 1:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**	**2**	NS304/-02: PK/PD in Caucasian patients AC-065-B201: PK/PD in Japanese patients
Phase 3 clinical trial:	**X**	**1**	**1**	AC-065-A302 (GRIPHON): Collected PK (approx. 50%) and PD (approx. 90%)
Population Analyses -				
Pop PK	**X**	**2**	**2**	Healthy subjects and PAH patients
Pop PK/PD	**X**	**1**	**1**	Response variables: 6MWD, BP, HR, NT pro-BNP (PD/efficacy); occurrence of prostacyclin mediated AEs (safety)
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**1**	AC-065-108: Strength equivalence 8 x 200 µg and 1 x 1600 µg (multiple dose study)
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**	**1**	QGUY/2006/NS304/-01 (Part B)
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total		**39**	**39**	In-vitro: 15 In-vivo: 16 Bioanalytical methods: 5 Pop-PK and -PK/PD reports: 3

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			

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3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			Information request for population PK and PK/PD analyses dataset was sent to the applicant on 2/5/2015
	Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)				
	Data				
11	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
12	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
13	Is the appropriate pharmacokinetic information submitted?	X			
14	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			Drug is proposed to be titrated based on tolerability
15	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Response variables: 6MWD, BP, HR, NT pro-BNP (efficacy/PD); occurrence of

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

					prostacyclin mediated AEs (safety)
16	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
17	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
18	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
19	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
20	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
21	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

Sudharshan Hariharan & Luning Zhuang 02/09/2015
Primary reviewer(s) Date

Rajanikanth Madabushi 02/09/2015
Team Leader/Supervisor Date

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