CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214275Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	214275
Link to EDR	\\CDSESUB1\evsprod\NDA214275
Submission Date	29 September 2020
Submission Type	Standard
Brand Name	Uptravi for injection
Generic Name	Selexipag
Dosage Form and Strength	Sterile lyophilized powder for solution containing 1.8 mg selexipag
Route of Administration	Intravenous infusion
Proposed Indication	For the treatment of Pulmonary Arterial Hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
Applicant	Actelion Pharmaceuticals Ltd.
Associated IND	IND 104504
OCP Review Team	Harisudhan Thanukrishnan, PhD Sudharshan Hariharan, PhD
OCP Final Signatory	Doanh Tran Ph.D., Deputy Director, Division of Cardiometabolic and Endocrine Pharmacology

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1. EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 214275. The application primarily relied on the data from the study AC-065A309, an open-label, single sequence, cross-over study in 20 adult participants that were on Uptravi (oral selexipag) for treatment of pulmonary arterial hypertension (PAH). The study established that a switch from a stable oral dose of selexipag to the intravenous (IV) dose provided comparable exposure to the active metabolite (ACT-333679) and the switching back to the initial oral dose of selexipag was safe and well tolerated across the entire oral dose range, in participants with stable PAH. From the clinical pharmacology perspective, the information provided supports the approval of Uptravi for injection for the treatment of patients with WHO (World Health Organization) Group 1 PAH who cannot swallow Uptravi tablets.

1.2 Post-Marketing Requirements and Commitments

None

2.CLINICAL PHARMACOLOGY REVIEW

2.1 General attributes of the drug product

2.1.1 What are the key features of the drug product

The selexipag drug substance (ACT 293987) is same as that in the Uptravi tablets that was approved under NDA 207947. The drug product for Uptravi for injection contains 1800 µg of selexipag drug substance as a lyophilized sterile powder in a single-dose vial. The excipients in this formulation include (b) (4) NaOH ((b) (4)), glycine (b) (4)) and (b) (4) Polysorbate 20 (b) (4)). Prior to IV infusion, the vial should be first reconstituted with 0.9% (w/v) sodium chloride (saline) for injection to obtain the nominal concentration of 225 µg/mL of selexipag. An exact volume of this solution should be withdrawn ((b) (4)) for mixing with 100 mL of saline followed by infusion for 80 minutes. The commercial formulation is identical to the clinical formulation except for an increase in the fill weight of selexipag per vial (to provide the extractable volume needed at the highest dose).

2.1.2 What is the Applicant's rationale in developing this drug product

Selexipag is a prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. The primary reason stated by applicant for developing this IV formulation was to provide an uninterrupted selexipag treatment option for patients with PAH who are temporarily unable to swallow oral medications. The IV formulation would allow:

- the patient to remain on selexipag treatment and thereby avoid the need to switch to a parenteral formulation of another IP-receptor agonist that may require continuous infusion
- patients to maintain plasma concentrations of active metabolite (ACT-333679) similar to the oral regimen, throughout the temporary oral interruption period
- avoidance of repeat up-titration following re-introduction of oral selexipag.

Overall, the IV formulation would help to maintain drug exposure and therapeutic effects in PAH patients who may temporarily be unable to swallow oral selexipag, eg: patients hospitalized for elective surgery or intensive care.

2.1.3 What is the regulatory history associated with the submission of this NDA?

Selexipag tablets for oral use (NDA 207947, submitted 22 December 2014) was approved for treatment of PAH (WHO Group 1) to reduce the risks of disease progression and hospitalization for PAH on 21 December 2015. In May 2016, the applicant proposed to develop an IV formulation for selexipag, and advice was provided by the Agency via Type C meeting in Jul 2016 under IND 104504. The applicant shared data from a previously completed absolute bioavailability study (AC-065-110) in healthy volunteers using a single IV 80-minute infusion of 200 µg selexipag compared to 400 µg of oral selexipag. Based on this study, the oral bioavailability was determined to be 49% for selexipag and the exposure ($AUC_{0\text{-}inf}$ and C_{max}) to selexipag was comparable after the IV (200 µg) versus the oral (400 µg) doses of selexipag. However, exposure to the active metabolite of selexipag ACT-333679 (37-fold as potent as selexipag) was 2.5 and 2.4-fold higher for the $AUC_{0\text{-}inf}$ and C_{max}, respectively after the oral (400 µg) selexipag dosing in comparison to the exposure after the IV selexipag (200 µg).

Since ACT-333679 is responsible for majority of the drug's effect, the Agency agreed with the applicant that bridging oral and iv route of administration by matching exposures of the active metabolite was appropriate. The applicant had determined via modeling and simulation that using 1.115 times higher IV dose is required to match exposure to active metabolite across the oral doses (200-1600 µg) and will result in up to a 3-fold higher exposure to selexipag compared to the corresponding oral dose. The final IV transition dose was rounded off to 1.125 times of oral dose for clinical convenience (eg: 450 instead of 446 µg for transitioning from 400 µg oral dose).

As a part of NDA 207947 (selexipag tablets), it was also shown that the pharmacokinetics (PK) of selexipag and active metabolite, ACT-333679 were dose proportional up to oral doses of 1600 µg and PK was similar between healthy volunteers and PAH patients. Hence, the Agency recommended a tolerability study of transitioning selexipag from the oral to IV route of administration following the highest oral dose in PAH patients and evaluation of PK could be an optional consideration. The applicant decided to conduct the study (AC-065A309) with PK assessment included.

2.2 Clinical Development Program

2.2.1 What are the design features of the clinical pharmacology and clinical studies that supported this development program?

The rationale for development of an IV formulation of selexipag was to provide an uninterrupted treatment option for PAH patients who may be temporarily unable to swallow oral medications. The Applicant conducted one study (AC-065A309) in support of this NDA for IV administration of selexipag. The study was a multicenter, open-label, single-sequence, cross-over study to assess safety, tolerability,

and PK of intravenous selexipag in 20 adult stable PAH subjects switching from a stable oral dose of selexipag. The study assessed if temporary switching from a stable oral dose of selexipag to an IV dose of selexipag for a total of 3 doses (36 hours) and switching back to the initial oral dose of selexipag was safe and well tolerated in participants with stable PAH. Selexipag is given twice daily (bid) and there is no accumulation of selexipag or its metabolite upon repeat dosing up to the highest oral dose. Hence, steady state assumption after 3 IV doses repeated over 36 hours was considered a reasonable duration for tolerability assessment. In addition, the AC-065A309 study verified if the IV dose of selexipag provided a comparable exposure to the active metabolite ACT-333679.
Twenty PAH patients who received Uptravi (oral selexipag) as a part of their standard therapy were enrolled. Patients were on a stable oral dose of Uptravi that ranged between 400-1600 µg bid with 9 patients on the highest 1600 µg bid dose. All 20 patients received oral selexipag in Period 1, followed by 3 IV infusions of selexipag in Period 2. The infusion rate was set to 20 mL/h for the first 15 min (as a safety precaution) followed by 37.5 ml/h for 72 min, across all doses resulting in a total 87-min infusion time. All subjects transitioned back to their stable oral dose in Period 3. The applicant submitted a modeling and simulation report (Document Number: D-19.333) to provide supportive evidence for the appropriateness of using a one step 80-minute infusion time for selexipag dosing.

2.3 Basis for Regulatory Action

2.3.1 Is there an adequate dosing characterization of the intravenous formulation to support the proposed dosing regimen?

Yes. The proposed dosing regimen for the intravenous selexipag is acceptable and supported by 1. modelling and simulation of relative bioavailability between oral and IV doses of selexipag, 2. the results from Study AC-065A309, that established tolerability, safety as well as similarity in the PK and exposure to the active metabolite when transitioning from the oral dosing of selexipag (Tables 1 and 2), and 3. modelling and simulation showing similar exposure between the proposed 80-minute constant infusion rate and the two step 87-minute infusion used in Study AC-065A309.

During development of IV selexipag, it was agreed that because the absolute bioavailability for selexipag and ACT-333679 was known, modeling could be used to predict the IV transition doses across the range of oral doses, as the linear PK for selexipag and ACT-333679 was already established up to the maximum oral dose of 1600 µg. In addition, because PK of selexipag and ACT-333679 were established to be similar between healthy volunteers (HV) and PAH patients, the applicant did not need to characterize the PK of IV selexipag in two separate studies in HV and PAH patients. Modelling and simulation results showed that an IV dose 1.125 times the corresponding oral dose would result in similar exposure to active metabolite ACT-333679 (Reference ID 3972986, IND 104504, Meeting minutes dated 16th Aug 2016). This IV dose conversion was used for evaluation of the safety and tolerability in 20 PAH patients (Study AC-065A309).

The switch from oral to IV selexipag and back to oral was well tolerated with similar tolerability reported for Uptravi tablets and IV selexipag. There was mild infusion site erythema reported in two subjects but

there were no unexpected safety findings observed during the IV treatment period (Refer to section 3.1.3).

Due to the range of doses evaluated in the enrolled patients, the exposures were dose-normalized using 200 µg or 225 µg for oral and IV regimen, respectively. The dose-normalized geometric mean ratios (IV/oral selexipag) and their 90% CIs for selexipag, ACT-333679 and combined exposure adjusted for their relative potencies are shown in Tables 1 and 2. The mean combined exposure for the IV and oral regimen (as shown in Table 2) were comparable but the confidence interval was not within the standard bioequivalence criterion. The dose-normalized mean concentration vs time profiles of the active metabolite ACT-333679 showed a slightly lower mean concentration after IV selexipag dosing (Figure 2). However, a high inter-subject variability was observed with overlapping standard deviations and the study was not powered for a standard bioequivalence comparison. As a worst-case scenario, there is a potential for the combined exposure to the active moiety after intravenous switch to be less than 80% of the corresponding oral dose, in individual patients. However, the possibility of this marginal decrease in exposure is not concerning from an efficacy perspective, as the individual patients are stabilized on the maximum tolerated oral dose and not based on a fixed dose or exposure criterion. Hence, the comparable exposures provided in the interim by IV selexipag during the interruption of oral therapy are considered acceptable.

The T_{max} was comparable for both selexipag and ACT-333679 between the IV and oral selexipag periods. The increased exposure to selexipag after the IV dose was as expected, considering oral bioavailability was 49% and the absence of first-pass metabolic conversion of selexipag to ACT-333679 for the IV product.

Table 1. Ratio of geometric means for the dose-normalized $AUC_{\tau,ss}$ and $C_{max,ss}$ of Selexipag and ACT-333679 after IV and oral selexipag administration

PK parameter	Ratio of geometric means (IV/oral)[#] (90% CI)	
	Selexipag	**ACT-333679**
$AUC_{\tau,ss}$* (h.ng/mL)	2.13 (1.67, 2.70)[§]	0.79 (0.71, 0.90)
C_{max} (ng/mL)	1.98 (1.62, 2.43)	0.79 (0.65, 0.96)

Source: Table 11-1 CSR for study AC-065A309, Doc No D-18.330;
$AUC_{\tau,ss}$=area under the plasma concentration-time curve during a dose interval at steady state; * Dose normalized to 200 and 225 µg for oral and IV exposures, respectively; IV=intravenous; [#]geometric mean ratios were obtained by computing the anti-log of the treatment group difference of a mixed model with treatment as fixed and subject as random effect to the log-transformed data.

Table 2. Summary of dose-normalized combined exposure of selexipag plus ACT-333679, adjusted for their relative potencies and ratio of geometric means after IV and oral selexipag administration

$AUC_{\tau, ss,combined}$* (h.ng/mL)	Oral selexipag	IV selexipag	Ratio of geometric means (IV/oral)#
n	20	18	20
Geometric Mean (95% CI)	19.0 (13.3, 27.1)	15.9 (11.2, 22.5)	0.82 (0.72, 0.93)§

Source: Tables 15-63 and 15-64 in CSR for study AC-065A309, Doc No D-18.330;
$AUC_{\tau,ss}$=area under the plasma concentration-time curve during a dose interval at steady state;
$AUC_{\tau,ss,combined} = 1/38 \times AUC_{\tau,ss,selexipag} + 37/38 \times AUC_{\tau,ss,ACT-333679}$; CI=confidence interval; * Dose normalized to 200 and 225 µg for oral and IV exposures, respectively; IV=intravenous; n=number of subjects analyzed; #geometric mean ratios were obtained by computing the anti-log of the treatment group difference of a mixed model with treatment as fixed and subject as random effect to the log-transformed data; § 90% CI.

The study AC -065A309 used a two-step IV infusion rate where the first 10% of the dose was given at approximately half-maximal infusion rate over 15 min, as a precautionary measure for tolerability issues, followed by 90% of the dose given in 72 minutes at the maximal infusion rate. Modeling and simulation of the IV data was used to describe exposure metrics (C_{max} and AUC_{0-12h}) for selexipag and ACT-333679 resulting from a one-step constant infusion rate that would be more clinically convenient. A 80-minute constant infusion rate was shown to result in similar exposure and the geometric mean ratios (90% CI) for both selexipag and ACT-333679 were shown to be within the 80–125% interval compared with the two step 87-minute infusion. Based on the above assessments of safety, tolerability, and PK for active metabolite the evaluated IV dosing regimen for selexipag is considered an appropriate transition for the oral dose of selexipag during PAH therapy (Refer to section 3.2).

2.4 Summary of Bioanalytical Method Validation and Performance

Plasma levels of selexipag and ACT-333679 were determined by a validated Ultra high-performance liquid chromatography with tandem mass spectrometric detection (UPLC-MS-MS) method using a triple quadrupole mass spectrometer (Triple Quad 5500).

The method validation report pertaining to quantification of the current study samples was (b) (4)NL-SML-2092 (sponsor number BA13061). The calibration range was 0.01-20 ng/mL for both the analytes with a 5-fold dilution for quantification up to 100 ng/mL. The quality controls (QCs) were 0.03, 1, 10 and 16 ng/mL for both analytes. Accuracy and precision of QC samples were ≤15% (and ≤20% at LLOQ), as shown in the table 3 and calibration curves for the assay were within the acceptable limits.

Results of selectivity, stability and incurred sample reanalysis using this method were within acceptable limits for both the analytes. Incurred samples reanalysis was carried out on roughly 11% of randomly selected samples from the total of 280 study samples (140 per analyte). The results of incurred sample reanalysis showed 90 and 93% of samples were within 20% deviation for selexipag and ACT-333679, respectively.

Table 3. Summary of accuracy and precision of the method used in quantification of the analytes selexipag and ACT-333679

Method/report Number	Study		Accuracy* (bias)	Precision* (% CV)
Selexipag				
(b) (4)-NL-SML-2092 (sponsor number BA13061)	Method validation	LLOQ	6.6 %	7.6 %
		QC L/M/H	-6.0 to 4.1 %	2.5 to 3.7 %
(b) (4)-NL-SML-2092 (sponsor number AC-065A309)	Bioanalytical report (Doc No D-18.330)	LLOQ	1.0 %	3.0 %
		QC L/M/H	-2.5 to 3 %	2.2 to 7.9 %
ACT-333679				
(b) (4)-NL-SML-2092 (sponsor number BA13061)	Method validation	LLOQ	17.1 %	5.4 %
		QC L/M/H	-3.6 to 7.1 %	1.6 to 3.6 %
(b) (4)-NL-SML-2092 (sponsor number AC-065A309)	Bioanalytical report (Doc No D-18.330)	LLOQ	4.0 %	3.8 %
		QC L/M/H	-1.0 to 3.0 %	2.1 to 3.9 %

* represent total inter-batch values in method validation

Source: Tables 8 and 9 in validation report BA13061; Tables 7 and 8 in bioanalytical report (b) (4) 020EL-180203-A

The bioanalytical method used in analysis of the AC-065A309 study samples fulfilled the required criterion for 'method validation' and 'application to routine analysis' provided in the 'Guidance for Industry: Bioanalytical Method Development' and is considered acceptable.

3. INDIVIDUAL STUDY REVIEWS

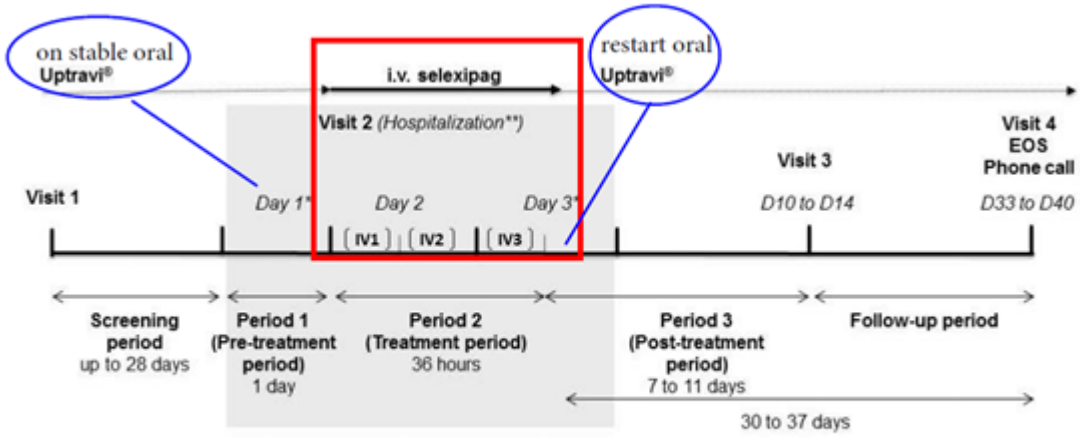
3.1 Study AC-065A309 - Tolerability study of IV regimen in PAH patients

A multicenter, open-label, single-sequence, cross-over study to assess safety, tolerability, and pharmacokinetics of intravenous selexipag in subjects with stable pulmonary arterial hypertension switching from an oral stable dose of selexipag

3.1.1 Study summary:

The primary objective of the study was to assess whether switching from a stable oral dose of selexipag to an IV dose of selexipag provides comparable exposure to active metabolite ACT-333679 and switching back to the initial oral dose of selexipag was safe and well tolerated in subjects with stable PAH. A total of 20 PAH patients diagnosed with Group 1 PAH in WHO functional class I-III and who were prescribed Uptravi (oral selexipag) as part of their standard treatment for PAH were enrolled in the study. Patients were required to be on a stable dose of Uptravi for at least 28 days prior to enrollment. Based on the Uptravi dose at study entry, subjects were allocated to either groups, Uptravi 200–1000 µg bid or Uptravi 1200–1600 µg bid.

Figure 1. Study design for AC-065A309 in PAH patients on standard therapy that included a stable dose of Uptravi (oral selexipag)



* 12-hour PK profile after the morning dose.
** For convenience hospitalization may be extended to the night before Day 1 and to the night of Day 3.
D = day; EOS = End-of-Study; IV1–IV3 = dose of i.v. selexipag; V = visit
Source: adapted from Figure 9-1 CSR for study AC-065A309, Doc No D-18.330

Uptravi oral dose was temporarily interrupted for 36 hours during the administration of 3 repeat infusions of IV selexipag bid. Each subject received an IV selexipag dose that corresponded to the individual's stable dose of Uptravi multiplied by 1.125, as in table 4. All 20 patients received oral selexipag in Period 1, followed by the 3 IV infusions of selexipag in Period 2. No subject prematurely discontinued study treatment in Period 2. All subjects entered Period 3 and subsequently completed the study, as in the figure 1.

Table 4. Oral and corresponding IV* doses for selexipag in PAH patients

Uptravi oral dose (µg)	Corresponding i.v. selexipag dose (µg)
200	225
400	450
600	675
800	900
1000	1125
1200	1350
1400	1575
1600	1800

Source: Table 9-1 CSR for study AC-065A309, Doc No D-18.330;
* All doses prepared in a total of 50 mL using sterile normal saline; For the first 5 mL: an infusion rate of 20 mL/h (0.33 mL/min) for 15 min, for the remaining 45 mL: an infusion rate of 37.5 mL/h (0.63 mL/min) for 72 min.

PK samples were collected in this study at steady state for both selexipag and ACT-333679 during Period 1 and after the last IV dose in Period 2. Blood samples for PK included a pre-dose prior to drug

administration and a 12-h sample prior to the administration of the evening dose of oral or IV selexipag. The additional 5 blood samples were obtained at 1,2,4,6 and 8 h or at 25 min, 87 min (end of infusion), 4,6 and 8 h following the oral or IV doses, respectively. PK analysis included the parameters of AUC, t_{max} and C_{max} for both analytes compared between the IV and oral selexipag doses.

The safety and tolerability assessments included injection-site reactions, ECG recordings, prostacyclin related adverse events including blood pressure and standard laboratory tests. The safety and tolerability analysis set, and PK analysis set included all 20 patients.

3.1.2 Study results:

Of the 20 subjects, 16 (80 %) were females. Median age at baseline was 54 years (range: 40–75 years) and mean BMI was 28.48 kg/m2 (range: 21–40 kg/m2). All subjects were White, except (b) (6) subject with 65% of patients from Germany and rest from the US.

The dose normalized selexipag and ACT-333679 plasma concentrations per time point and treatment are summarized in figure 2. The PK parameters following IV dosing of selexipag are summarized per dose level for selexipag and ACT-333679 in table 5.

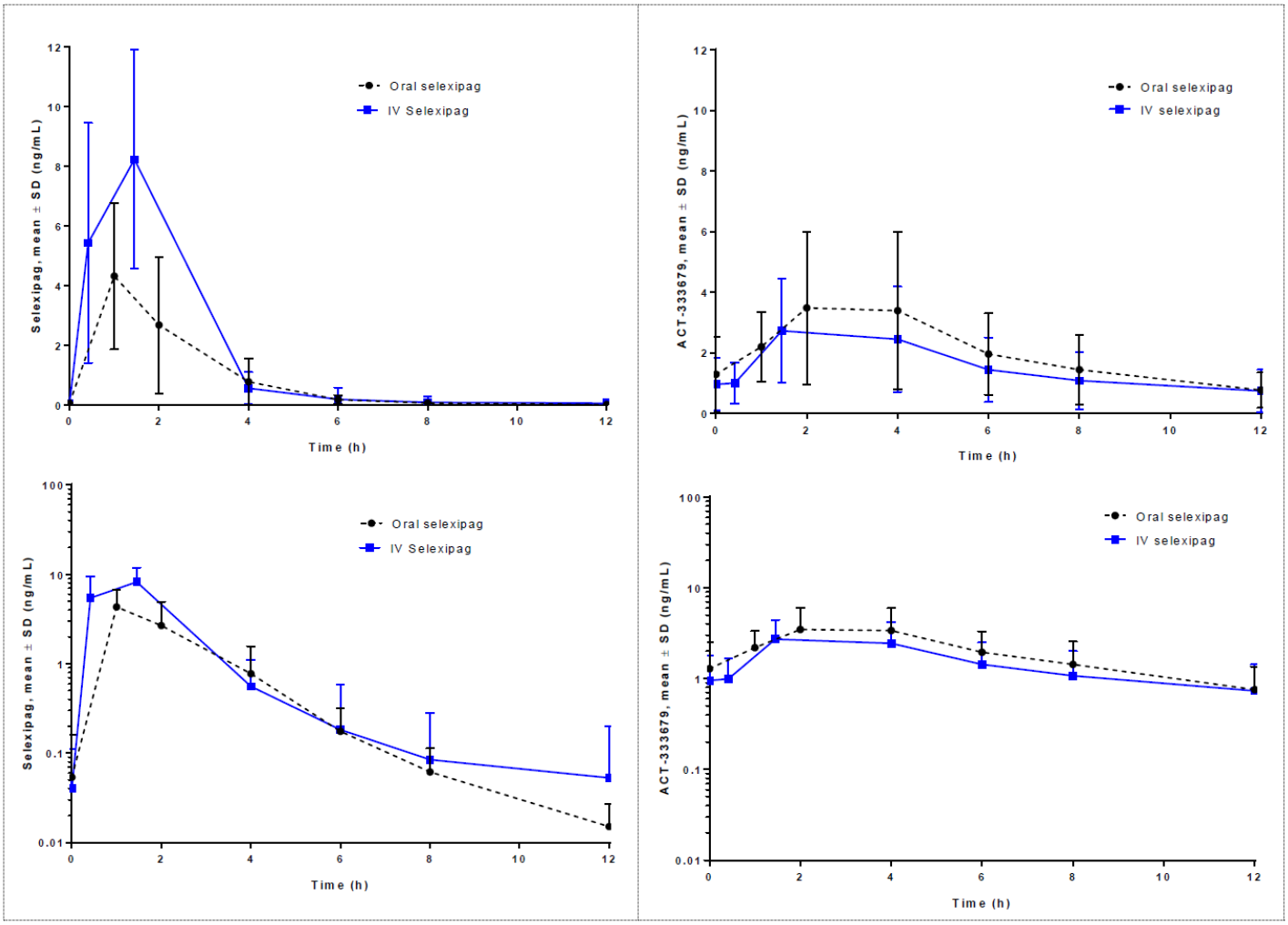
The mean concentration for selexipag increased during IV infusion followed by a rapid decline after the end of infusion (87 min). The mean concentrations and exposures for selexipag after IV administration were higher than those after the oral administration. Overall, administering the 1.125-fold higher IV selexipag dose in participants with PAH resulted in a 2.1-fold higher exposure ($AUC_{\tau, ss}$) to selexipag as compared to oral administration (Refer to 2.3.1). The exposure ratio of ACT-333679 to selexipag was 0.83 (95% CI: 0.56–1.22) after IV administration, whereas it was 2.21 (CI: 1.81-2.69) after oral administration of selexipag in PAH participants. Based on the results of this study, the absolute bioavailability (F) of selexipag following oral administration in participants with PAH was found to be 56 % (90% CI: 42–75), which was similar to the previous healthy volunteer study.

From an efficacy perspective the exposure to ACT-333679 or the combined AUC of selexipag plus ACT-333679 (adjusted for their relative potencies) were comparable following oral and IV administration, supportive of the 1.125-times higher IV dose (Refer to 2.3.1). For both selexipag and ACT-333679, $t_{max,ss}$ was comparable between the IV and oral selexipag periods.

Dose proportionality in exposures of selexipag and ACT-333679 were evaluated using a power model approach and the 90% CI for the slopes for $AUC_{\tau, ss}$ of selexipag and ACT-333679 was shown to include 1, indicating proportionality (selexipag: slope = 0.80, 90% CI: 0.39, 1.21; ACT-333679: slope = 0.70, 90% CI: −0.003, 1.40). . However, the observation is limited by the few number of patients at each dose level except for the highest dose. The inter-subject variability (CV%) in exposure ($AUC_{\tau,ss}$) after IV dosing was 44 and 22% for selexipag and ACT-333679, respectively. The selexipag concentration in the infusion solution was reported to be less than nominal (median: -47.1 range: -15.4 to -90.5 %) in samples corresponding to five subjects. However, the corresponding patient PK profiles did not show sub-optimal values for either selexipag or ACT-333679, when compared to other patients receiving the same dose for selexipag and when compared to corresponding oral profile for ACT-333679. The reason for low

selexipag concentration in the infusion solution was unknown and but the absence of impact on PK could be indicative of stability issues related to storage or handling of the test sample aliquot.

Figure 2. Study AC-065A309: Dose-Normalized Mean plasma concentration-time profiles of selexipag and ACT-333679 in PAH patients after oral and IV selexipag dosing (linear and semilogarithmic scales)



Source: Figure 11-1, 11-2 in CSR for study AC-065A309, Doc No D-18.330; Data are presented as arithmetic means (±SD or +SD), normalized to doses of 200 and 225 µg for oral and IV dosing, respectively. IV=intravenous; h=hours; SD=standard deviation.

Table 5. PK parameters for selexipag and ACT-333679 following IV doses of selexipag in PAH patients

Dose level (µg, bid)	N	$AUC_{\tau, ss}$ (ng.h/mL)	$C_{max, ss}$ (ng/mL)	$C_{trough, ss}$ (ng/mL)	$t_{max, ss}$ (h)
Selexipag					
450	1	46.4	19.5	0.0*	1.5
675	2	44.5 (20.9, 94.8)	18.0 (6.3, 51.8)	0.0* (0.0, 0.3)	1.0 (0.5, 1.5)
900	2	140.9 (126.6, 156.8)	64.0 (51.4, 79.6)	0.1 (0.0, 257.7)	1.5 (1.4, 1.6)
1125	3[$]	71.9	40.6 (21.4, 77.3)	0.1	1.4 (1.4, 1.5)
1350	2	160.6 (0.6, 40879.5)	76.6 (0.1, 42542.3)	0.1 (0.0, 7.0)	0.9 0.4, 1.4
1575	1	80.2	33.9	0.0*	1.4
1800	9	137.8 (104.0, 182.5)	51.6 (37.8, 70.5)	0.2 (0.1, 0.6)	1.5 (1.4, 1.5)
Dose normalized to 225	20[#]	18.8 (15.2, 23.2)	7.8 (6.2, 9.7)	0.0* (0.0, 0.0)	
ACT-333679					
450	1	47.6	6.7	1.9	1.5
675	2	45.9 (0.1, 21969.3)	7.1 (0.2, 233.3)	1.7 (0.0, 38326.6)	2.7 (1.4, 4.0)
900	2	90.0 (35.6, 227.8)	23.3 (0.8, 697.3)	1.7 (0.0, 470.7)	1.5 (1.4, 1.6)
1125	3[$]	81.0 (1.5, 4276.6)	11.6 (6.7, 19.8)	3.5 (0.0, 1700.0)	4.0 (1.4, 4.0)
1350	2	117.4 (9.4, 1467.9)	14.4 (4.0, 51.7)	5.5 (0.0, 6134.0)	4.0 (3.9, 4.1)
1575	1	72.1	15.7	2.3	1.4
1800	9	115.1 (53.9, 246.1)	18.9 (9.8, 36.4)	5.3 (1.9, 14.6)	1.5 (1.4, 4.0)
Dose normalized to 225	20[#]	15.9 (11.2, 22.5)	2.6 (1.9, 3.5)	0.6 (0.4, 1.0)	

Source: Tables 15-20 and 15-21 of CSR for study AC-065A309, Doc No D-18.330;
Data are geometric means (95% CI). t_{max} is presented as median (min, max);
* values zero due to rounding to 1 digit;
[$]N= 1 and 2 for $AUC_{\tau, ss}$ and $C_{trough,ss}$ of selexipag and ACT-333679, respectively due to implausible values
[#]N= 18 and 19 for $AUC_{\tau, ss}$ and $C_{trough,ss}$ of selexipag and ACT-333679, respectively due to implausible values

3.1.3 Summary of safety and tolerability:

Overall, during the entire 3 periods of the study, 15 out of the 20 patients (75%) had at least 1 adverse event (AE), which occurred in similar proportion when compared in the Uptravi 200–1000 and 1200–1600 µg b.i.d. sub-groups, respectively. Headache was the most frequent prostacyclin-associated AE reported in 4 (20%) patients after IV dosing, 1 and 3 in the Uptravi 200–1000 and 1200–1600 µg b.i.d. groups, respectively. After IV dosing, 7 subjects (35 %; 3 and 4 subjects enrolled in the Uptravi 200–1000 and 1200–1600 µg b.i.d. groups, respectively) had at least 1 injection site reaction (pain, erythema, or swelling). Injection site reactions with onset during infusion 2 or 3 were reported for 3 subjects; between infusions 1 and 2 were reported for 2 subjects; and after infusion 3 for 2 subjects.

Clinically significant infusion site erythema was reported in 2 patients (10%), both in the Uptravi 1200–1600 µg b.i.d. group. These were mild intensity infusion site erythema with swelling (1 patient) and mild-to-moderate infusion site erythema (1 patient) and these clinically significant injection site reactions were considered by the investigator to be study-treatment-related. During Period 2, QTcF prolongation to > 450 ms was reported for 3 subjects (16%) and QTcF prolongation to > 480 ms was reported for 4 subjects (20%). Six of these 7 patients reportedly had QTcF prolongation to > 450 ms in Period 1 (prior to the start of IV infusion of selexipag).

During Period 3 including safety follow-up (up to 37 days; oral selexipag), 8 subjects (40%) had at least 1 AE. An AE of peripheral edema was reported for 2 subjects (10%), with one event reported on Day 16 and the other on Day 35. The AE profile was consistent with the known safety profile of selexipag, with no unexpected safety findings observed during treatment with IV selexipag.

3.1.3 Reviewer's comment:

An IV dose which was 1.125-times of the corresponding oral dose of selexipag was selected for clinical evaluation of safety, tolerability and the PK profiles of selexipag and the active metabolite in this study. The pharmacokinetic profiles and exposure of the active metabolite were comparable between both routes of administration. Based on the comparable exposures to the active metabolite after oral and IV selexipag administration, the evaluated dosing regimen for IV selexipag is considered appropriate for clinical treatment of PAH patients. The patient tolerability was also similar between selexipag injection and tablets, except for cases of injection site reactions with IV selexipag. There was no unexpected safety finding reported during treatment with IV selexipag.

3.2 Modeling and simulations of different intravenous infusion rates/times

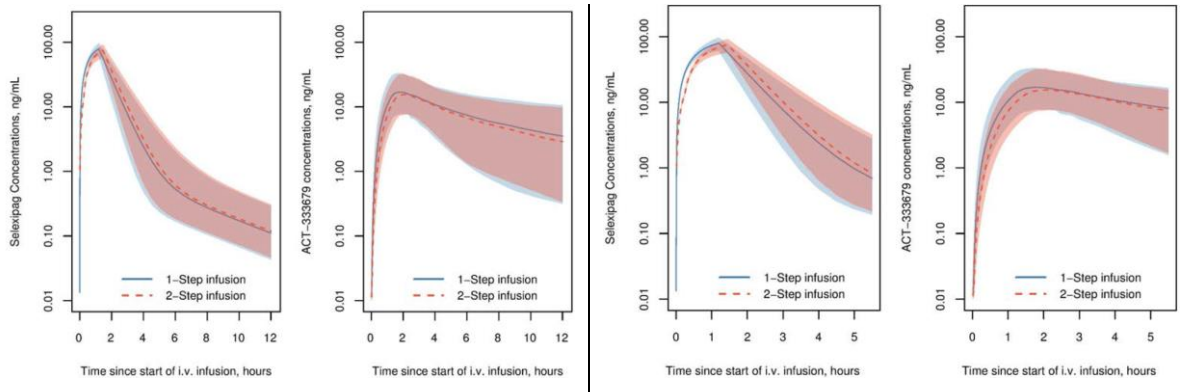
Population pharmacokinetic analysis of intravenous selexipag and model-based simulations of different intravenous infusion times

The main objective of this simulation exercise was to demonstrate that a clinically convenient one-step constant rate infusion would result in equivalent exposures to selexipag and its active metabolite (ACT-333679) to those that resulted after a two-step infusion in Study AC-065A309. The clinical study had evaluated IV regimen using a two-step infusion rate where doses were prepared in a total of 50 mL and 10% of the total dose was delivered within the first 15 min (5 mL @ 20mL/h) and the remaining 90%

delivered during the last 72 min (45 mL @ 37.5 mL/h) of the infusion. The initial 15-min infusion at slower infusion rate was implemented as a precautionary measure to assess any tolerability issues, especially at the higher selexipag dose levels. The highest IV dose of 1800 µg bid was tolerated by PAH patients in the AC-065A309 study when infused over 87 min as above. However, it is a reasonable rationale from applicant that the one-step constant rate of infusion would be easy for clinical use and less prone for dosing errors provided the PK profiles are demonstrated to be similar for selexipag and ACT-333679. An 80-minute infusion that was previously used in the single dose AC-065-110 study was evaluated for appropriateness using simulations. The constant rate of infusion in µg/h or mL/h would depend on the target dose or total volume containing the dose, respectively.

The simulations were performed with the IV regimen of 1800 µg bid that corresponds to the maximum oral selexipag dose of 1600 µg bid. An integrated population PK model was developed to describe the PK profiles of both selexipag and ACT-333679, assuming a first-order formation process for ACT-333679 from selexipag. The model-based simulations were used to generate selexipag and ACT-333679 plasma concentration-time profiles after administration of the two-step or one-step infusion rate for a total of 500 subjects. individual exposure metrics C_{max} and $AUC_{0\text{-}12h}$ were derived for both analytes and compared between both IV infusion rates using geometric mean ratios (GMRs). The GMR of the one-step infusion versus two-step infusion for C_{max} and $AUC_{0\text{-}12h}$ for selexipag were 1.07 (90% CI: 1.06–1.08) and 1.00 (90% CI: 0.97–1.03), respectively, while the GMR of the one-step infusion versus two-step infusion for C_{max} and $AUC_{0\text{-}12h}$ for ACT-333679 were 1.08 (90% CI: 1.03–1.13) and 1.09 (90% CI: 1.04–1.14), respectively. The concentration-time profiles were also similar for both analytes between both the infusion rates, as shown in the figure 3.

Figure 3. Study AC-065A309: Dose-Normalized Mean plasma concentration-time profiles of selexipag and ACT-333679 in PAH patients after oral and IV selexipag dosing (linear and semilogarithmic scales)



Source: Figure 7, in modeling and simulation report study AC-065A309, Doc No. D-19.333; solid blue line with its associated blue shaded represents the median (90% prediction interval) based on the IIV of the 1800 µg in 80 min (one-step infusion); the dashed red line with its associated red shaded represents the median (90% prediction interval) based on the IIV of the 180 µg in 15 min followed by 1620 µg in 72 min rates (two-step infusion); Panels on right show a zoom-in to the first 5 h after IV dosing

Conclusion:

Based on the model-based PK simulations, the 80-min infusion is suitable and results in a similar PK profile for selexipag and ACT-333679 to that observed in the AC-065A309 study in PAH patients.

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/s/

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