Office of Clinical Pharmacology Review

NDA or BLA Number	207947
Link to EDR	\\CDSESUB1\evsprod\NDA207947\0446
Submission Date	7/31/2025
Submission Type	Pediatric supplement
Brand Name	Uptravi
Generic Name	Selexipag
Dosage Form and Strength	Tablets: 100 mcg, 150 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg
Route of Administration	Oral
Proposed Indication	Pediatric Patients (2 to 17 years old) - UPTRAVI is indicated for the treatment of PAH (WHO Group I) in pediatric patients aged two years and older. UPTRAVI reduces NT-proBNP and is expected to delay disease progression and reduce the risk of hospitalization for PAH.
Applicant	Actelion Pharmaceuticals US, Inc.
Associated IND	104504
OCP Review Team	Nora Lee, Ph.D., Elly Moon, Pharm.D., Abiy Eyakem, Ph.D., Vishnu Sharma, Ph.D

Reference ID: 5737631

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1. EXECUTIVE SUMMARY

This supplemental application submitted by Janssen Research & Development (Janssen) on behalf of Actelion Pharmaceuticals, Inc. on July 31, 2025, is to seek the extension of the indication of UPTRAVI (selexipag) for use in pediatric patients with pulmonary arterial hypertension (PAH) aged 2 years and older. The Applicant pursued a pediatric program under the Best Pharmaceuticals for Children Act (BPCA) to obtain pediatric exclusivity.

The Applicant is seeking the following pediatric indication in this NDA supplement:
For the treatment of pulmonary arterial hypertension (PAH, WHO Group I):

- In adults to delay disease progression and reduce the risk of hospitalization for PAH.
- *In pediatric patients aged 2 years and older. UPTRAVI reduces NT-proBNP and is expected to delay disease progression and reduce the risk of hospitalization for PAH.*

This NDA supplement discusses the results of 2 clinical studies and 1 supportive clinical study in the pediatric PAH population:

- Phase 3, pivotal placebo-controlled safety and efficacy study (AC-065A310 [SALTO])
- Phase 2, open-label, single-arm pharmacokinetic (PK) study (AC-065A203)
- Phase 2, open-label, single-arm, exploratory study conducted in Japanese patients (NS304P-P2-1)

Study AC-065A310 (SALTO) was a randomized, multicenter, double-blind, placebo controlled, parallel-group study with open-label extension period to assess the efficacy and safety of selexipag as add-on treatment to standard of care in children aged ≥2 to <18 years with PAH (open label extension period is ongoing). Total 138 children with PAH were enrolled and randomized in a 1:1 manner to either selexipag (n=69) or placebo (n=69). Study intervention consisted of selexipag 200 µg, 150 µg, 100 µg, and 50 µg film-coated tablets or matching placebo. Up to the end of double-blind treatment period, median duration of exposure was 87.9 weeks (78.0 weeks and 92.7 weeks in the selexipag group and the placebo group, respectively). For the primary endpoint, the median time to first Clinical Efficacy Committee (CEC)-confirmed disease progression event was not estimable for the selexipag group and 35.29 months for the placebo group. For the key secondary endpoint, the model-adjusted geometric least square (LS) mean ratio (selexipag vs. placebo) for the change from baseline to Week 24 in NT-proBNP was 0.93 (p=0.57).

In SALTO, the selexipag starting dose and up-titration scheme were based on body weight groups (≥50 kg, ≥25 to <50 kg, and ≥9 to <25 kg), targeting the exposure observed in adults at a dose range of 200 to 1600 µg twice daily (BID). The maximum allowed dose was tolerated by 63.6% in the ≥50 kg body weight group (1600 µg), by 50.0% in the ≥25 to <50 kg group (1200 µg), and by 69.2% in the ≥9 to <25 kg group (800 µg).

Study AC-065A203 was an open-label, single-arm phase 2 study to assess the safety, tolerability, and PK of selexipag in children with PAH (Cohort 1: ≥12 to <18, Cohort 2: ≥6 to <12, Cohort 3: ≥2 to <6 years of age). The primary objective of this study was to determine whether the selected selexipag dosing regimen result in exposure similar to the those observed with adult dosing regimen.

For pediatric formulations, smaller, film-coated tablets of 3 mm diameter containing 50, 100, and 150 µg of selexipag were developed and were used in both SALTO and Study AC-065A203. As supportive data, results from a relative bioavailability study (AC-065-112) were submitted. In this

study, the PK of selexipag following a single oral administration of 4 film-coated pediatric tablets of 50 µg was compared with that following administration of 1 film-coated tablet of 200 µg selexipag tablet.

Based on an exposure matching approach using population PK model analysis and a biomarker bridging approach using exposure-response (E-R) analysis for NT-proBNP change in pediatric patients (SALTO and Study AC-065A203) and adult patients (GRIPHON), the Applicant proposed the weight-based dosing in the pediatric patients aged 2 years and older. The review focuses on the appropriateness of the population PK and E-R analyses and relevant clinical pharmacology information for the proposed dose and indication.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted to NDA 207947 and found it acceptable to support approval of UPTRAVI (selexipag) for the treatment of PAH (WHO Group I) in pediatric patients aged 2 years and older: UPTRAVI reduces NT-proBNP and is expected to delay disease progression and reduce the risk of hospitalization for PAH.

We recommend the following revisions to the labeling (refer to Sections 2.4 and 3.3.1):

- Revise the pediatric dosing regimen (b) (4). For pediatric patients with body weight ≥40 kg to <50 kg, the recommended initial dose is 150 mcg with a maximum dose of 1600 mcg.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Selexipag is a prostacyclin receptor agonist (IP receptor) 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.

This supplemental NDA application proposes to add pediatric patients aged 2 years and older for the use of selexipag for treatment of PAH based on the findings of Study AC-065A310 (SALTO) entitled " A randomized, multicenter, double-blind, placebo-controlled, parallel-group study with open-label extension period to assess the efficacy and safety of selexipag as add-on treatment to standard of care in children aged ≥2 to <18 years with pulmonary arterial hypertension.

Refer to details of general clinical pharmacology information of selexipag in clinical pharmacology review under NDA 207947 (DARRTS, dated 11/06/2025; reference ID: 3844340).

Smaller, film-coated tablets of 3 mm diameter containing 50, 100, and 150 µg of selexipag were developed and these (b) (4) pediatric formulation were used in both SALTO and AC-065A203 studies. As supportive data, results from a relative bioavailability study (AC-065-112) were submitted. In this study, the PK of selexipag following a single oral administration of 4 film-coated pediatric tablets of 50 µg was compared with that following administration of 1 film-

coated tablet of 200 µg. The 90% confidence intervals (CIs) of geometric mean ratios (GMRs) for C_{max}, AUC_t, and AUC_{inf} of active metabolite (JNJ-68006861/ACT-333679) were within the bioequivalence (BE) criteria of 80.00% to 125.00%. The 90% CIs of GMRs for AUC_t and AUC_{inf} of selexipag were within the prespecified BE criteria while the lower limit for C_{max} was slightly below it (0.75) which was considered not clinically significant.

A population pharmacokinetic (popPK) model was established previously to simultaneously characterize selexipag and its active metabolite (JNJ-68006861 / ACT-333679) in adult patients with PAH. The final model included bodyweight, sex, total bilirubin and comedications as significant covariates. In addition, an exposure-response (E-R) relationship was recognized between the combined exposures ($AUC_{\tau, ss, combined}$) weighed by potency of selexipag and its active metabolite (JNJ-68006861/ACT-333679) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a bridging biomarker for PAH.

The adult popPK model was employed as a starting model to develop the model on phase 2 pediatrics data (AC-065A203). Bayesian approach was utilized to update the pediatric model with the prior adult model parameters. The pediatric popPK model was externally evaluated and updated based on pediatric data from Phase 3 (SALTO) study. The current final pediatric model was used to predict selexipag and its active metabolite (JNJ-68006861/ACT-333679) combined PK exposure metrics in pediatric PAH patients. The E-R analysis for changes in NT-proBNP from baseline over time was performed in a pooled pediatric data from AC-065A203 and SALTO after stratifying into two subgroups based on baseline NT-proBNP level (≥300 and < 300 ng/L). The magnitude of NT-proBNP change from baseline was modeled as a function of $AUC_{\tau,ss,combined}$ of selexipag and the active metabolite at individual maximum tolerated dose (iMTD).

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed indication is the treatment of PAH (WHO Group I) in pediatric patients aged two years and older. The recommended starting dose is determined based on the patient's body weight and is given twice daily (BID). The recommended starting doses, titration increments, and maximum allowed doses based on body weight categories in pediatric patients are shown in **Table 1**.

Table 1. Proposed Pediatric Dosing Regimen.

Body weight (kg)	Recommended starting dose (µg), twice daily	Recommended titration increments (µg), twice daily	Maximum dose allowed (µg), twice daily

Source: M1.14 - Labeling

Increase the dose in increments equivalent to the starting dose (i.e., 100, 150, of 200 µg given twice daily), at weekly intervals, to the highest tolerated dose up to the maximum dose allowed for the patient's body weight (**Table 1**). If a patient reaches a dose that cannot be tolerated or

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medically managed, the dose should be reduced to the previous tolerated dose. The UPTRAVI tablets should be swallowed whole and splitting or crushing is not allowed.

Alternative methods of administration of UPTRAVI tablets

For patients who cannot swallow the tablets whole, 100 µg or 150 µg UPTRAVI tablets can be dispersed and administered in apple or orange juice. Dispersion in water or milk is not allowed. Alternatively, 100 µg and 150 µg UPTRAVI tablets can also be administered with soft foods such as yogurt, applesauce, or mashed banana.

2.2.2 Therapeutic individualization

For details, refer to the clinical pharmacology review under NDA 207947 (DARRTS, dated 11/06/2025; reference ID: 3844340).

No adjustment to the dosing regimen is needed in patients with mild hepatic impairment (Child-Pugh class A) while a once-daily regimen is recommended in adult and pediatric patients with moderate hepatic impairment (Child-Pugh class B) due to the increased exposure to selexipag and its active metabolite. Use of UPTRAVI in patients with severe hepatic impairment is not recommended.

No adjustment to the dosing regimen is needed in patients with estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2. There is no clinical experience with UPTRAVI in patients undergoing dialysis or in patients with eGFR <15 mL/min/1.73 m^2.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following preliminary labeling concepts be included in the final package insert:

Label Section	Acceptable to OCP?			Recommendation
	A	AWE	U	
DOSAGE AND ADMINISTRATION in highlights of prescribing information	x			(b) (4)

				(b) (4)
2 DOSAGE AND ADMINISTRATION		x		

				(b) (4)
8.4 Pediatric Use		x		

				(b) (4)
12.3 Pharmacokinetics		x		

A = Acceptable; AWE=Acceptable with minor edits; U=Unacceptable/substantive disagreement (must provide comment); Updates proposed by reviewer are in red font or with strikethrough.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

As part of the pediatric development program under BPCA, three pediatric studies (SALTO, AC-065A203, NS304P-P2-1) were conducted to assess the safety, efficacy and PK/PD of selexipag in pediatric patients aged 2 to less than 18 years with PAH.

Date	Communication/Meeting Type	Key Communication Points
22 December 2015	NDA Approval Letter	Selexipag has orphan drug designation and no pediatric obligations exist. The Applicant pursued a pediatric program under the Best Pharmaceutical for Children Act to obtain pediatric exclusivity.
30 July 2025	Written Request	FDA issued a formal written request (WR) that requires the submission of full study reports and analyses from three pediatric

		studies - the Phase 3 SALTO trial, the Phase 2 pharmacokinetic study (AC-065A203), and a Phase 2 study in Japanese patients (NS304P-P2-1) - leveraging the agreed-upon supplementary analyses of NT-proBNP to support pediatric extrapolation.
31 Jul 2025	Supplement S-014 Submission	The three pediatric studies (SALTO, AC-065A203, NS304P-P2-1) were submitted for approval of selexipag in the pediatric patients aged 2 years and older.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Refers to details of general clinical pharmacology information of selexipag in clinical pharmacology review under NDA 207947 (DARRTS, Reference ID: 3844340).

3.3 Clinical Pharmacology Review Questions

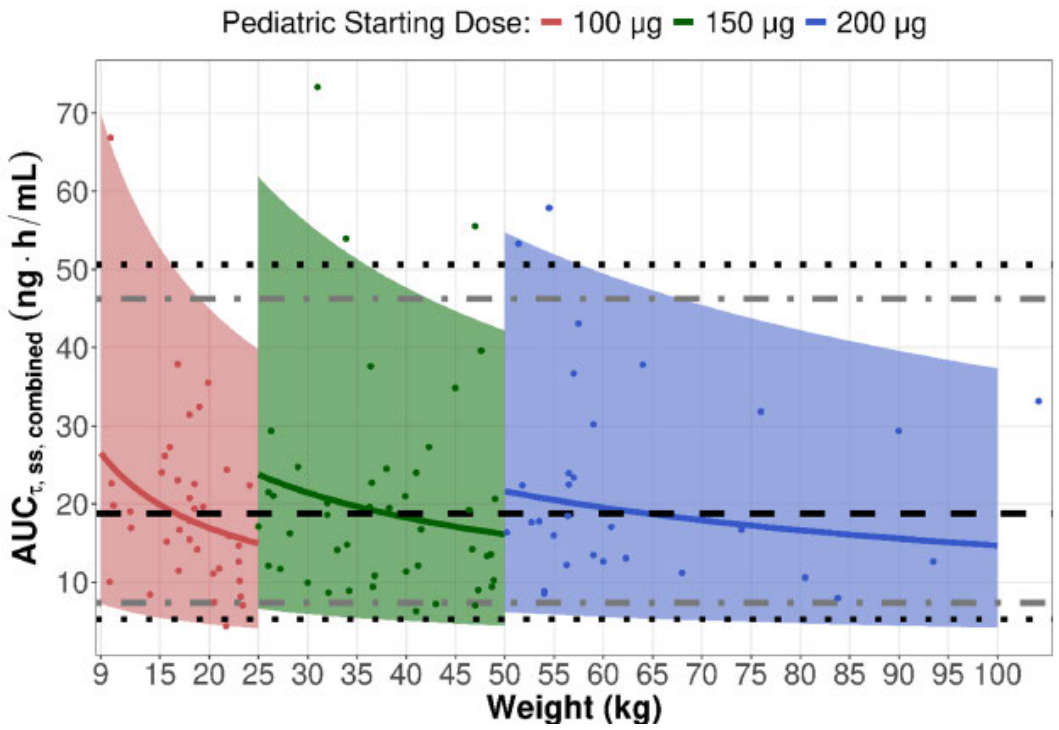
3.3.1 Is selexipag exposure similar between pediatric and adult patient populations, justifying the body weight-based dosing regimen in children aged 2 years and older?

Yes, the estimated selexipag exposure in pediatric patients in SALTO and Study AC-065A203 across body weight groups and corresponding starting doses were comparable to the range observed in adult patients (GRIPHON) (**Figure 1**).

The (b) (4) bodyweight-tiered pediatric dosing was based on PK exposure-matching with the approved 200 µg adult dose for the treatment of PAH. To support adult to pediatric extrapolation, the Applicant refined the adult popPK model by applying allometric scaling on the pediatric data obtained from SALTO and Study AC-065A203. Using this model, PK exposures were derived (AUC, C_{max} and C_{trough}) from 500 simulated pediatric patients at the (b) (4) bodyweight-tiered starting doses. The observed PK exposures were overlayed on the simulated exposures for the pediatric population and were compared with the adult reference exposures in terms of median and 10th and 90th percent prediction interval similarities (**Figure 1**).

The observed and simulated pediatric exposures are largely contained within the exposure ranges seen in the adult population. Further, the simulated median with 90% prediction interval of pediatric patients appears to be comparable with that observed in adults (**Figure 1**). Overall, the (b) (4) bodyweight-tiered pediatric dosage regimen resulted in similar exposures as those observed in adults with a flat 200 µg starting dose.

Figure 1. Predicted Median and 90% Prediction Interval of $AUC_{T,ss,combined}$ for the Pediatric Dosing Groups



$AUC_{\tau,ss,combined}$=combined area under the plasma concentration-time curve of selexipag and JNJ-68006861 over a 12-hour dosing interval at steady-state, weighed by their relative potencies. Solid circles show $AUC_{\tau,ss,combined}$ for participants from pediatric studies AC-065A203 and SALTO. Black lines show a median (black-dashed line) and 90% prediction interval (black-dotted lines) of $AUC_{\tau,ss,combined}$ of adult population (GRIPHON), for body weights ranging from 39.5 to 148 kg with the other intrinsic/extrinsic factors, i.e., co-PAH medication, sex, and bilirubin concentration bootstrapped from the GRIPHON trial data at individual level. Grey lines show the 90% prediction interval (grey-dotted-dashed lines) of $AUC_{\tau,ss,combined}$ in the adult population estimated from random effects and intrinsic factors from the GRIPHON data.

Source: Response to the information request dated October 14, 2025 (SDN 755, received October 24, 2025), Figure 1, page 6

In GRIPHON, the patients' body weight ranged from 39.5 to 148 kg, indicating that the adult patients with body weight ≥40 kg received a starting dose of 200 µg while the pediatric patients with body weight ≥40 kg to <50 kg received a starting dose of 150 µg in accordance with the proposed pediatric dosing regimen.

To align the bodyweight dosing in pediatric patients with adult patients, the review team conducted additional simulations based on the recommended bodyweight-tiered dosing indicated in **Table 2**.

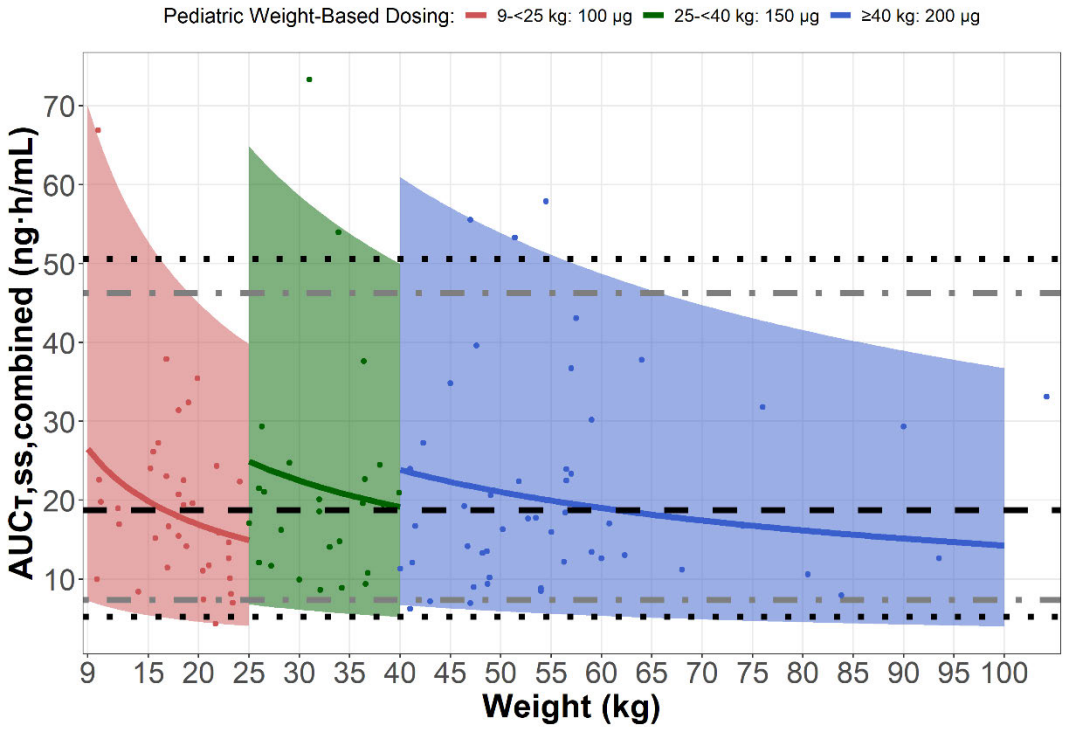
The FDA analysis demonstrated that the estimated exposure in pediatric patients weighing ≥40 kg to <50 kg with a starting dose of 200 µg was comparable to those in other body weight categories and in adult patients although the model tended to marginally overpredict exposures for pediatric patients with bodyweight falling between 40 – 50kg (**Figure 2**).

Table 2. Bodyweight based Dose Regimens Comparing the Applicant's Proposal and OCP team's Recommendation.

Proposed By the Applicant			Recommended By the OCP team		
Body-weight tier (kg)	Starting dose (µg) BID	Maximum tolerated dose (µg) BID	Body-weight tier (kg)	Starting dose (µg) BID	Maximum tolerated dose (µg) BID
(b) (4)			≥ 9 to < 25	100	800
			≥ 25 to < 40	150	1200
			≥40	200	1600

Source: Reviewer's Analysis

Figure 2. Predicted Median and 90% Prediction Interval of $AUC_{T,ss,combined}$ for the Pediatric Dosing Groups with Body Weight Categories of 9 to <25 kg, 25 to <40 kg and ≥40 kg (FDA's Analysis).



Solid circles show $AUC_{T,ss,combined}$ for participants from pediatric studies AC-065A203 and SALTO. Black lines show a median (black-dashed line) and 90% prediction interval (black-dotted lines) of $AUC_{T,ss,combined}$ of adult population (GRIPHON), for body weights ranging from 39.5 to 148 kg with the other intrinsic/extrinsic factors, i.e., co-PAH medication, sex, and bilirubin concentration bootstrapped from the GRIPHON trial data at individual level. Grey lines show the 90% prediction interval (grey-dotted-dashed lines) of $AUC_{T,ss,combined}$ in the adult population estimated from random effects and intrinsic factors from the GRIPHON data.
Source: FDA's analysis

Based on the FDA's analysis, the Clinical Pharmacology team proposed the pediatric dosing regimen (b) (4) body weight categories as indicated in **Table 2**. In response to the information request dated January 7, 2026, the Applicant addressed a higher frequency of vomiting and abdominal pain, which are likely prostacyclin-related adverse events, in the pediatric population which may warrant cautious, individualized up-titration with close monitoring

to optimize tolerability, safety and treatment adherence. To ensure optimal short- and long-term tolerability in the pediatric patients with body a weight of 40 kg to <50 kg, the Applicant proposes an initial dose of a 150 µg with up-titration in 150 µg increments up to a maximum of 1600 µg (**Table 3**).

Table 3. Pediatric Dosing Regimen (b) (4) Body Weight Categories.

Body-weight tier (kg)	Starting dose (µg) BID	Titration increment (µg) BID	Maximum tolerated dose (µg) BID
≥ 9 to < 25	100	100	800
≥ 25 to < 40	150	150	1200
≥ 40 to < 50	150	150	1600
≥ 50	200	200	1600

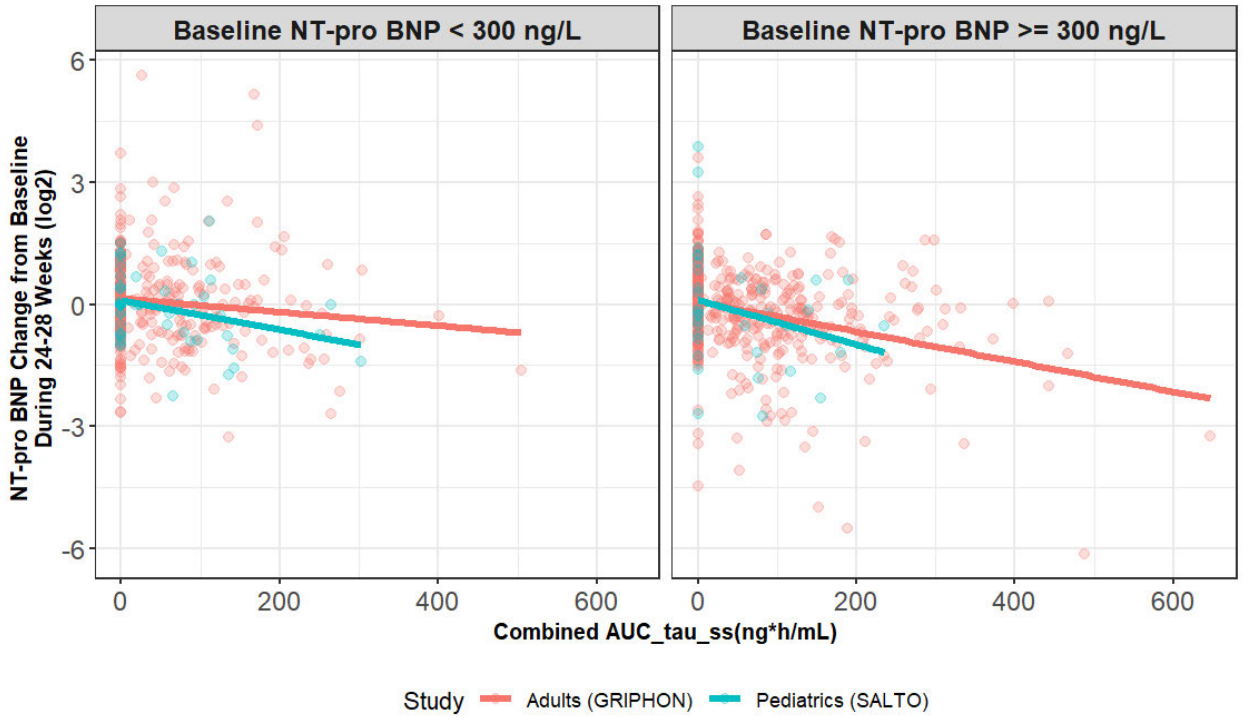
The Clinical Pharmacology team considers the proposed pediatric dosing regimen acceptable based on the tolerability and adverse event data in pediatric patients.

3.3.2. Is exposure-response relationship similar between pediatric and adult populations?

A negative linear E-R relationship was shown between changes in NT-proBNP from baseline overtime and $AUC_{\tau,ss,combined}$ at iMTD mainly in pediatric subjects with elevated baseline NT-proBNP level (≥300 ng/L) but not in those with non-elevated baseline NT-proBNP level (< 300 ng/L). To illustrate if similar E-R relationship was observed in adults, the review team compared the E-R relationships between adults (GRIPHON) and pediatrics (SALTO) data. Regardless of baseline NT-proBNP levels, similar E-R relationships between pediatric and adult populations were observed (**Figure 3**).

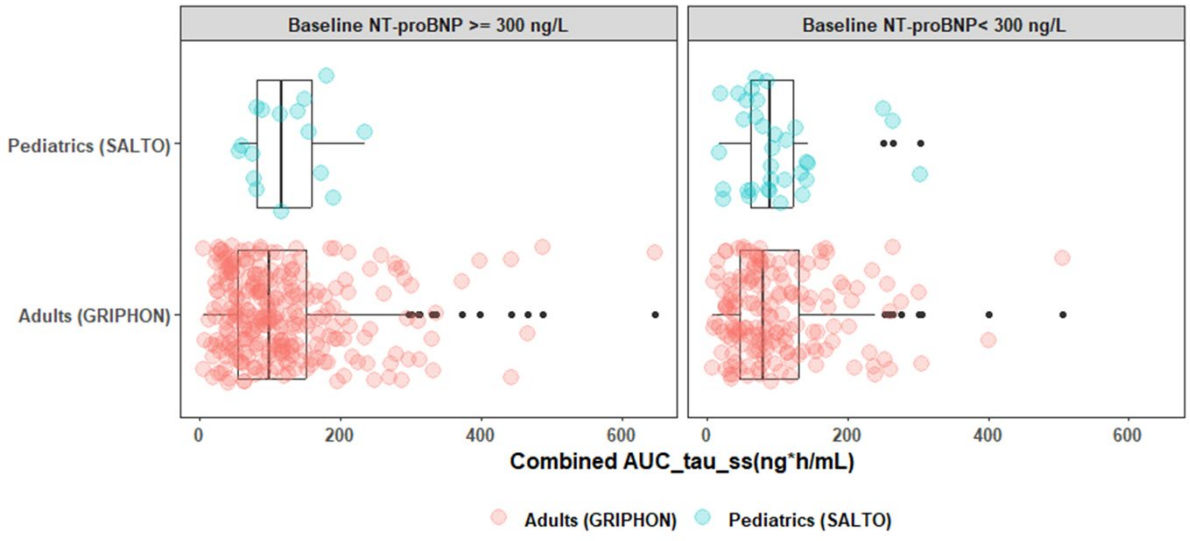
However, based on the **Figure 3,** differences in the observed PK exposure ranges between pediatrics and adults appear to exist despite comparable central tendencies (**Figure 4**). The review team believes that the differences are likely due to smaller sample size of SALTO study that are largely influenced by subjects with baseline NT-proBNP <300 ng/L and differential placebo responses in SALTO study across NT-proBNP levels (**Table 4**).

Figure 3. Comparing E-R Relationships Between Pediatric (SALTO) and Adult (GRIPHON) Studies Stratified by Baseline NT-proBNP levels



Source: Reviewer's Analysis

Figure 4. Exposure Comparison Between Pediatric (SALTO) and Adult (GRIPHON) Studies Stratified by Baseline NT-proBNP levels.



Source: Reviewer's Analysis

Table 4. Comparison of NT-proBNP Change Ratios Between Pediatric and Adult Patients by Treatment

	Selexipag	Placebo
Adults (GRIPHON)	0.84 (n=460)	1.10 (n=449)
NT-ProBNP <300 ng/L	0.95 (n=178)	1.08 (n=173)
NT-ProBNP ≥300 ng/L	0.78 (n=282)	1.10 (n=276)
Pediatrics (SALTO)	0.87 (n=59)	1.03 (n=64)
NT-ProBNP <300 ng/L	1.0 (n=40)	1.0 (n=42)
NT-ProBNP ≥300 ng/L	0.70 (n=20)	1.10 (n=22)

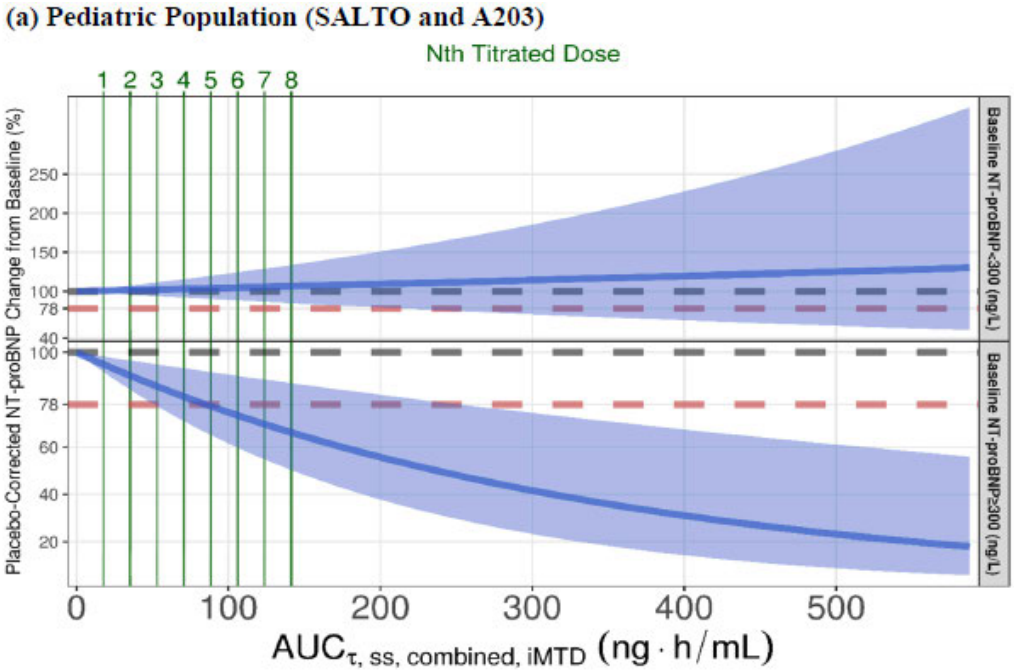
*Geometric mean ratio to baseline at Week 24/26

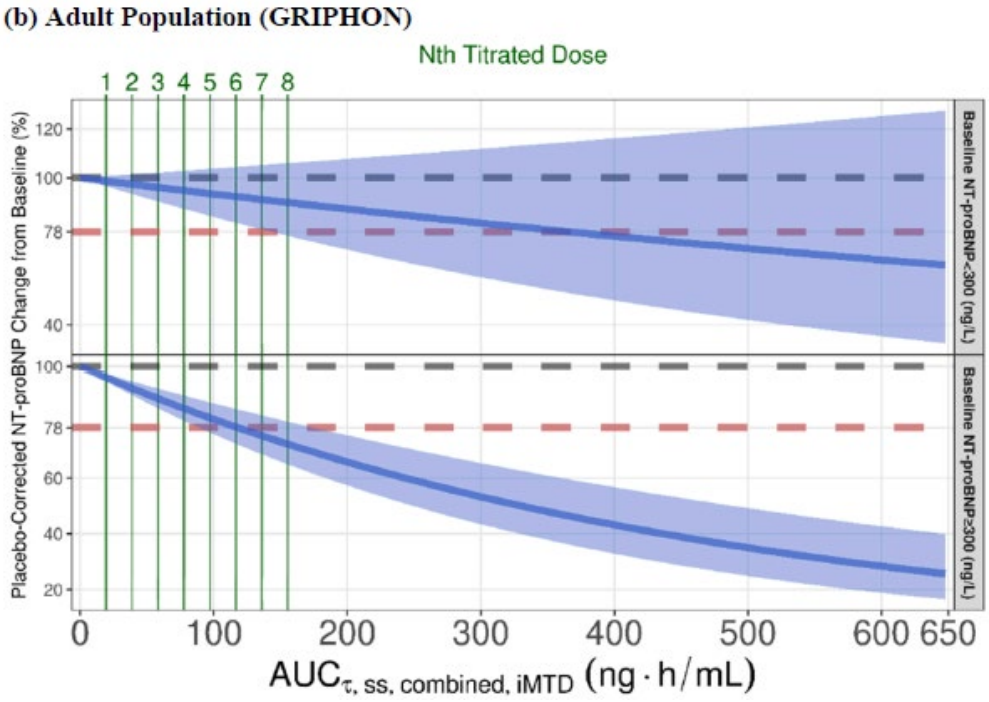
Source: Response to the information request dated August 25, 2025

3.3.3 Does the exposure-response relationship in pediatric patients support the treatment effect in pediatric patients as observed in adult patient population?

Yes, the E-R relationships for both disease progression (efficacy) and changes in NT-proBNP (PD response) were comparable between pediatric and adult patient populations with elevated baseline NT-proBNP levels (≥300 ng/L) (**Figure 5** and **Table 5**).

Figure 5. Placebo-corrected NT-proBNP Change From Baseline Versus $AUC_{\tau,ss,combined,iMTD}$ by NT-proBNP Baseline Subgroup in Pediatric and Adult Populations





A203=Study AC-065A203; AUCτ,ss,combined,iMTD=combined area under the plasma concentration-time curve of selexipag and JNJ- 68006861 at the individual maximal tolerated dose over a 12-hour dose interval at steady state, weighed by their relative potencies; NT-proBNP=N-terminal pro-type natriuretic peptide. The solid-blue line represents the point estimate of the exposure-response relationship; the shaded-blue area represents the 95% confidence interval; the dashed-red line represents the minimal clinically relevant reduction; the solid-green lines represent the geometric means of AUCτ,ss,combined,iMTD corresponding to titrated doses; and the dashed-black line represents the line of no change.

Source: Response to the information request dated October 14, 2025 (SDN 757, received October 30, 2025), Figure 1, page 12-13

Table 5. Probability of First Disease Progression Event at Month 6 and Slope of NT-proBNP E-R Model for Pediatric (SALTO and A203) and Adult Patients (GRIPHON)

Parameters	Population	Baseline NT-proPNP Subgroup	
		Non-elevated	Elevated
Probability of first disease progression event at Month 6 (odds ratio)	Adult	0.692	0.398
	Pediatric	2.07	0.556
Slope of NT-proBNP E-R model	Adult	-0.00098	-0.00303
	Pediatric	0.0000647	-0.00422

Source: Response to the information request dated October 14, 2025 (SDN 757, received October 30, 2025), Tables 1 and 2 (pages 8 and 10); Tables 3 and 4 (page 11)

In the non-elevated baseline NT-proBNP group, a decreasing trend in the E-R relationship for disease progression and NT-proBNP change from baseline was observed in adults, but not in pediatric patients (**Figure 5** and **Table 5**). This difference between adult and pediatric patients may be attributed to limited sample size in pediatric studies and differences in background PAH therapy between the studies: GRIPHON had 20.4% participants without background, 47.1%

received endothelin receptor antagonist (ERA) or Phosphodiesterase Type 5 inhibitor (PDE5i) monotherapy and 32.5% received ERA+PDE5i combination therapy; Study A203 had 6.3% participants without background therapy, 41.3% received monotherapy, and 52.4% received combination therapy; SALTO had all participants with background therapy and 74.6% received combination therapy.

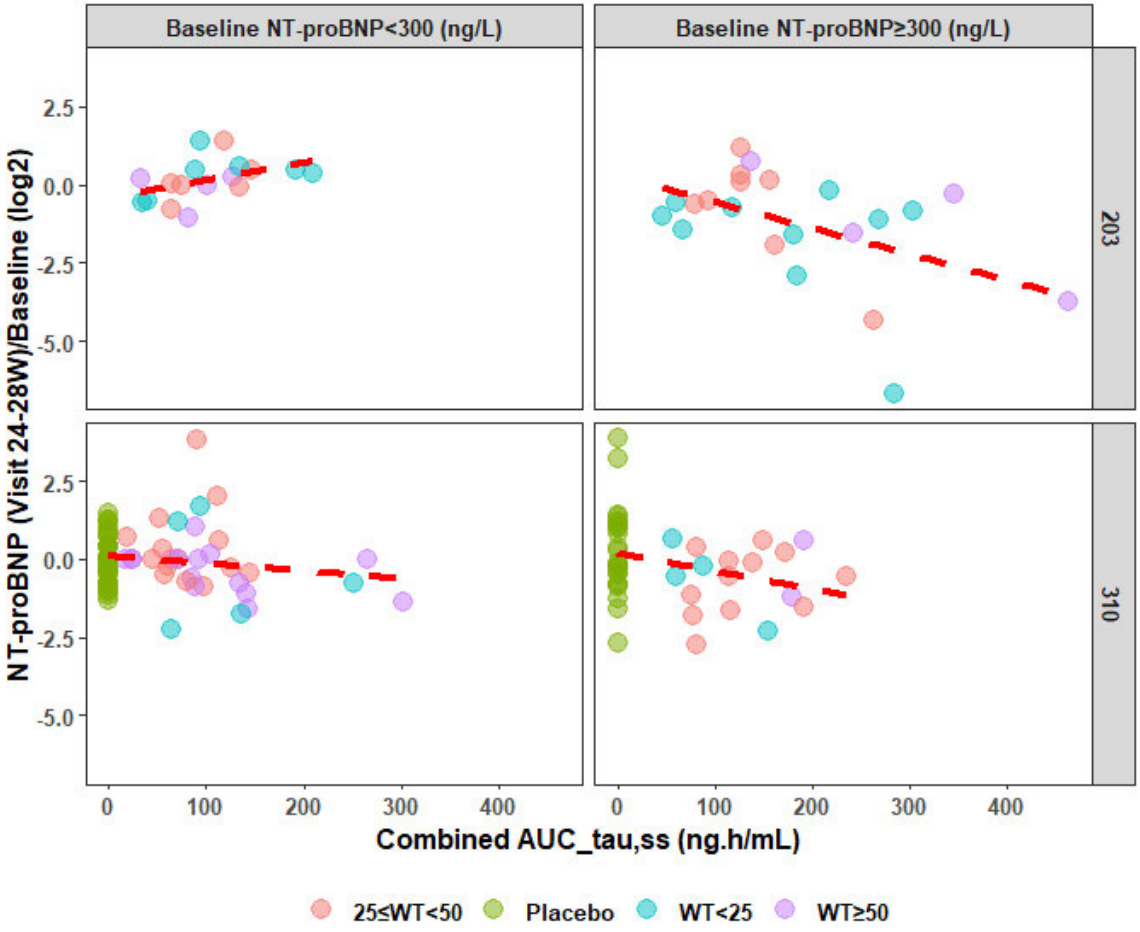
At Week 24 or Week 26, changes from baseline NT-proBNP were comparable between SALTO and GRIPHON (**Table 4**). In GRIPHON, there was a 58% treatment effect with this observed NT-proBNP reduction.

Given the similar NT-proBNP reductions at Week 24 or 26 and E-R relationship in the elevated baseline group, the treatment effect in pediatric patients is expected to be similar to that observed in adult patients when the proposed dose is administered.

3.3.4. What might have caused differential E-R relationship between elevated and non-elevated baseline NT-proBNP levels within pediatric?

While clear E-R relationship appears to be observed in subgroups with elevated baseline NT-proBNP level, to investigate the absence of an E-R relationship in the pediatric subgroup with non-elevated baseline NT-proBNP levels (<300 ng/L), the review team created a four-way plot by stratifying the pediatric data based on both baseline NT-proBNP level and study type [AC-065A203 versus SALTO] (**Figure 6**). This visual analysis revealed distinct patterns between the two baseline NT-proBNP subgroups. In patients with elevated baseline NT-proBNP levels, the E-R relationship appears to show similar trends between AC-065A203 and SALTO (right-panel in **Figure 6**). However, in patients with non-elevated baseline NT-proBNP levels, SALTO demonstrated a decreasing trend similar to that observed in GRIPHON, whereas AC-065A203 showed no apparent trend. The absence of a trend in AC-065A203 may be attributed to either the absence of a placebo arm and/or lower drug exposure ($AUC_{\tau,ss,\ combined}$) that truncated at about 200 ng*h/mL relative to SALTO in the subgroup of pediatric subjects with non-elevated baseline NT-proBNP levels (top-left in the **Figure 6**).

Figure 6. E-R Relationship Stratified by Baseline NT-proBNP levels and Study in Pediatric Patients.



Key: 203 = AC-065A203 (Pediatric Phase 2 Study); 310 = SALTO (Pediatric Phase 3 Study)

Source: Reviewer's Analysis

3.3.5 Is the proposed alternative methods of administration – administration with soft foods or dispersion in apple or orange juice, without allowing tablet splitting or crushing adequate for children aged 2 years and older?

As alternative methods of administration, the Applicant recommends that UPTRAVI tablets be administered with soft food or dispersed in apple or orange juice while crushing or splitting the tablets is not allowed.

Younger children may have difficulty swallowing the tablets even if the tablets are given with soft food and it was unclear why dispersion in apple or orange juice is acceptable whereas dispersion in milk in water is not permitted. The Clinical Pharmacology review team requested the Applicant to provide additional information and justification to support the proposed recommendations.

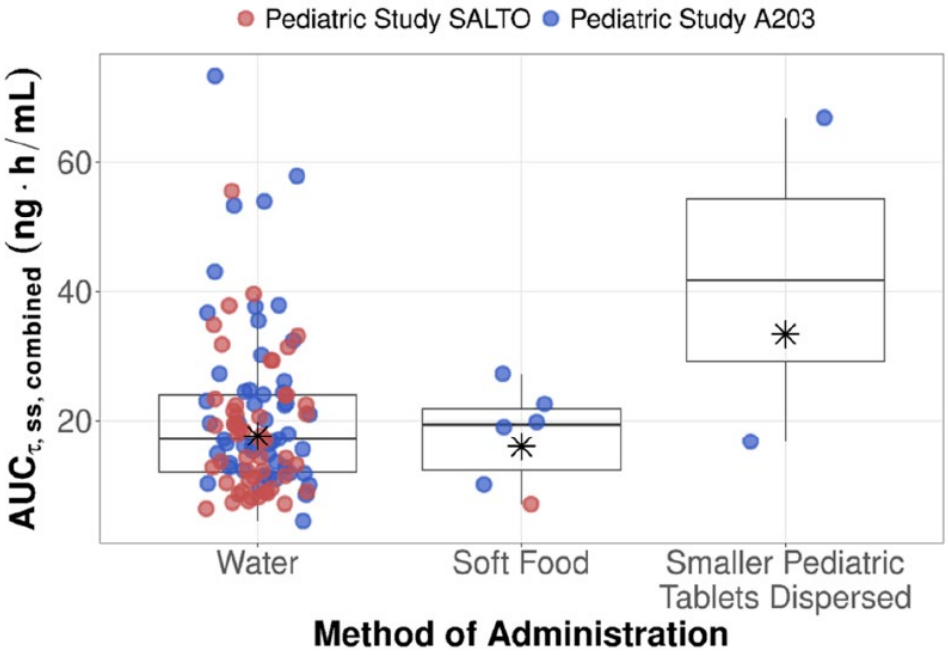
In response to the information request dated December 3, 2025, the Applicant stated that the tablets are small (3 mm in diameter) and not scored, therefore are not intended to be split. The Applicant also addressed that crushing is not recommended to minimize potential loss of active material. The CMC review team concurred that tablet splitting is not appropriate due to the lack of scoring. Overall, the recommendation to avoid crushing or splitting the tablets appears acceptable.

Given that the tablets taken with soft food can be inadvertently chewed during intake, the review team requested that the Applicant provide clear dosing instruction with supportive data. In the response, the Applicant proposed to include additional instruction as follows:

(b) (4)

As a supporting data, the Applicant provided the data of 6 subjects who were administered the tablets with soft food in SALTO and Study AC-065A203, demonstrating PK (**Figure 7)**, efficacy and safety profiles that were consistent with the overall study population.

Figure 7. Distribution of $AUC_{\tau,ss,combined}$ across Administration Methods in Pediatric Studies



A203=Pediatric PK Study AC-065A203; $AUC_{\tau,ss,combined}$=combined area under the plasma concentration-time curve over 1 dose interval at steady state; IQR=interquartile range; SALTO=Study AC-065A310. Stars denote geometric means of distributions. The median and the IQR are indicated by the thick lines and the boxes, respectively. The whiskers extend to the largest/smallest value not more than 1.5 times the IQR.
Source: M 5.3.3.5AC-065A310/CSR Analysis3/PopPK Report/Figure 5, Response to the information request dated December 3, 2025

Additionally, the Applicant provided the results of study (67896049PAH001) that assessed the acceptability, swallowability (swallowing all tablets without chewing), and palatability of a single administration of multiple film-coated, 3 mm diameter selexipag/placebo tablets, taken with soft food or water in children aged ≥2 to <7 years. In this study, 100 children (median age 4 years) who were administered 16 tablets with soft food showed the acceptability rate of 88%, the swallowability rate of 53% and the palatability rate of 90%. Among 35 children who chewed or swallowed some of the tablets, 34 did not have any leftover tablets in the oral cavity and were able to swallow within 2 attempts.

Given that the size of tablet is small (3 mm in diameter) and majority of children with median age of 4 in Study 67896049PAH001 were able to swallow the tablets either with soft food or water, the proposed recommendation including additional instruction to take the tablets with soft food appears acceptable.

The Applicant provided the compatibility data in water or milk and dissolution data in orange or apple juice to support the proposed recommendation for tablet dispersion. The review of these data is deferred to Office of Pharmaceutical Quality (OPQ) and biopharmaceutics review team.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Bioanalytical method for quantification of selexipag and JNJ68006861 in SALTO, Study AC-065A203, and Study AC065-112

Bioanalysis of selexipag and its active metabolite (JNJ68006861) was performed using a mass spectrometry (LC-MS/MS). The methods BA13451/BA13061, BA13061 and BA-14.045 were used in SALTO, Study AC-065A203, and Study AC065-112, respectively. The calibration range for the three assays was 0.0100 to 20.0 ng/mL with the quality control (QC) samples at 0.03 ng/mL, 0.8 ng/mL, 8.0 ng/mL and 15.0 ng/mL. The assays were adequately validated for accuracy, precision, sensitivity, selectivity/specificity and stability.

The study samples were analyzed within the validated stability period at -20°C and the assay performance was found acceptable, as shown in **Table 6**. The overall accuracy and precision of the standard curve and QC samples were acceptable. Incurred sample reproducibility was assessed by re-assaying ≥ 12% of the study samples and ≥67% of the re-assayed samples results were within the acceptance criteria. Overall, the bioanalytical method validation and performance to quantify selexipag and its active metabolite in the study plasma samples were found to be acceptable.

Table 6. Summary of method performance

Validation Parameters	Method Performance Summary	Acceptability
SALTO (SH-J01-R4803)/Method BA13541		
Assay passing rate	83.3% (5/6 runs) for selexipag, 88.9% (8/9 runs) for JNJ-68006861 - Total runs: 6 for selexipag and 9 for JNJ-68006861 - Accepted runs: 5 for selexipag and 8 for JNJ-68006861 - Total samples tested and reported: 40 samples - Total samples reassayed: 20 samples (reasons for reassay: Sponsor/client request or the value being above upper limit of the standard calibration curve)	Acceptable
Standard curve performance	Accuracy (bias%): • selexipag: -12.0 to 3.4% • JNJ-68006861: -1.4 to 2.0% Precision (%CV): • selexipag: 10.2% • JNJ-68006861: 8.6%	Acceptable
QC performance	Accuracy (bias%): • selexipag: 0.7 to 4.3% • JNJ-68006861: -0.4 to 1.7% Precision (%CV): • selexipag: 9.6% • JNJ-68006861: 11.7%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 12.5% (5/40) of study samples for both selexipag and JNJ-68006861 and 100.0% samples were within the acceptance criteria.	Acceptable
Study sample analysis/ stability	- Long term stabilities were established at -20°C for 755 days. - Samples were received from July 13, 2023 to September 12, 2024 and stored at -20°C. The experimental start date was August 22, 2023 and completion date was September 24, 2024. The sample storage time (from collection to analysis end) was 406 days from first shipment which did not exceed the established long term stability duration.	Acceptable
SALTO (JJP19870-19870X-A)/Method BA13061		
Assay passing rate	90% (9/10 runs) for both selexipag andJNJ-68006861 - Total runs: 10 - Accepted runs: 9 - Total samples tested and reported: 205 samples - Total samples reassayed: 2 samples	Acceptable
Standard curve performance	Accuracy (bias%): • selexipag: -6.5 to 5.5% • JNJ-68006861: -4.0 to 3.5%	Acceptable

	Precision (%CV): • selexipag: ≤5.3% • JNJ-68006861: ≤5.5%	
QC performance	Accuracy (bias%): • selexipag: -6.3 to 3.0% • JNJ-68006861: -3.8 to 1.3% Precision (%CV): • selexipag: ≤5.8% • JNJ-68006861: ≤5.6%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 12.7% (26/205) and 12.2% (25/205) for selexipag and JNJ-68006861 study samples, and at least 2/3 of the samples were within the acceptance criteria.	Acceptable
Study sample analysis/ stability	- Long term stabilities were established at -20°C for 951 days. - Samples were received from February 11, 2021 to September 17, 2024 and stored at -20°C. The experimental start date was September 1, 2021 and completion date was October 1, 2024. The maximum storage period between collection and analysis of the samples did not exceed the established long term stability duration.	Acceptable
AC-065A203 (SH-J01-R3728)/Method BA13061		
Assay passing rate	100% (9/9 runs) for both selexipag andJNJ-68006861 - Total runs: 9 - Accepted runs: 9 - Total samples tested and reported: 65 samples - Total samples reassayed: 18 samples (reason for reassay: the original result is above the upper limit of the standard calibration curve)	Acceptable
Standard curve performance	Accuracy (bias%): • selexipag: -6.1 to 3.5% • JNJ-68006861: -6.1 to 3.1% Precision (%CV): • selexipag: 9.7% • JNJ-68006861: 9.8%	Acceptable
QC performance	Accuracy (bias%): • selexipag: -2.3 to -2.0% • JNJ-68006861: -1.7 to -0.1% Precision (%CV): • selexipag: 12.8% • JNJ-68006861: 15.5%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 13.8% (9/65) of study samples for both selexipag and JNJ-68006861 and 100.0% samples were within the acceptance criteria.	Acceptable
Study sample analysis/ stability	- Long term stabilities were established at -20°C for 379 days.	Acceptable

	- Samples were received from August 27, 2021 to June 8, 2022 and stored at -20°C. The experimental start date was September 17, 2021 and completion date was June 13, 2022. The sample storage time (from collection to analysis end) was 692 days from first shipment which exceeds the established long term stability duration. In the report, it was indicated that longer duration of storage would be evaluated to cover the sample storage time, but the data was not provided. In general, stability is not a concern as the maximum long term stability established in another study (JJP103XL-181033-A) but using the same method (BA13061) was 695 days at -20°C which covers the sample storage duration for this study.	
AC-065A203 (JJP103XL-181033-A)/Method BA13061		
Assay passing rate	100.0% (18/18 runs) for selexipag, 94.4% (17/18 runs) for JNJ-68006861 - Total runs: 18 for both selexipag and JNJ-68006861 - Accepted runs: 18 for selexipag and 17 for JNJ-68006861 - Total samples tested and reported: 540 samples - Total samples reassayed: 36 samples for selexipag and 66 samples for JNJ-68006861 (reasons for reassay: the original result is above the upper limit of the standard calibration curve)	Acceptable
Standard curve performance	Accuracy (bias%): • selexipag: -2.5 to 4.0% • JNJ-68006861: -2.5 to 4.0% Precision (%CV): • selexipag: ≤4.7% • JNJ-68006861: ≤5.0%	Acceptable
QC performance	Accuracy (bias%): • selexipag: -0.6 to 6.7% • JNJ-68006861: 0.0 to 5.0% Precision (%CV): • selexipag: ≤7.4% • JNJ-68006861: ≤6.4%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 10.6% (57/540) for both selexipag and JNJ-68006861 study samples, and 93% and 96.5% of the samples for selexipag JNJ-68006861 respectively were within the acceptance criteria.	Acceptable
Study sample analysis/ stability	- Long term stabilities were established at -20°C for 695 days. - Samples were received from December 5, 2017 to February 24, 2022 and stored at -20°C. The experimental start date was February 19, 2019 and completion date was May 4, 2022.The maximum	Acceptable

Reference ID: 5737631

	storage period between collection and analysis of the samples did not exceed the established long term stability duration.	
AC065-112 (BA-15.049)/Method BA-14.045		
Assay passing rate	90.0% (9/10 runs) for selexipag, 80.0% (8/10 runs) for JNJ-68006861 - Total runs: 10 for both selexipag and JNJ-68006861 - Accepted runs: 9 for selexipag and 8 for JNJ-68006861 - Total samples tested and reported: 678 samples - Total samples reassayed: 12 samples for selexipag and 55 samples for JNJ-68006861 (reasons for reassay: verification of measurement)	Acceptable
Standard curve performance	Accuracy (bias%): • selexipag: -3.9 to 3.0% • JNJ-68006861: -2.3 to 3.0% Precision (%CV): • selexipag: ≤3.6% • JNJ-68006861: ≤3.2%	Acceptable
QC performance	Accuracy (bias%): • selexipag: -4.4 to 0.9% • JNJ-68006861: -4.7 to 2.2% Precision (%CV): • selexipag: ≤6.0% • JNJ-68006861: ≤6.9%	Acceptable
Method reproducibility	Incurred sample re-analysis was performed in 10.0% (68/678) and 11.2% (76/678) for selexipag and JNJ-68006861 study samples, respectively, and 95.6% and 94.7% of the samples for selexipag and JNJ-68006861, respectively were within the acceptance criteria.	Acceptable
Study sample analysis/ stability	- Long term stabilities were established at -20°C and -80°C for 367 days. - Samples were received on June 23, 2016 and stored at -80°C. The experimental start date was May 26, 2016 (date for preparation of stock solutions) and completion date was July 6, 2016. The maximum storage period between collection and analysis of the samples did not exceed the established long term stability duration.	Acceptable

Bioanalysis for quantification of NT-proBNP in SALTO and Study AC-065A203

NT-proBNP levels in all plasma samples from SALTO and Study AC-065A203 were measured by electrochemiluminescence immunoassay (ECLIA) using a commercial assay, Elecsys® proBNP II by Roche. The two assay kits were used during the studies. As Roche upgraded the Elecsys® proBNP II assay to address biotin interference in 2020, the second-generation assay

with the modified reagent formulations was used for all subsequent analyses. The method validation reports for the assays were submitted in response to the information request dated November 7, 2025. The assays were adequately validated for accuracy, precision, sensitivity, selectivity/specificity and stability with the calibration range of 6 to 2950 pmol/L and 2.5 to 2950 pmol/L (upgraded assay).

4.2 Assessment of Applicant's Population PK Analyses

Executive Summary

The pharmacometrics assessment did not identify any concern with the proposed starting doses of selexipag for the proposed indication based on pediatric extrapolation. Further, the E-R analysis appears to be consistent between pediatric and adult populations.

Population Pharmacokinetic Modeling and Simulation Assessment

The Applicant's population PK model adequately characterized selexipag and its active metabolite JNJ-68006861 (ACT333679) PK following the [redacted] bodyweight-tiered dose in pediatric patients with PAH aged ≥2 to <18 years in all the bodyweight categories (≥9 to < 25 kg, ≥ 25 to < 50 kg and ≥50 kg).

The population PK analysis utilized PK data from patients with PAH participating in SALTO. **Table 7** summarizes patient characteristics from SALTO study.

Table 7. Summary of Population Demographics and Baseline Characteristics from SALTO

Reference ID: 5737631

Group	Subgroup	N (%)
Number of participants		52
	Male	28 (53.8)
	Female	24 (46.2)
Race	White, Not Hispanic or Latino	23 (44.2)
	White, Hispanic or Latino	8 (15.4)
	Asian	17 (32.7)
	Black, of African heritage or African American	2 (3.85)
	Other	2 (3.85)
Co. PAH Med.	ERA	7 (13.5)
	PDE-5i	9 (17.3)
	ERA+PDE-5i	36 (69.2)
Administration method	Water	51 (98.1)
	Soft food	1 (1.92)
	Smaller pediatric tablets dispersed	0 (0.000)
Weight (kg)	≥50	18 (34.6)
	≥25 to <50	25 (48.1)
	≥9 to <25	9 (17.3)
Age (years)	≥12 to <18	29 (55.8)
	≥6 to <12	20 (38.5)
	≥2 to <6	3 (5.77)
Continuous Variables		
Group	**Range**	**Mean / Median (SD)**
Total bilirubin (µmol/L)	3.00 to 29.0	10.1 / 7.00 (6.63)
Weight (kg)	12.1 to 104	45.2 / 46.6 (19.9)
Age (years)	3.67 to 17.8	12.6 / 13.2 (3.49)

Abbreviations: Co. PAH Med.=concomitant pulmonary arterial hypertension medications; ERA=endothelin receptor antagonist; PDE-5i=phosphodiesterase type-5 inhibitor; SALTO=Study AC-065A310; SD=standard deviation.
Source: Reviewer's Analysis

The pediatric popPK model of selexipag and JNJ-68006861 was developed based on the final Phase 2 PK data of AC-065A203 using the prior adult model . The final pediatric popPK model updated based on AC-065A203 data was applied to SALTO study. The parameter estimates of selexipag and JNJ-68006861 model based on SALTO data are provided in **Table 8**

Table 8. Population PK model parameter estimates of selexipag and JNJ-68006861 based on SALTO study

Parameter	Estimate	RSE[a]	Transformed Estimate[b]
ka (1/h)	0.663	3.67%	-
kmet (1/h)	0.868 (fix)	-	-
CL (L/h)	18.9	6.71%	-
Vp (L)	12.4	7.32%	-
k12 (1/h)	0.115	8.48%	-
k21 (1/h)	0.0563	16%	-
km (1/h)	0.445	6.52%	-
k34 (1/h)	0.83	8.35%	-
k43 (1/h)	0.168	12.5%	-
Vm (L)	6.05	4.04%	-
Tlag (h)	0.668 (fix)	-	-
Body weight on CL	0.828	12.1%	-43.7%
Total bilirubin on CL	-0.363	22.5%	28.6%
Body weight on Vp	0.805	11.3%	-42.8%
Body weight on Vm	0.542	11.4%	-31.3%
Male versus female sex on km	0.145	29.1%	15.6%
ERA comedication on km	0.186	34.8%	20.5%
PDE-5i comedication on km	0.0495	116%	5.07%
ERA+PDE-5i comedication on km	0.368	15.3%	44.5%
IIV ka	0.180	3.27%	44.4%
IIV kmet	0 (fix)	-	-
IIV CL	0.648	3.02%	95.5%
IIV Vp	0.125	3.05%	36.5%
IIV k12	0.194	3.22%	46.2%

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IIV k21	1.24	3.15%	156%
IIV km	0.0726	3.06%	27.4%
IIV k34	0.0977	3.13%	32.0%
IIV k43	0.657	3.2%	96.4%
IIV Vm	0.00849	3.06%	9.24%
IIV Tlag	3.13	3.17%	-
Residual error selexipag	0.694	4.28%	69.5%
Residual error JNJ-68006861	0.455	3.62%	45.5%

Abbreviations:
CL = apparent selexipag clearance via other routes; ERA = endothelin receptor antagonist; h = hours; IIV = interindividual variability; ka = first-order absorption rate constant; km = first-order rate constant of elimination for JNJ-68006861; kmet = selexipag first-order metabolic rate constant resulting in formation of JNJ-68006861; k12 = first-order rate constant from central to peripheral compartment for selexipag; k21 = first-order rate constant from peripheral to central compartment for selexipag; k34 = first-order rate constant from central to peripheral compartment for JNJ-68006861; k43 = first-order rate constant from peripheral to central compartment for JNJ-68006861; NONMEM = nonlinear mixed-effects modeling; PDE-5i = phosphodiesterase type-5 inhibitor; PK = pharmacokinetic(s); RSE = residual standard error; SE = standard error; Tlag = absorption lag-time; Vm = volume of distribution of JNJ-68006861 central compartment; Vp = volume of distribution of selexipag central compartment.

Footnotes:

[a] Calculated as SE×100 for parameters from ka to Tlag, SE/estimate×100 for covariate parameters, IIV and residual error variances.

[b] Transformed estimates shown in relative percentage scale and calculated as follows: for the covariate effects of male versus female sex, ERA, PDE-5i, and ERA+PDE-5i comedication on km: 100×(exp(estimate)-1) where estimate represents the untransformed estimate as returned by NONMEM; for the covariate effects of body weight on CL, Vp, and Vm: $100\times(0.5^{estimate-1})$ (ie, halving of body weight compared with the reference body weight of 70 kg); for the covariate effect of total bilirubin on CL: $100\times(0.5^{estimate-1})$ (ie, halving of total bilirubin compared with the reference total bilirubin of 10 µmol/L); for the IIV of log-normally distributed parameters (ie, all parameters except Tlag), 100×sqrt(exp(var)-1), where var represents the variance estimate as returned by NONMEM; for residual error, 100×sqrt(var), where var represents the variance estimate as returned by NONMEM.

Source: Reproduced by Reviewer

The popPK model adequately characterized the PK of selexipag and JNJ-68006861 in pediatric patients aged 2 to < 18 years based on overall goodness-of-fit and prediction-corrected visual predictive check (pc-VPC) plots. No clear differences in model fit were observed with goodness of fit across bodyweight category (≥9 to < 25 kg, ≥25 to < 50kg and ≥50kg; see **Figure 8**). The pc-VPC plots indicate that the 10th, 50th and 90thpercentiles of the observed and predicted concentrations appear in alignment, further showing the model captures both the central tendency and the magnitude of the variability of the observed data (**Figure 9**).

The final pediatric popPK model was utilized to simulate PK exposures across the bodyweight range of 9–100 kg based on the (b) (4) bodyweight-based dosing regimen. The simulated exposures were predominantly contained within the 90% prediction interval (**Figure 1**), confirming model adequacy. Additionally, the central tendency (median) and variability (90% prediction interval) of the simulated exposures were consistent with those observed in the

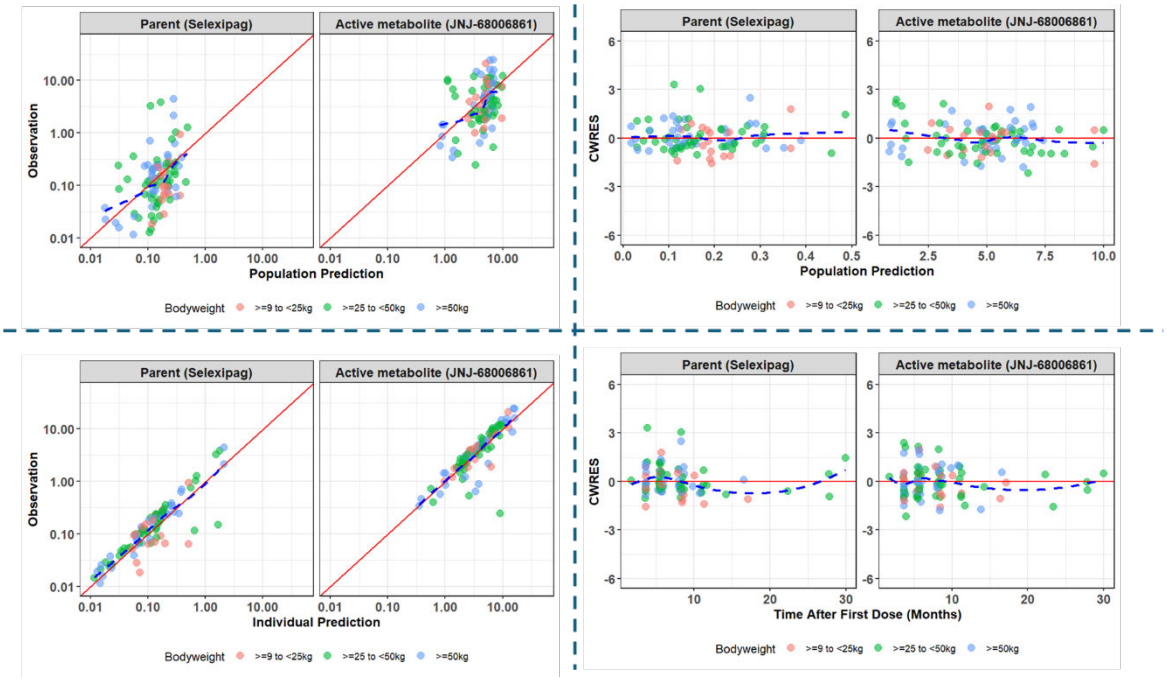
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GRIPHON study, supporting the appropriateness of the [redacted] (b) (4) bodyweight-based dosing strategy.

Conclusions

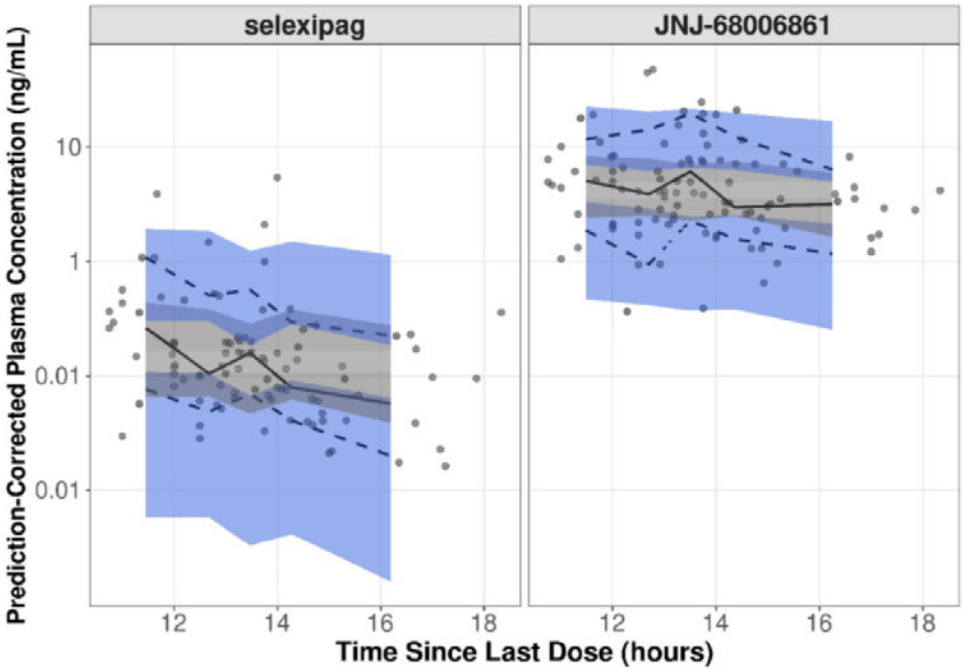
The pharmacometric evaluation did not identify any exposure-based safety or efficacy concerns regarding the [redacted] (b) (4) selexipag starting doses or dose titration strategy for the intended pediatric indication.

Figure 8. Goodness-Of-Fit plots of PopPK model for selexipag and JNJ-68006861



Source: Reviewer's Analysis

Figure 9. Prediction-Corrected Visual Predictive Check for selexipag and JNJ-68006861



The pcVPC shows the 95% CI for: 10th, 50th, and 90th percentiles of prediction-corrected concentrations for simulated data (shaded areas) and 10th, 50th, and 90th quantiles of measured concentrations (black continuous lines).

Source: Applicant's Population Pharmacokinetics and Exposure-response Report (EDMS-RIM-1459522, 3.0), Figure 17, Page 59

4.3 Assessment of Applicant's Exposure-Response Analyses

Review Summary

The Applicant explored the exposure-response (E-R) analysis to characterize the relationship between combined $AUC_{\tau,ss}$ at individual maximum tolerated dose (iMTD) as exposure metric and change from baseline in NT-proBNP as a response biomarker for patients with PAH. The analysis showed a negative E-R relationship in a subgroup of patients with elevated-baseline NT-proBNP (≥300 ng/L) but not in those patients with non-elevated NT-proBNP (<300 ng/L) at baseline.

The OCP review team investigated if a similar E-R relationship was observed in adults and additionally requested the Applicant to compare the E-R relationship between pediatric and adult patients. According to the Applicant's response, the E-R relationships were consistence between pediatrics and adults in both elevated (≥300 ng/L) and non-elevated (< 300ng/L) baseline NT-proBNP subgroups as the slopes of E-R relationship in adults and pediatric appear similar. The review team agrees that the E-R relationship exists, furthermore, the team also believes that the observed relationship is likely to exist regardless of baseline NT-proBNP level.

The E-R relationship between $AUC_{\tau,ss,\ combined}$ at iMTD and NT-proBNP changes from baseline was explored in pediatric patients aged ≥2 to <18 years with PAH using pooled data from studies AC-065A203 (Phase 2) and SALTO/AC-065A310 (Phase 3). The analytical approach incorporated baseline stratification of the participants into two distinct subgroups based on established pediatric risk stratification guidelines. The pediatric patients were categorized into elevated-baseline (NT-proBNP ≥300 ng/L) and non-elevated-baseline (NT-proBNP <300 ng/L) subgroups.

Linear mixed-effects modeling approach was used to explore the relationship assuming constant NT-proBNP change from baseline over time with $AUC_{\tau,ss,\ combined}$ at iMTD as the exposure metric . NT-proBNP change from baseline (log2-transformed) was modeled with a linear E-R relationship (slope × $AUC_{\tau,ss,combined,\ iMTD}$). Separate intercepts and slopes were estimated for elevated- and non-elevated-baseline NT proBNP subgroups. According to the previous adult study (GRIPHON), the minimal clinically relevant reduction was defined as ≥22% placebo-corrected NT-proBNP reduction. The model parameter estimates are presented in **Table 9**. The E-R linear model relationship was evaluated by visual inspection of diagnostic GoF and VPC scatterplot. **Figure 10** shows GoF plot of the model.

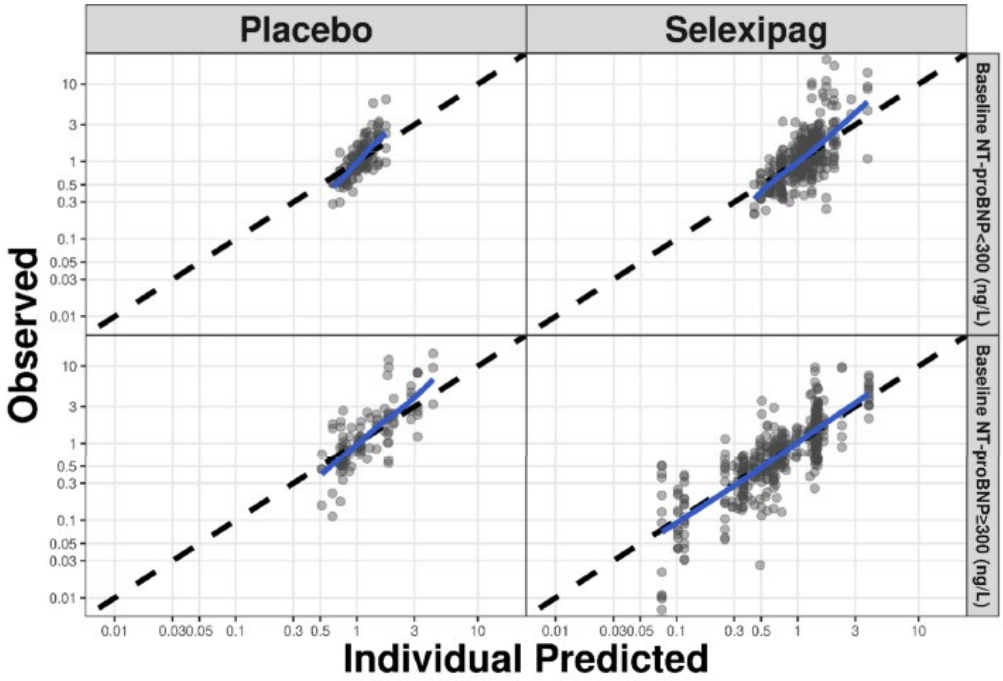
Table 9. NT-proBNP E-R Model Parameter Estimates

Parameter	Estimate (95% CI)	RSE (%)
Intercept, elevated-baseline	0.218 (-0.120, 0.557)	79.1
Intercept, non-elevated-baseline	0.0849 (-0.0767, 0.246)	97.1
Difference between slopes for elevated- and non-elevated-baselines (ng*h /mL)	-0.00487 (-0.00851, -0.00123)	38.2
Slope, elevated-baseline (ng*h/mL)	-0.00422 (-0.00702, -0.00142)	33.8
Slope, non-elevated-baseline (ng*h/mL)	0.000647 (-0.00168, 0.00297)	183
IIV intercept, elevated-baseline	0.738	29.3
IIV intercept, non-elevated-baseline	0.212	37.1
IIV slope	1.75e-05	57.9
Sigma, elevated-baseline	99.7	6.61
Sigma, non-elevated-baseline	76.0	6.75

CI = confidence interval; CV = coefficient of variation; E-R = exposure-response; IIV = interindividual variability; NT-proBNP = N-terminal pro-type natriuretic peptide; RSE = residual standard error
Data were analyzed on a log2 scale. Sigmas are reported as percentage of CV
Elevated-baseline refers to NT-proBNP ≥300 ng/L and non-elevated-baseline refers to NT-proBNP <300 ng/L

Source: Reviewer's Analysis

Figure 10. Goodness-of-fit Plot of Showing Observed Versus Individual Model Predicted NT-proBNP Change from Baseline



Source: Applicant's Population Pharmacokinetics and Exposure-response Report (EDMS-RIM-1459522, 3.0), Figure 34, Page 78.

An additional exposure-response (E-R) analysis was performed to evaluate whether the relationship between $AUC_{T,ss,\ combined}$ and NT-proBNP changes is comparable between pediatric and adult patients.

Key E-R findings

The E-R relationship between drug exposure and NT-proBNP changes appears fundamentally similar between pediatric and adult populations (**Figure 3**). In pediatric patients with elevated baseline NT-proBNP levels (≥300 ng/L), a statistically significant E-R relationship was identified. The analysis revealed a slope of -0.00422 ng*h/ mL (95% CI: -0.00702 to -0.00142) (**Table 9**). The geometric mean $AUC_{T,ss,\ combined}$ of 88.4 ng*h/mL was associated with a 22.8% placebo-corrected NT-proBNP reduction, which was marginally above the predefined minimal clinically relevant reduction threshold of 22%. However, pediatric patients with non-elevated baseline NT-proBNP levels (< 300 ng/L) did not demonstrate a statistically significant E-R relationship. The slope was 0.000647 ng*h/mL (95% CI: -0.00168 to 0.00297).

The above finding was attributed to notable differences in the range of exposures observed between the elevated and non-elevated subgroups. Higher exposures were consistently observed in the elevated compared to the non-elevated subgroup, with a geometric mean ratio of 1.58 (90% CI: 1.30-1.92). The exposure differences were explained by several factors, including a higher proportion of participants in the elevated-baseline group who were up-titrated to higher individual maximal tolerated doses. Additionally, an imbalance in intrinsic clearance factors was observed, specifically lower bodyweight and higher total bilirubin concentrations in

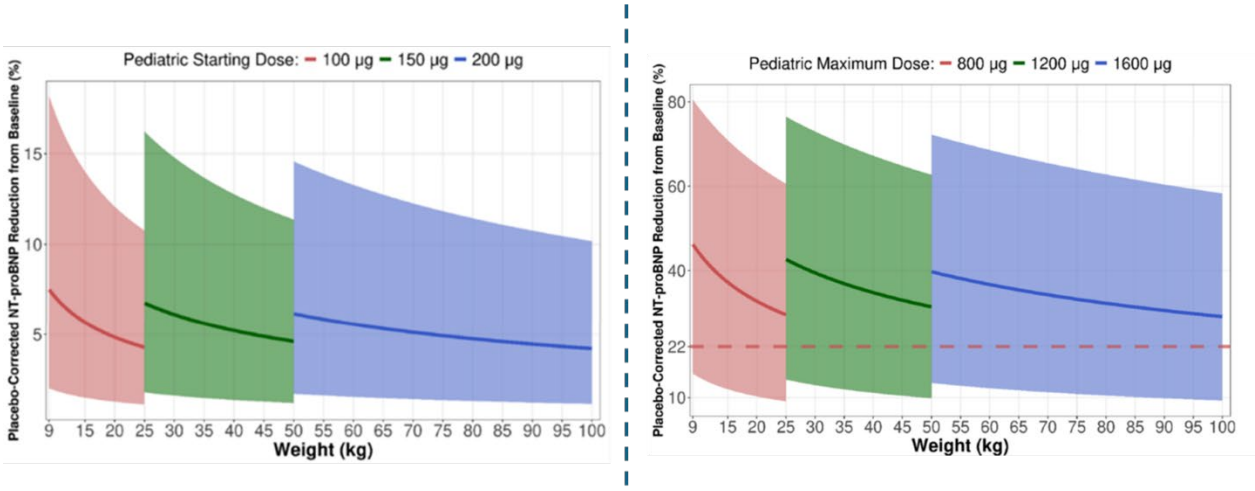
the elevated subgroup. Importantly, no inherent difference in drug clearance was identified between groups when adjustments were made for these confounding factors.

The [redacted] (b) (4) weight-based starting dose and titration regimen demonstrated consistent efficacy across different bodyweight categories. Similar placebo-corrected NT-proBNP reductions were achieved across weight categories of ≥9 to <25 kg, ≥25 to <50 kg, and ≥50 kg (**Figure 11**).

Conclusions

The review team generally agrees that the E-R model describes the observed data demonstrating a linear E-R relationship. A negative E-R relationship exists between $AUC_{T,SS,combined}$ at iMTD and NT-proBNP change from baseline in PAH patients, regardless of baseline NT-proBNP level. This E-R relationship is consistent between pediatric (≥2 to <18 years) and adult populations in both elevated (≥300 ng/L) and non-elevated (<300 ng/L) baseline subgroups. The [redacted] (b) (4) weight-based starting dose and titration regimen demonstrated consistent placebo-corrected NT-proBNP reductions across all bodyweight categories (≥9 to <25 kg, ≥25 to <50 kg, and ≥50 kg).

Figure 11. Model-Predicted NT-proBNP Reduction from Baseline by Body Weight at Starting Dose (Left-panel) and Maximum Dose (Right-panel)



Source: Applicant's Population Pharmacokinetics and Exposure-response Report (EDMS-RIM-1459522, 3.0), Figure 32 & 32, Page 76-7.

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NORA LEE
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ABIY H EYAKEM
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VISHNU D SHARMA
02/03/2026 11:44:12 AM

ELLY Y MOON
02/03/2026 11:47:15 AM