U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 207947
Supplement #:	#14
Drug Name:	Uptravi ® (Selexipag)
Indication(s):	Reduction of NT-proBNP and expected delay in disease progression and reduction of the risk of hospitalization for pediatric patients aged 2 years and older with Pulmonary Arterial Hypertension (PAH)
Applicant:	Actelion Pharmaceuticals US, Inc.
Date(s):	Submission date: July 31, 2025 PDUFA due date: January 31, 2026
Review Priority:	6-month review period for Pediatric Written Request
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Table of Contents

1 EXECUTIVE SUMMARY 5

2 INTRODUCTION 7

2.1 OVERVIEW 7
2.2 DATA SOURCES 7

3 STATISTICAL EVALUATION 8

3.1 DATA AND ANALYSIS QUALITY 8
3.2 EVALUATION OF EFFICACY 8
3.2.1 Study Design and Endpoints 8
3.2.2 Statistical Methodologies 9
3.2.3 Patient Disposition, Demographic and Baseline Characteristics 10
3.2.4 Results and Conclusions 11

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 17

4.1 RACE, AGE, AND GEOGRAPHIC REGION 17
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 19

5 SUMMARY AND CONCLUSIONS 20

5.1 STATISTICAL ISSUES 20
5.2 COLLECTIVE EVIDENCE 20
5.3 CONCLUSIONS AND RECOMMENDATIONS 21
5.4 LABELING RECOMMENDATIONS (AS APPLICABLE) 21

APPENDICES (ADD WHEN NEEDED) 22

Reference ID: 5737060

LIST OF TABLES

Table 1: List of all studies included in analysis
Table 2: Patient Disposition for the Double-Blind Study (AC-065A310) (Full Analysis Set)
Table 3: Patient Demographics and Baseline Characteristics (FAS) for SALTO study
Table 4: Main Analysis on NT-proBNP

Reference ID: 5737060

LIST OF FIGURES

Figure 1. Applicant Created Schematic Overview of Study AC-065A310 (SALTO)
Figure 2. Comparison of treatment effects for various datasets
Figure 3. KM plot of time to first CEC-confirmed disease progression event
Figure 4. KM plot of time to first CEC-confirmed hospitalization for PAH or death due to PAH
Figure 5. Forest plot of subgroup analyses

Reference ID: 5737060

1 EXECUTIVE SUMMARY

On 31 July 2025, the Applicant, Actelion Pharmaceuticals submitted a supplemental NDA to support a pediatric indication to assess the efficacy and safety of selexipag as add-on treatment to standard of care in children with Pulmonary Arterial Hypertension (PAH). The application included three pediatric studies in children with Pulmonary Arterial Hypertension (PAH): AC-065A310 (referred to as SALTO), AC-065A203 phase 2 study, and NS304P-P2-1 phase 2 study. SALTO is a randomized, double-blind pivotal Phase 3 study (n=138), with an ongoing open-label extension period. AC-065A203 is an ongoing open-label, single-arm Phase 2 study (n=63) and NS304P-P2-1 is an open-label, single-arm Phase 2 study done in Japan (n=6). Given the limitations of AC-065A203 and NS304P-P2-1 (single arm, small sample size), the focus of this review will be on the SALTO study results.

SALTO was originally designed as an event-driven study with a primary endpoint of time to first CEC-confirmed disease progression event. Due to the lower than anticipated event rates, the Agency agreed to elevate NT-proBNP from an exploratory endpoint to a secondary endpoint that could be used as a bridging biomarker for pediatric extrapolation of efficacy from the adult GRIPHON study upon which the original approval was based (Type A Meeting 2 November 2022).

The adjusted geometric mean ratio (GMR) comparing selexipag to placebo for NT-proBNP levels from baseline to Week 24 was 0.93 (95% confidence interval: 0.71, 1.21), with a p-value of 0.575. This estimated GMR had noticeably less reduction than the 0.78 (with common standard deviation of 1) assumed in the sample size calculation, and less than the estimated GMR of 0.8 (95% CI: 0.73, 0.88) in adult patients with PAH in the GRIPHON study. Based on the pre-specified NT-proBNP analyses in the full SALTO population, selexipag failed to demonstrate a treatment effect in pediatric patients

In the submission, the Applicant flagged that there was a "low proportion of study participants with elevated NT-proBNP or reasonably detectable level at baseline." In order to have adequate equipoise for pediatric patients, all participants had to be on stable PAH therapy prior to enrollment and were heavily pretreated (Table 3). The Applicant makes the argument that "…the effectiveness of these standard of care therapies in the pediatric population resulted in a lowering of NT-proBNP levels in many patients enrolled in the SALTO study. Consequently, the absolute treatment effect of selexipag on NT-proBNP may have been too limited, given variations in baseline values to confirm the target treatment effect in SALTO, falling below the sensitivity of the extrapolation framework when considering only 1 study." While these are valid points that could have attenuated the treatment effect in the SALTO study population, these should have been brought up and addressed a priori when the Applicant reached agreement with the Agency on using an NT-proBNP bridging endpoint in lieu of the primary outcomes endpoint. Enrollment criteria (e.g., background medication) and baseline demographics for the enrolled patients would have been available at the time of the agreement. Relevant thresholds were not specified at the time of the amendment although the strong prognostic nature of baseline NT-proBNP was

Reference ID: 5737060

established at the time (Chin et al. 2019, Mauritz et al. 2011). Thus, it is difficult to consider further subgroup analyses based on NT-proBNP thresholds as anything but exploratory.

Given the debilitating nature of this disease and unmet medical for pediatric patients, and factoring in that this was a well-run study, further analyses were done adjust for differences in underlying baseline characteristics between the adult GRIPHON population and pediatric SALTO population. Interpretation of these results relies on the strong underlying assumption that treatment effects for NT-proBNP seen in the pediatric PAH population would be similar in a matching adult PAH population. Please see the clinical review by Dr. Ji and Dr. Garnett for clinical rationale on this assumption. Results from the matched exploratory analysis did not conclude with estimates from the adult study that aligned with the pediatric study (section 3.2.4.1, Figure 2). Thus, we were unable to draw supportive evidence from this exploratory analysis.

Even allowing for flexibility using NT-proBNP results from the SALTO study instead of the primary endpoint of disease progression outcome to establish efficacy, the statistical team cannot conclude that efficacy has been established in the pediatric study. Thus, the statistical team does not recommend that a pediatric claim be given based on results in this submission.

Reference ID: 5737060

2 INTRODUCTION

2.1 Overview

The purpose of this submission is to support the fulfillment of the written request (WR) issued under the Best Pharmaceuticals for Children Act (BPCA) dated July 30, 2025. The Applicant considered the data generated from the double-blind treatment period of the placebo-controlled Phase 3 pediatric SALTO study (study ID # AC-065A310), in conjunction with two phase 2 studies (AC-065A203 (A203) in pediatrics and Japanese pediatric study NS304P-P2-1), meets the objectives of the Written Request. This review mainly focuses on the SALTO study.

SALTO was a randomized, multicenter, double-blind (DB), placebo-controlled, parallel group, phase 3 study with an open-label extension period to assess the efficacy and safety of selexipag as add-on treatment to standard of care in children with Pulmonary Arterial Hypertension (PAH). The participants were ≥2 years old and randomized in a 1:1 ratio to either receive selexipag or placebo. Randomization was stratified by WHO Function Class (FC) (II vs III) and for presence of background PAH-specific medication (monotherapy vs combination therapy) at baseline. The study consists of a screening period of up to 6 weeks and a DB treatment period, including up-titration and maintenance periods, followed by a 3-year open-label extension period, and a 30-day safety follow-up period.

A high-level summary of the results for the DB period is shown in Table 1. Note: based on discussions with the Agency, the outcomes for both the primary endpoint (Time to confirmed disease progression) and the secondary endpoint (Time to confirmed hospitalization or death for PAH) were considered exploratory (b) (4).

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
AC-065a310	*Phase 3*	*24 weeks (this is an interim analysis of the study)*	*Still ongoing*	*N=69 in Selexipag arm and N=69 in Placebo arm*	*Children Aged ≥2 to <18 years with Pulmonary Arterial Hypertension*

Source: Reviewer's Table

2.2 Data Sources

The pediatric study data used for this review is located at:
\\CDSESUB1\evsprod\NDA207947\0446\m5\datasets\ac-065a310\analysis\adam\datasets

The review also used NT-proBNP data from the adult trial GRIPHON, which can be found at:
\\CDSESUB1\evsprod\NDA207947\0000\m5\datasets\ac-065a302\analysis\adam\datasets

Reference ID: 5737060

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

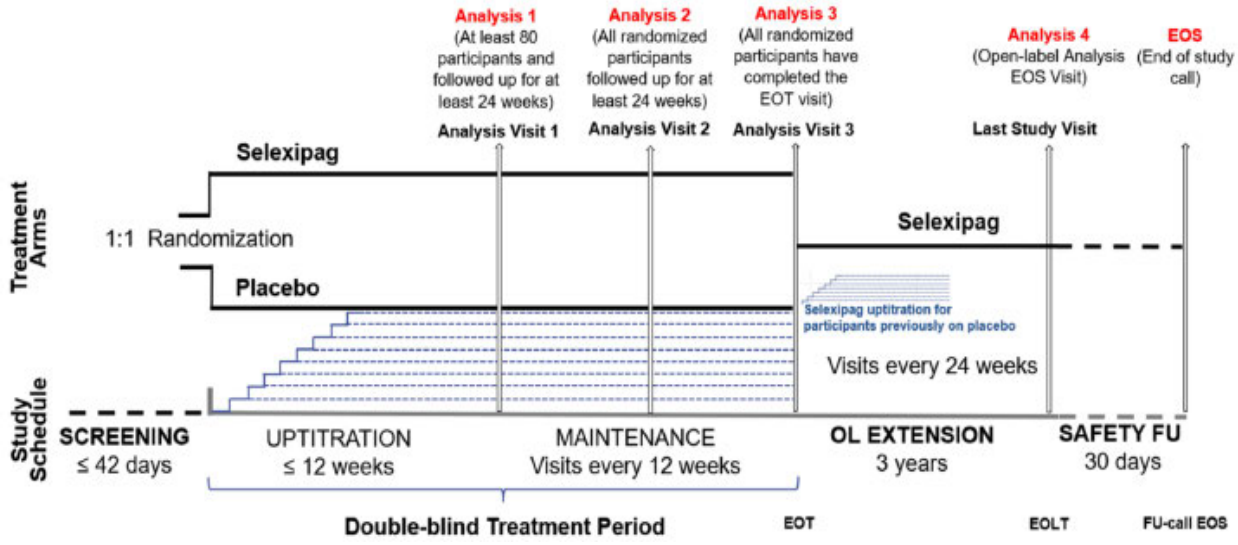
The statistical reviewer was able to reproduce the results from main analyses conducted by the Applicant. The largest site enrolled <10 full analysis set (FAS) subjects. No single site drives the overall results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study AC-065A310 is an ongoing randomized, multicenter, DB, placebo-controlled, parallel-group study with an OLEP to assess the efficacy and safety of selexipag as add-on treatment to standard of care in children ≥2 to <18 years of age with Group 1 PAH, with a severity of WHO FC II or III. Participants were randomized in a 1:1 ratio to either selexipag or placebo, stratified by WHO FC (II vs III) and for presence of background PAH-specific treatment (monotherapy vs combination therapy) at baseline. The study design is depicted in Figure 1. The study consists of a screening period of up to 6 weeks and a DB treatment period, including up-titration and maintenance periods, followed by a 3-year open-label extension period, and a 30-day safety follow-up period.

Figure 1. Applicant Created Schematic Overview of Study AC-065A310 (SALTO):



Source: Figure 1 in Applicant's clinical study report

Reference ID: 5737060

The primary endpoint is time to CEC-confirmed disease progression from randomization up to 7 days after study treatment discontinuation. The key secondary endpoint is change in log2(NT-proBNP) from baseline to week 24. The Applicant's clinical study report and this review mainly focused on the NT-proBNP change from baseline to week 24.

This study was originally designed as an event-driven group sequential study to evaluate the primary time to disease progression endpoint. However, by 2022, the SALTO trial faced significant recruitment challenges and a lower-than-anticipated event rate, making its original event-driven primary endpoint difficult to achieve. In a November 2022 Type A meeting, the Agency agreed to the use of NT-proBNP as a bridging biomarker for pediatric extrapolation. The protocol was amended to elevate change in NT-proBNP at week 24 from exploratory to a secondary endpoint which would be used as the primary source of evidence for efficacy for the Agency review.

Sample Size Determination
In the Statistical Analysis Plan (SAP), a sample size of 125 was chosen to allow for the detection of a critical geometric mean ratio target of ≤0.78 and common standard deviation of 1 for NT-proBNP between selexipag and control arms, for 80% power at 2-sided type I error rate 0.05.

3.2.2 Statistical Methodologies for Efficacy Analyses

Primary endpoint analysis

The primary endpoint, time (in days) from randomization to the first CEC-confirmed disease progression event up to DBED + 7 days/OL Day 1, was analyzed via unstratified Cox proportional hazards model on FAS. Model covariates include treatment and Interactive Web Response System (IWRS) stratification factors at randomization [WHO FC (II, III) and the number of PAH-specific therapies (monotherapy vs. combination therapy)]. The results were presented as estimated Hazards Ratio (HR) of selexipag versus placebo, with 95% confidence interval. Additionally, time to disease progression was descriptively summarized with Kaplan-Meier (KM) estimates.

Secondary endpoint analyses

NT-proBNP:
The key secondary efficacy endpoint, change from baseline in $\log_2$(NT-proBNP) at week 24, was analyzed using ANCOVA. Model covariates included intervention group, randomization stratification factors [WHO FC (II, III) and PAH-specific therapy (monotherapy vs. combination therapy)], and baseline NT-proBNP. The between-arm ratio of geometric means with corresponding 2-sided 95% Confidence Interval (CI) and p-value will be displayed as the placebo-corrected treatment effect.

Reference ID: 5737060

Subgroup analyses were conducted for NT-proBNP as that was the endpoint meant to support efficacy. No sensitivity analyses were prespecified or conducted.

Handling of Missing Data:
Multiple imputation (MI) was used to handle missing NT-proBNP values under a missing at random (MAR) assumption, with a modification for selexipag participants who discontinued due to disease progression. For participants with CEC-confirmed disease progression before week 24 and missing week 24 NT-proBNP assessments, the imputation assumes their trajectory resembles placebo participants rather than their original treatment arm, treating these cases as missing not at random (MNAR). All other dropouts will follow standard MAR imputation.

The imputation will proceed in two steps using $\log_2$-transformed NT-proBNP values. First, missing week 16 values were imputed using Markov Chain Monte Carlo (MCMC) with monotone regression (SAS PROC MI), generating 100 partially completed datasets. The imputation model includes treatment arm, $\log_2$-transformed baseline NT-proBNP, and randomization stratification variables. Second, missing week 24 values will be imputed using sequential regression (MONOTONE REG option in SAS PROC MI).

For MNAR imputation of selexipag participants who discontinued due to disease progression, missing values at time t used only placebo observations through time t plus selexipag disease progression dropouts through time t-1. Treatment arm will be excluded from the imputation model for these cases. Each of the 100 completed datasets will be analyzed individually, with results aggregated using Rubin's rules via SAS PROC MIANALYZE.

Time to First CEC-confirmed Hospitalization for PAH or Death Due to PAH:
The secondary endpoint of first CEC-confirmed Death or Hospitalization due to PAH event is defined as the earlier of: death due to PAH or PAH-related hospitalization occurring from randomization until DBED + 7 days/OL Day 1. This endpoint was analyzed via unstratified Cox proportional hazards model on the full analysis set. Model covariates include treatment and IWRS stratification factors at randomization (WHO FC (II, III) and the number of PAH-specific therapies (monotherapy vs. combination therapy)). The results were presented as estimated HR of selexipag versus placebo, with 95% CI. Additionally, time to disease progression was descriptively summarized with Kaplan-Meier estimates.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

There were 138 patients who were randomized and received at least one dose of study drug. The FAS included 138 patients (Table 2). A similar number of participants prematurely discontinued study intervention in both treatment arms (25 in placebo vs. 26 in selexipag), however more participants in the selexipag arm discontinued before or on week 24 (11.6% in selexipag vs 4.3% in placebo). The OLE phase of the study is still ongoing.

Reference ID: 5737060

Table 2: Patient Disposition for the Double-Blind Study (AC-065A310) (Full Analysis Set)

Category	**Placebo**	**Selexipag**	**Total**
Analysis set: Full	69	69	138
Participants treated with study treatment	69 (100.0%)	69 (100.0%)	138 (100.0%)
Participants who completed DB study treatment	44 (63.8%)	43 (62.3%)	87 (63.0%)
Participants who prematurely discontinued DB study treatment	25 (36.2%)	26 (37.7%)	51 (37.0%)
COVID-19-related	0	0	0
Reason for discontinuation of DB study treatment			
Progressive Disease	16 (23.2%)	8 (11.6%)	24 (17.4%)
Death	5 (7.2%)	8 (11.6%)	13 (9.4%)
Withdrawal by Subject	1 (1.4%)	4 (5.8%)	5 (3.6%)
Initiated Prohibited Medication	1 (1.4%)	2 (2.9%)	3 (2.2%)
Withdrawal by Parent or Guardian	1 (1.4%)	1 (1.4%)	2 (1.4%)
Lost To Follow-up	0	1 (1.4%)	1 (0.7%)
Physician Decision	0	1 (1.4%)	1 (0.7%)
Subject Refused Further Study Treatment	1 (1.4%)	0	1 (0.7%)
Other	0	1 (1.4%)	1 (0.7%)
Participants who prematurely discontinued DB study treatment before or on Week 24	3 (4.3%)	8 (11.6%)	11 (8.0%)
COVID-19-related	0	0	0
Reason for discontinuation of DB study treatment before or on Week 24			
Progressive Disease	3 (4.3%)	3 (4.3%)	6 (4.3%)
Death	0	1 (1.4%)	1 (0.7%)
Initiated Prohibited Medication	0	1 (1.4%)	1 (0.7%)
Withdrawal by Parent or Guardian	0	1 (1.4%)	1 (0.7%)
Withdrawal by Subject	0	1 (1.4%)	1 (0.7%)
Other	0	1 (1.4%)	1 (0.7%)

Source: Statistical Reviewer Analysis; adsl.xpt, addisp.xpt

Demographic and baseline characteristics are listed in Table 3. Generally, characteristics were balanced between the two arms but selexipag had fewer Asian patients (33.3%) and more White patients (55.1%) than in the placebo. More selexipag-treated participants had a baseline weight ≥50 kg (31.9% vs 24.6% in placebo).

Reference ID: 5737060

Table 3: Patient Demographics and Baseline Characteristics (FAS) for SALTO study

Category	Placebo N=69	Selexipag N=69
Sex, n (%)		
Female	32 (46.4)	35 (50.7)
Male	37 (53.6)	34 (49.3)
Age		
Mean (SD)	11.1 (3.54)	11.6 (3.76)
Pooled Age Group 1, n (%)		
>=12 to <18 years	35 (50.7)	36 (52.2)
>=2 to <6 years	6 (8.7)	5 (7.2)
>=6 to <12 years	28 (40.6)	28 (40.6)
Race, n (%)		
American Indian or Alaska Native	2 (2.9)	2 (2.9)
Asian	32 (46.4)	23 (33.3)
Black or African American	0	3 (4.3)
Multiple	2 (2.9)	1 (1.4)
Not Reported	2 (2.9)	2 (2.9)
White	31 (44.9)	38 (55.1)
Geographic Region 2, n (%)		
Asia	32 (46.4)	22 (31.9)
Eastern Europe	11 (15.9)	19 (27.5)
Latin America	13 (18.8)	11 (15.9)
North America and Western Europe	13 (18.8)	17 (24.6)
WHO FC, n (%)		
II	53 (76.8)	54 (78.3)
III	16 (23.2)	15 (21.7)
BMI		
Mean (SD)	18.1 (4.60)	18.7 (4.67)
Weight (kg) at Baseline Group 1, n (%)		
>=25 to <50 kg	36 (52.2)	34 (49.3)
>=50 kg	17 (24.6)	22 (31.9)
>=9 to <25 kg	16 (23.2)	13 (18.8)
NT-proBNP at Baseline		
Mean (SD)	787.4 (2366.74)	756.0 (1456.17)
Grouped NT-proBNP at Baseline, n (%)		
BNP BL<300	43 (62.3)	43 (62.3)
BNP_BL>=300	26 (37.7)	25 (36.2)
Missing	0	1 (1.4)
PAH specific therapy, n (%)		
Combination Therapy	52 (75.4)	53 (76.8)
Monotherapy	17 (24.6)	16 (23.2)

Reference ID: 5737060

Category	Placebo N=69	Selexipag N=69
PAH etiology, n (%)		
CHD post-operative	19 (27.5)	21 (30.4)
Idiopathic PAH, Heritable PAH, PAH associated with HIV infection, Drug- and toxin-induced PAH, PAH with coincidental CHD	50 (72.5)	48 (69.6)

Abbreviations: FAS=full analysis set, SD = standard deviation
Source: Statistical Reviewer Analysis; adsl.xpt adbdc.xpt

Note: WHO FC and PAH-specific therapy classifications are based on the Interactive Web Response System (IWRS) definitions that serve as stratification factors at randomization and are used for data analyses throughout the study. However, the baseline characteristic summary in Table 6 of the applicant's clinical study report (CSR) and the information for these two factors in the labeling the Applicant provided were based on the electronic case report form (eCRF) data. For the summary of these two factors, there is a discrepancy between the eCRF data and the IWRS data: one participant discrepancy for the WHO FC and two participant discrepancy for the PAH specific therapy. According to the Applicant's response to the Information Request dated January 8, 2026, the discrepancy is due to the eCRF being revised after receiving a response to queries, but the IWRS data were not revised. Analyses in this review were done using the IWRS specifications. Given the small discrepancies, differences in analysis results would be minimal and would not alter the conclusions.

3.2.4 Results and Conclusions

3.2.4.1 Analyses for NT-proBNP:

The missing data rate for NT-proBNP was 10.1% in the SALTO trial. Using the pre-specified multiple imputation with the ANCOVA model, the adjusted geometric mean ratio (GMR) for NT-proBNP was 0.93 (95% CI: 0.71, 1.21) (Table 4). NT-proBNP decreased slightly from baseline in the selexipag arm, while it increased slightly in the placebo arm. However, the between-arm comparison was not statistically significant (p-value = 0.575).

Table 4: Main Analysis on NT-proBNP

	Selexipag (N=69)	Placebo (N=69)
Geometric Mean (Wk24/Baseline) (95% CI)	0.98 (0.78, 1.22)	1.05 (0.85, 1.31)
Geometric Mean (Wk24/Baseline) ratio: Selexipag/Placebo (95% CI)	0.93 (0.71, 1.21)	
p-value	0.575	

* Geometric mean and geometric mean ratio are covariate-adjusted. CI: confidence interval.
Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt

Reference ID: 5737060

Supplementary Analyses:
Since results for the pre-specified NT-proBNP failed to show statistical significance, no sensitivity analyses were run. Given the evidence seen in the adult GRIPHON study population, and the feasibility issues of running a clinical trial in the pediatric PAH population, along with the clinical argument that extrapolation of adult data to pediatrics is reasonable, further supplementary analyses were run. These analyses rely on the strong clinical assumption that effects seen in the adult population can be reasonably extrapolated to the pediatric population.

Re-evaluation of the Adult Trial (GRIPHON) Using a Propensity Score Approach

In the selexipag program, the adult GRIPHON study provided evidence supporting NT-proBNP as a meaningful bridging biomarker. Exploratory analyses indicated that changes in NT-proBNP explained a substantial portion (58%) of the treatment effect on important clinical outcomes (refer to the meeting minutes of Type A meeting on November 2, 2022).

Extrapolation of information from adult trials for pediatric studies can be justifiable when the disease, drug pharmacology, and response to treatment are similar (U.S. Food and Drug Administration "E11A Pediatric Extrapolation Guidance for Industry."). The amount of extrapolation from the adult population often depends on the comparability of the expected treatment effect in adults and the corresponding pediatric population.

The comparison in trial design between the pediatric SALTO trial and adult GRIPHON trial is shown in Appendix Table A1. There are 1,156 participants in the adult trial, vs 138 in the pediatric trial. The selection criteria for GRIPHON were different from those for SALTO: participants with WHO FC I or IV and participants without PAH-specific background therapy (naïve) were eligible for GRIPHON, but such participants were ineligible for SALTO. The most comparable visit to the week 24 NT-proBNP values in the SALTO study was at week 26 for the GRIPHON study.The comparison on demographic and baseline characteristics between the two studies is shown in Appendix Table A2. In the SALTO trial, the stratification factors are WHO FC (II and III), and PAH-specific background therapy (monotherapy vs combination). With respect to baseline WHO FC and PAH-specific background therapy, pediatric patients were much more tightly controlled to be at a better baseline (e.g., everyone on background therapy) so they would be healthy enough to be randomized to placebo.

To evaluate the similarity in response to treatment between the adult and pediatric populations despite the differences in baseline disease characteristics, we re-evaluated the adult study using a propensity score approach. This approach selects a subset of the adult population that has more similar baseline characteristics to the pediatric population. This approach was implemented by first filtering subjects from GRIPHON using the following SALTO based exclusion criteria: baseline WHO FC I or IV, absence of PAH-specific background therapy, or missing baseline NT-proBNP values. For this filtered GRIPHON dataset (containing 445 participants in the placebo arm and 454 in the selexipag arm), missing week 26 NT-proBNP values were imputed using the same multiple imputation (MI) approach applied to SALTO. The efficacy analysis results for NT-proBNP in this filtered dataset are presented in Appendix Table A3. For

Reference ID: 5737060

comparison, results for the full GRIPHON and SALTO datasets are also included in this table. Missing data rates for week 26 NT-proBNP were 24.1% in the GRIPHON trial and 23.3% in the filtered GRIPHON data. Additionally, the same ANCOVA model was applied to completers from these datasets (i.e., on those with observation thus no need for imputation), the results are shown in Appendix Table A4. Comparing results across these scenarios, we see that selexipag has a stronger effect on NT-proBNP for both the full [GMR (95% CI): 0.76 (0.68, 0.84)] and filtered [GMR (95% CI): 0.78 (0.70, 0.87)] GRIPHON datasets than what was seen in the SALTO completers [GMR (95% CI): 0.88 (0.68, 1.14)]. The effect size is smaller in datasets with multiple imputation (FDA preferred analysis) for the unfiltered [GMR (95% CI): 0.80 (0.73, 0.88)], filtered GRIPHON [GMR (95% CI): 0.83 (0.76, 0.92)], and primary NT-proBNP SALTO [GMR (95% CI): 0.93 (0.71, 1.21)] results, compared to using only the completers without imputation for missing data.

To further adjust for the strong prognostic differences between the studies, such as baseline NT-proBNP, we focused on exploratory results using the filtered GRIPHON. For simplicity, this is done without data imputation, while the FDA preferred method is using MI. It should be noted that these results are meant only as exploratory, and results would need to be appropriately discounted to reflect impacts from subjects who have missing NT-proBNP measurements who typically do not have the same outcomes as those with measurements. This is important to note as we do see impacts on the treatment effect when adjusting for missing data in the overall analyses for both studies (Appendix Tables A3 and A4). Additionally, all extrapolation for pediatrics using adult data implicitly assumes that treatment effects seen in the adult population will translate, in some degree, to the pediatric population. Please see the clinical review signed by Dr. Ji and Dr. Garnett for clinical rationale on extrapolation from the adult population and on how baseline NT-proBNP influences outcomes and should be matched when extrapolating from adult data. Hence, propensity score matching was applied to select a subset from the filtered GRIPHON data with similar characteristics and sample size to SALTO.

In the propensity score calculation, the baseline NT-proBNP, WHO Function Class, and PAH specific background therapy were included in the model. For this analysis, we used the assumption that the PAH-specific background therapies (combination and monotherapy) used in the filtered adult trial are similar to those used in the pediatric population in clinical practice. For simplicity, the filtered GRIPHON dataset is referred to as "GRIPHON" throughout the remainder of this analysis.

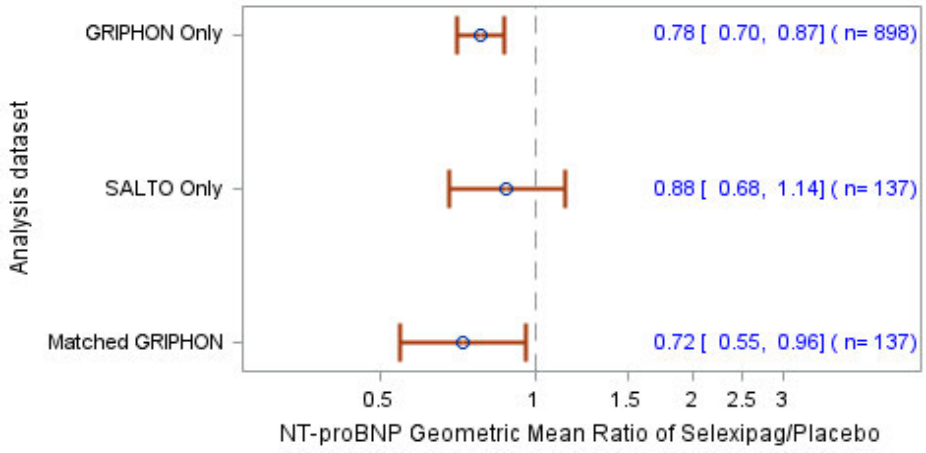
After matching, there were 137 subjects from the GRIPHON study in the matched cohort (70 in placebo and 67 in selexipag) based on the optimal matching approach (Austin 2014). For comparison, analysis results are presented in Figure 2 for the following datasets: GRIPHON only, SALTO only, the matched subset from GRIPHON. Balance checking was also performed for all the covariates included in the propensity score model. After propensity score matching, the standardized mean differences (SMD) for all covariates in the matched sample were <0.1 (see Table A5 in Appendix), suggesting good balance was achieved between trials (i.e., SALTO and matched GRIPHON).

Reference ID: 5737060

We expected that the matched GRIPHON cohort would have an estimated treatment effect that is more similar to the SALTO study than what was seen in the GRIPHON study. Surprisingly, estimated effects for NT-proBNP appear stronger in the matched GRIPHON cohort indicating that treatment effects could actually be stronger in an adult cohort that, at baseline, looked more like the pediatric SALTO population based on NT-proBNP, WHO function class, and background PAH therapies. Proportionally, the SALTO population had more subjects with lower NT-proBNP and more background combination therapy (see Appendix Table A2). If differences between these studies were only based on prognostic characteristics such as NT-proBNP and background therapy, then having a cohort that is better matched to the SALTO population on these characteristics (see Appendix Table A6) we would expect effects in the matched population to look more similar to that of the SALTO study results. Results from the matched analysis suggest that there are either

1) Further prognostic differences in these populations that should be adjusted for when using a matching approach, or
2) There are strong differences in how NT-proBNP behaves when using selexipag in adult vs. pediatric PAH populations.

Figure 2. Comparison of treatment effects based on completers analyses for various datasets



Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt
Note: n represents the number of participants with non-missing baseline NT-proBNP.

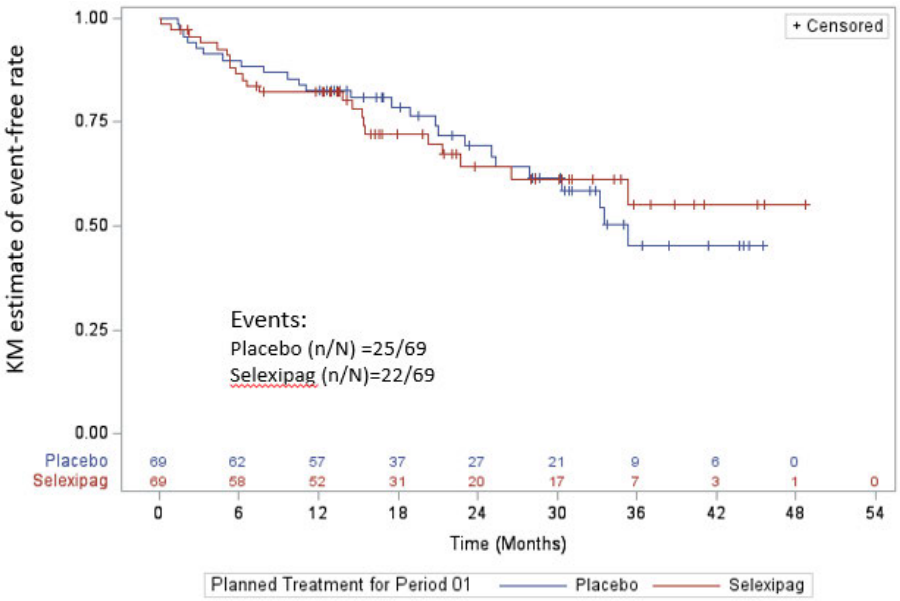
3.2.4.2 Analysis Result for Time to CEC-Confirmed Disease Progression

For the pre-specified primary time-to-event endpoint, 22 participants experienced a CEC-confirmed disease progression event in the selexipag arm and 25 participants with progression events in the placebo arm. The analysis of time to first progression event yielded an HR of 1.08 with a 95% confidence interval of (0.61, 1.93). Thus, selexipag failed to show evidence of any reduction in the time to progression events in pediatric PAH participants with trends that favored placebo. Based on earlier discussions before data unblinding, it was known that the study would

Reference ID: 5737060

be underpowered for this endpoint, thus it was agreed that regulatory evidence for efficacy would be based on results using the bridging biomarker NT-proBNP. This was supported by results in the literature (Chin et al. 2019) which showed baseline and follow-up NT-proBNP were highly prognostic for future morbidity/mortality events with selexipag. The Kapler-Meier (KM) plot of time to first CEC-confirmed disease progression event is shown in Figure 3.

Figure 3. KM plot of time to first CEC-confirmed disease progression event



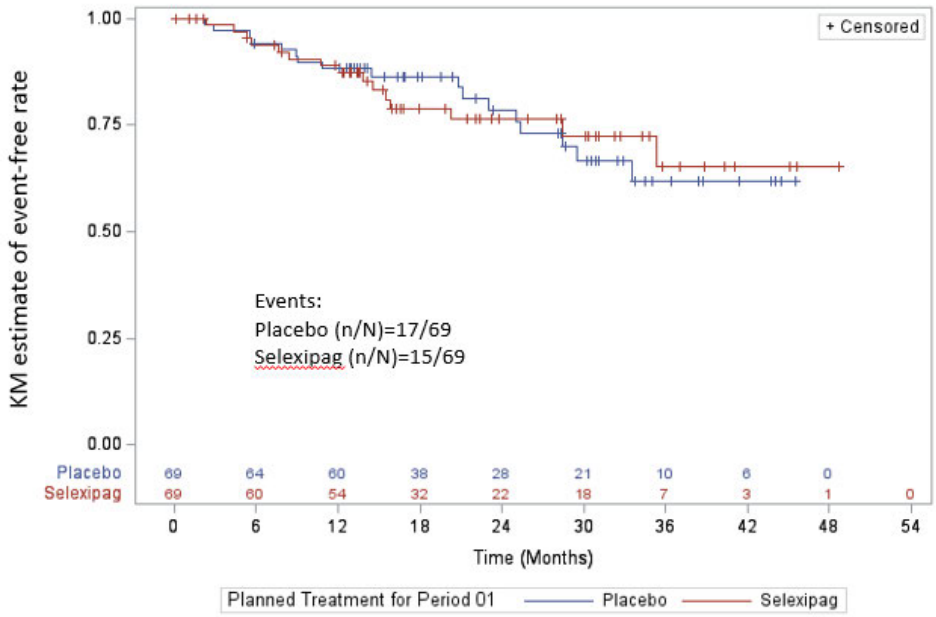
Source: Statistical Reviewer Analysis; adsl.xpt adtte.xpt

3.2.4.3 Analysis Result for Time to First CEC-confirmed Hospitalization for PAH or Death Due to PAH

For the pre-specified secondary time-to-event endpoint, 15 participants experienced a CEC-confirmed death or hospitalization due to PAH in the selexipag arm and 17 participants in the placebo arm. The analysis of time to first such event yielded an HR of 1.10 with a 95% confidence interval of (0.55, 2.21), which indicates that selexipag failed to show evidence of any reduction in the time to PAH events in pediatric PAH participants. The Kapler-Meier (KM) plot of time to first CEC-confirmed PAH event is shown in Figure 4. Components for this endpoint overlap with the primary outcome composite endpoint (i.e., both composites contain death due to PAH and PAH-related hospitalization), hence the similar resulting point estimates. Kaplan-Meier curves also indicate no difference between the arms and assumptions for the proportional odds assumption were not met.

Figure 4. KM plot of time to first CEC-confirmed hospitalization for PAH or death due to PAH

Reference ID: 5737060



Source: Statistical Reviewer Analysis; adsl.xpt adtte.xpt

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 [redacted], Race, Age, and Geographic Region

Subgroup analyses were conducted by [redacted] age groups, race, ethnicity, region, body weight, PAH etiology, background therapy, NT-proBNP baseline groups, and WHO functional class (Figure 5).

Overall, the results (highlighted in blue) showed a consistent pattern of either modest treatment effects or no effect for selexipag across most subgroups. However, the CHD post-operative subgroup within PAH etiology demonstrated a negative treatment effect. Notably, patients of Hispanic or Latino ethnicity showed a nominally significant treatment benefit with selexipag, as did patients from the Latin America region. Patients with body weight >50kg demonstrated a modest treatment effect, along with those in the 12-18 years age group. The subgroup with baseline NT-proBNP >300 showed a relatively larger effect size compared to those with NT-proBNP <300, though neither group achieved statistical significance.

Additionally, we conducted shrinkage analyses to address potential random variation in subgroup treatment effect estimates that may arise from small sample sizes and/or large variability. The shrinkage analysis employed a Bayesian hierarchical model with non-informative priors based on summary sample estimates. The shrinkage estimate of the subgroup log ratio borrows information from other subgroups while estimating the log ratio for a specific subgroup, creating

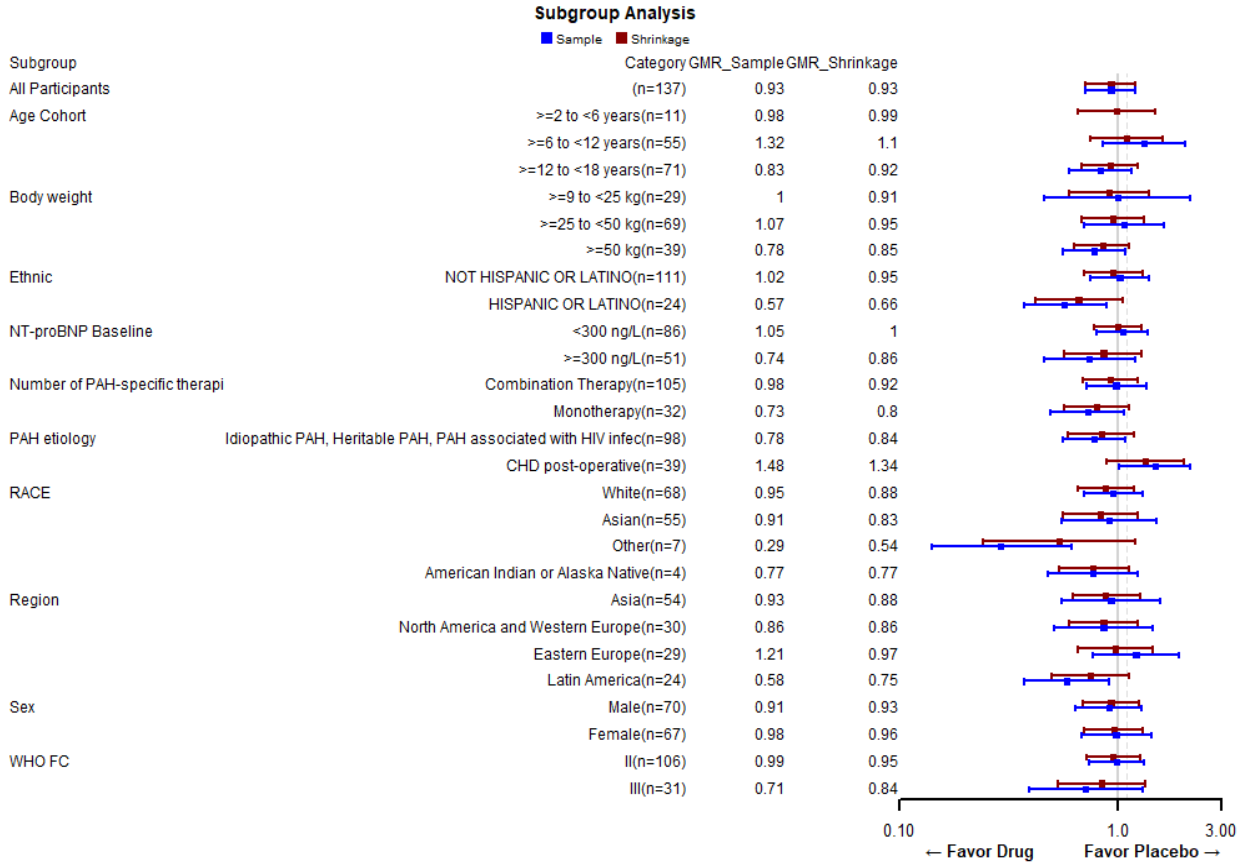
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a weighted average of the individual sample estimate and the overall estimate. We applied the same flat prior to derive shrinkage estimates across all subgroups.

Specifically, let Y_i represent the observed sample estimate of treatment effect (i.e., log ratio) for subgroup i (i=1, 2, ...), where $Y_i \sim N(\mu_i, \sigma_i^2)$, with σ_i^2 representing the observed variance for sample estimates, and $\mu_i \sim N(\mu, \tau^2)$. The hyperpriors were specified as $\mu \sim N(0, 16)$ and $\tau^2 \sim$ Half-Cauchy(0, 1). These distributions, $N(0, 16)$ and Half-Cauchy(0, 1), were selected as weakly informative priors for the hyper-mean μ and hyper-standard deviation τ, respectively.

The shrinkage method results are displayed in red in Figure 3. Notably, a consistent pattern was observed between the two analytical approaches.

Figure 5. Forest plot of subgroup analyses



Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt
Note: A confidence interval for the Age cohort of ≥2 to <6 cannot be estimated in the original subgroup analysis because the between-imputation variance is zero for the estimated treatment effect.

Reference ID: 5737060

4.2 Other Special/Subgroup Populations

Given the Applicant's rationale for efficacy based on grouping NT-proBNP baseline values into two categories due to its prognostic nature (Chen et al., 2019), we conducted analyses for each subgroup across primary and exploratory analyses. The results are shown in Appendix Figure A1. The GMR was stronger 0.69 [95% CI: 0.39, 1.20] for the subgroup with baseline NT-proBNP >300 (n=51) for the completers in the SALTO study, while the GMR value was 0.78 [95% CI: 0.47, 1.27] for the subgroup with baseline NT-proBNP >300 for the completers in the matched GRIPHON population. This difference could be attributed to the impact of PAH background therapy, which served as a stratification factor in the SALTO study but not in the GRIPHON study. Therefore, using information from GRIPHON for the SALTO study analysis may introduce noise or bias. See clinical rational for extrapolation between adult and pediatric populations when looking at treatment effects for selexipag for treatment of PAH. While extrapolation may be reasonable to support approval, data and results from, GRIPHON and SALTO, even based on filtered and matched data, should remain separate.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

- The pediatric SALTO study showed a much smaller GMR reduction in change from baseline NT-proBNP than in the adult PAH patients, which was what was assumed in the sample size determination for NT-proBNP (Section 3.2.1).
    - Sample size assumptions came from the adult GRIPHON study; differences add uncertainty to using the relationship established in adult patients for predicting the likely treatment effect in pediatrics.
- Supplementary analyses on more closely match the adult GRIPHON population to the SALTO population did not support extrapolation of adult treatment effects into the pediatric population (Section 3.2.4.1, Figure 2).
    - There were a number of potential confounding issues, including changing clinical practice for background therapy and differences in baseline NT-proBNP. NT-proBNP has been shown to be a prognostic factor for the adult patient population treated with selexipag, which is not considered first-line therapy (see clinical review).
    - Changing practices and other approved effective therapies means patients are likely to already be on background therapy with lower NT-proBNP.
- Although the study was ultimately not powered for the primary disease progression event endpoint, there were no trends indicating efficacy in the pediatric population (Section 3.2.4.2, Figure 3).
    - Contrasted with the strong efficacy findings seen in the adult GRIPHON results (Tables 3-5 and 3-7 from the statistical review of the GRIPHON study signed by Dr. Steven Bai on July 29, 2015, for NDA 207947).

Reference ID: 5737060

5.2 Collective Evidence

In the selexipag program, the adult GRIPHON study provided evidence supporting NT-proBNP as a meaningful bridging biomarker (refer to the meeting minutes of Type A meeting on November 2, 2022). Often, the basis for approval in pediatric patients relies on demonstrating a similar treatment effect, here on NT-proBNP, as was observed in adult patients with comparable pathophysiology. Having such evidence would support the reasonable conclusion that selexipag would likely provide clinical benefit in pediatric PAH patients. However, the analysis results do not provide evidence regarding similar efficacy magnitude. Using similar imputation analyses, NT-proBNP GMR was 0.93 (95% CI: 0.71, 1.21) in the SALTO pediatric study compared to 0.8 (95% CI: 0.73, 0.88) in the full adult GRIPHON study, and 0.83 (95% CI: 0.76, 0.92) in the filtered GRIPHON analysis. Matching using propensity scores to adjust for confounding between these populations does not alleviate this issue.

Additionally, although the study was not adequately powered for statistical inference, outcomes in the pre-specified primary and secondary endpoints for disease progression showed no evidence or even trends that would favor selexipag over placebo in the pediatric population events (sections 3.2.4.2 and 3.2.4.3).

5.3 Conclusions and Recommendations

The statistical team agrees that the pediatric Written Request was fulfilled by the Applicant in this submission. Based on the findings discussed in this review, there appears to be insufficient evidence to support that selexipag provides clinical benefit in pediatric patients. The statistical review team does not recommend approval of the pediatric indication based on the current results, including biomarker analysis.

5.4 Labeling Recommendations (as applicable)

This section should address any major areas of disagreement with the applicant's proposed label, for example not to include subgroup or secondary endpoint analyses without multiplicity adjustments. It may be amended after the label is finalized.

Section 1
The statistical team recommends not including a pediatric indication.

Section 8.4
Based on the results presented in this review, the statistical team does not believe effectiveness has been established for pediatric PAH patients.

Section 14

Given that the SALTO study failed to achieve significance for both the primary outcomes composite and the NT-proBNP endpoint, we do not recommend including results beyond descriptive statistics in the label. (b) (4)

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APPENDICES (Add When Needed)

Table A1. Design comparison between the pediatric SALTO trial and adult GRIPHON trial

	GRIPHON	**SALTO**
Population	Adult patients (aged 18 ~75 years) with PAH (WHO, Group I)	Pediatric patients ≥2 to <18, with PAH (WHO Group I)
Treatment	Starting 200mcg twice daily, to highest tolerated dose up to 1600 mcg twice daily	Starting dose, up-titration scheme, and maximum allowed doses are based on are based on body weight groups
Trial duration (median)	70.7 weeks	Up to the end of DB treatment period, median duration is 87.9 weeks
Sample size	1,156	138
WHO functional class	I, II, III, IV	II, III
PAH-specific background therapy	Naïve Monotherapy Combination therapy	Monotherapy Combination therapy
Primary endpoint	Time to first CEC-confirmed MM event	Time to CEC-confirmed disease progression event
Secondary endpoint	Change from baseline to Week 26 in 6MWD	Change in NT-proBNP from baseline to Week 24 on log scale
NT-proBNP endpoint	Week 26; Exploratory endpoint: Descriptive summary	Week 24; Key secondary endpoint for powering the trial

Source: Statistical Reviewer's table

Reference ID: 5737060

Table A2. Demographics and Baseline Characteristics (FAS), GRIPHON and SALTO studies

	GRIPHON		SALTO	
	Placebo N=582	**Selexipag N=574**	**Placebo N=69**	**Selexipag N=69**
Sex, n (%)				
F	466 (80.1)	457 (79.6)	32 (46.4)	35 (50.7)
M	116 (19.9)	117 (20.4)	37 (53.6)	34 (49.3)
Age				
Mean (SD)	47.9 (15.55)	48.2 (15.19)	11.1 (3.54)	11.6 (3.76)
Race, n (%)				
American Indian or Alaska Native	0	0	2 (2.9)	2 (2.9)
Asian	120 (20.6)	125 (21.8)	32 (46.4)	23 (33.3)
Black or African American	14 (2.4)	13 (2.3)	0	3 (4.3)
Hispanic	63 (10.8)	51 (8.9)	0	0
Multiple	0	0	2 (2.9)	1 (1.4)
Not Reported	0	0	2 (2.9)	2 (2.9)
Other	10 (1.7)	9 (1.6)	0	0
White	375 (64.4)	376 (65.5)	31 (44.9)	38 (55.1)
WHO FC, n (%)				
I	5 (<1)	4 (<1)	0	0
II	255 (43.8)	274 (47.7)	53 (76.8)	54 (78.3)
III	314 (54.0)	293 (51.0)	16 (23.2)	15 (21.7)
IV	8 (1.4)	3 (<1)	0	0
PAH specific therapy, n (%)				
Combination Therapy	197 (33.8)	179 (31.2)	52 (75.4)	53 (76.8)
Monotherapy	261 (44.8)	283 (49.3)	17 (24.6)	16 (23.2)
No PAH-Specific Med	124 (21.3)	112 (19.5)	0	0
NT-proBNP baseline				
Mean (SD)	1275.3 (1953.60)	1135.7 (1548.64)	787.4 (2366.74)	756.0 (1456.17)
NT-proBNP group, n (%)				
BNP_BL<300	197 (33.8)	210 (36.6)	43 (62.3)	43 (62.3)
BNP_BL>=300	377 (64.8)	358 (62.4)	26 (37.7)	25 (36.2)
Missing	8 (1.4)	6 (1.0)	0	1 (1.4)

Abbreviations: FAS=full analysis set, SD = standard deviation
Source: Statistical Reviewer Analysis; adsl.xpt adbdc.xpt adlb.xpt

Table A3: Analysis result of NT-proBNP with multiple imputation for missing data

Trial	GRIPHON (full) [a]		GRIPHON (filtered) [a]		SALTO	
Treatment	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
n	568	574	453	445	68	69
Geometric Mean (Post/Baseline) (95% CI)	0.89 (0.82, 0.96)	1.11 (1.04, 1.18)	0.91 (0.84, 0.98)	1.09 (1.02, 1.16)	0.98 (0.78, 1.22)	1.05 (0.85, 1.31)

Reference ID: 5737060

Geometric Mean (Post/Baseline) ratio: Selexipag/Placebo (95% CI)	0.80 (0.73, 0.88)	0.83 (0.76, 0.92)	0.93 (0.71, 1.21)
p-value	<0.001	<0.001	0.575

Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt
CI=confidence interval; GM=geometric mean for NT-proBNP (Post/Baseline) ratio; GMR=ratio of (GM of selexipag) vs (GM of placebo); Post =26 Week for GRIPHON, 24 Week for SALTO; n=number of participants included in the analysis.
[a]: The Applicant provided the results following an information request.

Table A4: Completer analysis result of NT-proBNP

Trial	GRIPHON (full)		GRIPHON (filtered)		SALTO	
Treatment	Selexipag	Placebo	Selexipag	Placebo	Selexipag	Placebo
Observed n	439	428	340	339	60	64
Geometric Mean (Post/Baseline) (95% CI)	0.85 (0.70,1.04)	1.12 (0.92,1.37)	0.85 (0.79, 0.92)	1.09 (1.01, 1.17)	0.93 (0.74,1.17)	1.06 (0.85,1.33)
Geometric Mean (Post/Baseline) ratio: Selexipag/Placebo (95% CI)	0.76 (0.68, 0.84)		0.78(0.70, 0.87)		0.88 (0.68, 1.14)	
p-value	<0.001		<0.001		0.329	

Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt
CI=confidence interval; GM=geometric mean for NT-proBNP (Post/Baseline) ratio; GMR=ratio of (GM of selexipag) vs (GM of placebo); Post =26 Week for GRIPHON, 24 Week for SALTO; n=number of participants included in the analysis.

Table A5. Standardized Mean Differences between the SALTO and Filtered GRIPHON studies for variables included in the PS calculation

Variable	Observations	Mean Difference	Standardized Difference
Log2(NT-proBNP) baseline	All	-1.19	-0.60
	Matched	-0.04	-0.02
WHO FC	All	0.35	0.76
	Matched	0.0	0.0
PAH background therapy	All	0.36	0.78
	Matched	0.02	0.05

Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt

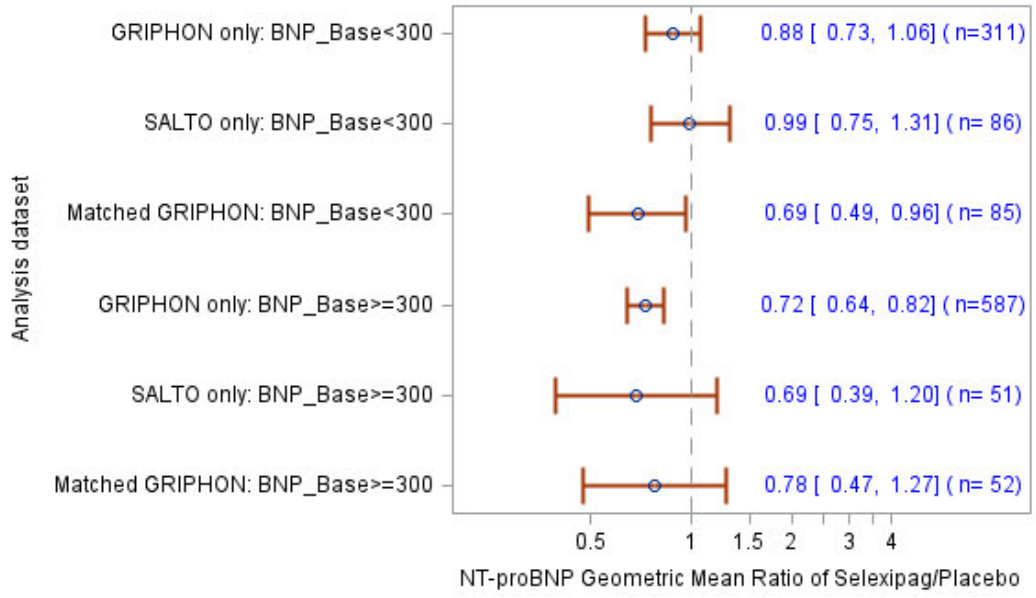
Reference ID: 5737060

Table A6. Baseline characteristics for matched GRIPHON and SALTO studies

	GRIPHON			SALTO		
	Placebo N=70	**Selexipag N=67**	**Total N=137**	**Placebo N=69**	**Selexipag N=68**	**Total N=137**
WHO FC, n (%)						
II	49 (70.0)	57(85.1)	106 (77.4)	53 (76.8)	53 (77.9)	106 (77.4)
III	21 (30.0)	10 (14.9)	31 (22.6)	16 (23.2)	15 (22.1)	31 (22.6)
PAH specific therapy, n (%)						
Combination Therapy	57 (81.4)	45 (67.2)	102 (74.5)	52 (75.4)	53 (77.9)	105 (76.6)
Monotherapy	13 (18.6)	22 (32.8)	35 (25.5)	17 (24.6)	15 (22.1)	32 (23.4)
NT-proBNP baseline						
Mean (SD)	839.1 (3409.4)	499.3 (621.4)	672.9 (2473.2)	787.4 (2366.7)	756.0 (1456.2)	771.9 (1960.3)
NT-proBNP group, n (%)						
BNP_BL<300	46 (65.7)	39 (58.2)	85 (62.0)	43 (62.3)	43 (63.2)	86 (62.8)
BNP_BL>=300	24 (34.3)	28 (41.8)	52 (38.0)	26 (37.7)	25 (36.8)	51 (37.2)

Abbreviations: SD = standard deviation
Source: Statistical Reviewer Analysis; adsl.xpt adbdc.xpt adlb.xpt
N: number of participants included in the analysis

Figure A1: Comparison of treatment effects using only completers for within baseline NT-proBNP subgroups across various datasets



Source: Statistical Reviewer Analysis; adsl.xpt adeff.xpt

Reference ID: 5737060

References:

U.S. Food and Drug Administration. "E11A Pediatric Extrapolation Guidance for Industry." December 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation-guidance-industry.

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