Efficacy and safety of selexipag in pediatric pulmonary arterial hypertension: results from the randomized controlled phase 3 SALTO study

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Background and Aim

- Pediatric pulmonary arterial hypertension (PAH) has shown important similarities to adult PAH,[1] and it is characterized by high morbidity and mortality, reflecting the high unmet medical need[2,3]
- While therapies targeting four pathways are approved for use in adult PAH, options for pediatric patients are limited to therapies that target the endothelin and nitric oxide pathways[2–9]
- Selexipag is an oral, selective IP receptor agonist that targets the prostacyclin pathway and is approved for use in adult PAH patients[10]
- **The SALTO study of selexipag in pediatric PAH was designed to provide further information on the efficacy and safety of selexipag versus placebo on top of standard of care in patients with PAH**

1. Fleming et al. *Ther Innov Regul Sci* 2023;57:109–20; 2. Humbert et al. *Eur Heart J* 2022;43:3618–731; 3. Humbert et al. *Eur Respir J* 2022; 61:2200879; 4. Volibris SmPC 2024: https://www.ema.europa.eu/en/documents/product-information/volibris-epar-product-information_en.pdf; 5. Tracleer SmPC 2024: https://www.ema.europa.eu/en/documents/product-information/tracleer-epar-product-information_en.pdf; 6. Opsumit SmPC 2025: https://www.ema.europa.eu/en/documents/product-information/opsumit-epar-product-information_en.pdf; 7. Revatio SmPC: https://www.ema.europa.eu/en/documents/product-information/revatio-epar-product-information_en.pdf; 8. Adcirca SmPC 2024: https://www.ema.europa.eu/en/documents/product-information/adcirca-epar-product-information_en.pdf; 9. Adempas SmPC 2024: https://www.ema.europa.eu/en/documents/product-information/adempas-epar-product-information_en.pdf; 10. Uptravi SmPC 2025: https://www.ema.europa.eu/en/documents/product-information/uptravi-epar-product-information_en.pdf [All URLs last accessed May 2025].

PAH, pulmonary arterial hypertension; SmPC, Summary of Product Characteristics.

SALTO study design

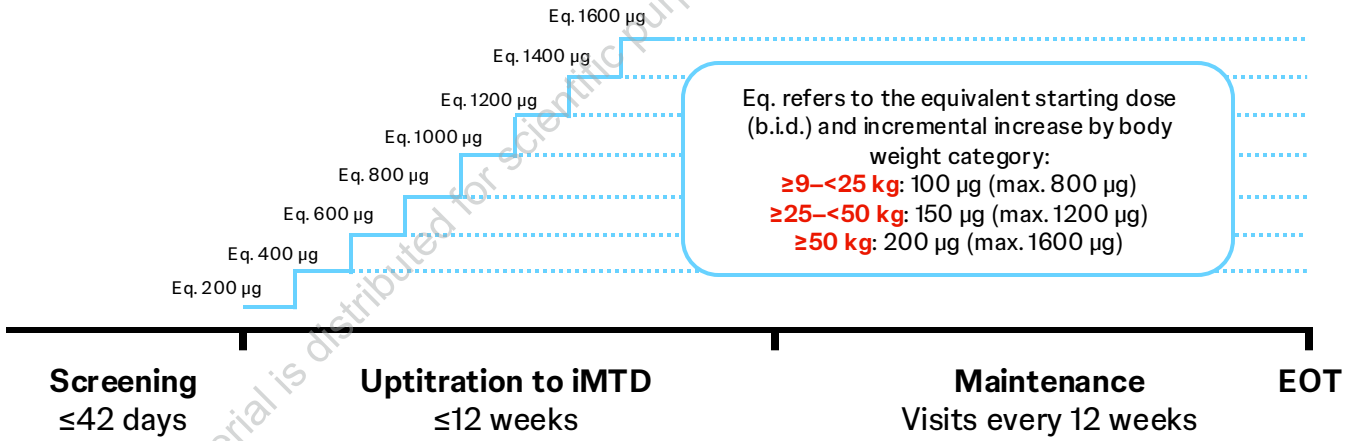
- SALTO was a pivotal, randomized, multi-center, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of selexipag vs placebo in pediatric PAH (NCT04175600)

Patients
- Aged ≥2–<18 years
- RHC-confirmed (historical) PAH
- IPAH, HPAH, PAH-CHD, drug/toxin-induced PAH, or PAH-HIV etiology
- WHO FC II–III symptoms
- Stable (≥3 months) background therapy with ≥1 PAH-specific therapy

Selexipag (dosed according to body weight category)

1:1 randomization stratified by WHO FC (II vs III) and background therapy (mono vs combination therapy)

Placebo



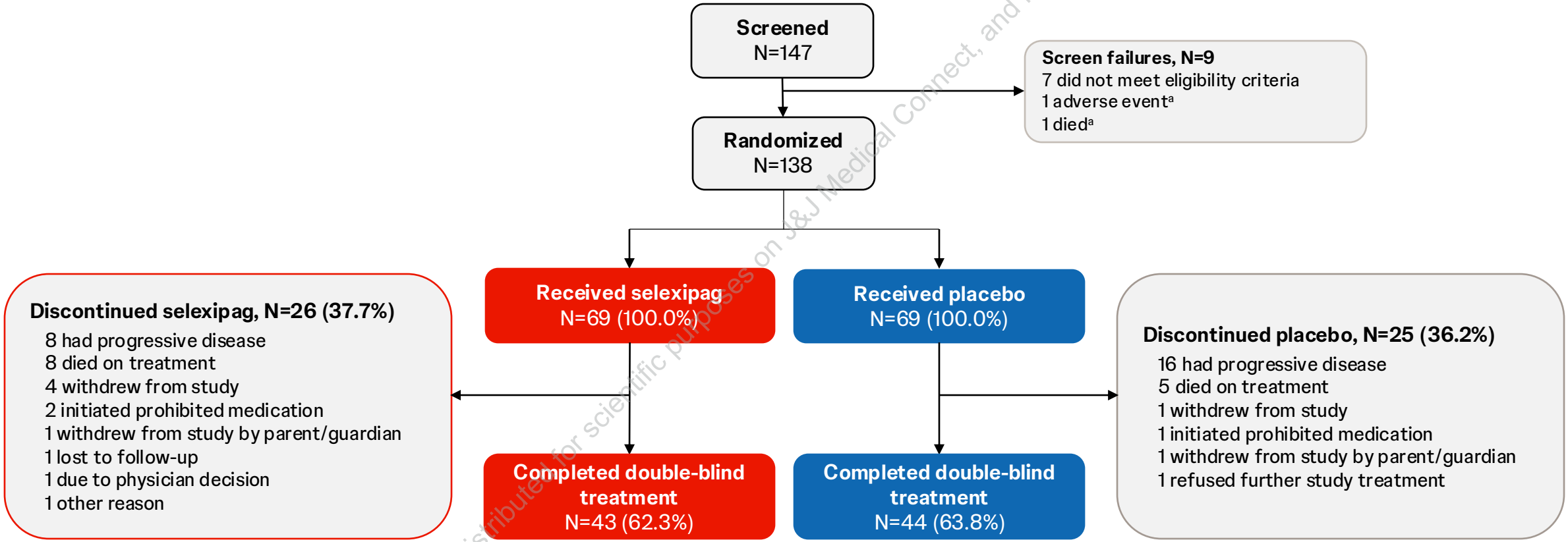
Primary endpoint:
Descriptive analysis of time to first CEC-confirmed disease progression event[a]

Secondary endpoints included:
- *Powered* analysis of change in NT-proBNP from baseline to Week 24
- *Descriptive* analysis of safety and tolerability
- *Descriptive* analysis of time to first CEC-confirmed hospitalization for PAH or death due to PAH[a]

Exploratory endpoints included:
Descriptive analysis of change from baseline in WHO FC and 6MWD[b]

[a]Time to outcomes measured from randomization to 7 days after study treatment discontinuation; [b]6MWD measured in patients aged ≥6 years and developmentally able to perform the test.
6MWD, 6-minute walk distance; b.i.d., twice daily; CEC, clinical events committee; EOT, end of trial; HPAH, heritable PAH; iMTD, individualized maximum tolerated dose; IPAH, idiopathic PAH; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH-CHD, PAH associated with congenital heart disease; PAH-HIV, PAH associated with human immunodeficiency virus; RHC, right heart catheterization; WHO FC, World Health Organization functional class.

Patient disposition



[a]Not related to COVID-19

Baseline demographics and characteristics

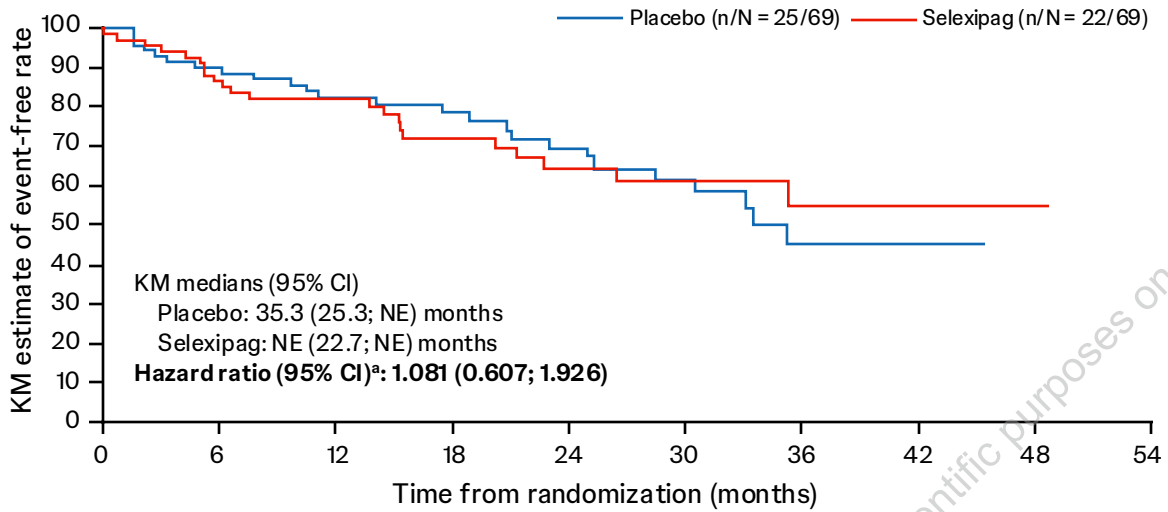
Demographic/characteristic	Selexipag, N=69	Placebo, N=69
Age category, n (%)		
≥2–<6 years	5 (7.2)	6 (8.7)
≥6–<12 years	28 (40.6)	28 (40.6)
≥12–<18 years	36 (52.2)	35 (50.7)
Body weight category, n (%)		
≥9–<25 kg	13 (18.8)	16 (23.2)
≥25–<50 kg	34 (49.3)	36 (52.2)
≥50 kg	22 (31.9)	17 (24.6)
Female, n (%)	35 (50.7)	32 (46.4)
Race, n (%)[a]		
White	38 (55.1)	31 (44.9)
Asian	23 (33.3)	32 (46.4)
Black or African American	3 (4.3)	0
Other[b]	3 (4.3)	4 (5.8)

Disease characteristic	Selexipag, N=69	Placebo, N=69
PAH etiology, n (%)		
IPAH	38 (55.1)	38 (55.1)
PAH-CHD	29 (42.0)	26 (37.7)
Post-operative PAH	21 (30.4)	19 (27.5)
PAH with co-incidental CHD	8 (11.2)	7 (10.1)
HPAH	2 (2.9)	5 (7.2)
Median (range) time from PAH diagnosis, years	2.43 (0.07–16.64)	3.87 (0.18–16.04)
WHO FC, n (%)		
II	54 (78.3)	52 (75.4)
III	15 (21.7)	17 (24.6)
Median (range) NT-proBNP, ng/L	231.0 (51–7626)[c]	168.0 (51–18740)
Background PAH-specific therapies, n (%)		
Monotherapy (ERA/PDE5i)	18 (26.1)	17 (24.6)
Combination therapy (ERA + PDE5i)	51 (73.9)	52 (75.4)

[a]Information on race was not available for two patients in each treatment arm.
[b]Two patients in each arm identified as American Indian or Alaskan Native, and three patients (one in selexipag arm, two in placebo arm) selected multiple races.
[c]NT-proBNP measurements were not available at baseline for one patient in the selexipag arm.
ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase type 5 inhibitor.

Descriptive primary endpoint
Time to first CEC-confirmed disease progression event

Kaplan–Meier plot of time to first CEC-confirmed disease progression event through double-blind end date +7days



Participant at risk

Placebo	69	62	57	37	27	21	9	6	0	0
Selexipag	69	58	52	31	20	17	7	3	1	0

Cumulative number of events

Placebo	0	7	12	14	18	21	25	25	25	25
Selexipag	0	9	12	17	20	21	22	22	22	22

Parameter	Selexipag, N=69	Placebo, N=69
Median observation time, months	16.2	19.6
No. (%) of patients with an event	22 (31.9)	25 (36.2)
Component events		
Death	5 (7.2)	0
Atrial septostomy or Potts' anastomosis or registration on lung transplant list	0	0
Hospitalization due to worsening PAH	3 (4.3)	5 (7.2)
Clinical worsening of PAH	14 (20.3)	20 (29.0)
Worsening in WHO FC	7 (10.1)	14 (20.3)
New or worsening syncope	1 (1.4)	2 (2.9)
New occurrence or worsening of ≥2 PAH symptoms	5 (7.2)	4 (5.8)
New or worsening signs of right heart failure not responding to oral diuretics	1 (1.4)	0
KM estimates of event-free rates at 1 year (95% CI), %	82.1 (70.7; 89.4)	82.6 (71.4; 89.7)

No difference between treatment groups for the primary endpoint

Data based on full analysis set.
[a]Hazard ratio (HR) is from unstratified proportional hazards model; HR <1 favors selexipag.
CI, confidence interval; KM, Kaplan–Meier; NE, not estimable.

Post-hoc assessment of cumulative disease progression events

Parameter	Selexipag, N=69	Placebo, N=69
Cumulative number of events	44	64
Cumulative number of events by component		
Death	8	9
Atrial septostomy or Potts' anastomosis or registration for lung transplant	2	1
Hospitalization due to worsening PAH	14	19
Clinical worsening of PAH	20	35
Total patient-years of observation	118.78	134.57
Average annualized event rate[a]	0.37	0.48

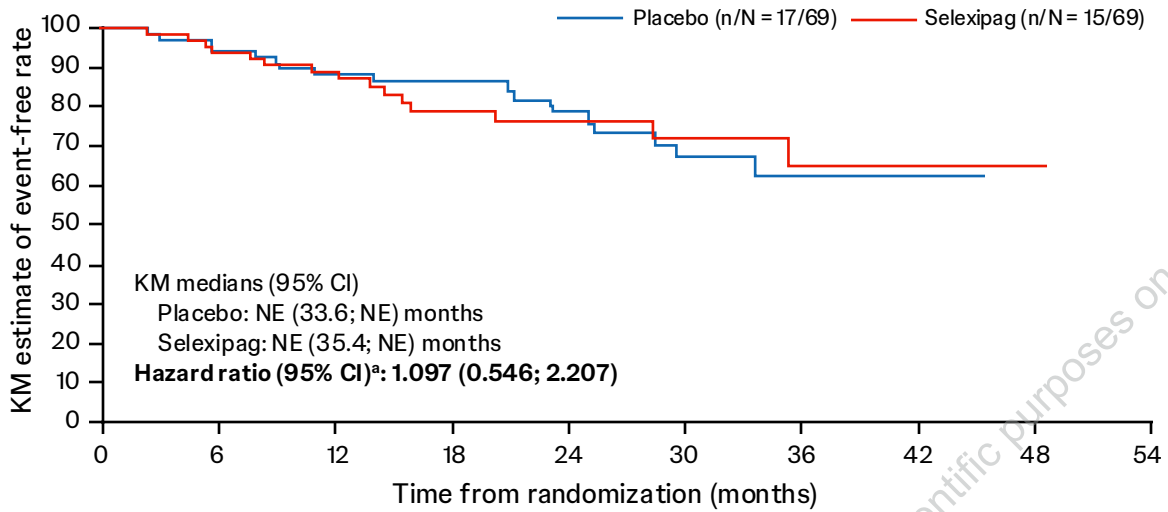
Smaller annualized cumulative disease progression event rate with selexipag versus placebo

Data based on full analysis set.

[a]Average annualized event rate is defined as the total number of recurrent events/components across all participants in analysis set divided by the total participant-years of observation.

Descriptive secondary endpoint
Time to first CEC-confirmed death or hospitalization due to PAH

Kaplan–Meier plot of time to first CEC-confirmed death or hospitalization due to PAH through double-blind end date +7days



Participant at risk

Placebo	69	64	60	38	28	21	10	6	0	0
Selexipag	69	60	54	32	22	18	7	3	1	0

Cumulative number of events

Placebo	0	4	8	9	12	16	17	17	17	17
Selexipag	0	4	7	12	13	14	15	15	15	15

Parameter	Selexipag, N=69	Placebo, N=69
Median observation time, months	16.6	20.3
No. (%) of patients with an event	15 (21.7)	17 (24.6)
Component events, n (%)		
Death due to PAH	4 (5.8)	3 (4.3)
Hospitalization due to PAH	11 (15.9)	14 (20.3)
KM estimates of event-free rates at 1 year (95% CI), %	89.0 (78.3; 94.6)	88.3 (78.0; 94.0)

No difference between treatment groups

Data based on full analysis set.
[a]Hazard ratio (HR) is from unstratified proportional hazards model; HR <1 favors selexipag.

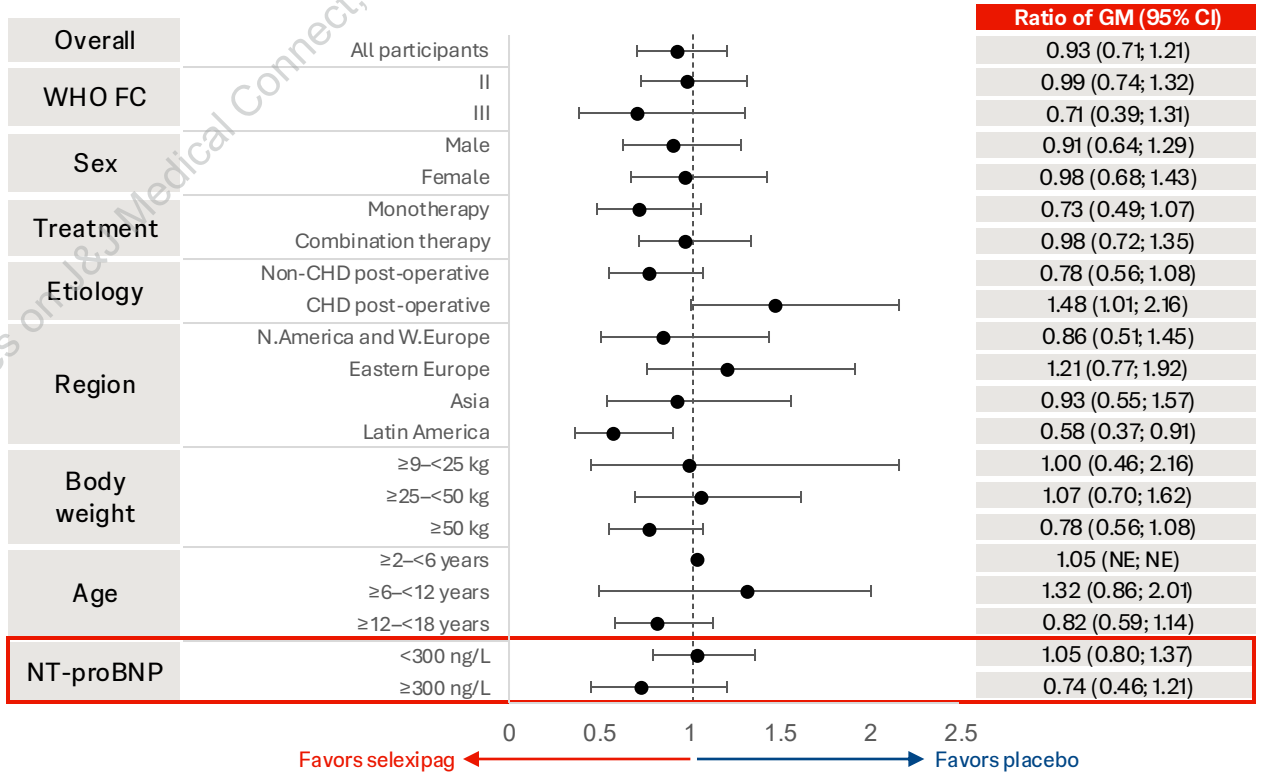
Powered secondary endpoint
NT-proBNP change from baseline to week 24

Change from baseline to Week 24 in NT-proBNP

Parameter	Selexipag, N=69	Placebo, N=69
Baseline NT-proBNP, ng/L Median (range)	231.0 (51–7626)	168.0 (51–18740)
Ratio of Week 24 to baseline (model-adjusted)[a] N GM 95% CI of GM	 68 0.98 (0.78; 1.22)	 69 1.05 (0.85; 1.31)
Treatment effect: ratio of selexipag over placebo (model-adjusted)[b] Geometric LS means ratio 95% CI 2-sided p-value	 0.93 (0.71; 1.21) 0.5748	

[a] Multiple imputation methodology is applied to handle all missing NT-proBNP values at Week 24 (nine missing in selexipag arm; five missing in placebo arm). Imputation is based on $\log_2$ transformed values of NT-proBNP. [b] Analysis is based on an ANCOVA of the $\log_2$ transformed ratio of NT-proBNP (Week 24/Baseline).

Treatment effect estimates of ratio of week 24 to baseline NT-proBNP by subgroup



No significant difference in secondary endpoint, subgroup analysis shows greater numerical difference in favor of selexipag among patients with NT-proBNP ≥300 ng/L

Data based on full analysis set.
ANCOVA, analysis of covariance; GM, geometric mean; LS, least squares.

Post hoc analysis of NT-proBNP subgroups

- A standardized NT-proBNP Zlog threshold of 2.58 is equivalent to the Zlog NT-proBNP for an individual aged 18 years with NT-proBNP level of 300 ng/L[1]

Baseline NT-proBNP Zlog ≥2.58

Parameter	Selexipag	Placebo
Ratio of Week 24 to baseline (model-adjusted)[a]		
N	22	20
GM	0.80	1.27
95% CI of GM	(0.53; 1.20)	(0.88; 1.84)
Treatment effect: ratio of selexipag over placebo (model-adjusted)[b]		
Geometric LS means ratio	0.63	
95% CI	(0.37; 1.08)	
2-sided p-value	0.0938	

Baseline NT-proBNP Zlog <2.58

Parameter	Selexipag	Placebo
Ratio of Week 24 to baseline (model-adjusted)[a]		
N	46	49
GM	1.04	0.97
95% CI of GM	(0.82; 1.34)	(0.83; 1.14)
Treatment effect: ratio of selexipag over placebo (model-adjusted)[b]		
Geometric LS means ratio	1.08	
95% CI	(0.81; 1.43)	
2-sided p value	0.6172	

Subgroup analysis shows greater numerical difference in favor of selexipag among patients with NT-proBNP Zlog ≥2.58

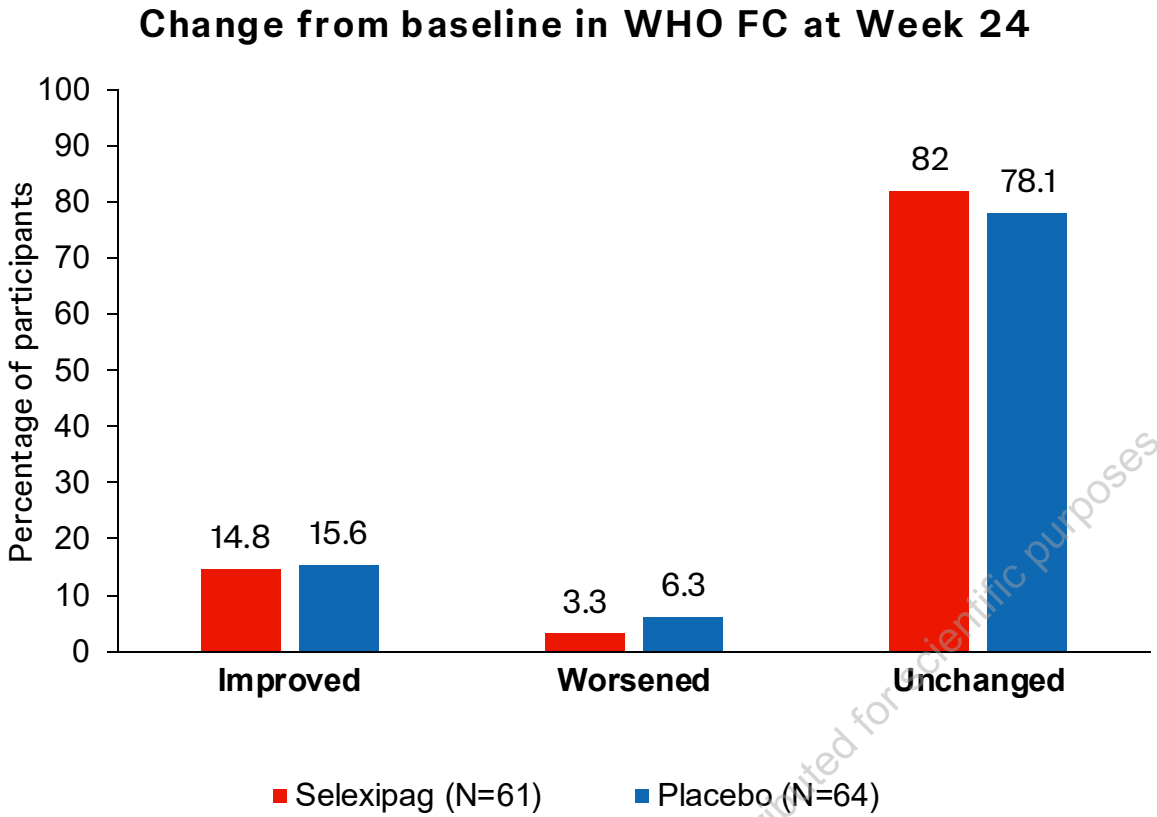
Data based on full analysis set.

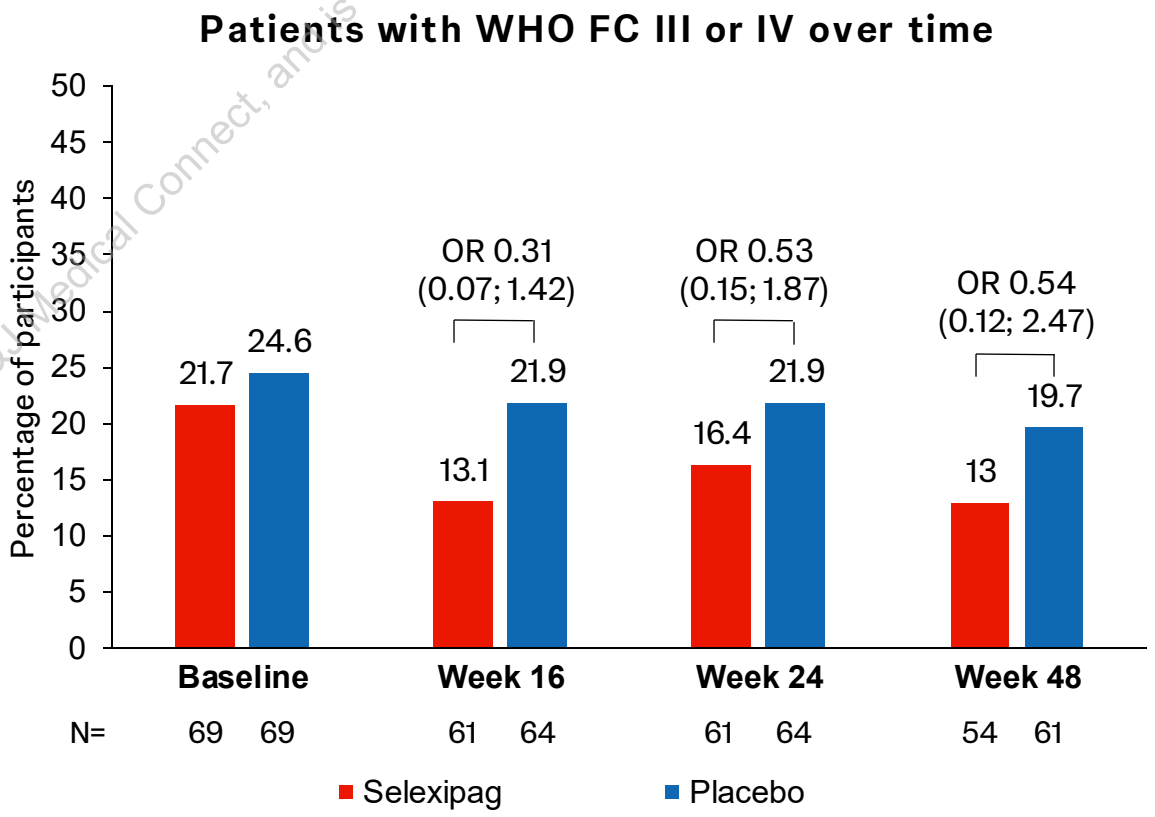
[a] Multiple imputation methodology is applied to handle all missing NT-proBNP values at Week 24 (nine missing in selexipag arm; five missing in placebo arm). Imputation is based on $\log_2$ transformed values of NT-proBNP.

[b] Analysis is based on an ANCOVA of the $\log_2$ transformed ratio of NT-proBNP (Week 24/Baseline).

1. Palm et al. *Clin Chem Lab Med*. 2020;58:1509–16.

Exploratory assessment
WHO FC change from baseline





Lower proportion of patients in WHO FC III/IV over time with selexipag versus placebo

Observed data based on full analysis set.
OR, odds ratio.

Safety and tolerability

- Most common AEs were well known prostacyclin-related AEs
- Other AEs were associated with disease progression or other comorbidities known to occur in the pediatric population

Characteristic	Selexipag, N=69	Placebo, N=69
Median (range) exposure, weeks	78.0 (0–212)	92.7 (10–198)
Median (range) individualized maximum tolerated dose, ug b.i.d.		
≥9–<25 kg *(N=13 selexipag, N=16 placebo)*	800 (450–800)	800 (300–800)
≥25–<50 kg *(N=34 selexipag, N=36 placebo)*	1200 (300–1200)	1200 (600–1200)
≥50 kg *(N=22 selexipag, N=17 placebo)*	1600 (200–1600)	1600 (800–1600)
Patients with 1 or more, n (%)		
TEAE	68 (98.6)	65 (94.2)
Study drug-related TEAE[a]	47 (68.1)	32 (46.4)
Serious TEAE	32 (46.4)[b]	26 (37.7)
TEAE leading to death	9 (13.0)	8 (11.6)
TEAE leading to treatment discontinuation	9 (13.0)	13 (18.8)
Deaths,[c] n (%)	10 (14.5)	11 (15.9)
Most frequent TEAEs (>15% of selexipag-treated participants), n (%)		
Headache	38 (55.1)	12 (17.4)
Vomiting	27 (39.1)	13 (18.8)
Nausea	23 (33.3)	13 (18.8)
Upper respiratory tract infection	23 (33.3)	19 (27.5)
Diarrhea	18 (26.1)	13 (18.8)
PAH	13 (18.8)	13 (18.8)
COVID-19	11 (15.9)	14 (20.3)
Pyrexia	11 (15.9)	8 (11.6)

Data are based on safety analysis set. [a]As assessed by the investigator; [b]Serious TEAE of urticaria considered related to selexipag treatment by the investigator; [c]There were 21 deaths in total (11 in patients randomized to placebo and 10 in patients randomized to selexipag), 15 were treatment-emergent (eight with selexipag and seven with placebo); no deaths in either arm wereconsidered related to study treatment. AE, adverse event; TEAE, treatment-emergent AE.

Conclusions

- In SALTO, the descriptive primary endpoint of time to first CEC-confirmed disease progression event did not show a difference between the treatment groups, potentially reflecting low patient number and lack of power
- For the powered secondary endpoint of NT-proBNP, the treatment effect was numerically in favor of selexipag, however, the difference was not statistically significant
  - Subgroup analyses show greater numerical difference in favor of selexipag among patients with baseline NT-proBNP levels indicative of greater disease severity (≥300 ng/L and Z-score ≥2.58)
- A number of exploratory and *post hoc* analyses showed numerical differences that favored selexipag
  - Smaller annualized cumulative disease progression event rate
  - Lower proportion of patients in WHO FC III/IV over time
- Adverse events were consistent with the known safety profile of selexipag in adults
- These results suggest a potential role for selexipag in the treatment of pediatric patients with PAH