ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

ORIGINAL CLINICAL SCIENCE

Selexipag for the treatment of children with pulmonary arterial hypertension: First multicenter experience in drug safety and efficacy

Georg Hansmann, MD, PhD,[a] Katharina Meinel, MD,[b] Mila Bukova, MD,[a] Philippe Chouvarine, PhD,[a] Håkan Wåhlander, MD, PhD,[c] and Martin Koestenberger, MD[b], on behalf of the European Pediatric Pulmonary Vascular Disease Network (EPPVDN)

From the [a]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany; [b]Division of Pediatric Cardiology, Department of Pediatrics, Medical University of Graz, Graz, Austria; and the [c]The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Institution of Clinical Sciences, Gothenburg University, Gothenburg, Sweden.

KEYWORDS:
prostacyclin;
IP receptor agonist;
pulmonary hypertension;
pulmonary vascular disease;
heart failure;
right ventricle

BACKGROUND: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN) investigated the safety and efficacy of add-on selexipag, an oral prostacyclin receptor agonist approved for pulmonary arterial hypertension (PAH) in adults, in the largest, exploratory pediatric cohort to date.
METHODS: This is a prospective observational study of 15 consecutive children with PAH, treated with oral add-on selexipag at 3 centers. Most patients underwent cardiac catheterizations at baseline and median of 8 months follow-up. All patients had clinical, echocardiographic, and N-terminal pro b-type natriuretic peptide studies, including the EPPVDN pediatric pulmonary hypertension (PH) risk score.
RESULTS: There was no death during the use of selexipag. Two of 15 patients ultimately underwent lung transplantation. One patient with heritable PAH died on intravenous treprostinil (off selexipag). The mean right atrial pressure, the ratio of pulmonary arterial pressure (PAP) to systemic arterial pressure (SAP) (mean PAP/mean SAP, diastolic PAP/diastolic SAP: −17%), and transpulmonary pressure gradients (TPG) (mean TPG: −17%; $p < 0.01$; diastolic TPG: −6 mm Hg; $p < 0.05$) were improved after the therapy ($n = 10$). Selexipag therapy was associated with a better right ventricular systolic function (tricuspid annular plane systolic excursion: +14.5%; $p < 0.01$) and functional class. Improvement was seen in non-invasive and combined invasive/non-invasive PH risk scores (lower risk: +18%−22%, higher risk: −35%−37%; $p < 0.05$). Overall, the efficacy of selexipag was variable, often with a better response in less sick patients.
CONCLUSIONS: Oral selexipag use in children with PAH is well tolerated and safe when closely monitored. Add-on selexipag therapy improved several outcome-relevant variables in about 50% of patients and prevented disease progression in additional 27% of patients. The novel EPPVDN pediatric PH risk score indicated these drug effects properly, can be useful in clinical follow-up, and should be validated in larger prospective studies.

Reprint requests: Georg Hansmann, MD, PhD, FESC, FAHA, Department of Pediatric Cardiology and Critical Care, Pulmonary Vascular Research Center, Hannover Medical School, Carl-Neuberg-Street 1, Hannover 30625, Germany. Telephone: +49 511-532-9594. Fax: +49 511-532-18533.
E-mail address: georg.hansmann@gmail.com

https://doi.org/10.1016/j.healun.2020.03.029

J Heart Lung Transplant 000;000:1−12

Progressive pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling/pulmonary vascular disease (PVD), leading to elevated pulmonary arterial pressure (PAP), right ventricular (RV) dysfunction, underfilling/compression of the left ventricle, and terminal heart failure.[1−3] Pulmonary hypertension (PH)−associated mortality has decreased over the past 2 decades in children[3−5] and adults.[6] These advancements are probably due to increased awareness of this condition and its multiple etiologies, more accurate diagnosis, better risk stratification, and an early initiation of combination PAH-targeted pharmacotherapy.[4−8] Nevertheless, transplant-free survival with various forms of Group 1 PH (refer to Supplementary Table S1 available online at www.jhltonline.org) remains poor in both children and adults.[3,4,9,10] Particularly in children and young adults, the clinical course of PAH is often characterized by the rapid progression of PVD and a rather late but sharp decline of RV performance.[3,5] Without any PAH-targeted pharmacotherapy, the average survival of children with idiopathic PAH is only 10 months. Even with mono or dual pharmacotherapy, the mortality remains high (25%−29%) 5 years after diagnosis[9] and is even higher in patients with PAH-related gene mutations and those with other risk factors such as scleroderma and human immunodeficiency virus. Oral combination PAH-targeted therapy for children, although not approved in this age group to date, commonly consists of a phosphodiesterase 5 inhibitor (sildenafil and tadalafil) and endothelin receptor antagonists (bosentan, macitentan, and ambrisentan).[5,7] However, only sildenafil and bosentan have been approved by the European Medicines Agency for use in children, and only for those older than 1 year.

However, emerging therapeutic strategies for adult PAH, such as upfront or rapid sequence oral dual or triple combination therapy,[6] have not been studied at all in children.[5] In addition, so far, only case reports on pediatric therapy within the novel drug classes such as prostacyclin (IP) receptor agonists (selexipag)[11,12] or soluble guanylate cyclase stimulators (riociguat) exist.[13] Overall, the off-label use of established PAH medication approved for adult use, such as macitentan, epoprostenol, or treprostinil, is frequently pursued at experienced PH centers. Until recently, agents targeting the prostacyclin pathway have only been available through the parenteral administration of epoprostenol (intravenous [IV]), treprostinil (IV, subcutaneous, inhalation), or iloprost (inhalation).

Selexipag is the first orally administered IP receptor agonist with a non-prostanoid structure. The major known therapeutic effects of selexipag are vasodilation and the inhibition of both inflammation and proliferation of vascular smooth muscle cells. Pharmacodynamics, pharmacokinetics, and pre-clinical studies of selexipag and its active metabolite, ACT-333679, have been recently reviewed.[14] In the large, event-driven GRIPHON trial in 1,156 adult patients with PAH,[15] the risk of the primary composite endpoint death or a complication related to PAH was significantly lower with selexipag than with placebo (hazard ratio [HR]: 0.60). In May 2016, selexipag was approved by the European Medicines Agency for oral use in adults with PAH, and subsequently, the first-in-child use of selexipag was reported in 2017.[11,16] Here, we present safety and efficacy data for add-on selexipag in a prospective observational multi-institutional study of 15 children and adolescents with pre-capillary PH. These PAH patients had neither clinical (New York Heart Association Functional Classification) nor echocardiographic or hemodynamic improvement on dual oral PAH-targeted therapy over at least 6 months, and thus received add-on oral selexipag pharmacotherapy for PAH treatment. Apart from clinical, echocardiographic, and hemodynamic variables, we evaluated the efficacy of selexipag with the European Pediatric Pulmonary Vascular Disease Network (EPPVDN) pediatric PH risk factor score originally introduced in the updated EPPVDN guidelines for pediatric PH.[5]

Methods

Patient population

This was a prospective observational study of 15 children with pre-capillary PH, treated consecutively with oral add-on selexipag at the 3 tertiary PH centers in Hannover, Germany ($n = 7$); Graz, Austria ($n = 6$); and Gothenburg, Sweden ($n = 2$; Table 1 and Supplementary Table S2 online). Pre-capillary PH was defined according to the 2015 international guidelines by the European Society of Cardiology/European Respiratory Society (ESC/ERS)[5]: mean PAP (mPAP) ≥ 25 mm Hg, pulmonary arterial wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) index > 3 Wood unit•m^2 when > 3 months old, at sea level. Furthermore, all patients also fulfilled the ESC/ERS adjunct criterion of a diastolic transpulmonary pressure gradient (dTPG or diastolic pulmonary gradient) ≥ 7 mm Hg (Supplementary Tables S3 and S4 online). Patients with any significant intra- or extra-cardiac shunt, World Health Organization (WHO) functional class (FC) 4, and any recent clinical instability or infection were not considered for further analysis.

The compiled EPPVDN pediatric PH risk factor score consists of 17 clinical, echocardiographic, and hemodynamic variables and was introduced in the 2019 updated EPPVDN guidelines for pediatric PH[5] but has not been evaluated in published patient cohorts. We applied the EPPVDN pediatric PH risk factor score (Supplementary Figure S1 online) to the observation period between Time 0 and Time 1 (on selexipag). We defined clinical improvement as a reduction in the number of high risk criteria without a concomitant reduction in the number of low risk criteria, and defined progression as an increase in the number of high risk

Table 1 Characteristics of All 15 Patients with PH at Baseline and Follow-up

Patients #1–15 Cities: Hannover, Graz, Gothenburg	Baselinetime point #0$n = 15$	On selexipagtime point #1$n = 15$	p-value
Demographics			
Age (years)	7.4 ± 1.6	8.3 ± 1.7	—
Sex, female, n (%)	11 (73)	11 (73)	—
Height (m)	1.2 ± 0.1	1.2 ± 0.1	—
Weight (kg)	25.7 ± 5.1	27.6 ± 5.3	—
BSA (kg/m^2)	0.9 ± 0.1	0.9 ± 0.1	—
Clinical diagnosis			
PH Group, n (%)			—
PH Group 1			
1.1 IPAH	8	8	
1.2 HPAH	1	1	
1.4.4 PAH–CHD	3	3	
PH Group 3 (lung disease)			
3.5 developmental (BPD)	2	2	
PH Group 5 (multifactorial)			
5.4 complex (CHD)	1	1	
Comorbidities, n			—
Abernethy malformation Ib	1	1	
Marfan syndrome	1	1	
HHT (Osler's disease)	1	1	
DGUOK deficiency	1	1	
Trisomy 21	2	2	
Functional status			
FC	2.8 ± 0.1	2.4 ± 0.2	
6-minute walk distance (m), $n = 6$	396.3 ± 40.5	453.4 ± 54.6	0.204
Biomarker			
NT-proBNP (pg/ml)	3,571 ± 2,302	1,194 ± 629	0.277
Risk stratification (EPPVDN)			
Patients (with 2 caths)[a], n	10	10	
Risk	Intermediate risk	Intermediate risk	
HR score (max. 21)	5.5 ± 1.1	4.2 ± 1.3	0.034
LR score (max. 20)	9.7 ± 1.1	11.2 ± 1.3	0.049
Patients (< 2 caths)[b], n	15	15	
Risk	Intermediate risk	Intermediate risk	
HR score (max. 15)	4.5 ± 0.8	3.6 ± 0.9	0.031
LR score (max. 14)	6.5 ± 0.9	7.8 ± 1.1	0.018
Selexipag dose			
Daily discharge dose (μg)	827 ± 211	N/A	
Daily discharge dose (μg/kg)	43.8 ± 10.4	N/A	
Daily dose at follow-up (μg)	N/A	1,427 ± 265	
Daily dose at follow-up (μg/kg)	N/A	67.2 ± 10.0	
Daily final dose (μg)	N/A	1,267 ± 212	
Months on selexipag at f/u cath, $n = 10$	0	8.9 ± 1.3	
Months on selexipag (November 2019), alive and no LuTx, $n = 12$	0	22.5 ± 3.0	

BPD, bronchopulmonary dysplasia; BSA, body surface area; Cath, catheterization; CHD, congenital heart disease; DGUOK, deoxyguanosine kinase; EPPVDN, European Pediatric Pulmonary Vascular Disease Network; FC, functional class; HHT, hereditary hemorrhagic telangiectasia; HPAH, hereditary PAH; HR, higher risk; IPAH, idiopathic PAH; LR, lower risk; LuTx, lung transplantation; Max., maximum; mRAP, mean right atrial pressure; N/A, not applicable; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

[a]If the patient had a recent cardiac catheterization (within the preceding 12 months), then the maximum LR score (including 4 *criteria) is 20 and the maximum HR score (including 4 *criteria) is 21. For risk stratification, see Supplementary Figure S1 online.The starred criteria (*) in the new 2019 EPPVDN risk score are risk determinants/prognostic variables with a high prognostic impact on clinical outcome on the basis of retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP) and are counted as 2 points.

[b]If the patient did not have any recent cardiac catheterization within the preceding 12 months, then the maximum LR score (including 2 *criteria) is 14 and the maximum HR score (including 2 *criteria) is 15. Accordingly, the actual LR and HR scores can be provided as points per max. score (e.g., 8 of 20 LR score for a patient with recent cardiac catheterization data in the preceding 12 months).

The normalized EPPVDN risk scores (actual score divided by the max. score) are shown in Figure 5A-D (range 0-1). Values are presented as mean ± SEM. A Wilcoxon's signed-rank test was applied. $p < 0.05$ was considered as significant. All patients with PAH–CHD had the repair > 12 months before cardiac catheterization.

criteria and/or switch to parenteral prostacyclin analog, listing for lung transplantation (LuTx), or death.

Pharmacotherapy with oral add-on selexipag

A total of 15 patients were started on oral selexipag (right after Time Point #0). Patients were inpatients at the initiation of therapy (Supplementary Table S5 online), taking possible drug−drug interactions into account (Supplementary Table S6 online). All patients had moderate to severe PH (Supplementary Tables S6−S21 online). The starting dose was individualized at the discretion of the treating physician. The starting doses in children >10 kg, children 10−20 kg, and children > 20 kg were 50−100 μg, 100−200 μg and usually 200 μg, respectively. Doses were escalated as tolerated by the increments of 50−100 μg in the smallest children and 100−200 μg in larger children. Doses were increased every 2−3 days by increasing firstly the evening dose in the inpatient setting. Patients could finalize the dose escalation to the higher doses with longer intervals (1−2 weeks) in an outpatient setting. The target dose was the maximally tolerated dose, with respect to side effects (Supplementary Table S2 online).

Statistical analysis

The statistical analysis was based on clinical, laboratory, and hemodynamic data sets. The Wilcoxon's signed-rank test was used for the pairwise comparisons of data collected at baseline and follow-up. Spearman's correlation analysis was used to investigate the relationships between the hemodynamic variables relevant to disease progression and the proposed risk scores. All statistical analysis was performed in R. The changes in the examined parameters (Figures 1−5) were visualized using R and GraphPad Prism software. Details on the outcome variables and statistical analysis can be found in the Supplementary Materials online.

Ethics statement

This is a prospective, observational, exploratory study that does not fulfill the criteria of a trial (no fixed enrollment criteria and a variable follow-up period). All cardiac catheterizations were clinically indicated, and all clinical data were anonymized. Informed consent for study participation was obtained from the legal caregivers during the collection of biomarkers at Hannover Medical School, according to the principles expressed in the Declaration of Helsinki (Ethics Committee approval #2200).

Results

Demographic and clinical characteristics at baseline

Demographic characteristics of the 15 children with precapillary PH are summarized in Table 1 and are also shown individually in Supplementary Table S2 online, including FC, N-terminal pro b-type natriuretic peptide (NT-proBNP) at baseline, diagnosis, dosing, adverse events, medication, and clinical outcomes. The ranges of age and body weight were 7 months to 17 years and 5 kg to 73 kg, respectively. In FC 2 or 3, all patients were symptomatic with median serum NT-proBNP at baseline (Time 0) of 818 pg/ml (range 110 to > 35,000 pg/ml).

Individual drug response to oral selexipag, clinical follow-up, and outcomes

Here, we report the safety and efficacy of add-on oral selexipag for a median of 8 months (range: 4.5−20.0 months). The median clinical follow-up (outcome) for each patient who was started on selexipag between April 2016 and June 2018 is 24.5 months as of November 2019 (range: 6−43 months). There were no deaths during selexipag therapy. Two patients ultimately underwent bilateral LuTx and are doing well. One cachectic patient with heritable, rapid progressive PAH, initially improved on selexipag but died 18 months later from RV failure while on intravenous treprostinil. The remaining 12 children with chronic PAH are alive and currently stable on combination therapy with 3−4 oral PAH-targeted medications (Supplementary Table S2 online).

In our data analysis, we focused on the diagnostic determinants of risk, as published by the ESC/ERS,[8] World Symposium on Pulmonary Hypertension (2018),[6] and the EPPVDN (2019).[5] We applied the new 2019 EPPVDN pediatric PH risk score[5] in this observational, prospective study (Supplementary Figure S1 online; Supplementary Tables S7−S21 online; see text further below).

The individual drug response to oral add-on selexipag, as judged by cardiac catheterization (Figure 1) and echocardiography (Figure 2), was variable, with apparent better drug responses in less sick patients (for data per patient, see Supplementary Tables S7−S21 online and Figures 1 and 2). This result was consistent with the wide range of disease severity/stages and etiology of this Group 1 PH cohort (Table 1; Supplementary Tables S2−S4 online). The sicker, less drug-responsive patients tended to be older, that is, most likely had a longer history of PAH onset and RV pressure load (Patients #1, #6, #14, and #15; Supplementary Tables S7, S12, S20, and S21 online). However, this was not a consistent finding (Patients #2 and #8; Supplementary Tables S8 and S14 online).

Oral add-on selexipag improves the prognostic invasive hemodynamics at clinical follow-up

In the 10 patients with comparable sedation at both cardiac catheterizations (Figure 3), selexipag significantly improved mean right atrial pressure (mRAP, −2 mm Hg; Figure 3A), mPAP to mean systemic artery pressure (mSAP) ratio (−17%; Figure 3B), diastolic PAP to diastolic SAP ratio (−17%; $p < 0.05$; Figure 3C), mean TPG (mTPG, −17%; $p < 0.01$; Figure 3D), and dTPG (−5.8 mm Hg; $p < 0.05$, Figure 3E) at 5−18 months follow-up vs baseline. Moreover, at follow-up, patients treated with selexipag tended to have a lower PVR index (−13%; $p = 0.131$; Figure 3F) and PVR to systemic vascular resistance ratio (−20%; $p = 0.097$; Figure 3G) and a higher cardiac index (Qsi, +18%, $p = 0.322$; Figure 3H). Overall, the efficacy of selexipag on invasive hemodynamic was variable and often better in less sick patients, as outlined above.

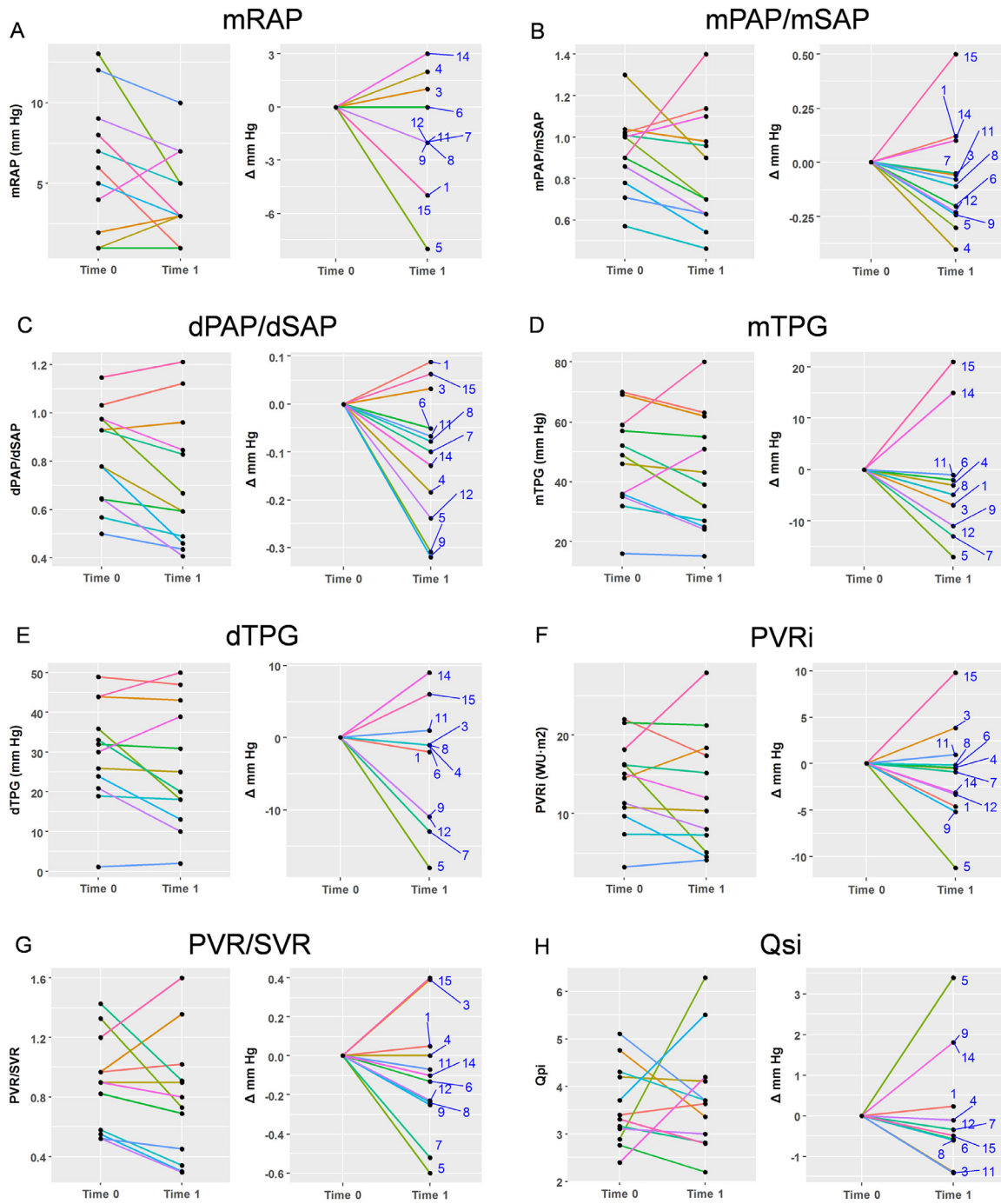


Figure 1 The direction of changes in catheterization variables between baseline and follow-up indicates a positive response to selexipag treatment in most patients. All patients with catheterization data at baseline and follow-up ($n = 12$), including patients #14 and #15 with different modes of anesthesia at Time 0 and Time 1, are shown. Perhaps because of various etiologies, disease stages, and treatment regimens, 3 patient clusters can be observed: non-responders (whose condition continues to deteriorate), moderate responders (deterioration stopped, condition mildly improved), and good responders (significant improvement in echo variables). dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; dSAP, diastolic systemic artery pressure; mSAP, mean systemic artery pressure; dTPG, transpulmonary pressure gradient; diastolic mTPG, mean transpulmonary pressure gradient; PVRi, pulmonary vascular resistance index; Qsi, cardiac index; SVR, systemic vascular resistance.

Oral add-on selexipag improves the echocardiographic variables of RV systolic function, exercise capacity, and NT-proBNP at follow-up

All 15 patients underwent clinical assessment and transthoracic echocardiography both at baseline and follow-up. The RV anterior wall diameter (Figure 4A) and RV end-diastolic diameter (Figure 4B) did not significantly and consistently change in the entire cohort (Supplementary Tables S7–S21 online). Likewise, the RV to left ventricular end-systolic ratio of the ventricular inner diameters (Figure 4C), as a surrogate of RV dilation, did not significantly change in the entire cohort. The add-on selexipag therapy was

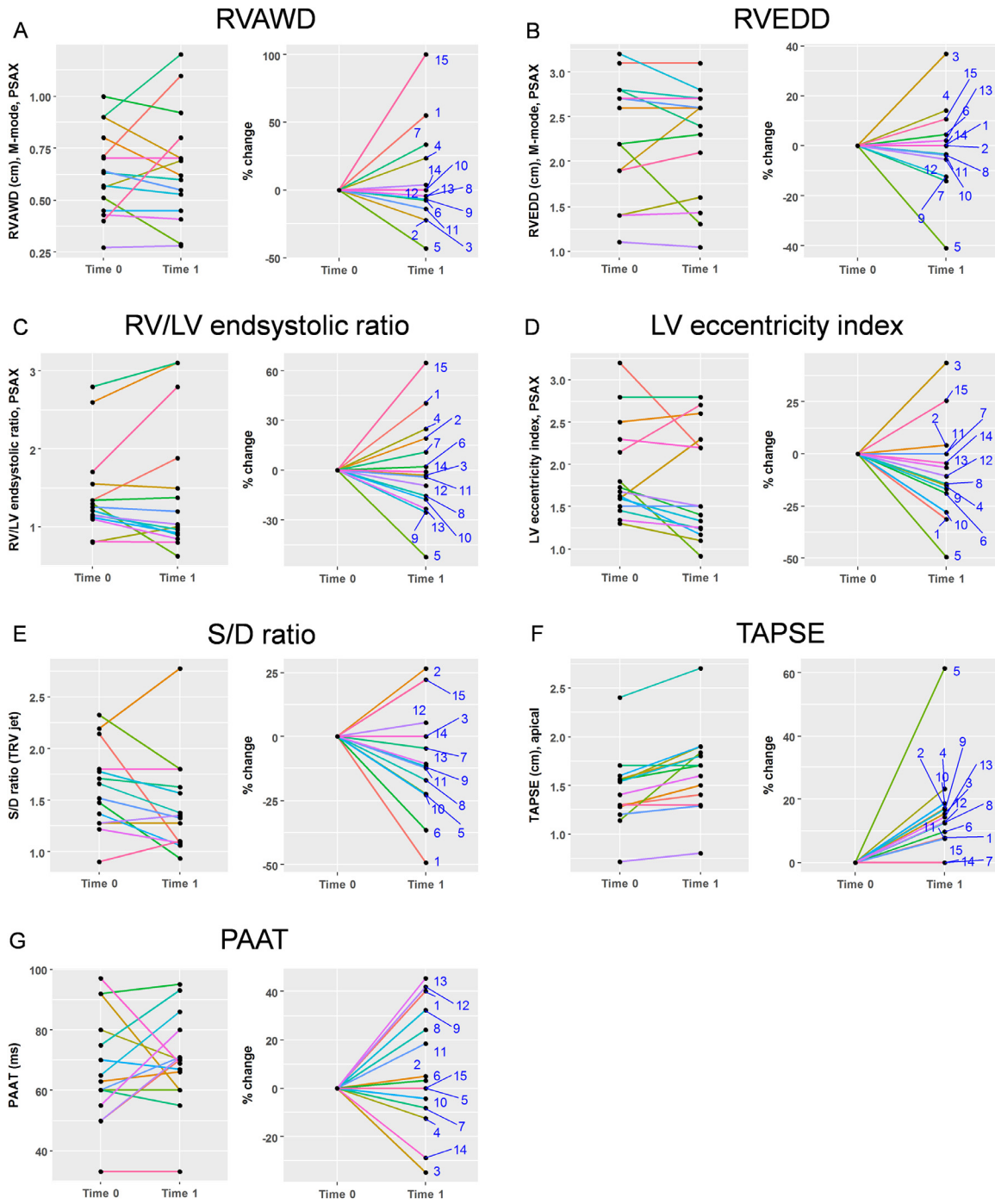


Figure 2 The direction of changes in the echocardiographic variables between baseline and follow-up indicate a positive response to selexipag treatment in most patients. All patients with catheterization data at baseline and follow-up ($n = 15$), including patients #14 and #15 with different modes of anesthesia at Time 0 and Time 1, are shown. The 3 clusters of responders (see legend for Figure 1) appear to exist in the echo variables as well. LV, left ventricular; PAAT, pulmonary artery acceleration time; RV, right ventricular; RVWAD, RV anterior wall diameter; RVEDD, RV end-diastolic diameter; S/D ratio, systolic to diastolic ratio; TAPSE, tricuspid annular plane systolic excursion.

associated with the improvement of longitudinal systolic RV function, as judged by tricuspid annular plane systolic excursion (TAPSE in cm, $p < 0.01$, Figure 4F; for TAPSE z-score by age, $p < 0.05$, see Supplementary Figure S2A online), consistent with the significantly improved invasive indicators of PVD severity such as mPAP to mSAP ratio and mTPG (Figure 3B−G). The pulmonary artery acceleration time displayed a large variability but tended to improve with selexipag therapy (Figure 4G; for pulmonary artery acceleration time z-scores,[17] see Supplementary Figure S2B online).

All patients were in FC 2 or 3 at baseline (Time 0; median FC = 3). In total, 6 patients changed FC from 3 to 2, which resulted in the median change from 3 to 2 between baseline (Time 0) and follow-up (Time 1; $p = 0.020$; data not shown). The 6-minute walk distance (6MWD) varied

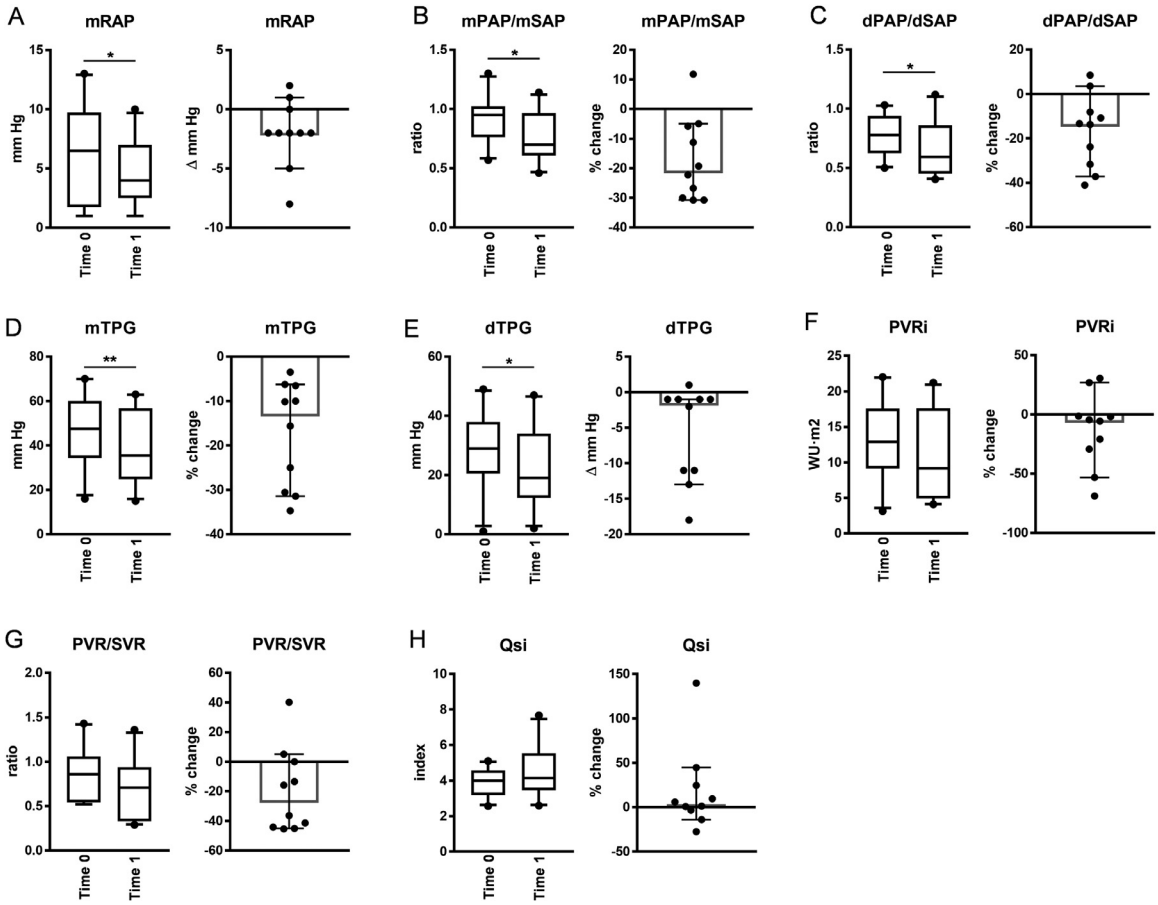


Figure 3 Patients with PAH treated with add-on selexipag show improvement in the invasive hemodynamic variables mRAP, mPAP/mSAP, dPAP/dSAP, mTPG, and dTPG at follow-up. Follow-up catheterization took place at a median of 8 months (5−18 months) after the start of selexipag. The Wilcoxon's signed-rank test was used. $*p < 0.05$, $**p < 0.01$, $n = 10$. The box and whisker plots (left) show the median, IQR, and 10th−90th percentile. The scatter plots (right) show the median with 95% CI. dSAP, diastolic systemic artery pressure; dTPG, diastolic transpulmonary pressure gradient; IQR, interquartile range; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; mSAP, mean systemic artery pressure; mTPG, mean transpulmonary pressure gradient; PAH, pulmonary arterial hypertension; PVRi, pulmonary vascular resistance index; Qsi, cardiac index; SVR, systemic vascular resistance.

greatly among the 7 patients and did not change significantly with selexipag at follow-up, confirming that 6MWD is not always a good indicator of exercise capacity, at least in children (Figure 4H). Serum NT-proBNP also varied greatly among the 15 patients with PAH at baseline (range 110−35,000) and improved in approximately half of the patients, while remaining nearly unchanged or worsened in the other half (Figure 4I, −24.7%, $p = 0.277$).

The new 2019 EPPVDN risk score can aid in the assessment of children with PH

We applied the new 2019 EPPVDN pediatric PH risk score[5] (Supplementary Figure S1 online) for the first time in a prospective analysis of a pediatric PAH cohort (Supplementary Tables S7−S21 online). By dividing the actual score by the maximum HR and lower risk (LR) score, we obtained normalized risk scores (on a scale from 0 to 1) as shown in Figure 5A−D. Add-on selexipag therapy improved both the combined non-invasive/invasive (echocardiography + cardiac catheterization, $n = 10$; Figure 5A and B) and the non-invasive only risk scores ($n = 15$; Figure 5C and D), meaning that the HR score was decreased and the LR score was increased at follow-up (Time 1) vs at baseline (Time 0; $p < 0.05$). Overall, by applying the compiled EPPVDN risk score, 7 of 15 patients with PAH improved with add-on selexipag, 4 of 15 stabilized, and 3 of 15 progressed with selexipag (Figures 1−4; Table 2).

We performed Spearman's correlation analysis to test whether the EPPVDN pediatric PH risk scores correlate with the already established, single indicators of risk such as NT-proBNP, mTPG, (Figure 5E and F), Qsi, and TAPSE (Supplementary Figure S3A and B online). Because NT-proBNP values varied greatly among the patients, we correlated the risk scores with serum NT-proBNP concentration as percent changes. NT-proBNP change was strongly correlated with both the non-invasive LR score ($\rho = -0.72$, $p = 0.006$; $n = 15$) and the combined non-invasive/invasive LR score ($\rho = -0.71$, p-value; $n = 10$; Figure 5E). Importantly, we found a good correlation of mTPG with the non-invasive HR score ($\rho = 0.71$, $p = 0.022$ at baseline and $\rho = 0.69$, $p = 0.027$ at follow-up) and LR score ($\rho = -0.64$, $p = 0.046$ at follow-up; $n = 15$; Figure 5F). Combined non-

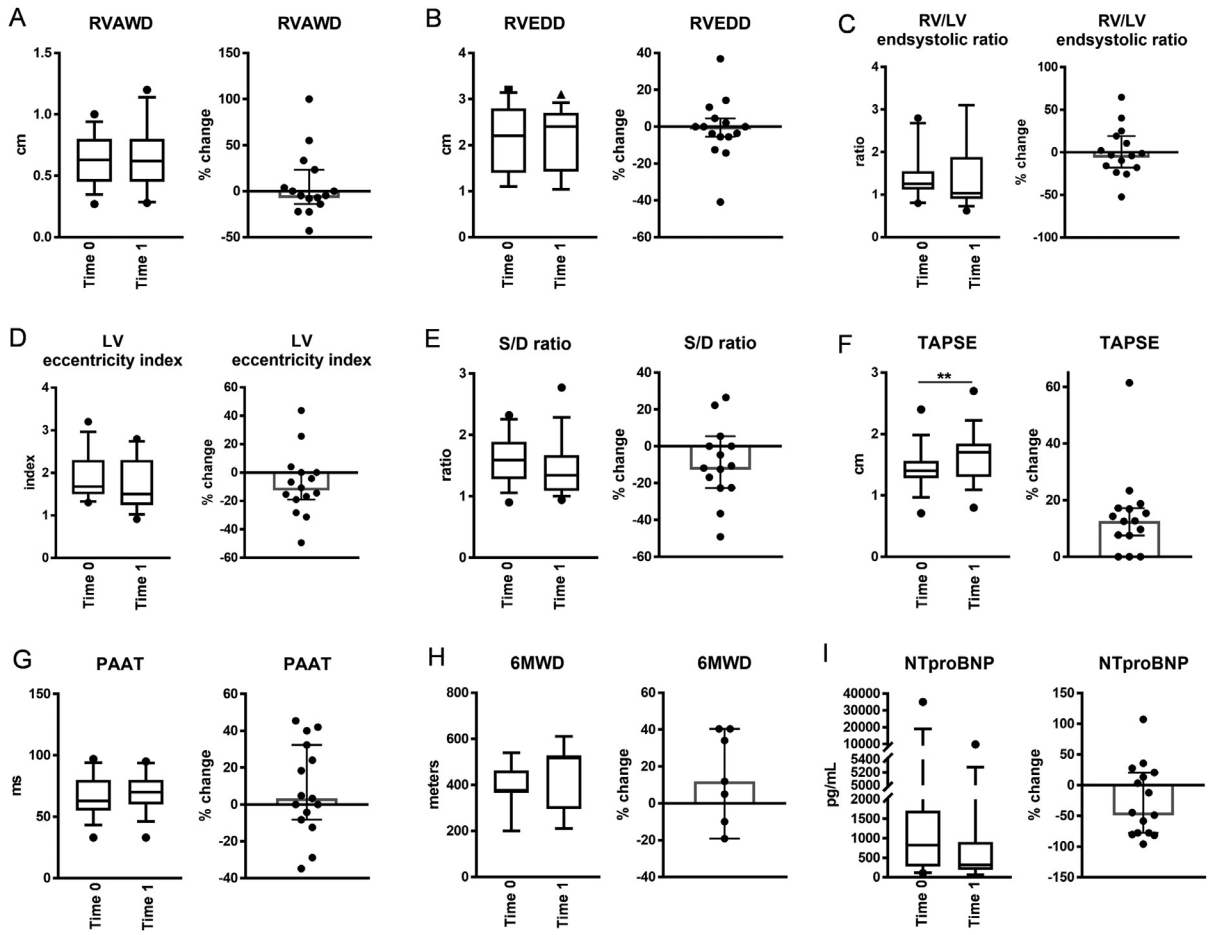


Figure 4 Patients with PAH treated with add-on selexipag show improvement in echocardiographic variable TAPSE (longitudinal RV systolic function) and a clear trend toward better 6MWD and serum NT-proBNP at follow-up. All 15 patients were included in the analysis, except for the 6MWD that only included 7 patients old enough to complete it. The Wilcoxon's signed-rank test was used. $*p < 0.05$, $**p < 0.01$. The box and whisker plots (left) show the median, IQR, and 10th−90th percentile. The scatter plots (right) show the median with 95% CI. 6MWD, 6-minute walk distance; IQR, interquartile range; LV, left ventricular; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAAT, pulmonary artery acceleration time; PAH, pulmonary arterial hypertension; RV, right ventricular; RVAWD, RV anterior wall diameter; RVEDD, RV end-diastolic diameter; S/D ratio, systolic to diastolic ratio; TAPSE, tricuspid annular plane systolic excursion.

invasive/invasive HR scores also correlated well (and slightly better) with mTPG ($\rho = 0.82$, $p = 0.004$ at baseline and $\rho = 0.77$, $p = 0.010$ at follow-up; $n = 10$; Figure 5F).

Taken together, our data show that the new EPPVDN risk score (Supplementary Figure S1 online), be it combined invasive/non-invasive or non-invasive only, can reliably indicate a change of clinical status with medication (Figure 5A−D) and can reliably determine the risk when compared with the established single determinants of risk and outcome. In contrast, only 2 patients decreased with their gross risk class (low, intermediate, high). Thus, the EPPVDN score is more sensitive than risk class only.

Adverse effects of oral selexipag in children with PH

None of the patients discontinued oral selexipag because of the adverse events (1 death, 2 LuTx). Individual adverse events are listed in Supplementary Table S2 online. The most common adverse events on selexipag were transient, predominantly occurred during the initiation of the drug, and mainly included nausea ($n = 7$ of 15), headaches ($n = 6$ of 15), and vomiting (n = 1 of 15). Jaw ($n = 2$ of 15) or extremity pain (1 of 15) occurred less frequently than described for adults in the GRIPHON trial (17%−26%)[15] (Supplementary Table S2 online). Start and up-titration of selexipag was conducted in the hospital for 4−10 days depending on the patient's condition. Up-titration was then continued as an outpatient every 2 weeks, as recommended for adults (Supplementary Table S2 online for dosing and individual adverse events). In most instances, the final selexipag dose was reached after 4−8 weeks. In 2 patients, the maximal selexipag dose had to be reduced slightly (minus 100−200 μg) because of significant, persistent decrease in oxygen saturation (drop by 5%−7% points).

Discussion

A substantial number of children, adolescents, and young adults with PAH may not tolerate parenteral prostacyclin analog therapy (IV administration of epoprostenol or IV/

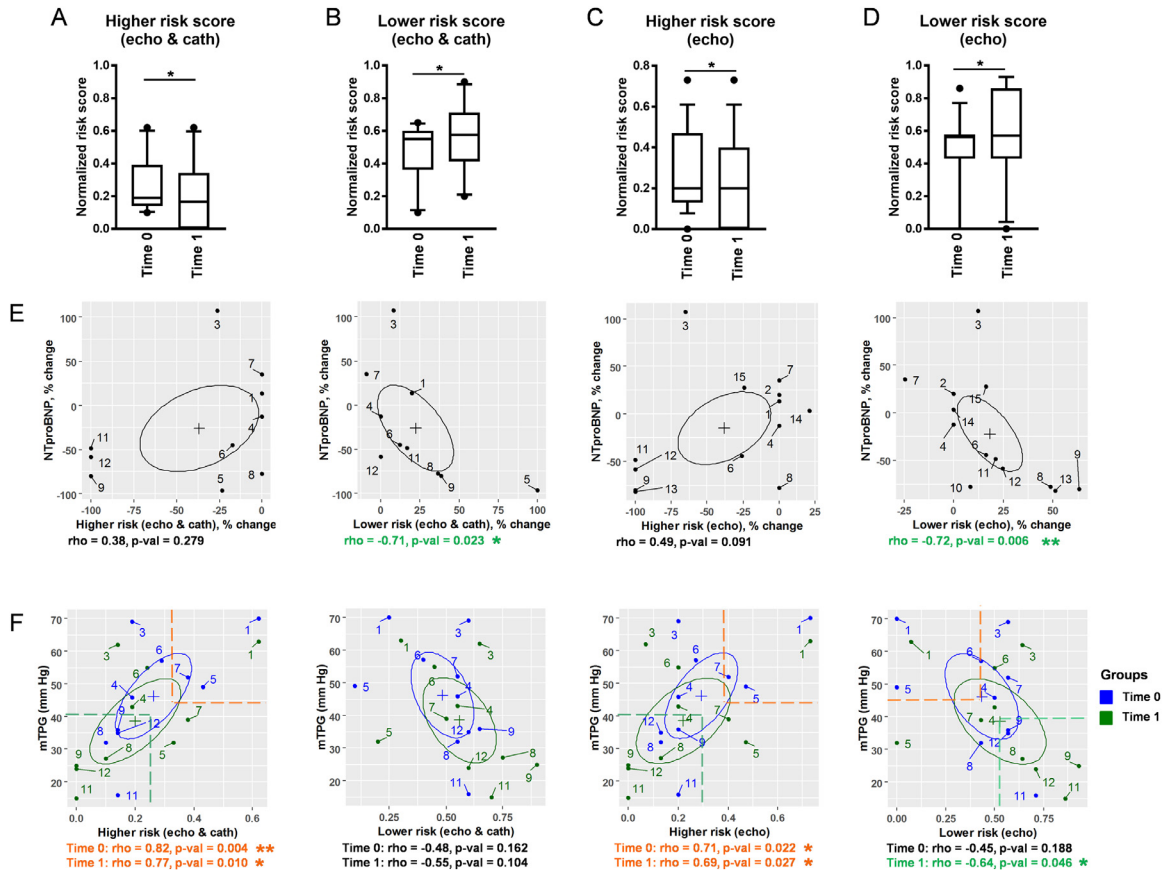


Figure 5 Improvement of combined invasive/non-invasive and non-invasive only EPPVDN pediatric PH risk scores with selexipag therapy at follow-up is supported by strong correlation of these scores with NT-proBNP and mTPG. In total, 10 patients underwent cardiac catheterization at baseline (Time 0, before add-on selexipag) and follow-up (5−18 months later)—see sub-headers or y axes "echo and cath" (a, b, and the 2 left panels in e, f). All 15 patients were included in the graphs showing non-invasive only risk scores—see sub-headers or y axes "echo" (c, d, and the 2 right panels in e, f). The Wilcoxon's signed-rank test was used. $*p < 0.05$, $**p < 0.01$. The box and whisker plots show the median, IQR, and 10th−90th percentile. (E and F) Spearman's rank correlation test, $*p < 0.05$, $**p < 0.01$. The correlation plots show means (cross) and 95% confidence ellipses. Cath, catheterization; EPPVDN, European Pediatric Pulmonary Vascular Disease Network; IQR, interquartile range; mTPG, mean transpulmonary pressure gradient; NT-proBNP, N-terminal pro b-type natriuretic peptide; PH, pulmonary hypertension.

subcutaneous administration of treprostinil) from a compliance or hemodynamic standpoint. Moreover, in pediatrics, it is quite common that caregivers and/or patients may refuse an invasive procedure or therapy such as a permanent central venous line for the continuous prostacyclin analog infusion. Even PH experts may be hesitant to pursue a central venous line that comes with possible adverse events such as thrombosis and line infection (1−2% per year), especially when the clinical status appears stable with few reported symptoms of mild/moderate severity. In this situation, oral selexipag, oral treprostinil (not available in Europe), or inhaled prostacyclin (6−9 times a day) can be therapeutic add-on options; however, it is unproven that either of these therapies can prevent RV failure in long-term PAH.

We conducted a prospective multicenter study to determine the safety and efficacy of oral selexipag in children with PAH. We found that selexipag treatment was associated with improvement in invasive hemodynamics (Figure 3), RV systolic function (Figure 4F), FC (median FC 3 was down to 2), and EPPVDN pediatric PH prognostic risk score (Figures 4 and 5) and a trend toward lower serum NT-proBNP concentrations (Figures 4I and 5E).

Most of the aforementioned variables have been shown to predict the clinical outcomes in adult PAH (FC, 6MWD, NT-proBNP or BNP plasma levels, Qsi, RAP, mixed venous oxygen saturation),[6] and recent studies indicate that this holds true for pediatric PAH: FC, NT-proBNP, mRAP, PVRi, Qsi, and positive acute vasoreactivityt test have been consistently reported to be predictive factors for clinical outcomes in pediatric PAH.[18−20] There was no death during oral selexipag use in our study. However, 3 of 15 patients showed disease progression and 2 ultimately underwent LuTx. One cachectic patient with PAH with an ACVRL1 mutation and hereditary hemorrhagic telangiectasia initially responded well to selexipag, gained weight, and was switched to an intravenous treprostinil pump, but eventually died (off selexipag) from right heart failure. It should be noted that patients with ACVRL1 mutations who do develop PAH are particularly young and have a worse prognosis than those with BMPR2 mutations,[21] or those without evidence for a known PAH gene mutation.

The efficacy of oral selexipag on clinical, invasive, and echocardiography variables was heterogeneous, as were disease stages and etiology of disease. There seemed to be a better drug response to the add-on selexipag in less sick patients. Overall, approximately 50% of our pediatric patients with PAH improved with add-on selexipag, 25% were stabilized, and 20% of the patients deteriorated during the observation period (Figures 1 and 2), similar to the clinical worsening rate of 22% in the adult patients in the GRIPHON trial.[15]

Pediatric experience with oral prostacyclin analog treprostinil vs oral IP receptor agonist selexipag

A recent, descriptive, observational North American study investigated the use of oral treprostinil in 28 children with PAH (prostanoid-naive or transitioning from parenteral or inhaled prostanoids; minimum 4 years, mean body weight of 16 kg)[22]: gastrointestinal adverse reactions were common, and half of the patients discontinued therapy within the 2-year study period.[22] An additional open-label study investigated add-on oral treprostinil in a small number of prostacyclin-naive children with PAH ($n = 12$),[23] similarly to our study but without invasive hemodynamic follow-up cardiac catherization. Add-on treprostinil had no significant beneficial effects on 6MWD, exercise capacity (cardiopulmonary exercise testing), cardiac magnetic resonance imaging variables, or Pediatric Quality of Life Inventory score.[23] Prostanoid-related adverse events with oral treprostinil were very common (56%−81%) and similar to those reported in adults.[23] In contrast, although the typical adverse effects were observed at the initiation of treatment (Supplementary Table S2 online), none of our patients discontinued selexipag because of adverse events.

A strength of our study is the comprehensive, invasive hemodynamic follow-up at baseline and after a median of 8 months pharmacotherapy of oral add-on selexipag (Figure 3). As outlined above, selexipag therapy was associated with the improvement of several key determinants of clinical outcomes and the EPPVDN risk scores. Based on our experience, the longitudinal RV systolic function as assessed by TAPSE stays normal for a long time and then turns abnormal rather late in pediatric PAH, probably explaining why it correlates well with survival in pediatric[18] and adult[24] PAH studies. The finding that the mean TAPSE z-score[25] was abnormal at baseline and increased to the normal values during selexipag therapy (Supplementary Figure S2a online) suggests a potential for RV function improvement with the lowering of mPAP/mSAP, mTPG, and dTPG or a direct beneficial effect of selexipag on RV performance (Figure 3B, D, and E).

First application of the novel 2019 EPPVDN pediatric PH risk score

The predictors of outcome have been defined that characterize a child or adolescent with PH at high risk.[5] In particular, WHO FC, NT-proBNP, and TAPSE have been identified as the surrogate variables for survival and thus can serve as treatment goals. A simplified adult PAH risk score based on the 2015 ESC/ERS guidelines particularly emphasizes the prognostic values of mRAP, Qsi, WHO FC, and NT-proBNP. The EPPVDN has introduced a new pediatric PH risk score (2019)[5] based on the simplified ESC/ERS (2016)[8] and World Symposium on Pulmonary Hypertension (2018)[6] adult risk scores, and pediatric-specific echocardiographic z-scores, for example, those for TAPSE.

We systemically applied the novel EPPVDN pediatric PH risk score in our cohort of patients with PAH, at baseline and after 4.5−20 months on selexipag pharmacotherapy. By combining the known predictors of clinical outcomes, including the starred, more important criteria (WHO FC; NT-proBNP; Qsi; mRAP; positive AVT), the EPPVDN pediatric PH risk score (Supplementary Figure S1 online) reflected the changes in those patients who responded well to add-on selexipag (Figure 5). Only 2 of 15 patients (#9 and #14) changed the gross risk category during the selexipag therapy. In contrast, the 2019 EPPVD risk score was more sensitive in detecting improvement in the overall cohort, be it total (combined non-invasive/invasive) risk scores (Figure 5A and B) or only non-invasive risk scores (Figure 5C and d, $p < 0.05$).

To explore whether HR and LR scores correlate significantly with the established variables of clinical outcomes, we performed Spearman's correlation and cluster analysis (mean and 95% confidence ellipse) of each risk score with mTPG (Figure 5F), Qsi (Supplementary Figure S3A), TAPSE z-score (Figure S3B), and serum NT-proBNP concentration (Figure 5E). We found that both total and non-invasive only HR scores showed strong positive correlations with mTPG. Moreover, the non-invasive LR score showed a strong negative correlation with mTPG. Both total and non-invasive LR scores showed strong negative correlations with serum NT-proBNP percent change.

Based on our current, observational (uncontrolled) study results, we speculate that the addition of selexipag to dual oral PAH therapy may be particularly useful in the early disease stages, which are characterized by moderately elevated PAP, mPAP to mSAP ratio, PVRi, and NT-proBNP; low to midrange intermediate risk scores (Supplementary Figure S1 online); and still normal systolic RV function. Careful dose escalation (Supplementary Table S5 online) and possible drug−drug interactions (Supplementary Table S6 online) must be considered when starting a pediatric patient with PAH in a tertiary PH center off-label on oral selexipag.

This study is limited by the low number of patients enrolled, the heterogenous etiology including genetic mutations, the wide age range, and the lack of randomization, blinding, and placebo control. Although these are typical limitations in the pediatric studies on a rare but fatal disease, we feel that our data collection and data analysis still provide very valuable information on the safety and efficacy of oral selexipag in children, adolescents, and probably young adults with PAH. To minimize the selection bias, we *consecutively* analyzed patients treated with selexipag at all 3 PH centers. Especially the systemic, combined

invasive/non-invasive hemodynamic comparison in 10 patients at baseline vs follow-up is quite comprehensive and provides new information not even available in previous adult PAH selexipag studies. Moreover, we used validated and rather new hemodynamic variables and the novel PH risk score (EPPVDN 2019),[5] all of which have not been reported in any single PAH study and also not in studies on the use of selexipag in adult PAH.

Conclusions

Oral add-on therapy with selexipag in children with PAH, although not approved in this age group to date, is well tolerated and appears to be safe when closely monitored. In children who underwent invasive cardiac catheterization at baseline and follow-up, selexipag treatment was associated with the improvement or stabilization of several outcome-relevant variables (mRAP, mPAP/mSAP, mTPG, dTPG, TAPSE, FC; Figure 3) in 12 of 15 patients at a median follow-up of 8 months (range: 6−43 months; Figures 1−5). The novel EPPVDN pediatric PH risk score (Supplementary Figure S1 online)[5] seemed to properly indicate these beneficial drug effects. It may, thus, be useful in the clinical follow-up but needs to be validated in larger prospective PAH studies to elucidate its broader applicability and usefulness in clinical care.

Disclosure statement

The authors have no conflicts of interest to disclose.

M.K. has served as a consultant for Actelion and received fees outside this work. H.W. has served on the then Speaker's Bureau and the advisory board for AbbVie and Actelion and received fees outside this work. G.H., K. M., M.B., and P.C. have no relationship with industry. G.H. received additional funding from the German Research Foundation (DFG, HA4348/6-2 KFO311).

This work was supported by the European Pediatric Pulmonary Vascular Disease Network (http://www.pvdnetwork.org), (https://nam03.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.pvdnetwork.org&data=02%7C01%7Cj.yee%40elsevier.com%7Ca4173accec674854e54708d7d4b37e18%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637211739706009880&sdata=g5IL6b79EXQmLKYvBzbQg2 × 5JCIlC6D%2FdzlELLISMvQ%3D&reserved=0), an international non-for-profit organization.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2020.03.029.

References

1. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J 2019;53:1801887.
2. Vonk Noordegraaf A, Chin KM, Haddad F, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. Eur Respir J 2019;53:1801900.
3. Hansmann G. Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol 2017;69:2551-69.
4. Frank BS, Ivy DD. Diagnosis, evaluation and treatment of pulmonary arterial hypertension in children. Children (Basel) 2018;5:E44.
5. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38:879-901.
6. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53:1801889.
7. Hansmann G, Apitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102(Suppl 2):ii67-85.
8. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
9. Barst RJ, McGoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012;125:113-22.
10. Maxwell BG, Nies MK, Ajuba-Iwuji CC, Coulson JD, Romer LH. Trends in hospitalization for pediatric pulmonary hypertension. Pediatrics 2015;136:241-50.
11. Geerdink LM, Bertram H, Hansmann G. First-in-child use of the oral selective prostacyclin IP receptor agonist selexipag in pulmonary arterial hypertension. Pulm Circ 2017;7:551-4.
12. Gallotti R, Drogalis-Kim DE, Satou G, Alejos J. Single-center experience using selexipag in a pediatric population. Pediatr Cardiol 2017;38:1405-9.
13. Spreemann T, Bertram H, Happel CM, Kozlik-Feldmann R, Hansmann G. First-in-child use of the oral soluble guanylate cyclase stimulator riociguat in pulmonary arterial hypertension. Pulm Circ 2018;8:2045893217743123.
14. Skoro-Sajer N, Lang IM. Selexipag for the treatment of pulmonary arterial hypertension. Expert Opin Pharmacother 2014;15:429-36.
15. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373:2522-33.
16. Koestenberger M, Hansmann G. Should we use the oral selective IP receptor agonist selexipag off-label in children with pulmonary arterial hypertension? Pulm Circ 2018;8:2045894018793580.
17. Koestenberger M, Grangl G, Avian A, et al. Normal reference values and z scores of the pulmonary artery acceleration time in children and its importance for the assessment of pulmonary hypertension. Circ Cardiovasc Imaging 2017;10:e005336.
18. Ploegstra MJ, Douwes JM, Roofthooft MT, Zijlstra WM, Hillege HL, Berger RM. Identification of treatment goals in paediatric pulmonary arterial hypertension. Eur Respir J 2014;44:1616-26.
19. Ploegstra MJ, Roofthooft MT, Douwes JM, et al. Echocardiography in pediatric pulmonary arterial hypertension: early study on assessing disease severity and predicting outcome. Circ Cardiovasc Imaging 2014;8:e000878.

20. Ploegstra MJ, Zijlstra WM, Douwes JM, Hillege HL, Berger RM. Prognostic factors in pediatric pulmonary arterial hypertension: a systematic review and meta-analysis. Int J Cardiol 2015;184:198-207.
21. Girerd B, Montani D, Coulet F, et al. Clinical outcomes of pulmonary arterial hypertension in patients carrying an ACVRL1 (ALK1) mutation. Am J Respir Crit Care Med 2010;181:851-61.
22. Kanaan U, Varghese NP, Coleman RD, et al. Oral treprostinil use in children: a multicenter, observational experience. Pulm Circ 2019; 9:2045894019862138.
23. Ivy DD, Feinstein JA, Yung D, et al. Oral treprostinil in transition or as add-on therapy in pediatric pulmonary arterial hypertension. Pulm Circ 2019;9:2045894019856471.
24. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 2006;174:1034-41.
25. Koestenberger M, Nagel B, Ravekes W, et al. Systolic right ventricular function in pediatric and adolescent patients with tetralogy of Fallot: echocardiography versus magnetic resonance imaging. J Am Soc Echocardiogr 2011;24:45-52.

Supplementary Material

Selexipag for the treatment of children with pulmonary arterial hypertension: first multicenter experience in drug safety and efficacy

Georg Hansmann[1], Katharina Meinel[2], Mila Bukova[1], Philippe Chouvarine[1], Håkan Wåhlander[3], Martin Koestenberger[2], on behalf of the European Pediatric Pulmonary Vascular Disease Network (EPPVDN).

Author affiliations:

[1]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany

[2]Divison of Pediatric Cardiology, Department of Pediatrics, Medical University Graz, Graz, Austria

[3]The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Institution of Clinical Sciences, Gothenburg University, Gothenburg, Sweden

Keywords: prostacyclin – IP receptor agonist – pulmonary hypertension – pulmonary vascular disease – heart failure – right ventricle

Online Supplement: supplemental text, 1 supplemental figure, 21 supplemental tables, 31 supplemental references

*** Correspondence should be addressed to:**

Prof. Dr. Georg Hansmann, MD, PhD, FESC, FAHA
Department of Pediatric Cardiology and Critical Care
Pulmonary Vascular Research Center
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany
Phone: +49 511 532 9594
Email: georg.hansmann@gmail.com
Website: http://www.pvdnetwork.org

ABBREVIATIONS and ACRONYMS

AVT = acute pulmonary vasoreactivity testing
BPD = bronchopulmonary dysplasia
CHD = congenital heart disease
CI = cardiac index
cGMP = cyclic guanosine monophosphate
DPD = diastolic pressure difference
EMA = European Medicines Agency
EPPVDN = European Pediatric Pulmonary Vascular Disease Network
ERS = European Respiratory Society
ESC = European Society of Cardiology
HIV = human immunodeficiency virus
IPAH/FPAH/HPAH = idiopathic/familial/heritable pulmonary arterial hypertension
LV = left ventricle
mRAP = mean right atrial pressure
dPAP = diastolic pulmonary artery pressure
mPAP = mean pulmonary artery pressure
sPAP = systolic pulmonary artery pressure
dSAP = diastolic systemic artery pressure (aorta)
mSAP = mean systemic artery pressure (aorta)
sSAP = systolic systemic artery pressure (aorta)
mTPG = mean transpulmonary pressure gradient
dTPG = diastolic transpulmonary pressure gradient (syn. DPG)
iNO = inhaled nitric oxide
NT-proBNP = NT-pro B-type natriuretic peptide
PAH = pulmonary arterial hypertension
PAWP = pulmonary artery wedge pressure
PAAT = pulmonary artery acceleration time
PCA = prostacyclin analog (alternative spelling: analogue)
PDA = persistent ductus arteriosus
PDE5 = phosphodiesterase 5
PH = pulmonary hypertension
PHVD = pulmonary hypertensive vascular disease
PVRi = pulmonary vascular resistance index (PVR indexed to body surface area)
Qpi = pulmonary blood flow index (Qp indexed to body surface area)
Qsi = systemic blood flow index (Qs indexed to body surface area), syn. cardiac index
RAP = right atrial pressure
RCT = randomized controlled trial
RV = right ventricle
RVAWD = right ventricular wall diameter (in diastole)
RVEDD = right ventricular enddiastolic diameter (syn. RVIDd)
RV/LV endsystolic ratio = ratios of inner diameters of RV over LV in endsystole
S/D ratio = systolic/diastolic duration ratio, CW Doppler flow of tricuspid regurgitation flow
SVRi = systemic vascular resistance (SVR indexed to body surface area)
TAPSE = tricuspid annular plane systolic excursion
TPG = transpulmonary pressure gradient
TR = tricuspid regurgitation
TRV = tricuspid regurgitation velocity (m/s)
VO_2 = oxygen consumption
WHO = World Health Organization
WSPH = World Symposium on Pulmonary Hypertension

SUPPLEMENTARY TEXT

SUPPLEMENTARY INTRODUCTON

The European Pediatric Pulmonary Vascular Disease Network

The European Pediatric PVD Network (EPPVDN) is a registered non-profit organization that is independent of any medical-scientific society and industry. The network strives to define and develop effective, innovative diagnostic methods and treatment options in all forms of pediatric pulmonary hypertensive vascular disease (PHVD), including specific forms such as PAH-congenital heart disease (CHD), pulmonary hypertension associated with bronchopulmonary dysplasia (BPD), persistent pulmonary hypertension of the newborn, and related cardiac dysfunction.

Pharmacodynamics and pharmacokinetics of the oral IP-receptor agonist selexipag

Pharmacodynamics, pharmacokinetics and preclinical studies of selexipag and ACT-333679 have been recently reviewed elsewhere (1). Briefly, selexipag is rapidly hydrolyzed to the active metabolite ACT-333679 (i.e., {4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino] butoxy}acetic acid), in hepatic microsomes. In healthy volunteers, selexipag at a 100µg dose, was metabolized to ACT-333679 with an elimination half-life of 7.9 h, while selexipag itself has a half-life of 1-2 h. The metabolite's long half-life enables a twice-a-day oral dosing regimen. In the event-driven GRIPHON trial in 1,156 adult PAH patients (2), the risk of the primary composite end point of death or a complication related to PAH was significantly lower with selexipag than with placebo. Subsequently, in May 2016, selexipag was ultimately approved by the European Medicines Agency (EMA) for oral use in adult PAH. This was followed by our report on the first pediatric use of selexipag in 2017 (3)

SUPPLEMENTARY METHODS

DEFINITIONS

Pulmonary Hypertension (PH), according to the recent WSPH (Nice, 2018)
mPAP > 20 mmHg in children >3 months of age at sea level

Pre-capillary PH (e.g., IPAH, PAH-CHD, also developmental PH such as PH-BPD):
mPAP > 20 mmHg
PAWP ≤ or left ventricular end-diastolic pressure (LVEDP) ≤ 15 mmHg*
PVR index ≥ 3 WU · m^2 (PVR ≥ 3 WU in adults), indicates pulmonary vascular disease (PVD)
Diastolic TPG (DPG) ≥ 7 mmHg (adjunct criterion)

Patient population

Patients were closely monitored as in- and outpatients, and treated medically according to the most recent consensus statement of the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC), European Society for Pediatric Research (ESPR) and the International Society of Heart and Lung Transplantation (ISHLT) (4). The three lead investigators agreed upfront to record all patients that they start on selexipag when treatment goals are not met, in order to jointly gather unique clinical data (prospective study). However, since patient analysis was based on compassionate, off-label use in consecutively treated, but selected patients, with no specifically defined, narrow inclusion and exclusion criteria, and because the follow-up period was variable, this study does not fulfill the definition of a trial. Different levels of consciousness or cardiodepressive agents during general anesthesia vs. sedation at two subsequent cardiac catheterizations (#14, #15 – both left out of Figure 3), can also bias the hemodynamic numbers and their interpretation.

Co-medication at baseline

All patients were on dual oral PAH-targeted medication at the time they were considered for add-on selexipag (**Table S2**). In most instances, the co-medication consisted of a PDE5-inhibitor and an endothelin receptor antagonist. One patient (#7) also received a calcium channel blocker. No patient was treated with prostacyclin or prostacyclin analog during the treatment with selexipag.

Cardiac catheterization

Patients underwent right and left heart catheterization in room air at baseline (timepoint 0), either under conscious, intravenous sedation (S) and local anesthesia for femoral access (n=13 catheterizations), or general anesthesia (GA; n=13 catheterizations). At the discretion of the PH-specialized pediatric cardiologist, 12 patients underwent a second cardiac catheterization 4.5-20 (median 8) months after the start of selexipag (time point 1 = follow up). Two of the 12 patients were excluded from the subsequent analysis of drug efficacy on invasive hemodynamics due to divergent mode of anesthesia (S vs. GA) during the subsequent cardiac catheterizations. Thus, 10 patients with similar sedation at both cardiac catheterizations (5 x S, 5 x GA), underwent more detailed statistical analysis.

Clinical assessment, echocardiography and biomarkers

All patients underwent clinical assessment, transthoracic echocardiography, and determination of serum NTproBNP at each inpatient visit. Moreover, patients were seen as outpatients at a minimum every 3 months, according to the EPPVDN consensus recommendations (4). Functional class was determined as defined by World Health Organization (WHO) or - for children less than 12 years of age - as defined by the EPPVDN

(5). Seven patients were old enough to perform a 6-minute walk test (6MWT) at baseline (time 0) and follow-up (time 1).

Statistical Analysis

The statistical analysis was based on clinical (WHO functional class, novel EPPVDN pediatric PH risk score), laboratory (NT-proBNP) and hemodynamic data sets (echocardiography, cardiac catheterization). The Wilcoxon signed-rank test was used to make pairwise-comparisons for data collected at baseline and follow-up. Spearman correlation analysis was used to investigate relationships between the hemodynamic variables relevant to disease progression and the proposed risk scores. To trace the treatment effects such as improvement of risk scores in relationship to individual hemodynamic variables in the entire cohort, we clustered Time 0 and Time 1 data points in the correlation graphs by displaying their mean and 95% confidence ellipses. A 95% confidence ellipse is a two-dimensional confidence interval with the property that multiple resampling of the underlying distribution and recalculation of the confidence region performed the same way would result in inclusion of the underlying mean in the 95% of the resampled confidence regions. All statistical analysis was performed in R. The changes in the examined parameters (Fig. 1-5) were visualized using R and GraphPad Prizm software.

SUPPLEMENTARY RESULTS

Changes in z scores for TAPSE

After 6-20 months of add-on therapy with oral selexipag, PH patients had significantly better z scores for TAPSE as surrogate of RV systolic longitudinal function (median TAPSE z score -2.73 → -1.26)(6). In contrast, PAAT, an inverse indicator of PAP and PVR elevation, (median PAAT z score -3.12 → -3.28) (7), showed high variability in the 15 children of various ages, and significant differences between the two time points. **See Supplementary Figure S2 further below.**

Selexipag dosing and possible desaturation

In two patients, the maximal selexipag dose had to be reduced slightly (minus 100-200 µg) because of significant, persistent desaturation (ca. 5-7 % points, e.g. patient #2). The mild selexipag dose reduction resulted in significant improvement of systemic saturations, probably due to less intrapulmonary arteriovenous (right-to-left) shunting and subsequently lower circulating drug metabolite levels.

Oral selexipag used to bridge a patient to intravenous PCA pump implantation

One patient with severe heritable PAH (ACVRL1 mutation) and hereditary hemorrhagic telangiectasia (HHHT, Osler's disease) initially responded well to the add-on of oral selexipag and demonstrated substantial clinical and hemodynamic improvement (patient #2, **Table S8**). The teenager had denied listing for lung transplantation as a first treatment option or a permanent central venous Broviac catheter and was judged not to be a lung transplant candidate. Fifteen months after the start of selexipag, and substantial weight gain (+3kg), the patient was transitioned from oral selexipag to continuous intravenous treprostinil, as

initially planned because of very progressive disease (3). Treprostinil was then administered via a subcutaneously implanted intravenous 20 mL pump (OMT Lenus pro) when sufficient body weight (30kg) for surgical implantation was reached. We conducted an overlapping dosing regimen, i.e. escalating intravenous treprostinil and weaning oral selexipag. Unfortunately, the patient experienced then rapid PAH progression and died on continuous intravenous treprostinil (off selexipag) from RV failure.

Oral add-on selexipag improves prognostic invasive hemodynamics further at later clinical follow-up (time 2) in one patient at the third cardiac catheterization

One patient with moderate PAH-repaired CHD (#12; now 20 months old) underwent a second follow-up catheterization 14 months after initiation of add-on selexipag (**Table S19**), and was found to have no PH anymore, under the current medication (spironolactone, sildenafil, macitentan, selexipag): mPAP 19 mmHg (-10 mmHg), mPAP/mSAP ratio 0.41 (-0.45), mTPG 13 mmHg (- 22 mmHg), dTPG 6 mmHg (-15 mmHg), PVR/SVR ratio 0.32 (-0.2).

The new 2019 EPPVDN risk score for pediatric PH, at baseline (no selexipag) and follow-up (on selexipag), can aid in the clinical assessment of risk

For each of the invasive hemodynamic, echocardiographic or biomarker PAH variables at timepoint 1 vs. 0, ≈50% of patients improved with add-on selexipag (≥ 10% positive change), ≈20-30% stabilized, and ≈20-30% progressed on selexipag (≥ 10% negative change; **Figures 1, 2, Tables S7-S21**). The change in overall PH risk score is discussed further below.

Overall, by applying the EPPVDN risk score to the patients at the time points 0 and 1, ≈50% of PAH patients improved with add-on selexipag (7/15; patient IDs: 3, 4, 6, 9, 11, 12, 13),

≈20-30% (4/15) did not change/stabilized (patient IDs: 4, 7, 8, 14), and ≈20-30% (3/15) progressed (IDs: 2, 10, 15), as defined under **Methods**. One PAH patient with an ACVRL1 mutation and hereditary hemorrhagic telangiectasia initially responded well to selexipag, gained weight, and was switched to intravenous treprostinil, but eventually died (off selexipag) from right heart failure.

SUPPLEMENTARY DISCUSSION

Clinical trial data on the efficacy and safety of selexipag in adults with PAH

In the large *GRIPHON trial (n=1156)*, adult PAH patients were eligible for enrollment if they were not receiving treatment for PAH or if they were receiving a stable dose of an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both (2). The primary end point was a composite of death from any cause or a complication related to PAH up to the end of the treatment period (defined for each patient as 7 days after the date of the last intake of selexipag or placebo). A primary end-point event occurred in 397 patients-41.6% of those in the placebo group and 27.0% of those in the selexipag group (HR in the selexipag group 0.60; 99% CI, 0.46 to 0.78; P<0.001) (2). A subsequent subgroup analysis of the large GRIPHON trial (2) included 110 adult PAH patients after repair of so-called simple congenital heart disease (CHD) shunt lesions (ASD, VSD, PDA): The rate of the primary composite endpoint of morbidity/mortality was lower in patients with corrected CHD-PAH (age 40.3±15.1 years) who were treated with selexipag compared with those treated with placebo (HR 0.58; 95% CI 0.25, 1.37) (8).

A *Cochrane meta-analysis* investigated the efficacy of parenteral prostacyclin/PCAs and oral PCAs/prostacyclin mimetics, including oral treprostinil and oral selexipag, in PAH (9). It demonstrated clinical and statistical benefit for intravenous prostacyclin with improved functional class, 6MWD, mortality, symptoms scores, and cardiopulmonary hemodynamics, but at a cost of adverse events (9). There was a statistical and small clinical benefit in functional class and hemodynamics for inhaled prostacyclin, but the effect was uncertain for mortality. However, the effect of oral “prostacyclins” was less evident (9). This Cochrane analysis suggests that both pediatric and adult PAH patients with symptoms and signs of severe disease (**Figure S1**), still should receive intravenous prostacyclin/PCA therapy according to the treatment algorithm (4, 10), while our exploratory data may indicate a role

for oral selexipag as add-on treatment in patients in the earlier disease stages. Oral selexipag may be used “off-label” in children with no sufficient response to dual oral PAH therapy (as in the current study), or potentially as upfront triple oral therapy, in selected cases when a sufficient clinical response to dual PAH-therapy is not expected.

Previously reported experience with oral selexipag in pediatric PAH

We began treating the first child with severe PAH in 2016 with oral selexipag, very soon after the medication became available (3). Add-on selexipag achieved hemodynamic and clinical improvement in this patient with very severe, heritable PAH, hereditary hemorrhagic telangiectasia (HHT=Osler’s disease, ACLVRL1 mutation, small atrial septal defect), including weight gain (+ 3kg bodyweight), so that the patient could be stabilized and transitioned to intravenous treprostinil therapy via an subcutaneously implantable intravenous pump (3). However, the patient died 15 months after selexipag start from rapid disease progression and RV failure (off selexipag, on intravenous treprostinil). It is well known that patients with ACVRL1 mutations who do develop PAH are particularly young and have a worse prognosis than those with BMPR2 mutations(11), or those without a known PAH gene mutation.

Pediatric experience with oral prostacyclin analog treprostinil vs. oral IP receptor agonist selexipag (full discussion)

A recent, descriptive, observational North American study investigated the use of oral treprostinil in a total of 28 children with PAH (prostanoid-naïve or transitioning from parenteral or inhaled prostanoids) (12): The youngest patient in this study was four years old and the smallest weighed 16 kg. Gastrointestinal adverse reactions were common, and half of the patients discontinued therapy within the two-year study period (12). An additional

open-label, uncontrolled study investigated the safety and efficacy of add-on oral treprostinil in a small number of prostacyclin-naïve children with PAH (n=12) (13), similarly to our study, but without invasive hemodynamic follow-up cardiac catheterization. Prostanoid-related adverse events with oral treprostinil were most common (56-81%) and similar to those reported in adults (13). Overall, oral add-on treprostinil had no significant beneficial effects on 6MWD, exercise capacity by cardiopulmonary exercise testing, clinically meaningful cardiac MRI variables, or Pediatric Quality of Life Inventory score (PedsQL™) (13).

In our current prospective study, 5 of the 15 patients had a body weight under 10 kg at start of selexipag, and 6 patients were under 4 years of age (an eight-month-old infant being the youngest). Although the typical adverse effects were seen at the initiation of treatment (**Table S2**), none of our patients discontinued selexipag because of adverse events.

Weaning parenteral prostacyclin analogs (treprostinil) to oral selexipag in "stable" children with PAH?

Intravenous treprostinil has been reported to be successfully transitioned to oral selexipag in 4 children with apparently "stable" PAH and a biventricular circulation, using a standardized, careful combined in-/outpatient protocol over several weeks, thereby overlapping intravenous treprostinil (weaning) with oral selexipag (up-titration) (14). Others reported on the transition of an infant with PAH (11.5 months, 8.6kg) from intravenous treprostinil (40 ng/kg/minute) to enteral selexipag (400 µg twice daily) with a good response and no adverse effects (15).

Oral selexipag use in small and/or very sick pediatric PAH patients

The three youngest, smallest patients in our multicenter cohort were 0.6-1.3 years old, with a body weight of 5-8 kg. One of these patients (#5; 8kg) could only be weaned from mechanical ventilation and inhaled nitric oxide (iNO) with add-on selexipag, because life-threatening pulmonary vascular crisis occurred immediately after any careful iNO weaning, despite concomitant intravenous sildenafil and oral macitentan therapy. We suggest oral selexipag may be used to transition a PAH patient from the intensive to the intermediate care unit, and to long-term oral (triple) combination therapy (14). In the two adolescent (14-15 years), very sick patients in functional class 3b (patients #14, 15) and 6 MWD below 400 m, oral selexipag did not seem to have any consistent beneficial effect on exercise capacity, invasive hemodynamics or RV function (**Tables 1b, S21, S22**; **Figures 1, 2, 3**). It is noteworthy that the EPPVDN risk scores did not correlate with cardiac index (Qsi). The cardiac index (Qsi) is the estimated flow over time variable that is based on multiple assumptions when applying the commonly used Fick principle (**Figure S3A**). However, estimations of Qsi (and Qpi, in the absence of a shunt), using chart reference values of maximum oxygen consumption (VO_2 max.) of healthy children, may be inaccurate, especially in sick patients in intermediate or intensive care units (16, 17).

Management of children with severe PAH resistant to dual oral combination therapy

In severe, largely resistant PAH, right atrial (atrial septostomy) or RV-decompressing therapies (such as reverse Potts shunt, i.e. a connection between left pulmonary artery and descending aorta) must be considered, in combination with PAH pharmacotherapy, to prevent death from pulmonary vascular crisis and low cardiac output. If right ventricular systolic function is still normal or only mildly decreased by cardiac MRI in children with systemic or slightly suprasystemic PAH, a reverse Potts shunt (18-22) may serve as bridge

to lung transplantation or palliative destination therapy (4, 23, 24), although the worldwide experience with Potts shunt is still very limited and must be considered experimental therapy at this stage.

Rapid progressive pediatric PAH and Listing for Bilateral Lung Transplantation

Based on our experience of the last 10 years, children with PAH and a known disease-causing mutation such as BMPR2 or ACVRL1, usually have very severe and aggressive disease (systemic or suprasystemic PAH) and thus, should be considered for early listing for lung transplantation. Moreover, pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are important differential diagnoses of severe PAH. The correct diagnosis of PVOD/PCH (joint as group 1.6 PH; **Table S1**) is difficult to make based on chest computed tomography and lung function criteria. However, correct diagnosis is critical as patients with PVOD/PCH can deteriorate on vasodilator therapy, including PCAs (epoprostenol, treprostinil, iloprost) and probably also selexipag. In any case, careful dose escalation (**Table S4**) and possible drug-drug interactions (**Table S5**) must be considered when starting a pediatric PAH patient in a tertiary PH center off-label on selexipag.

CONCLUSIONS

Pediatric and adult PAH patients with symptoms and severe disease, i.e. those in the “higher risk class”, still should receive intravenous prostacyclin/PCA therapy (9) according to the treatment algorithm. Whether oral selexipag can really serve as alternative or bridge to parenteral prostacyclin analog (PCA) therapy in pediatric patients at earlier disease stages must be determined in future studies. Our exploratory study indicates that oral selexipag may be more effective in earlier disease stages of PAH than in more advanced stages.

Children with severe, treatment-resistant, progressive PAH, should still be considered for early lung transplantation listing.

Take home message

The add-on use of oral selexipag in children must still be considered ‘‘experimental therapy” but appears to be safe when pursued carefully. Enrollment in any appropriate, future clinical selexipag study may become available and then should include frequent echocardiographic evaluations and also cardiac catheterization before and approximately six months after the start of selexipag. The decision to add selexipag as a third oral PAH agent, or to replace intravenously administered PAH prostacyclin analogs with oral selexipag in rather ‘stable’’ pediatric PAH patients, might become a future strategy, but should be substantiated in larger prospective studies.

CONFLICTS OF INTEREST

All authors declare they have no conflict of interest related to the content of this work.

M.K. has served as consultant for Acetlion and received fees outside this work. H.W. has served on then speaker’s bureau and the advisiory board for Abbvie and Actelion and received fees outside this work. G.H., K.M., M.B. and P.C. indicate no relationship with industry (RWI). The European Pediatric Pulmonary Vascular Disease Network is a non-for profit organization and has received annual donations or small grants for research purposes and travel to scientific conferences; such donors included pharmaceutical industry (Bayer, Pfizer and Actelion/Johnson&Johnson; < 10,000 Euro per year). Actelion/Johnson&Johnson, the producer of selexipag (Uptravi), had no influence on this publication, was not aware of the work being done, has not seen the data or the manuscript,

and had no role in the production of this manuscript. None of the authors was financially reembursed for her/his contributions to this manuscript.

SUPPLEMENTARY FIGURES

Figure S1. Risk Score Sheet for a Child with Pulmonary Hypertension (EPPVDN, 2019)

Patient

....

Surname, First Name **Date of Birth** **Patient´s ID**

Parameter	Measured Variable	Lower Risk Criteria		Higher Risk Criteria	
Clinical Presentation	**Clinical evidence of RV failure** (e.g. exertional dyspnoea, fatigue, dizziness, ankle swelling, epigastric fullness and right upper abdominal discomfort or pain)	no	☐	yes	☐
	Progression of symptoms	no	☐	yes	☐
	Syncope	no	☐	yes	☐
	Growth	Normal (height, BMI)	☐	Failure to thrive	☐
	WHO functional class	*I, II	☐	*III, IV	☐
Laboratory Results	**Serum NT-proBNP**	*Minimally elevated for age or not elevated	☐	*Greatly elevated for age, i.e. >1200 pg/mL (>1yr old) Rising NT-proBNP level	☐
Medical Imaging	**Echocardiography, CMR**	Minimal RA/RV enlargement No RV systolic dysfunction RV/LV endsystolic ratio < 1 (PSAX) TAPSE normal (z > -2) S/D ratio <1.0 (TR jet) PAAT > 100 ms (>1yr old)	☐ ☐ ☐ ☐ ☐ ☐	Severe RA/RV enlargement RV systolic dysfunction RV/LV endsystolic ratio >1.5 (PSAX) TAPSE (z < -3) S/D ratio >1.4 (TR jet) PAAT <70 ms (>1yr old) Pericardial effusion	☐ ☐ ☐ ☐ ☐ ☐ ☐
Cardiac Catheterization Last CATH study (date): ..... (preceding 12 months)	**Invasive Hemodynamics**	*Cardiac index >3.0 l/min/m^2 *mRAP <10 mm Hg mPAP/mSAP <0.5 Acute vasoreactivity +	☐ ☐ ☐ ☐	*Cardiac index <2.5 l/min/m^2 *mRAP >15 mm Hg mPAP/mSAP >0.75 PVRi >15 WU x m^2	☐ ☐ ☐ ☐

Lower Risk	Intermediate Risk	Higher Risk
= at least 3 starred (*) lower-risk and no higher-risk criteria (CATH available). or = at least 5 non-starred lower-risk and no higher-risk criteria (CATH not available). Date:…… ☐	= definitions of lower or higher risk not fulfilled. Date:…….. ☐	= at least 2 starred (*) higher-risk criteria including cardiac index (CATH available). or = greatly elevated NT-proBNP* and at least 5 non-starred higher-risk criteria (CATH not available). Date:…….. ☐

Figure S1: Pediatric Pulmonary Hypertension - Individual Risk Stratification. The above 2019 EPPVDN risk score sheet for a child with PH may be used in follow-up in clinics. While serum NT-proBNP and many of the listed echocardiographic variables have normative reference values (z-scores, range) and have been validated to some extent in children with PH, this is not the case for most invasive hemodynamic criteria. Thus, the risk stratification and combination of criteria in this figure is primarily a consensus of the EPPVDN. Changes in PAH medication and/or clinical condition often are associated with changes in hemodynamics. Only cardiac catheterization data from the preceding 12 months should be taken into account. The *starred criteria (*)* are risk determinants with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.

• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.

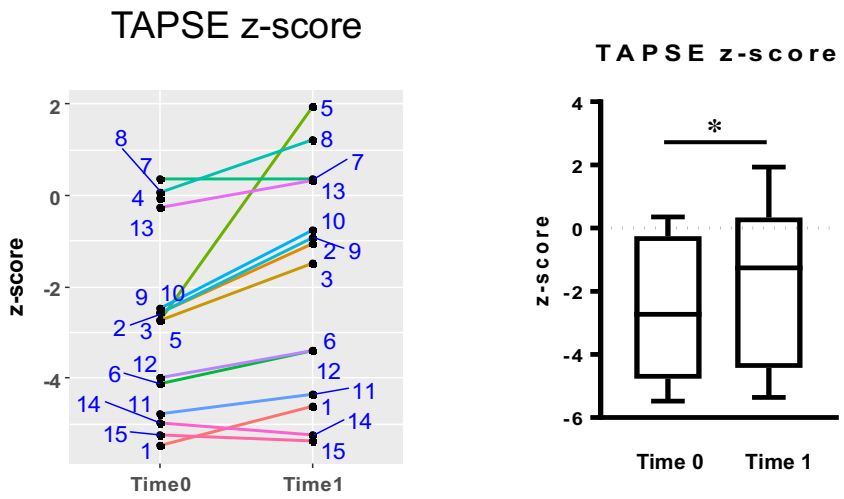
• If the patient has not had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.

• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).

Starred criteria (*) are taken from Dardi F, Manes A, Lo Russo GV, Rinaldi A, Gotti E, Zuffa E, De Lorenzis A, Pasca F, Cassani A, Guarino D, Palazzini M, Galiè N. A pragmatic approach to risk assessment in pulmonary arterial hypertension using the ESC/ERS Guidelines, Nov 2018, Circulation. 2018;138:A15572 (abstract). The risk criteria in this figure are modified Hansmann G, Koestenberger M et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019 Sep;38(9):879-901. doi: 10.1016/j.healun.2019.06.022 (ref.(4)). Abbreviations: CMRI-cardiac magnetic resonance imaging ; mPAP – mean pulmonary arterial pressure ; mRAP – mean right atrial pressure ; NT-proBNP - brain natriuretic peptide ; PVRI - pulmonary vascular resistance index; RA – right atrium ;RV – right ventricle ; TR – tricuspid regurgitation.

Figure S2 Analysis of selexipag efficacy on non-invasive hemodynamics TAPSE and PAAT expressed as z-scores showed significant improvement at follow-up only in TAPSE z-score.

A



B

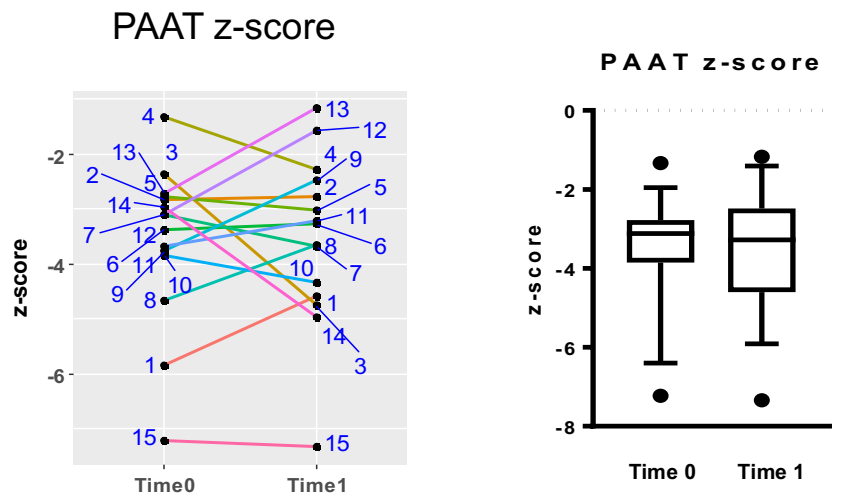


Figure S2. Analysis of selexipag efficacy on non-invasive hemodynamics TAPSE and PAAT expressed as z-scores showed significant improvement at follow-up only in TAPSE z-score. All 15 patients were included in the analysis. The Wilcoxon signed-rank test was used, * $P < 0.05$, ** $P < 0.01$. The box and whisker plots (right) show the median, IQR and 10-90th percentile.

Figure S3. Correlations of Cardiac Index (Qsi) and TAPSE z-score with risk scores show improvement in patients at follow-up

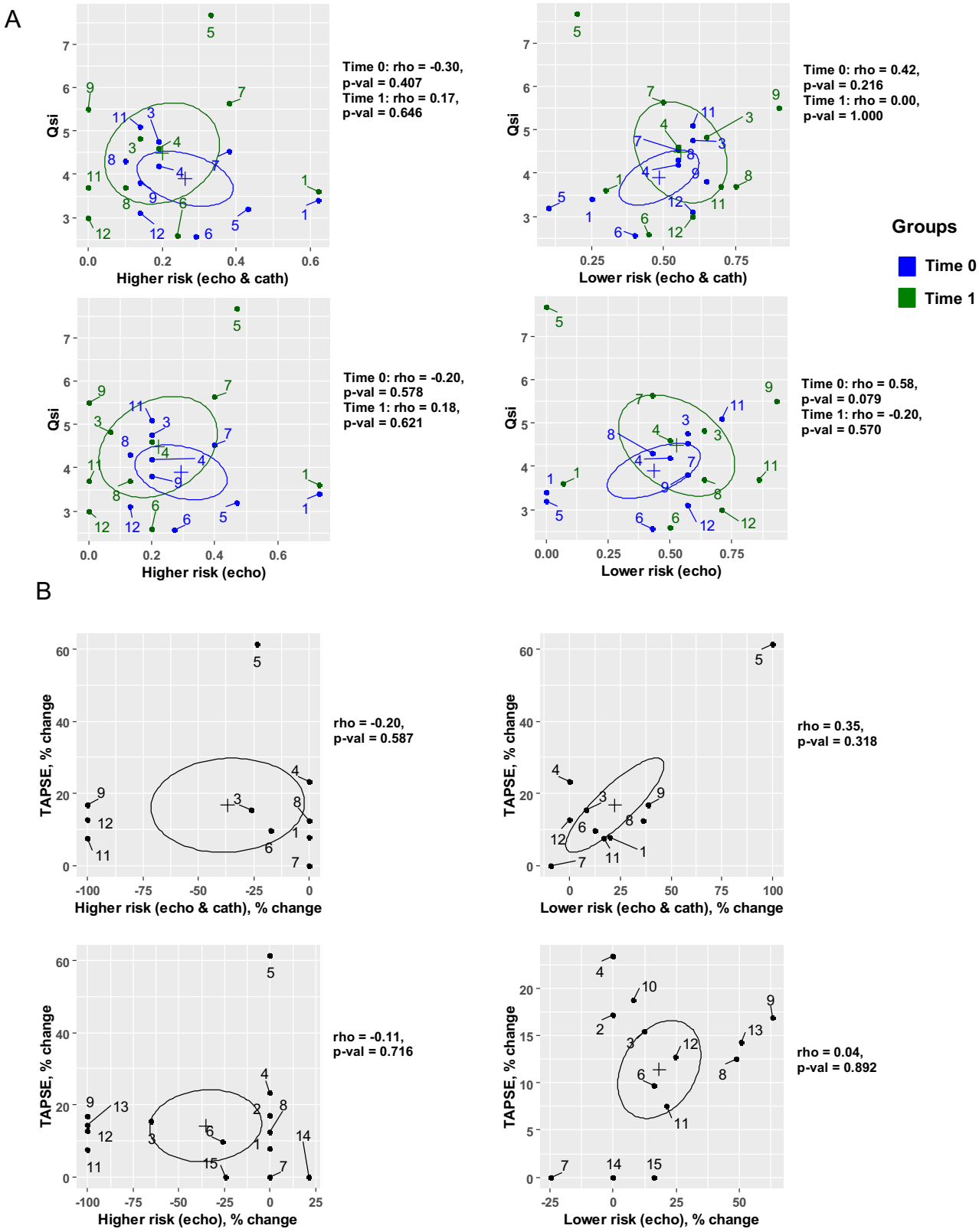


Figure S3: Correlations of Cardiac Index (Qsi) and TAPSE z-score with risk scores show improvement in patients at follow-up. All 15 patients were included in TAPSE correlations with the non-invasive risk scores. All other graphs are related to catheterization variables and limited to the 10 patients with the catheter data obtained under general anesthesia. (A-D) Spearman's rank correlation test was used, * P < 0.05, ** P < 0.01. The correlation plots show means (cross) and 95% confidence ellipses.

SUPPLEMENTARY TABLES

Table S1. Classification of Pulmonary Hypertension (6th World Symposium on Pulmonary Hypertension, Nice 2018)

Group 1-5 Pulmonary Hypertension	
1. Pulmonary arterial hypertension (PAH)	
1.1 Idiopathic PAH	
1.2 Heritable PAH	e.g. BMPR2, ACVRL1*, TBX4*, ENG, SOX17, KCNK3 and additional genes. See Table 4. (*enriched in pediatric vs. adult PAH)
1.3 Drug and toxin induced	e.g., amphetamines, methamphetamines, dasatinib, toxic rapseed oil
1.4 Associated with: 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease (CHD) 1.4.5 Schistosomiasis	CHD: of note, PH associated with complex CHD is classified as group 5.4 (see Table S7), and PH due to obstructive post-capillary lesions is classified as group 2.4 PH (see Table S8). For PH associated with HIV or schistosomiasis, see Table 12.
1.5 PAH long-term responders to calcium channel blockers	See main text for acute vasoreactivity testing (AVT).
1.6 PAH with overt features of venous/capillary (PVOD/PCH) involvement	Pulmonary function tests: Decreased DLCO (frequently <50%) Chest HRCT: e.g. Septal lines; Centrilobular ground-glass opacities/nodules Response to PAH therapy: possible pulmonary edema. PVOD/PCH may be associated with EIF2AK4 mutations.
1.7 Persistent PH of the newborn syndrome	See Table S9.
2. Pulmonary hypertension due to left heart disease	2.1 PH due to heart failure with preserved LVEF 2.2 PH due to heart failure with reduced LVEF 2.3 Valvular heart disease 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3. Pulmonary hypertension due to lung diseases and/or hypoxia	3.1 Obstructive lung disease 3.2 Restrictive lung disease 3.3 Other lung disease with mixed restrictive/obstructive pattern 3.4 Hypoxia without lung disease 3.5 Developmental lung disorders (s. Table S10)
4. PH due to pulmonary artery obstructions	4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions
5. Pulmonary hypertension with unclear multifactorial mechanisms	5.1 Hematological disorders 5.2 Systemic and metabolic disorders 5.3 Others 5.4 Complex congenital heart disease

Table S1. PVOD, pulmonary veno-occlusive disease, PCH, pulmonary capillary hemangiomatosis

Table S2. Individual PAH patient characteristics and medication at the time of selexipag start

ID	Age (years)	Gender (M/F)	Weight (kg)	BSA (m^2)	FC (1-4)	NTproBNP (pg/mL)	Diagnosis	Selexipag 1st dose (µg) Final dose (µg) Months on drug Adverse events	Medication	Outcome
1	12.8	F	27.7	1.0	3	703	HPAH, HHT, ACVRL1-mutation (group 1.2 PH)	200 - 0 - 200 1600 - 0 – 1600 On SEL: 8/15 →TREP AEs: nausea, vomiting, headaches, dizziness	SIL, BOS Add other meds	No LuTx; PH Progression. Transitioned to i.v. TREP; Died off selexipag→ RV failure
2	2	F	8	0.42	3	8069	IPAH, large ASD II (group 1.1 PH)	100 - 0 - 100 400 - 0 - 400 On SEL: 4.5/- →LuTx AEs: none	SIL+MAC+ILO inhal. (stopped) Add other meds	Progression of PH. LuTx, 5/2017
3	8.4	F	27	0.95	2	124	IPAH, PDA, s/p PDA banding Nov. 11, 2012 s/p PDA stenting Jun. 13, 2017 (group 1.1 PH)	200 - 0 - 200 1000 - 0 - 1000 On SEL: 7/29 AEs: nausea, headaches	SIL+MAC Add other meds	alive
4	1.5	M	9.6	0.50	2	330	PAH-CHD, large VSD (12mm); treat to close (fenestrated VSD patch) (group 1.4.4 PH)	100 - 0 - 100 600 - 0 - 600 On SEL: 7/26 months AEs: none	SIL+MAC Add other meds	alive
5	1.5	F	7	0.39	3	>35000	IPAH, mito-gene deletion (DGUOK), s/p liver Tx x 2 (group 1.1 PH)	100 - 0 - 100 500 - 0 - 500 On SEL: 6/26 months AEs: none	SIL+MAC Add other meds	alive
6	17	M	44	1.45	3	110	IPAH (genetic testing pending), small ASD II, undefined CTD (group 1.1 PH)	200 - 0 - 200 800 - 0 - 800 On SEL: 8/11 AEs: nausea, headaches	SIL+MAC+ILO inhal. (stopped) Add other meds	alive
7	2	F	9.6	0.44	2	1710	IPAH, PDA, ASD II, trisomy 21 (group 1.1 PH)	100- 0 - 100 400 - 0 - 400 ON SEL: 6/10 AEs: none	SIL, BOS, AML, SPI Add other meds	alive
8	16.8	F	73	1.9	3	345	PAH, portal hypertension Abernethy malformation 1b (group 1.4.3 PH)	200 -0- 200 600 – 0 - 600 On SEL: 16/43 AEs: headaches	MAC, SIL, FUR, SPI, PPI, UDC	alive

ID	Age (years)	Gender (M/F)	Weight (kg)	BSA (m^2)	FC (1-4)	NTproBNP (pg/mL)	Diagnosis	Selexipag 1st dose (µg) Final dose (µg) Months on drug Adverse events	Medication	Outcome
9	6.6	M	22	0.89	3	981	IPAH PFO, mild biliary cirrhosis (group 1.1 PH)	200 -0- 200 400 – 0 - 400 On SEL: 12/31 AEs: extremity pain, jaw pain, dizziness	MAC, SIL, UDC	alive
10	10.7	F	47.1	1.45	2	274	PH-BPD (group 3.5 PH) Preterm 25+0 (group 3.5 PH)	200 -0- 200 200–0- 200 On SEL: 20/24 AEs: nausea, headaches, jaw pain, cough	MAC, SIL, SAB	alive
11	4.5	M	17.5	0.71	2	1233	PAH-CHD PA-VSD, XXY MAPCAs (group 1.4.4 PH)	200 -0- 200 200 –0- 200 On SEL: 20/24 AEs: nausea, diarrhea, myalgia, headache	MAC, SAB, SIL, FUR, SPI, PPI, KA	alive
12	0.6	F	5.5	0.28	3	2181	PAH-CHD/ PH-BPD AV Canal, Trisomy 21, s/p banding, Preterm 30+0 weeks (group 1.4.4 + 5.4/ 3.5 PH)	50 -0- 50 200 –0- 200 On SEL: 5/15 AEs: diarrhea, arterial hypotension	SPI, ASA, SIL, MAC	alive
13	0.8	F	5	0.29	3	1710	PH-BPD,VSD, preterm 26+2 (group 3.5 PH)	50 - 0- 50 200 –0- 200 On SEL: 6/6 AEs: diarrhea	SIL, MAC, FUR	alive
14	14.5	F	36.9	1.26	3b	818	IPAH, Marfan, restrictive lung disease, mitral regurgitation, atrial flutter, IBD (group 1.1 PH/1.4.1 PH)	200 - 0 – 200 1000 – 0 - 1000 On SEL: 12/25 AEs: nausea, headache, retroorbital pressure	SIL, BOS, DIG, FRU, SPI, PRED, AZA, LOS, SOT, PPI	alive
15	15.4	F	41.5	1.34	3b	244	IPAH, left bronchial stenosis, s/p ALL and EBV-lymphoma, atrial septostomy before selexipag (group 1.1 PH)	200 - 0 - 200 1200 – 0 - 1200 On SEL: 8/25 →LuTx AEs: nausea, jaw pain, low appetite, weight loss	SIL, BOS, DIG FRU SPI, O_2	Progression of PH. LuTx 2/2019

Table 2. *Individual PAH patient characteristics and medication at the time of selexipag start.* Full legend on the next page

Table S2. *Individual PAH patient characteristics and medication at the time of selexipag start.* Medication was unchanged 3 months prior to start of selexipag.
First dose means the very first starting dose (always start with evening dose, followed by twice daily dosing; oral selexipag should be taken with food).
Final dose means here the long-term dose achieved with acceptable adverse effects.
Months on drug x/y means that a patient was x months on oral add-on selexipag (SEL) between the baseline (time 0) and first follow up cardiac catheterization (time 1), and a total of y months on add-on oral selexipag on November 30, 2019.
When applying the compiled EPPVDN pediatric PH risk factor score (**Figure S1**) to the observation period between time 0 and time 1 (on selexipag), we defined "clinical improvement" as a reduction in the number of high risk criteria without concomitant reduction in the number of low risk criteria, and "progression" as increase in the number of high risk criteria and/or switch to parenteral prostacyclin analog (PCA), listing for lung transplantation (LuTx), or death.
Overall, by applying the EPPVDN risk score, ≈50% (7/15) of PAH patients improved with add-on selexipag (#3, 5, 6, 9, 11, 12, 13), ≈20-30% (4/15) stabilized (#4, 7, 8, 14), and ≈20-30% (3/15) progressed on selexipag (#2, 10, 15; Figures 1-4).
One patient with very severe, heritable PAH (ACVRL1 mutation) and hereditary hemorrhagic telangiectasia, who refused a Broviac-type permanent central venous catheter, initially responded well to oral selexipag, gained weight, and was then switched to intravenous treprostinil via a subcutaneous intravenous pump (OMMT Lenus Pro, 20ml), but eventually died from right heart failure.
All patients experienced flush at initiation of therapy (not mentioned as adverse event).
Abbreviations: AEs, adverse events; ALL, acute lymphocytic leukemia; AML, amlodipine; ASA, acetylsalicylic acid; (P.O.); ASD, atrial septal defect; AZA, azathioprine (P.O.); BSA, body surface area; BOS, bosentan (P.O.); BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CTD, connective tissue disease; DIG, digoxin (P.O.); EBV, ebstein barr virus; FC, functional class; FUR, furosemide (Lasix) (P.O.); HPAH, heritable PAH; IBD, intestinal bowel disease; AH, idiopathic PAH (WPSH 2018 category 1.1); i.v., intravenous; KA, potassium (Rekawan); KI, potassium iodide (P.O.); LuTx, lung transplantation; MAC, macitentan (P.O.); MAPCAs, main aortopulmonary collateral arteries; mo., months; O_2, oxygen by nasal canula; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PH, pulmonary hypertension; PPI, proton pump inhibitor (P.O.); PRED, prednisone (P.O.); RV, right ventricle; SAB, salbutamol (P.O.); SIL, sildenafil (P.O.); SOT, sotalol (P.O.); SPI, spironolactone (P.O.); TREP, treprostinil; UDC, ursodiol; VSD, ventricular septal defect

.

Table S3. Classification of Pediatric Pulmonary Hypertensive Vascular Disease (PPHVD) (PVRI, Panama, 2011): 10 Basic categories of PPHVD

#	Basic PPHVD Category
1	Prenatal or developmental pulmonary hypertensive vascular disease
2	Perinatal pulmonary vascular maladaptation
3	Pediatric cardiovascular disease
4	Bronchopulmonary dysplasia
5	Isolated pediatric pulmonary hypertensive vascular disease (isolated pediatric PAH)
6	Multifactorial pulmonary hypertensive vascular disease in congenital malformation syndromes
7	Pediatric lung disease
8	Pediatric thromboembolic disease
9	Pediatric hypobaric hypoxic exposure
10	Pediatric pulmonary vascular disease associated with other system disorders

Table S3. Ten Basic categories of Pediatric Pulmonary Hypertensive Vascular Disease (PPHVD); Paediatric Taskforce of the Pulmonary Vascular Research Institute, Panama 2011 From *del Cerro Pulm Circ, 2011(25).*

.

Table S4. Hemodynamic Definitions, Invasive Measures and Clinical Implications

Table S4a. Hemodynamic Definitions of Pulmonary Hypertension

Definition [a, b, c, d]	**Invasive measures** [a, b, c]	**PH-group**
Pulmonary hypertension (PH) [a, b]	mPAP > 20 mmHg	1-5
Pre-capillary PH [a, b]	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVRi ≥ 3 WU · m^2	1, 3, 4 and 5
• Isolated post-capillary PH (Ipc-PH, as defined for adults) [a, b] or • Combined post-capillary and pre-capillary PH (Cpc-PH, as defined for adults)	mPAP > 20 mmHg PAWP > 15 mmHg PVRi < 3 WU · m^2 DPD < 7mmHg (adults) [c] mPAP > 20 mmHg PAWP > 15 mmHg PVRi ≥ 3 WU · m^2 DPD ≥ 7mmHg (adults) [c]	2 and 5 2 and 5

Table S4b Invasive Measures and Clinical Implications

Measure [a-f]	**Abnormality**	**Clinical implications**
Mean RAP	Mean RAP >15mmHg Mean RAP >20mmHg	"Higher risk", RV failure, higher mortality Contraindication for atrial septostomy
mPAP (mmHg) [a, b, e]	mPAP > 20mmHg	Definition of PH (WSPH, 2018)
mPAP/mSAP	mPAP/mSAP >0.3 mPAP/mSAP >0.75	Adjunct criterion for presence of PH Higher mortality
PAWP (mmHg)	PAWP > 15 mmHg	Criterion for post-capillary component [c]
PVR index (Wood units · m^2) [b, e]	PVR index >3 WU · m^2 PVR index >8 WU · m^2 PVR index >15 WU · m^2	Criterion for pre-capillary component [c] Inoperability in PAH-CHD "Higher risk", higher mortality
Cardiac index (L/min · m^2) by Fick principle or thermodilution	CI < 2.5 L/min · m^2	"Higher risk", low cardiac output, higher mortality
SVO_2, %	SVO_2 < 55%	Low cardiac output, higher mortality
Acute vasoreactivity testing [f]	AVT negative	see Tables 5 and 8; Figures 2, 3 and S1

.

Table S4. Hemodynamic definitions according to 2015 ESC/ERS guidelines on PH (Galie et al Eur Heart J, 2016)(26), modified according to WSPH 2018 (Simonneau G et al. Eur Resp J, 2018)(27).

[a]The definitions of the PH subtypes in table 3a apply only when cardiac index is either normal or decreased (but not in hyperdynamic states with significantly increased cardiac index, e.g. patients receiving high dose prostacycline analog infusion or those with sepsis).

[b]Of note: At the WSPH 2018, the definition of PH has changed to a lower mPAP cut off value (mPAP > 20mmHg) and now also includes a PVR and PVR index cut off value of 3 WU (adults) and 3 WU · m^2 (children) to distinguish pre-capillary from isolated post-capillary PH (Ipc-PH). The 2015 ESC/ERS guidelines had defined a higher mPAP cut off value (mPAP ≥ 25mmHg). All patients (#1-15) fulfilled both definitions of PH.

[c] Of note: Diastolic transpulmonary pressure gradient (DPG, syn. dTPG) is an adjunct criterion to determine pre- and postcapillary components in adults with PH. DPD (dTPG) has been a criterion in the 2015 ESC/ERS guidelines but was omitted in the WSPH 2018 consensus documents.

[d] Of note: Previous terms such as “reactive PH” or “out of proportion PH” were removed.

[e] It should also be noted that there is inconsistency in the published literature on the cut off values that define the different types of PH (pre-capillary, isolated postcapillary, combined pre- and post-capillary PH>; mPAP, PAWP, PVR, PVR index) and mPAP cut off values for AVT, mostly due to inaccurate use of mathematical symbols (> vs. ≥ and < vs. ≤, for mPAP and PVR).

[f]It should be noted that the WSPH 2018 has recommended the use of the Sitbon criteria for a positive AVT in children with IPAH/HPAH, as defined by a decrease in mPAP by at least 10 mmHg to a mPAP value below 40 mmHg without a fall in cardiac output (Rosenweig EB et al. Eur Resp J, 2018)(28). However, the majority of the EPPVDN’s voting group found there is insufficient evidence for such a recommendation in children, and prefered to continue to recommend the modified Barst criteria that define a positive AVT, as outlined in the above table.

See also Table 5, Table 8, Figure 2 (determinants of risk), Figure 3. (algorithm on PAH associated with congenital heart disease), and Figure S1 (risk score sheet for a child with PH).

Abbreviations: CI = cardiac index; dPAP = diastolic pulmonary arterial pressure; DPD = diastolic pressure difference (dPAP-PAWP; synonym2: diastolic transpulmonary pressure gradient, dTPG); mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure;

.

Table S5. Oral Pharmacotherapy with Selexipag for Pediatric PAH

Agent	Indication	Dosing	Expected benefit	Possible Side Effects	COR / LOE Comments
Prostacyclin Analogs (Prostanoids)					
Selexipag (oral use)	• Prostacyclin IP receptor agonist. Pending approval for adult PH group 1 (PAH). Limited pediatric data.	• Adult dosing: Starting dose: 200 mcg PO twice daily. Dosing increase in 200mcg twice daily steps. Max. dose is 1.6 mg twice daily PO • No published comprehensive pediatric pharmacokinetic data on pediatric dosing in 2020 (case reports and small case series). • overall, limited pediatric data.	• Reduction of morbidity/mortality event. • Improved CI • Improved PVR	• To be determined (RCT and post marketing surveillance pending)	**COR IIb** **LOE C** GRIPHON trial (1,156 PAH patients): Significant risk reduction of morbidity/mortality events.

Table S5. COR, class of recommendation; LOE, level of evidence. COR and LOE grading (higher than COR IIb and LOE C) is based on pediatric study data, adult RCTs that included > 10% children, and studies on adults on congenital heart disease (ACHD). Adapted from Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, Budts W, D'Alto M, Gatzoulis MA, Hasan BS, Kozlik-Feldmann R, Kumar RK, Lammers AE, Latus H, Michel-Behnke I, Miera O, Morrell NW, Pieles G, Quandt D, Sallmon H, Schranz D, Tran-Lundmark K, Tulloh RMR, Warnecke G, Wåhlander H, Weber SC, Zartner P. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019 Sep;38(9):879-901. doi: 10.1016/j.healun.2019.06.022. Epub 2019 Jun 21. PMID: 31495407

Table S6. Potential Drug-Drug Interactions of oral Selexipag

PAH drug	Mechanism of Interaction	Interacting drug	Interaction
Selexipag	CYP2C8 substrate	moderate CYP2C8 inhibitor Clopidogrel Deferasirox Teriflunomid	Limited data. Selexipag and active metabolite could potentially increase. Consider dose adjustment of Selexipag. Follow-up unpublished study on clopidogrel (NCT03496506).
	CYP2C8 substrate	Strong CYP2C8 inhibitor Gemfibrozil	Combination contraindicated Exposure to selexipag 2-fold increased, active metabolite 11-fold increased(29)
	CYP2C8 substrate	CYP2C8 inducers Rifampicin	active metabolite of Selexipag reduced 50 %, consider dose adjustment
	CYP2C8 substrate	CYP2C8 inducers Carbamazepine Phenytoin	No data Active metabolite could be reduced, consider dose adjustment
	CYP3A4 substrate	Strong CYP3A4 inhibitor Lopinavir/Ritonavir	Selexipag increased 50 %, active metabolite unchanged. As active metabolite is 37fold stronger, no clinical relevance of interaction (CYP3A4 pathway seems of no clinical relevance)
	CYP3A4 substrate	CYP3A4 substrate Midazolam	No dose adjustment (CYP3A4 pathway seems of no clinical relevance)
	CYP3A4 substrate	CYP3A4 substrate Hormonal contraceptives	No data, no interaction, as contraceptives are CYP3A4 substrates (see Midazolam) and CYP2C9 substrates (see S-Warfarin)
	UGT1A3 und UGT2B7 glucuronidation	Inhibitors of UGT1A3 and UGT2B7 Valproat Probenecid Fluconazol	No data potential interaction with strong inhibitors cannot be excluded
	CYP2C9 substrate and CYP3A4 substrate	CYP2C9 substrate: (S-Warfarin): Warfarin CYP3A4 substrate (R-Warfarin): Warfarin	No interaction, no dose adjustment of Warfarin or Selexipag necessary(30)

Table S6. cGMP: cyclic guanosine monophosphate. Please note that most of the listed RCT data is derived from studies in adults with PAH. Healthcare providers must obtain valid information on the approval of any of the listed medications for use in pediatric PAH in the according country. Please be aware that only the unilateral effects of “interacting drug” (3rd column) on the PAH drug (left column) and related adverse effects are listed. This table most likely does not indicate all possible drug-drug-interaction and adverse effects, so that health care providers should always consult their local pharmacy service. This table is adapted from National Pulmonary Hypertension Centers of the UK and Ireland. Consensus Statement on the Management of Pulmonary Hypertension in Clinical Practice in the UK and Ireland. Heart 2008;94 (suppl I):i1–41(31) and Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, Budts W, D'Alto M, Gatzoulis MA, Hasan BS, Kozlik-Feldmann R, Kumar RK, Lammers AE, Latus H, Michel-Behnke I, Miera O, Morrell NW, Pieles G, Quandt D, Sallmon H, Schranz D, Tran-Lundmark K, Tulloh RMR, Warnecke G, Wåhlander H, Weber SC, Zartner P. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019 Sep;38(9):879-901. doi: 10.1016/j.healun.2019.06.022. Epub 2019 Jun 21. PMID: 31495407
Additional specific references are cited in the left column and can be found at the end of this supplement.

Table S6. Complex Congenital Heart Disease (group 5.4 PH)

Complex Congenital Heart Disease (group 5.4 PH)
Segmental pulmonary hypertension
Isolated pulmonary artery of ductal origin
Absent pulmonary artery
Pulmonary atresia with ventricular septal defect and major aorto-pulmonary collateral arteries
Hemitruncus
Other
Single ventricle
Unoperated
Operated
Scimitar syndrome

Table S6: This table on complex heart diseases specific for the pediatric age group which are associated with congenital anomalies of the pulmonary vasculature such as segmental disorders, single ventricle physiology and the scimitar syndrome. From Rosenzweig EB et al. Eur Resp J, 2018. DOI: 10.1183/13993003.01916-2018

Table S7. Characteristics of PAH patient 1 at baseline (cath #0) and follow up (cath #1)

ID: #1	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	12.7	13.3	
Sex (M/F)	F	F	
Height (m)	1.36	1.44	
Weight (kg)	27.7 (< 3rd Perc)	30.8	
BSA (m^2)	1.0	1.2	
Clinical Diagnosis			
PH Group	HPAH ACVRL 1 mutation (group 1.2 PH)	HPAH ACVRL 1 mutation (group 1.2 PH)	
Co-morbidities	Absence epilepsy	Absence epilepsy	
Functional Status			
Functional Class	3	2	-1
6-min. walk distance (m)	376	528	
Biomarker			
NTproBNP (pg/mL)	406	460	+13%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	11/15, 13/21	11/15, 13/21	
Lower Risk Score	0/14, 5/20	1/14, 6/20	
Selexipag dose			
Discharge and f/u dose (µg)	1600-0-1600	1600-0-1600	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	S	S	
Cardiac catheterization			
Date	4/2016	12/2016	
Months before selexipag	0	N/A	
Months on selexipag	0	8	
mRAP (mm Hg)	6	1	-83%
sPAP (mm Hg)	114	94	-17%
mPAP (mm Hg)	85	72	-15%
dPAP (mm Hg)	64	56	-13%
sSAP/mSAP/dPAP (mmHg)	116/83/62	80/56/50	
mPAP/mSAP	1.02	1.14	+11%
PAWP (mm Hg)	15	9	-40%
LVEDP (mm Hg)	6	7	+16%
mTPG (mm Hg)	70	63	-10 %
dTPG (mm Hg)	49	47	
PVRi ($WU \cdot m^2$)	22	17.4	-21 %
PVR/SVR	0.97	1.02	
Qpi	3.4	3.64	
Qsi (= cardiac index)	3.4	3.6	
Qp/Qs	1.0	1.0	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.71	1.1	+14%
RVEDD (cm), M-mode, PSAX	3.1	3.1	
RV/LV endsystolic ratio, PSAX	1.34	1.88	+41%
LV eccentricity index, PSAX	3.2	2.2	+32%
S/D ratio (TRV jet)	2.14	1.09	-49%
TAPSE (cm), apical	1.3 (z -5,48)	1.4 (z -4.62)	
PAAT (ms), PSAX	50	70	+40%
LVEF (%)	54	59	

Table S7. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; HPAH, hereditary pulmonary hypertension; IPAH, idiopathic pulmonary hypertension; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S8. Characteristics of PAH patient 2 at baseline (cath #0) and follow up (cath #1)

ID: #2	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	2.0	2.5	
Sex (M/F)	F	F	
Height (m)	0.78	0.78	
Weight (kg)	8	8.1	
BSA (m^2)	0.4	0.4	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	ASD II.	ASD II	
Functional Status			
Functional Class	3	3	
6-min. walk distance (m)	N/A	N/A	
Biomarker			
NTproBNP (pg/mL)	8069	9720	+20%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	8/15, 9/21	8/15, 8/21	
Lower Risk Score	3/14, 7/20	3/14, 3/20	
Selexipag dose			
Discharge and f/u dose (µg)	400-0-400	400-0-400	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	S	-	
Cardiac catheterization			
Date	1/2017	**No Cath.**	
Months before selexipag	0	N/A	
Months on selexipag	0	3 (LuTx 5/2017)	
mRAP (mm Hg)	8	-	
sPAP (mm Hg)	89	--	
mPAP (mm Hg)	57	-	
dPAP (mm Hg)	36	-	
sSAP/mSAP/dPAP (mmHg)	80/51/39	-	
mPAP/mSAP	1,1	-	
PAWP (mm Hg)	7	-	
LVEDP (mm Hg)	missing	-	
mTPG (mm Hg)	50	-	
dTPG (mm Hg)	29	-	
PVRi ($WU \cdot m^2$)	14.3	-	
PVR/SVR	1.29	-	
Qpi	3.55	-	
Qsi (= cardiac index)	4.04	-	
Qp/Qs	0.88	-	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.8	0.62	-23%
RVEDD (cm), M-mode, PSAX	2.6	2.6	
RV/LV endsystolic ratio, PSAX	2.6	3.1	+19%
LV eccentricity index, PSAX	2.5	2.6	
S/D ratio (TRV jet)	2.19	2.77	+26%
TAPSE (cm), apical	1.28 (z -2.58)	1.5 (z -1.05)	+17%
PAAT (ms), PSAX	63	66	
LVEF (%)	60	68	

Table S8. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
ASD, atrial septal defect; BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; IPAH, idiopathic pulmonary hypertension; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S9. Characteristics of PAH patient 3 at baseline (cath #0) and follow up (cath #1)

ID: #3	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	8.5	9.3	
Sex (M/F)	F	F	
Height (m)	1.24	1.19	
Weight (kg)	27	29	
BSA (m^2)	0.96	0.95	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	PDA, PFO, L-SVC, Preterm 34 GW	PDA-Stent, PFO, L-SVC, Preterm 34 GW	
Functional Status			
Functional Class	3	2	-1
6-min. walk distance (m)	376	528	
Biomarker			
NTproBNP (pg/mL)	124	257	+107%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	3/15, 4/21	1/15, 3/21	
Lower Risk Score	8/14, 12/20	9/14, 13/20	
Selexipag dose			
Discharge and f/u dose (µg)	600-0-600	1000-0-1000	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	S	S	
Cardiac catheterization			
Date	6/2017	2/2018	
Months before selexipag	0	N/A	
Months on selexipag	0	7	
mRAP (mm Hg)	2	3	
sPAP (mm Hg)	111	92	
mPAP (mm Hg)	76	67	
dPAP (mm Hg)	51	48	
sSAP/mSAP/dPAP (mmHg)	89/73/55	87/68/50	
mPAP/mSAP	1.04	0.98	
PAWP (mm Hg)	7	5	-29%
LVEDP (mm Hg)	7	-	
mTPG (mm Hg)	69	62	-10 %
dTPG (mm Hg)	44	43	
PVRi ($WU \cdot m^2$)	14.5	18.39	+27%
PVR/SVR	0.97	1.36	+40%
Qpi	4.76	3.37	+30%
Qsi (= cardiac index)	4.76	4.82	
Qp/Qs	1	0.7	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.9	0.7	-22%
RVEDD (cm), M-mode, PSAX	1.9	2.6	+37%
RV/LV endsystolic ratio, PSAX	1.55	1.5	
LV eccentricity index, PSAX	1.6	2.3	44 %
S/D ratio (TRV jet)	1.28	1.28	
TAPSE (cm), apical	1.56 (z -2.73)	1.8 (z -1.47)	+15%
PAAT (ms), PSAX	92	60	-35 %
LVEF (%)	68	72	

Table S9. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has not had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; GW, gestational week; IPAH, idiopathic pulmonary arterial hypertension; LV, left ventricle; L-SVC, left superior vena cava; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PDA, persistent ductus arteriosus; PFO, patent foramen ovale; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S10. Characteristics of PAH patient 4 at baseline (cath #0) and follow up (cath #1)

ID: #4	**Baseline Cath #0**	**On Selexipag Cath #1**	
Demographics			
Age (years)	1.8	2.3	
Sex (M/F)	M	M	
Height (m)	0.80	0.84	
Weight (kg)	9.6	9.5	
BSA (m^2)	0.45	0.46	
Clinical Diagnosis			
PH Group	PAH-CHD (group 1.4.4 PH)	PAH-CHD (group 1.4.4 PH)	
Co-morbidities	Large VSD	Large VSD	
Functional Status			
Functional Class	3	3	
6-min. walk distance (m)	N/A	N/A	
Biomarker			
NTproBNP (pg/mL)	360	316	-13%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	3/15, 4/21	3/15, 4/21	
Lower Risk Score	7/14, 11/20	7/14, 11/20	
Selexipag dose			
Discharge and f/u dose (µg)	200-0-200	600-0-600	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	S	S	
Cardiac catheterization			
Date	10/2017	5/ 2018	
Months before selexipag	0	N/A	
Months on selexipag	0	7	
mRAP (mm Hg)	1	3	
sPAP (mm Hg)	74	73	
mPAP (mm Hg)	48	50	
dPAP (mm Hg)	28	32	
sSAP/mSAP/dPAP (mmHg)	67/51/36	73/39/54	
mPAP/mSAP	1.3	0.9	-31 %
PAWP (mm Hg)	2	7	
LVEDP (mm Hg)	5	-	
mTPG (mm Hg)	46	43	
dTPG (mm Hg)	26	25	
PVRi ($WU \cdot m^2$)	10.82	10.34	
PVR/SVR	0.9	0.9	
Qpi	4.2	4.1	
Qsi (= cardiac index)	4.2	4.6	
Qp/Qs	1	0.9	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.56	0.69	
RVEDD (cm), M-mode, PSAX	1.4	1.6	+14%
RV/LV endsystolic ratio, PSAX	0.8	1	+25%
LV eccentricity index, PSAX	1.3	1.1	-16%
S/D ratio (TRV jet)	no TR	no TR	
TAPSE (cm), apical	1.54 (z -0.07)	1.9 (z 1.74)	+23%
PAAT (ms), PSAX	80	70	-13%
LVEF (%)	62	66	

Table S10. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; CHD, congenital heart disease; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity; VSD, ventricular septal defect

.

Table S11. Characteristics of PAH patient 5 at baseline (cath #0) and follow up (cath #1)

ID: #5	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	1.3	1.9	
Sex (M/F)	F	F	
Height (m)	0.73	0.78	
Weight (kg)	7	8.4	
BSA (m^2)	0.36	0.41	
Clinical Diagnosis			
PH Group	IPAH / PH multifactorial (group 1.1 PH /group 5.2 PH)	IPAH / PH multifactorial (group 1.1 PH /group 5.2 PH)	
Co-morbidities	Desoxyguanosin Deficiency Liver Tx 3/2017 Hypothyroidism	Desoxyguanosin Deficiency Liver Tx 3/2017 Hypothyroidism	
Functional Status			
Functional Class	3	2	
6-min. walk distance (m)	N/A	N/A	
Biomarker			
NTproBNP (pg/mL)	>35,000	1437	
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	7/15, 9/21	7/15, 7/21	
Lower Risk Score	0/14, 2/20	0/14, 4/20	
Selexipag dose			
Discharge and f/u dose (µg)	500-0-500	500-0-500	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	S	S	
Cardiac catheterization			
Date	11/2017	4/2018	
Months before selexipag	0	N/A	
Months on selexipag	0	6	
mRAP (mm Hg)	13	5	
sPAP (mm Hg)	68	59	
mPAP (mm Hg)	53	42	
dPAP (mm Hg)	40	28	
sSAP/mSAP/dPAP (mmHg)	73/52/41	77/58/42	
mPAP/mSAP	1	0.7	-30 %
PAWP (mm Hg)	4	10	
LVEDP (mm Hg)	-	-	
mTPG (mm Hg)	49	32	-35 %
dTPG (mm Hg)	36	18	-50 %
PVRi ($WU \cdot m^2$)	16.24	5.06	-70%
PVR/SVR	1.33	0.73	-46%
Qpi	2.88	6.28	+118%
Qsi (= cardiac index)	3.2	7.67	+138%
Qp/Qs	0.9	0.82	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.51	0.29	
RVEDD (cm), M-mode, PSAX	2.2	1.3	-41%
RV/LV endsystolic ratio, PSAX	1.3	0.62	-53%
LV eccentricity index, PSAX	1.8	0.91	-50%
S/D ratio (TRV jet)	2.32	1.8	-37%
TAPSE (cm), apical	1.14 (z -2.73)	1.84 (z 1.93)	+67%
PAAT (ms), PSAX	60	60	
LVEF (%)	73	56	

Table S11. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).

BSA, body surface area; CHD, congenital heart disease; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; LTX, liver transplantation; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S12. Characteristics of PAH patient 6 at baseline (cath #0) and follow up (cath #1)

ID: #6	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	16.1	16.9	
Sex (M/F)	M	M	
Height (m)	1.73	1.73	
Weight (kg)	44	50	
BSA (m^2)	1.5	1.5	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	ASD II, undefined CTD	ASD II, undefined CTD	
Functional Status			
Functional Class	3	3	
6-min. walk distance (m)	540 (stopped b/o cyanosis+dyspnea)	486	
Biomarker			
NTproBNP (pg/mL)	110	61	-45%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	4/15, 6/21	3/15, 5/21	
Lower Risk Score	6/14, 8/20	7/14, 9/20	
Selexipag dose			
Discharge and f/u dose (µg)	200-0-200	1600-0-1600	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	S	S	
Cardiac catheterization			
Date	1/2019	Sep. 10, 2019	
Months before selexipag	0	N/A	
Months on selexipag	0	8	
mRAP (mm Hg)	1	1	
sPAP (mm Hg)	102	98	
mPAP (mm Hg)	63	63	
dPAP (mm Hg)	36	39	
sSAP/mSAP/dPAP (mmHg)	88/69/56	100/81/66	
mPAP/mSAP	0.9	0.7	-22%
PAWP (mm Hg)	5	8	
LVEDP (mm Hg)	-	7	
mTPG (mm Hg)	57	55	
dTPG (mm Hg)	32	31	
PVRi ($WU \cdot m^2$)	21.6	21.2	
PVR/SVR	0.82	0.69	-25%
Qpi	2.77	2.19	-21%
Qsi (= cardiac index)	2.57	2.59	
Qp/Qs	1.08	1.18	

Echocardiography			
RVAWD (cm), M-mode, PSAX	1	0.92	
RVEDD (cm), M-mode, PSAX	2.2	2.3	
RV/LV endsystolic ratio, PSAX	1.34	1.37	
LV eccentricity index, PSAX	1.73	1.4	-20%
S/D ratio (TRV jet)	1.48	0.94	-36%
TAPSE (cm), apical	1.55 (z -4.13)	1.7 (z -3.39)	
PAAT (ms), PSAX	92	95	
LVEF (%)	61	59	

Table S12. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has not had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
ASD, atrial septal defect; BSA, body surface area; CTD, connective tissue disease,;D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; IPAH, idiopathic pulmonary arterial hypertension; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S13. Characteristics of PAH patient 7 at baseline (cath #0) and follow up (cath #1)

ID: #7	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	2.1	2.7	
Sex (M/F)	F	F	
Height (m)	0.78	0.82	
Weight (kg)	10	10.5	
BSA (m^2)	0.45	0.48	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	ASD II, PDA Trisomy 21	ASD II, PDA Trisomy 21	
Functional Status			
Functional Class	2	2	
6-min. walk distance (m)	-	-	
Biomarker			
NTproBNP (pg/mL)	1710	2320	+35%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	6/15, 8/21	6/15, 8/21	
Lower Risk Score	8/14, 11/20	6/14, 10/20	
Selexipag dose			
Discharge and f/u dose (µg)	200-0-200	600-0-600	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	GA	
Cardiac catheterization			
Date	Jan. 23, 2019	Aug. 07, 2019	
Months before selexipag	0	N/A	
Months on selexipag	0	6	
mRAP (mm Hg)	9	7	-22%
sPAP (mm Hg)	84	69	-18%
mPAP (mm Hg)	61	48	-21%
dPAP (mm Hg)	39	29	-26%
sSAP/mSAP/dPAP (mmHg)	79/60/42	68/50/35	
mPAP/mSAP	1.01	0.96	-11 %
PAWP (mm Hg)	9	9	
LVEDP (mm Hg)	-	4	
mTPG (mm Hg)	52	39	-25 %
dTPG (mm Hg)	33	20	-34 %
PVRi ($WU \cdot m^2$)	16.12	15.23	
PVR/SVR	1.43	0.91	-37 %
Qpi	3.16	2.81	-12 %
Qsi (= cardiac index)	4.52	5.63	+24%
Qp/Qs	0.7	0.5	-29 %

.

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.9	1.2	+33%
RVEDD (cm), M-mode, PSAX	2.8	2.4	-15 %
RV/LV endsystolic ratio, PSAX	2.8	3.1	+10%
LV eccentricity index, PSAX	2.8	2.8	.
S/D ratio (TRV jet)	1.71	1.63	
TAPSE (cm), apical	1.7 (z 0.35)	1.7 (z 0.35)	
PAAT (ms), PSAX	60	55	
LVEF (%)	72	79	

Table S13. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
ASD, atrial septal defect; BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; IPAH, idiopathic pulmonary arterial hypertension; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PDA, persistent ductus arteriosus; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S14. Characteristics of PAH patient 8 at baseline (cath #0) and follow up (cath #1)

ID: #8	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	16.8	17.9	
Sex (M/F)	F	F	
Height (m)	1.78	1.78	
Weight (kg)	73	72	
BSA (m^2)	1.9	1.9	
Clinical Diagnosis			
PH Group	PAH, portal hypertension (group 1.4.3 PH)	PAH, portal Hypertension (group 1.4.3 PH)	
Co-morbidities	Abernethy Malformation Ib	Abernethy Malformation Ib	
Functional Status			
Functional Class	3	3	
6-min. walk distance (m)	462	517	+12%
Biomarker			
NTproBNP (pg/mL)	345	77	-78%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	2/15, 2/21	2/15, 2/21	
Lower Risk Score	6/14, 11/20	9/14, 15/20	
Selexipag dose			
Discharge and f/u dose (µg)	200-0-200	600-0-600	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	GA	
Cardiac catheterization			
Date	3/2016	3/2017	
Months before selexipag	0	N/A	
Months on selexipag	0	12	
mRAP (mm Hg)	7	5	
sPAP (mm Hg)	53	41	
mPAP (mm Hg)	38	32	
dPAP (mm Hg)	25	25	
sSAP/mSAP/dPAP (mmHg)	85/59/44	101/70/51	
mPAP/mSAP	0.57	0.46	-19%
PAWP (mm Hg)	10	8	
LVEDP (mm Hg)	6	5	
mTPG (mm Hg)	32	27	-16%
dTPG (mm Hg)	19	18	
PVRi ($WU \cdot m^2$)	7.4	7.3	
PVR/SVR	0.58	0.34	-41%
Qpi	4.30	3.7	
Qsi (= cardiac index)	4.30	3.7	
Qp/Qs	1	1	

Echocardiography			
RVAWD (cm), M-mode, PSAX	6.3	6	
RVEDD (cm), M-mode, PSAX	2.8	2.7	
RV/LV endsystolic ratio, PSAX	1.15	0.97	-16%
LV eccentricity index, PSAX	1.45	1.24	-15%
S/D ratio (TRV jet)	1.66	1.38	-16%
TAPSE (cm), apical	2.4 (z 0.05)	2.7 (z 1.21)	+13%
PAAT (ms), PSAX	75	93	+24%
LVEF (%)	67	64	

Table S14. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S15. Characteristics of PAH patient 9 at baseline (cath #0) and follow up (cath #1)

ID: #9	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	6.6	7.6	
Sex (M/F)	M	M	
Height (m)	1.28	1.34	
Weight (kg)	22	23	
BSA (m^2)	0.89	0.93	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	Mild Biliary Cirrhosis	Mild Biliary Cirrhosis	
Functional Status			
Functional Class	3	2	-1
6-min. walk distance (m)	455	610	
Biomarker			
NTproBNP (pg/mL)	981	192	-80%
Risk Stratification			
Risk	Intermediate Risk	Lower Risk	
Higher Risk Score	3/15, 3/21	0/15, 0/21	
Lower Risk Score	8/14, 13/20	13/14, 18/20	
Selexipag dose			
Discharge and f/u dose (µg)	200-0-200	400-0-400	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	GA	
Cardiac catheterization			
Date	4/2017	4/2018	
Months before selexipag	0	N/A	
Months on selexipag	0	12	
mRAP (mm Hg)	5	3	
sPAP (mm Hg)	58	47	-18%
mPAP (mm Hg)	45	34	-24%
dPAP (mm Hg)	35	22	-37%
sSAP/mSAP/dPAP (mmHg)	74/58/45	90/63/48	
mPAP/mSAP	0.78	0.54	-31%
PAWP (mm Hg)	11	9	
LVEDP (mm Hg)	8	9	
mTPG (mm Hg)	36	25	-31%
dTPG (mm Hg)	24	13	-46%
PVRi ($WU \cdot m^2$)	9.73	4.55	-53%
PVR/SVR	0.55	0.3	-46%
Qpi	3.7	5.5	+49%
Qsi (= cardiac index)	3.8	5.5	+45%
Qp/Qs	1	1	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.57	0.53	
RVEDD (cm), M-mode, PSAX	3.2	2.8	-13%
RV/LV endsystolic ratio, PSAX	1.21	0.90	-26%
LV eccentricity index, PSAX	1.60	1.33	-17%
S/D ratio (TRV jet)	1.78	1.57	-11%
TAPSE (cm), apical	1.54 (z -2.57)	1.8 (z -0.93)	+17%
PAAT (ms), PSAX	65	86	+32%
LVEF (%)	64	62	

Table S15. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S16. Characteristics of PAH patient 10 at baseline (cath #0) and follow up (cath #1)

ID: #10	Baseline Cath #0	On Selexipag Cath #1
Demographics		
Age (years)	8.2	9.9
Sex (M/F)	F	F
Height (m)	1.58	1.65
Weight (kg)	47.1	61
BSA (m^2)	1.45	0.8
Clinical Diagnosis		
PH Group	PH-BPD (group 3.5 PH)	PH-BPD (group 3.5 PH)
Co-morbidities	Preterm 26 GW	Preterm 26 GW
Functional Status		
Functional Class	2	2
6-min. walk distance (m)	N/A	N/A
Biomarker		
NTproBNP (pg/mL)	274	61
Risk Stratification		
Risk	Intermediate Risk	Intermediate Risk
Higher Risk Score	0/15, 0/21	1/15, 1/21
Lower Risk Score	12/14, 14/20	13/14, 13/20
Selexipag dose		
Discharge and f/u dose (µg)	200-0-200	200-0-200
Key hemodynamics		
Sedation (S) or general anesthesia (GA)	GA	-
Cardiac catheterization		
Date	Oct. 12, 2017	**Cath denied**
Months before selexipag	0	N/A
Months on selexipag	0	20
mRAP (mm Hg)	10	-
sPAP (mm Hg)	60	-
mPAP (mm Hg)	45	-
dPAP (mm Hg)	26	-
sSAP/mSAP/dPAP (mmHg)	82/63/48	-
mPAP/mSAP	0.71	-
PAWP (mm Hg)	14	-
LVEDP (mm Hg)	9	-
mTPG (mm Hg)	36	-
dTPG (mm Hg)	17	-
PVRi ($WU \cdot m^2$)	9	-
PVR/SVR	0.54	-
Qpi	4	-
Qsi (= cardiac index)	4,0	-
Qp/Qs	1	-

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.45	0.45	
RVEDD (cm), M-mode, PSAX	1.1	1.04	
RV/LV endsystolic ratio, PSAX	1.12	0.92	-18%
LV eccentricity index, PSAX	1.63	1.17	-28%
S/D ratio (TRV jet)	1.37	1.06	-22%
TAPSE (cm), apical	1.6 (z -2.47)	1.9 (z -0.77)	+18%
PAAT (ms), PSAX	70	67	
LVEF (%)	67	62	

Table S16. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; BPD, bronchopulmonary dysplasia; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; GW, gestational week; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S17. Characteristics of PAH patient 11 at baseline (cath #0) and follow up (cath #1)

ID: #11	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	4.5	6	
Sex (M/F)	M	M	
Height (m)	1.05	1.14	
Weight (kg)	17.5	20.5	
BSA (m^2)	0.71	0.8	
Clinical Diagnosis			
PH Group	PAH-CHD (group 1.4.4 PH)	PAH-CHD (group 1.4.4 PH)	
Co-morbidities	PA-VSD, 47 XXY, MAPCAs	PA-VSD, 47 XXY, MAPCAs	
Functional Status			
Functional Class	2	2	
6-min. walk distance (m)	N/A	N/A	
Biomarker			
NTproBNP (pg/mL)	1233	631	-49%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	3/15, 3/21	0/15, 0/21	
Lower Risk Score	10/14, 12/20	12/14, 14/20	
Selexipag dose			
Discharge and f/u dose (µg)	200-0-200	200-0-200	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	GA	
Cardiac catheterization			
Date	10/2017	6/2019	
Months before selexipag	0	N/A	
Months on selexipag	0	18	
mRAP (mm Hg)	12	10	
sPAP (mm Hg)	52	43	-17%
mPAP (mm Hg)	30	25	-17%
dPAP (mm Hg)	15	13	-13%
sSAP/mSAP/dPAP (mmHg)	69/42/30	71/47/30	
mPAP/mSAP	0.71	0.63	
PAWP (mm Hg)	15	11	
LVEDP (mm Hg)	14	10	
mTPG (mm Hg)	16	15	
dTPG (mm Hg)	1	2	
PVRi ($WU \cdot m^2$)	3.14	4.1	+30%
PVR/SVR	0.52	0.45	-14%
Qpi	5.1	3.7	
Qsi (= cardiac index)	5.1	3.7	
Qp/Qs	1	1	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.64	0.55	-14%
RVEDD (cm), M-mode, PSAX	2.7	2.6	
RV/LV endsystolic ratio, PSAX	1.25	1.20	
LV eccentricity index, PSAX	1.5	1.5	
S/D ratio (TRV jet)	1.52	1.33	-13%
TAPSE (cm), apical	1.2 (z -4.77)	1.29 (z -4.36)	
PAAT (ms), PSAX	60	71	+18%
LVEF (%)	65	62	

Table S17. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; CHD, congenital heart disease; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; MAPCA, major aortopulmonary collateral artery; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PFO, patent foramen ovale; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity; VSD, ventricular septal defect

.

Table S18. Characteristics of PAH patient 12 at baseline (cath #0) and follow up (cath #1)

ID: #12	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	0.6	0.7	
Sex (M/F)	F	F	
Height (m)	0.55	0.65	
Weight (kg)	5.5	8	
BSA (m^2)	0.28	0.38	
Clinical Diagnosis			
PH Group	PAH-CHD / PH-BPD (group 1.4.4. + 5.4/ 3.5 PH)	PAH-CHD / PH-BPD (group 1.4.4 + 5.4 / 3.5 PH)	
Co-morbidities	Preterm GW AV Canal, Trisomy 21	Preterm GW, AV Canal, Trisomy 21	
Functional Status			
Functional Class	3	2	-1
6-min. walk distance (m)	N/A	N/A	
Biomarker			
NTproBNP (pg/mL)	2181	908	-58%
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	2/15, 3/21	0/15, 0/21	
Lower Risk Score	8/14, 12/20	10/14, 12/20	
Selexipag dose			
Discharge and f/u dose (µg)	50-0-50	200-0-200	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	GA	
Cardiac catheterization			
Date	Sept. 6, 2018	Jan. 21, 2019	
Months before selexipag	0	N/A	
Months on selexipag	0	5	
mRAP (mm Hg)	9	7	-22%
sPAP (mm Hg)	71	45	-37%
mPAP (mm Hg)	43	31	-30%
dPAP (mm Hg)	29	17	-41%
sSAP/mSAP/dPAP (mmHg)	75/50/45	71/49/42	
mPAP/mSAP	0.86	0.63	-27%
PAWP (mm Hg)	8	7	
LVEDP (mm Hg)	10	9	
mTPG (mm Hg)	35	24	-31%
dTPG (mm Hg)	21	10	-52%
PVRi ($WU \cdot m^2$)	11.3	8	-29%
PVR/SVR	0.52	0.29	-44%
Qpi	3.1	3.0	
Qsi (= cardiac index)	3.1	3.0	
Qp/Qs	0.9	0.9	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.27	0.28	
RVEDD (cm), M-mode, PSAX	1.1	1.04	
RV/LV endsystolic ratio, PSAX	1.14	1.03	
LV eccentricity index, PSAX	1.68	1.5	-11%
S/D ratio (TRV jet)	1.28	1.35	
TAPSE (cm), apical	0.71 (z - 4.0)	0.8 (z -3.4)	+13%
PAAT (ms), PSAX	50	71	+42%
LVEF (%)	67	65	

Table S18. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
AV, atrioventricular; BSA, body surface area; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; GW, gestational week; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S19. Characteristics of PAH patient 13 at baseline (cath #0) and follow up (cath #1)

ID: #13	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	0.6	1,2	
Sex (M/F)	F	F	
Height (m)	0.62	0.68	
Weight (kg)	5	9	
BSA (m^2)	0.29	0,41	
Clinical Diagnosis			
PH Group	PH-BPD (group 3.5 PH)	PH-BPD (group 3.5 PH)	
Co-morbidities	Preterm 26 + 2 GW, severe BPD	Preterm 26 + 2 GW, severe BPD	
Functional Status			
Functional Class	3	2	-1
6-min. walk distance (m)	N/A	N/A	
Biomarker			
NTproBNP (pg/mL)	1710	313	-82%
Risk Stratification			
Risk	Intermediate Risk	Lower Risk	
Higher Risk Score	2/15, 2/21	0/15, 0/21	
Lower Risk Score	8/14, 8/20	12/14, 12/20	
Selexipag dose			
Discharge and f/u dose (µg)	50-0-50	200-0-200	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	N/A	N/A	
Cardiac catheterization			
Date	**Cath. denied**	**Cath. denied**	
Months before selexipag	0	N/A	
Months on selexipag	0	6	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.43	0.41	
RVEDD (cm), M-mode, PSAX	1.4	1.43	
RV/LV endsystolic ratio, PSAX	1.1	0.84	-24%
LV eccentricity index, PSAX	1.34	1.25	
S/D ratio (TRV jet)	1.22	1.09	-11%
TAPSE (cm), apical	1.4 (z -0.26)	1,6 (z 0,33)	
PAAT (ms), PSAX	55	80	+45%
LVEF (%)	68	66	

Table S19. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has not had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; BPD, bronchopulmonary dysplasia; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S20. Characteristics of PAH patient 14 at baseline (cath #0) and follow up (cath #1)

ID: #14	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	14.5	15.9	
Sex (M/F)	F	F	
Height (m)	1.56	1.53	
Weight (kg)	36.9	36.5	
BSA (m^2)	1.26	1.25	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	Marfan, Scoliosis, MR, IBD	Marfan, Scoliosis, MR, IBD	
Functional Status			
Functional Class	3	3	
6-min. walk distance (m)	200	210	
Biomarker			
NTproBNP (pg/mL)	818	844	
Risk Stratification			
Risk	High Risk	Intermediate Risk	
Higher Risk Score	4/15, 8/21	6/15, 8/21	
Lower Risk Score	8/14, 10/20	8/14, 12/20	
Selexipag dose			
Discharge and f/u dose (µg)	800-0-800	1200-0-1200	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	S	
Cardiac catheterization			
Date	May 2, 2017	Oct 29, 2018	
Months before selexipag	5	N/A	
Months on selexipag	0	12	
mRAP (mm Hg)	4	7	+75%
sPAP (mm Hg)	60	81	+48%
mPAP (mm Hg)	46	62	+34%
dPAP (mm Hg)	40	50	+20%
sSAP/mSAP/dPAP (mmHg)	61/46/41	98/73/59	
mPAP/mSAP	1.0	1.1	+10%
PAWP (mm Hg)	10	11	
LVEDP (mm Hg)	missing	missing	
mTPG (mm Hg)	36	51	+18%
dTPG (mm Hg)	30	39	+30%
PVRi ($WU \cdot m^2$)	15.1	12.0	-21%
PVR/SVR	0.9	0.8	
Qpi	2.4	4.2	+75%
Qsi (= cardiac index)	2.4	4.2	+75%
Qp/Qs	1.0	1.0	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.7	0.7	
RVEDD (cm), M-mode, PSAX	2.7	2.7	
RV/LV endsystolic ratio, PSAX	0.81	0.8	
LV eccentricity index, PSAX	2.3	2.2	
S/D ratio (TRV jet)	1.8	1.8	
TAPSE (cm), apical	1.3 (z -4.97)	1.3 (z -5.24)	
PAAT (ms), PSAX	97	69	-33%
LVEF (%)	55	56	

Table S20. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has <u>not</u> had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; IBD, intestinal bowel disease; IPAH, idiopathic pulmonary arterial hypertension; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, MR, mitral regurgitation; mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

.

Table S21. Characteristics of PAH patient 15 at baseline (cath #0) and follow up (cath #1)

ID: #15	Baseline Cath #0	On Selexipag Cath #1	
Demographics			
Age (years)	15.4	16.8	
Sex (M/F)	F	F	
Height (m)	1.57	1.57	
Weight (kg)	41.5	37	
BSA (m^2)	1.34	1.27	
Clinical Diagnosis			
PH Group	IPAH (group 1.1 PH)	IPAH (group 1.1 PH)	
Co-morbidities	Left bronchial stenosis	Left bronchial stenosis	
Functional Status			
Functional Class	3	3	
6-min. walk distance (m)	365	295	
Biomarker			
NTproBNP (pg/mL)	244	311	
Risk Stratification			
Risk	Intermediate Risk	Intermediate Risk	
Higher Risk Score	8/15, 10/21	6/15, 8/21	
Lower Risk Score	6/14, 10/20	7/14, 11/20	
Selexipag dose			
Discharge and f/u dose (µg)	800-0-800	1400-0-1400	
Key hemodynamics			
Sedation (S) or general anesthesia (GA)	GA	S	
Cardiac catheterization			
Date	Jan. 23, 2017	July 5, 2018	
Months before selexipag	10	N/A	
Months on selexipag	0	8	
mRAP (mm Hg)	8	3	-62%
sPAP (mm Hg)	93	137	+47%
mPAP (mm Hg)	70	84	+20%
dPAP (mm Hg)	55	52	-5%
sSAP/mSAP/dPAP (mmHg)	77/56/48	88/59/43	
mPAP/mSAP	0.9	1.4	+56%
PAWP (mm Hg)	11	2	
LVEDP (mm Hg)	-	-	
mTPG (mm Hg)	59	80	+36%
dTPG (mm Hg)	44	50	+14%
PVRi ($WU \cdot m^2$)	18,1	27.9	+54%
PVR/SVR	1.2	1.6	+33%
Qpi	3.3	2.8	-15%
Qsi (= cardiac index)	3.3	3.1	
Qp/Qs	1.0	0.9	

Echocardiography			
RVAWD (cm), M-mode, PSAX	0.4	0.8	
RVEDD (cm), M-mode, PSAX	1.9	2.1	
RV/LV endsystolic ratio, PSAX	1.7	2.8	+65%
LV eccentricity index, PSAX	2.15	2.70	+25%
S/D ratio (TRV jet)	0.9	1.1	
TAPSE (cm), apical	1.3 (z -5.24)	1.3 (z -5.36)	
PAAT (ms), PSAX	33	33	
LVEF (%)	81	81	

Table S21. Values are presented as mean ± SEM. A Mann-Whitney U test was applied. $P < 0.05$ was considered significant. All PAH patients with repaired congenital heart disease (PAH-CHD) had the repair > 12 months prior to cardiac catheterization. LV eccentricity index is measured at end systole.
For risk stratification, see also Figure S1:
The *starred criteria (*)* are risk determinants/prognostic variables with high prognostic impact on clinical outcome, based on retrospective analyses of adult PAH study data (WHO FC, NT-proBNP, cardiac index, mRAP), and are counted as 2 points.
• If the patient had a recent cardiac catheterization (within the preceding 12 months), the maximum lower risk score (including 4 * criteria) is 20, and the maximum higher risk score (including 4 * criteria) is 21.
• If the patient has not had any recent cardiac catheterization within the preceding 12 months, the maximum lower risk score (including 2 * criteria) is 14 and the maximum higher risk score (including 2 * criteria) is 15.
• Accordingly, the actual lower risk and higher risk scores can be given as points per max. score (e.g., “8/20 lower risk score for a patient with recent cardiac catheterization data in the preceding 12 months”).
BSA, body surface area; D, diastolic; dPAP, diastolic pulmonary arterial pressure; dTPG, diastolic transpulmonary pressure gradient; IPAH, idiopathic pulmonary hypertension; LV, left ventricle; LVEDP, left ventricular enddiastolic pressure; LVEF, left ventricular ejection fraction, LVOTO, left ventricular outflow tract obstruction; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; mTPG, mean transpulmonary pressure gradient; n.s., not significant; PAAT, pulmonary artery acceleration time; PAWP, pulmonary arterial wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PSAX, parasternal short axis; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index; RV, right ventricle; RVAWD, right ventricular anterior wall diameter; RVEDD, right ventricular end-diastolic diameter; S, systolic; sPAP, systolic pulmonary arterial pressure; sSAP, systolic systemic arterial pressure; SVR, systemic vascular resistance; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity

SUPPLEMENTARY REFERENCES

The references below refer to the references in this Online Supplement only.

1. Skoro-Sajer N, Lang IM: Selexipag for the treatment of pulmonary arterial hypertension. Expert Opin Pharmacother 2014;15:429-36.
2. Sitbon O, Channick R, Chin KM, et al.: Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med 2015;373:2522-33.
3. Geerdink LM, Bertram H, Hansmann G: First-in-child use of the oral selective prostacyclin IP receptor agonist selexipag in pulmonary arterial hypertension Pulm Circ 2017;7:551-4.
4. Hansmann G, Koestenberger M, Alastalo T, et al.: 2019 Updated Consensus Statement on the Diagnosis and Treatment of Pediatric Pulmonary Hypertension. The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant 2019;38:879-901.
5. Lammers AE, Apitz C, Zartner P, Hager A, Dubowy KO, Hansmann G: Diagnostics, monitoring and outpatient care in children with suspected pulmonary hypertension/paediatric pulmonary hypertensive vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102 Suppl 2:ii1-ii13.
6. Koestenberger M, Nagel B, Ravekes W, et al.: Systolic right ventricular function in pediatric and adolescent patients with tetralogy of Fallot: echocardiography versus magnetic resonance imaging. J Am Soc Echocardiogr 2011;24:45-52.
7. Koestenberger M, Grangl G, Avian A, et al.: Normal Reference Values and z Scores of the Pulmonary Artery Acceleration Time in Children and Its Importance for the Assessment of Pulmonary Hypertension. Circ Cardiovasc Imaging 2017;10.
8. Beghetti M, Channick RN, Chin KM, et al.: Selexipag treatment for pulmonary arterial hypertension associated with congenital heart disease after defect correction: insights from the randomised controlled GRIPHON study. Eur J Heart Fail 2019;21:352-9.
9. Barnes H, Yeoh HL, Fothergill T, Burns A, Humbert M, Williams T: Prostacyclin for pulmonary arterial hypertension. Cochrane Database Syst Rev 2019;5:CD012785.
10. Galie N, Channick RN, Frantz RP, et al.: Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53.
11. Girerd B, Montani D, Coulet F, et al.: Clinical outcomes of pulmonary arterial hypertension in patients carrying an ACVRL1 (ALK1) mutation. American journal of respiratory and critical care medicine 2010;181:851-61.
12. Kanaan U, Varghese NP, Coleman RD, et al.: Oral treprostinil use in children: a multicenter, observational experience. Pulm Circ 2019;9:2045894019862138.
13. Ivy DD, Feinstein JA, Yung D, et al.: Oral treprostinil in transition or as add-on therapy in pediatric pulmonary arterial hypertension. Pulm Circ 2019;9:2045894019856471.
14. Gallotti R, Drogalis-Kim DE, Satou G, Alejos J: Single-Center Experience Using Selexipag in a Pediatric Population. Pediatr Cardiol 2017;38:1405-9.
15. Koo R, Lo J, Bock MJ: Transition from intravenous treprostinil to enteral selexipag in an infant with pulmonary arterial hypertension. Cardiol Young 2019;29:849-51.
16. Li J: Accurate measurement of oxygen consumption in children undergoing cardiac catheterization. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2013;81:125-32.
17. Seckeler MD, Hirsch R, Beekman RH, 3rd, Goldstein BH: A new predictive equation for oxygen consumption in children and adults with congenital and acquired heart disease. Heart 2015;101:517-24.
18. Baruteau AE, Belli E, Boudjemline Y, et al.: Palliative Potts shunt for the treatment of children with drug-refractory pulmonary arterial hypertension: updated data from the first 24 patients. Eur J Cardiothorac Surg 2015;47:e105-10.
19. Schranz D, Kerst G, Menges T, et al.: Transcatheter creation of a reverse Potts shunt in a patient with severe pulmonary arterial hypertension associated with Moyamoya syndrome. EuroIntervention 2015;11:121.
20. Sizarov A, Raimondi F, Bonnet D, Boudjemline Y: Vascular anatomy in children with pulmonary hypertension regarding the transcatheter Potts shunt. Heart 2016;102:1735-1741
21. Gorbachevsky SV, Shmalts AA, Barishnikova IY, Zaets SB: Potts shunt in children with pulmonary arterial hypertension: institutional experience. Interact Cardiovasc Thorac Surg 2017;25:595-9.
22. Aggarwal M, Grady RM, Choudhry S, Anwar S, Eghtesady P, Singh GK: Potts Shunt Improves Right Ventricular Function and Coupling With Pulmonary Circulation in Children With Suprasystemic Pulmonary Arterial Hypertension. Circ Cardiovasc Imaging 2018;11:e007964.

23. Hansmann G, Apitz C: Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102 Suppl 2:ii67-ii85.
24. Hansmann G: Pulmonary hypertension in infants, children, and young adults. J Am Coll Cardiol 2017;69:2551-69.
25. Cerro MJ, Abman S, Diaz G, et al.: A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulmonary circulation 2011;1:286-98.
26. Galie N, Humbert M, Vachiery JL, et al.: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
27. Simonneau G, Montani D, Celermajer DS, et al.: Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2018;52:pii1800678
28. Rosenzweig EB, Abman SH, Adatia I, et al.: Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:pii 1801916
29. Bruderer S, Petersen-Sylla M, Boehler M, Remenova T, Halabi A, Dingemanse J: Effect of gemfibrozil and rifampicin on the pharmacokinetics of selexipag and its active metabolite in healthy subjects. Br J Clin Pharmacol 2017;83:2778-88.
30. Bruderer S, Okubo K, Mukai H, Mant T, Dingemanse J: Investigation of Potential Pharmacodynamic and Pharmacokinetic Interactions Between Selexipag and Warfarin in Healthy Male Subjects. Clin Ther 2016;38:1228-36 e1.
31. National Pulmonary Hypertension Centres of the UK, Ireland: Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Heart 2008;94 Suppl 1:i1-41.