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PULMONARY HYPERTENSION

Real-Life Experience with Selexipag as an Add-On Therapy to Oral Combination Therapy in Patients with Pulmonary Arterial or Distal Chronic Thromboembolic Pulmonary Hypertension: A Retrospective Analysis

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Abstract

Background Patients with pulmonary arterial hypertension (PAH) and distal chronic thromboembolic pulmonary hypertension (CTEPH) who still reveal risk factors of worse prognosis on double combination therapy may benefit from add-on therapy with the novel oral selective prostacyclin receptor agonist selexipag.

Methods We reviewed all patients with PAH/distal CTEPH in the Zurich cohort who received selexipag as add-on to oral combination therapy and retrieved New York Heart Association (NYHA) functional class, 6-min walk distance (6MWD), NT-pro-BNP, quality of life questionnaires (CAMPHOR and EuroQoL), tricuspid pressure gradient (TPG) by echocardiography and cardiopulmonary exercise test parameters (power output and oxygen uptake).

Results Twenty-three patients with PAH/CTEPH (20/3), 14 females, median (quartiles) age 56 (46; 66) years received an oral triple therapy containing selexipag at a median dose of 2000 (1600; 3100) mcg during 221 (113; 359) days. The following parameters were stabilized from baseline to last FU: 6MWD (440 (420; 490) to 464 (420; 526) m), NYHA class (three to two), NT-pro-BNP (326 (167; 1725) to 568 (135; 1856) ng/l), TPG, power output, and oxygen uptake. Quality of life reflected by the CAMPHOR and EuroQoL improved.

Conclusions Early initiation of triple oral combination therapy including selexipag in PAH/CTEPH with intermediate risk factor profile may help to stabilize functional class, exercise performance, and pulmonary hemodynamics in a real-life setting and potentially improves quality of life. Whether these beneficial effects can be truly attributed to the addition of selexipag should be addressed in future randomized controlled trials.

Keywords Pulmonary hypertension · Pulmonary arterial hypertension · Vasodilator therapy · Endothelin receptor antagonist · Phosphodiesterase inhibitor · Selexipag · Chronic thromboembolic pulmonary hypertension

Introduction

Precapillary pulmonary hypertension (PH) is a serious condition leading to impaired exercise tolerance, quality of life, and reduced life expectancy if untreated [1]. In the absence of relevant lung or heart disease, the two major forms are pulmonary arterial and chronic thromboembolic pulmonary hypertension (PAH and CTEPH). Whereas symptoms in many patients with CTEPH can substantially improve with pulmonary endarterectomy or balloon-pulmonary angioplasty, different medical therapies ameliorate symptoms, exercise capacity, and quality of life in PAH and in persisting CTEPH after treatment or inoperable CTEPH, which share pathogenic features with PAH [1–5]. PH is characterized by the vasoconstriction of pulmonary artery smooth muscles, vascular remodeling, and endothelial cell proliferation [6]. Three majorly involved pathogenic pathways are therapeutically addressed to date: the nitric oxide, endothelin, and prostacyclin pathways.

Oral drugs targeting the endothelin and nitric oxide pathways are commonly initiated in ambulatory patients, whereas

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initial intravenous prostanoids are used in patients presenting with advanced disease stages in right heart failure [1]. Recent randomized controlled trials like the AMBITION [7], PATENT PLUS [8], and SERAPHIN trial [9] have shown that initial early combination therapy addressing both the endothelin and nitric oxide pathways have higher efficacy in improving symptoms, clinical worsening, and exercise capacity in PAH, and thus current recommendations support the early use of combination therapy, which is widely initiated as initial oral combination therapy [1, 7, 9–12]. Initial use of triple combination therapy addressing all available pathways was mainly reserved for severe cases in NYHA functional class IV due to the need of an indwelling catheter for continuous prostanoid therapy. Selexipag is an oral highly selective prostacyclin receptor agonist and has been approved by the FDA in December 2015 allowing an oral combination therapy targeting the prostacyclin pathway. In a placebo-controlled phase 2 study with PAH patients receiving single or double therapy, addition of selexipag significantly reduced the pulmonary vascular resistance (PVR) by 30.3% after 17 weeks of treatment [13]. In a large randomized placebo-controlled phase 3 study (GRIPHON) including PAH patients on oral mono or dual therapy for PAH, selexipag reduced the primary composite endpoint of death or a complication related to PAH by 40% (hazard ratio in the selexipag group as compared with the placebo group 0.6, $p < 0.001$) [14]. This treatment effect was driven by differences in disease progression and hospitalization as there was no significant difference in mortality between the two study groups as disease progression was a predefined endpoint and terminated the study for the patient in investigation [14]. Subgroup analysis in PAH associated with connective tissue disease (CTD) revealed similar improvements of the same primary composite endpoint [15]. The role of combination therapy in distal inoperable or postoperative persisting CTEPH is less clear. However, many experts agree that distal CTEPH is medically treated in analogy to PAH as both share similar pathogenic features [5, 10, 16, 17].

Early combination therapy is commonly used in clinical practice [10, 16] and since the availability of selexipag in Switzerland, triple oral combination therapy including selexipag is commonly offered to patients not fulfilling all criteria of favorable prognosis. Currently, there are very scarce data available on the clinical course of patients with PAH or CTEPH receiving selexipag in real-life conditions. We therefore analyzed all patients in the Zurich PH cohort who received triple therapy with selexipag.

Methods

This retrospective cohort study complied with the ethical laws in Switzerland and all patients have signed informed consent for the Zurich PH cohort study (KEK 2014-0214).

Study Design and Patients

This is a retrospective analysis of data from all adults (> 18 years) with PAH or distal CTEPH in whom selexipag was initiated at the University Hospital Zurich between July 2016 and April 2018 due to not fulfilling all criteria for favorable prognosis according to the latest guidelines [1]. The data from the last visit before starting selexipag were considered as baseline. Right heart catheterization (RHC) data of the last RHC available before the start of selexipag were retrieved. Variables assessed at baseline, at 2–4 months follow-up (FU), and at the last visit or at the last visit before stopping selexipag included the NYHA class, the 6-min walk distance (6MWD), the N-terminal pro brain natriuretic peptide (NT-proBNP), echocardiographic assessments of the tricuspid pressure gradient (TPG) as surrogate for pulmonary artery pressure, the tricuspid annular plane systolic excursion (TAPSE), and the systolic/diastolic fractional area change of the right ventricle (FAC%) as markers of cardiac function [18], and also the maximal power output, oxygen uptake and VE/VCO_2 slope retrieved from maximal ramp cycle cardiopulmonary exercise test (CPET). Quality of life questionnaires [Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), EuroQoL and Minnesota living with heart failure questionnaire (MLHF)] as well as patient self-reported therapeutic effect (I feel better, worse, equal), and self-reported health status (scaled from very bad, bad, not so good, good, very good, and excellent) were retrieved at baseline and after on average 6 months of FU. We compared and statistically analyzed the variables between baseline and FU as well as between baseline and 'last visit'. The 'last visit' consisted in the last available visit or the last visit before stopping selexipag. In patients who stopped selexipag, the last visit was additionally analyzed separately. We used the risk stratification strategy of the last guidelines [1] to categorize patients as low, intermediate, or high risk at baseline, following the validation strategy of Kylhammar et al. [19].

Treatment Regimen

All patients received an oral double therapy with endothelin receptor antagonist (ERA) and phosphodiesterase type 5 (PDE-5) inhibitors or soluble guanylate cyclase (sGC) stimulator. One patient on inhaled Iloprost was switched to selexipag and one patient was pretreated also with imatinib since years. Selexipag treatment was initiated at a dose of 200 mcg bid and increased weekly in increments of 200 mcg bid until the maximal dose of 1600 mcg bid was reached or until unmanageable adverse effects developed

(headache, jaw pain, nausea, or diarrhea). Specialized nurses controlled the up-titration with weekly telephone calls according to clinical practice.

Statistical Analysis

Data were stored in the secure database of the Zurich PH cohort. Analysis was performed using the SPSS Statistics 25. All data are expressed as median (quartiles). Comparison of NYHA class, 6MWD, blood, echocardiography and CPET parameters were performed using non-parametric Wilcoxon test due to non-normal distribution of the majority of data. A p value < 0.05 was considered statistically significant. We calculated the Cohen's effect size for quality of life parameters as the mean change during follow-up divided by the standard deviation at baseline for the quality of life questionnaire items. Due to the exploratory nature of our clinical study, we did not perform an a priori sample size calculation. However, we computed non-parametric 95% confidence intervals of changes in quality of life to assess the precision of these outcomes.

Results

Baseline Patient Characteristics

Baseline characteristics and therapy of 23 patients (14 females, median age 56 years) who had selexipag added to oral combination therapy are shown in Tables 1 and 2. There were only three patients with distal CTEPH in this observational study, two of them with persisting PH after pulmonary endarterectomy, and one patient was inoperable. Functional class, 6MWD, and echocardiography were available for all patients at baseline and CPET in 12 patients. CPET at baseline showed a reduced maximal oxygen uptake (peak VO_2max), a reduced power output, and increased VE/VCO_2 slope. According to the risk classification proposed by Boucly et al. [1, 20], seven patients were in the low risk, 15 in the intermediate risk, and 1 patient in the high risk group, but all revealed at least one factor of worse prognosis.

Follow-up at 2–4 months

Follow-up data at visit 2–4 months after start of selexipag was available in 20 patients (Table 2; Fig. 1). The daily selexipag dose achieved was 2200 (1600; 3200) mcg. The 6MWD improved significantly to 447 (420; 507) m (+ 7 m, $p = 0.035$). The resting peripheral oxygen saturation (SpO_2) and the Borg scale at peak 6MWD improved significantly (SpO_2 from 96% (92; 97) to 97% (94; 98), $p = 0.043$, Borg from 5 (4, 7) to 4 (3, 5) points, $p = 0.009$).

Table 1 Patient's baseline characteristics

Subjects (n)	23
Age (years)	56 (46; 66)
Time from diagnosis to start of selexipag (months)	24 (6; 70)
Female	14 (61%)
Body mass index (kg/m^2)	25.6 (23; 29)
PH classification	
PAH WHO group 1	20
Idiopathic	14
Associated with congenital heart disease	3
Associated with connective tissue disease	2
Associated with schistosomiasis	1
CTEPH	3
After endarterectomy	2
Inoperable	1
NYHA FC	
I	1
II	8
III	13
IV	1
Baseline hemodynamics right heart catheter n = 22	
Mean pulmonary artery pressure (mmHg)	48 (42; 54)
Right atrium pressure (mmHg)	8.5 (5; 13)
Pulmonary capillary wedge pressure (mmHg)	11 (9; 12)
Pulmonary vascular resistance (WU)	8 (6; 10)
Cardiac output (l/min)	4.8 (4; 5.8)
Cardiac index (l/min/m^2)	2.8 (2.4; 3.3)
PAH targeted therapy	
Endothelin receptor antagonist	23
Phosphodiesterase 5 inhibitor	20
Soluble guanylate cyclase stimulator	3
Imatinib	1
Iloprost inhalation	1
Other therapies	
Diuretics	17
Anticoagulation	15
Betablocker	3
ACEI/ATII	5
Oxygen: only nocturnal/16–24 h/day	6/7

Values are expressed as median (quartiles) or number (%)

PH pulmonary hypertension, *PAH* pulmonary arterial hypertension, *CTEPH* chronic thromboembolic pulmonary hypertension, *NYHA FC* New York heart association functional class, *ACEI* angiotensin converting enzyme inhibitor, *ATII* angiotensin receptor 2 antagonist

The NYHA class and NT-pro-BNP remained stable. Individually analyzed, 12 patients remained in the same NYHA class, five patients improved, and three deteriorated. Follow-up echocardiographic and CPET variables from eight, respectively five, patients showed no difference compared to baseline.

Table 2 Baseline data and outcomes at 2–4 months of follow-up and at the last visit

		Baseline		2–4 months of follow-up after start of selexipag		Last visit
NYHA functional class						
I	$n=23$	1	$n=20$	1	$n=22$	1
II		8		7		13
III		13		12		8
IV		1		0		0
Median		3		3		2
6-min walk test	$n=23$		$n=19$		$n=19$	
Distance (m)		440 (420; 490)		447 (420; 507)*		464 (420; 526)
SpO_2 resting (%)		96 (92; 97)		97 (94; 98)*		95 (92; 97)
SpO_2 peak exercise (%)		88 (79; 94)		90 (84; 92)		83 (76; 93)
Heart rate peak exercise (bpm)		128 (114; 137)		121 (110; 135)		116 (104; 134)
Systolic blood pressure peak exercise (mmHg)		140 (121; 169)		126 (116; 145)		137 (114; 148)
Diastolic blood pressure peak exercise (mmHg)		74 (71; 95)		73 (66; 81)		75 (68; 79)
Borg scale		5 (4; 7)		4 (3; 5)*		4 (4; 6)
Blood parameter	$n=22$		$n=20$		$n=22$	
NT-pro-BNP (ng/l)		326 (167; 1725)		243 (130; 892)		568 (135; 1856)
Cycle cardiopulmonary exercise test	$n=12$		$n=5$		$n=13$	
Peak VO_2 (ml/kg/min)		12 (10; 15)		17 (14; 20)		16 (12; 17)
VE/VCO_2 slope		40 (33; 49)		30 (29; 34)		37 (30; 43)
Power output (watt)		71 (62; 91)		69 (66; 105)		94 (66; 105)
Echocardiography	$n=23$		$n=8$		$n=18$	
Tricuspid pressure gradient (mmHg)		54 (46; 72)		50 (38; 57)		48 (37; 66)
Tricuspid annual plane systolic excursion (mm)		17 (13; 21)		13 (12; 17)		16 (13; 20)
Right ventricular systolic/diastolic fractional area change (%)		29 (25; 36)		31 (28; 37)		29 (21; 36)
Left ventricular ejection fraction (%)		61 (59; 65)		62 (60; 64)		61 (56; 65)
Selexipag dose per day (mcg)				2200 (1600; 3200)		2000 (1600; 3100)
Therapy duration (days)				89 (59; 116)		221 (113; 359)

Values are expressed as median (quartiles). $p<0.05$ was considered as statistically significant change from baseline and is marked with asterisk

SpO_2 peripheral oxygen saturation, *NT-pro-BNP* N-terminal brain natriuretic peptide, *peak VO_2* maximal oxygen uptake, *VE* minute ventilation, *VCO_2* carbon dioxide output

Last Visit

Data for the last visit were available from 22 patients, after 221 (113; 359) days of observation (Table 2; Fig. 1). The 6MWD remained stable with 464 (420; 526) m in comparison with the baseline 6MWD. The SpO_2 at rest and at peak exercise, the Borg scale, and the NT-pro-BNP remained stable. Even though the median pro-BNP doubled at the last visit in comparison with the baseline, this increase was not significant. Overall, there was no difference in the NYHA class from baseline to the last visit (median 3 vs. 2, $p = 0.14$). Individually analyzed, 13 patients remained in the same NYHA class, seven patients improved, and two deteriorated (Fig. 2). The echocardiographic ($n=18$) and the CPET ($n=13$) variables remained stable. The daily selexipag dose achieved was 2000 (1600; 3100) mcg.

Quality of Life

Quality of life questionnaires were available in half of the patients (Table 3). There was a significant improvement in the symptoms and quality of life items of the CAMPHOR questionnaire, whereas the activity item remained stable. The effect size of the change of the CAMPHOR was between 0.4 and 0.8. There was also a significant improvement in the EuroQoL visual analog scale from 55 to 65 (a higher score meaning a better quality of life), with a good effect size of 0.8. More patients rated themselves as better under additional selexipag therapy as shown in the patient self-reported therapeutic effect questionnaire and the self-reported health status stayed stable (a lower score indicating a better status), with a good effect size of 1.2 and 0.5, respectively. The MLHF questionnaire was low at baseline and remained

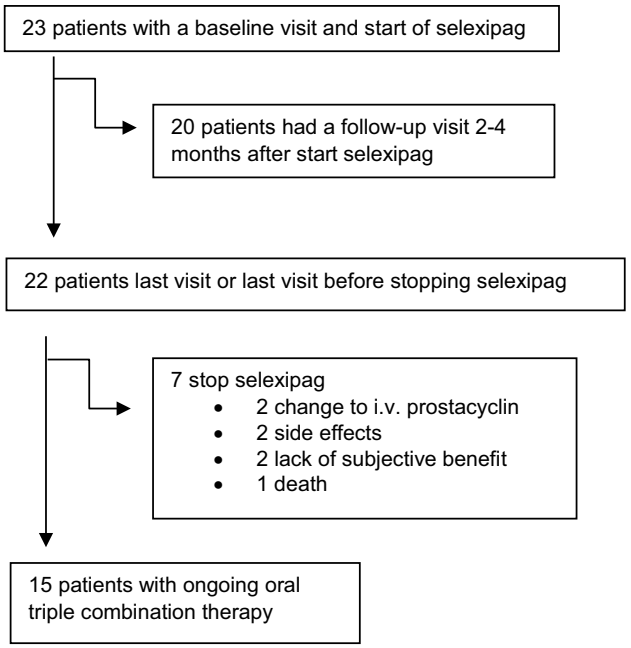

Fig. 1 Flow chart of the patients treated with selexipag as add-on therapy

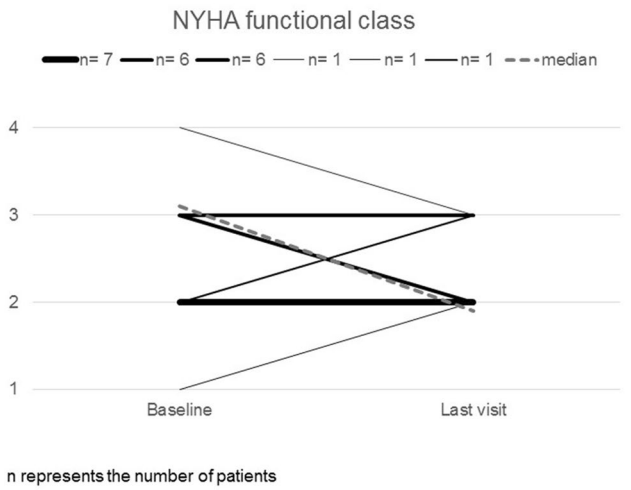

Fig. 2 NYHA functional class at baseline and at the last visit

stable under therapy (a lower score indicating a better quality of life).

Stop of Selexipag

Six patients stopped selexipag during the observational period. Two patients (1 PAH, 1 CTEPH) were switched to intravenous prostacyclin after 345 respectively 111 days due to insufficient clinical stabilization and listing for lung transplantation. One patient with congenital heart disease stopped selexipag because of intense head and muscle ache and worsening of SpO_2. One PAH patient stopped selexipag due to persistent diarrhea and pruritus and two because of lack of subjective benefit. The therapy duration for the patients who stopped selexipag was 218 (111; 254) days and the selexipag dose 2400 (1000; 3000) mcg.

Mortality and Hospitalization

A 73-year-old patient died during the observational period due to a septic shock with *Staphylococcus aureus* 283 days after the initiation of selexipag therapy. This death was not related to PAH and its therapy. One patient was hospitalized due to an influenza infection and one due to progressive right heart failure necessitating intravenous diuretic therapy.

Discussion

Our retrospective study describes for the first time the clinical outcome of patients with PAH or distal CTEPH treated with selexipag as add-on to oral combination therapy in a real-life setting. We found that triple oral combination therapy adding selexipag was generally well tolerated and may help to stabilize exercise capacity, NYHA class, NT-proBNP, pulmonary artery pressure and right heart function, and available questionnaire assessment revealed improved quality of life scores and symptoms.

Initial combination therapy has shown efficacy in randomized trials and delayed disease progression and its early initiation even in patients with more favorable risk factor profiles may be beneficial [1]. According to recently published risk assessments strategies, 7, 15, and 1 patients of the present collective would be assigned to low, intermediate, and high risk [19–21]. But even in the low-risk group, the patients did not fulfill all beneficial criteria, which is why we proposed escalation of drug therapy.

The post hoc analysis of the GRIPHON study [22] analyzed the subgroup of patients ($n=376$) who received double oral therapy with ERAs and PDE-5 inhibitors before adding selexipag versus placebo. In this subgroup, selexipag reduced the composite endpoint of death or a complication related to PAH by 37% compared to placebo, indicating an effect similar to that in the overall GRIPHON population [14].

The 6MWD is one of the most widely used prognostic marker and study endpoint; however, the observed changes are usually less in combination therapy trials [23]. In our retrospective real-life cohort after a median treatment time of 8 months, the median 6MWD increased by 24 m; however, due to small number and variable response, this was not significant but relates to the treatment effect of 12 m in GRIPHON [12]. Exercise capacity assessed by CPET was

Table 3 Quality of life at baseline and during therapy with selexipag

	n	Baseline	*n*	Follow-up	*p* value	Effect size (CI)
CAMPHOR	14		13			
Symptoms		8 (5; 11)		4 (3; 8)	0.014	−0.68 (−1.26 to −0.11)
Activity		9 (6; 10)		7 (5; 9)	0.303	−0.36 (−1.07 to 0.35)
Quality of life		3 (1; 5)		1 (0; 2)	0.041	−0.42 (−0.80 to −0.03)
EuroQoL visual analog scale	14	55 (43; 64)	12	65 (60; 72)	0.039	0.65 (0.09 to 1.21)
Self-reported therapeutic effect	11	2 (2; 3)	11	1 (1; 2)	0.046	−1.26 (−2.38 to −0.13)
Self-reported health status	11	4 (3; 4)	11	3 (3; 4)	0.317	−0.49 (−1.65 to 0.67)
Minnesota living with heart failure questionnaire	14		11			
General score		22 (9; 43)		23 (17; 31)	0.45	−0.27 (− 0.86 to 0.32)
Physical		12 (7; 20)		11 (9; 15)	0.44	−0.34 (−0.95 to 0.26)
Emotional		4 (1; 11)		3 (2; 7)	0.26	−0.36 (−1.01 to 0.29)

Values are expressed as median (quartiles). CI 95% confidence interval. *p* values by Wilcoxon matched pair test from baseline to follow-up are shown. *CAMPHOR* Cambridge pulmonary hypertension outcome review. CAMPHOR, self-reported therapeutic effect, self-reported health status and Minnesota living with heart failure questionnaire: a lower score indicates a better status. *EuroQoL* a higher score indicates a better quality of life. Effect size is calculated as mean change during follow-up divided by the pooled standard deviation (Cohen's *d*)

also stabilized, reflected by a trend towards an improved peakVO_2, VE/VCO_2 slope, and power output. Improving CPET would be of high relevance for patients, as CPET parameters have a prognostic value predicting survival and time to clinical worsening [24]. NYHA class remained stable in the majority of patients (13 patients), improved in seven, and deteriorated in two patients. Thus, the percentage of patients not revealing a worsening of the NYHA class in our cohort is slightly higher than in GRIPHON (91 vs. 78%) and reassuring in a real-life setting. Echocardiographic assessment at the last visit showed that all assessed parameters remained stable on oral triple combination therapy and so did the NT-pro-BNP.

An improved quality of life is an important and patient-relevant outcome parameter, and the measurement of the quality of life endpoint enables to have a more comprehensive and relevant assessment of therapeutic effects. A better quality of life was furthermore predictive of the prognosis in PAH/CTEPH [4]. The CAMPHOR was designed as a disease-specific score to assess symptoms, activity limitations, and quality of life. It has a good internal consistency and reproducibility and its German version has also been validated [25, 26]. Significant improvement was observed in the symptoms and quality of life items of the CAMPHOR questionnaire with an effect size ranging from 0.4 to 0.8 depending on the items, which is concordant with the described ranges of the effect size in the literature and is clinically relevant [27]. It is thus patient relevant and underscores the potential use of early initiated triple combination therapy. The fact that the item activity of the CAMPHOR questionnaire remained stable again points towards a stabilization on therapy and underscores the fact that further improvement in exercise capacity/activity might be difficult to achieve in pretreated patients. There was also a significant improvement in the EuroQoL visual analog scale (similar to a thermometer), which is a standardized non-disease-specific instrument for assessing quality of life [28]. The MLHF questionnaire has been shown to be a significant predictor of outcome in a prospective study investigating the performance and clinical relevance of the MLHF in PAH and CTEPH patients [4]. The patient self-reported therapeutic effect and health status showed also an amelioration and stabilization, also with a high effect size of ≥ 0.5. To our knowledge, this is the first report on quality of life measures on selexipag, showing an amelioration in two important disease-specific scores and parameters of global assessments.

Our study has several limitations. The major one is that this is a retrospective analysis in a relatively small number of patients, particularly the CTEPH group was very small and thus will not allow subgroup analysis concerning CTEPH alone. As we have no control group available, it remains speculative whether stabilization in this cohort was due to the addition of selexipag to the established double combination therapy and lead-time bias may apply. Although all patients had some factor of unfavorable prognosis, the majority was in an intermediate-to-low risk profile. The fact that two patients were switched to an intravenous prostanoid during the course of the analysis underscores the importance of close follow-up of this patients in a tertiary care center.

In conclusion, oral triple combination therapy by adding selexipag to an established double combination therapy may contribute to stabilization of the NYHA class, exercise capacity and hemodynamics, and improves quality of life in patients with PAH or distal CTEPH with risk parameters

for unfavorable prognosis. Further randomized trials should assess the value of triple oral combination therapy in PAH or distal CTEPH not fulfilling all favorable risk criteria.

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Compliance with Ethical Standards

Conflict of interest None of the authors declares any conflict of interest in relation to the present work. SU received grant money from the Swiss National Science Foundation, Zurich Lung, Actelion SA, Bayer SA, Orpha Swiss. SU; EIS, SS, ML and CB received travel support and lecture fees from Actelion SA, Bayer SA, MSD SA and Orpha Swiss.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective cohort study complied with the ethical laws in Switzerland and all patients have signed informed consent for the Zurich PH cohort study (KEK 2014-0214).

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