Real-world retrospective cohort study of oral selexipag in methamphetamine-associated pulmonary arterial hypertension: An interim analysis from TEAM PAH

Samuel B Brusca, MD[1]; Amanda Schnell Heringer, MS, RN, AGCNS-BC[1]; Sumeet Panjabi, PhD[2]; Sarah Walden, PharmD, BCPS[2]; Gurinderpal Doad, PharmD[2]; Michelle Cho, PharmD[2]; Ambika Satija, ScD[3]; Gayatri Marathe, PhD[4]; Henrietta Blinder, MSc[4]; Marjolaine Gauthier-Loiselle, PhD[4]; Teresa De Marco, MD, FACC, FHFSA[1]

[1]University of California San Francisco, San Francisco, CA, USA; [2]Johnson & Johnson, Titusville, NJ, USA; [3]Analysis Group, Inc., Boston, MA, USA; [4]Analysis Group, Inc., Montreal, QC, Canada

Introduction

- Pulmonary arterial hypertension (PAH) is a complex disease that leads to progressive right ventricular failure[1]
- Selexipag is an oral prostacyclin receptor agonist that delays disease progression and reduces the risk of hospitalization for PAH (GRIPHON trial)[2,3]
- Methamphetamine-associated PAH (meth-PAH) is increasingly recognized as a common, severe form of PAH with increased risk of heart failure and death compared to idiopathic PAH[4,5]
- The meth-PAH patient population remains understudied, with limited clinical data and recommendations from guidelines
- To our knowledge, there are no data on selexipag titration and persistence in this population

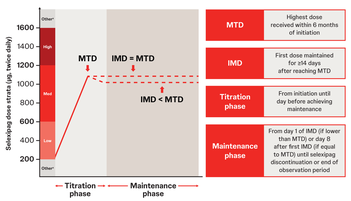
Objective

- To describe oral selexipag dosing patterns and persistence in patients with and without a history of methamphetamine use at an expert center in California, USA, that uses a customized, site-specific, multidisciplinary, nurse-directed protocol (RN-protocol)

Methods

- This was a single-center, retrospective chart review of all adult patients with a primary diagnosis of PAH initiated on oral selexipag between January 1, 2018, and March 31, 2023. Patients were titrated to an individualized maintenance dose (IMD) using an RN-protocol that entailed frequent follow-up to individually manage side effects and tailor selexipag titration
- Dosing patterns and persistence were reported during follow-up, which spanned from selexipag initiation (i.e., the index date) to the earliest of 14 months after index, the last assessment, lung transplant or death
- Study definitions for titration and dosing were adapted from the SelexiPag: tHe usErs dRug rEgistry (SPHERE) (**Figure 1**)[6]
- Demographic and clinical characteristics, including history of methamphetamine use (defined as documentation by a pulmonary hypertension clinician in the patient's medical record), were assessed at selexipag initiation, and dosing patterns and persistence were reported during follow-up
- Data were summarized using descriptive statistics, chi-square testing, and Kaplan–Meier analysis

Figure 1. Study definitions adapted from SPHERE[6]



*The 'other' dose category includes doses <200 or >1600 µg.
BID, twice daily; **IMD**, individualized maintenance dose; **Med**, medium; **MTD**, maximum tolerated dose; **SPHERE**, SelexiPag: tHe usErs dRug rEgistry.

Results

Baseline demographic and clinical characteristics

- This was an interim analysis of 119 patients who initiated oral selexipag, with a median observation period of 14 months
  - 56/119 (47%) patients had a history of methamphetamine use; of these, 13 (23%) reported active use
  - One patient whose history of methamphetamine use was recorded as 'unknown' was excluded
- Patients with a history of methamphetamine use were significantly more likely to be male, White, World Health Organization functional class III/IV, and initiated on selexipag as a part of triple therapy relative to those with no history of methamphetamine use (**Table 1**)

Table 1. Baseline demographic and clinical characteristics (N=119)*

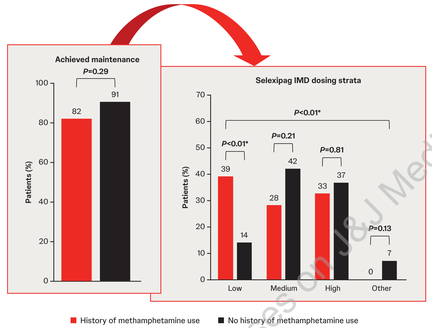
	History of methamphetamine use (n=56)	No history of methamphetamine use (n=63)
Median age	50 years	52 years
Female sex	50%	79%*
Race[b]		
White	70%	41%*
Hispanic/Latino	9%	22%
PAH etiology/ disease factors		
Drug- or toxin-induced[c,d]	91%	8%*
WHO FC III/IV PAH	63%	41%*
Median time from diagnosis[d]	1.3 years	1.5 years
Median REVEAL Lite 2 risk score[e]	6.0	6.0
Comorbidities[b]		
Hypertension	36%	33%
Obstructive sleep apnea	36%	32%
CAD	21%	18%
Obesity (BMI ≥30 kg/m^2)	20%	24%
COPD	13%	10%
Triple therapy regimen (selexipag + ERA + PDE5i)	80%	64%

*P<0.05 (chi-square test for difference between cohorts). [b]One patient who reported history of methamphetamine use as 'unknown' was excluded. [c]Categories shown represent the most common and are not mutually exclusive. [d]Drug- or toxin-induced etiology included drugs such as methamphetamine and fenfluramine/phentermine. Five patients with a history of methamphetamine use without documented drug- or toxin-induced PAH etiology had a multifactorial PAH etiology. [e]Diagnosis date was unknown in 25% of patients with a history of methamphetamine use and 24% of patients with no history of methamphetamine use. [e]REVEAL Lite 2 scores were available for 30% of patients with a history of methamphetamine use and 25% of patients with no history of methamphetamine use. WHO functional class, vital signs (SBP and HR), 6MWD, BNP/NT-proBNP, and renal insufficiency (eGFR) were used to calculate the REVEAL Lite 2 score. Only patients with (i) no missing values, (ii) missing values for one of the six components, and (iii) missing values for two or more of renal insufficiency, SBP, and HR were included in the risk score calculation, based on Benza et al, 2021,[7] which showed good discrimination; c-statistic ≥0.70.
6MWD, 6-minute walk distance; **BMI**, body mass index; **BNP**, B-type natriuretic peptide; **CAD**, coronary artery disease; **COPD**, chronic obstructive pulmonary disease; **eGFR**, estimated glomerular filtration rate; **ERA**, endothelin receptor antagonist; **HR**, heart rate; **NT-proBNP**, N-terminal pro-B-type natriuretic peptide; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor; **REVEAL**, Registry to Evaluate Early and Long-Term PAH Disease Management; **SBP**, systolic blood pressure; **WHO FC**, World Health Organization functional class.

Titration and individualized dosing

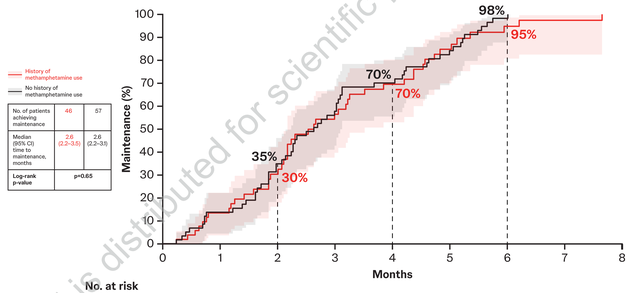
- More than 80% of patients with a history of methamphetamine use achieved maintenance on oral selexipag, which was similar to those with no history of use (82% vs 91%; *P*=0.29) (**Figure 2**)
- Patients with a history of methamphetamine use had a lower IMD (median IMD, 700 vs 1000 µg twice daily), with more patients in the low-dose category (39% vs 14%, *P*<0.01) than those without a history of methamphetamine use (**Figure 2**)
- Time to maintenance was similar across the two cohorts, with roughly one-third achieving maintenance within 2 months of initiation and >90% within 6 months (median, 2.6 months in both cohorts) (**Figure 3**)
- Median time between dose escalations was longer for patients with a history of methamphetamine use than for those without, during titration (15.5 vs 14.3 days) and during maintenance (59.1 vs 41.7 days)

Figure 2. Selexipag dosing strata among patients who achieved maintenance



*Chi-square test for difference between cohorts. **IMD**, individualized maintenance dose.

Figure 3. Kaplan–Meier plot for time to maintenance



No. at risk									
Methamphetamine use	56	44	32	20	14	7	2	1	0
No methamphetamine use	63	50	37	24	17	9	1	0	0

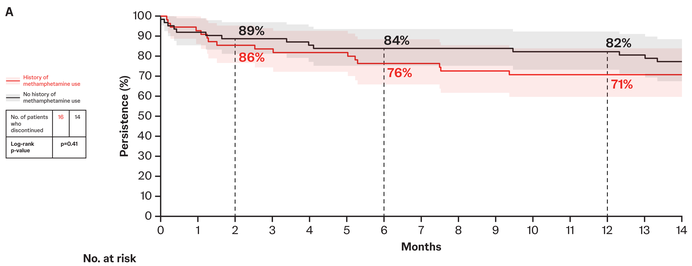
No. of patients achieving maintenance	46	57
Median (95% CI) time to maintenance, months	2.6 (2.2–3.5)	2.6 (2.2–3.1)
Log-rank p-value	p=0.65	

CI, confidence interval.

Selexipag persistence

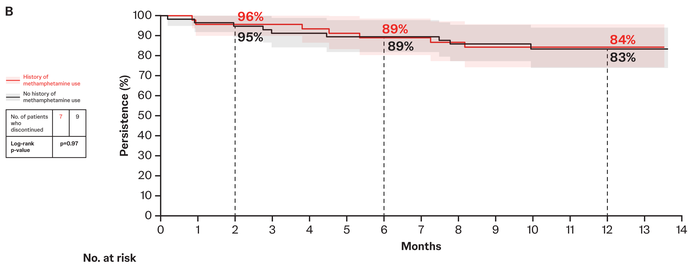
- At 12 months, 71% of patients with a history of methamphetamine use remained persistent on oral selexipag, compared with 82% of those with no history of use (**Figure 4A**)
- Among patients achieving maintenance, patients with versus without a history of methamphetamine use had similar persistence at 12 months (84% vs 83%) (**Figure 4B**)
- In both groups, the highest rate of discontinuation occurred within 2 months of selexipag initiation, and more than two-thirds of discontinuations were due to an inability to tolerate treatment
- In total, 39% of patients with and 40% of patients without a history of methamphetamine use experienced severe adverse events during the observation period

Figure 4. Kaplan–Meier plot for selexipag persistence during (A) the entire observation period, and (B) the maintenance phase among those who reached maintenance



No. at risk															
Methamphetamine use	56	51	47	46	45	45	41	41	39	39	38	38	38	38	38
No methamphetamine use	63	57	55	55	53	52	52	52	52	52	50	50	50	49	47

No. of patients who discontinued	10	14
Log-rank p-value	p=0.41	



No. at risk															
Methamphetamine use	46	44	43	43	42	41	40	39	37	32	26	19	10	5	0
No methamphetamine use	57	55	54	52	52	51	51	51	47	40	33	26	14	5	0

No. of patients who discontinued	7	9
Log-rank p-value	p=0.97	

Limitations

- **Methamphetamine use may not be reliably reported and the study findings pertain only to patients with documented use**
- **The study reports results for patients with a documented history of methamphetamine use, which does not necessarily equate to meth-PAH etiology**
- **Other limitations include missing data elements (e.g., risk parameters), lack of information on variables not ascertained in routine patient care, and limited generalizability to patients with any barriers to accessing or receiving care**

Conclusions

- **To our knowledge, this is the first study describing oral selexipag dosing patterns in patients with PAH and a history of methamphetamine use**
- **Most patients with a history of methamphetamine use were successfully titrated to their IMD and persisted on treatment, thereby supporting oral selexipag as a viable option targeting the prostacyclin pathway in a population that may have challenges with parenteral prostacyclin formulations**
- **Despite similar time to maintenance and comparable levels of persistence in both groups, patients with a history of methamphetamine use had a slower escalation schedule and lower IMDs, highlighting the importance of a multidisciplinary, nurse-directed protocol with frequent patient contact and titration individualization**

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