BREEZE: Clinical Outcomes and Pharmacokinetics of Treprostinil Inhalation Powder (Tyvaso DPI)

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BACKGROUND

- Inhaled treprostinil (Tyvaso®) is indicated in the United States for WHO Groups I (PAH) and III (PH-ILD) to improve exercise ability and is currently delivered via a handheld ultrasonic nebulizer[1]
- Prostacyclins are valuable medications for the treatment of PAH but their use is limited by their delivery systems
- A dry powder formulation of treprostinil (Tyvaso DPI) is in development to improve ease of use
- Previous evaluation of Tyvaso DPI in healthy volunteers demonstrated it was safe and well-tolerated at doses of 30, 60, 90, 120, and 150 µg[2]

METHODS

- BREEZE is an open label safety and tolerability study in which subjects on a stable regimen of Tyvaso® switched to a corresponding dose of Tyvaso DPI
- After 3 weeks, subjects underwent safety evaluations and completed a six- minute walk distance (6MWD) test, device preference and satisfaction (PQ-ITD), and completed symptoms and impact (PAH-SYMPACT) questionnaires
- After Week 3, subjects could continue receiving Tyvaso DPI by participating in an Optional Extension Phase (OEP) of the study, with follow up visits every 8 weeks. The OEP is ongoing
- The primary objective was to evaluate the safety and tolerability of Tyvaso DPI in subjects with PAH previously treated with Tyvaso®
- Secondary objectives include changes in 6MWD, device preference and satisfaction (PQ-ITD), and PAH symptoms and impact (PAH-SYMPACT) from Baseline to Week 3
- Pharmacokinetic (PK) samples were also collected at Baseline and Week 3. Plasma concentrations were used to derive PK parameters using noncompartmental methods and were compared between Tyvaso and Tyvaso DPI across all dose levels

RESULTS

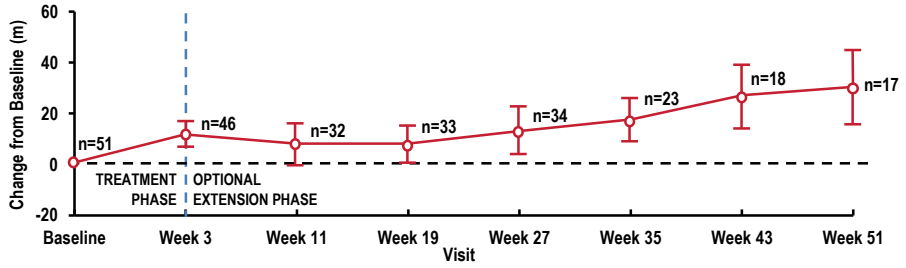
- Fifty-one subjects enrolled and transitioned from a stable dose of Tyvaso to an equivalent dose of Tyvaso DPI
- Significant improvements were seen in 6MWD (11.5 m; p=0.0217) (Figure 1), and PQ-ITD (p≤0.0003) after 3 weeks; PAH-SYMPACT scores were improved for all domain scores (range: -0.05 to -0.22) after 3 and 11 weeks
- Adverse events (AEs) were consistent with other inhaled treprostinil studies in subjects with PAH [cough (35%), headache (16%)] (Table 2); there were no study drug related serious AEs
- Overall, systemic exposure between Tyvaso DPI and Tyvaso was similar in this study and time of maximum plasma concentration occurred rapidly for Tyvaso DPI and Tyvaso at all doses. (Figure 2)
- When comparing exposures of Tyvaso DPI versus Tyvaso following pooling of doses for each treatment, geometric mean AUC was 13% greater for Tyvaso DPI compared to Tyvaso and geometric mean Cmax was 33% greater for Tyvaso DPI compared to Tyvaso
- Between-subject variability for AUC and Cmax parameters was similar within treatment (Tyvaso DPI or Tyvaso); however, variability in these parameters was approximately 2- to 3-fold lower for Tyvaso DPI compared to Tyvaso

RESULTS (cont.)

Table 1. Baseline Characteristics

	Tyvaso DPI Dose in Treatment Phase			
	32 mcg (n=2)	48 mcg (n=27)	64 mcg (n=22)	Overall (n=51)
Age (years), Mean (SD)	48.0 (28.3)	54.7 (13.1)	58.0 (12.8)	55.9 (13.4)
Sex, n (%)				
Male	0	5 (18.5)	3 (14)	8 (16)
Female	2 (100)	22 (81.5)	19 (86)	43 (84)
Baseline BMI (kg/m^2), Mean (SD)	30.20 (11.03)	27.89 (5.94)	32.18 (6.91)	29.87 (6.74)
Time Since PAH Diagnosis (years), Mean (SD)	5.675 (7.333)	7.973 (7.172)	9.834 (5.634)	8.686 (6.509)
Current PAH Diagnosis, n (%)				
Idiopathic/Familial	1 (50)	17 (63)	11 (50)	29 (57)
Associated with Unrepaired or Repaired Congenital Systemic-to-Pulmonary Shunts	0	2 (7)	2 (9)	4 (8)
Associated with Collagen Vascular Disease	1 (50)	6 (22)	7 (32)	14 (28)
Associated with HIV	0	0	1 (5)	1 (2)
Associated with Appetite Suppressant/ Other Drug or Toxin Use	0	2 (7)	1 (5)	3 (6)
WHO Functional Class at Screening, n (%)				
I	1 (50)	5 (19)	0	6 (12)
II	1 (50)	18 (67)	12 (55)	31 (61)
III	0	4 (15)	10 (46)	14 (28)
Background PAH Medications, n (%)				
Any Medication	2 (100)	27 (100)	21 (96)	50 (98)
ERA	2 (100)	22 (82)	19 (86)	43 (84)
PDE5-I	1 (50)	23 (85)	17 (77)	41 (80)
sGC	0	3 (11)	4 (18)	7 (14)
Number of Background PAH Medications in Addition to Tyvaso, n (%)				
None	0	0	1 (4.5)	1 (2)
1	1 (50)	6 (22)	2 (9)	9 (18)
2	1 (50)	21 (78)	19 (86)	41 (80)
6MWD (m), Mean (SD)	362.0 (79.2)	426.8 (116.7)	414.4 (104.6)	418.9 (109.4)

Figure 1. Mean Change from Baseline in 6MWD from Baseline by Visit*



*Results for subjects completing up to 51 weeks of the treatment phase and OEP are reported. The OEP is currently ongoing

Figure 2: Mean Treprostinil Concentration vs. Time by Treatment with Pooled Dose Levels

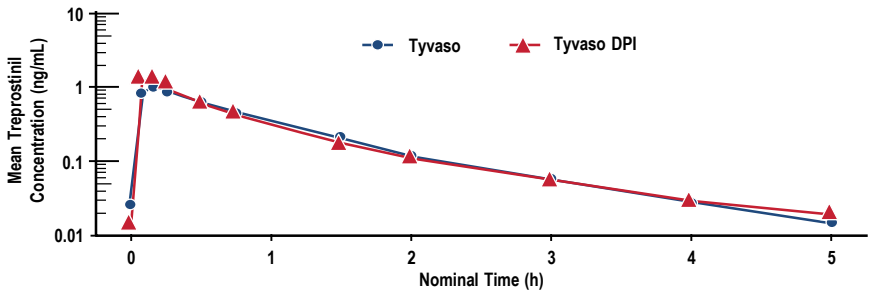


Table 2. Safety and Tolerability

	Tyvaso DPI Dose in Treatment Phase			
Preferred Term	32 mcg (n=2) n (%)	48 mcg (n=27) n (%)	64 mcg (n=22) n (%)	Overall (n=51) n (%)
Any	0	16 (59)	13 (59)	29 (57)
Cough	0	11 (41)	7 (32)	18 (35)
Headache	0	4 (15)	4 (18)	8 (16)
Dyspnea	0	2 (7)	2 (9)	4 (8)
Nausea	0	2 (7)	1 (5)	3 (6)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; Tyvaso DPI, treprostinil inhalation powder

[a] AE rate is calculated as the number of AEs divided by the total patient years of exposure per dose group

DISCUSSION

- In patients with PAH, transition from Tyvaso to Tyvaso DPI was safe and well tolerated with significant improvements in 6MWD, device preference and satisfaction, and patient reported outcomes
- Improvement in 6MWD was significant but should be viewed in the context that patients were not blinded and all patients received the study device and drug
- Overall, systemic exposure between Tyvaso DPI and Tyvaso was similar in this study and time of maximum plasma concentration occurred rapidly for Tyvaso DPI and Tyvaso at all doses

CLINICAL IMPLICATIONS

- Given the lower variability in PK parameters with Tyvaso DPI, the findings from this study suggest dosing compatibility with Tyvaso DPI formulation
- The ease of use, portability, accessibility, and ability to titrate Tyvaso DPI to higher dose levels may have a clinically significant, beneficial impact on patient compliance and persistence and quality of life,

REFERENCES

1. Tyvaso® (treprostinil) Prescribing Information. Research Triangle Park, NC: United Therapeutics Corporation; 2021
2. Smith PM. Poster presented at ERS International Conference; 2019 Sept 27 – Oct 2; Madrid, Spain

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