BREEZE: Open-label, Clinical Study to Evaluate the Safety and Tolerability of a Treprostinil Dry Powder Inhaler in Subjects with Pulmonary Arterial Hypertension Currently Using Tyvaso

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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]
- A dry powder formulation of treprostinil (Tyvaso DPI) containing an inhalation excipient, fumaryl diketopiperazine (FDKP), which acts to encapsulate and release drug into the lung for systemic absorption, is in development to improve ease of use[2]
- 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[3]

METHODS

- BREEZE is a single-sequence 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

RESULTS

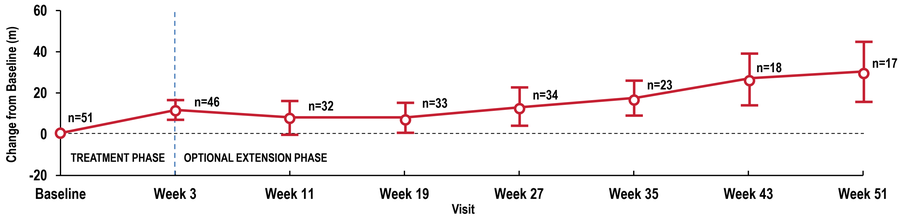
- Fifty-one subjects enrolled and transitioned from a stable dose of Tyvaso to an equivalent dose of Tyvaso DPI
- The majority of subjects 49/51 (96%) completed the 3-week treatment phase and elected to participate in the OEP; two subjects discontinued study treatment due to treatment-related AEs during the 3-week treatment phase
- 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
- Significant improvements were seen in 6MWD (11.5 m; p=0.0217) (Figure 1), and PQ-ITD (p≤0.0003) (Figure 2) after 3 weeks; PAH-SYMPACT scores were improved for all domain scores (range: -0.05 to -0.22) after 3 and 11 weeks (Figure 3)

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/m²), 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, 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. Patient Satisfaction (PQ-ITD) with Tyvaso DPI

Patient-Reported Satisfaction

Satisfaction with Tyvaso DPI inhaler was significantly improved at Week 3 compared to Tyvaso nebulizer at Baseline

- At Week 3, 44 (96%; p<0.0001) of 46 subjects agreed/strongly agreed that they were satisfied with the Tyvaso DPI inhaler, 1 (2%) subject was neutral
- In comparison, 16 (31%) subjects agreed/strongly agreed they were satisfied with Tyvaso nebulizer, 23 (45%) were neutral

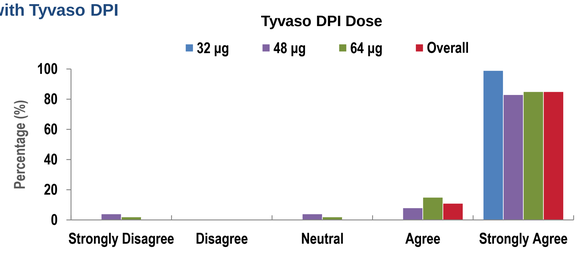
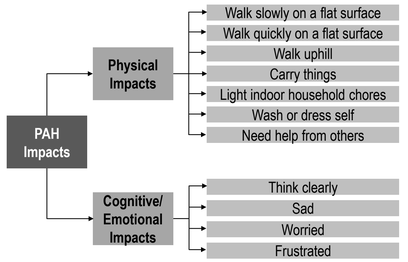


Figure 3. PAH-SYMPACT Questionnaire



PAH IMPACTS

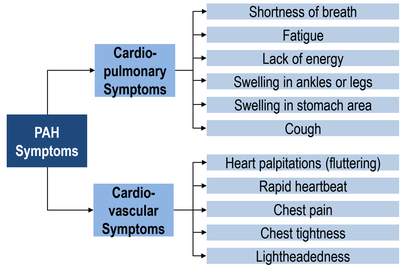
Significant improvements at Week 3 (n=46):

Physical impacts
Mean change from Baseline at Week 3: -0.14 (range: -1.1 to 1.0; p=0.0438)

Cognitive/emotional impacts:
Mean change from Baseline at Week 3: -0.17 (range: -1.3 to 0.5; p=0.0048)

Significant improvements at Week 11 (n=36):

Physical impacts
Mean change from Baseline at Week 11: -0.21 (range: -2.0 to 0.9; p=0.0429)



PAH SYMPTOMS

Cardiopulmonary Symptoms Score:
Mean change from Baseline at Week 3: -0.05 (p=0.2451) and Week 11: -0.04 (p=0.5433)

Cardiovascular Symptoms Score:
Mean change from Baseline at Week 3: -0.06 (p=0.2492) and Week 11: 0.05 (p=0.4685)

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

CONCLUSIONS

- In subjects 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
- The results of this study indicate that Tyvaso DPI is a convenient, tolerable formulation of inhaled treprostinil and may increase prostacyclin accessibility to more subjects earlier in the course of their disease, thereby potentially improving long-term outcomes

REFERENCES

1. Tyvaso® (treprostinil) Prescribing Information. Research Triangle Park, NC: United Therapeutics Corporation; 2021
2. Wang Q, Shen Y, Mi G, et al. Fumaryl diketopiperazine based effervescent microparticles to escape macrophage phagocytosis for enhanced treatment of pneumonia via pulmonary delivery. *Biomaterials* 2020;228: 119575 2.
3. Smith PM. Poster presented at ERS International Conference; 2019 Sept 27 – Oct 2; Madrid, Spain

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