Poster P1155

INSPIRE: A Phase 3, Open-Label, Multicenter Study to Evaluate the Safety and Tolerability of LIQ861 in PULMONARY ARTERIAL HYPERTENSION (PAH) (Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil NCT03399604)

Preliminary Assessment of the Safety and Exploratory Endpoints

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INTRODUCTION AND RATIONALE

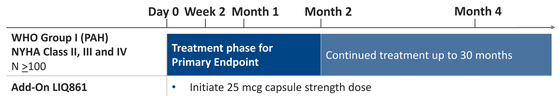
Pulmonary arterial hypertension (PAH) is a progressive disease characterized by elevated pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), leading to right ventricular failure and death.[1-3] Therapies are now available that target 3 different signal transduction pathways, and combination therapy may provide a standard of care in treating PAH. Initial therapy usually involves dual combination therapy with agents targeting the endothelin and nitric oxide/cyclic GMP pathways. Therapies targeting the prostacyclin pathway should be added for patients receiving dual combination therapy who do not achieve treatment goals.[4]

Treprostinil (TRE), a synthetic prostacyclin analogue, is approved for inhalation administration to patients with pulmonary arterial hypertension (PAH) via nebulized Tyvaso® Inhalation Solution with a target dose of 54 µg via 9 breaths, 4 times per day (QID). The time required for nebulizer preparation, dose administration, and cleaning can be a burden to patients. A more convenient system to deliver TRE directly and deeply to the lungs may offer a meaningful improvement over the current nebulized therapy.

Liquidia has developed LIQ861, a dry powder formulation of TRE utilizing PRINT® Technology, which is specifically designed to enhance deep-lung delivery and enable QID delivery of TRE doses in 1 to 2 breaths per capsule via a convenient, palm-sized dry powder inhaler (DPI). Proprietary PRINT Technology produces drug particles of a precise, uniform size, shape, and composition that are engineered for optimal deposition in the lung following oral inhalation using a DPI. LIQ861 may enhance lung delivery and pharmacodynamic effects of TRE in patients diagnosed with PAH. The primary endpoint of this study was to assess the safety of LIQ861 in cohorts of patients transitioned from Tyvaso® or added on to prior background therapy.

Tyvaso® is a registered trademark of United Therapeutics Corporation.

Figure 1 – Study Design



Sources: https://clinicaltrials.gov/ct2/show/NCT03399604; PGI – prostacyclin; TEAEs – treatment-emergent adverse events; SAEs – serious adverse events
Tyvaso is a registered trademark of United Therapeutics Corp.

METHODS

INSPIRE is a phase 3, open-label, multicenter study designed to assess the safety and tolerability of LIQ861 in subjects with PAH, New York Heart Association (NYHA) Class II–IV **(Figure 1)**. Enrollment was across 2 cohorts: (1) prostacyclin (PGI)-naive subjects stable on ≤2 approved, non-PGI oral PAH therapies (Add-on) or (2) subjects transitioning from Tyvaso® (Transition). Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) were assessed at every visit through spontaneous reporting by the patients and with non-leading questions from the study staff. Exploratory endpoints included 6 Minute Walk Distance (6MWD), which was assessed across visits following the guidelines published by the American Thoracic Society (ATS) in 2002, and administration of the Minnesota Living With Heart Failure Questionnaire (MLHFQ), also assessed across visits. Reviewed in this poster are these endpoints through Month 2.

RESULTS

Table 1 – Summary of Demographics and Baseline Characteristics

		No. Subjects (% of Study) at 2-Month Timepoint		
		LIQ861 Add-ons (N=65)	Transitions (N=44)	Overall (N=109)
Sex	Female	51 (78.5%)	39 (88.6%)	90 (82.6%)
	Male	14 (21.5%)	5 (11.4%)	19 (17.4%)
Age at Screening (y)	Mean ± SD	55 ± 14.7	54 ± 12.6	55 ± 13.9
BMI (kg/m²)	Mean ± SD	29.5 ± 7.8	29.3 ± 7.5	29.4 ± 7.7
NYHA Functional Class at Screening	Class II	36 (55.4%)	36 (81.8%)	72 (66.1%)
	Class III	29 (44.6%)	8 (18.2%)	37 (33.9%)

One hundred nine (109) patients (65 Add-on, 44 Transition) with Month 2 data are included in this preliminary assessment of the safety and exploratory endpoints mentioned in the Methods. At baseline, 72 of these subjects (66.1%) were NYHA Class II and 37 (33.9%) were NYHA Class III **(Table 1)**.

Table 2 – Treatment Emergent Adverse Events (TEAEs)

TEAEs at Month 2 in ≥4% of Patients Receiving LIQ861	LIQ861 Add-ons				Tyvaso® Transitions				Overall			
	No. (%) Subjects	No. of Events			No. (%) Subjects	No. of Events			No. (%) Subjects	No. of Events		
		Mld	Mod	Sev		Mld	Mod	Sev		Mld	Mod	Sev
Cough	30 (46.2%)	25	5	0	6 (13.6%)	5	1	0	36 (33.0%)	30	6	0
Headache	11 (16.9%)	9	4	0	9 (20.5%)	8	2	0	20 (18.3%)	17	6	0
Throat irritation	11 (16.9%)	12	2	0	4 (9.1%)	4	0	0	15 (13.8%)	16	2	0
Dizziness	7 (10.8%)	7	0	0	4 (9.1%)	3	1	0	11 (10.1%)	10	1	0
Diarrhea	7 (10.8%)	5	2	0	2 (4.5%)	1	1	0	9 (8.3%)	6	3	0
Oropharyngeal pain	5 (7.7%)	5	0	0	1 (2.3%)	1	0	0	6 (5.5%)	6	0	0
Nausea	4 (6.2%)	3	1	0	2 (4.5%)	1	1	0	6 (5.5%)	4	2	0
Dyspnea	3 (4.6%)	2	1	0	3 (6.8%)	3	1	0	6 (5.5%)	5	2	0
Flushing	5 (7.7%)	5	0	0	1 (2.3%)	1	0	0	6 (5.5%)	6	0	0
Chest discomfort	4 (6.2%)	3	1	0	1 (2.3%)	0	1	0	5 (4.6%)	3	2	0

- **No SAEs related to study drug**

LIQ861 doses of up to 125 mcg capsule strength (two capsules) were evaluated, with no study-drug–related SAEs or dose-limiting toxicities observed during the 2-month observation period. TEAEs were mostly mild and consistent with inhaled PGI therapy **(Table 2)**. To date, there have been no study-drug–related SAEs with up to 12 months of follow-up.

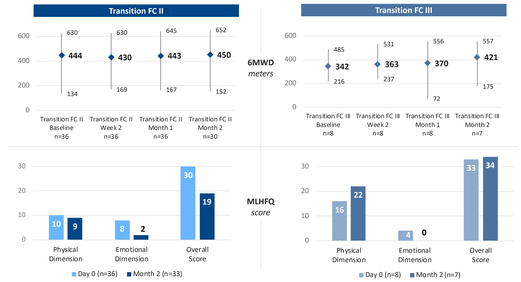
Table 3 – Patients Remaining on LIQ861 Through 2 Months of Treatment

Sustained Therapy at 2 Months	LIQ861 Add-ons	Tyvaso® Transitions	Overall
Total Patients Started	65	44	109
Withdrawn <2 Months	6	2	8
Sustained at 2 Months	59	42	101
% Patients Sustained	90.8%	95.5%	92.7%

- Patients withdrew due to: Adverse Events, Patient Choice, Investigator Decision, Lost to Follow-up

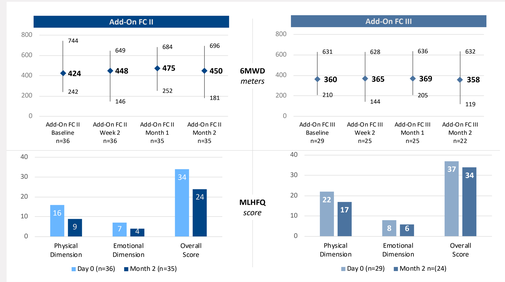
At Month 2, 42 of 44 (95.5%) Transition patients remained on LIQ861. Ninety-three percent (93%) of all patients completed 2 months of treatment, the primary safety endpoint, and remained in the study beyond their Month 2 visit **(Table 3)**. As of 8 May 2019, 6 patients have been treated for over 1 year.

Figure 2 – Transition Patients 6MWD and MLHFQ Score



NYHA functional classification (FC) was broken out by cohort at Baseline. Transition patients: NYHA Class II cohort maintained activity benefits in the 6MWD while improving quality of life (QOL), as reflected in the MLHFQ score; NYHA Class III cohort improved activity benefit in the 6MWD while sustaining QOL **(Figure 2)**.

Figure 3 – Add-on Patients 6MWD and MLHFQ Score



Add-on patients: NYHA Class II cohort improved activity benefits in the 6MWD while improving QOL; NYHA Class III cohort maintained 6MWD activity and QOL **(Figure 3)**.

CONCLUSIONS

- LIQ861 was observed to be safe and well-tolerated at Month 2, achieving the primary endpoint
- No study-drug–related SAEs have been reported, with some patients remaining on LIQ861 for over a year
- TEAEs were consistent with inhaled PGI therapy and mostly mild in nature
- Overall, 93% of patients completed 2 months of treatment and remained in the study beyond their Month 2 visit
- In the Transition patients, the NYHA Class II cohort maintained the 6MWD while reporting clinically meaningful improvement in QOL as reflected in the MLHFQ score, while the NYHA Class III cohort exhibited a marked improvement in the 6MWD while sustaining QOL
- In the Add-on patients, the NYHA Class II cohort demonstrated an increase in the 6MWD while improving QOL, whereas the NYHA Class III cohort maintained 6MWD activity and QOL
- LIQ861 may provide functional and QOL benefits to functional class II and III PAH patients

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Disclosures

- N.S. Hill: Consultant-Liquidia Technologies. Grant/Research Support Institution-Actelion, Bayer, Gilead, Liquidia Technologies, Reata, United Therapeutics. Scientific Medical Advisor-Liquidia Technologies.
- J.P. Feldman: Consultant-United Therapeutics, Gilead, Bayer, Actelion. Speaker's Bureau-United Therapeutics, Gilead, Bayer.
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