# INSPIRE: A Phase 3 Open-Label, Multicenter Study to Evaluate the Safety and Tolerability of LIQ861 in Pulmonary Arterial Hypertension (PAH) – Exploratory Efficacy Endpoints Analysis at Month 2

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## BACKGROUND

LIQ861 is a novel, inhaled, dry-powder formulation of treprostinil developed by Liquidia Technologies with PRINT® (Particle Replication in Nonwetting Templates) technology to enhance deep-lung drug deposition and enable delivery in 1-2 breaths per capsule via a convenient dry-powder inhaler. PRINT® technology produces drug particles that are precise and uniform in size, shape, and composition, and engineered for optimal deposition in the lung at higher doses than reached with currently approved inhaled PAH therapies. The clinical development program for LIQ861 includes two phase 1 studies enrolling healthy volunteers (LTI-101[1] and LTI-102[2]); INSPIRE (Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil), an open-label, phase 3, multicenter study of PAH patients (LTI-301; safety outcomes[3]); and a global, open-label extension trial of continued LIQ861 for patients who completed LTI-301 (LTI-302).

The INSPIRE study evaluated the safety and tolerability of LIQ861 in PAH patients who were on a stable dose of Tyvaso® or were receiving ≤2 approved oral PAH therapies. The exploratory efficacy endpoints of the INSPIRE study through Month 2 are reported.

## METHODS

- INSPIRE was a phase 3, open-label, multicenter trial conducted to support the New Drug Application submission for LIQ861 under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act.
- Patient eligibility criteria included:
  - Age ≥18 years
  - WHO Group 1 PAH, with diagnosis confirmed by right heart catheterization
  - New York Heart Association (NYHA) Functional Class (FC) II-IV
  - Six-minute walk distance (6MWD) ≥150 meters (m) at Screening
  - Forced expiratory volume in 1 second ($FEV_1$) ≥60% and $FEV_1$/forced vital capacity ratio ≥60% in the 6 months preceding enrollment
- Two patient cohorts were enrolled including those receiving:
  - A stable dose of Tyvaso® (treprostinil) for ≥3 months (Transitions)
  - ≤2 approved non-prostacyclin oral therapies for ≥3 months (Add-Ons)
- Transitions patients received an initial LIQ861 dose that was comparable to their Tyvaso® dose while Add-Ons patients initiated LIQ861 at 26.5 mcg four times daily.
- Dose increases were titrated in 26.5 mcg increments to tolerance and symptom relief in both cohorts.
- Scheduled study visits occurred at Screening (within 28 days of Baseline), Baseline (Day 1), Week 2, Month 1, and Month 2.
- The primary endpoint was the incidence of treatment-emergent adverse events and serious adverse events at the 2-month follow-up.
- Exploratory endpoints for all patients were changes from Baseline to Month 2 in 6MWD, NYHA FC, N-terminal risk assessment (ERS/ESC risk score), and time to and reason for discontinuation of LIQ861.
- An additional exploratory endpoint for Transitions patients only was patient-reported satisfaction with the LIQ861 dry-powder inhaler device compared with the Tyvaso® Inhalation System.

## References

1. Roscigno RF, et al. *Pulm Circ.* 2020. In press.
2. Roscigno RF, et al. Poster presented at: 14th Pulmonary VascularResearch Institute Annual World Congress: January 30-February 2, 2020; Lima, Peru.
3. Hill NS, et al. *J Heart Lung Transplant.* 2020;39(4):S17-S18.
4. Galiè N, et al. *Eur Heart J.* 2016;37:67-119.

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## Disclosures

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D. J. Levine: None

R. F. Roscigno: Consultant-Liquidia Technologies. Stock Shareholder-Liquidia Technologies.

T. A. Vaughn: Consultant-Liquidia Technologies. Stock Shareholder-Liquidia Technologies.

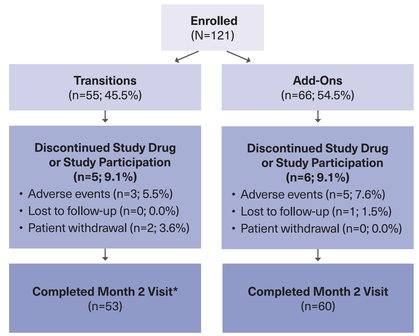
T. M. Bull: Institution-Bayer. Consultant-Liquidia Technologies.

## RESULTS

### *Patients*

- 121 patients were enrolled, including 55 (45.5%) in the Transitions group and 66 (54.5%) in the Add-Ons group **(Figure 1)**.

**FIGURE 1. PATIENT DISPOSITION**




*3 of the Transitions patients discontinued after the Month 2 timepoint.

- Adverse events were the most common reason for discontinuation in both groups, with no discontinuations due to lack of efficacy.
- Overall, the majority of patients were female (n=99; 81.8%); white (n=96; 79.3%), and non-Hispanic (n=101; 83.5%), with an overall mean age of 54.2 years at Baseline **(Table 1)**.

**TABLE 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS: SAFETY POPULATION**

| | Transitions (n=55) | Add-Ons (n=66) | Overall (N=121) |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 47 (85.5) | 52 (78.8) | 99 (81.8) |
| Male | 8 (14.5) | 14 (21.2) | 22 (18.2) |
| **Race, n (%)** | | | |
| American Indian or Alaska Native | 1 (1.8) | 2 (3.0) | 3 (2.5) |
| Asian | 3 (5.5) | 3 (4.5) | 6 (5.0) |
| Black | 11 (20.0) | 4 (6.1) | 15 (12.4) |
| White | 40 (72.7) | 56 (84.8) | 96 (79.3) |
| Other | 0 (0.0) | 1 (1.5) | 1 (0.8) |
| **Ethnicity, n (%)** | | | |
| Hispanic | 10 (18.2) | 10 (15.2) | 20 (16.5) |
| Non-Hispanic | 45 (81.8) | 56 (84.8) | 101 (83.5) |
| **Age, years** | | | |
| Mean (SD) | 53.3 (14.1) | 55.0 (14.6) | 54.2 (14.3) |
| **BMI, kg/m²** | | | |
| Mean (SD) | 30.1 (7.9) | 29.3 (7.9) | 29.7 (7.9) |
| **NYHA Functional Class** | | | |
| II | 43 (78.2) | 37 (56.1) | 80 (66.1) |
| III | 12 (21.8) | 29 (43.9) | 41 (33.9) |
| **PAH duration, years** | | | |
| Mean (SD) | 7.3 (5.1) | 4.7 (5.1) | 5.9 (5.2) |
| **Therapy at screening** | | | |
| PDE5i monotherapy | 8 (14.5) | 12 (18.2) | 20 (16.5) |
| $PGI_2$ monotherapy | 6 (10.9) | 0 (0.0) | 6 (5.0) |
| ERA monotherapy | 5 (9.1) | 3 (4.5) | 8 (6.6) |
| sGC monotherapy | 0 (0.0) | 2 (3.0) | 2 (1.7) |
| ERA plus PDE5i | 35 (63.6) | 46 (69.7) | 81 (66.9) |
| ERA plus sGC | 1 (1.8) | 3 (4.5) | 4 (3.3) |

BMI, body mass index; ERA, endothelin receptor antagonist; max, maximum; min, minimum; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; $PGI_2$, prostacyclin; SD, standard deviation; sGC, soluble guanylate cyclase.

### *Exposure*

- Among Transitions patients, 94% received an initial LIQ861 dose ≥53 mcg and 74% titrated to doses ≥79.5 mcg at Month 2 **(Figure 2a)**.
- The initial LIQ861 dose was 26.5 mcg for Add-Ons patients at baseline, with 71% of patients titrated to doses ≥79.5 mcg at Month 2 **(Figure 2b)**.

**FIGURE 2A. LIQ861 DOSE AT BASELINE AND MONTH 2: TRANSITIONS**

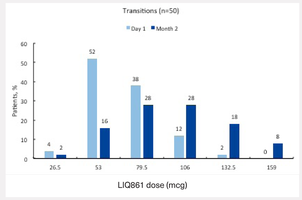
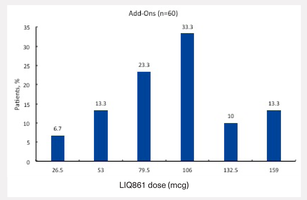



**FIGURE 2B. LIQ861 DOSE AT MONTH 2: ADD-ONS***

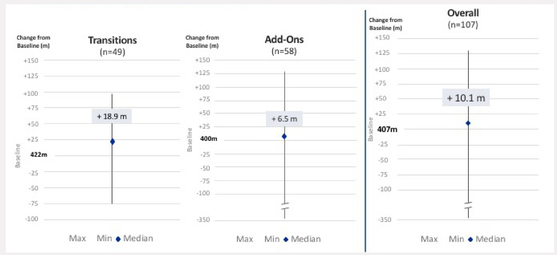



*All patients in the Add-Ons group initiated LIQ861 at 26.5 mcg.

### *Exploratory Endpoints*

- Improvement in 6MWD was observed with an overall median increase of 10.1 m at Month 2 **(Figure 3)**.

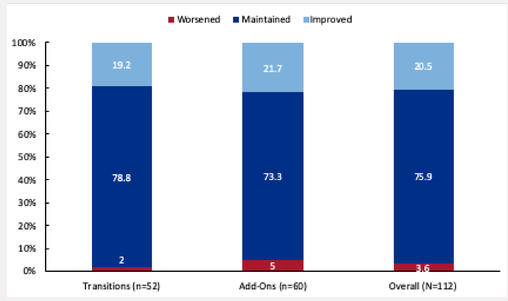
**FIGURE 3. CHANGE FROM BASELINE TO MONTH 2 IN SIX-MINUTE WALK DISTANCE: EFFICACY POPULATION**




6MWD decreased 344 m in one Add-Ons patient who reported symptoms of a serious treatment-emergent adverse event of parainfluenza virus.

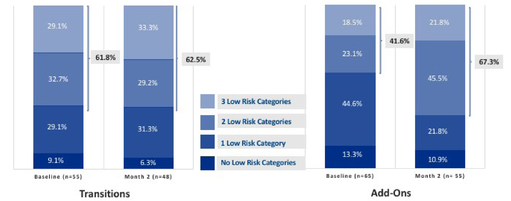
- Overall, from Baseline to Month 2, NYHA FC improved for 20.5% of patients (n=23) and was maintained in 75.9% of patients (n=85), with similar results for the Transitions and Add-Ons groups **(Figure 4)**.

**FIGURE 4. CHANGE FROM BASELINE TO MONTH 2 IN NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS: EFFICACY POPULATION**



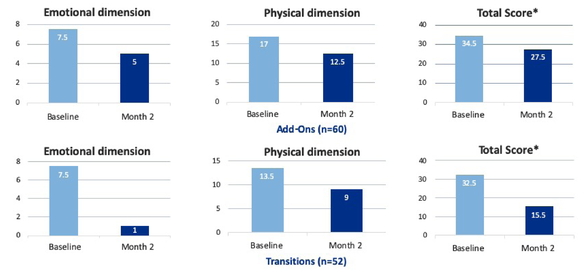

- The percentage of patients who met 2 or 3 PAH low-risk criteria (based on European guideline-specified criteria[4] increased from Baseline to Month 2, with a larger shift in Add-Ons patients compared with Transitions patients **(Figure 5)**.

**FIGURE 5. ONE-YEAR MORTALITY RISK AT BASELINE AND MONTH 2: EFFICACY POPULATION**



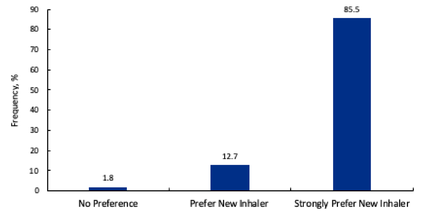

- Overall, there was a clinically meaningful improvement (defined as a >5-point decrease) from Baseline to Month 2 in the MLWHF questionnaire total score **(Figure 6)**; improvements were also noted for the overall Emotional and Physical Dimension scores.

**FIGURE 6. CHANGE IN MINNESOTA LIVING WITH HEART FAILURE QUESTIONNAIRE SCORES AT MONTH 2: EFFICACY POPULATION**




- No clinically meaningful change was observed in NT-proBNP, with an overall mean increase from Baseline to Month 2 of 43.3 ng/L.
- At Week 2, the majority of patients in the Transitions group strongly preferred the RS00 Model 8 dry-powder inhaler compared with their previously used device, the Tyvaso® Inhalation System **(Figure 7)**.

**FIGURE 7. DRY-POWDER INHALER DEVICE (RS00 MODEL 8) SATISFACTION SCORES: TRANSITIONS GROUP**




## CONCLUSIONS

- LIQ861 is a convenient, safe, well-tolerated option for inhaled prostacyclin therapy in PAH patients.
- More than 70% of patients titrated to a LIQ861 dose ≥79.5 mcg, which is approximately equivalent to 54 mcg of nebulized treprostinil.
- FC improved in 20.5% of patients and was maintained in 75.9%.
- Overall median 6MWD increased by 10.1 m.
- There was no clinically meaningful change in NT-proBNP.
- A larger percentage of patients met 2 or 3 PAH low-risk criteria at Month 2 compared with Baseline.
- The MLWHF questionnaire showed an improved total score (>5 point decrease) in addition to improvements in Emotional and Physical Dimension scores.
- The majority of Transitions patients preferred the RS00 Model 8 dry-powder inhaler to the Tyvaso® Inhalation System.