Phase 1 Safety and Pharmacokinetic Study of Inhaled LIQ861, a New Dry Powder Formulation of Treprostinil

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Introduction

Treprostinil (Tre) is a synthetic prostacyclin analogue approved for inhalation administration to patients with pulmonary arterial hypertension (PAH) via nebulized Tyvaso® Inhalation Solution (Tre Solution) administered four times daily. Liquidia is developing LIQ861, a convenient, dry powder inhalation formulation of Tre that offers a simple, portable alternative treatment regimen.

LIQ861 is specifically designed to improve the therapeutic profile of Tre by enhancing deep-lung delivery and achieving higher dose levels than current inhaled therapies. Using our proprietary PRINT® technology, LIQ861 particles are a precise, uniform size (1μm) and troffel pollen-like shape designed to have ideal aerodynamic properties for deep-lung delivery. Liquidia conducted a Phase 1 safety, tolerability and PK single ascending dose study in healthy volunteer subjects who received 25 mcg to 150 mcg in two inhalations per capsule using a palm-sized dry powder inhaler (DPI) device (RS00 Model 8, Plastiape SpA, Lecco, Italy). The study’s primary objectives were to characterize Tre PK, evaluate the safety and tolerability of inhaled LIQ861 and assess the performance of the DPI.

Methods: Phase 1 Ascending Single Dose Escalation Study Trial Design

Successive gender-balanced cohorts of 8 healthy volunteers were randomly assigned to active (n=6) or placebo (n=2). Dosing was initiated at a dose level of 25 mcg Tre. Additional cohorts of 8 subjects were enrolled to evaluate escalating single doses of LIQ861 at 50, 75, 100, 125, and 150 mcg Tre. PK samples and safety assessments were performed approximately 1 h before dosing and at 5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, 180, and 210 min and 4, 6, and 8 h post-dose. A Safety Review Committee was consulted after each cohort to review safety findings and interim PK results. Tre PK parameters and dose proportionality were characterized.

Results

Fifty-seven subjects (29 M/28 F; 18 to 44 years old) were enrolled. The median Tre Tremax within cohorts was between 10 and 20 min post-dose and both Cmax and AUCinf were dose proportional. The 90% CI for the ratio of dose-normalized geometric means ranged from 0.514 to 1.02 for Cmax, and 0.65 to 1.4 for AUCinf.

All reported treatment-emergent adverse events (AEs) that were related to treatment were mild, with the most frequent AEs reported as a mild cough and throat irritation. No dose-limiting toxicities were observed and no SAEs were reported. Events deemed unrelated by physician include vasovagal symptoms (11.6%), headache (2.3%), lightheadedness (12.5%), and throat irritation. No dose-limiting toxicities were observed and no SAEs were reported. Events deemed unrelated by physician include vasovagal symptoms (11.6%), headache (2.3%), lightheadedness (12.5%), rhinorrhea (7.1%), and throat irritation. No dose-limiting toxicities were observed and no SAEs were reported. Events deemed unrelated by physician include vasovagal symptoms (11.6%), headache (2.3%), lightheadedness (12.5%), rhinorrhea (7.1%), and venipuncture site pain (1.1%).

LIQ861 was generally well tolerated at all dose levels evaluated in the study. No notable or significant findings were reported with vital signs, physical examinations and laboratory evaluations.

Phase 1 Study Conclusions

1. Tre exposure (Cmax & AUCinf) from LIQ861 was dose proportional from 25 to 150 mcg.
2. No dose limiting toxicity was observed and the maximum tolerated dose (MTD) was not reached.
3. At higher doses, 50% of subjects had measurable Tre at 4 hrs.
4. No observed proportional increase in frequency or severity of AEs from 25 to 100 mcg.
5. LIQ861 was well tolerated at Tre doses up to 150 mcg with no SAEs and all treatment related AEs were mild in severity.
6. The 150 mcg dose of LIQ861 is approximately double the maximum recommended dose of Tyvaso®.

LIQ861: Rapid Systemic Uptake

LIQ861: No SAEs; only mild AEs

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PRINT Technology: http://liquidia.com/print-technology/

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