An Open-Label Safety Study of L606 (Liposomal Treprostinil) in Patients With PAH and PH-ILD

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Background

Inhaled treprostinil, a prostacyclin (PGI_2) analog, is approved for the treatment of pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD). Current inhaled formulations are immediate-release and require frequent dosing (every 4 hours). L606 is a novel investigational liposomal formulation of treprostinil that is designed to prolong lung retention, maximize efficacy, and limit toxicity (Fig 1). Pharmacokinetic studies in healthy volunteers demonstrated therapeutic levels of L606 up to 12 hours and 7x lower peak plasma concentration (C_{max}) compared to Tyvaso®[1]. The increased apparent half-life ($t_{1/2}$) of L606, in concert with comparable systemic exposure and clearance rate, suggests that L606 provides controlled, continuous drug coverage during sleeping and waking hours, and supports twice daily administration using a breath actuated smart technology nebulizer.

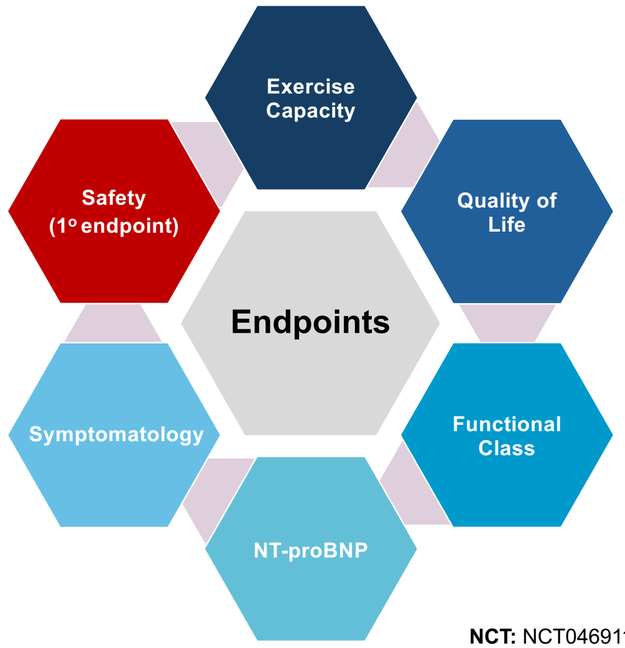
Methods

This Phase 3, 2-part, open-label, multicenter study aims to demonstrate the safety and tolerability and efficacy of L606 in patients with PAH or PH-ILD:

COHORT A
- PAH or PH-ILD patients
- On stable dose of Tyvaso (nebulized or DPI)
- Endpoints measured at 2 weeks and up to 48 weeks

SCREEN

COHORT B
- PAH patients
- Prostacyclin-naïve patients on ≤2 non-prostacyclin oral therapies
- Endpoints measured at 12 weeks and up to 48 weeks



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Results

Twenty-four patients were enrolled in the study (22 in cohort A and 2 in cohort B) at the time of this analysis. Thirteen (54.2%) patients have been treated for greater than 6 months; 7 (29.2%) for greater than 1 year. The majority of patients were female (75%), and non-Hispanic (91.7%) with a mean age of 61 years. At baseline, 54.2% of patients were NYHA FC II and 45.8% were FC III. Sixteen (66.7%) patients received triple and 3 (12.5%) received dual combination PH therapy. Combinations included inhaled treprostinil and 1-2 of the following: ERA, PDE-5i, or sGC agonist. Two patients discontinued study drug: one discontinued by physician decision due to methamphetamine use after 134 days of exposure at a L606 dose of 229 µg BID; the second discontinued due to patient choice after an unrelated mild TEAE of dyspnoea after 39 days of exposure at a L606 dose of 207 µg BID.

Of the 24 enrolled patients, 16 (66.7%) experienced TEAEs (Table 1). Five (20.8%) patients experienced suspected drug related TEAEs. Of these patients, 4 (16.7%) experienced mild and 1 (4.2%) experienced moderate suspected drug related TEAEs. Six SAEs (pneumonia, cholecystitis, acute respiratory failure, fall, hypoxia, cardiac ventricular thrombosis) have been observed in 4 patients, all of them classified as unrelated, and no emerging safety signals have been identified. Three (12.5%) patients experienced a mild cough, and 1 (4.2%) experienced a moderate cough. The median dose achieved at the time of this analysis was 207 µg BID (~14-16 bps equivalent Tyvaso QID) with doses ranging from 42 to 378 µg BID (< 5 bps to 26-28 bps equivalent Tyvaso QID).

Figure 1. Liposomes in Aerosol. A, During treatment, L606 liposomal solution is nebulized into respirable particles. This formulation enables slow-release of encapsulated treprostinil upon delivery to alveoli. **B,** Schematic of liposome-encapsulated treprostinil.

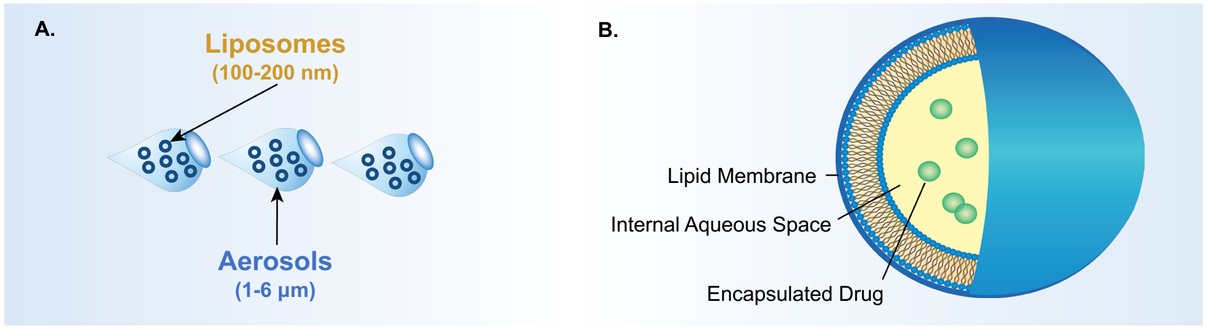

Table 1. Treatment-Emergent Adverse Events (TEAEs)

	Overall (N=24)			
	No. (%)	Severity of TEAEs		
	Subjects	Mild	Moderate	Severe
Respiratory, thoracic, and mediastinal disorders (Cough, Dyspnoea, Dysphonia, Hypoxia, Orthopnoea, Rhinorrhoea)	8 (33.3)	4	4	0
Nervous system disorders (Syncope, Dizziness, Headache, Metabolic encephalopathy, Nerve compression)	6 (25)	4	2	0
Gastrointestinal disorders (Diarrhoea, Diverticulum, Nausea)	2 (8.4)	1	1	0
Cardiac disorders (CVT, Palpitations)	2 (8.4)	2	0	0
Eye disorders (Dry eye, Vision blurred)	2 (8.4)	1	1	0
Infections and infestations (COVID-19, Nasopharyngitis, Pneumonia, Upper respiratory tract infection)	8 (33.3)	4	3	1
General disorders and administration site conditions (Fatigue, Asthenia, Feeling abnormal, Feeling hot, Oedema peripheral, Pain)	7 (29.1)	6	1	0
Hepatobiliary disorders (Cholecystitis)	1 (4.2)	0	0	1
Investigations (NT-ProBNP increase, Blood bicarbonate decreased, Prothrombin time prolonged, PAP increased, Weight increased)	6 (25)	4	2	0
Metabolism and nutrition disorders (Hypokalaemia, Milk-alkali syndrome)	2 (8.4)	0	2	0
Musculoskeletal and connective tissue disorders (Arthralgia, Muscle spasms, Myalgia)	4 (16.7)	3	1	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (Basal cell carcinoma)	1 (4.2)	1	0	0
Renal and urinary disorders (Acute kidney injury)	2 (8.4)	0	2	0
Skin and subcutaneous tissue disorders (Alopecia, Night sweats, Pruritis, Urticaria)	3 (12.5)	3	0	0
Vascular disorders (DVT, Hypotension, Thrombophlebitis superficial)	2 (8.4)	0	2	0

Conclusions

L606 was safe and well tolerated in naïve patients and in patients who transitioned from Tyvaso. TEAEs were generally mild or moderate, consistent with known AEs for treprostinil, and did not hinder the titratability of L606. Results from the continuation of this study will be pivotal in establishing the long-term safety and efficacy of L606 in patients with PAH and PH-ILD.

References and Disclosures

1. Tully, J., Saggar, R., Prabel, J., Garcia, A., Patel, S., Chen, K., Kan, P. Clinical Pharmacokinetics of an Extended-Release Formulation of Inhaled Liposomal Treprostinil (L606) to Reduce Dosing Frequency [POSTER]. Pulmonary Vascular Research Institute (PVRI) 2024 Annual Congress; 2024 Feb 2, London.

Conflict of Interest disclosures: **N. Habib** receives consulting fees for Janssen Pharmaceuticals, United Therapeutics Corporation (UTC), Aerovate Therapeutics, and Liquidia Corporation, along with speaking for Janssen, UTC, and Liquidia Corporation. **R. Restrepo** receives research support from Liquidia Corporation, UTC, Janssen Pharmaceuticals, and Insmed Incorporated, and receives fees for being a speaker for Bayer Pharmaceuticals, UTC, and Janssen Pharmaceuticals. **M. Trivieri** and **S. Shapiro** receive research support from Liquidia Corporation. **C. Burger** receives consulting fees for Insmed Incorporated and serves on advisory boards for Merck and Janssen Pharmaceuticals. **P. Kan** is a salaried employee and shareholder of Pharmosa BioPharm Inc. **S. Patel**, **A. Galloway**, and **R. Saggar** are salaried employees and shareholders of Liquidia Corporation.