Clinical Pharmacokinetics of an Extended-Release Formulation of Inhaled Liposomal Treprostinil (L606) to Reduce Dosing Frequency

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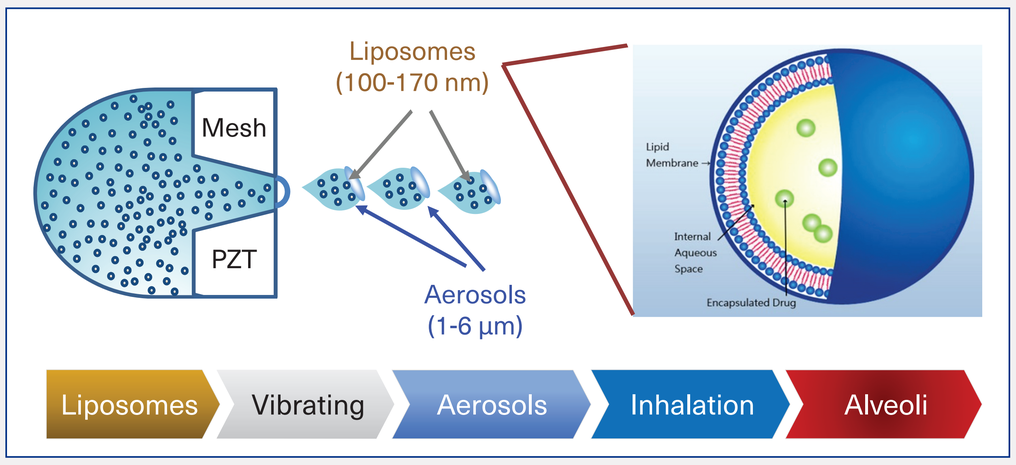
BACKGROUND

Treprostinil is a prostacyclin (PGI_2) analog with a short half-life used for the treatment of pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD). Current inhaled therapies are immediate-release formulations and require frequent dosing, up to every 4 hours, due to the short half-life. These immediate-release formulations result in exposure only during the waking hours (14-16 hours).

Inhaled liposomal treprostinil (L606) is a novel extended-release formulation designed to provide sustained plasma levels to reduce dosing frequency while extending daily exposure (**Figure 1**). L606 suspension is designed to control the release of the encapsulated treprostinil upon delivery to the lung, potentially reducing local respiratory tract irritation during treatment.

Figure 1. Liposomes in Aerosol



METHODS

A comparative bioavailability study in healthy volunteers was conducted to evaluate the pharmacokinetics of L606 (liposomal treprostinil). Subjects received L606 administered by a vibrating-mesh nebulizer or a Tyvaso comparator. Blood samples were collected for 24 hours after dosing and analyzed by LC-MS-MS. Systemic pharmacokinetics were evaluated for total exposure and dosing frequency.

RESULTS AND DISCUSSION

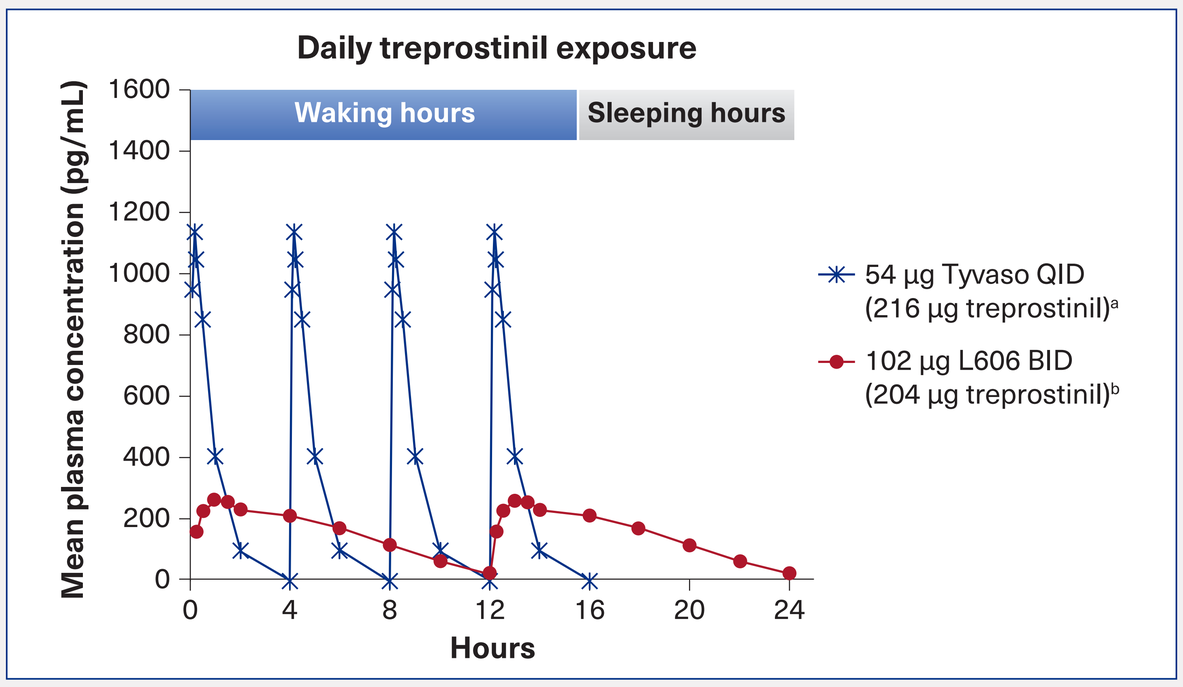
The systemic exposures of a single dose of L606, 51 µg, and Tyvaso, 54 µg, were compared. L606 resulted in a similar systemic exposure (AUC_{inf}) compared with the equivalent dose of Tyvaso, with a significantly reduced peak plasma concentration (C_{max}). The increased apparent half-life ($t_{1/2}$) of L606, combined with a plasma clearance rate comparable to that of Tyvaso, suggests that the liposomal formulation drives the controlled release of treprostinil after delivery to the lung (**Table 1**).

Table 1. Clinical Pharmacokinetics of an Extended-Release Formulation of Inhaled Liposomal Treprostinil (L606) to Reduce Dosing Frequency

PK Parameter	51 µg L606 n = 12	54 µg Tyvaso n = 12
Geometric mean (geometric CV%)		
C_{max}, pg/mL	140 (24.0)	1090 (38.4)
AUC_{inf}, h*pg/mL	1050 (18.3)	1040 (27.5)
$t_{1/2}$, h	4.81 (29.2)	0.445 (14.6)
CL/F, L/h	48.8 (18.3)	52.0 (27.5)
Median		
t_{max}, h	1.25	0.18

L606 demonstrates extended plasma concentrations up to 12 hours after a single dose, supporting a reduction in dosing frequency to twice daily, or every 12 hours. Peak and total exposure of treprostinil increased with increasing dose (data not shown). When evaluating the same total daily dose as Tyvaso, L606 provides sustained plasma concentrations with a similar total daily exposure. The extended-release formulation results in a reduced peak-to-trough ratio to provide continuous coverage during waking and sleeping hours (**Figure 2**).

Figure 2. Treprostinil Plasma Concentration in Healthy Volunteers Following Administration of Tyvaso or L606



[a]Tyvaso data over 4 hours are from the comparative bioavailability study and the remaining data are simulated to show Tyvaso 24-hour exposure.

[b]L606 data over 12 hours are from the comparative bioavailability study and the remaining data are simulated to show L606 24-hour exposure.

CONCLUSION

The clinical pharmacokinetics of L606 in healthy volunteers demonstrate sustained plasma levels up to 12 hours, supporting twice daily administration. Although total dose-normalized systemic exposure (AUC_{0-t}/D and AUC_{inf}/D) was generally comparable between treatment groups, dose-normalized peak exposure to treprostinil (C_{max}/D) was approximately 7.3-fold lower for L606 than for Tyvaso. An open-label study to assess the safety of L606 in up to 60 patients with PAH and patients with PH-ILD transitioning from Tyvaso (nebulizer or dry-powder inhaler) or patients with PAH naïve to prostacyclins, is currently ongoing in the United States. Liquidia plans to initiate a global Phase 3 placebo-controlled efficacy study in PH-ILD in late 2024.

References

Kan P, Chen K, Pan C. Comparative pharmacokinetics between Tyvaso® and L606, extended-release formulation of treprostinil for inhalation therapy. Poster presented at: ATS 2020 International Conference; May 15-20, 2020; Philadelphia, PA.

Kan P, Chen K, Hunt T. Preclinical and clinical pharmacokinetics of L606, an extended-release formulation of treprostinil for inhalation therapy. Poster presented at: 2019 PH Professional Network Symposium; September 5-7, 2019; Washington, DC.

Liquidia Data on File.