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## Preclinical and Clinical Pharmacokinetics of L606, An Extended-Release Formulation of Treprostinil for Inhalation Therapy

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**Background:** For treatment of pulmonary hypertension (PH), inhalation therapy features a target delivery, low systemic side-effect and ventilation/perfusion match over oral and injection administration. However, the current inhaled prostacyclin therapy (Tyvaso<sup>®</sup>) is associated with frequent, cumbersome treatment regimen mainly because of its short half-life and nebulizer design.

The time required for nebulizer preparation, dose administration and cleaning of Tyvaso<sup>®</sup> is a burden to patients. A novel combination of liposome formulation and mesh-vibrating nebulizer offers a simple, convenient and portable treatment regimen that is a clinically meaningful improvement over the current nebulized therapy.

Pharmosa has been developing L606, a sustained-release inhalation combination of treprostinil, specifically designed to improve dosing schedule and safety profile of nebulized treatment.

**Methods:** L606 and treprostinil solution were administered intratracheally by micro-sprayer into rats for single-dose PK study.

A mesh-vibrating nebulizer was operated by healthy subjects to deliver L606 inhalation solution. Healthy subjects in each cohort are randomized in a double-blinded fashion to receive a single dose of L606 for Inhalation in a dose escalation manner (starting from an emitted dose of 51 µg) or placebo in a 3:1 ratio. Eight cohorts are planned to examine safety and tolerability profile of L606.

**Results:** In rat PK study, L606 was delivered and deposited in lungs as the drug depots which release treprostinil slowly and steadily for more than 8 hours without burst. Peak plasma concentration (C<sub>max</sub>) of L606 at the eightfold dose is comparable to that of treprostinil solution.

L606 also demonstrated a sustained plasma level in healthy adult subject. Treprostinil concentrations are detectable for more than 10 hrs. Peak plasma concentration is significantly reduced as compared the reported C<sub>max</sub> of Tyvaso<sup>®</sup> at the comparable dose level.

**Conclusions:** Pharmacokinetic profiles of L606 in rat and human were investigated. It is a proof-of-concept evidence that L606 may provide a convenient dosing schedule and mitigate adverse events caused by either inhaled therapy or systemic exposure.



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