Single and Multiple Dose Pharmacokinetics of YPL-001, a Novel Botanical Drug Product in Development for the Treatment of Respiratory Inflammatory Diseases.


Background

YPL-001 is an oral dosage form of the extract from the plant Speedwell used in traditional Asian medicine to treat respiratory inflammatory diseases including chronic obstructive pulmonary disease (COPD). The botanical drug product is a mixture of 5 identified active inodins and other related compounds. Biological activity is considered to be due to the interaction of multiple active ingredients. Current long term control medications for the treatment of COPD include corticosteroids, bronchodilators, anti-inflammatory agents, and immunomodulators. YPL-001 belongs most closely with the leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

Pharmacokinetic Results:

YPL-001 was well tolerated in a panel of standard animal toxicology studies. Based on NOAEL values of 150 mg/kg/day and 1000 mg/kg/day established in rats and dogs, respectively, 4-week repeated dose oral toxicology studies, the human equivalent doses were calculated to be 28.6 mg/kg and 540 mg/kg, respectively (i.e., 1056 mg and 3500 mg, respectively based on a 70 kg human).

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.89 mg/kg in rats, respectively), the maximum concentration (Cmax) for veropside was rapidly absorbed. AUC and Cmax of veropside increased linearly with YPL-001 dose. Other parameters were not comparable among animals across the different dose levels studied, indicating that the pharmacokinetic (PK) profile of veropside was independent of dose.

YPL-001 inhibited neutrophil accumulation in bronchoalveolar lavage (BAL) fluid and several pro-inflammatory cytokines and chemokines (including interleukin (IL)-8) and activated the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) anti-oxidative pathway.

YPL-001 may down-regulate neutrophil influx and production of tumor necrosis factor alpha (TNF-α), IL-6, chemokine ligand-1 (CXCL-1), and macrophage inflammatory protein-2 (MIP-2).

Rationale

Assess single-dose and multiple-dose PK of veropside and picroside II, 2 of the active iridoids components of YPL-001, in healthy subjects and in COPD patients to assess single-dose and multiple-dose PK of veropside and picroside II.

Study Design:

Methods

Study Design:

Study Design

Safety

All AEs observed in healthy subjects were mild to moderate and the majority were unlikely related or unrelated to treatment.

In the POC study, 5% of patients experienced AEs, with the majority of the following placebos.

Summary

Veropside and picroside II exposure appeared to increase in a dose-dependent manner only to the 240 mg BD dose level, after which no further increases in exposure were observed suggesting capacity-limitation absorption.

The 240 mg dose of YPL-001 is expected to contain amounts of identified compounds relative to those observed in traditional Chinese medicine.

Conclusion

Multiple doses of YPL-001 up to 240 mg BD in healthy subjects and multiple doses of YPL-001 up to 160 mg BD in patients with moderate to severe COPD were safe and well tolerated. Beneficial therapeutic effects seen in patients were consistent with traditional use in Asian medicine. The PK profile of veropside and picroside II and the beneficial therapeutic effects observed in the POC study provide a basis for future studies of longer duration at doses up to 240 mg BD.

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