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INTRODUCTION

EDP-297 is a potent FXR agonist under development for the treatment of non-alcoholic steatohepatitis (NASH). EDP-297 activates FXR-related pathways of steatosis, liver injury, fibrosis, and hyperlipidemia. In preclinical studies, we present pharmacokinetic (PK), pharmacodynamic (PD), toxic effect (TE), and safety results of a single ascending dose (SAD) and multiple ascending dose (MAD) phase 1 study in healthy subjects (HS).

METHODS

Study Design:
A randomized, placebo-controlled, parallel-group study was conducted to evaluate the safety, tolerability, PD, and PK of single and multiple doses of EDP-297 in healthy subjects. Subjects received EDP-297 or placebo (PBO) in 15 cohorts of 6 subjects each. Single doses of EDP-297 were 5 µg, 15 µg, 60 µg, and 300 µg. Multiple ascending dose (MAD) phase 1 study in healthy subjects (HS).

EDP-297: A Novel, Highly Potent, Farnesoid X Receptor Agonist: Results of a Phase 1 Study in Healthy Subjects

RESULTS

Subject Disposition and Demographics

- Inclusion Criteria:
  - Healthy male or female subjects
  - BMI of 18 to 30 kg/m² with a minimum body weight of 50 kg
  - No history of GI disorders
  - No history of abnormal liver function tests
  - No current tobacco smokers or use of tobacco within 1 month prior to screening
  - None of the subjects were pregnant or nursing females
  - None of the subjects were having high risk factors of contracting COVID-19

- Exclusion Criteria:
  -Subjects with hepatic, renal, or cardiovascular disorders
  - Subjects with a history of alcohol abuse
  - Subjects with a history of hepatic or GI infections
  - Subjects with a history of psychiatric disorders

- Cohort Design:
- A total of 82 subjects (n=42 in SAD; n=40 in MAD) received at least one dose of EDP-297 or PBO. Demographics are summarized in Table 1 (SAD) and Table 2 (MAD).

Pharmacokinetics

- PK data is summarized in Figure 1/Table 3 (SAD) and Figure 2/Table 4 (MAD).
- FGF-19 Cmax did not show clear dose response as EDP-297 doses were increased, with ≥50% target engagement for multiple doses of 30 µg and higher, and up to 95% decrease from baseline was observed at the highest multiple dose of 90 µg.
- FGF-19 AUC0-24 generally increased as doses of EDP-297 were increased, with 94.7% increase from baseline observed at the highest multiple dose of 90 µg.
- The two lowest MAD doses (5, 15 µg) were not associated with pruritus, and resulted in modest C4 target engagement (<50%)
- C4 Mean AUC0-24 decreased as the doses of EDP-297 were increased, with 52.7% decrease from baseline observed at the highest multiple dose of 90 µg.

Pharmacodynamics – MAD

- C4 and FGF-19 are displayed in Figure 3 and 4, respectively. Table 5 shows % change from baseline for C4 and FGF-19 for both Day 1 and Day 14.
- C4 mean % decrease from baseline at MAD 90 µg was 75.9 (±8.1) at day 14 and 36.3 (±41.8) at day 1.
- FGF-19 % decrease from baseline at MAD 90 µg was 90 (±40) at day 14 and 7.4 (±12) at day 1.
- Summary of % changes from baseline in C4 and FGF-19 mean (SD) (MAD) is presented in Table 5.

Safety

- Overall EDP-297 was well tolerated except for pruritus and liver enzyme elevations observed especially at highest MAD dose (90 µg).
- There were no clinically significant haematological or abnormal ECG findings, nor for grade 1 ALT elevation (MAD 90 µg) that was not associated with other liver enzyme abnormalities.
- There were no clinically meaningful changes in the lipid profile, except for a trend towards decrease in HDL and increase in LDL at MAD 90 µg; and mean lipid values were within normal range during the entire study (Figures 5-8).

CONCLUSIONS

- EDP-297 was generally well tolerated following single and multiple doses for 14 days. No SADs or discontinuations due to TEAEs or MAD (up to 90 µg) were observed. Most TEAEs were mild and were not related/likely related to study drug (Table 7).
- In the MAD phase, all TEAEs were mild except for 3 subjects with Grade 2 events: pruritis (pruritis), elevated transaminases (ALT, AST), elevated creatine kinase (CK).
- Pruritis was observed at single dose 300 µg and multiple doses 150 µg in 3 subjects due to pruritis in the MAD phase.

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REFERENCES

DISCLOSURES

For references and disclosures please refer to the full manuscript and the PLoS ONE Special Issue on the study.