Single Dose Inhalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of a Fibrinolytic, the Prodrug Debio 1450 and its Active Moiety Debio 1452, Administered Orally in Healthy Subjects

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RESULTS

Baseline characteristics and study population (Table 1)

The active treatment and placebo groups were comparable with respect to demographic characteristics and baseline laboratory values. The two treatment groups were also comparable with regard to smoking and alcohol consumption history. All randomized subjects completed the study and were included in the Safety analysis; all 48 patients who received Debio 1450 were included in the PK analysis.

Pharmacokinetic evaluation (N = 48)

• only 10% subjects had some samples with quantifiable but limited Debio 1452 levels; the remaining samples were below the lower limit of quantification (< 5 SLM).
• plasma concentrations are plotted in Figure 1 and a summary of the PK parameters is shown in Table 2.
• for plasma concentrations, non-compartmental analysis was used and the lower limit of quantification was 5 SLM.
• for renal clearance, non-compartmental analysis was used and the lower limit of quantification was 0.03% of the dose.
• for the prodrug Debio 1450, the active form Debio 1452 plasma exposure increased in a dose-dependent manner.
• the prodrug Debio 1450 has excellent oral bioavailability and a long plasma elimination half-life.
• the renal clearance of Debio 1452 was a minor route for drug elimination.
• Debio 1452 plasma concentrations increased in a dose-dependent manner when compared with PK data from a previous Phase I study with Debio 1450.
• the PK parameters of Debio 1452 from this study are similar to those of a previous Phase I trial with Debio 1450.

Safety assessment (N = 48)

1. Gastrointestinal:
• nausea, vomiting, eructation, belching, and anorexia were reported by 3, 3, 2, and 2 patients, respectively.
• vomiting was also a feature in 2 patients.
• none of the patients showed any clinically significant abnormalities.

2. Nervous system:
• headache (74%), dizziness (58%), somnolence (22%), and anxiety (11%) were the most frequently reported events.
• no clinically significant abnormalities were reported in the clinical laboratory results or vital sign measurements.

3. Other:
• 1 case of worsening of pre-existing depression was reported in the placebo group.

No clinically significant abnormalities were reported in the clinical laboratory results or vital sign measurements.

Preliminary data presented at ECCMID 2014

Debio 1450 is a prodrug of Debio 1452, which is a novel antimicrobial agent currently in clinical development for the treatment of complicated acute infections. The safety, tolerability, and PK of Debio 1452 were evaluated in a randomized, placebo-controlled, double-blind Phase I trial, which included six dose cohorts (9–12 mg, 9–12 mg, 100 mg, 320 mg, 12 mg, and 640 mg). The randomization scheme was stratified by age (< 18 years, 18–30 years, 31–60 years, > 60 years). Inclusion criteria included:

• age ≥ 18 years, ≤ 65 years
• male or female of non-childbearing potential
• assignment to treatment arm (active treatment or placebo)
• provided written informed consent

Exclusion criteria included:

• active or recent history of severe infection
• any condition requiring chronic antibacterial therapy within the 30 days prior to dosing
• history of alcohol or substance abuse or dependence
• history of bleeding tendencies
• any clinically significant abnormality identified in the clinical laboratory results or vital sign measurements

A total of 136 subjects were randomized to one of the dosing cohorts (18–30 years: 36 subjects; 31–60 years: 52 subjects; > 60 years: 48 subjects). The mean (SD) age of randomized subjects (N = 136) was 33.4 (8.7) years across the six dosing cohorts. There were 80 male and 56 female participants. The active treatment and placebo groups were comparable with regard to demographic characteristics. In the placebo group, 47.8% of patients were male. The active treatment and placebo groups were comparable with regard to smoking and alcohol consumption history. All randomized subjects completed the study and were included in the Safety analysis; all 136 patients who received Debio 1450 were included in the PK analysis.

Target population (if resulting from licencing of Debio 1450 designed to activate Debio 1452 and habitually addicted patients)

• 50% severely addicted smokers
• 10% moderately addicted smokers
• 30% habitually addicted patients
• 10% non-smokers

REFERENCE