ABSTRACT
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EB8018, A NOVEL FIMH BLOCKER IS WELL TOLERATED IN A RANDOMIZED, DOUBLE-BLIND, PLACEBO -CONTROLLED PHASE I STUDY IN HEALTHY VOLUNTEERS

EB8018 is a novel, first-in-class oral small molecule that is a minimally absorbed, gut restricted molecule that represents a non-biologic, non-steroidal, non-immunomodulatory approach for the treatment of Crohn's Disease. EB8018 inhibits adhesion of FimH expressed by some pro-inflammatory bacteria such as Adherent, Invasive E Coli and Klebsiella to mannosylated receptors in the gut wall, thereby reducing the generation of inflammatory cytokines.

STUDY DESIGN

The primary objective of the study was to determine the tolerability and safety of single and multiple doses of EB8018 in healthy male subjects.

The secondary objectives were to determine the PK profile of single and multiple doses of EB8018 and to assess preliminary effects of EB8018 on the gut microbiome.

This randomized, double-blind, placebo-controlled study was split in 2 parts with the following assessments: adverse events, laboratory data, electrocardiograms, plasma, urine and fecal concentrations of EB8018, and microbiome analysis.

- Part 1 of the study was the single ascending dose (SAD) part: 5 cohorts with 8 male subjects (40 subjects in total) enrolled in each (6 treated with EB8018 and 2 with placebo) in a sequential escalating manner with a sentinel group of 2 subjects. The EB8018 single doses assessed were 50 mg, 250 mg, 750 mg, 1500 mg and 3000 mg.
- Part 2 of the study was the multiple ascending dose (MAD) part: 2 cohorts with 10 male subjects enrolled (20 subjects in total) in each (7 treated with EB8018 and 3 with placebo) in a sequential escalating manner with a sentinel group of 2 subjects. The EB8018 multiple doses assessed were 750 mg and 1500 mg B.I.D.

STUDY RESULTS

The PK results of the MAD part are presented in the table below (Geo. means and CV):

DOSE (mg)	C_{max} (ng/mL)	C_{min} (ng/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-last}}$ (ng.h/mL)	T ½ (h)	Ae (F) (%D)	Ae (U) (%D)
DAY 1							
750	16.7 (48)		102 (35)	102 (35)	9.2	4.7	0.035
1500	16.6 (57)		123 (39)	123 (39)	NC	88	0.027
DAY 14							
750	28.2 (28)	17 (48)	257 (22)	258 (22)	29	0.6	0.07
1500	44.1 (49)	24 (33)	376 (36)	377 (36)	10.5	107	0.05

EB8018 was rapidly but minimally absorbed and the systemic exposure was increased in a non-dose proportional manner. The accumulation ratios, comparing the Day 1 and Day 14, Cmax and AUC values were between 1.68 and 3.07. With the 1500 mg BID dose, approximately 97% of the administered dose was recovered in the feces.

The safety results of the MAD part show that EB8018 was well tolerated with no serious or severe Adverse Events (AEs) and no AEs leading to drug discontinuation. All AEs resolved spontaneously.

The following AEs (all mild) were each reported by a single subject except for headache. Only one 750 mg treated subject reported a study drug considered as possibly related AE (decrease appetite)

- Placebo: no adverse events
- 750 mg B.I.D: fatigue, vessel puncture site bruise, headache, abdominal discomfort, pharyngitis, decreased appetite, neck pain, pain in extremity and seborrheic dermatitis.
- 1500 mg B.I.D: vessel puncture site pain, headache (2 subjects), dizziness, upper airway cough.

In addition, there were no clinically significant changes in any safety laboratory data, ECG, vital or physical signs. Microbiome analysis is currently on-going.

Based on these results, EB8018 will be progressed into the next phase of clinical development in patients with Crohn's Disease.