First-in-Human Study with EHP-101 Oral Solution of a Synthetic Cannabidiol Derivative Enables the Initiation of a Phase II Study in Multiple Sclerosis

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BACKGROUND

EHP-101 is an oral formulation of VCE-004.8, a patented new chemical entity derived from synthetic cannabidiol (CBD) with dual peroxisome proliferator-activated receptor gamma (PPARγ) and cannabinoid receptor type 2 (CB2) agonist activity that prevents microglia activation, axonal degeneration, and demyelination in vivo. EHP-101 has also demonstrated the stabilization of the expression of hypoxia inducible factor (HIF)-1α in microglia, oligodendrocytes, and endothelial microvascular cell lines. Recently, EHP-101 was shown to induce significant remyelination of brain neurons in murine cuprizone models within an anticipated therapeutic dose range in healthy volunteers (see ACTRIMS 2020 Poster 289).

OBJECTIVES

To evaluate the safety, tolerability, pharmacokinetics (PK), including food-effect and exploratory pharmacodynamics (PD) of single ascending doses (SAD) and multiple ascending doses (MAD) of orally administered EHP-101 or placebo.

METHODS

This randomized, double-blind, placebo-controlled Phase I study comprised 8 SAD cohorts (0.91 mg to 185 mg), including one food effect cross-over cohort (25 mg) and 4 MAD cohorts (20 mg once daily (QD) to 50 mg twice daily (BID)) with 7 days of treatment. Safety was assessed clinically by the incidence of treatment-emergent adverse events (TEAEs), vital signs, laboratory, cardiovascular and ophthalmological assessments. Evaluations were conducted under clinic confinement and in the outpatient setting.

RESULTS (Demographics)

A total of 104 subjects were randomized with 80 subjects exposed to active drug. In Part 1 (SAD cohorts), 6 subjects each received a single dose of either 0.91 mg, 1 mg, 9 mg, 20 mg, 25 mg (fasted and fed), 50 mg, 100 mg or 185 mg of EHP-101 and placebo was dosed in 2 subjects per cohort. In Part 2 (MAD cohorts), 8 subjects each received daily repeated doses for 7 days of either 20 mg QD, 25 mg BID, 50 mg BID, or 51.9 mg QD of EHP-101 and placebo was dosed in 2 subjects per cohort.

RESULTS (Safety)

Plasma samples for pharmacokinetic assessments were collected at prespecified time points. The determination of VCE-004.8 in plasma samples was performed using a validated liquid chromatography coupled to tandem mass spectrometry detection (LC-MS/MS) method. The Lower Limit of Quantification (LLQ) was 1 ng of VCE-004.8 per ml of plasma.

Maximum VCE-004.8 plasma levels (Cmax) occurred within 4 hours of dosing in all cohorts.

RESULTS (Pharmacokinetics)

A tendency for a greater-than-proportional increase in Cmax and Area under the Curve (AUC) parameters with increasing dose was observed in Part 1, however, broadly, despite intrachip variability, a proportional increase in Cmax and AUCmax was observed with increasing doses.

In Part 1 or 2 of the study, there were no drug-related, clinically relevant changes from baseline on vital signs, electrocardiograms, telemetry, echocardiograms, ophthalmological examinations or clinical laboratory results. There were two serious adverse events reported as a result of hospitalization for clarification of mild paraesthesia in the left arm and leg (possibly related) and asymptomatic second-degree AV block on telemetry (unlikely related).

Overall the TEAEs related to EHP-101 observed in the healthy volunteers at different dose levels were:

- mild to moderate headache
- mild to moderate somnolence
- mild to moderate photophobia
- mild to moderate paresthesia
- mild dizziness
- mild blurred vision
- mild palpitations
- mild abdominal pain (at highest dose)

Subjects showed the distinct double peak profile expected following BID dosing at steady state. Concentration profiles and PK parameters obtained after BID administration of 25 mg and 50 mg over 7 days indicated minimal accumulation between Day 1 and Day 7 in terms of AUC0-7d and Cmax.

RESULTS (Exploratory Pharmacodynamics)

In this first-in-human (FIH) study with EHP-101, single doses up to 185 mg and multiple doses up to 50 mg BID for 7 days were well tolerated by healthy subjects. The predicted Anticipated Therapeutic Dose (ATD) of EHP-101 in humans is about 30 mg (calculated based on 90% of anticipated effect level from efficacy data in an experimental autoimmune encephalomyelitis (EAE) mouse model). The Cmax for the predicted ATD was reached with a 20 mg single dose and the targeted exposure based on AUC was approached with a 50 mg single dose and 25 mg BID multiple dosing, respectively. In consequence, the initial recommended Phase II doses are 25 mg QD, 25 mg BID, 50 mg QD, and 50 mg BID. The encouraging FIH data enable the start of Phase II clinical studies in MS patients and other autoimmune disorders.

CONCLUSIONS

A mean increase of 1.5-fold in Cmax and AUC was observed post-administration with food. The half-life of a 25 mg single dose was about 2 hours during fasting and about 7 hours during fed state.

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