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

P061

ACTRIMS 2020

Joachim Schupp [1], Maria del Mar Municio [1], Jim DeMesa[1], David Fuller [2], Ben Snyder [3], Alain Rolland [1]

[1] Emerald Health Pharmaceuticals, San Diego, USA

[2] Syneos Health, Sydney, Australia; [3] Nucleus Network, Melbourne, Australia

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 (CB_2) 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[a], 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, cardiological 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, 3 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.

		Part 1 Total (n=64)	Part 2 Total (n=40)
Age (years)			
	Mean (SD)	27.8 (9.98)	29.3 (8.62)
	Median	24.5	28.5
	Min, Max	18, 64	19, 57
Gender			
	Male	28 (43.8%)	21 (52.5%)
	Female	36 (56.3%)	19 (47.5%)
Race			
	White	56 (87.5%)	35 (87.5%)
	Black	2 (3.1%)	1 (2.5%)
	Asian	4 (6.3%)	2 (5.0%)
	Other	2 (3.1%)	2 (5.0%)
Body Mass Index (kg/m^2)			
	Median	23.96	23.96
	Min, Max	17.86, 33.66	19.61, 30.77

RESULTS (Safety)

Summary of Exposure and Treatment-emergent Adverse Events Overall Incidence Part 1 and Part 2 (Safety Population)

	Daily Dose (mg)	N	Total EHP-101 Exposure (mg)	S (%) E	Relationship to Study Drug: Related
Part 1	Placebo	16	0	11 (68.8%) 20	7
	0.91	6	0.91	2 (33.3%) 3	2
	3	6	3	4 (66.7%) 5	2
	9	6	9	5 (83.3%) 9	4
	20	6	20	4 (66.7%) 8	2
	25 (fasted)	6	25	4 (66.7%) 6	1
	25 (fed)	6	25	3 (50%) 3	0
	50	6	50	4 (66.7%) 5	2
	100	6	100	3 (50%) 3	2
	185	6	185	5 (83.3%) 19	12
Part 2	Placebo	8	0	7 (87.5%) 15	5
	20 QD	8	140	6 (75%) 13	4
	25 BID	8	350	6 (75%) 17	8
	50 BID	8	700	8 (100%) 31	18
	51.9 QD	8	363.3	7 (87.5%) 15	1

Abbreviations: BID, twice daily; E, number of events; N, number of subjects in the group; QD, once daily; S, number of subjects. Note: Drug-related TEAEs were defined as possible, probable, or very likely/certain.

Treatment-emergent Adverse Events by Relationship to Study Drug per Cohort - Part 1 (Safety Population)

	Placebo fasted/ fed	0.91 mg	3 mg	9 mg	20 mg	25 mg fasted	25 mg fed	50 mg	100 mg	185 mg
	N=16 S (%) E	N=6 S (%) E	N=6 S (%) E	N=6 S (%) E	N=6 S (%) E	N=6 S (%) E	N=6 S (%) E	N=6 S (%) E	N=6 Part S (%) E	N=6 S (%) E
≥ 1 study drug-related	5 (31.3) 7	1 (16.7) 2	2 (33.3) 2	3 (50.0) 4	2 (33.3) 2	1 (16.7) 1	0	2 (33.3) 2	2 (33.3) 2	4 (66.7) 12

Abbreviations: E, events; N, number of subjects in the group; S, subjects.
Note: Drug-related is defined as possible, probable, or very likely/certain.

Treatment-emergent Adverse Events by Relationship to Study Drug per Cohort - Part 2 (Safety Population)

	Placebo fasted	20 mg QD	25 mg BID	50 mg BID	51.9 mg QD
	N=8 S (%) E	N=8 S (%) E	N=8 S (%) E	N=8 S (%) E	N=8 S (%) E
≥ 1 study drug-related TEAE	4 (50.0) 5	3 (37.5) 4	4 (50.0) 8	6 (75.0) 18	1 (12.5) 1

Abbreviations: E, events; N, number of subjects in the group; S, subjects.
Note: Drug-related is defined as possible, probable, or very likely/certain.

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).

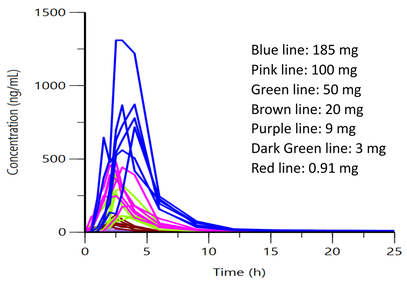
Overall the TEAEs related to EHP-101 observed in the study in healthy volunteers at different dose levels were:

- 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)

RESULTS (Pharmacokinetics)

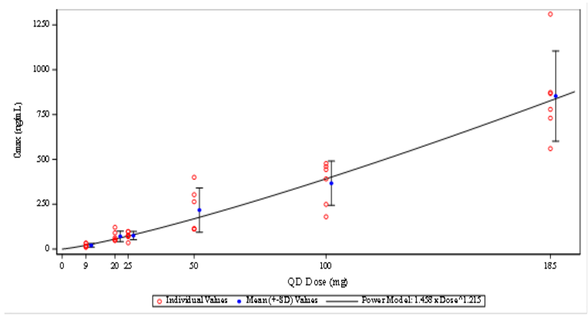
Plasma samples for pharmacokinetic assessments were collected at prespecified time points. The determination of VCE-004.8 in plasma samples was performed using a validated liquid chromatography coupled to tandem mass spectrometry detection (LC-MS/MS) method. The Lower Limit of Quantification (LLOQ) was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

Plasma Concentrations of Single Doses (Part 1)



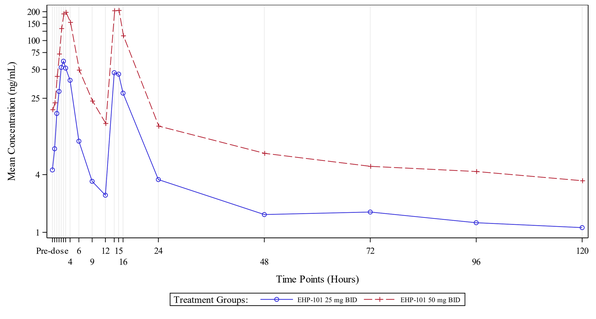
Maximum VCE-004.8 plasma levels (C_{max}) occurred within 4 hours of dosing in all cohorts.

Dose Proportionality of C_{max} for Single Doses (Part 1)



A tendency for a greater-than-proportional increase in C_{max} and Area under the Curve (AUC) parameters with increasing dose was observed in Part 1, however, broadly, despite intracohort variability, a proportional increase in C_{max} and AUC_{last} was observed with increasing doses.

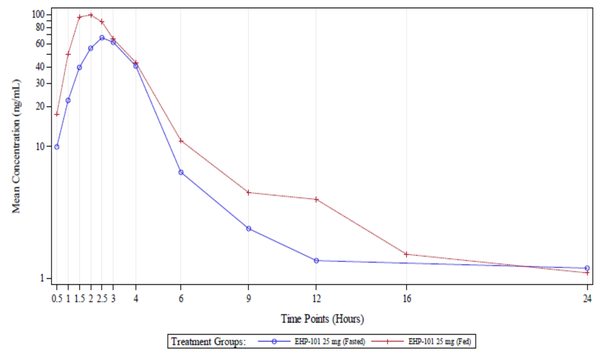
Plasma Concentration Profiles for 25 mg BID and 50 mg BID on Day 7 (Part 2)



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 $AUC_{0\text{-}12}$ and C_{max} .

RESULTS (Pharmacokinetics continued)

Food-Effect Cohort 25 mg (Part 1)



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

RESULTS (Exploratory Pharmacodynamics)

Preliminary SWATH analysis on Day 7 supports the mechanism of action of EHP-101 after dosing with 50 mg BID:

- 19 proteins were up-regulated 6 hours post administration on Day 7 (T_{max} 2 - 4h)
  - 7 related to vascular endothelial cell function (HIF pathway activation), such as VCAM1, NCAM1 and ECM1
  - 4 related to lipid metabolism and control of inflammation (PPARγ activation), such as APO1, APOA4, APOE and APOM
- 39 proteins were down-regulated at 6 hours post administration
  - Several related to CB_2 and PPARγ activation (e.g., FGB, LDHB, PCOLCE) (inflammation and immunomodulation)

Further biomarker analyses by Multiplex and ELISA are ongoing.

CONCLUSIONS

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 (calculation based on 90% of anticipated effect level from efficacy data in an experimental autoimmune encephalomyelitis mouse model). The C_{max} 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.

Acknowledgements

Dr. Eduardo Muñoz, Córdoba, Spain for biomarker assessments
Syneos Health and Nucleus Network Team, Melbourne, Australia
Emerald Health Pharmaceuticals Team

For questions please contact **jschupp@emeraldpharma.life**

References

[a] Navarrete C, Carrillo-Salinas F, Palomares B, et al. Hypoxia mimetic activity of VCE-004.8, a cannabidiol quinone derivative: implications for multiple sclerosis therapy. *J Neuroinflammation*, 2018; **15**(1):64.