A Phase 1 Single- and Multiple-Rising Dose Study of the Safety & PK of EMB-001, a Potential Treatment for Substance Use Disorders

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Abstract

Background: EMB-001 is a combination of two drugs: metyrapone (MET), a cortisol synthesis inhibitor, and oxazepam (OX), a benzodiazepine. EMB-001's mechanism targets the stress response to help maintain abstinence in the face of stressors and related triggers. EMB-001 reduced nicotine self-administration in rats and, at the highest dose tested, did so to a greater degree than did varenicline (Chantix®).

Methods: This was a single- and multiple-rising dose study. Healthy volunteers who smoked at least 10 cigarettes/day for at least a year were enrolled. They were not seeking to quit smoking. Each received a single am dose on Day 1, BID dosing on Days 3-9 and a single am dose on Day 10. Three sequential dose cohorts of 8 subjects (6 drug, 2 placebo) received the following doses of MET and OX, respectively: 270 and 12 mg; 540 and 24 mg; and 720 and 24 mg. Primary outcomes were safety and PK. Exploratory outcomes included cigarettes smoked; breath CO; urinary cotinine; and the Smoking Urges Questionnaire and Minnesota Nicotine Withdrawal Symptoms scale (assessed on day 9 after a 12-hr enforced period of smoking abstinence).

Results: The most frequent adverse event was somnolence. Most AEs were mild; all were mild or moderate. There were no SAEs and no discontinuations due to AEs. There were no clinically significant changes in vital signs, ECGs or other safety labs. The half-lives of MET, metyrapol its active metabolite, and OX were approximately and respectively 2, 8 and 7.5 hr. There were numerical changes that favored EMB-001 on both the Smoking Urges Questionnaire and the Minnesota Nicotine Withdrawal Symptoms scale. Assessment with inferential statistics is underway and will be available by the time of the conference.

Conclusions: EMB-001 was well-tolerated in this study and no new safety signals were identified. PK results suggest that twice-daily dosing may provide appropriate duration of exposure for efficacy. Exploratory efficacy measures in tobacco use disorder suggest further analysis is needed and future studies may be warranted. Future plans include a Phase 1b/2a study in a human laboratory model of tobacco use disorder.

Background

- The corticosterone synthesis inhibitor, metyrapone, decreases cocaine self-administration in rats (Goeders and Guerin, 1996; Goeders and Guerin, 2008).
- Benzodiazepines, like alprazolam and oxazepam, also decrease cocaine-related behaviors in rats (Goeders et al., 2009; Goeders et al., 1993).
- Combining low doses of metyrapone (MET) and oxazepam (OX) to form a combination drug product (MET/OX; EMB-001) may mitigate the side effects of each drug alone.
- MET/OX combination significantly reduced cocaine self-administration in rats and cocaine use in human addicts (Goeders and Guerin, 2008; Kablinger, et al., 2012).
- MET/OX combination significantly reduced nicotine self-administration in rats (Goeders, et al., 2012).

Disclosures

One or more authors report potential conflicts which are described in the program and as follows: All have been employees or contractors of Embera NeuroTherapeutics, Inc. which provided funding for this study.

Study Design and Demographics

- Healthy Volunteers who smoke cigarettes, ages 18-65
- Single Dose Day 1; BID dosing Days 3-9 and AM dose Day 10
- 3 Sequential Dose Cohorts. N=8/cohort (6 drug, 2 placebo)
- Doses: Metyrapone (MET) & Oxazepam (OX)*
  - 270mg MET & 12mg OX
  - 540mg MET & 24mg OX
  - 720mg MET & 24mg OX
- Primary Outcomes:
  - Safety
  - PK of MET, OX and metyrapol (active metabolite of MET)
- Exploratory Outcomes
  - Cigarettes smoked, CO, cotinine
  - MNWS & QSU prior to BID dosing and on Day 9 after 12-hr smoking abstinence

		n	(%)
Gender	Male	19	79%
	Female	5	21%
Race	Black	12	50%
	Caucasian	8	33%
	Hispanic	3	13%
	Asian	1	4%

	Age (yr)	Height (m)	Weight (kg)
Mean	38	1.7	79
Range	19-57	1.6-1.9	51-105

Highest daily doses given in this study: 1440mg MET & 48mg OX
Highest FDA-approved daily doses: 4500mg MET & 120mg OX
MET only approved for one-day use

Safety Results: Tolerability

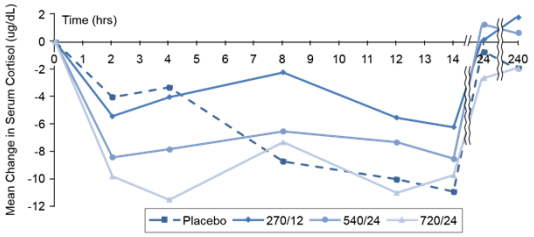
	Placebo (n=6)	EMB-001 270/12 (n=6)	EMB-001 540/24 (n=6)	EMB-001 720/24 (n=6)
Any AE:	4 (67%)	4 (67%)	4 (67%)	5 (83%)
Somnolence	1 (17%)	2 (33%)	4 (67%)	4 (67%)
Extremity Pain	0 (0%)	0 (0%)	1 (17%)	2 (33%)
Headache	1 (17%)	0 (0%)	0 (0%)	3 (50%)
Abnormal Dreams	0 (0%)	0 (0%)	2 (33%)	0 (0%)
Nausea	1 (17%)	0 (0%)	0 (0%)	2 (33%)
Diarrhea	0 (0%)	0 (0%)	0 (0%)	2 (33%)

No deaths, SAEs or discontinuations due to adverse events
Most AEs were mild; all were mild or moderate
Summary: tolerability consistent with MET & OX labeling

Safety Results: Vitals, ECGs, Safety Labs

- Vital signs were assessed multiple times/day on dosing days. Investigators reported no clinically significant changes in vital signs during the study.
- ECGs were assessed at Screening, Day 1, Day 10 and Day 17 (Follow up). No clinically significant changes in ECG were reported.
- Safety Labs were drawn at Screening, Day 1, Day 10 and Day 17 (Follow up). No clinically significant changes in laboratory values were reported, with the exception of the single morning decreased cortisol in one subject described in Safety Results: HPA Labs, Signs, Symptoms.

Safety Results: HPA Labs, Signs, Symptoms

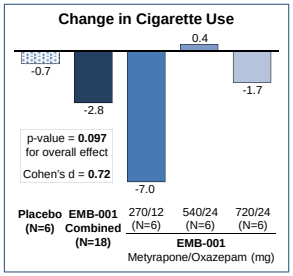


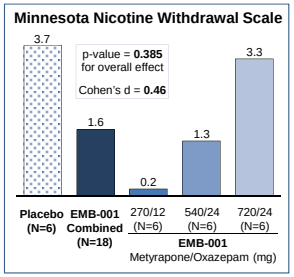
- Cortisol and ACTH were evaluated throughout the study.
- While some subjects experienced reductions in cortisol, none exhibited symptoms of adrenal insufficiency that required discontinuation of study drug or treatment.
- One subject in Dose Cohort 2 experienced a decrease in morning cortisol >50% versus screening. The subject was asymptomatic. Study drug was withheld for one day (Day 8) and subsequent ACTH stimulation testing revealed sufficient adrenal response. Dosing was resumed the next day and the subject completed the study.
- Daily Adrenal Insufficiency Review Checklist (AIRC) responses displayed no clinically significant signs or symptoms.
- Cortisol was dose-dependently reduced 2-4 hours after dosing, but returned to normal by the next morning and the morning after the week of BID dosing.

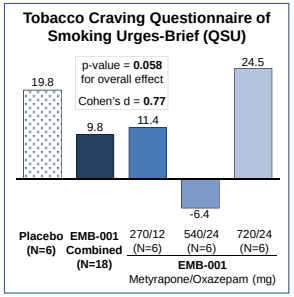
Results: Pharmacokinetics

- Half-lives:
  - MET: ~ 2 hours, OX: ~ 7.5 hours, Metyrapol (active metabolite of MET): ~ 8 hours
  - Half-lives do not change substantially at different doses or with repeated dosing
  - Half-life data suggest twice daily dosing may be appropriate.
- MET and OX exposures increase with increasing dose; OX exposure at 24 mg BID does not change with increased MET dose.
- Modest accumulation of MET and OX was observed with repeated dosing at most doses tested.

Results: Smoking Cessation Parameters



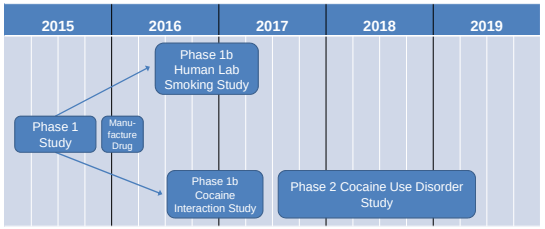




- Reduction in number of cigarettes smoked per day from baseline to steady state was numerically greater in the EMB-001 combined group than placebo.
- Following 12-hr nicotine abstinence, change in nicotine withdrawal (MNWS) from baseline to steady state was numerically lower in the EMB-001 combined group than placebo.
- Following 12-hr nicotine abstinence, change in tobacco craving (QSU brief) score from baseline to steady state was numerically lower in the EMB-001 combined group than placebo.

Conclusions and Clinical Trial Plan

- EMB-001 was well-tolerated in this study and no new safety signals were identified.*
- AEs were mostly mild and consistent with approved labeling.
- Cortisol was dose-dependently reduced 2-4 hours after dosing, but returned to normal by the next morning and the morning after the week of BID dosing.
- No clinically significant changes were observed in other safety labs, vital signs and ECGs.
- PK results suggest that twice-daily dosing may provide appropriate duration of exposure for efficacy.
- Exploratory efficacy measures in tobacco use disorder were not powered for statistical significance, but effect sizes were encouraging, and support future studies.



** These safety findings are generally consistent with MET and OX approved labeling and with safety data in 6 published studies in which MET doses of 500-4000 mg/day were given for 2-8 weeks in depressed (4 studies), heavy drinking (1 study) and cocaine-dependent (1 study) subjects.*