The Discovery and Development of EMB-001 for the Treatment of Substance Use Disorders

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Abstract

Background: No pharmaceutical treatments are currently available for cocaine use disorder, and treatments for tobacco use disorder are effective 25% of the time at best. EMB-001 is a combination of two FDA-approved drugs: metyrapone, a cortisol synthesis inhibitor, and oxazepam, a benzodiazepine. Metyrapone is approved for one day only as a test; oxazepam is approved for acute and chronic treatment of anxiety. We hypothesized that a combination of drugs working by different stress-related mechanisms may be efficacious for the treatment of substance use disorders, at doses that minimize the safety/tolerability risks of each individual drug.

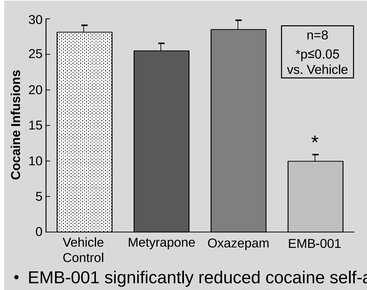
Methods: We summarize preclinical and clinical data supporting the potential efficacy and safety of EMB-001 for the treatment of substance use disorders, including a pilot human study in cocaine-dependent subjects, and a recently completed Phase 1 combined single/multiple ascending dose safety and PK study.

Results: EMB-001 reduced cocaine self-administration in rats at doses of each individual drug that were ineffective alone (Goeders, 2008). EMB-001 also reduced nicotine self-administration in rats (Goeders, 2012), and attenuated cocaine and methamphetamine cue reactivity in rats (Keller, 2013). A pilot human study of EMB-001 in cocaine dependence (Kablinger, 2012) showed a significant reduction in cocaine use and EMB-001 was generally well-tolerated. A new Phase 1 safety and PK study revealed EMB-001 to be well tolerated with no new safety signals identified. These safety results are generally consistent with 5 other published studies (O'Dwyer 1995; Murphy 1998; Eriksson, 2001; Jahn, 2004; Rogoz 2004). PK results from this new study suggest twice-daily dosing may provide appropriate duration of exposure for efficacy.

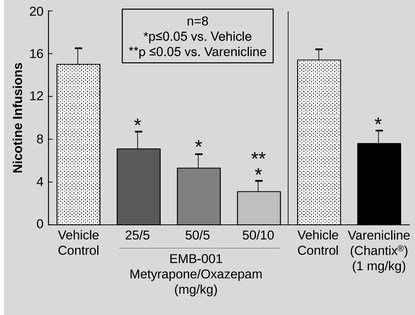
Conclusions: EMB-001 is effective in several animal models of drug addiction. A pilot human study suggested efficacy in cocaine-dependent subjects, and good tolerability. New data from a Phase 1 study extend the safety and tolerability findings and PK support BID dosing. EMB-001 has potential to treat cocaine and methamphetamine use disorders, for which no FDA-approved treatments exist. It also has potential for tobacco use disorder, for which a large unmet need and limited treatment options exist.

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.*

Preclinical Data and Clinical Pilot Study



- Male Wistar rats were trained to self-administer cocaine (0.25 mg/kg/inf) and food on a concurrent alternating FR4 schedule. VEH, MET (25-100 mg/kg IP) or OX (5-40 mg/kg IP) were administered 30 minutes prior to the self-administration session in a random dose order.
- EMB-001 significantly reduced cocaine self-administration at doses which did not affect food self-administration.



- Separate groups of rats were trained to self-administer nicotine (0.03 mg/kg/inf) on an FR and PR schedule.
- EMB-001 pretreatment reduced both reinforcement by nicotine (comparable to varenicline) and break point attained in these rats.

Phase 1 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

Phase 1 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

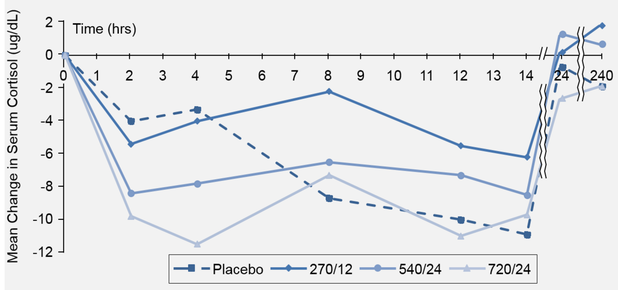
Phase 1 Safety Results: Vitals, ECGs, Safety Labs

- 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.

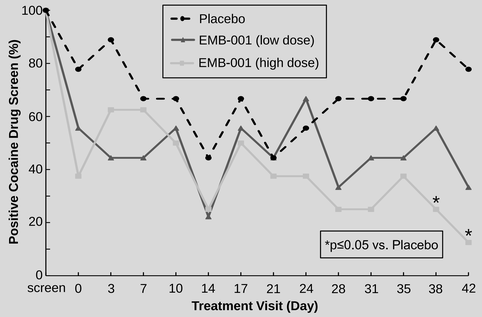
Phase 1 Results: Pharmacokinetics

- 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.

Phase 1 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.



- Statistically significant reduction in craving at several time points
- Significant reduction in visits positive for cocaine in the high dose group at end of study
- Data trend in direction of dose response

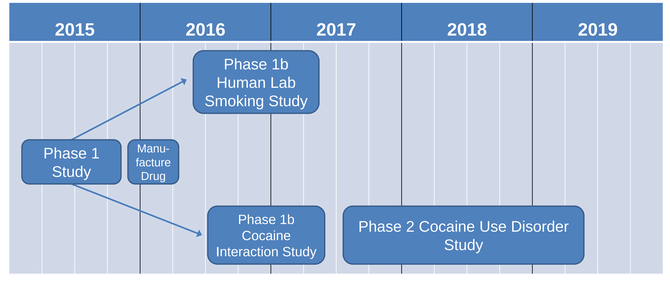
- LSUHSC-S IRB-approved trial.
- 45 subjects: 6 weeks of twice daily treatment
  - 15 subjects; low dose EMB-001 (500mg MET, 20mg OX per day)
  - 15 subjects; high dose EMB-001 (1500mg MET, 20mg OX per day)
  - 15 subjects; placebo
- Twice weekly study visits
- Endpoints:
  - Cocaine craving (CCQ-Brief)
  - Cocaine use (urinary benzoylecgonine)

Phase 1 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 has been shown in preclinical models to have potential efficacy in cocaine, methamphetamine and nicotine use disorders
- In a prior pilot study, EMB-001 reduced cocaine use in human subjects with cocaine dependence
- In a recently completed Phase 1 Safety/PK study:
  - EMB-001 was well-tolerated 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
  - 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.*