A Phase 1b Study of Potential Safety and Pharmacokinetic Interactions between Cocaine and EMB-001 with Exploratory Efficacy Measures

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Abstract

Introduction: EMB-001 is a combination of metyrapone (MET), a cortisol synthesis inhibitor, and oxazepam (OX), a benzodiazepine. EMB-001 reduced cocaine and nicotine self-administration in rats, reduced cocaine use in a human pilot study, and showed trends of decreased tobacco use, craving and withdrawal symptoms in a small study in humans. The present study was required by the FDA to investigate potential drug-drug interactions between EMB-001 and cocaine prior to planned Phase 2 and 3 studies in cocaine use disorder (CUD).

Methods: This was a double-blind, placebo-controlled crossover study of non-treatment-seeking subjects with CUD. Each subject received one week of oral BID dosing of MET/OX 720/24 mg and one week of oral BID placebo, randomized for order and separated by a one-week washout. On the last day of each dosing week, each subject received 40 mg IV cocaine. Primary outcomes were safety and PK. The potential effects of cocaine on EMB-001 PK were assessed with a cross-study meta-analytic approach, leveraging data from a previously completed safety/PK study of EMB-001 at the same dose(s) and without cocaine. Exploratory outcomes included craving and subjective measures, as well as cortisol biomarker response to cocaine infusion.

Results: 93% of AEs were mild; all were mild or moderate. There were no SAEs. There were few clinically significant changes in vital signs, ECGs or other safety lab measurements. There were no significant PK interactions, either within study or across studies. Exploratory biomarker measures showed that EMB-001 significantly blunted the cortisol response to cocaine, supporting the mechanistic hypothesis.

Conclusions: EMB-001 was well-tolerated and no new safety signals were observed. The crossover design allowed for greater statistical power with fewer subjects, and the meta-analytic approach for the PK data leveraged data from an already-completed Phase 1 safety and PK study (ERL-001). This allowed Embera to conclude that no clinically significant interactions between EMB-001 and cocaine were observed in PK, safety or exploratory craving/subjective measures. Assessment of a cortisol biomarker allowed for an observation that supports the novel mechanistic hypothesis involving effects of EMB-001 on the stress axis. Overall, these results support future studies of this novel mechanistic approach in CUD and tobacco use disorder, areas of unmet need with few or no approved treatments.

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.
- The MET/OX combination significantly reduced cocaine self-administration in rats and cocaine use in human addicts (Goeders and Guerin, 2008; Kablinger et al., 2012).
- The MET/OX combination significantly reduced nicotine self-administration in rats (Goeders et al., 2012).

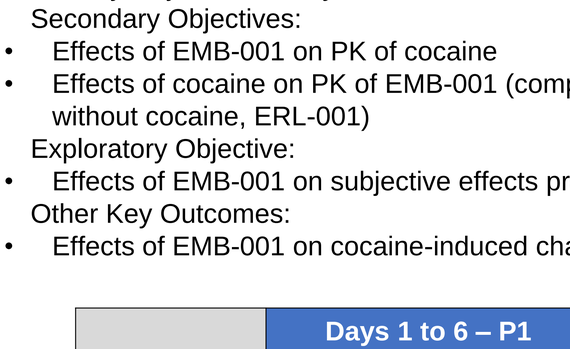
Study Design and Demographics

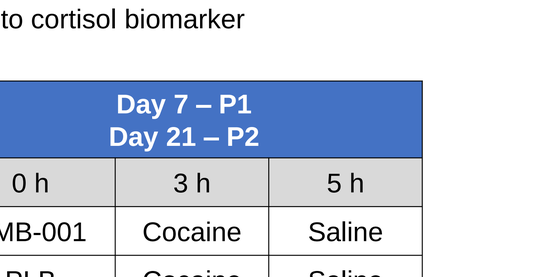
- Subjects: Non-treatment seeking subjects with cocaine use disorder, ages 21-55
- Design: Single center, randomized, double-blind (DB), placebo-controlled (PLB), 2-period crossover design
- Dosing:
  - One week of dosing with EMB-001 and one week of placebo, separated by one-week washout (randomized, DB, counterbalanced)
  - 40 mg IV cocaine & saline infusions on 7th day of dosing of EMB-001 and placebo
  - Dose of EMB-001: 720 mg MET & 24 mg OX, BID (highest dose to be used for future development)
- Primary Objective: Safety of EMB-001 when co-administered with cocaine
- Secondary Objectives:
  - Effects of EMB-001 on PK of cocaine
  - Effects of cocaine on PK of EMB-001 (compared across this study, ERL-002, and a prior study without cocaine, ERL-001)
- Exploratory Objective:
  - Effects of EMB-001 on subjective effects produced by cocaine
- Other Key Outcomes:
  - Effects of EMB-001 on cocaine-induced changes to cortisol biomarker

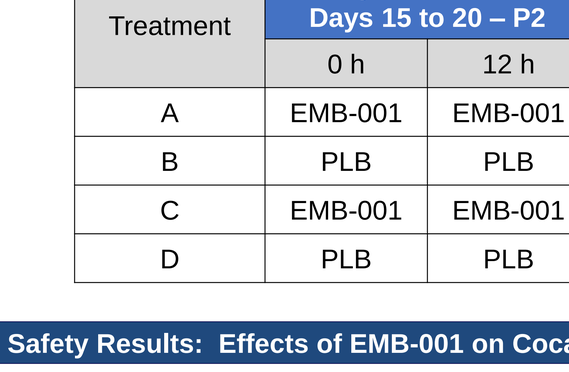
Treatment	Days 1 to 6 – P1 Days 15 to 20 – P2		Day 7 – P1 Day 21 – P2		
	0 h	12 h	0 h	3 h	5 h
A	EMB-001	EMB-001	EMB-001	Cocaine	Saline
B	PLB	PLB	PLB	Cocaine	Saline
C	EMB-001	EMB-001	EMB-001	Saline	Cocaine
D	PLB	PLB	PLB	Saline	Cocaine

Safety Results: Effects of EMB-001 on Cocaine Cardiovascular Effects

- Cocaine is known to increase blood pressure and heart rate significantly, and to cause cardiac arrhythmias, sometimes fatal.
- There were no clinically significant effects of EMB-001 (vs. placebo) on the effects of cocaine on ECGs, systolic/diastolic blood pressure, heart rate







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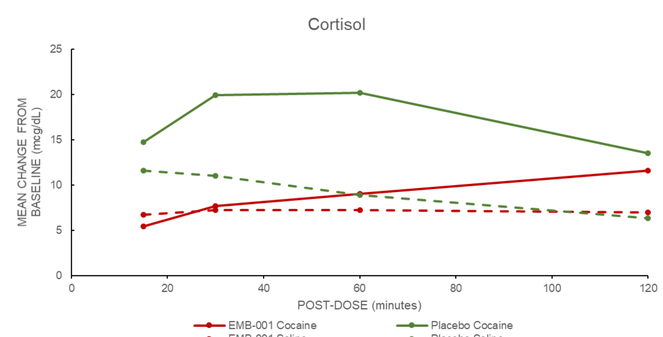
Safety Results: Tolerability and Vital Signs

All TEAEs present in >2 subjects that received EMB-001	Placebo N=14	EMB-001 720 mg MET / 24 mg OX N=18
Any AE	12 (86%)	16 (89%)
Euphoric Mood	8 (57%)	9 (50%)
Somnolence	1 (7%)	6 (33%)
Headache	1 (7%)	4 (22%)
ACTH increased and/or cortisol decreased	1 (7%)	4 (22%)

- No deaths or SAEs; 93% of all TEAEs were mild (mild/moderate/severe scale)
- Summary: tolerability consistent with MET and OX labeling

Results: Biomarker



Cortisol rises more during cocaine infusion than saline infusion, and the rise is blunted by EMB-001.

This is consistent with the hypothesized mechanism of EMB-001 and supports potential efficacy in mitigating stress-induced relapse.

Results: Pharmacokinetics*

Cocaine	Cmax (ng/mL)	$AUC_{0-\infty}$ (ng*hr/mL)
Cocaine + EMB-001	343 +/- 165	434 +/- 92
Cocaine + Placebo	361 +/- 169	455 +/- 95
Major Metabolites of Cocaine	**Cmax (ng/mL)**	**$AUC_{0-\infty}$ (ng*hr/mL)**
Benzoylecgonine + EMB-001	198 +/- 55	3080 +/- 689
Benzoylecgonine + Placebo	199 +/- 45	2970 +/- 720
Ecgonine Methyl Ester + EMB-001	20.5 +/- 3.7	244 +/- 50
Ecgonine Methyl Ester + Placebo	21.5 +/- 3.7	234 +/- 45
EMB-001 (Oxazepam and Metyrapone)	**Cmax (ng/mL)**	**$AUC_{0-\infty}$ (ng*hr/mL)**
Oxazepam: EMB-001 + Cocaine (ERL-002)	602 +/- 183	6140 +/- 2970
Oxazepam: EMB-001 (ERL-001)	653 +/- 197	6160 +/- 2440
Metyrapone: EMB-001 + Cocaine (ERL-002)	581 +/- 832	911 +/- 769
Metyrapone: EMB-001 (ERL-001)	429 +/- 234	900 +/- 492
Major Metabolite of Metyrapone	**Cmax (ng/mL)**	**$AUC_{0-\infty}$ (ng*hr/mL)**
Metyrapol: EMB-001 + Cocaine (ERL-002)	1900 +/- 1180	6290 +/- 2790
Metyrapol: EMB-001 (ERL-001)	1850 +/- 1570	5480 +/- 4840

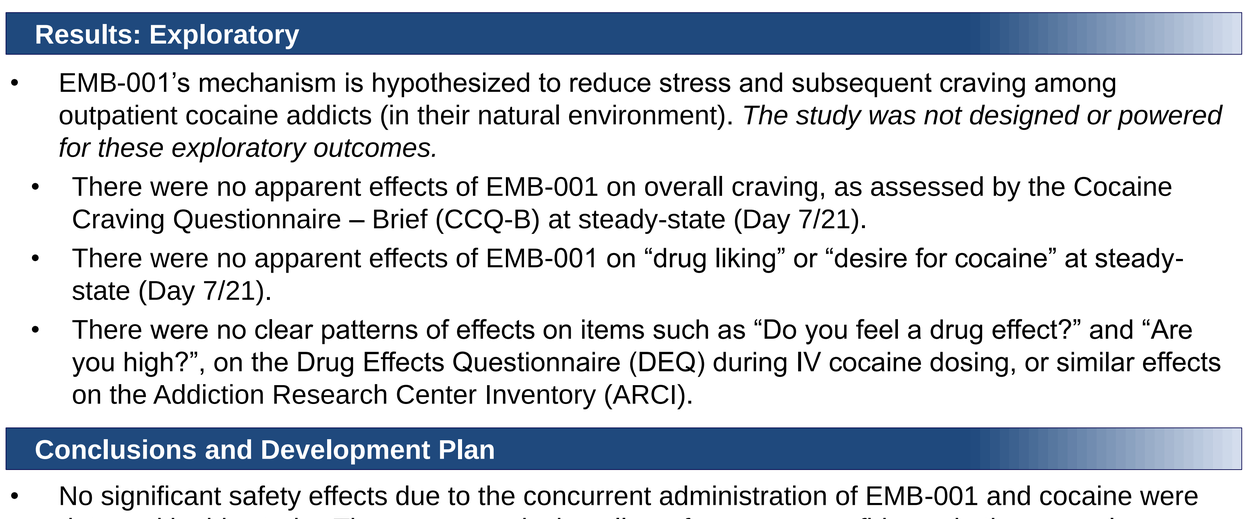
*Bioanalytical testing performed using LC-MS/MS analysis by AIT Bioscience.

Results: Exploratory

- EMB-001's mechanism is hypothesized to reduce stress and subsequent craving among outpatient cocaine addicts (in their natural environment). *The study was not designed or powered for these exploratory outcomes.*
  - There were no apparent effects of EMB-001 on overall craving, as assessed by the Cocaine Craving Questionnaire – Brief (CCQ-B) at steady-state (Day 7/21).
  - There were no apparent effects of EMB-001 on "drug liking" or "desire for cocaine" at steady-state (Day 7/21).
  - There were no clear patterns of effects on items such as "Do you feel a drug effect?" and "Are you high?", on the Drug Effects Questionnaire (DEQ) during IV cocaine dosing, or similar effects on the Addiction Research Center Inventory (ARCI).

Conclusions and Development Plan

- No significant safety effects due to the concurrent administration of EMB-001 and cocaine were detected in this study. The crossover design allows for greater confidence in these results.
- There were no significant effects of EMB-001 on the PK of cocaine or its major metabolites, and no significant effects of cocaine on the PK of EMB-001 (comparison to Clinical Study ERL-001). The meta-analysis leveraged data from a completed study to support the latter result.
- The tolerability of EMB-001 at this dose, in subjects with cocaine use disorder, was acceptable; no new safety signals were detected. Again, the crossover design allows for greater confidence in these results.
- Biomarker data support the hypothesis that EMB-001 mitigates cocaine-induced cortisol increase.
- These data support continued development of EMB-001 for the treatment of cocaine use disorder.



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