M206

Evaluation of M4 Muscarinic Receptor Occupancy by Emraclidine Using [^{11}C]MK-6884 PET in Healthy Volunteers

Sridhar Duvvuri,[1] Philip Iredale,[1] Sokhom S. Pin,[1] Deborah L. Smith,[1] Jianbo Zhang,[1] Amy Giugliano,[1] Michel Koole,[2] Koen Van Laere,[2] Jan de Hoon,[2] Vasily Belov,[3] Nicolas J. Guehl,[3] Georges El Fakhri,[3] Marc D. Normandin[3]

[1]Cerevel Therapeutics, Cambridge, MA, USA; [2]University Hospitals Leuven, Leuven, Belgium; [3]Gordon Center for Medical Imaging, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Presenting Author: Sridhar Duvvuri; sridhar.duvvuri@cerevel.com

CONCLUSIONS

- Simultaneous quantification of emraclidine M4 receptor occupancy (RO) via [^{11}C]MK-6884 PET imaging and emraclidine plasma concentrations demonstrated dose-dependent effects of emraclidine on striatal M4 RO and plasma exposure
- There was a positive relationship between M4 RO values in the striatum and emraclidine plasma concentration
  - Approximately 60% RO in striatum was observed across a wide concentration range of 350-900 ng/mL, suggesting potential saturation
  - Prespecified E_{max} model estimated the striatal E_{max} to be 80.1%, with a corresponding mean EC_{50} of 321 ng/mL
- In vitro binding data suggest potential underestimation of emraclidine ROs with MK-6884; additional in vitro studies are planned to understand the binding kinetics of emraclidine and MK-6884
- Single oral doses of emraclidine (30, 15, or 5 mg) were well tolerated in healthy volunteers
- The efficacy, safety, and tolerability of emraclidine for the treatment of adults with schizophrenia are being evaluated in ongoing phase 2 trials[1-3]

ACKNOWLEDGMENTS: This study was funded by Cerevel Therapeutics. Medical writing and editorial assistance were provided under the direction of the authors by MedThink SciCom with funding from Cerevel Therapeutics.

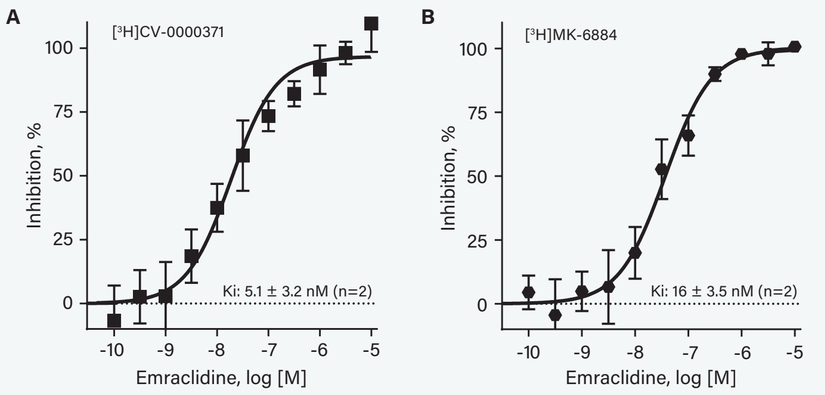
REFERENCES: 1. NCT05227703. https://clinicaltrials.gov/ct2/show/NCT05227703. Accessed October 11, 2023. **2.** NCT05227690. https://clinicaltrials.gov/ct2/show/NCT05227690. Accessed October 11, 2023. **3.** NCT05443724. https://clinicaltrials.gov/ct2/show/NCT05443724. Accessed October 11, 2023. **4.** Krystal et al. *Lancet.* 2022;400:2210-2220. **5.** Duvvuri et al. Presented at American College of Neuropsychopharmacology Annual Meeting; December 5-8, 2021; San Juan, Puerto Rico. **6.** Li et al. *Sci Transl Med.* 2022;14:eabg3684.

Presented at the 62nd Annual Meeting of the American College of Neuropsychopharmacology
December 3-6, 2023 ▪ Tampa, FL

INTRODUCTION

- Emraclidine is a novel, highly selective M4 muscarinic acetylcholine receptor–positive allosteric modulator currently in development for the treatment of schizophrenia and Alzheimer's disease psychosis[4]
- Preclinical characterization of emraclidine in rodents showed favorable brain penetration, direct target engagement, and robust in vivo activity in animal models of psychosis, including reversal of amphetamine-stimulated locomotion and prepulse inhibition[5]
- In vivo target engagement and an overall exposure-occupancy relationship of emraclidine was recently confirmed using the [^{11}C]MK-6884 radioligand in nonhuman primate positron emission tomography (PET) imaging studies evaluating M4 receptor occupancy (RO) as a function of emraclidine dose and plasma concentration[5]
- [^{11}C]MK-6884 was developed to evaluate target engagement of M4 receptors by positive allosteric modulators, with pharmacology and regional binding patterns consistent with that of an M4 positive allosteric modulator[6]; however, recent in vitro data demonstrate that competitive binding interactions between emraclidine and MK-6884 may differ from those observed between emraclidine and analogs with similar structure to emraclidine (**Figure 1**)
- As the M4 RO of emraclidine is anticipated to be directly related to its pharmacological effects, we sought to understand the relationship between M4 RO and plasma concentrations of emraclidine in healthy human volunteers

Figure 1. Competitive binding affinity (Ki) of (A) [^{3}H]CV-0000371 and (B) [^{3}H]MK-6884 at M4 receptors in the presence of emraclidine in vitro.



OBJECTIVES

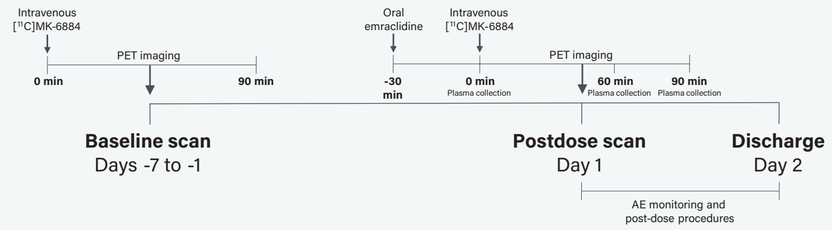
- The aim of this study was to evaluate M4 RO of emraclidine in the striatum of healthy adult volunteers and to assess the relationship between M4 RO and plasma concentration of emraclidine after single oral doses

METHODS

STUDY DESIGN

- This phase 1, open-label trial (NCT04787302) enrolled healthy adult volunteers in an adaptive study design across 3 cohorts (n=3 per cohort)
- Participants in the first cohort received a single 30-mg oral dose of emraclidine, participants in the second cohort received a single 15-mg oral dose of emraclidine, and participants in the third cohort received a single 5-mg oral dose of emraclidine
- Participants had 2 imaging sessions (**Figure 2**), baseline PET/computed tomography (CT) and magnetic resonance imaging (MRI) scans up to 1 week before emraclidine dosing, and a second PET/CT scan 30 minutes after dosing
  - Collection of PET data began concurrently with intravenous infusion of 10-20 mCi of [^{11}C]MK-6884
  - Serial arterial blood samples of approximately 1.0 mL were collected every 10 to 30 seconds at the start of each PET scan, with sampling every 15 to 30 minutes by the end of the sampling period
- Blood samples for determination of plasma concentrations of emraclidine were collected at 30, 90, and 120 minutes after emraclidine dosing

Figure 2. Baseline and postdose PET imaging and plasma sampling timeline.



AE, adverse event; PET, positron emission tomography.

OUTCOMES

- The primary endpoint was estimation of emraclidine RO (%) in the striatum (averaging values from the caudate and putamen), with the cerebellum as a reference region
  - Overall M4 RO (%) was calculated as follows:

$$RO\ (\%) = \frac{BP_{baseline} - BP_{treatment}}{BP_{baseline}} \times 100$$

- The secondary endpoint was the relationship between M4 RO and emraclidine plasma exposure, assessed using an exposure-response model informed by the maximum estimated RO (E_{max}), emraclidine plasma concentration (C), and the concentration at which 50% of maximum RO is achieved (EC_{50}), assuming a Hill coefficient (γ) of 1:

$$RO = \frac{E_{max} \times C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

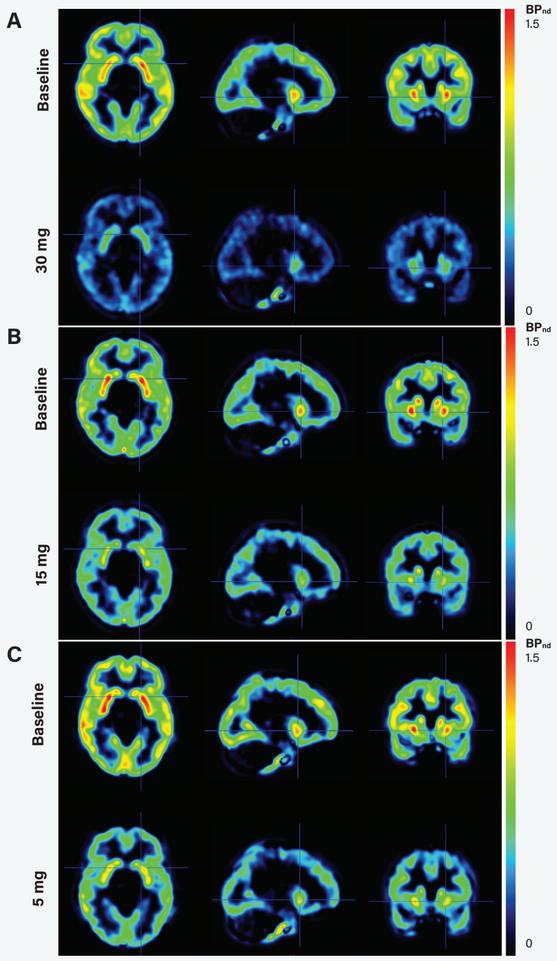
- Treatment-emergent adverse events (TEAEs), clinical laboratory assessments, vital sign measurements, and physical and neurological examination results were also evaluated after emraclidine dosing

RESULTS

STUDY PARTICIPANTS

- 68 participants were screened, and 9 were enrolled; all participants completed the trial and were included in the analyses
  - All participants were male, and most (89%) were White, with a mean (SD) age of 27.1 (10.1) years and a mean (SD) body mass index (kg/m^2) of 23.20 at screening

Figure 3. Individual [^{11}C]MK-6884 PET BP_{nd} parametric images at baseline and after dosing with (A) 30 mg, (B) 15 mg, and (C) 5 mg of emraclidine.



PET, positron emission tomography; BP_{nd}, nondisplaceable binding potential.

PHARMACOKINETICS (PK) OF EMRACLIDINE IN HEALTHY VOLUNTEERS

- Median plasma emraclidine PK exposure parameters decreased with decreasing emraclidine dose (**Table**)

Table. Summary of Plasma Emraclidine PK Parameters

	Plasma PK parameters, median (range)		
Parameter	Cohort 1: 30 mg (N=3)	Cohort 2: 15 mg (N=3)	Cohort 3: 5 mg (N=3)
$C_{avg\ scan\ duration}$, ng/mL	634 (425-888)	347 (186-374)	143 (128-167)

$C_{avg\ scan\ duration}$, average plasma concentration during the scan duration (area under the plasma concentration–time curve from time 0 to the end of the scan, calculated using the trapezoidal rule divided by 1.5); PK, pharmacokinetic.

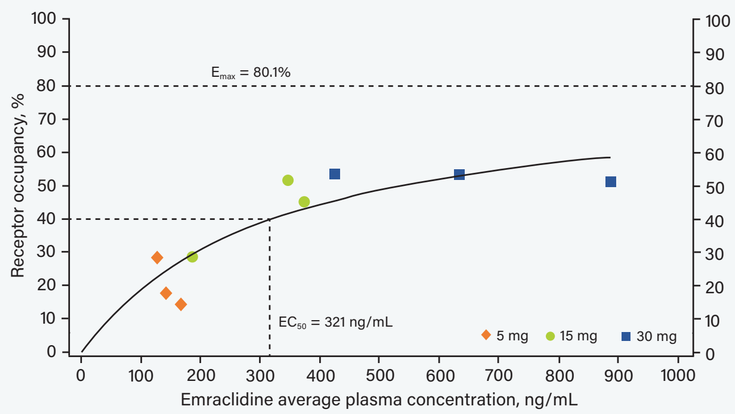
M4 RO AFTER ADMINISTRATION OF EMRACLIDINE

- Representative PET images at baseline and after administration of a 30-, 15-, or 5-mg dose of emraclidine are shown in **Figure 3**
  - After a single 30-, 15-, or 5-mg dose of emraclidine, mean (SD) M4 RO in the striatum was 52.7% (1.31%), 41.8% (11.9%), and 20.1% (7.30%), respectively

RELATIONSHIP BETWEEN M4 RO IN STRIATUM AND EMRACLIDINE PLASMA CONCENTRATION

- An E_{max} dose-response model was used to explore the relationship between plasma emraclidine concentration and M4 RO in the striatum (**Figure 4**)
- A positive relationship was observed when the M4 RO values in the striatum were plotted against the corresponding emraclidine plasma concentration data
  - The coverage of RO range was 14% to 54%
- Mean (SE; 95% CI) maximum RO (E_{max}) in the striatum was 80.1% (17.6%; 46.8% to 113%)
  - Corresponding mean (SE; 95% CI) EC_{50} was 321 (157; 23.9-618) ng/mL

Figure 4. Emraclidine M4 RO in the striatum vs emraclidine plasma concentrations.



EC_{50}, concentration at which 50% of maximum RO is achieved; Emax, maximum estimated RO; RO, receptor occupancy.

TEAES

- 2 participants in the 30-mg dose cohort and 1 participant in the 5-mg dose cohort experienced at least 1 TEAE; no participants in the 15-mg dose cohort reported any TEAEs
  - 1 participant in the 30-mg dose cohort experienced grade 1 TEAEs (fatigue, sinus tachycardia, increased blood pressure, orthostatic hypotension) that were considered to be related to emraclidine; all TEAEs resolved within 1 to 20 hours after onset
  - No AEs of special interest, serious TEAEs, or TEAEs leading to discontinuation from the trial were reported