Navacaprant (NMRA-140), A Novel and Highly Selective Kappa Opioid Receptor Antagonist, in Patients with Major Depressive Disorder: A Randomized Placebo-Controlled Phase 2 Trial

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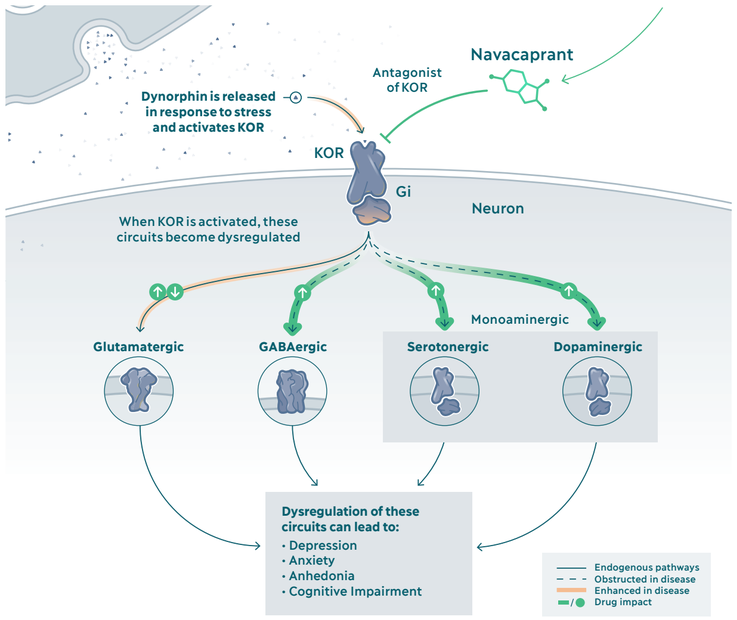
INTRODUCTION

- A significant unmet need remains in Major Depressive Disorder (MDD), as many patients do not adequately respond to approved pharmacotherapies and often experience residual symptoms and intolerable side effects[1-3]
- Current antidepressants also do not adequately treat anhedonia, a core clinical feature of MDD that affects approximately 70% of patients and is associated with more severe depressive symptoms and functional impairment[4,5]
- The kappa opioid receptor (KOR) / dynorphin system is a well-characterized pathway, and results from preclinical studies support its potential to modulate depression, anhedonia, and anxiety[6] (**Figure 1**)
- Navacaprant (NMRA-140, BTRX-335140) is a novel, oral, once-daily, highly selective KOR antagonist in development as monotherapy for the treatment of MDD
- Navacaprant has 300-fold selectivity for kappa over mu opioid receptors, and no agonist activity at kappa, mu, or delta opioid receptors[7]

Figure 1. KOR Antagonism in Major Depressive Disorder



GABA=gamma-aminobutyric acid; Gi=inhibitory signaling through a G-protein coupled receptor (GPCR); KOR=kappa opioid receptor.
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OBJECTIVE

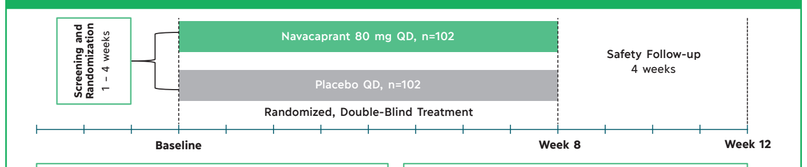
This Phase 2 randomized clinical trial was designed to assess the efficacy and safety of navacaprant monotherapy in adults with MDD

METHODS

Study Design

- This Phase 2 study was an 8-week, randomized, double-blind, placebo-controlled clinical trial conducted from Dec 2019 to Jun 2022; participants were enrolled at 31 U.S. sites
- After screening, participants were randomized to once-daily treatment with either navacaprant 80 mg or placebo for 8 weeks, followed by a 4-week follow-up
  - Study design, select inclusion criteria, primary/secondary outcomes, and prespecified analyses are shown in **Figure 2**

Figure 2. Study Design



Select Inclusion Criteria
- Primary diagnosis of MDD
- Current episode started within 3 wks to 12 mo. of screening
- Not failed ≥2 ADT in current episode
- 18 –65 years of age, BMI 18 –40 kg/m²
- Blinded rule list: HAMD-17 14 – 30; HAM-A ≥8; SHAPS ≥26

Study Endpoints

Primary Endpoint:
Δ from BL to Week 8 in HAMD-17

Prespecified Subgroup Analysis of Primary Endpoint:
Δ from BL to Week 8 in HAMD-17 (score ≥22 at BL)

Secondary Endpoints Included:
- Δ from BL to Week 4 in HAMD-17
- Δ from BL to Weeks 4 and 8 in SHAPS

Prespecified Analyses
- MMRM: primary analysis
- LOCF: if ≤10% of participants missing data

ADT=antidepressant treatments; BL=baseline; BMI=body mass index; HAM-A=Hamilton Anxiety Rating Scale; HAMD-17=Hamilton Depression Rating Scale – 17-item version; LOCF=last-observation-carried-forward; MDD=major depressive disorder; mo.=months; MMRM=mixed-models-repeated-measures; QD=once daily; SHAPS=Snaith-Hamilton Pleasure Scale; wks=weeks.

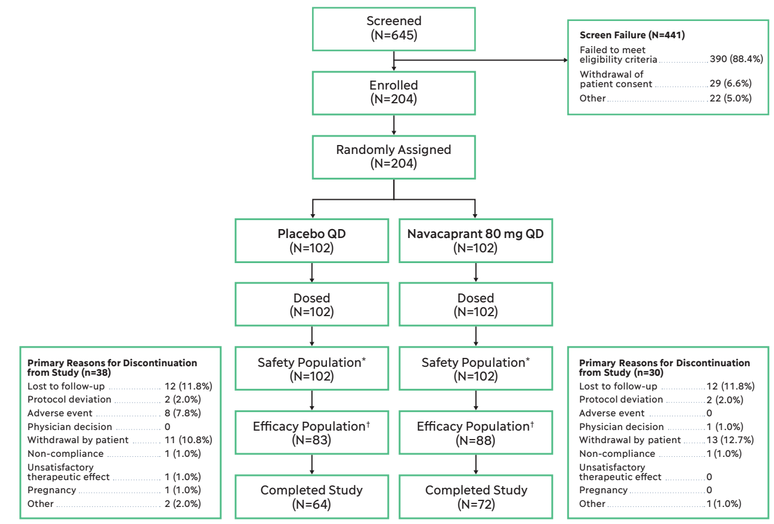
Neumora Amendments

- Neumora Therapeutics acquired this trial through its acquisition of BlackThorn Therapeutics and made several amendments to optimize the trial per FDA feedback and for consistency with other MDD trials, including:
  - Increased Hamilton Depression Rating Scale - 17 item version (HAMD-17) inclusion to allow for enrollment of participants with moderate-to-severe MDD (baseline HAMD-17 of **14 - 30**)
  - Increased target enrollment and number of sites

RESULTS

- In total, 204 participants (n=102 each group) were randomized and received study drug, comprising the safety population (**Figure 3**)
  - Of these, 171 participants (n=88 navacaprant, n=83 placebo) had ≥1 baseline (BL) and post-BL HAMD-17 assessment, comprising the efficacy population

Figure 3. Participant Disposition



BL=baseline; GCP=good clinical practice; HAMD-17=Hamilton Depression Rating Scale – 17-item version; QD=once daily.
*Participants who received ≥ 1 dose of study drug. †Participants with a BL HAMD-17 total score who received ≥ 1 dose of study drug & had ≥ 1 post-BL HAMD-17 assessment. Participants from 1 clinical site (navacaprant n=1, placebo n=4) that were otherwise eligible for inclusion in the efficacy population were excluded due to GCP violations; these participants were still included in the safety population.

- Treatment groups were well matched in terms of baseline characteristics and depression/anhedonia ratings (**Table 1**)
- In the efficacy population, 71 participants had BL HAMD-17 scores < 22 (more mild MDD) and 100 had BL HAMD-17 scores ≥ 22 (moderate-to-severe MDD)
  - Characteristics of participants with moderate-to-severe MDD (i.e., BL HAMD-17 of ≥ 22) were similar to those of the overall efficacy population (data not shown)

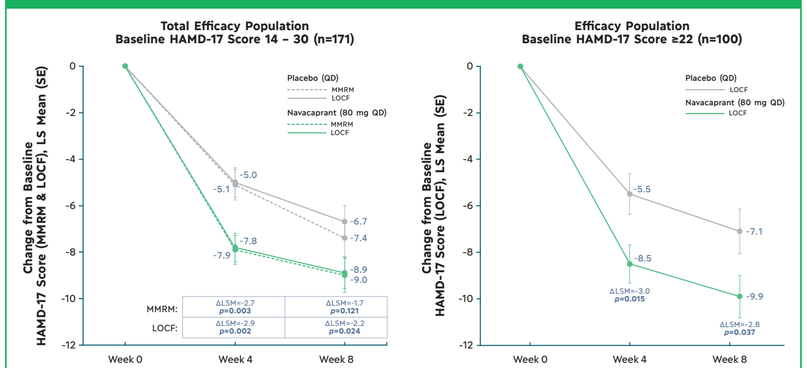
Table 1. Efficacy Population: Baseline Characteristics

	Navacaprant 80 mg QD n=88	Placebo QD n=83
Age, mean (SD), years	42.2 (13.3)	42.7 (13.4)
Female, n (%)	62 (70.5%)	58 (69.9%)
Race, n (%)		
White	54 (61.4%)	54 (65.1%)
Black/African American	30 (34.1%)	22 (26.5%)
Asian	4 (4.5%)	6 (7.2%)
Not collected	0	1 (1.2%)
Ethnicity, n (%)		
Not Hispanic or Latino	78 (88.6%)	69 (83.1%)
BMI, mean (SD), kg/m²	27.5 (4.8)	28.4 (4.7)
HAMD-17 score, mean (SD)	21.8 (3.5)	22.3 (3.4)
SHAPS score, mean (SD)	37.5 (5.8)	38.0 (5.7)

BMI=body mass index; HAMD-17=Hamilton Depression Rating Scale – 17-item version; QD=once daily; SD=standard deviation; SHAPS=Snaith-Hamilton Pleasure Scale.

- In the MMRM analysis of the efficacy population (which included mildly depressed participants with BL HAMD-17 scores as low as 14), navacaprant demonstrated statistically significant improvement vs. placebo at Week 4, but not Week 8 (**Figure 4**)
  - In the prespecified LOCF analysis, navacaprant was superior to placebo at both Weeks 4 and 8
- In the prespecified subgroup analysis of participants with moderate-to-severe MDD (BL HAMD-17 ≥ 22), statistically significant differences favoring navacaprant were seen at both Weeks 4 and 8

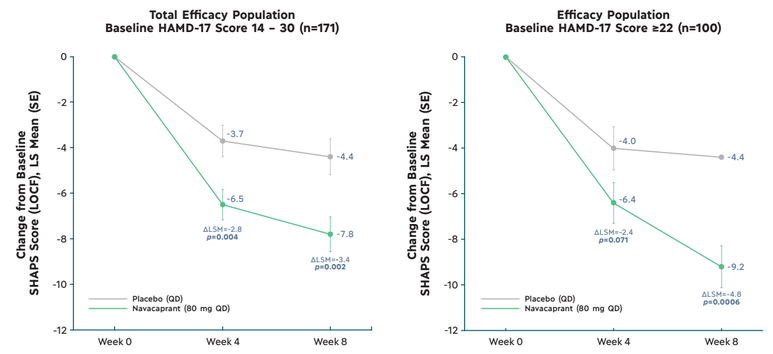
Figure 4. Efficacy Population: CFB in HAMD-17 Score



CFB=change from baseline; HAMD-17=Hamilton Depression Rating Scale – 17-item version; LOCF=last-observation-carried-forward; LSM=least squares mean; MMRM=mixed-model-repeated-measures; QD=once daily; SE=standard error

- For the SHAPS, significant differences favoring navacaprant were seen at both Weeks 4 and 8 in the efficacy population (**Figure 5**)
- In the subgroup of participants with moderate-to-severe MDD, a trend favoring navacaprant was found at Week 4, and a significant difference was detected at Week 8

Figure 5. Efficacy Population: CFB in SHAPS Score



CFB=change from baseline; HAMD-17=Hamilton Depression Rating Scale – 17-item version; LOCF=last-observation-carried-forward; LSM=least squares mean; QD=once daily; SE=standard error; SHAPS=Snaith-Hamilton Pleasure Scale

- The incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to TEAEs were higher in the placebo group compared to the navacaprant group (**Table 2**)
- No evidence of suicidal behavior was reported in the navacaprant group, as assessed by the Columbia Suicide Severity Rating Scale; one placebo-treated participant had 2 suicide attempts

Table 2. Safety Population: Treatment-Emergent Adverse Events

	Navacaprant 80 mg QD n=102	Placebo QD n=102
Total Number of TEAEs, n	65	83
Participants Reporting ≥ 1 TEAE, n (%)	36 (35.3%)	45 (44.1%)
Total Number of SAEs, n	0	2
TEAE by Severity, n (%)		
Mild	27 (26.5%)	30 (29.4%)
Moderate	9 (8.8%)	10 (9.8%)
Severe	0	5 (4.9%)
TEAE Leading to Discontinuation of Study Drug, n (%)	1 (1.0%)	12 (11.8%)
TEAEs Occurring at ≥ 2% in Either Group, n (%)		
Headache	5 (4.9)	5 (4.9)
Nausea	5 (4.9)	1 (1.0)
COVID-19	4 (3.9)	3 (2.9)
Upper respiratory tract infection	3 (2.9)	1 (1.0)
Diarrhea	2 (2.0)	3 (2.9)

QD=once daily; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
TEAEs reported in the safety population, which included participants receiving ≥ 1 dose of study drug.

CONCLUSIONS

Navacaprant is a novel, oral, once-daily, highly selective KOR antagonist with no agonist activity at kappa, mu, or delta opioid receptors that is in development as monotherapy for the treatment of MDD

Navacaprant resulted in statistically significant reductions in symptoms of depression and anhedonia compared with placebo following 8 weeks of treatment in participants with moderate-to-severe MDD

Participants receiving navacaprant reported fewer TEAEs vs. those receiving placebo, with lower TEAE-related discontinuation rates; no SAEs, suicidal behavior, or other clinically relevant safety findings were reported in navacaprant-treated participants

Navacaprant is currently in Phase 3 development (KOASTAL Program) as a monotherapy for MDD

Disclosures

This work was originally funded by BlackThorn Therapeutics, Inc. (San Francisco, CA, USA) and later by its parent company and eventual successor-in-interest, Neumora Therapeutics, Inc. (Watertown, MA, USA). Writing assistance and graphics support were provided by Prescott Medical Communications Group, Chicago, IL. Dr. Sanjay Mathew has served as a consultant to Almatica Pharma, Biohaven, BioXcel Therapeutics, Boehringer-Ingelheim, Brii Biosciences, Clexio Biosciences, COMPASS Pathways, Delix Therapeutics, Douglas Pharmaceuticals, Eleusis, EMA Wellness, Engrail Therapeutics, Levo Therapeutics, Liva Nova, Merck, Perception Neurosciences, Praxis Precision Medicines, Neumora, Neurocrine, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, Signant Health, Sunovion, and XW Pharma.

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