



NMRA-511 Phase 1b Results: Alzheimer's Disease (AD) Agitation

January 2026



Important disclosures

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Our Mission

We are focused on redefining neuroscience drug development by bringing forward the next generation of novel therapies that offer improved treatment outcomes and quality of life for patients



Advancing a leading neuroscience pipeline

Broad pipeline
addressing some of the
most prevalent diseases

Targeting novel
mechanisms across a
broad range of centrally
mediated indications

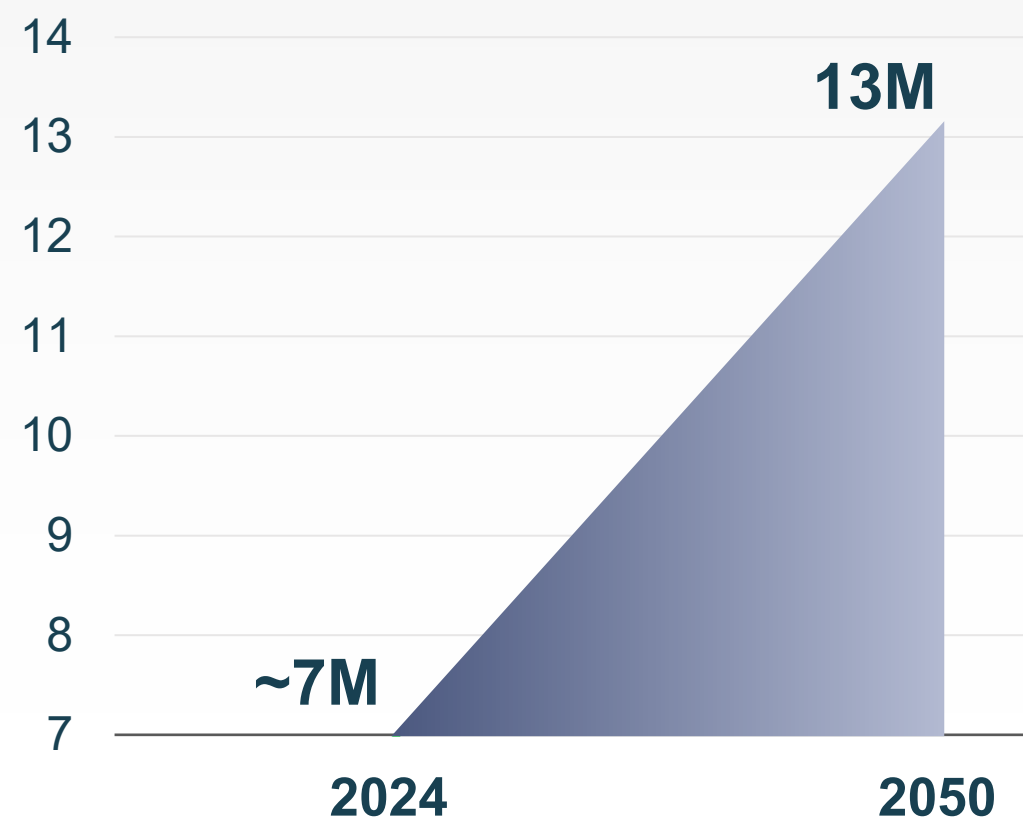
PROGRAM <i>Target/Mechanism</i>	INDICATION <i>U.S. Prevalence</i>	Preclinical	Phase 1	Phase 2	Phase 3
Navacaprant <i>KOR Antagonist</i>	Major Depressive Disorder 21M				
NMRA-511 <i>V1aR Antagonist</i>	Agitation in Alzheimer's Disease 7M				
NMRA-861 <i>M4 Modulator</i>	Schizophrenia 3M				
NMRA-898 <i>M4 Modulator</i>	Schizophrenia 3M				
NMRA-215 <i>NLRP3 Inhibitor</i>	Obesity/Parkinson's Disease 103M/1M				
NMRA-GCASE <i>GCCase Activator</i>	Parkinson's Disease 1M				
NMRA-CK1δ <i>CK1δ Inhibitor</i>	ALS/Parkinson's Disease 25K/1M				

Alzheimer's disease agitation represents large market opportunity with significant unmet need

Alzheimer's disease agitation is a large and growing health burden

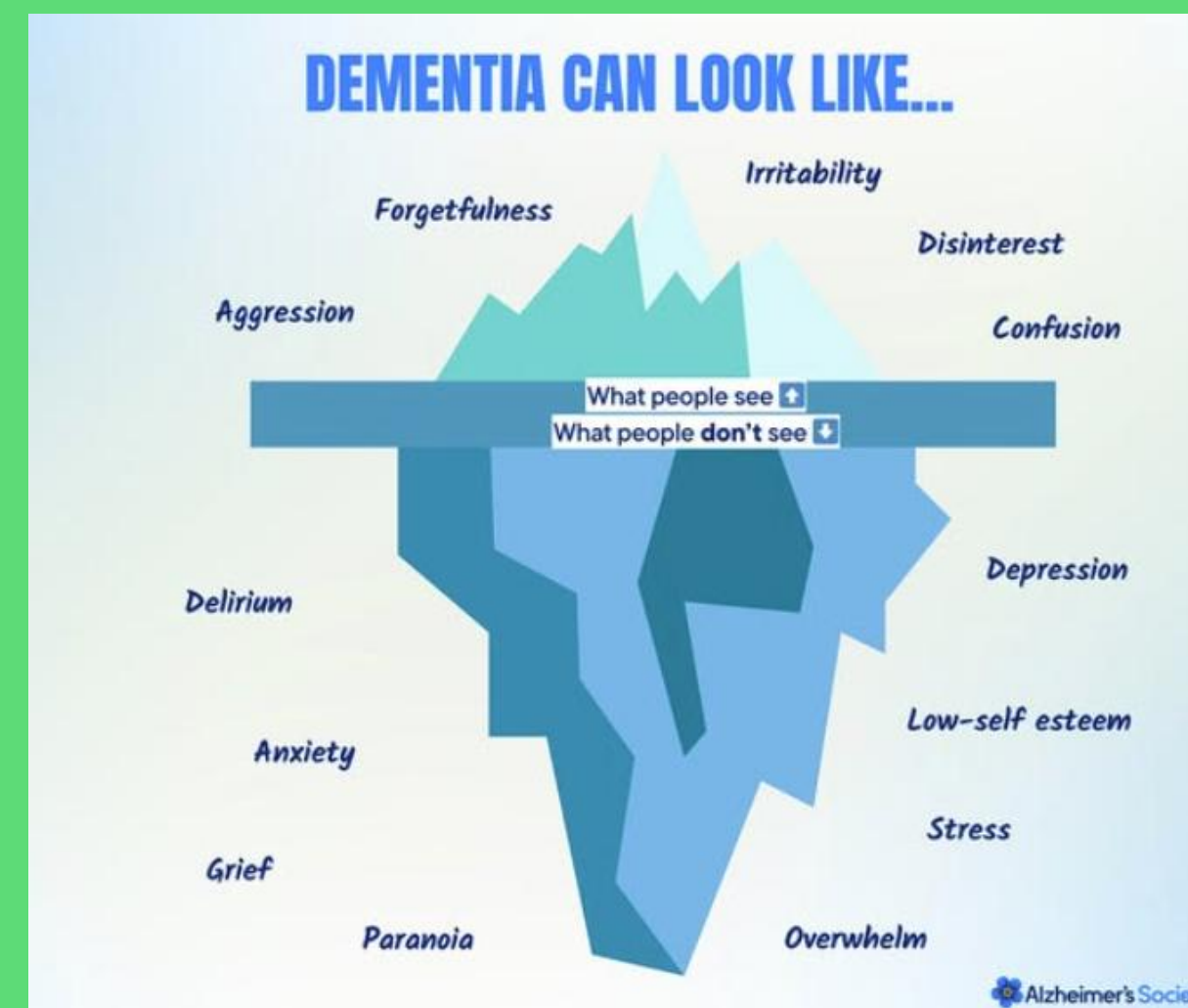
Millions currently living with AD; prevalence expected to increase as the population ages¹

U.S. Adults with Alzheimer's Disease (M)¹



>70%
of people with AD experience agitation at some point in their disease²

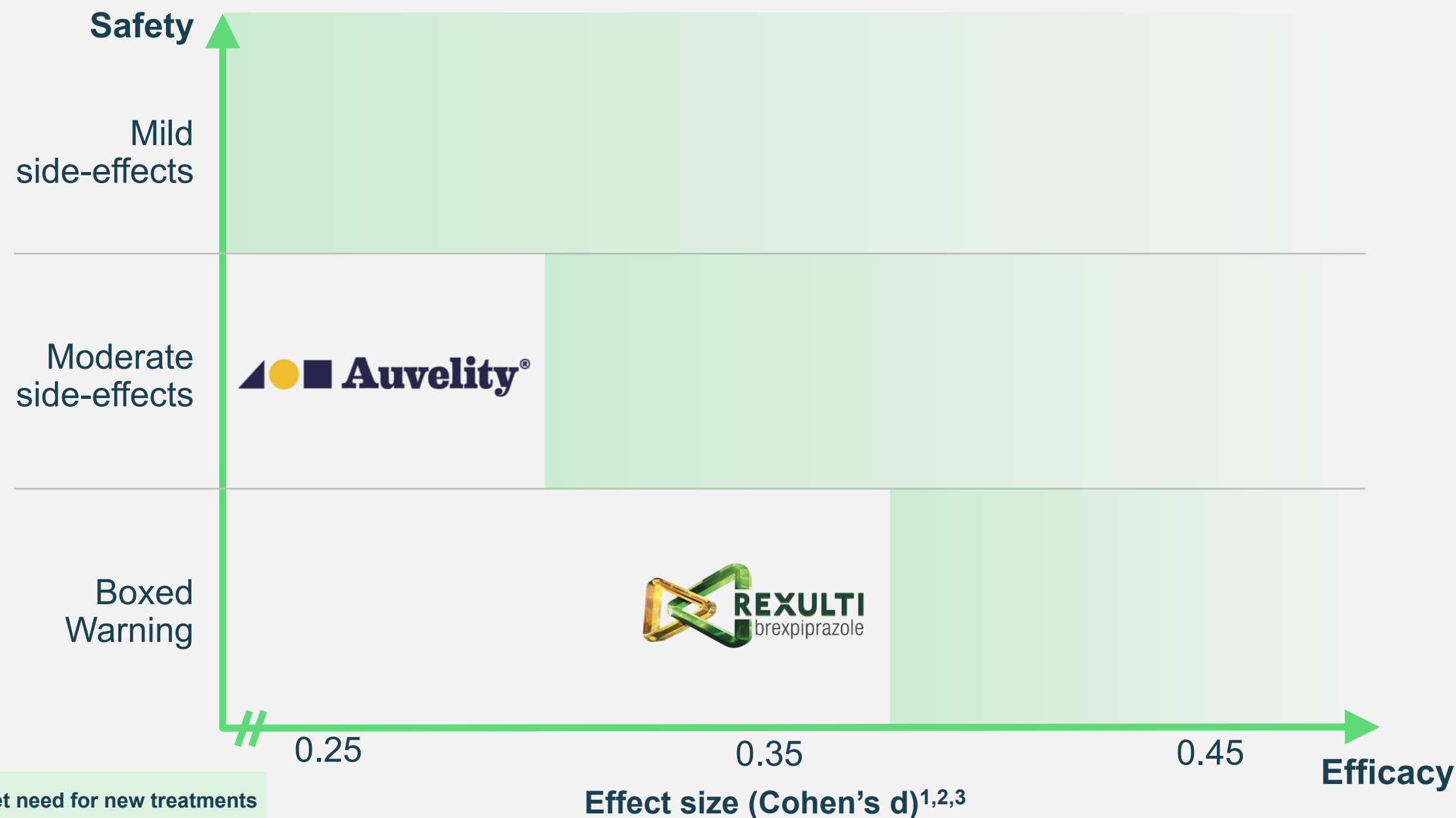
Anxiety is a key underlying driver of aggression and irritability in dementia³



¹Alzheimer's Association. 2025 Alzheimer's Disease Facts and Figures. Alzheimer's Dementia 2025;21(5). ²Van der Musselle S, et al. Aging Ment Health 2015;19(3):247-257. ³Image from Alzheimer's Society

Significant opportunity for a product with a differentiated benefit/risk profile

Simplified market segmentation and opportunities



There is an unmet medical need for therapies that reduce agitation with improved tolerability and safety profiles^{3,4}

AD agitation associated with:



Increased morbidity and mortality



Earlier placement in long-term care facilities



Reduced quality of life for patients and caregivers



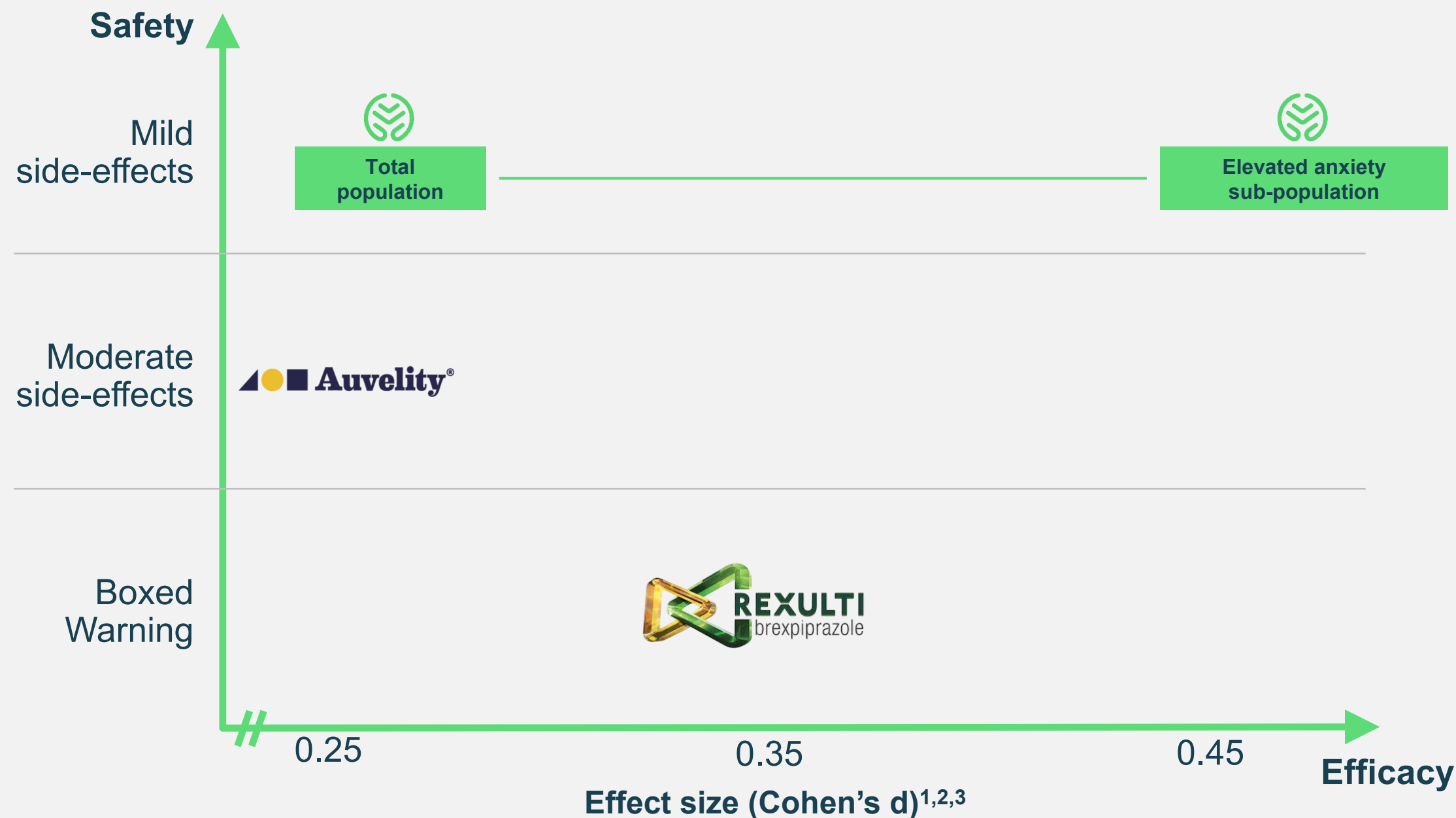
Inability to maintain independence

Standard-of-care treatment options are insufficient: The only currently approved therapy carries a boxed warning for mortality in elderly people with dementia-related psychosis.

For illustrative purposes only. NMRA-511 has not been studied in head-to-head trials against Auvelity or Rexulti, and there are differences in compounds, trial designs and other factors which must be considered. ¹Calculated from data: Addressing Dementia Via Agitation-Centered Evaluation (ADVANCE). <https://clinicaltrials.gov/study/NCT03226522?intr=AXS-05&page=1&rank=9&tab=results>. ²Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. JAMA Neurol. 2023;80(12):1307–1316. doi:10.1001/jamaneurol.2023.3810

NMRA-511 demonstrates positive signal in Phase 1b; potential to treat unmet need

Simplified market segmentation and opportunities



NMRA-511 Phase 1b key takeaways

- Well tolerated, with potential for higher dosing
- CMAI effect size similar to Auvelity in total population
- Unsurpassed CMAI effect size in patients with elevated anxiety

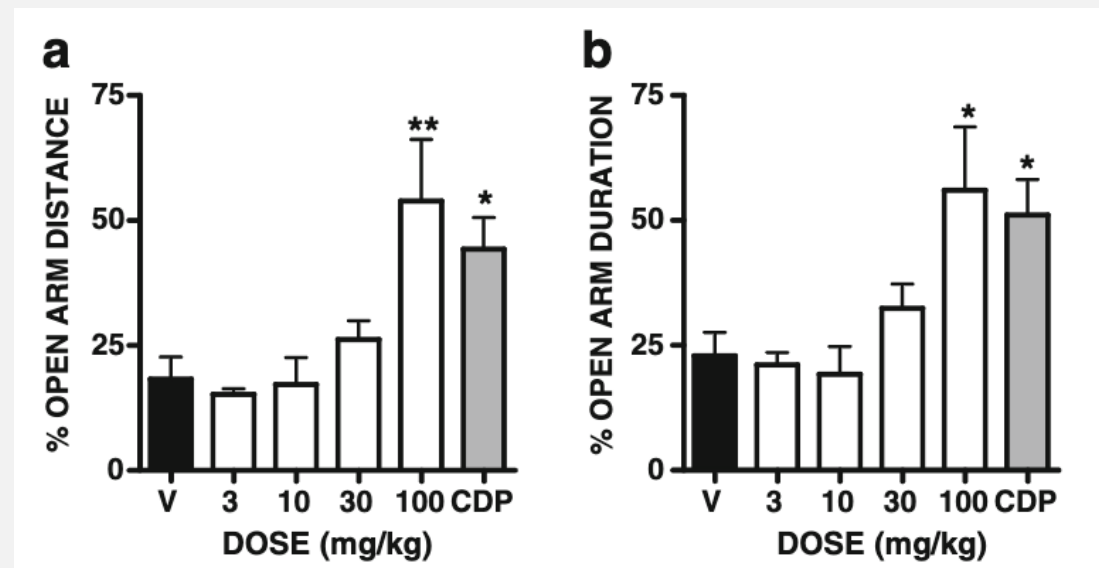
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Vasopressin/V1a receptor (V1aR) mediates anxiety-related behaviors

Robust preclinical data supports V1aR inhibition for treating anxiety in rodents

- V1a knock-out¹ or reduction by siRNA² drives reduced anxiety behaviors
- V1aR antagonists reduce anxiety and aggressive behaviors across models³
- Lines bred for aggression or anxiety show dysregulated AVP release and HPA axis functioning^{4, 5, 6, 7}

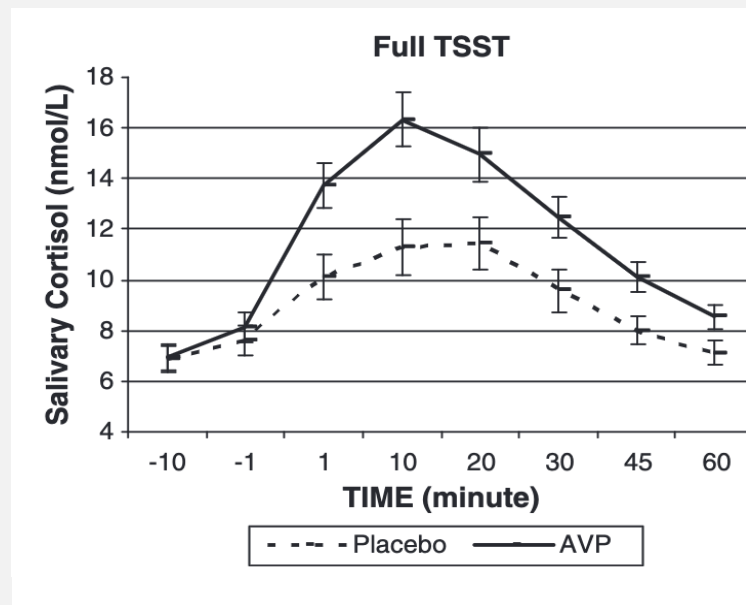
V1a receptor antagonist (JNJ-17308616) reduces anxiety behavior in rat



V1a antagonists and vasopressin modulate anxiety and stress related behaviors in humans

- Vasopressin administration exacerbates stress/anxiety behaviors in HVs^{1, 2, 3}
- V1a receptor antagonist reduced experimentally-induced anxiety in humans and attenuated aggression in Huntington's disease

AVP increases cortisol response to social stressors (TSST)¹



Psychopharmacology
<https://doi.org/10.1007/s00213-021-05861-4>

ORIGINAL INVESTIGATION

The novel vasopressin receptor (V1aR) antagonist SRX246 reduces anxiety in an experimental model in humans: a randomized proof-of-concept study

Tiffany R. Lago^{1,2,3}, Michael J. Brownstein⁴, Emily Page¹, Emily Beydler¹, Adrienne Manbeck¹, Alexis Beale¹, Camille Roberts¹, Nicholas Balderston^{1,5}, Eve Damiano⁴, Suzanne L. Pineles^{3,6}, Neal Simon^{4,7}, Monique Ernst¹, Christian Grillon¹

Journal of Personalized Medicine

Article

The Vasopressin 1a Receptor Antagonist SRX246 Reduces Aggressive Behavior in Huntington's Disease

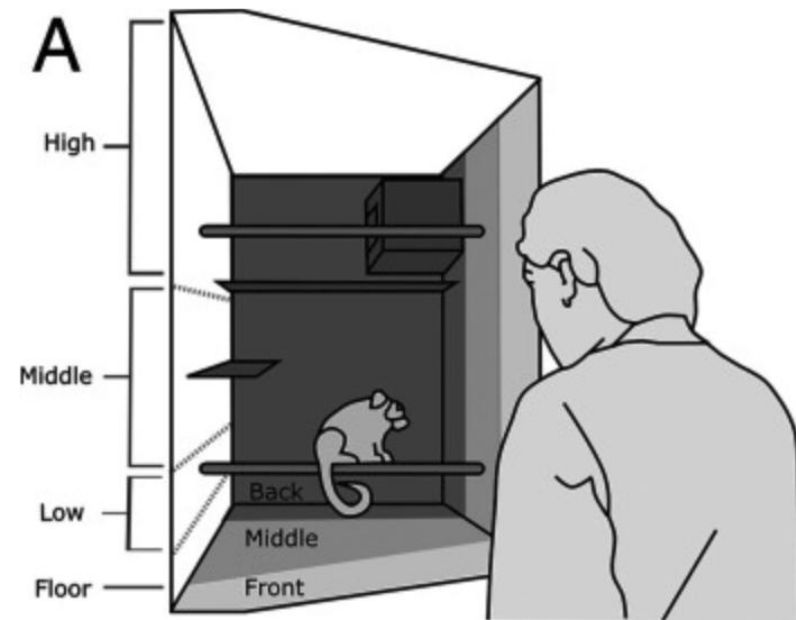
Hilda T. Maibach^{1,4}, Michael J. Brownstein^{1,4}, Steven M. Hersch^{2,3}, Karen E. Anderson⁴, Debra E. Itzkowitz¹, Eve M. Damiano¹ and Neal G. Simon^{1,5,*}

¹Bielsky et al., 2004, NPP; ²Barrett et al., 2013, *Horm. Behav.*; ³Bleickardt et al., 2009, *Psychopharmacology*; ⁴Veenema and Neumann, 2007, *Brain behavior, evolution*; ⁵Zelena et al., 2009 *J. Endo*; ⁶Mlynarik et al., 2007; ⁷Fodor et al., 2014, *Psychoneuroendocrin.*

¹Shalev et al., 2011, *Hormones and Behavior*; ²Thompson et al., 2006, *PNAS*; ³Kawada et al., 2019, *Sci. Reports*;

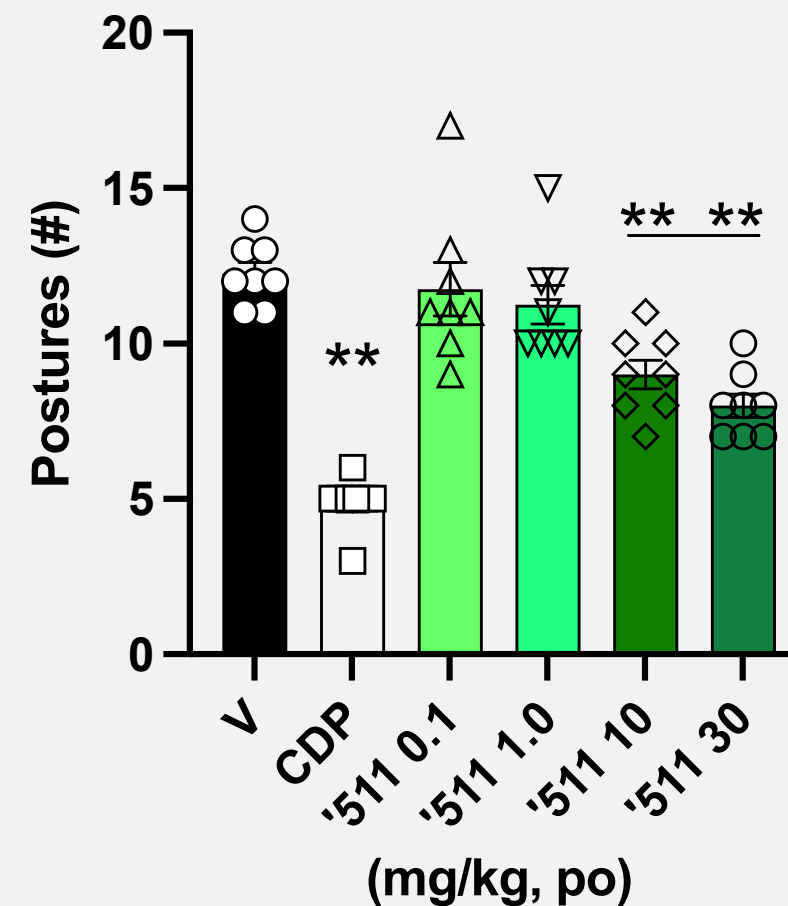
NMRA-511 reduced anxiety-related behaviors in a preclinical human threat test

Human threat test induces anxiety in marmosets¹



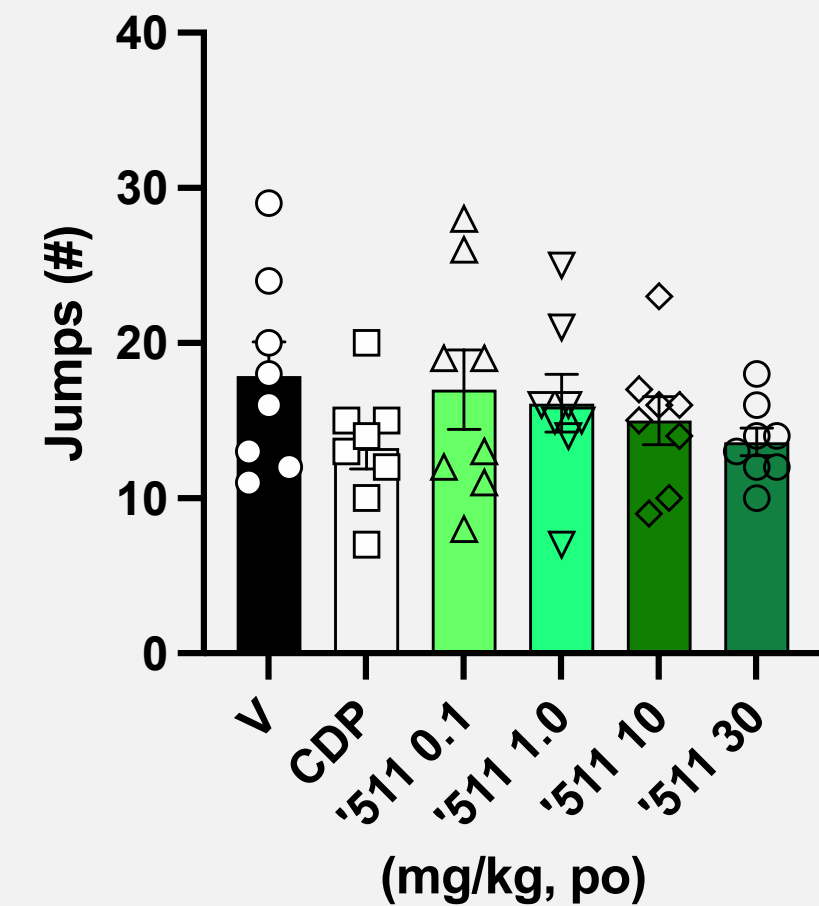
- Based on marmoset's behavioral response to situations of stress/uncertainty
- Set of characteristic postures are elicited
- Clinically effective anxiolytic drugs reduce the number of postures
- Locomotor activity is measured to control for sedative/stimulant effects of drugs

NMRA-511 reduces behavioral response to threat



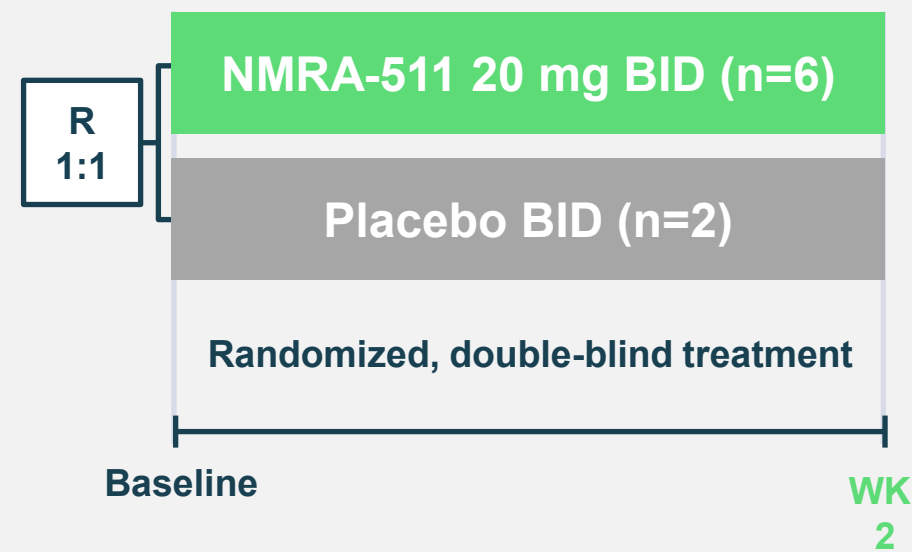
Orally administered NMRA-511 (10 and 30 mg/kg) and chlordiazepoxide (CDP, 2 mg/kg, SC) significantly reduced anxiety-related behaviors in marmosets (n=8) as measured by a decrease in the number of threat-elicited postures observed in the HTT without affecting locomotor activity or causing sedation. Testing occurred 90 mins after treatment to coincide with NMRA-511 maximal concentrations. *p<0.05 versus vehicle. Data plotted are mean± SE.

NMRA-511 does not reduce locomotor activity

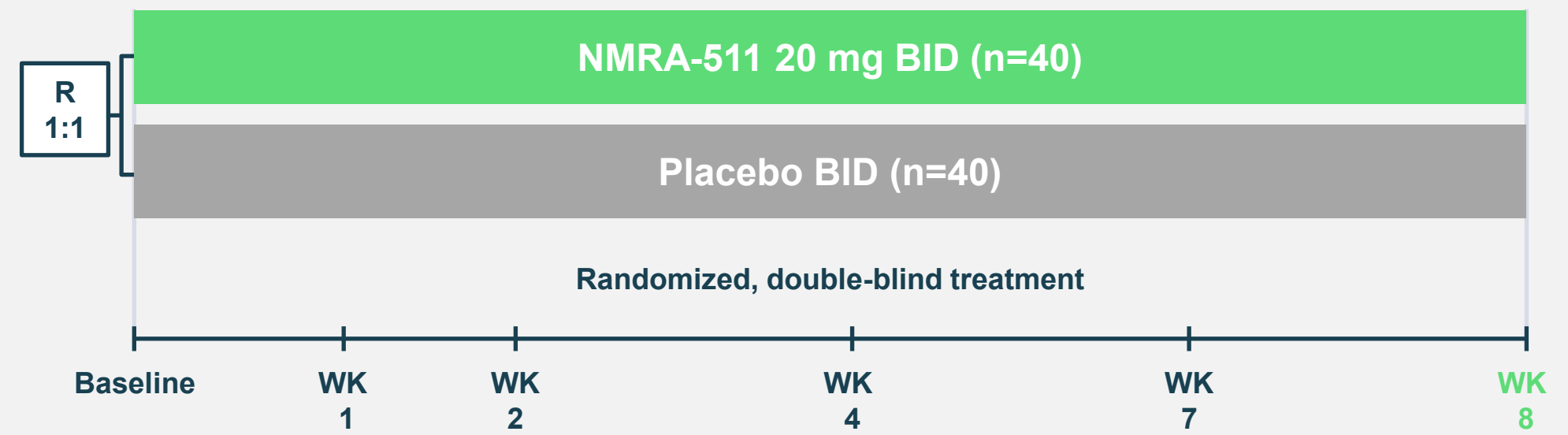


Study to evaluate the effects of NMRA-511 among healthy elderly and adults with agitation associated with dementia due to Alzheimer's disease

Part A: 2-Week Evaluation Period Enrolling Healthy Elderly Participants



Part B: 8-Week Evaluation Period Enrolling People with Alzheimer's Disease Agitation (ADA)



NMRA-511 Phase 1b Study

- Part A Inclusion Criteria:**
 - Healthy elderly adult participants aged 65-80 years
- Part B Inclusion Criteria:**
 - Adults aged 55-90 years with mild-severe dementia (MMSE score of 5-24) and clinically significant agitation (CMAI total score 45-100)
- Part B Primary Endpoint:**
 - Δ from baseline to Week 8 in CMAI total score
- Part B Other Endpoints Include*:**
 - Δ from baseline to Week 8 in:
 - CGI-S
 - NPI total score
- Prespecified Sub-Populations:**
 - Elevated anxiety (RAID)
- Statistics:**
 - **Study not powered to demonstrate statistical significance**
 - Designed as a signal-seeking study; effect size will inform the potential future development of NMRA-511 in ADA

*Safety Assessments include adverse events, clinical laboratory, vital signs, physical examination, 12-lead electrocardiogram (ECG), Columbia-Suicide Severity Rating Scale (C-SSRS). Δ = Change; BID = twice daily; CMAI = Cohen-Mansfield Agitation Inventory; MMSE = Mini-Mental State Examinations; CGI = Clinical Global Impression of Change for Agitation; NPI = Neuropsychiatric Inventory.

Demographics and baseline characteristics

	NMRA-511 n=40	Placebo n=40
Mean age	71.8	72.7
Sex, n (%)		
Male	18 (45.0%)	15 (37.5%)
Female	22 (55.0%)	25 (62.5%)
Race, n (%)		
White	27 (67.5%)	30 (75.0%)
Black	10 (25.0%)	9 (22.5%)
Asian	2 (5.0%)	0
Other	1 (2.5%)	1 (2.5%)
CMAI Total Score Mean (SD)	68.2 (14.7)	68 (14.3)
CGI-S (Agitation) Mean (SD)	4.3 (0.7)	4.2 (0.6)
NPI-AA Mean (SD)	5.1 (2.5)	5.9 (2.6)
MMSE Mean (SD)	19.0 (3.2)	19.5 (2.8)
Baseline anxiety as measured by RAID score (SD)	11.8 (6.4)	14.3 (8.6)
Protocol-Defined Medication Non-Adherence ¹	7 (17.5%)	0
Modified Analysis Set (n) ²	33	38
Pre-Specified Elevated Anxiety Population (n) ³	16	21

¹70% medication compliance required per protocol

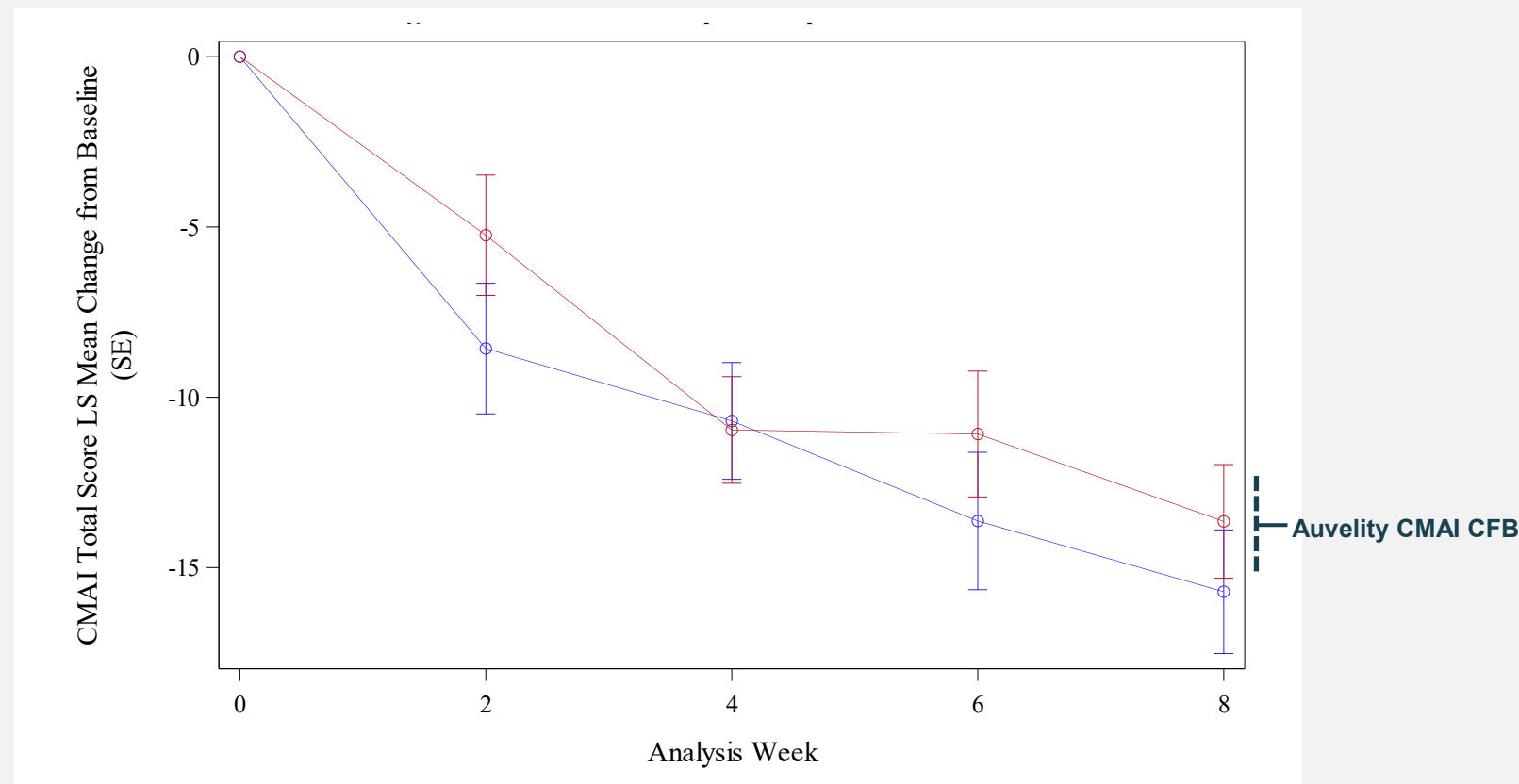
²2 placebo patients excluded based on rater change driving outlier data (>3 standard deviations from the mean)

³Defined as Rating Anxiety In Dementia (RAID) score ≥12

NMRA-511 demonstrated clinically meaningful reduction in CMAI total score and CMAI aggression sub-score

NMRA-511 demonstrated a 15.7-point reduction in CMAI total score at Week 8

CMAI Total Score Change from Baseline (Modified Analysis Set)

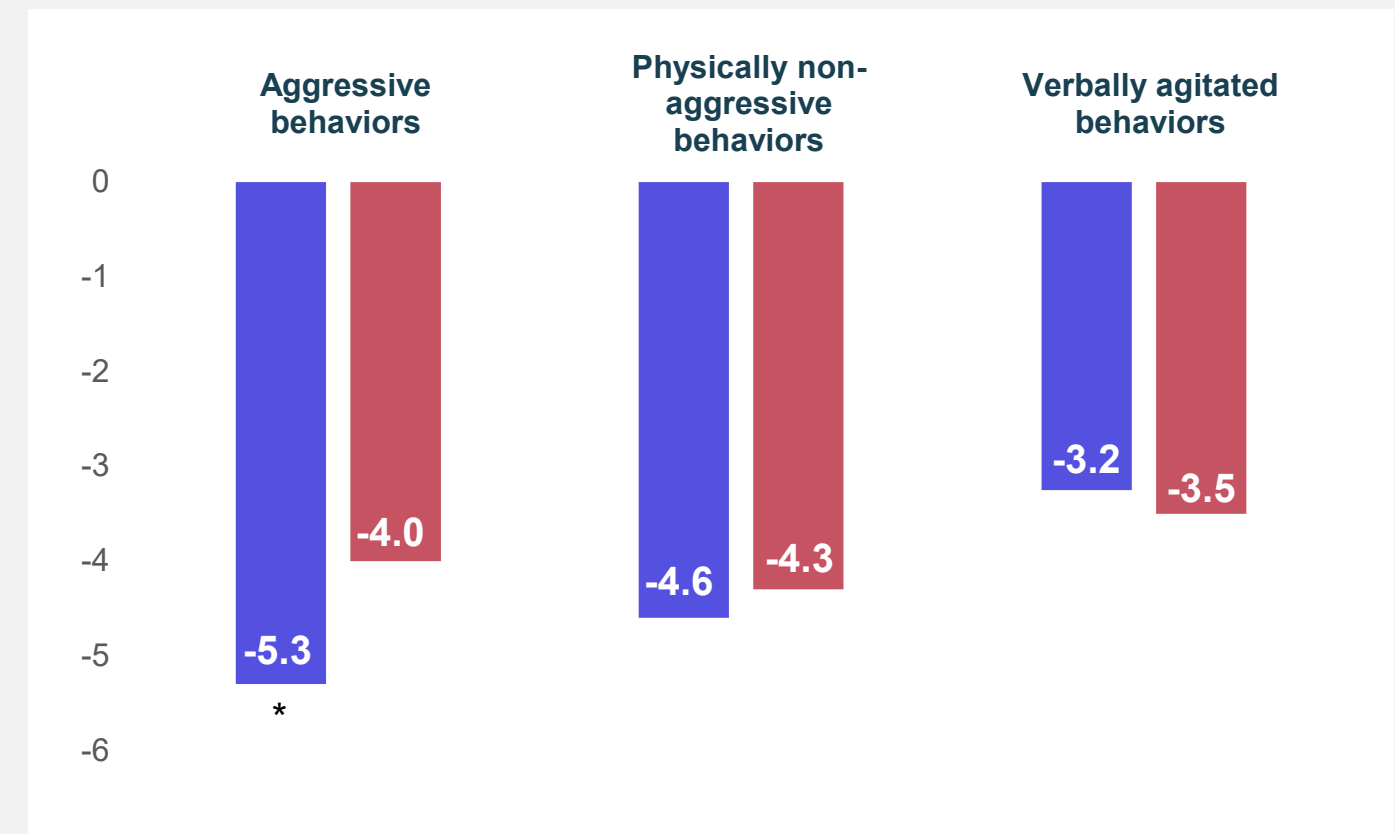


— NMRA-511 — Placebo

	Week 6	Week 8
LSMD (SE)	-2.6 (2.7)	-2.1 (2.5)
Effect size range (Cohen's d)	0.23	0.20

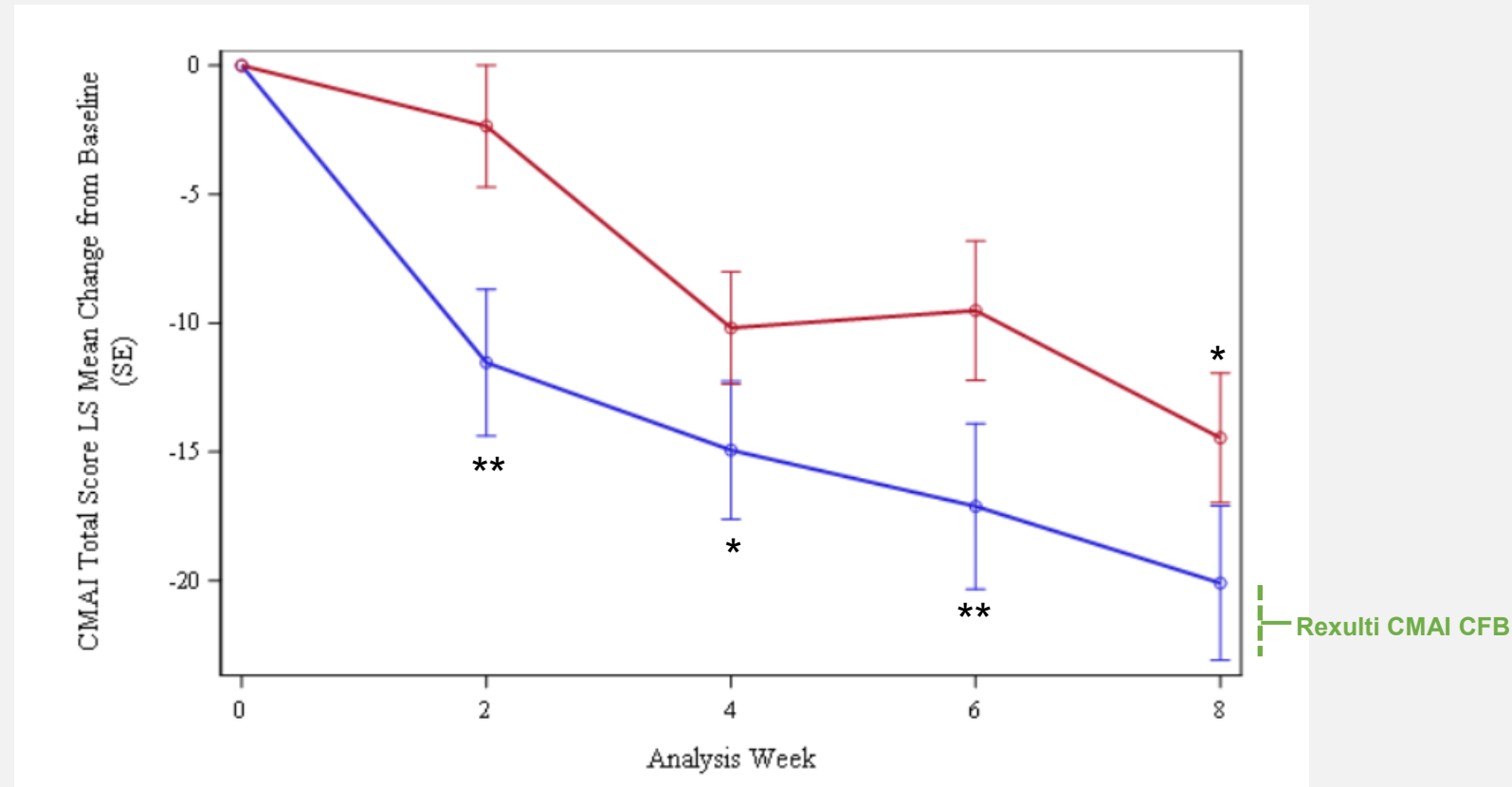
CMAI aggression sub-score results suggest improvement on clinically relevant symptoms of AD agitation

Mean Change in CMAI Sub-Scores at Week 8 (Modified Analysis Set)

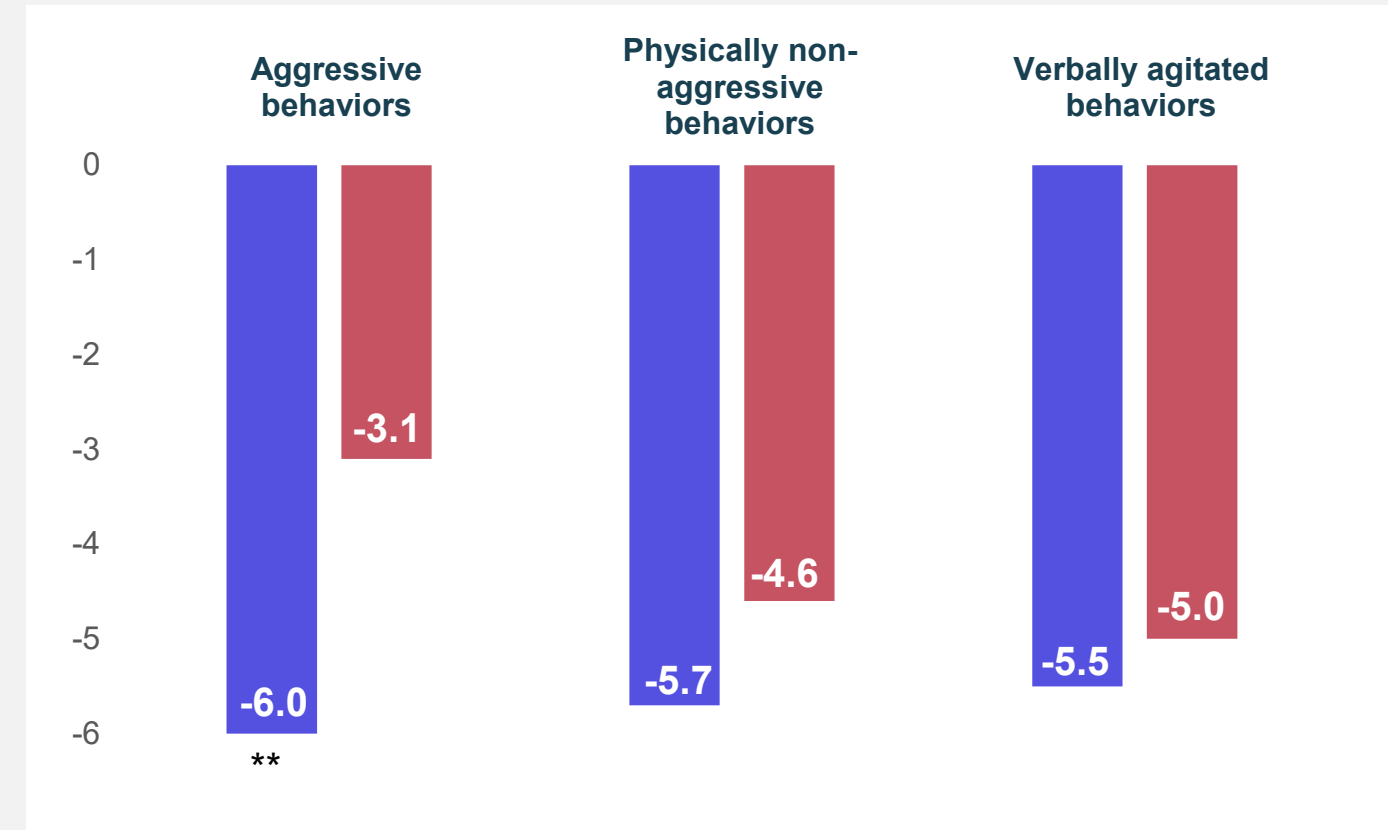


NMRA-511 demonstrated unsurpassed clinical effect size on CMAI total score in patients with elevated anxiety

CMAI Total Score Change from Baseline
(pre-specified elevated anxiety sub-population)



Mean Change in CMAI Sub-Scores at Week 8
(pre-specified elevated anxiety sub-population)



— NMRA-511 — Placebo

	Week 6	Week 8
LSMD (SE)	-7.6 (4.1)	-5.6 (3.8)
Effect size range (Cohen's d)	0.64	0.51

Favorable tolerability and safety profile demonstrated

NMRA-511 was safe and generally well tolerated

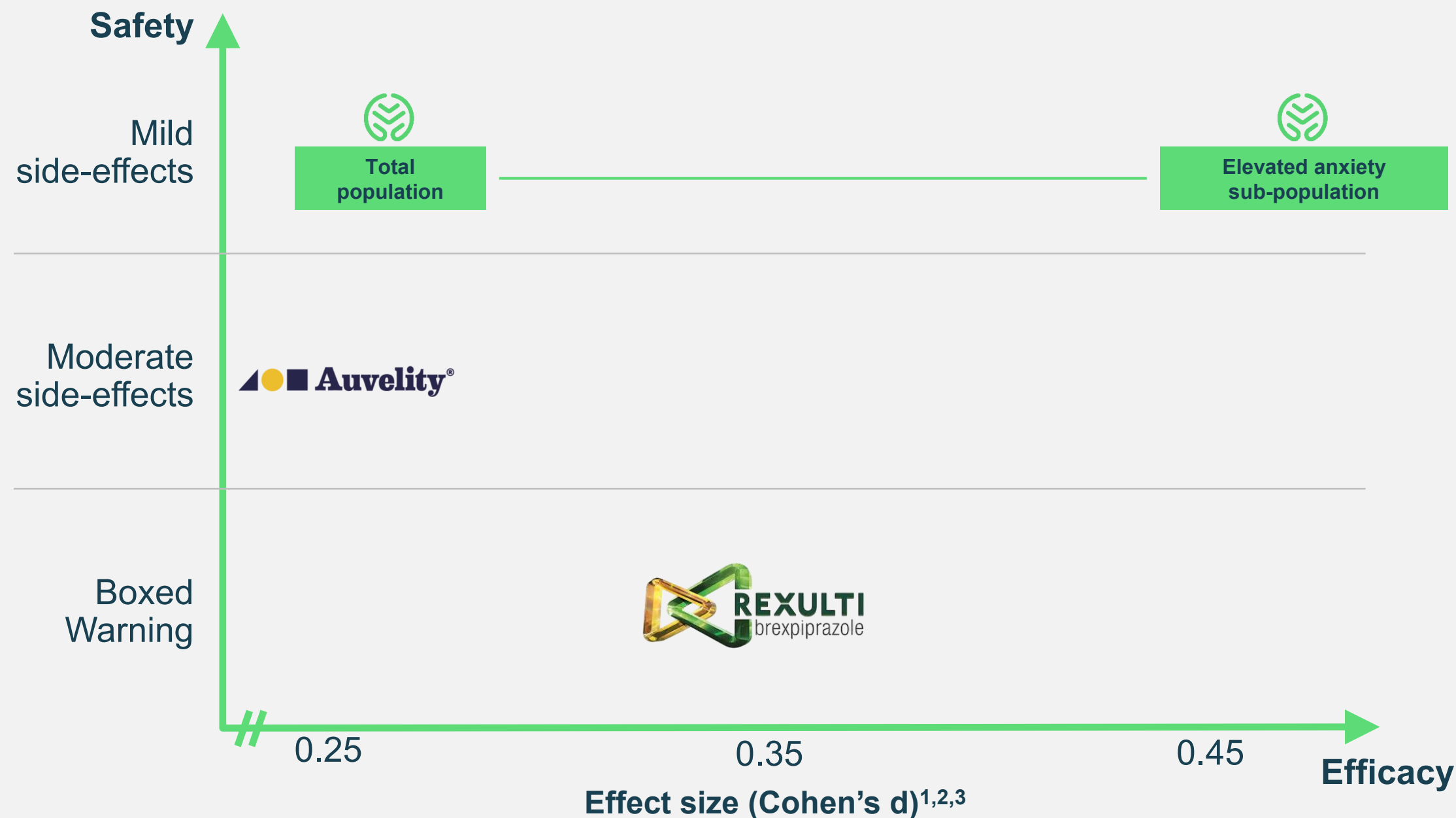
TEAEs Incidence (≥5% in either treatment group)	Placebo n=40	NMRA-511 n=40
Preferred Terms	n (%)	n (%)
Nasopharyngitis	3 (7.5%)	4 (10.0%)
Urinary tract infection	1 (2.5%)	4 (10.0%)
Anemia	1 (2.5%)	2 (5.0%)
Arthralgia	0	2 (5.0%)
Diarrhea	4 (10.0%)	2 (5.0%)
Dizziness	2 (5.0%)	2 (5.0%)
Headache	5 (12.5%)	2 (5.0%)
Hyponatremia	0	2 (5.0%)*
Myalgia	1 (2.5%)	2 (5.0%)
Nausea	1 (2.5%)	2 (5.0%)
Vomiting	1 (2.5%)	2 (5.0%)
Abdominal pain	2 (5.0%)	1 (2.5%)

- TEAEs were typically mild to moderate in severity
- Low treatment discontinuations due to TEAEs (2.5%)
- Opportunity to evaluate higher doses of NMRA-511 based on tolerability

*1 serious adverse event of hyponatremia that led to treatment discontinuation; resolved quickly following discontinuation

NMRA-511 demonstrates positive signal in Phase 1b; potential to treat unmet need

Simplified market segmentation and opportunities



NMRA-511 Phase 1b key takeaways

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Key takeaways: Study met goal to identify signal for NMRA-511

Planned next steps

1

Enable higher dosing:
initiate multiple
ascending dose
extension in 2026

2

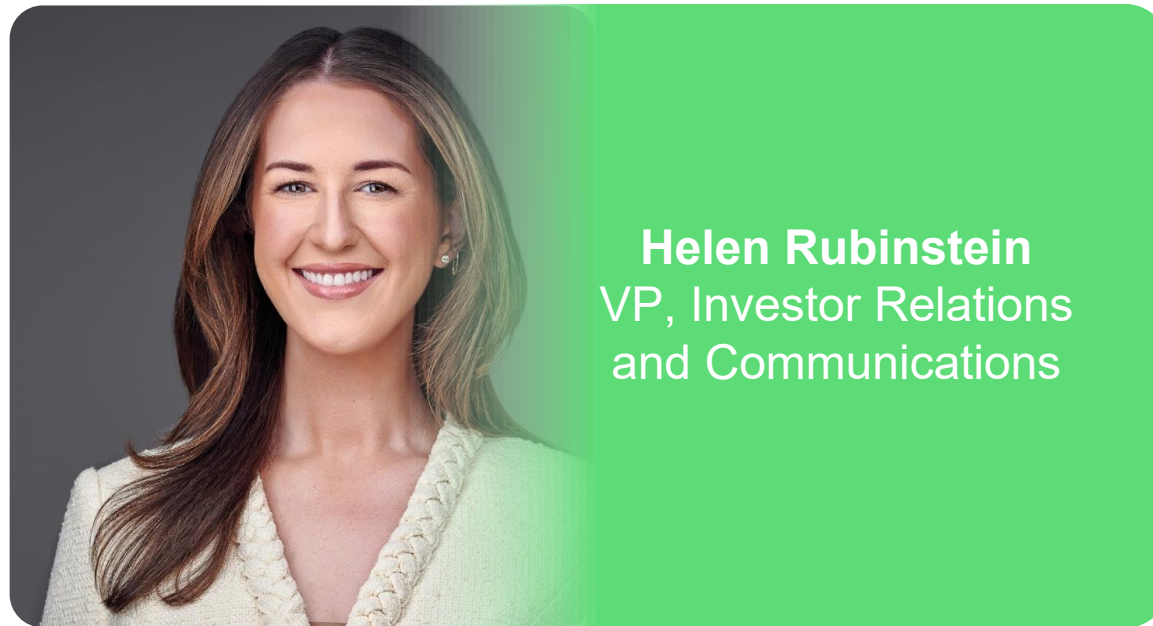
Transition BID to QD
formulation: Switch to
QD extended-release
formulation in 2026,
strengthening IP
(+4 years exclusivity)

3

Initiate Phase 2/3 dose
ranging study



HOSTED BY



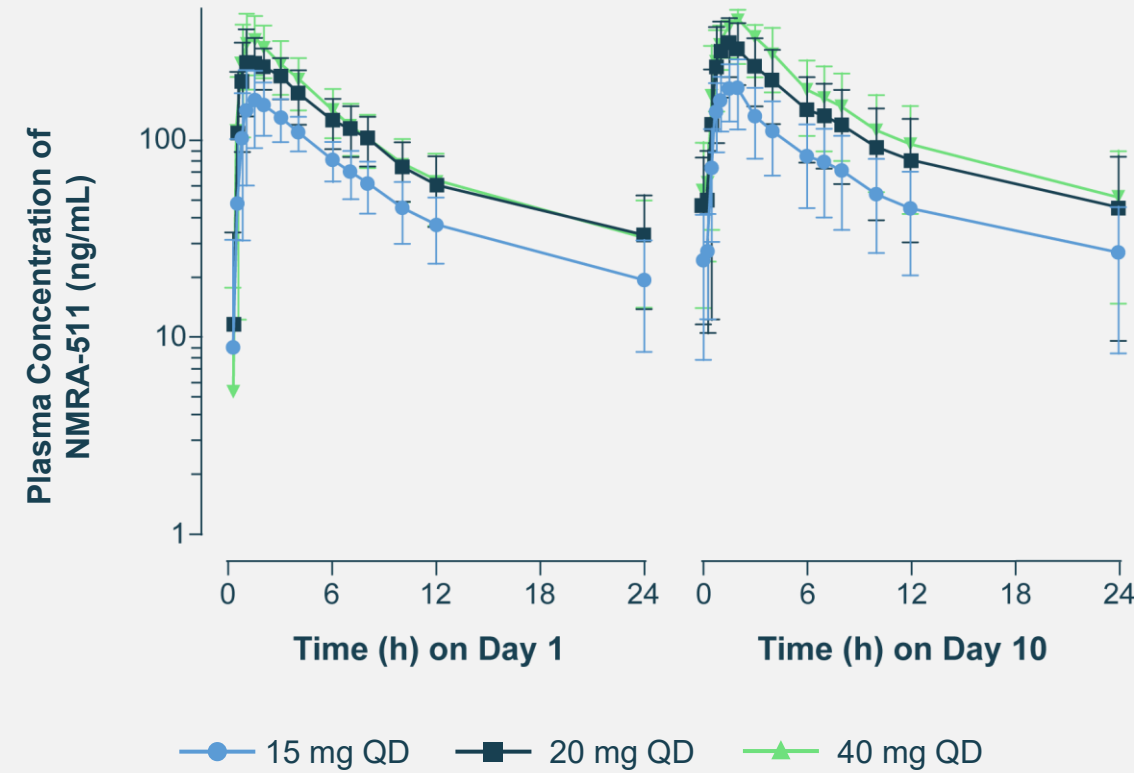
Appendix



NMRA-511 was safe and well-tolerated in healthy adults and healthy elderly participants

Phase 1 PK profile

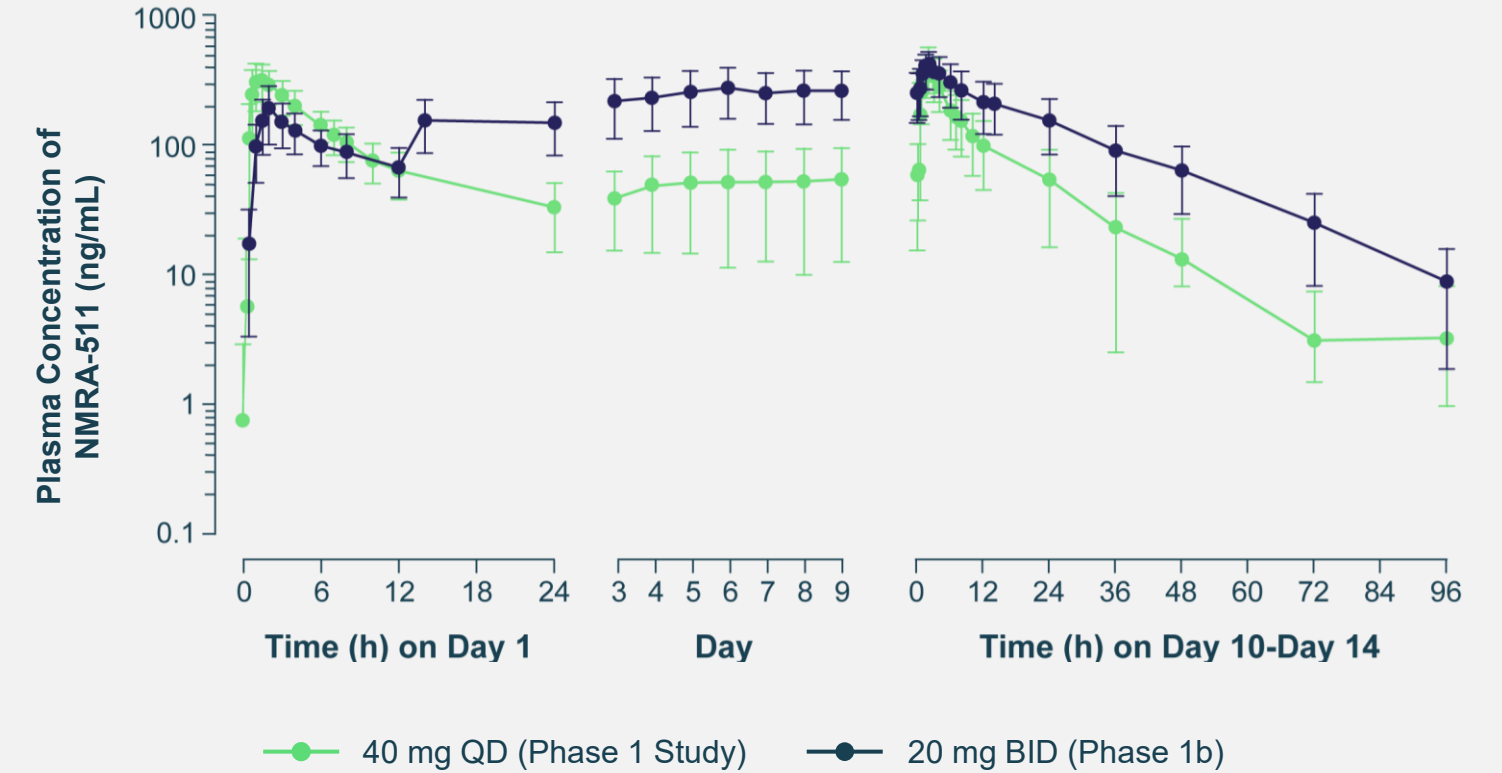
Healthy Adults



20 mg BID projected to achieve 97.7% to 99.3% receptor occupancy from trough to C_{max}

Dose selected for Phase 1b to maximize receptor occupancy over 24 hours

40 mg QD in healthy adults compared to 20 mg BID in healthy elderly participants



No SAEs, or discontinuation due to treatment-related AEs was observed



NMRA-511 was safe and well-tolerated

BID = twice-daily; QD = once-daily



Rexulti CMAI sub-scale data

Agitated behaviors as defined by CMAI⁴

The Cohen-Mansfield Agitation Inventory (CMAI) is a clinically validated scale measuring the frequency of 29 agitated behaviors.

- Grouped into 3 subscales
- Scored by clinicians based on caregiver input



VERBALLY AGITATED

- Complaining
- Constant unwarranted request for attention or help
- Repetitive sentences or questions
- Negativism



PHYSICALLY NON-AGGRESSIVE

- Pacing, aimless wandering
- General restlessness
- Inappropriate dress or disrobing
- Trying to get to a different place
- Handling things inappropriately
- Performing repetitive mannerisms



AGGRESSIVE

- Screaming
- Biting
- Hitting
- Kicking
- Hurting self or others
- Cursing or verbal aggression
- Pushing
- Scratching
- Throwing things
- Spitting
- Tearing things/destroying property
- Grabbing onto people

Additional behaviors assessed by CMAI total score that often have low rates of occurrence include making physical sexual advances, intentional falling, eating/drinking inappropriate substances, hiding things, hoarding things, making verbal sexual advances, and strange noises (weird laughter or crying).^{4,5}

