



Redefining Neuroscience Drug Development

August 2026



Important Disclosures

This presentation contains forward-looking statements about Neumora Therapeutics, Inc. (the “Company,” “we,” “us,” or “our”) within the meaning of the federal securities laws, including statements related to: Neumora’s intention to redefine neuroscience drug development by bringing forward the next generation of novel therapies that offer improved treatment outcomes and quality of life for patients; the timing, progress and plans for its therapeutic development programs, including the timing of clinical trial initiation and data readouts, including for the NMRA-215, NMRA-511 and NMRA-898 studies; support for continued development, and upcoming milestones and catalysts; expectations and projections regarding future operating results and financial performance, including the sufficiency of its cash resources and expectation of the timing of its cash runway; and other statements identified by words such as “could,” “expects,” “intends,” “may,” “plans,” “potential,” “should,” “will,” “would,” or similar expressions and the negatives of those terms. Other than statements of historical facts, all statements contained in this presentation are forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995. These statements are subject to risks and uncertainties that could cause the actual results to be materially different from the information expressed or implied by these forward-looking statements, including, among others: receipt and review of the histopathology report for the three-month toxicity study for NMRA-215, comparisons to efficacy results from other sponsors should be interpreted with caution due to differences in compounds, study designs, subject characteristics, and other factors that may limit direct comparability; the risks related to the inherent uncertainty of clinical drug development and unpredictability and lengthy process for obtaining regulatory approvals; risks related to the timely initiation and enrollment in our clinical trials; risks related to our reliance on third parties, including CROs; risks related to serious or undesirable side effects of our therapeutic candidates; risks related to our ability to utilize and protect our intellectual property rights; and other matters that could affect sufficiency of capital resources to fund operations. For a detailed discussion of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Neumora’s business in general, please refer to the risk factors identified in the Company’s filings with the Securities and Exchange Commission (SEC), including but not limited to its Quarterly Report on Form 10-Q for the quarter ended June 30, 2026 which was filed with the SEC on or about August 14, 2026. Forward-looking statements speak only as of the date hereof, and, except as required by law, Neumora undertakes no obligation to update or revise these forward-looking statements. Our results for the quarter ended June 30, 2026 are also not necessarily indicative of our operating results for any future periods.





Our Mission

We are focused on bringing forward the next generation of novel therapies with brain-penetrant chemistry that offer improved treatment outcomes and quality of life for patients



Led by experienced company builders and leading neuroscience drug developers

Leadership



Paul L. Berns
Co-Founder, Chief Executive Officer
& Chairman of Board of Directors





Jason Duncan
Chief Legal & Administrative Officer





Doron Sagman, MD, FRCPC
Chief Medical Officer





Joshua Pinto, Ph.D.
President





Nick Brandon, Ph.D.
Chief Scientific Officer





Michael Milligan
Chief Financial Officer





Bill Aurora, Pharm.D.
Chief Operating & Development Officer





Amy Sullivan
Chief Human Resources Officer





Pablo Gersberg
Chief Information Officer



Board of Directors

Paul L. Berns
Co-Founder, Chief Executive Officer, Chairman

Kristina Burow
Managing Director, ARCH Venture Partners

Matthew K. Fust
Biotechnology Advisor

Alaa Halawa
Executive Director, Mubadala Capital

Maykin Ho, Ph.D.
Retired Partner, Goldman Sachs

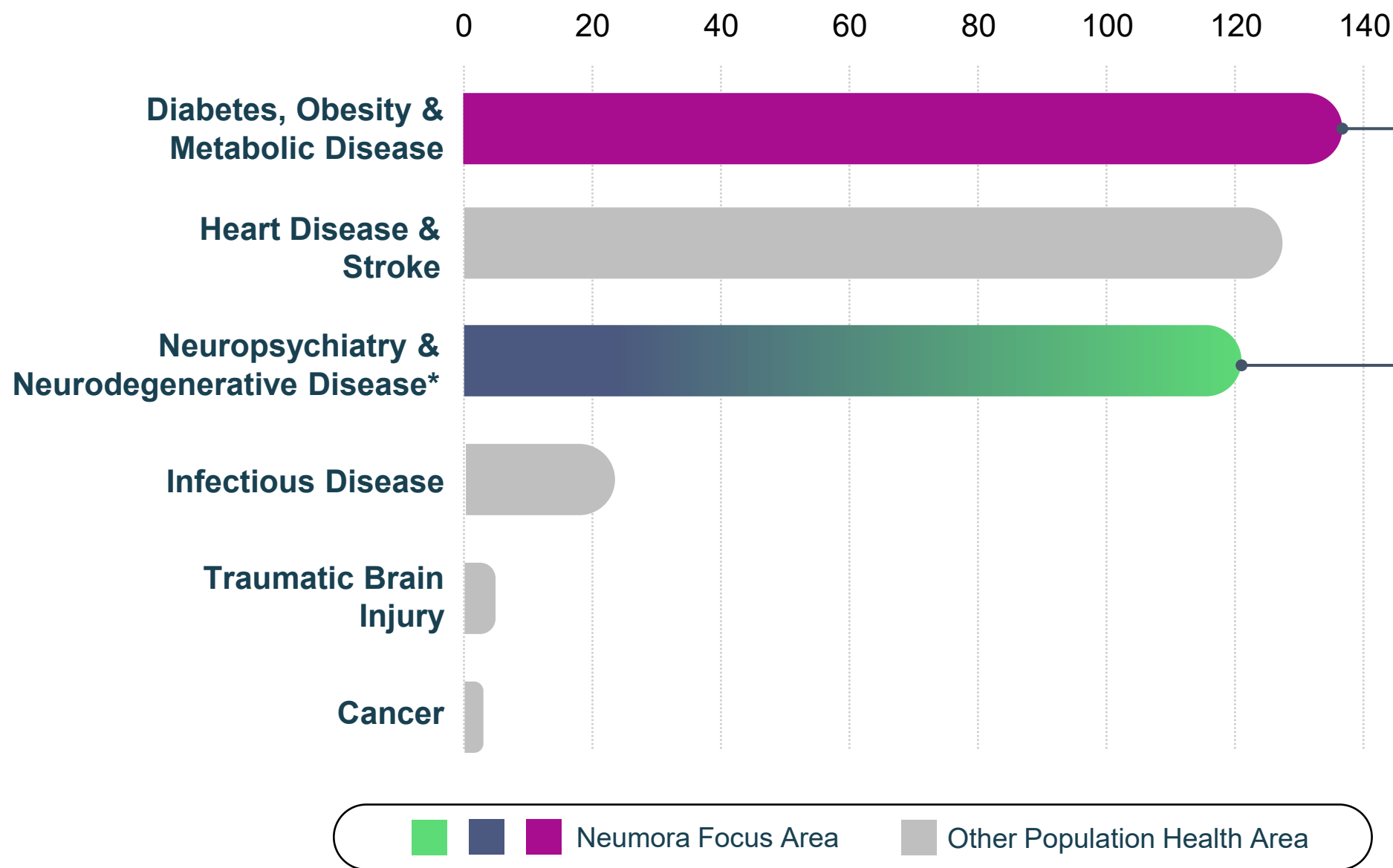
David Piacquad
Biotechnology Advisor



Goal to address unmet needs across large markets

Biggest Health Disorders Facing U.S.¹

Patients Impacted (M)



Goal To Address Unmet Needs

Cardiometabolic Disease

- Expanded oral treatment options
- Improved tolerability profile
- Novel mechanisms with potential for CV risk reduction, higher quality weight loss and maintenance

Neurodegenerative Disease

- Novel mechanisms with favorable benefit/risk profiles
- Oral treatments that reduce caregiver burden
- Improved tolerability and safety, particularly in elderly and high-risk populations

Neuropsychiatric Disease

- Effective treatments with favorable tolerability profiles
- Novel mechanisms with the potential to treat multiple elements of disease



¹Source: National Institutes of Health (NIH), “Our Biggest Health Challenges,” last reviewed January 21, 2025; CDC/NCHS, NHANES 2021–2023; The Lancet Diabetes & Endocrinology Commission, 2025; NIMH, 2025.

*Includes: major depressive disorder, bipolar depression, schizophrenia, generalized anxiety disorder, post traumatic stress disorder, substance use disorder, Alzheimer's disease, Parkinson's disease, attention-deficit hyperactivity disorder

Advancing three franchises, each anchored by a potential best-in-class program

PROGRAM <i>Target/Mechanism</i>	INDICATION <i>U.S. Prevalence</i>	Preclinical	Phase 1	Phase 2	Phase 3	EXPECTED CATALYSTS
CARDIOMETABOLIC DISEASE						
NMRA-215 <i>NLRP3 Inhibitor</i>	Obesity / Cardiometabolic Disease 103M					• Submit IND (4Q 2026) • Initiate Phase 1 study (year end 2026)
Undisclosed	Obesity / Cardiometabolic Disease 103M					
NEURODEGENERATIVE DISEASE						
NMRA-511 <i>V1aR Antagonist</i>	Agitation in Alzheimer's Disease 7M					• Report MAD extension data (4Q 2026) • Initiate Phase 2 study (year end 2026)
NMRA-GCASE <i>GCase Activator</i>	Parkinson's Disease 1M					
NEUROPSYCHIATRIC DISEASE						
NMRA-898 <i>M4 Modulator</i>	Schizophrenia 3M					• Report Phase 1 data (2H 2026)



NMRA-215: differentiated NLRP3 inhibitor for obesity and cardiometabolic diseases

NMRA-215 Target Profile

Rationale/Pharmacology

NLRP3-related inflammatory response via release of IL-1 β , IL-18 and IL-6 cytokines is associated with obesity^{1,2} and cardiovascular risk^{3,4,5}

Indication

Obesity, Cardiometabolic Disease

Target Administration

Oral, once-daily

IP

Composition of matter patent extending to 2043+*

Epidemiology

~1.13 billion patients in the world with obesity by 2030³

Multiple factors drive NLRP3-mediated inflammation resulting in disease

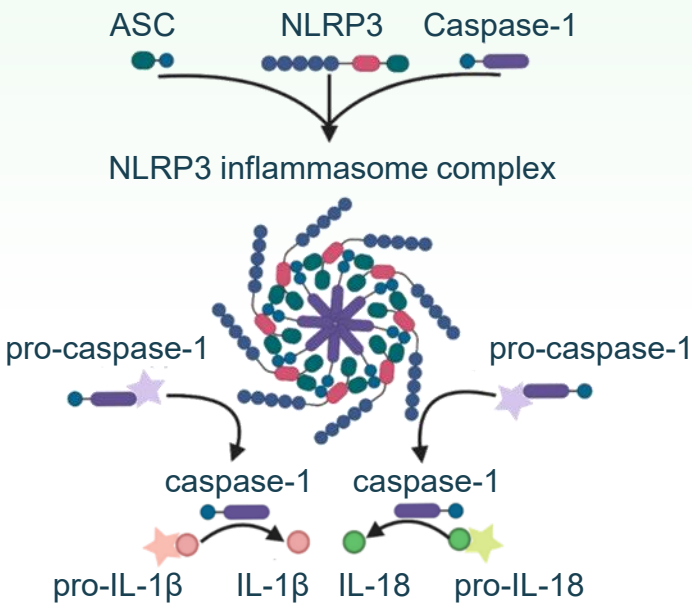


DRIVERS



- Diet (e.g., lipids)
- Environment
- Genetics
- Aging

NLRP3 Activation



DISEASES



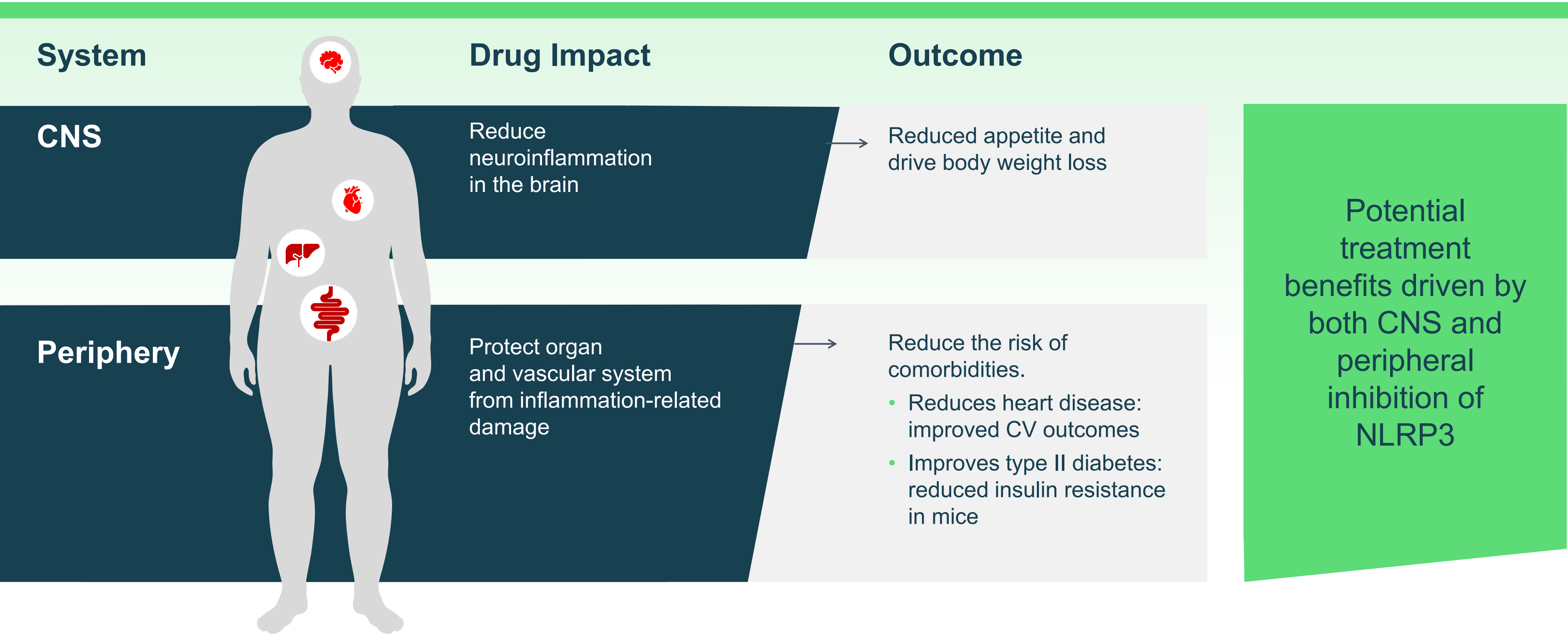
- Neurodegeneration (Parkinson's)
- Cardio-metabolic (obesity)
- Monogenic / autoimmune (CAPS)

*Excluding any patent term adjustment or extension

1. O'Brian et al. *J Neuroinflammation*. 2020;17(1):104. 2. Wani K et al. *Int J Environ Res Public Health*. 2021;18(2):511. 3. World Obesity Federation. World Obesity Atlas 2024. London: World Obesity Federation, 2024. <https://data.worldobesity.org/publications/?cat=22>. 3. Ridker PM. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. *Circ Res*. 2016 Jan 8;118(1):145-56. doi: 10.1161/CIRCRESAHA.115.306656. PMID: 26837745; PMCID: PMC4793711. 4. Ridker PM, Moorthy MV, Cook NR, Rifai N, Lee IM, Buring JE. Inflammation, cholesterol, lipoprotein(a), and 30-year cardiovascular outcomes in women. *N Engl J Med*. 2024;391(22):2087-2097. doi:10.1056/NEJMoa2405182. 5. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377(6):523-533. doi:10.1056/NEJMoa1706450.

Figure: AdipoGen Life Sciences. <https://adipogen.com/inflammasomes/rce>

CNS penetrant NLRP3 inhibition provides broad benefit



NMRA-215 has an optimized pharmacological profile including CNS exposure

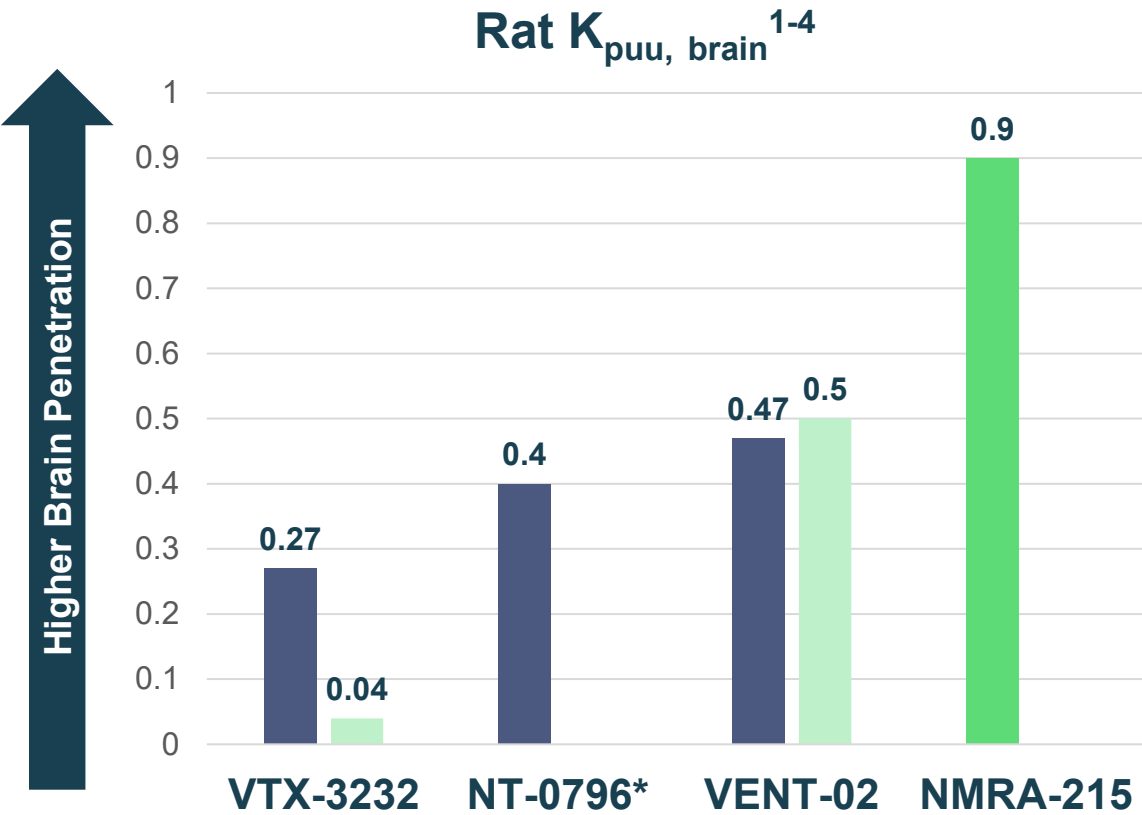
NMRA-215 is highly potent with low nM potency across a range of assays

NMRA-215 Assay Format	IC ₅₀
THP-1 (IL-1β)	3 nM
Target engagement (Nanobret)	5 nM
iMicroglia (IL-1β)	8 nM
Human whole blood (IL-1β)	16 nM

NMRA-215 is highly selective for NLRP3

- NMRA-215 is highly selective for NLRP3 versus other inflammasomes (NLRP1, NLRC4, AIM2)
- >250-fold selective for NLRP3 versus a broad panel of targets (Eurofins SafetyScreen87)
- Clean profile in cardiac ion channel and kinase screening panels

NMRA-215 is extensively characterized and optimized for brain exposure



MDCK permeability:	4.7	15	34	14.0
P-gp efflux ratio:	5.7	0.5	0.7	1.1

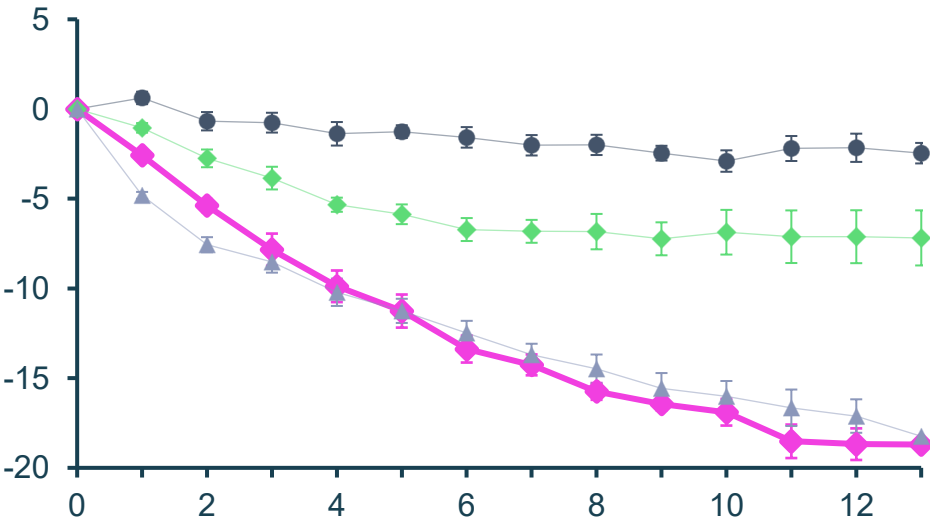
= characterized by Neumora = sponsor reported

*NT0796 = mouse K_{puu}
¹Neumora data on file. ²Thornton P, et al. *JPET*. 2024 Feb 15;388(3):813-826. ³Ventus Data Presented at 5th Annual Inflammasome Summit. November 28 – 30, 2023. Boston, MA. ⁴Ventyx R&D Day Presentation. Published Jan 2023, rat $K_{puu, CSF}$.
MDCK permeability, P-gp efflux ratio and K_{puu} brain data generated by Neumora. NT-0796 K_{puu} brain could not be evaluated without humanized CES1 mice.

DIO data supports utility of NMRA-215 across multiple treatment paradigms

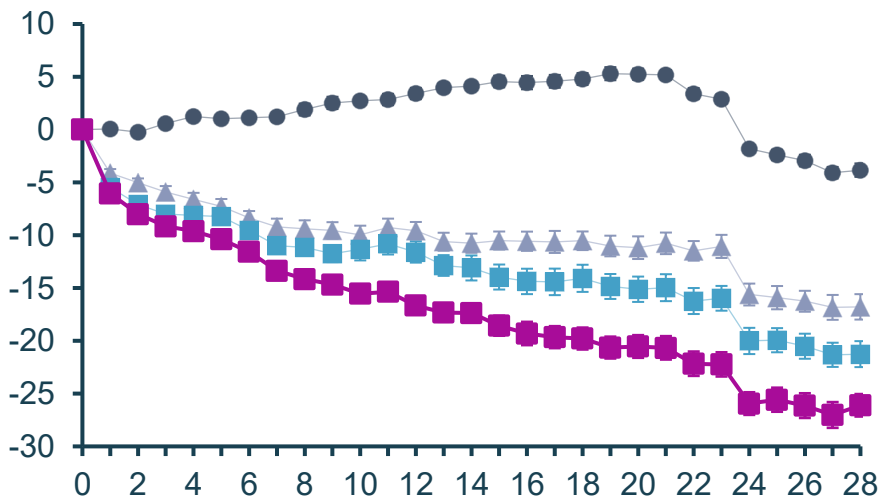
Monotherapy

- Up to 19% weight loss with incretin-like induction
- Reduced food intake equivalent to semaglutide



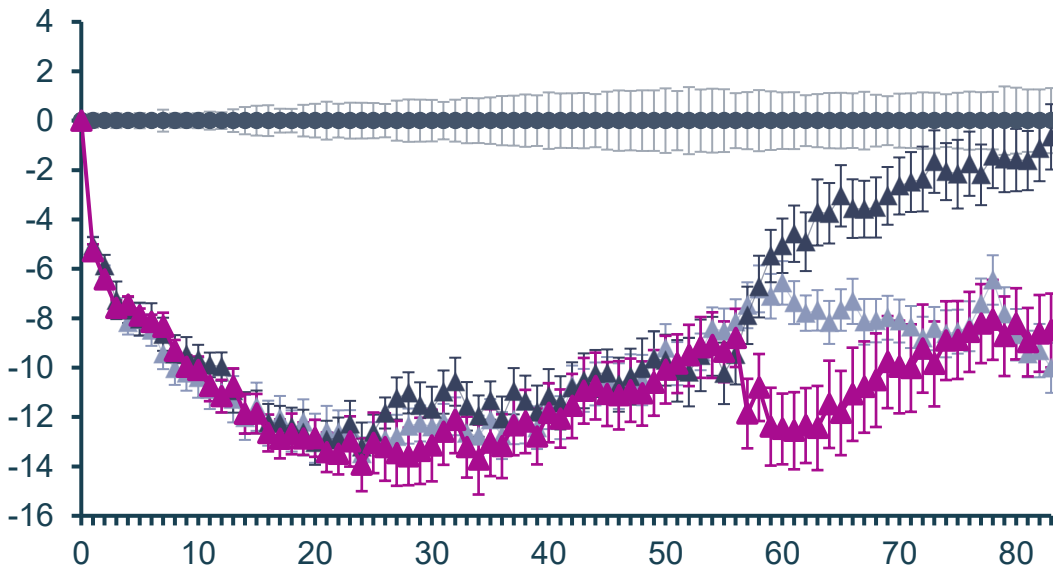
Combination Therapy

- Up to 26% weight loss when combined with therapeutically active dose of semaglutide
- Potential for incretin-sparing combination with better tolerability



Mechanism of Action Switch

- Sustained weight loss following switch from semaglutide to NMRA-215



Improvements across key biomarkers in all settings

Matched semaglutide weight loss, while preserving lean mass

Improved metabolic biomarkers relative to semaglutide

Improved liver health, cardiometabolic profile and insulin sensitivity

● Vehicle

◆ NMRA-215 Mid Dose

■ Combination with NMRA-215 Mid Dose

▲ semaglutide → Vehicle

▲ semaglutide

◆ NMRA-215 Target Dose

■ Combination with NMRA-215 Target Dose

▲ semaglutide → NMRA-215 Target Dose



Class-leading weight loss demonstrated with NMRA-215

		 Neumora®			BIOAGE	
		NMRA-215	VTX3232	VENT-02	BGE-102	NT-0796
NMRA-215 monotherapy demonstrates class-leading weight loss	NLRP3i (end of study)	15%–19%	2%	11%	6 %	17%
	semaglutide (end of study)	17%–19%	12%	21%^	5%	21%
NMRA-215 monotherapy matches semaglutide induction	NLRP3i (Day 7)	9% / 14% (Study 2) (Study 3)	3%	8%	6%	7%
	semaglutide (Day 7)	9% / 14% (Study 2) (Study 3)	9%	15%^	11%	11%
Combination demonstrates additive effects of NMRA-215	NLRP3i + semaglutide (Day 28)	26%	19%	29%^	21%	24%#

Studies in humanized transgenic obese mice are not directly comparable to other DIO studies



[^]Ventus semaglutide dose = 10 nmol/kg. [#]Nodthera combination study semaglutide dose = 5 µg/kg. Other market participant data obtained through company, scientific and Wall Street research publications
Note: Data on this slide presented for illustrative purposes only. These molecules have not been studied in head-to-head clinical trials and there are differences in compounds, trial design and other factors, which must be considered.

Totality of NMRA-215 non-clinical data support advancing to clinical studies

Study		Study Outcome	Study Supportive of Further Development
DOGS	GLP 28-Day <i>Dog Toxicity Study</i>	✓	✓
	GLP 3-Month <i>Dog Toxicity Study</i>	✓	✓
RATS	GLP 28-Day <i>Rat Toxicity Study</i>	✓	✓
	GLP 3-Month <i>Rat Toxicity Study 1</i>	Unexpected adverse findings	For-cause audit revealed various discrepancies resulting in a number of critical audit observations
	GLP 3-Month <i>Rat Toxicity Study 2*</i>	✓	✓

✓ = study supportive of progressing to human development
*study in reporting phase

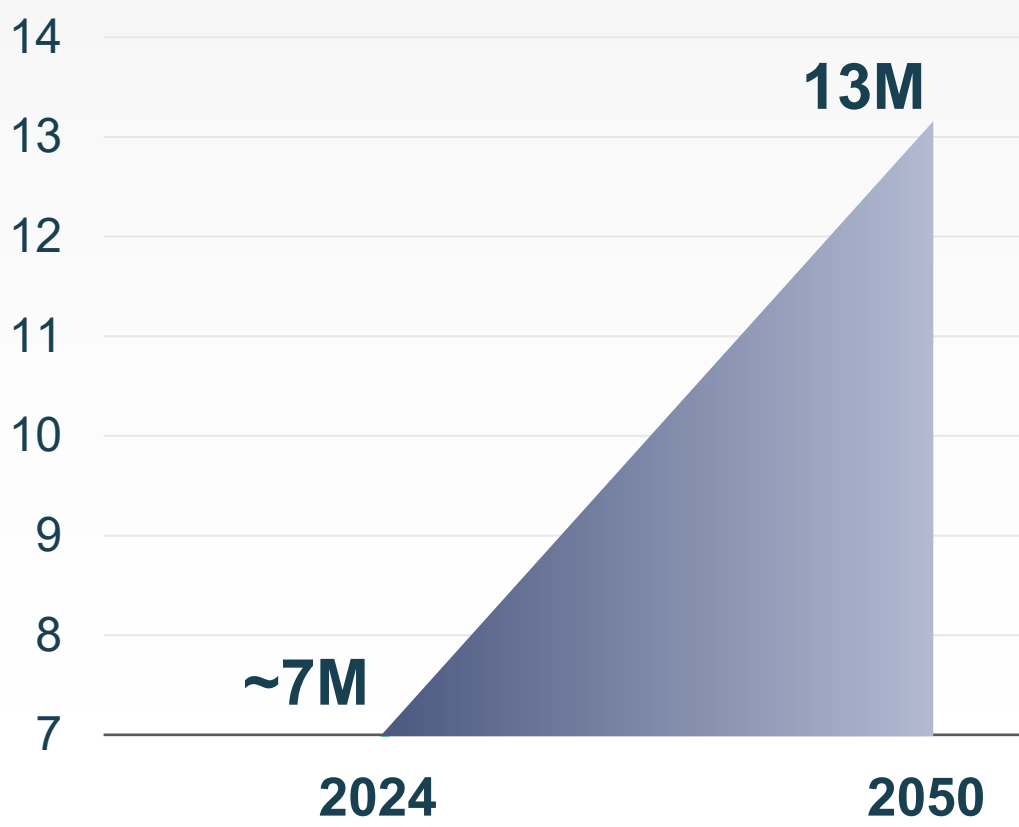


Alzheimer's disease agitation represents large market opportunity with significant unmet need

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

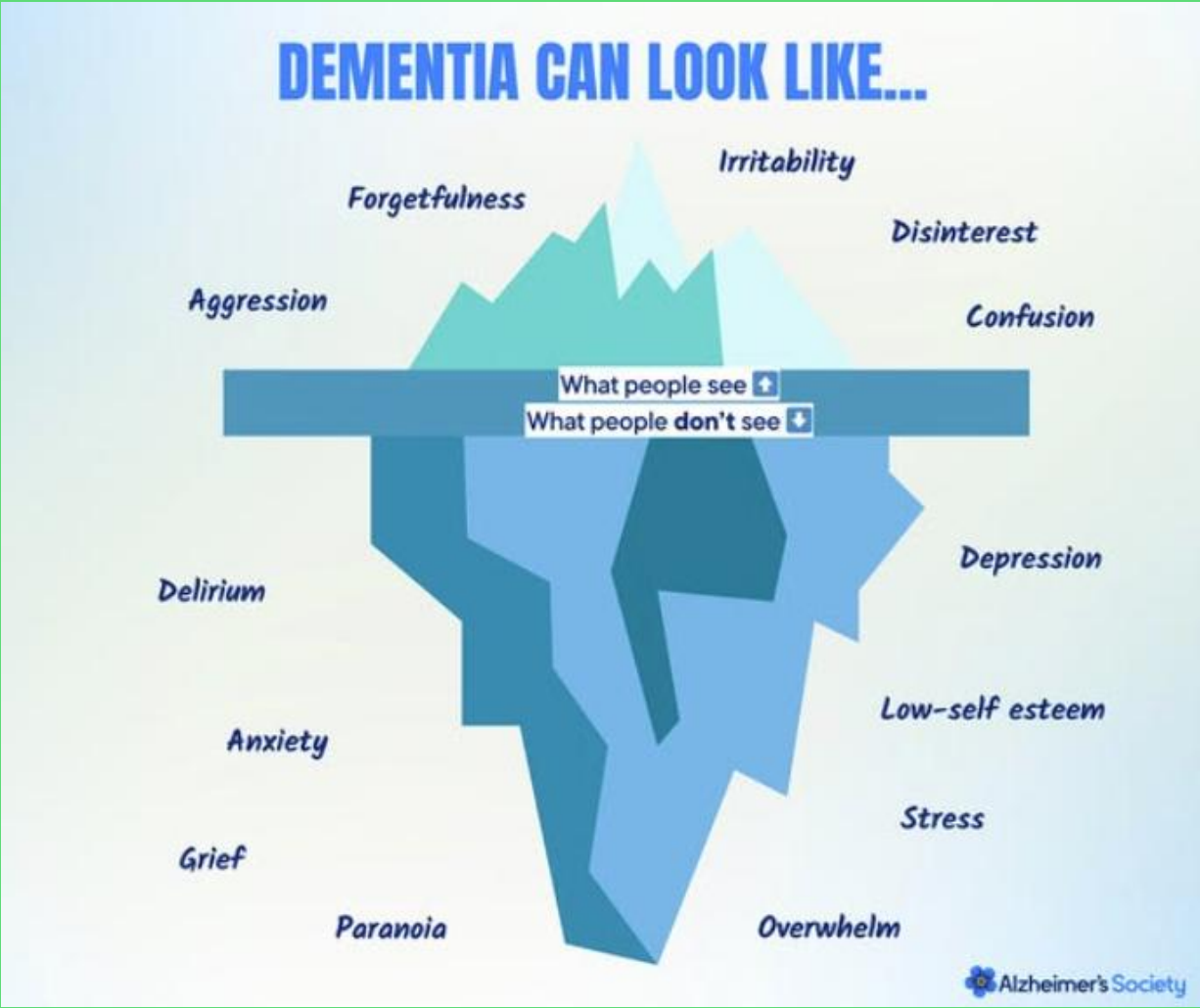
Millions currently living with AD; prevalence expected to increase as the population ages¹

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 Mussele S, et al. Aging Ment Health 2015;19(3):247-257. ³Image from Alzheimer's Society

NMRA-511 has potential as a treatment for AD agitation

Simplified market segmentation and opportunities



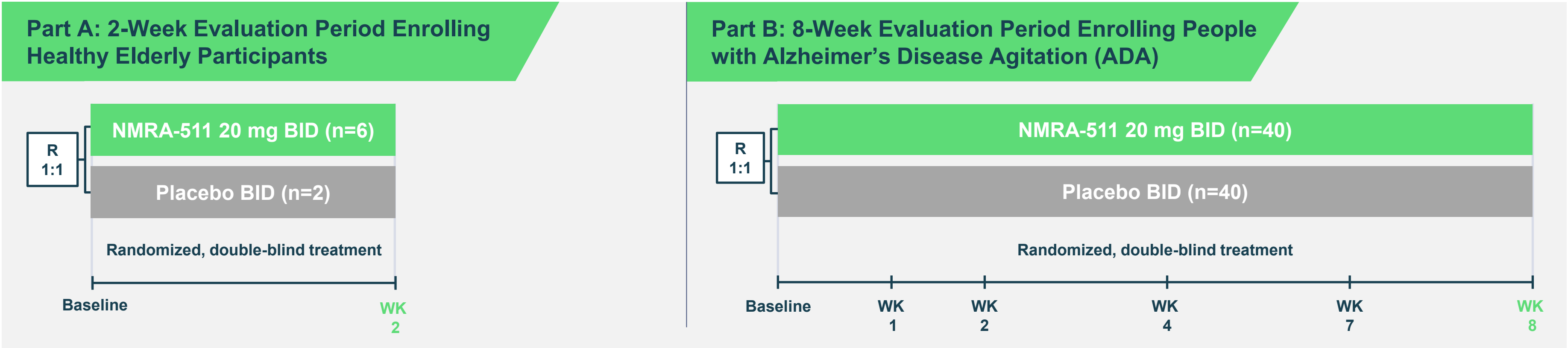
NMRA-511 Phase 1b key takeaways

- 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

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. ³NMRA data on file. CMAI = Cohen-Mansfield Agitation Inventory.

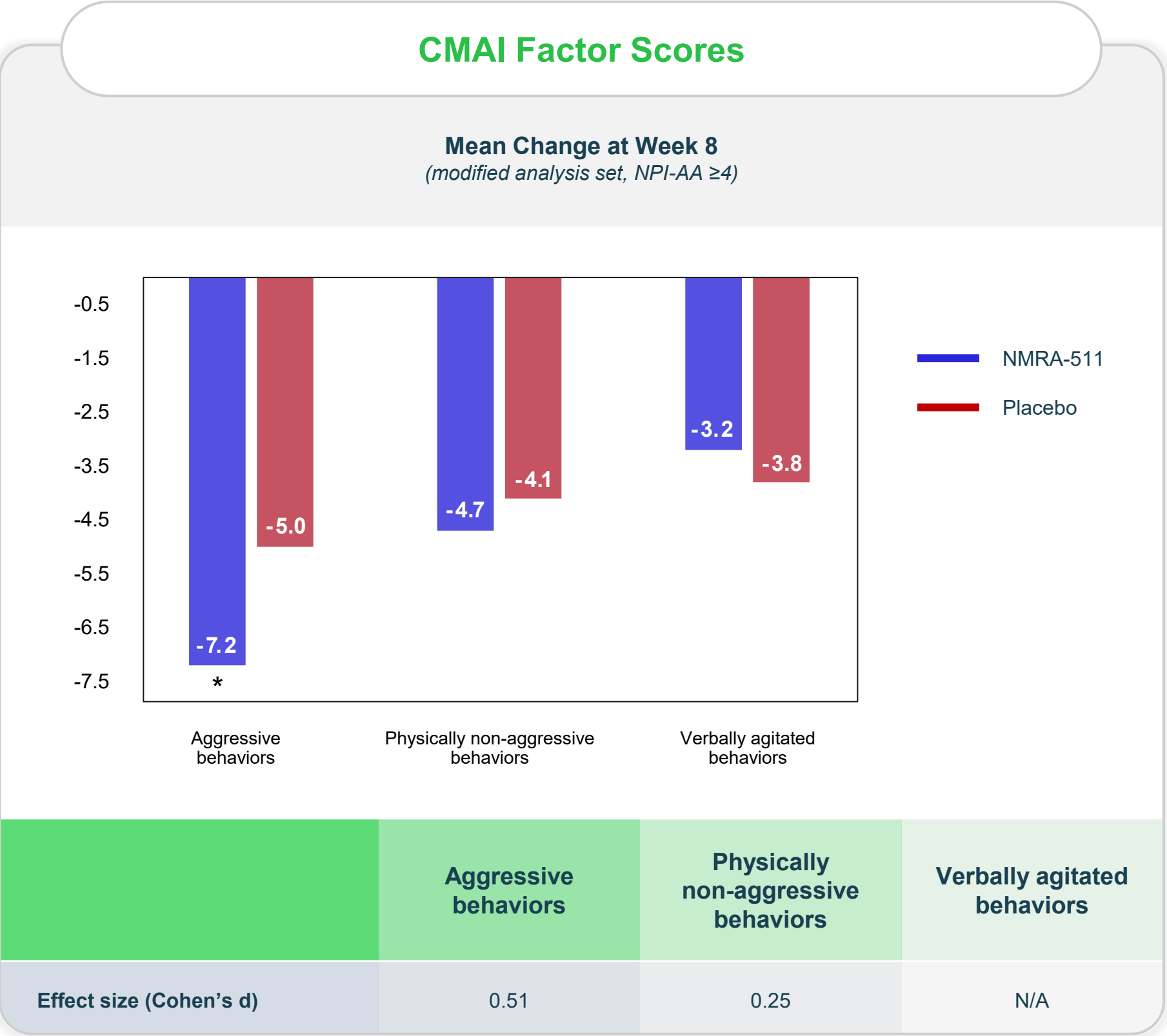
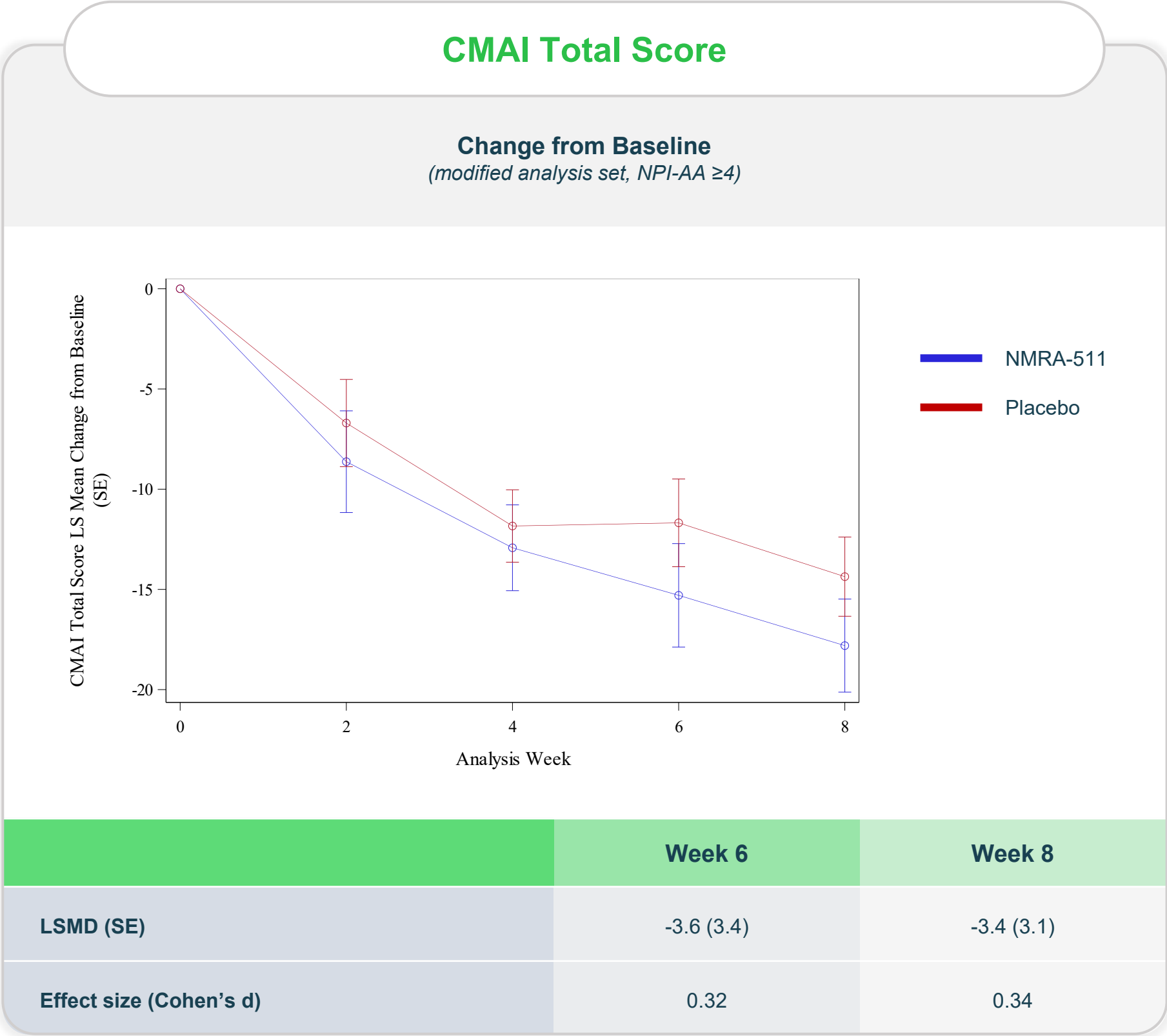
Confidential

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



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

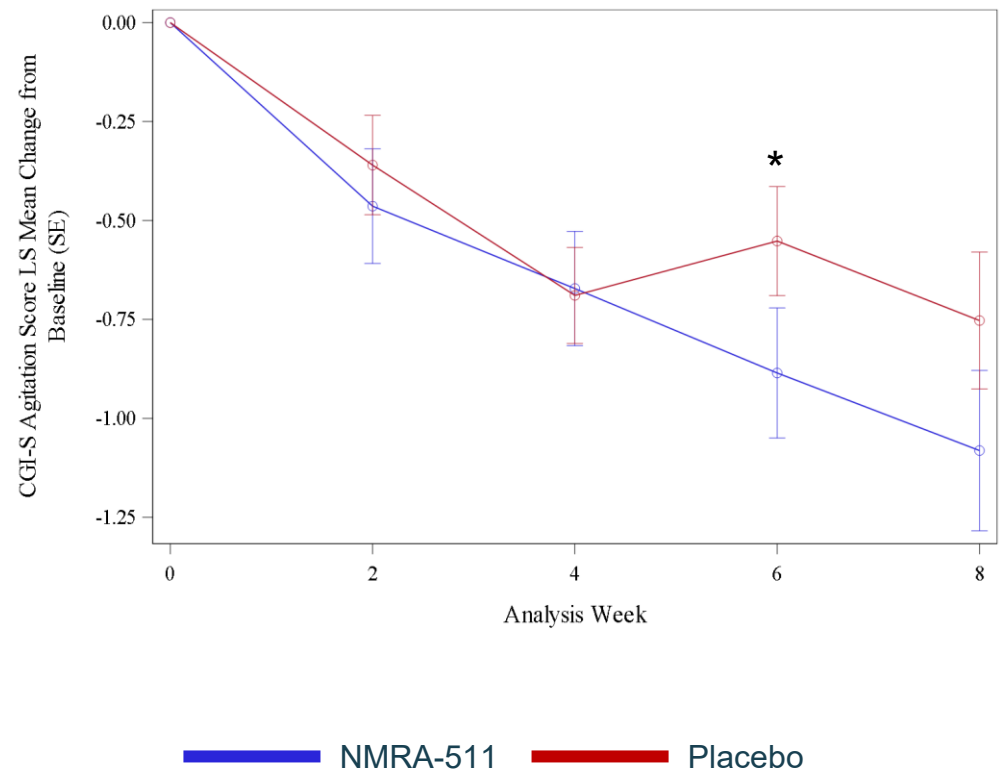
Data were consistent in the NPI-AA ≥4 population (matching other sponsors enrollment) showing an unsurpassed clinical effect size



With results in the NPI-AA ≥4 population supported by multiple endpoints

CGI-S Agitation

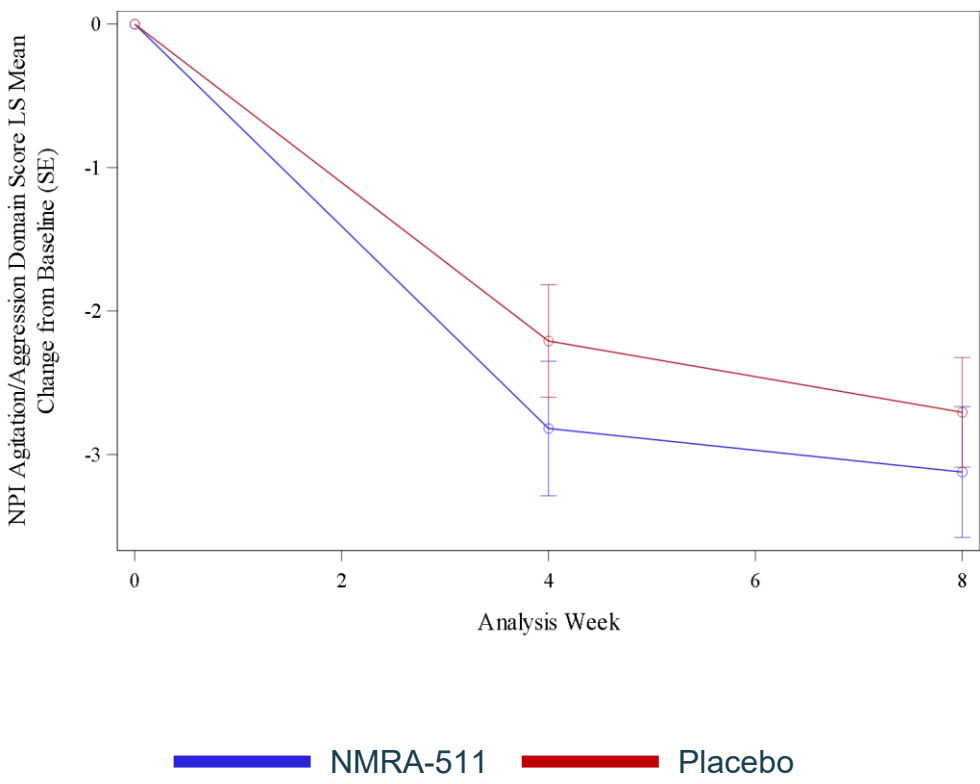
Change from Baseline
(modified analysis set, NPI-AA ≥4)



	Week 6	Week 8
LSMD (SE)	-0.3 (0.2)	-0.3 (0.3)
Effect size (Cohen's d)	0.46	0.36

NPI Agitation/Aggression Domain

Change from Baseline
(modified analysis set, NPI-AA ≥4)



	Week 4	Week 8
LSMD (SE)	-0.6 (0.6)	-0.4 (0.6)
Effect size (Cohen's d)	0.29	0.21

Favorable tolerability and safety profile of NMRA-511

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



One serious adverse event of asthenia (general weakness) reported; resolved by time of discharge from an overnight hospitalization and resolution was maintained at study follow up after treatment discontinuation

NMRA-511 demonstrated consistent unsurpassed efficacy across measures and populations

	CMAI Total Score	CMAI Aggressive Behaviors Score	CGI-S Agitation	NPI
NMRA-511 total population (NPI-AA ≥4)  	0.32 – 0.34	0.50 – 0.51	0.46 – 0.36	0.29-0.21*
	0.35	0.33	0.31	0.39^
	0.3	Not Reported	Not Reported	Not Reported
NMRA-511 elevated anxiety population	0.51-0.64	0.82-1.1	0.38-0.78	0.42-0.46*

NMRA-511 in AD agitation

- Well tolerated safety-profile, with potential for higher dosing
- Unsurpassed and consistent treatment effect across a range of measures
- Opportunity for convenient dosing with XR formulation
- Opportunity to enrich future studies for elevated anxiety (Phase 1b not enriched)

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. Data presented as Cohen's d effect size; elevated anxiety = RAID ≥12. *NPI-AA ^NPI-nursing home Neumora data on file.; Lee 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.; Axsome Therapeutics corporate materials. Rexulti and Auvelity studies were enriched with an NPI-AA domain cutoff ≥4 at baseline. NMRA-511 Phase 1b study included no enrichment. Baseline NPI-AA scores; NMRA-511: 5.1; Rexulti: 7.7 (Study 2); Auvelity: 7.2 (Advance-1)



M4 PAM franchise: differentiated M4R PAMs for schizophrenia

M4 Franchise Target Profile

Pharmacology

Neumora has multiple series of chemically distinct, highly selective M4 muscarinic receptor PAMs designed for antipsychotic-like efficacy with the potential for improved tolerability profile; NMRA-898 is the lead molecule in the franchise

Indication

Schizophrenia

Target Administration

Oral, once-daily

IP

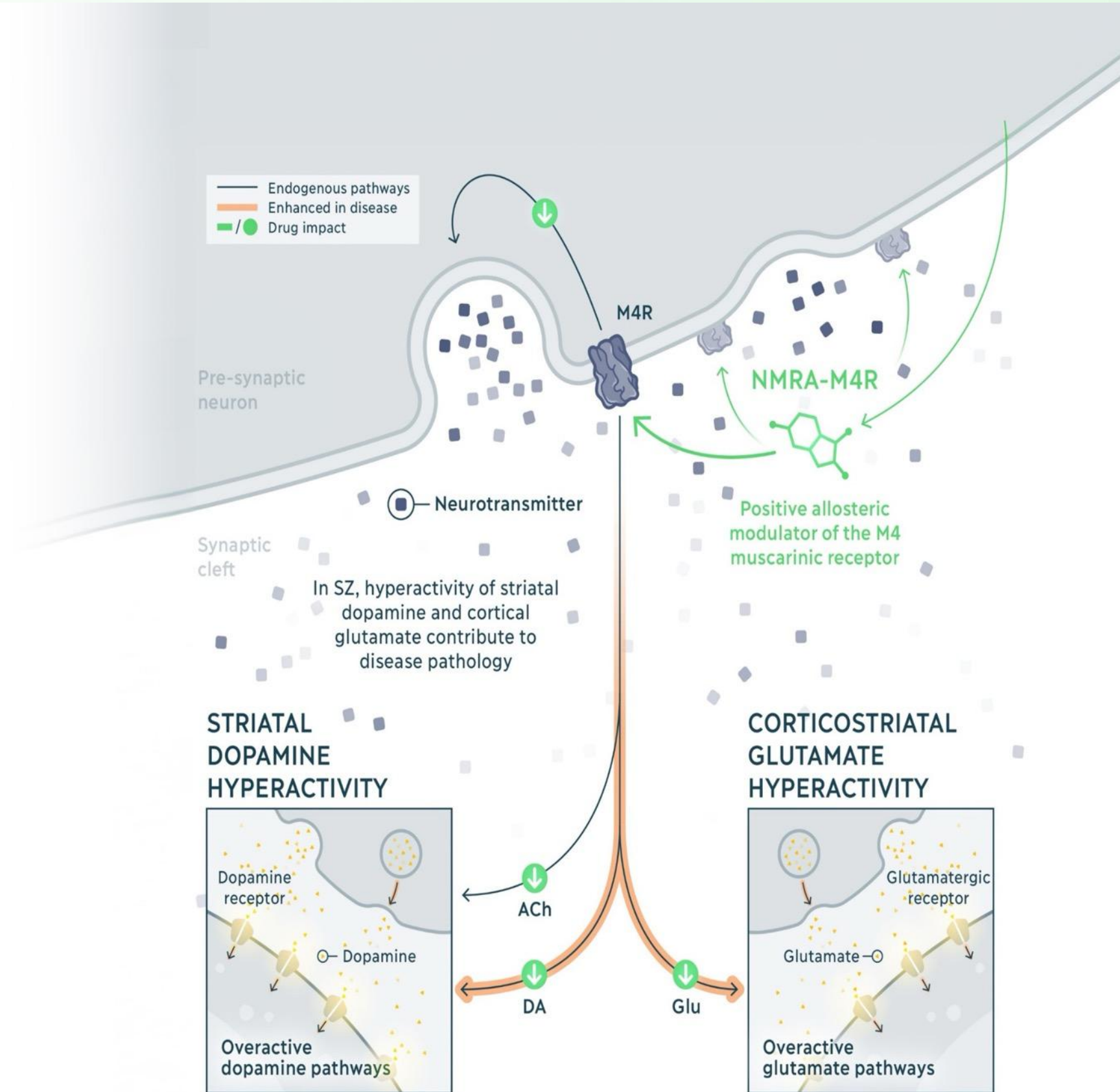
Composition of matter patent extending to 2044+*

Epidemiology

Estimated 3 million patients in the U.S. with schizophrenia¹

Expected Milestones

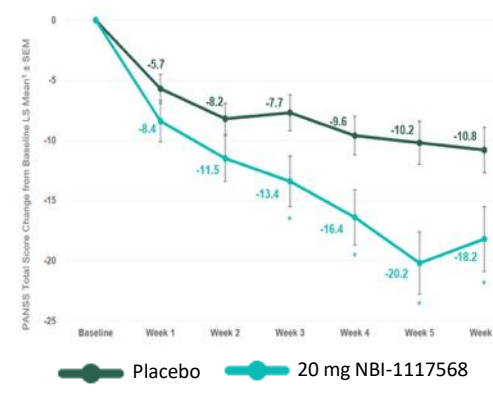
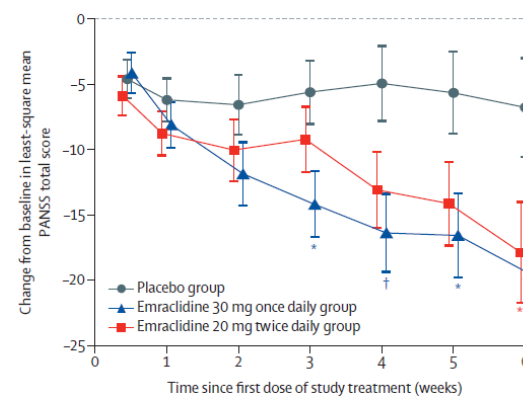
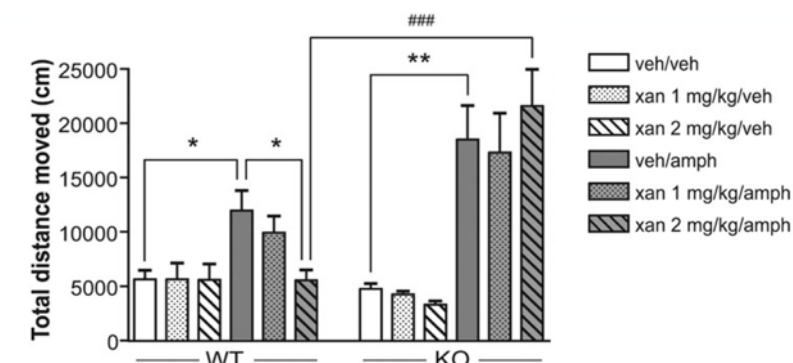
Report data from ongoing Phase 1 study with NMRA-898 in 2H 2026



An optimized muscarinic drug profile would include selectivity and potency in the CNS

Preclinical data and clinical data in acute schizophrenia supports M4 as a driver of antipsychotic activity

Activity of xanomeline (active component of Cobenfy™) is dependent on M4R in mice



Non-selective muscarinic agents are associated with a range of peripheral AEs

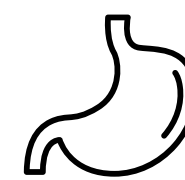
M4



Cardiovascular

Transient increased BP & heart rate

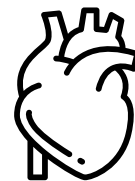
M1, M2, M3



GI Tract

Increased gastric secretion & gastric motility

M1, M2, M3



Cardiovascular

Direct effect on cardiac function – increased BP & heart rate

M1, M3



Glands

Increased salivation
Increased lacrimation
Increased sweating

PAMs offer the benefits of greater selectivity

- Targeting the allosteric site specifically allows for greater selectivity for M4 over other muscarinic sub-types than if targeting the orthosteric site due to binding site conservation
- To date the pharmacology of agonists targeting the orthosteric site are often thought to display 'partial' agonism which could contribute to variable clinical responses
- PAMs allow for more precise potentiation of M4, maintaining the spatial and temporal signaling dynamics of ACh

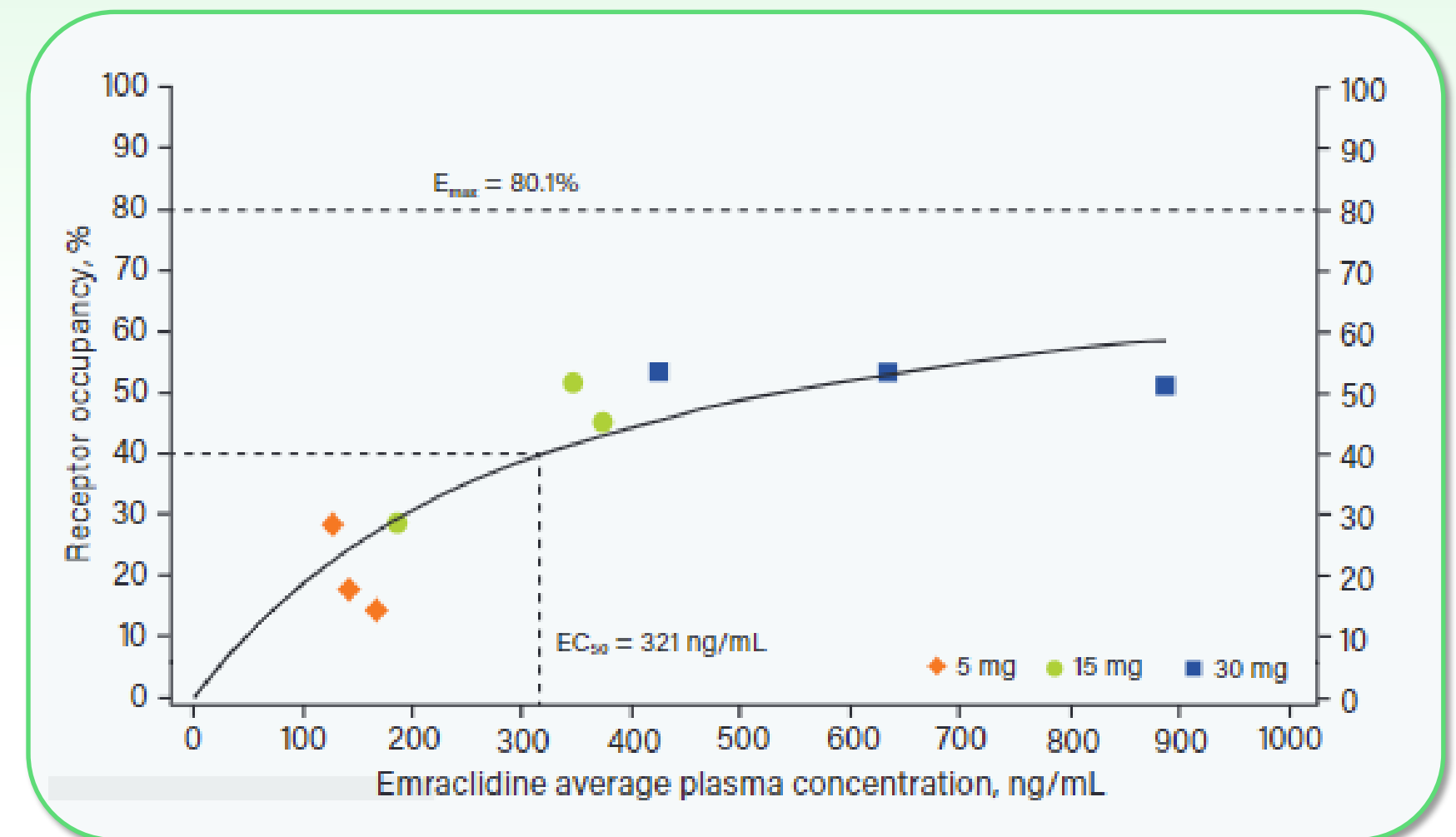


Emraclidine receptor occupancy disconnected from plasma exposures

Receptor Occupancy for Emraclidine in Humans Suggests the Compound has Limited Brain Exposure

- In a human PET study, peripheral concentration of emraclidine shows dose linear response
- However, CNS receptor occupancy unchanged when dose doubled from 15 to 30 mg
- Data suggests emraclidine may have limitations in engaging the M4 receptor in the brain

Low CNS exposure could limit efficacy



CNS = central nervous system; PET = positron emission tomography

Duvvuri S, et al. *Evaluation of M4 Muscarinic Receptor Occupancy by Emraclidine Using [^{11}C]MK-6884 PET in Healthy Volunteers*. Poster M206. Presented at the 62nd Annual Meeting of the American College of Neuropsychopharmacology, Tampa, FL: December 3 – 6, 2023.

NMRA-898 has potential best-in-class potency and optimized brain penetration

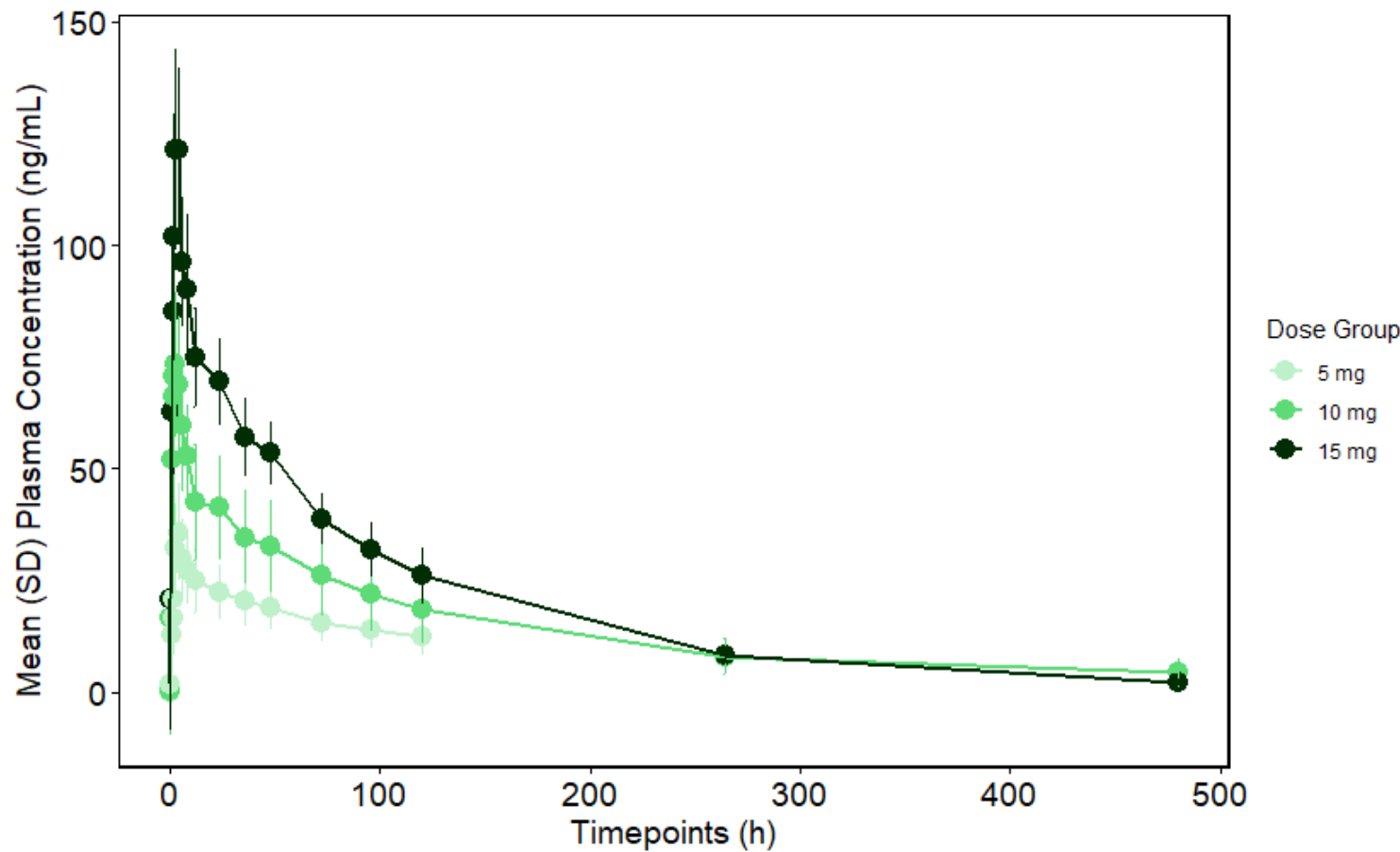
		NMRA-898 ¹	Emraclidine
NMRA-898 is potentially more potent than emraclidine across multiple assays	M4 EC ₅₀ (human; cAMP) ¹	13 nM	26 nM
	M4 EC ₅₀ (human; Ca ²⁺) ¹	8 nM	180 nM
NMRA-898 is selective for M4 over other muscarinic receptor subtypes	Selectivity at other muscarinic receptor subtypes (EC ₅₀) ¹	M1, M2, M3, M5 > 10 µM	M1, M3, M5 > 10 µM, M2 5.7 µM
NMRA-898 is optimized for high CNS exposure	Brain exposure MDCK permeability (target >10) P-gp efflux ratio (target <2) ^{1,2}	High 36.7 0.93	Moderate 9.5 3, 6.02 ^{1,2}
NMRA-898 is optimized for once daily dosing	Human half-life ^{^3}	80 – 100 hr	9 – 12 hr
NMRA-898 is well tolerated at exposures projected to achieve meaningful M4 potentiation	Estimated Free Brain C _{max} [^] (Fold cAMP EC ₅₀)	2 x Low PK variability	N/A High PK variability

Note: Data on this slide is presented for illustrative purposes only. These molecules have not been studied in head-to-head clinical trials. ^NMRA-898 data based on ongoing Phase 1 (SAD/MAD) study.
cAMP = cyclic adenosine monophosphate; CNS = central nervous system; PAM = positive allosteric modulator
1. Data generated by The Warren Center for Neuroscience Drug Discovery at Vanderbilt University on behalf of Neumora across NMRA-861, NMRA-898 and emraclidine. 2. Butler CR, et al. *J Med Chem.* 2024 Jul 11;67(13):10831-47. 3. Krystal JH, et al. *Lancet.* 2022 Dec 17;400(10369):2210-20.

Promising Phase 1 clinical results single ascending dose study

Exposures support program advancement

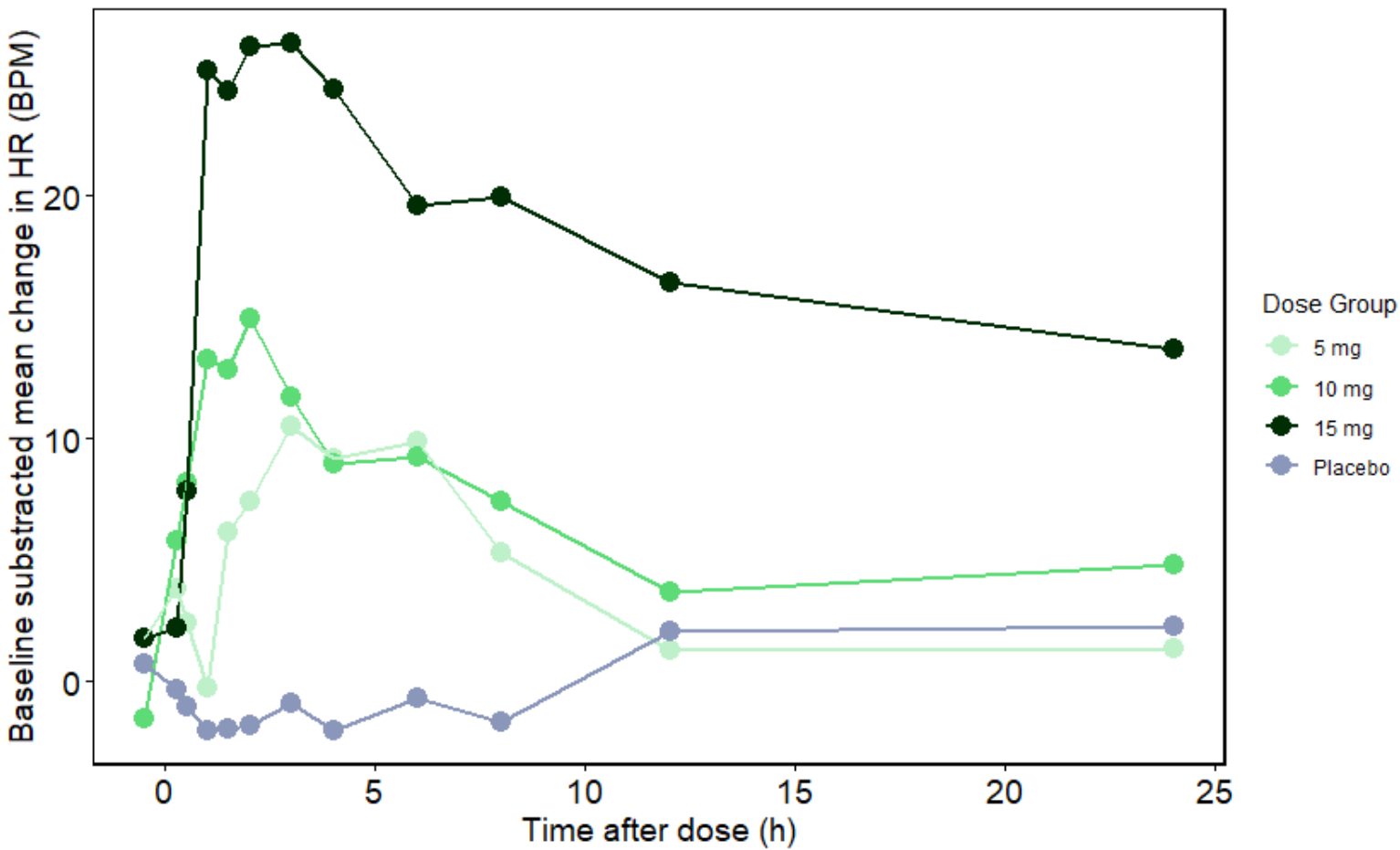
Phase 1 SAD PK Profile
(healthy adults)



Exposures were dose proportional with low variability and predicted free exposures in the brain above in vitro M4 EC50 levels

On-target changes in heart rate measures

Phase 1 SAD Heart Rate Changes
(healthy adults)



Exposure-dependent increases in heart rate, of similar magnitude to those demonstrated by Cobenfy (KarXT), providing pharmacodynamic evidence of target engagement



MAD study evaluating NMRA-898 in healthy adults and people with stable schizophrenia

Study Objectives

- Evaluate tolerable doses in people with stable schizophrenia
- Establish CNS penetration – based on CSF exposure

MAD – Part 2 CSP

	Dose	Participants	Randomization
Cohort 1	Dose to be determined	Healthy adults	6:2 active:placebo
Cohort 2	Dose to be determined	Healthy adults	
Cohort 3	Dose to be determined	Healthy adults OR with stable schizophrenia	
Cohort 4	Dose to be determined	Healthy adults OR with stable schizophrenia	
Cohort 5	Dose to be determined	Adults with stable schizophrenia	

Healthy adults Adults with stable schizophrenia





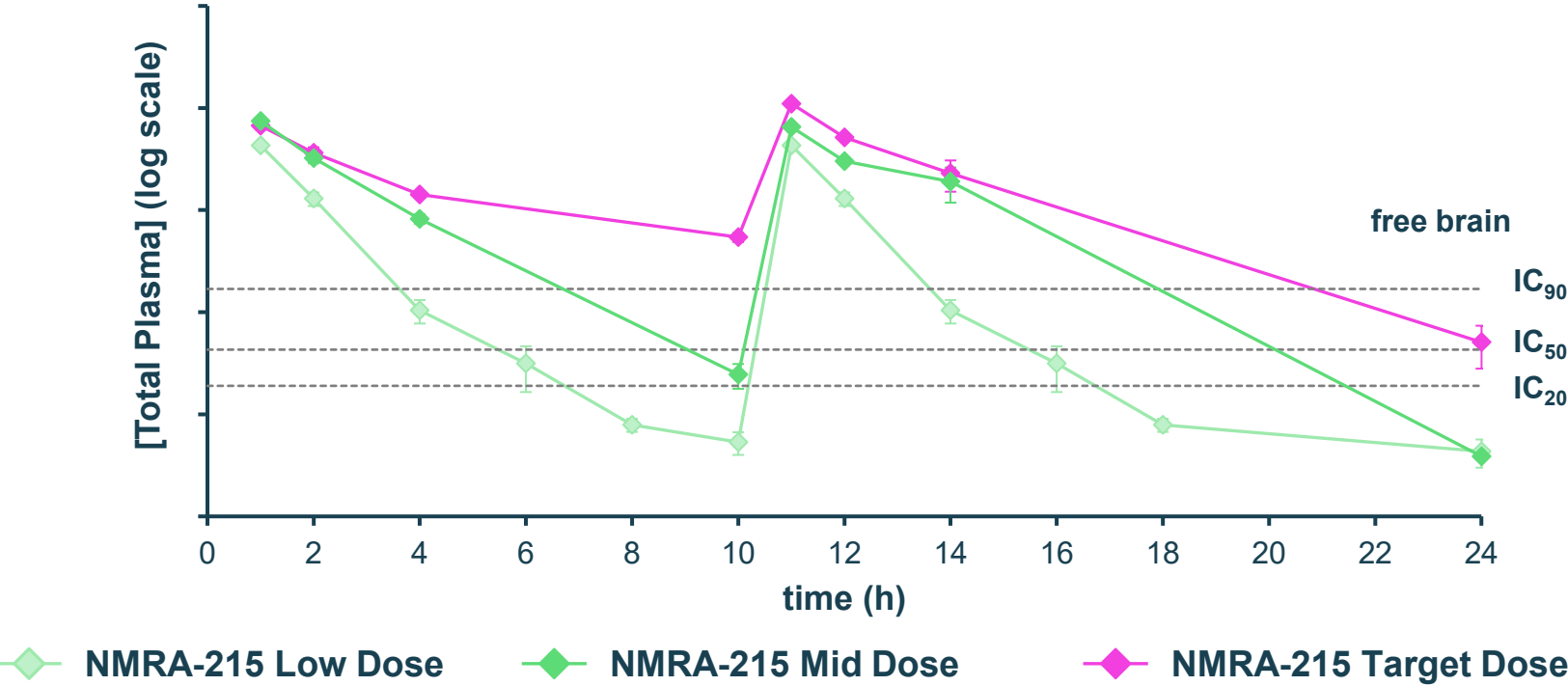
Appendix

Doses selected for DIO mouse studies to determine target coverage necessary for weight loss

NMRA-215 dose selection

Goal: Sustained IC₉₀ target coverage for 24 hours

Dose (BID)	IC
Target Dose	90
Mid-Dose	50
Low Dose	20



Target dose drives IC₉₀ in CNS and periphery over 24 hours based on human whole blood assay

Semaglutide dose selection

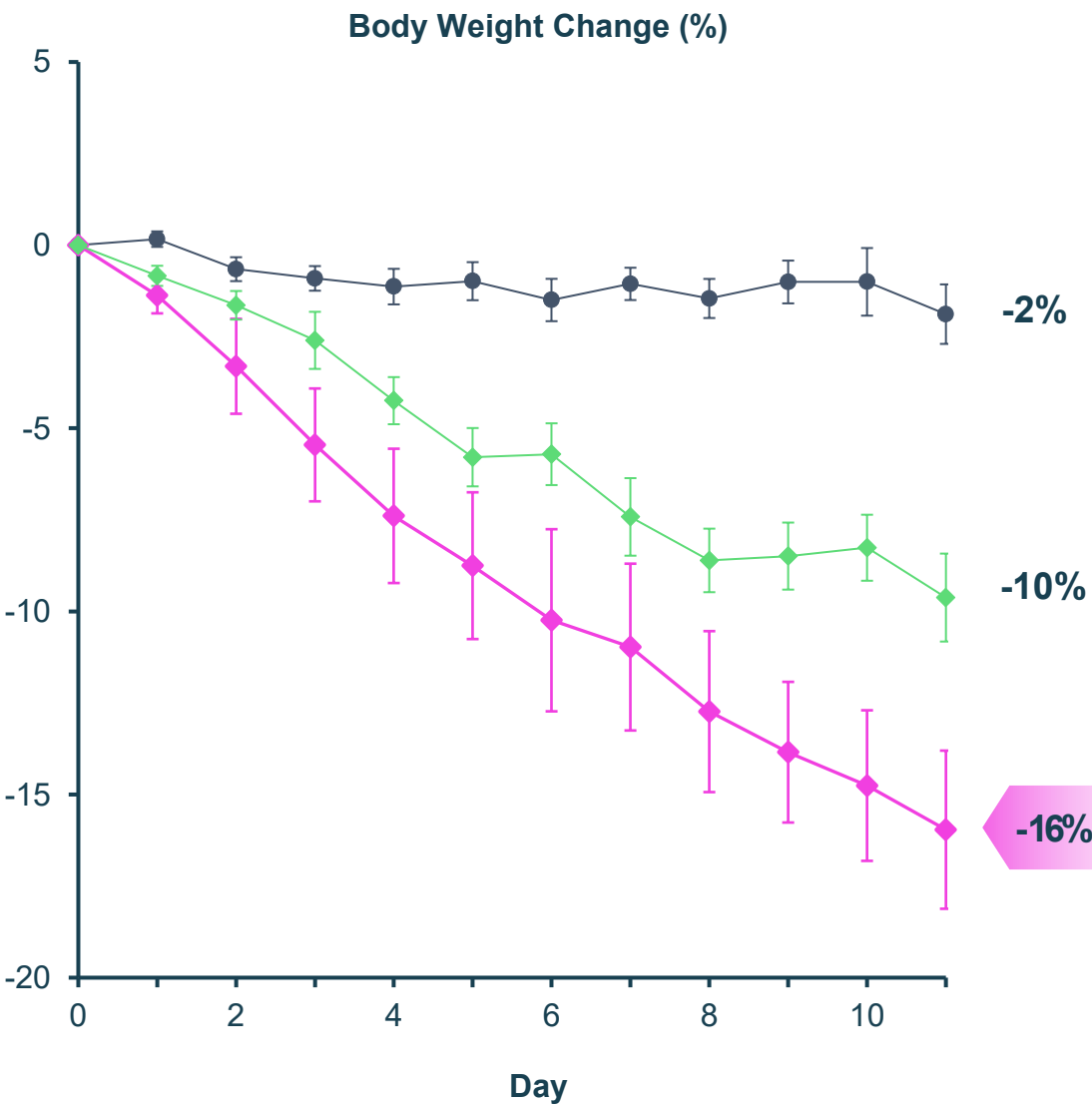
Goal: Select two doses that allow for evaluation of different treatment paradigms

- Ability to evaluate combination and dose sparing effects of NMRA-215
 - Therapeutic dose: 3 nmol/kg
 - Sub-therapeutic dose (incretin-sparing): 1 nmol/kg
- Similar dosing paradigm used by other sponsors allows for comparison across studies

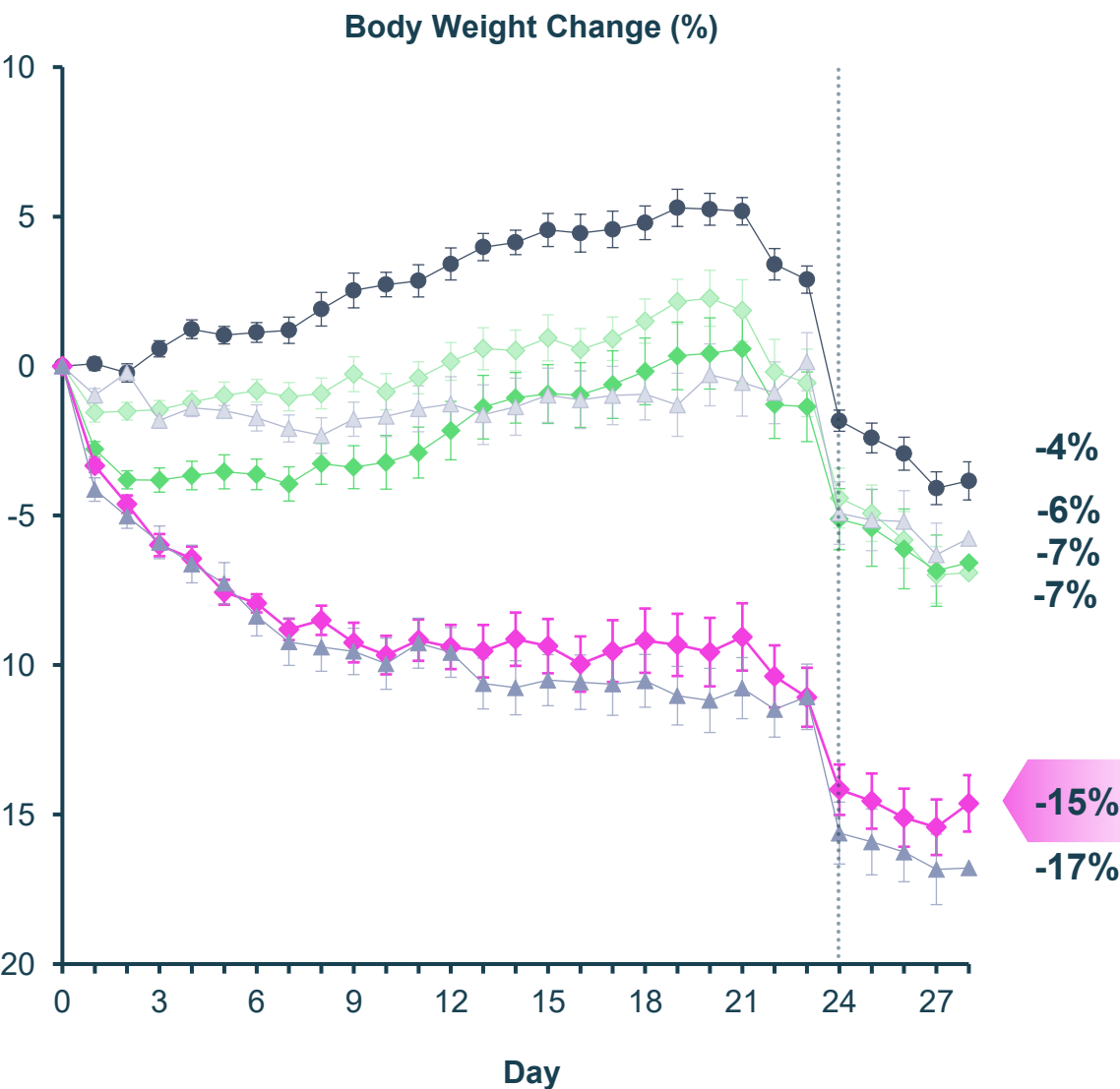


Monotherapy: Up to 19% weight loss with NMRA-215 with incretin-like induction

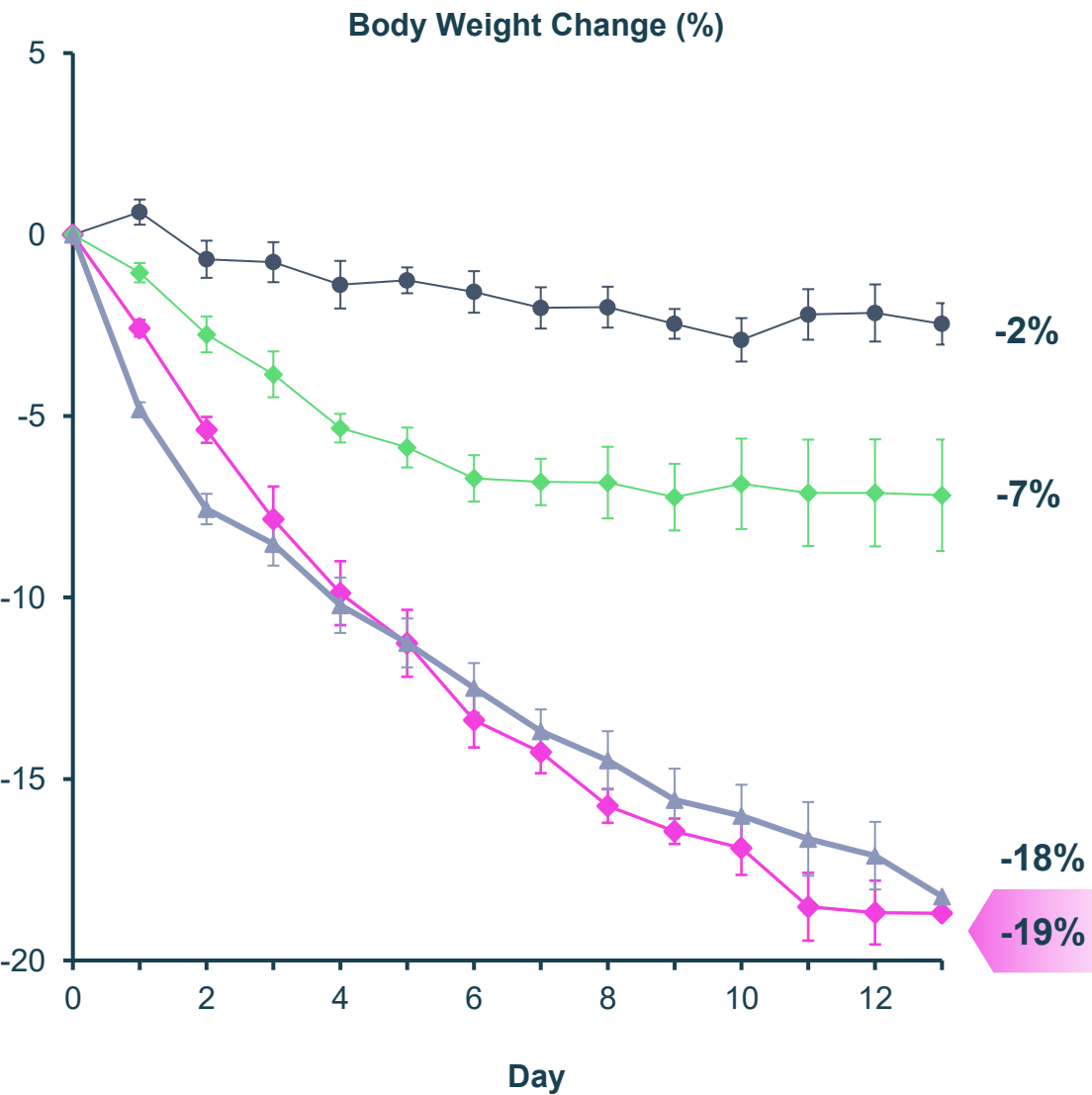
STUDY 1 Pilot Study



STUDY 2 Full DIO Study



STUDY 3 Induction Confirming Study*

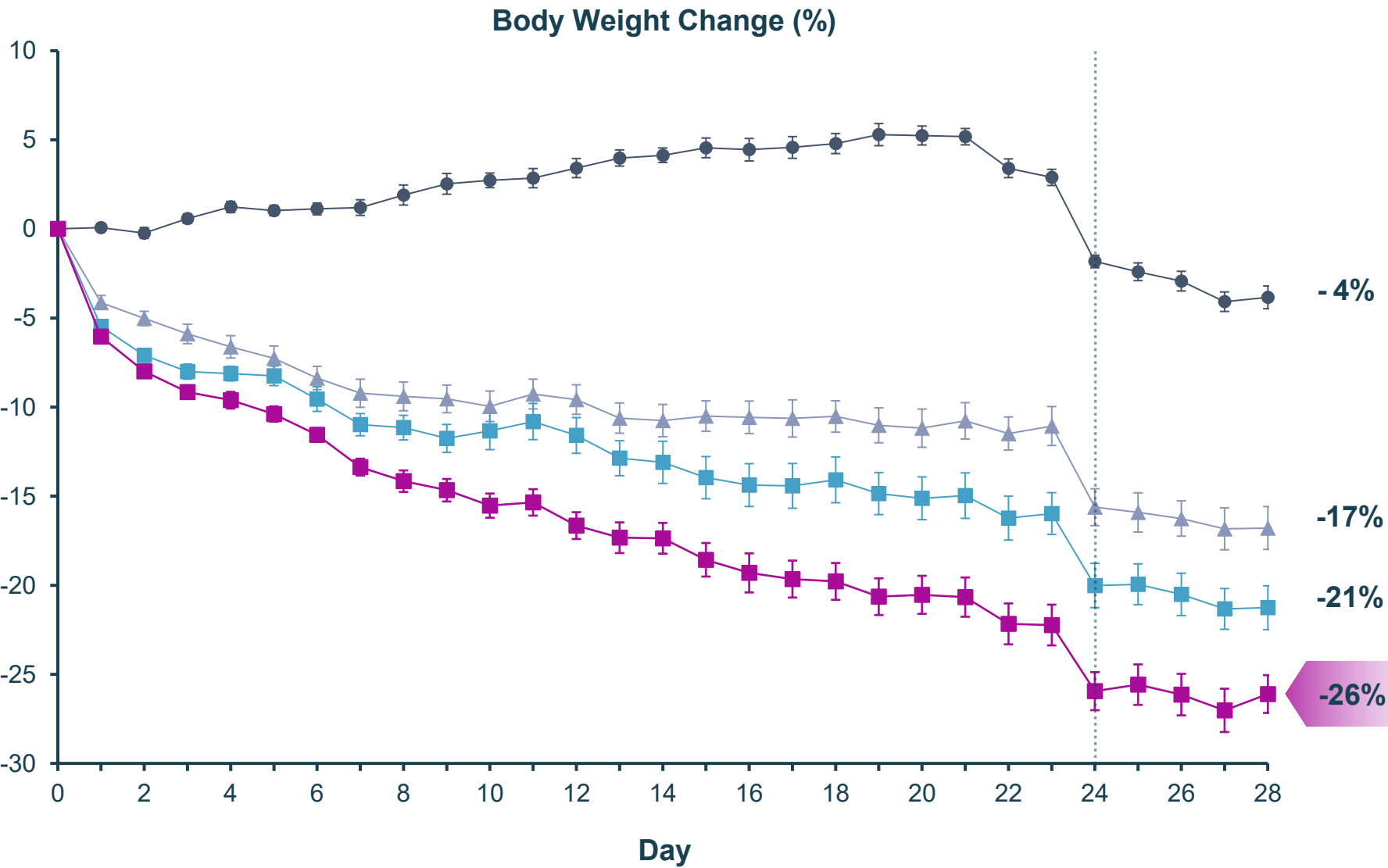


● Vehicle ◆ NMRA-215 Low Dose ◆ NMRA-215 Mid Dose ◆ NMRA-215 Target Dose ▲ semaglutide 1 nmol/kg ▲ semaglutide 3 nmol/kg

NMRA-215 administered subcutaneously in Studies 1 and 3 and administered orally in Study 2. Semaglutide administered subcutaneously in all studies. In Study 2 beginning on Day 22, mice underwent daily endpoint collections, including behavioral testing, MRI, and fasting on day 24 to support blood collection Days 25-27. *Study designed to run up to 28 days. Following achievement of study objective confirming incretin-like induction at Day 13, study was stopped due to injection site irritation, which will not be present in the clinical setting, as NMRA-215 is being developed as an oral therapy.

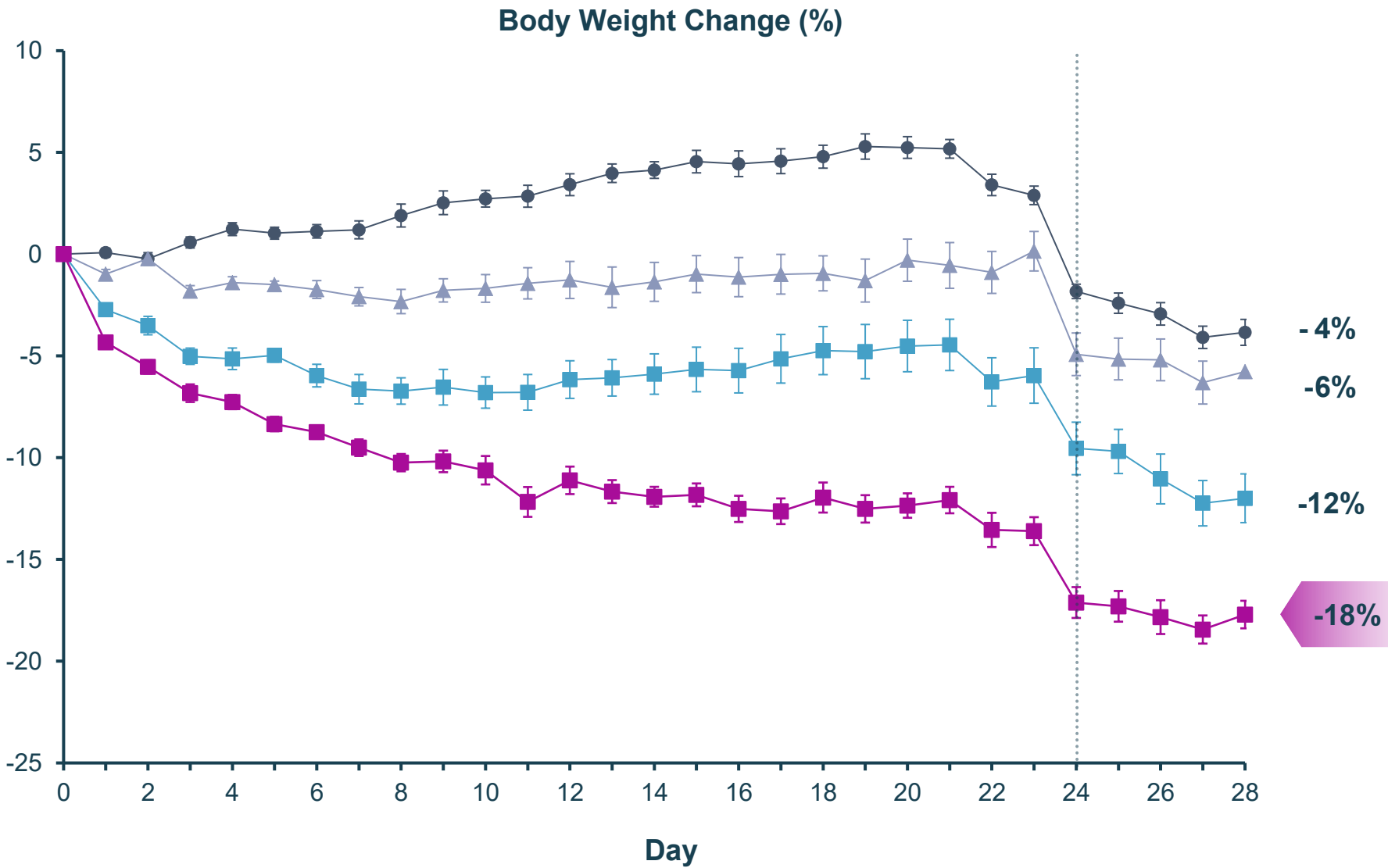
Combination therapy: Up to 26% weight loss with NMRA-215 + semaglutide

NMRA-215 + Combined with 3 nmol/kg semaglutide



Additive weight loss with therapeutically active incretin dose

NMRA-215 + Combined with 1 nmol/kg semaglutide



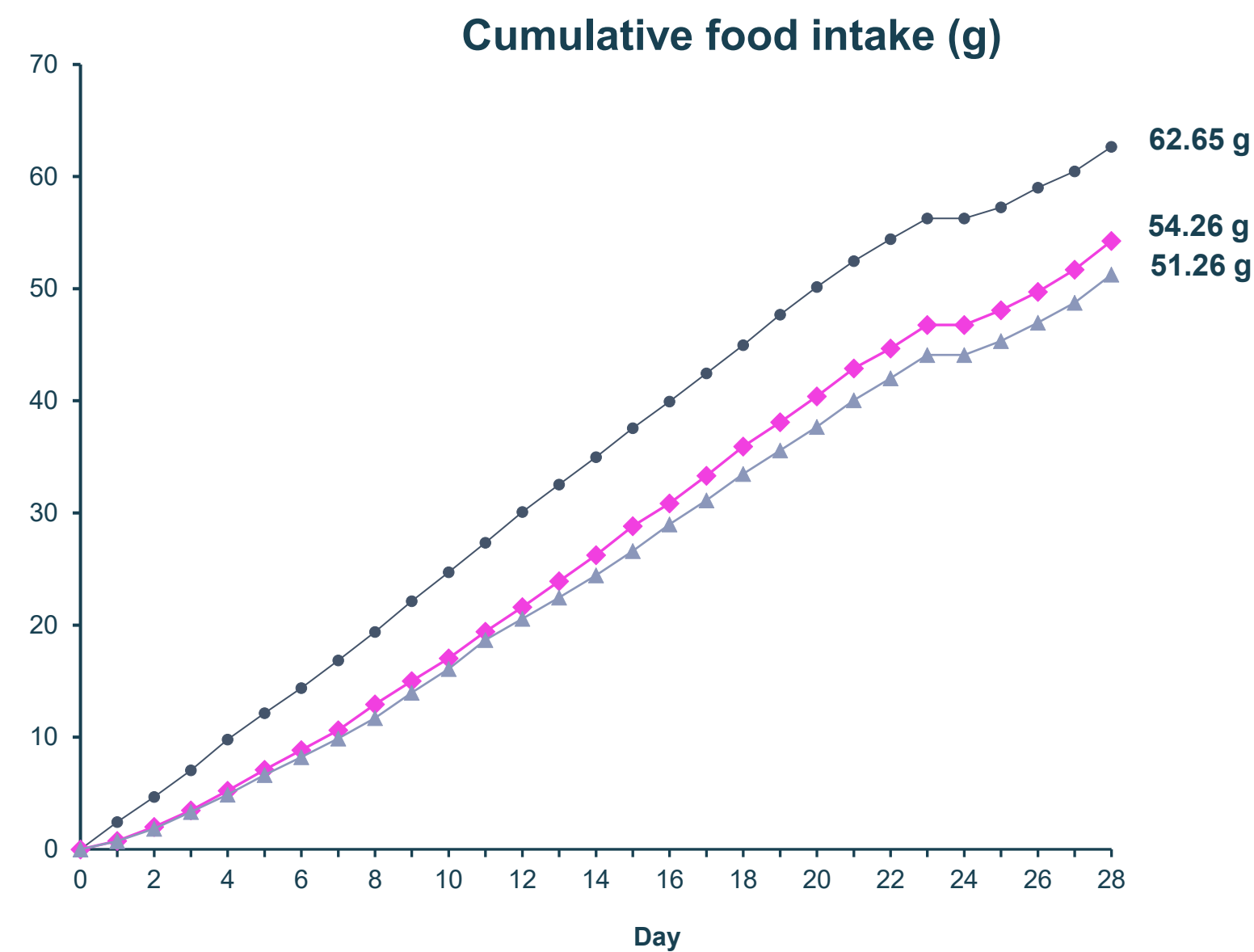
Potential for incretin-sparing combination with better tolerability



● Vehicle ▲ semaglutide ■ Combination with NMRA-215 Mid Dose ■ Combination with NMRA-215 Target Dose

NMRA-215 matches semaglutide weight loss with higher-quality outcomes

Reduced food intake
equivalent to semaglutide

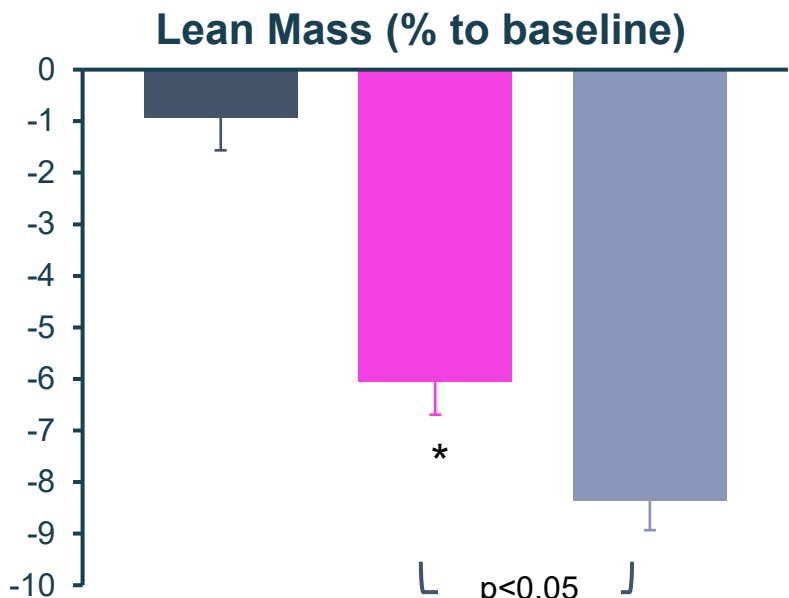
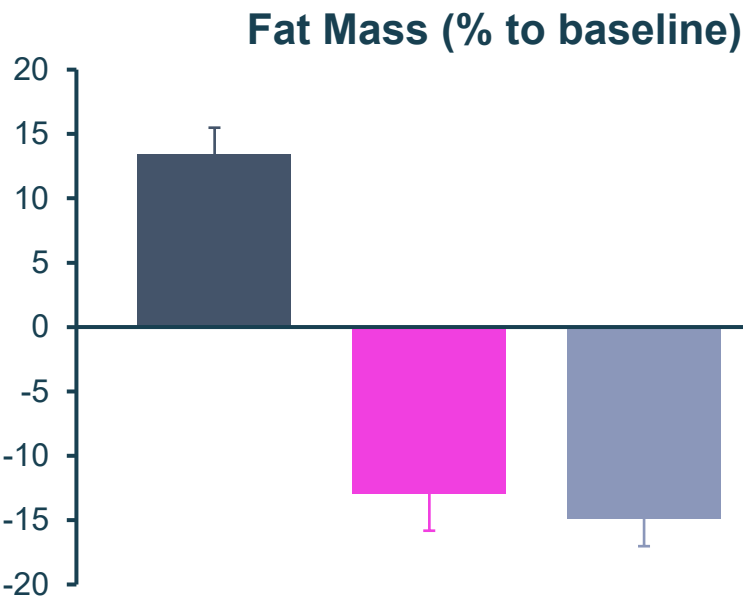


● Vehicle

◆ NMRA-215 Target Dose

▲ semaglutide 3 nmol/kg

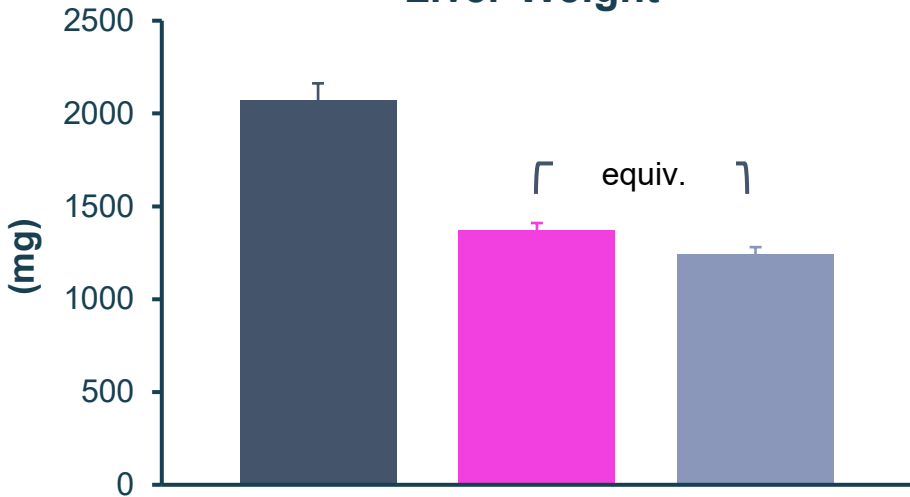
Matches semaglutide weight loss, while preserving
lean mass



NMRA-215 drove positive results across key biomarkers

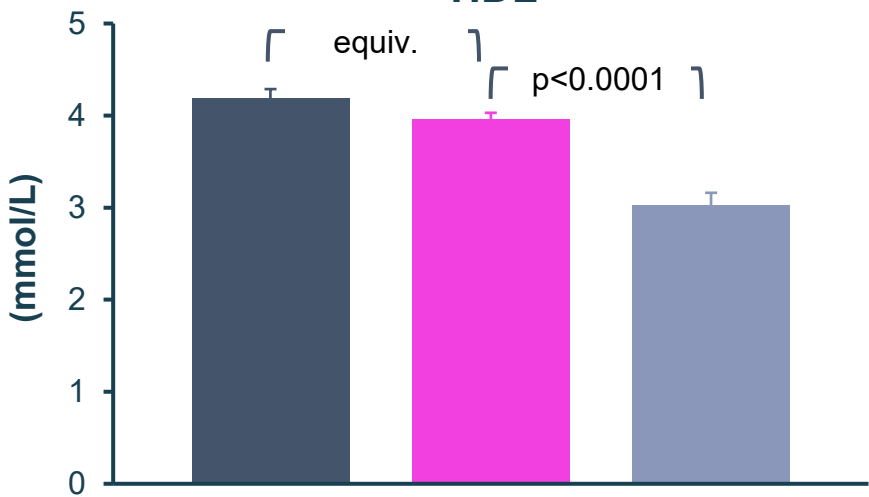
Improved liver health similar to semaglutide

Liver Weight

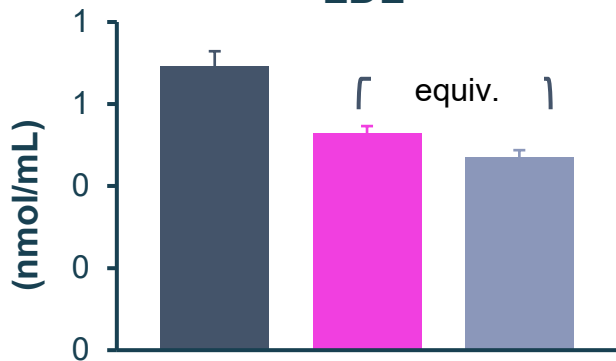


Improved cardiovascular/lipid profile relative to semaglutide

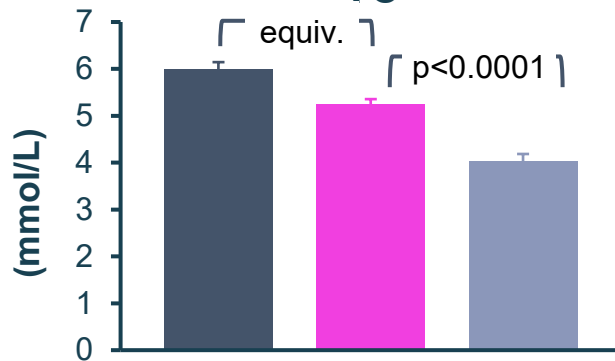
HDL



LDL

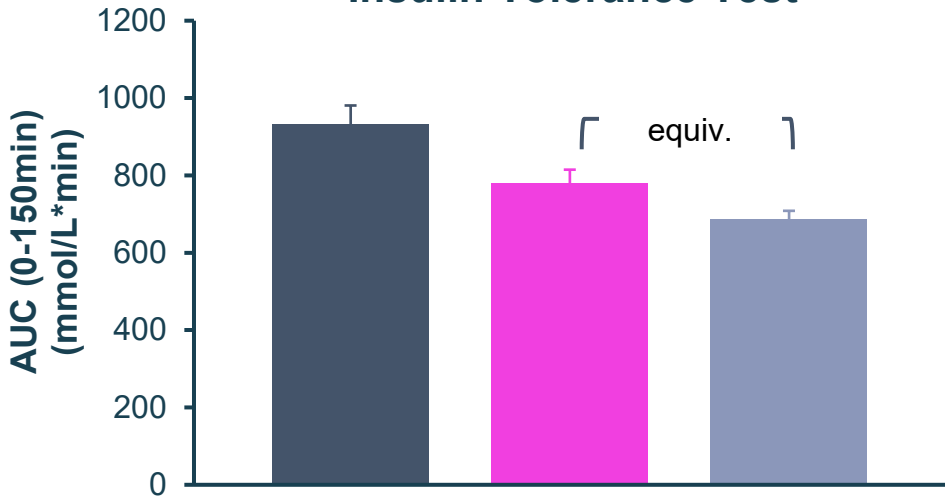


TC



Improved insulin sensitivity

Insulin Tolerance Test



● Vehicle

◆ NMRA-215 Target Dose

▲ semaglutide 3 nmol/kg



Sustained weight loss following switching from semaglutide to NMRA-215

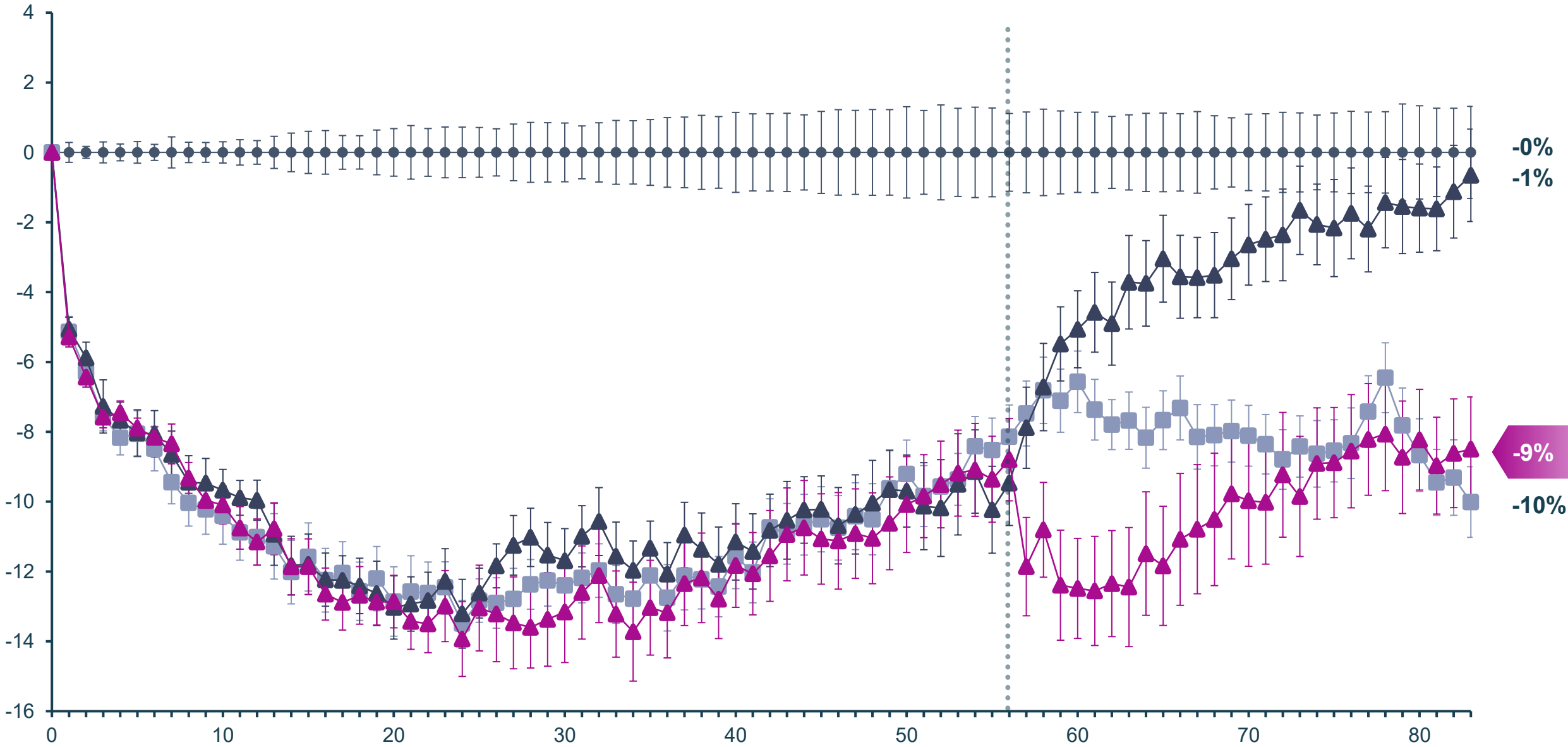
12-Week DIO Data

Full MoA Switch

Key Takeaway

NMRA-215 demonstrated sustained, semaglutide-like weight loss at 12 weeks following a switch from semaglutide monotherapy to NMRA-215 monotherapy at week 8

% Change in Body Weight (Vehicle Adjusted)



● Vehicle

■ semaglutide

▲ semaglutide → Vehicle

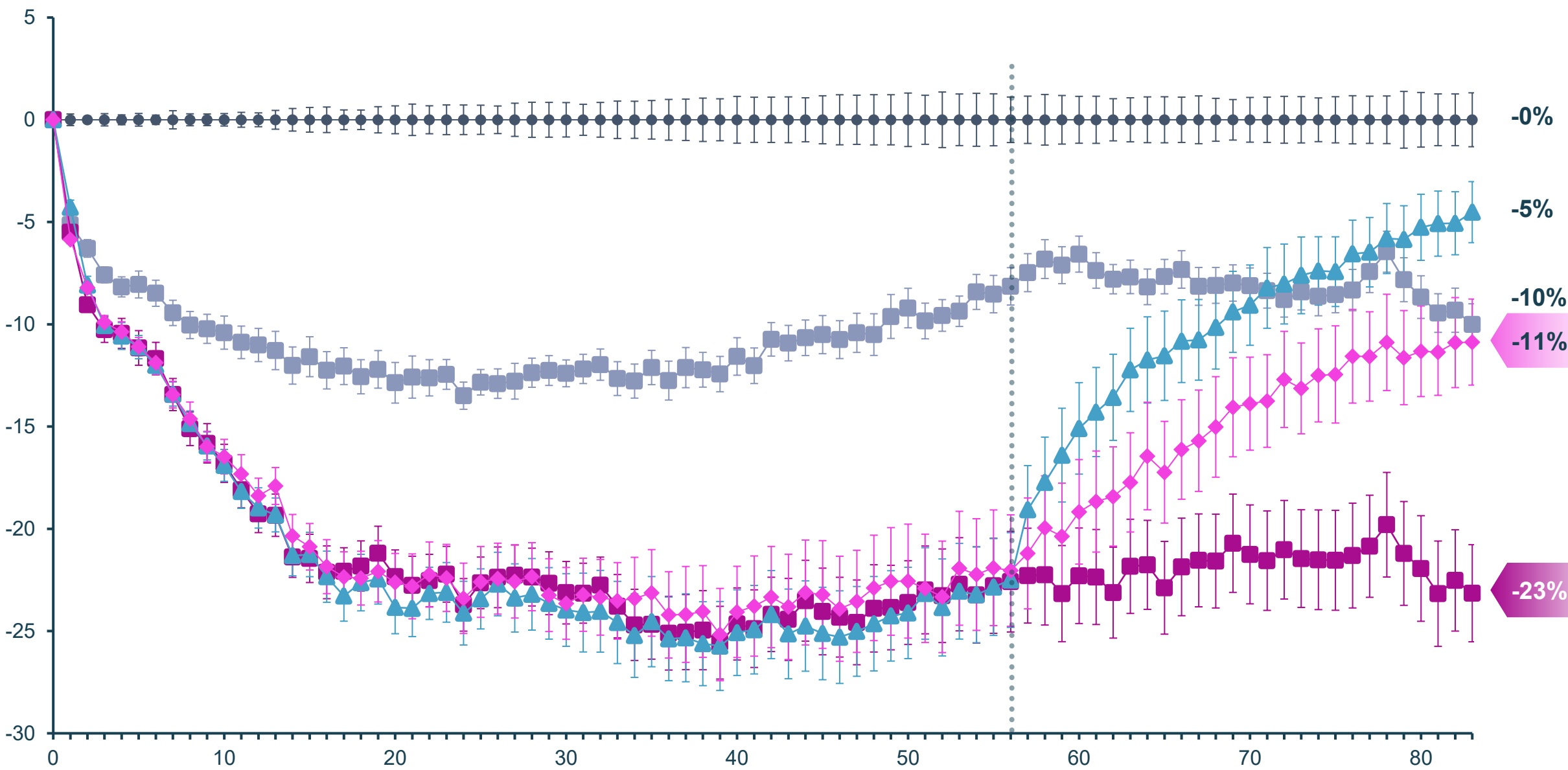
▲ semaglutide → NMRA-215 Target Dose

NMRA-215 offers maintenance of weight loss

12-Week DIO Data

Combination → NLRP3 maintenance

% Change in Body Weight (Vehicle Adjusted)



Key Takeaway

Following switch from semaglutide and NMRA-215 combination to NMRA-215 monotherapy at week 8, DIO mice maintained weight loss similar to mice who received semaglutide monotherapy for the entire duration



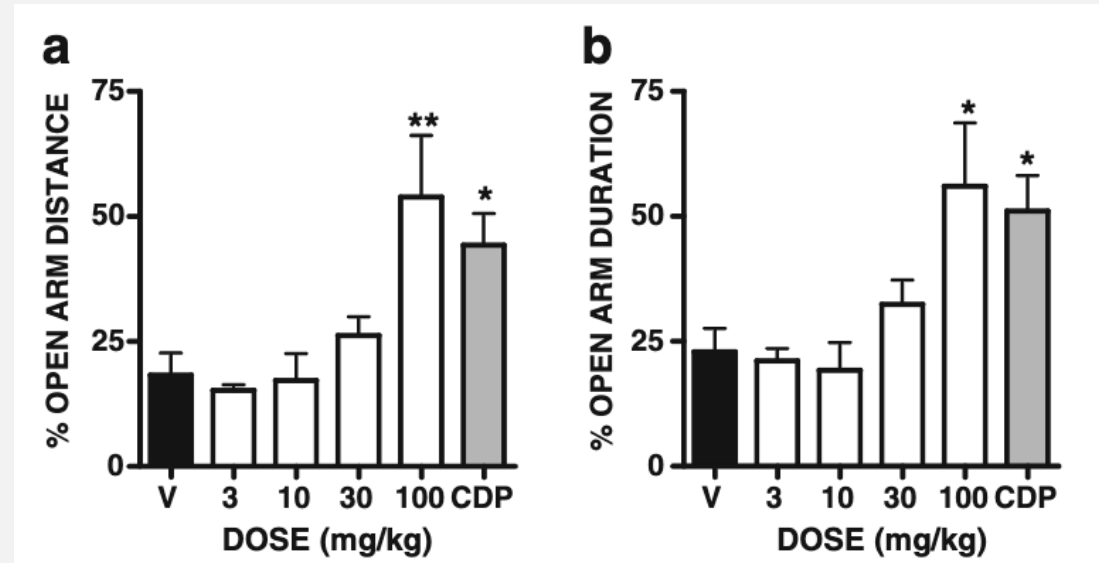
● Vehicle ■ semaglutide ■ Combination with NMRA-215 Target Dose ▲ Combination → Vehicle Maintenance ◆ Combination → NMRA-215 Maintenance

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}

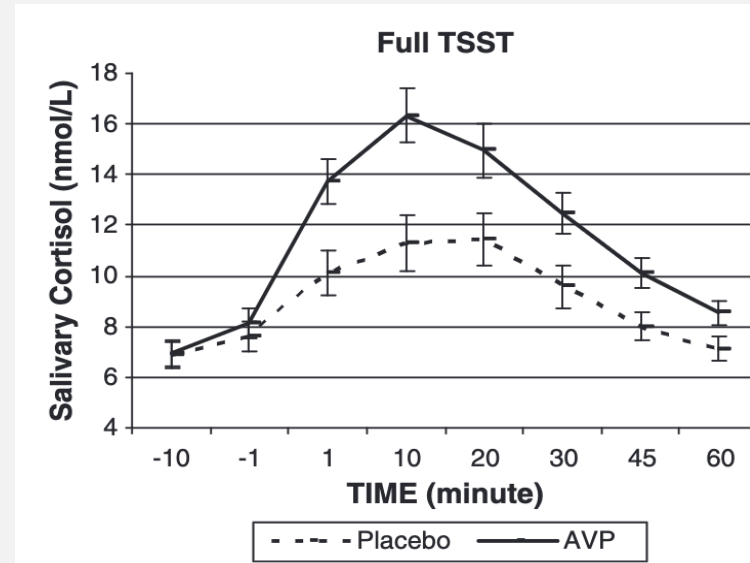
V1a receptor antagonist (JNJ-17308616) reduces anxiety behavior in rat



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

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

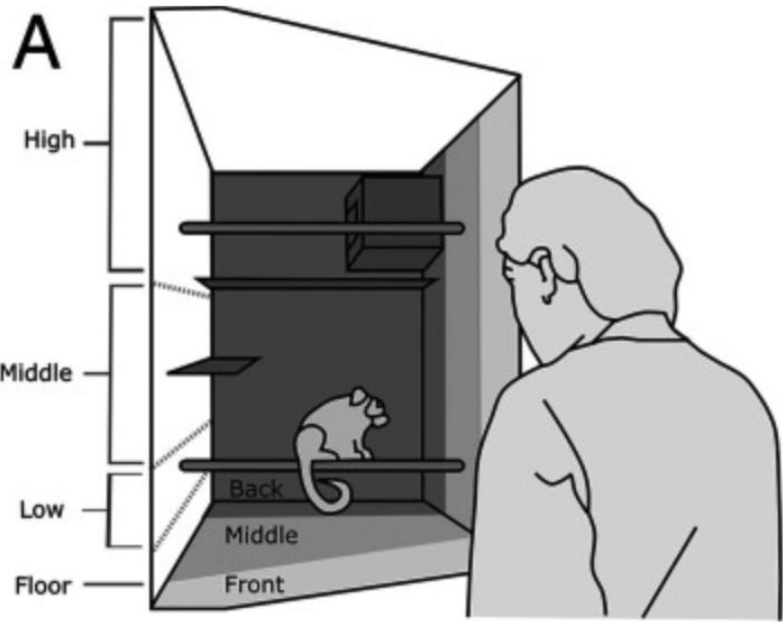
Hilda T. Maibach^{1,†}, Michael J. Brownstein^{1,†}, Steven M. Hersch^{2,3,‡}, Karen E. Anderson⁴, Debra E. Itzkowitz¹, Eve M. Damiano¹ and Neal G. Simon^{1,5,*}

¹Bielsky et al., 2004, NPP; ²Barrett et al., 2013, *Horm. Behav.*; ³Bleckardt 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;

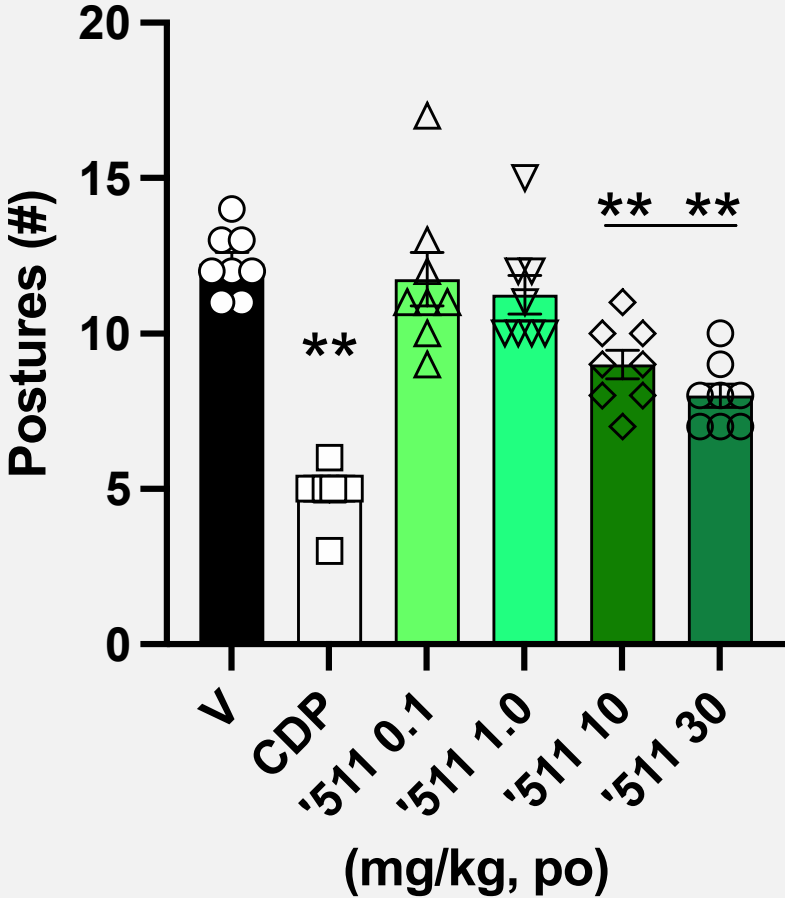
NMRA-511 reduced anxiety-related behaviors in a preclinical human threat test

Human threat test induces anxiety in marmosets¹



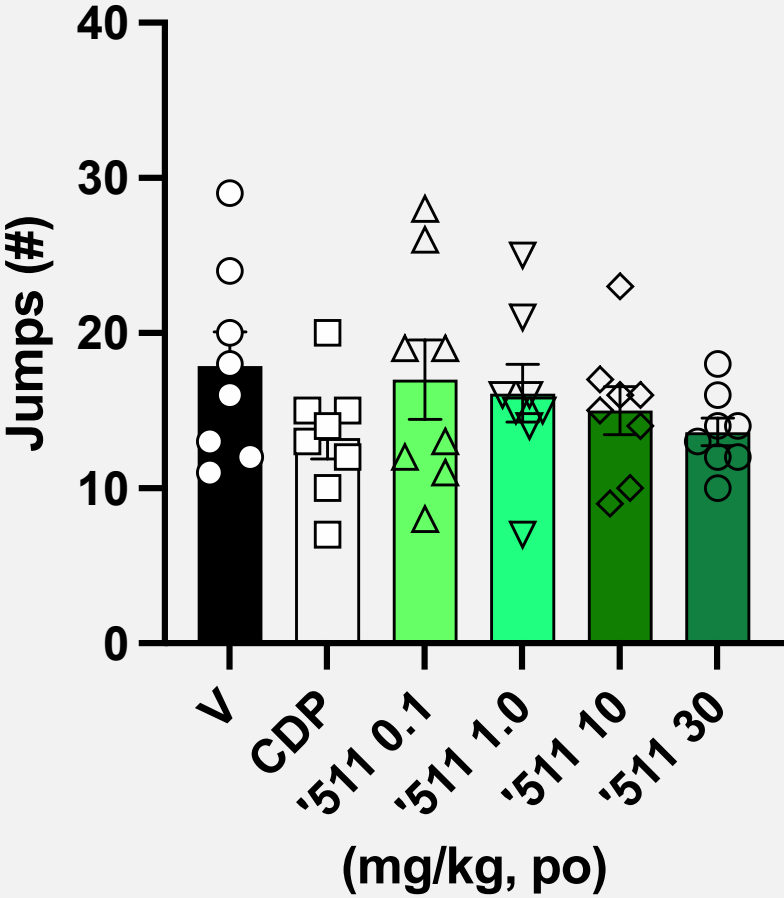
- Based on marmoset's behavioral response to situations of stress/uncertainty
- Set of characteristic postures are elicited
- Clinically effective anxiolytic drugs reduce the number of postures
- Locomotor activity is measured to control for sedative/stimulant effects of drugs

NMRA-511 reduces behavioral response to threat²



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 activity²



¹Stawicka *et al.* PNAS 2020 Sep 21;117(40): 25116-25127 ²Wallace *et al.*, 2022. American College of Neuropsychopharmacology Annual Meeting Poster.

Demographics and baseline characteristics

	Total Population		Pre-specified elevated anxiety population ³	
	NMRA-511 n=40	Placebo n=40	NMRA-511 n=16	Placebo n=21
Mean age	71.8	72.7	66.8	71.6
Sex, n (%)				
Male	18 (45.0%)	15 (37.5%)	7 (43.8%)	9 (42.9%)
Female	22 (55.0%)	25 (62.5%)	9 (56.3%)	12 (57.1%)
Race, n (%)				
White	27 (67.5%)	30 (75.0%)	11 (68.8%)	14 (66.7%)
Black	10 (25.0%)	9 (22.5%)	3 (18.8%)	6 (28.6%)
Asian	2 (5.0%)	0	1 (6.3%)	0
Other	1 (2.5%)	1 (2.5%)	1 (6.3%)	1 (4.8%)
CMAI Total Score Mean (SD)	68.2 (14.7)	68 (14.3)	69.3 (15.6)	67.7 (14.9)
CGI-S (Agitation) Mean (SD)	4.3 (0.7)	4.2 (0.6)	4.4 (0.8)	4.3 (0.6)
NPI-AA Mean (SD)	5.1 (2.5)	5.9 (2.6)	4.8 (2.7)	5.8 (2.8)
MMSE Mean (SD)	19.0 (3.2)	19.5 (2.8)	19.2 (2.9)	19.4 (2.9)
Baseline anxiety as measured by RAID score (SD)	11.8 (6.4)	14.3 (8.6)	18.3 (4.2)	18.7 (6.5)
Protocol-Defined Medication Non-Adherence ¹	7 (17.5%)	0	N/A	
Modified Analysis Set (n) ²	33	38		



¹70% medication compliance required per protocol

²2 placebo patients excluded based on rater change driving outlier data (>3 standard deviations from the mean) and protocol-defined medication non-adherent patients

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

