BREXPIPRAZOLE sNDA for Agitation Associated with Alzheimer's Dementia (AAD)

April 14, 2023

Psychopharmacologic Drugs Advisory Committee and Peripheral and Central Nervous System Drugs Advisory Committee

Otsuka Pharmaceutical Co.

Lundbeck Inc.

Introduction

Mary Hobart, PhD

Vice President, Global Regulatory Affairs

Otsuka Pharmaceutical

Agitation Associated with Alzheimer's Dementia (AAD)

Poor Health Outcomes

Increased Institutionalization

Caregiver Distress

No approved treatments

Seeking Supplemental Indication for Brexpiprazole

Proposed sNDA Indication

Treatment of agitation associated with AD

Recommended Dosing

- Target dose: 2 mg QD
- Maximum dose: 3 mg QD

Boxed Warning

- Not proposing to remove boxed warning

Brexpiprazole (REXULTI®) – Atypical Antipsychotic Approved for Schizophrenia and Major Depressive Disorder

- Approved in US for treatment of schizophrenia and for adjunctive treatment of major depressive disorder
  - First approved in US in 2015
  - Approved in > 60 countries, including EU and Canada

- 1,269,877 patient-years experience from clinical studies and post-approval

Brexpiprazole sNDA Key FDA Regulatory Interactions

Phase 3 Studies
283 (fixed 1 and 2 mg dose)
284 (flexible 0.5 – 2 mg dose)

Phase 3 Study 213
(fixed 2 and 3 mg dose)

Open-label Extension Study 182

2012	2015	2018	2022
Pre-IND meeting & IND submitted	**Fast Track Designation granted**	**FDA meeting to discuss Study 213 design**	**Pre-sNDA meeting & sNDA submission**

Three Phase 3 Studies Support Efficacy and Safety of Brexpiprazole

Study 283
Fixed-dose
1 or 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 284
Flexible-dose
0.5 to 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 213
Fixed-dose
2 or 3 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Brexpiprazole Positive Benefit / Risk for Treatment of AAD When Dosed 2 or 3 mg QD

Statistically significant and clinically meaningful improvements in key measures of agitation vs placebo

Favorable tolerability profile
AEs consistent with those previously reported for brexpiprazole and observed in this patient population

Addresses critical unmet clinical need and provides substantial improvement relative to currently utilized off-label treatments for AAD

Agenda

Unmet Need	**Zahinoor Ismail, MD, FRCPC** Professor of Psychiatry, Neurology, Epidemiology, and Pathology Hotchkiss Brain Institute & O'Brien Institute for Public Health University of Calgary
Efficacy	**Robert McQuade, PhD** Executive Vice President and Chief Strategy Officer Otsuka Pharmaceutical
Safety	**John Kraus, MD, PhD** Executive Vice President and Chief Medical Officer Otsuka Pharmaceutical
Clinical Perspective	**Alireza Atri, MD, PhD** Director Banner Sun Health Research Institute
Benefit / Risk Summary	**Mary Hobart, PhD** Vice President, Global Regulatory Affairs Otsuka Pharmaceutical

Additional Responders

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Unmet Need in AAD

Zahinoor Ismail, MD, FRCPC

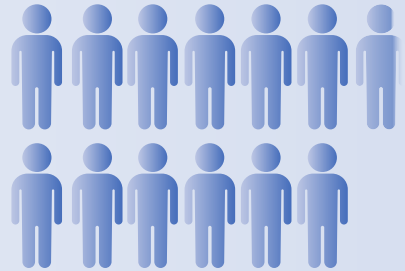
Professor of Psychiatry, Neurology, Epidemiology, and Pathology
Hotchkiss Brain Institute & O'Brien Institute for Public Health
University of Calgary

Alzheimer's Dementia Is Highly Prevalent and Expected to Increase Significantly in Coming Decades

Alzheimer's is most common form of dementia

~6.5 MILLION 2022

2050 ~12.7 MILLION



Alzheimer's Disease Facts and Figures, 2022

~ Half of Patients with Alzheimer's Dementia Develop Agitation

- International Psychogeriatric Association (IPA) defines agitation in dementia as ≥ 1 behavior persistent or frequently recurrent for ≥ 2 weeks[1,2]

Excessive Motor Activity Behaviors

- Pacing
- Rocking
- Gesturing
- Pointing fingers
- Restlessness
- Performing repetitious mannerisms

Verbal Aggression Behaviors

- Yelling
- Speaking in an excessively loud voice
- Using profanity
- Screaming
- Shouting

Physical Aggression Behaviors

- Grabbing
- Shoving
- Pushing
- Resisting
- Hitting others
- Kicking objects or people
- Scratching
- Biting
- Throwing objects
- Hitting self
- Slamming doors
- Tearing things
- Destroying property

1. Cummings et al. 2015; 2. Sano et al. 2023

AAD Worsens Impact of Already Devastating and Burdensome Disease for Patient and Caregiver

PATIENT[1-5]

- Accelerated disease progression
- Functional decline
- Poorer quality of life
- Greater mortality
- Higher rates of institutionalization

CAREGIVER[6-10]

- Anxiety and depression
- Further increases burden of care
- **> 20 hours per week** supervising and providing care to patients
- Caregiver distress can lead to institutionalization

1. Banerjee et al. 2006; 2. Halpern et al. 2019; 3. Koenig et al. 2016; 4. Peters et al. 2015; 5. Scarmeas et al. 2007;
6. Cohen-Mansfield 2008; 7. Allegri et al. 2006; 8. Grossberg et al. 2020; 9. Mohamed et al. 2010; 10. Okura et al. 2011

Evidence Based Approach to Treating AAD

- Nonpharmacological strategies are first line
- Both pharmacological and non-pharmacological treatments often initiated only after clinical emergency
  - Poor recognition of agitation
  - Lack of indicated treatments
  - Reluctance to treat early
- Goal is to reduce agitation and calm patient without sedation

No Approved Medication in US for Agitation in Patients with AD

- Current pharmacotherapy requires balance of risks and benefits
- Choice of medications (all off-label) can depend on acuity of agitation (i.e., frequency, severity, and safety issues)
  - Benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics (both typical and atypical)
- Off-label medications show inconsistent and modest effects and carry several notable safety limitations
    - Sedation, extrapyramidal symptoms, falls, worsened cognitive performance, and cardiovascular and cerebrovascular events
- No labeling to guide use

1. Ismail et al. 2019

Need for Better Identification of AAD and Approved, Well-Documented Pharmacological Treatments

- AAD worsens impact of already devastating and burdensome disease for patients, caregivers, and healthcare system

- Need for FDA-approved product that communicates efficacy and safety expectations in label
- Reduce AAD symptoms with better risk / benefit profile than currently used off-label pharmacotherapy
- Ultimate goal to not sedate patients but reduce AAD symptoms

Efficacy

Robert McQuade, PhD

Executive Vice President and Chief Strategy Officer

Otsuka Pharmaceutical

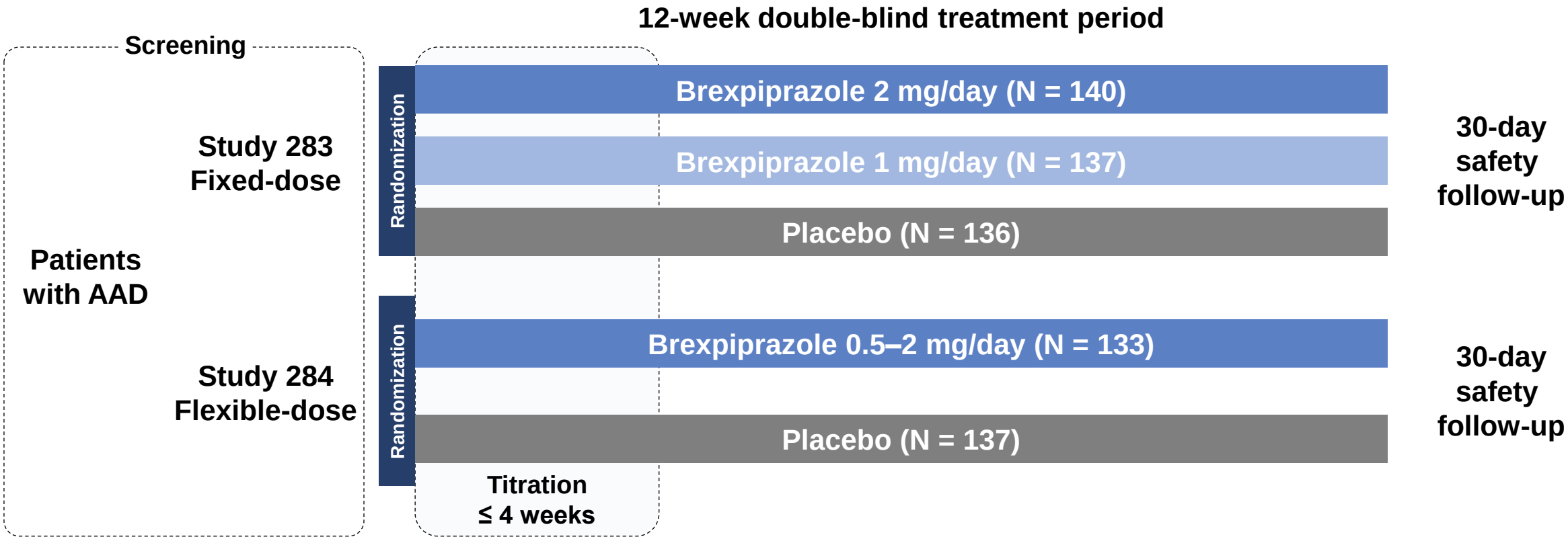
Three Phase 3 Studies Support Efficacy of Brexpiprazole 2 and 3 mg

Study 283
Fixed-dose
1 or 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 284
Flexible-dose
0.5 to 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 213
Fixed-dose
2 or 3 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Studies 283 and 284: Similar Clinical Designs



Titration, Study 283: Brexpiprazole 2 mg: Days 1–3, 0.25 mg; Days 4–14, 0.5 mg; Weeks 3 and 4, 1 mg/day; Weeks 5–12, 2 mg/day
Brexpiprazole 1 mg: Days 1–3, 0.25 mg; Days 4–14, 0.5 mg; Weeks 3 and 4, 1 mg/day; Weeks 5–12, 1 mg/day

Titration, Study 284: Brexpiprazole 0.5–2 mg: Days 1–3, 0.25 mg; Days 4–14, 0.5 mg; Weeks 3 and 4, 1 mg/day; Weeks 5–12, 2 mg/day

Study 283 originally had a 0.5 mg group which was removed based on new information from completed studies in other indications

Studies 283 and 284: Endpoint Selection

Primary Endpoint	**Mean change in Cohen-Mansfield Agitation Inventory (CMAI) Total Score at Week 12**
Key Secondary Endpoint	**Mean change on Clinical Global Impression of Severity (CGI-S) score as related to agitation at Week 12**

Cohen-Mansfield Agitation Inventory (CMAI): Well-Established Tool

	Factor 1 Aggressive	Factor 2 Physical Non-Aggressive	Factor 3 Verbally Agitated	Other Behaviors (Non-subscale)
Behaviors	▪ Hitting ▪ Kicking ▪ Pushing ▪ Scratching ▪ Hurting self or others ▪ Tearing things ▪ Throwing things ▪ Screaming ▪ Cursing or verbal aggression ▪ Grabbing ▪ Biting ▪ Spitting	▪ Pace, aimless wandering ▪ Inappropriate dress or disrobing ▪ Trying to get to different place ▪ Handling things inappropriately ▪ General restlessness ▪ Performing repetitive mannerisms	▪ Complaining ▪ Constant requests for attention ▪ Negativism ▪ Repetitious sentences or questions	▪ Hiding things ▪ Hoarding things ▪ Making strange noises ▪ Eating/drinking inappropriate substances ▪ Intentional falling ▪ Verbal sexual advances ▪ Physical sexual advances
Range of possible scores	**12 to 84 points**	**6 to 42 points**	**4 to 28 points**	**7 to 49 points**

7-point Scale

Rabinowitz et al. 2005

Studies 283 and 284: Key Enrollment Criteria

Inclusion Criteria

- Adults 55-90 years old
- Diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA criteria and MMSE score 5-22
- Diagnosis of agitation with onset of symptoms ≥ 2 weeks prior to screening
- NPI-NH or NPI/NPI-NH Agitation/Aggression Score ≥ 4 at screening and baseline

Exclusion Criteria

- Dementia or memory impairment not due to Alzheimer's disease
- Axis-1 disorders (schizophrenia, BD, current MDD)
- History of stroke, transient ischemic attack, or pulmonary or cerebral embolism
- Delirium or history of delirium within 30 days of screening
- Serious risk of suicide (Sheehan-STS scale)

MMSE = Mini-Mental State Examination

Studies 283 and 284: Demographics Similar Across and Within Studies

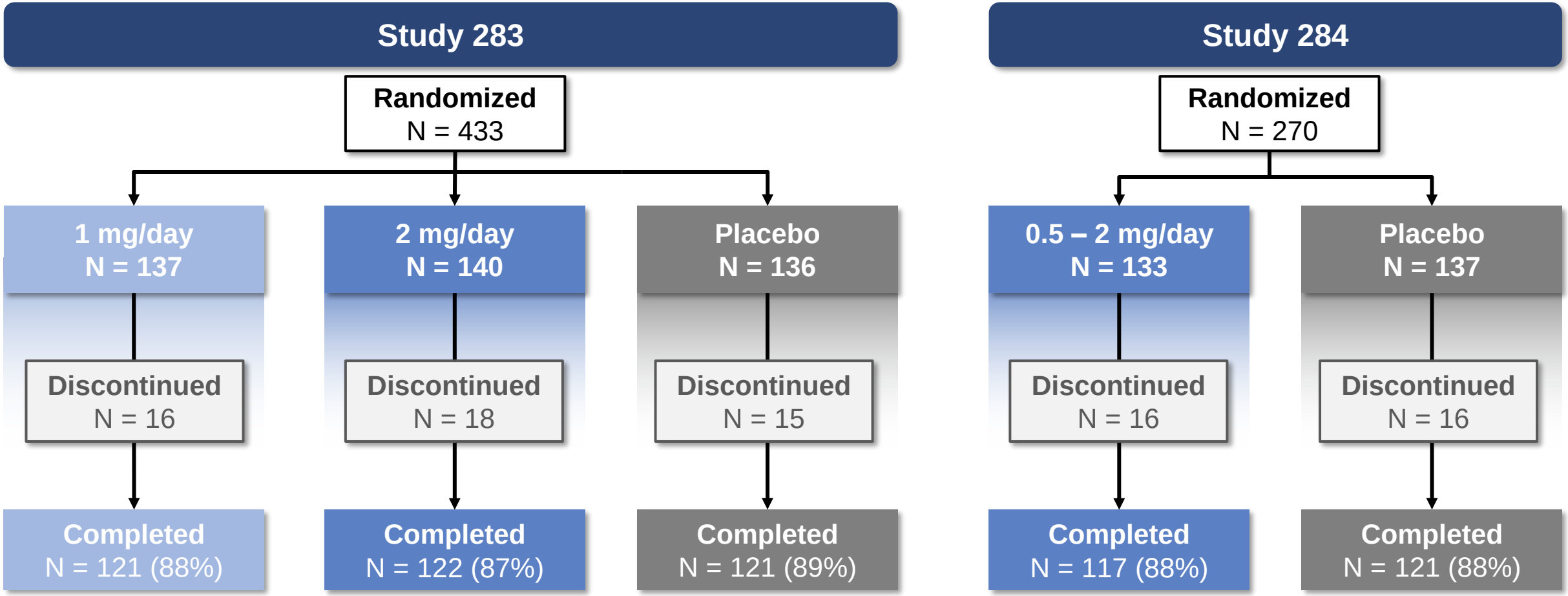
Characteristic	Study 283			Study 284	
	1 mg/day N = 137	2 mg/day N = 140	Placebo N = 136	0.5 – 2 mg/day N = 133	Placebo N = 137
Age (years), Mean	74	74	74	74	74
Female	57%	56%	51%	62%	64%
Race					
White	98%	95%	96%	96%	94%
Black / African-American*	1%	4%	4%	3%	4%
Other	0.7%	1%	0.7%	0.8%	2%
Hispanic or Latino	18%	16%	17%	5%	7%

* Black / African American patients represented 10% and 15% of randomized US patients

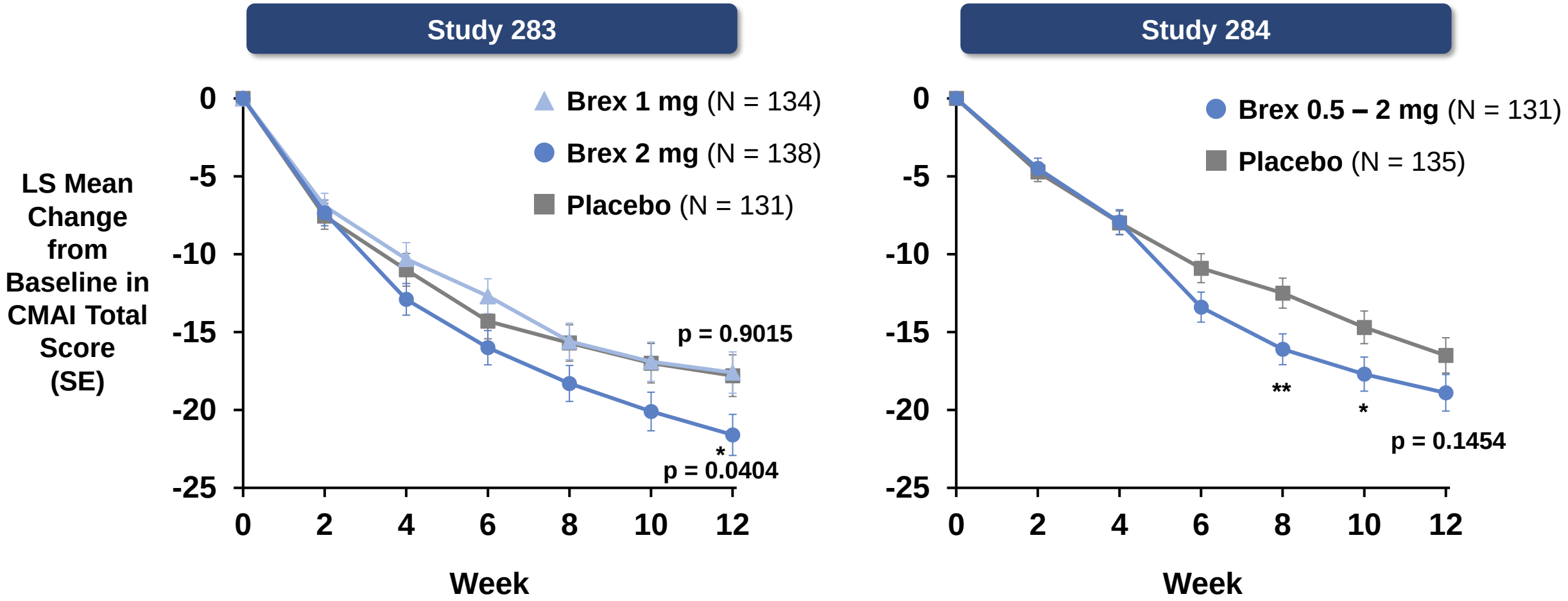
Studies 283 and 284: Representative of Patients with AAD with Similar Disease Characteristics

Characteristic	Study 283			Study 284	
	1 mg/day N = 137	2 mg/day N = 140	Placebo N = 136	0.5 – 2 mg/day N = 133	Placebo N = 137
CMAI total score, Mean	**70.7**	**71.0**	**72.0**	**71.4**	**68.5**
CGI severity score, Mean	**4.5**	**4.5**	**4.5**	**4.5**	**4.5**
Dementia severity (MMSE)					
Mild (> 18)	**5%**	**8%**	**14%**	**21%**	**25%**
Moderate (13 – 18)	**55%**	**62%**	**54%**	**48%**	**47%**
Severe (≤ 12)	**39%**	**30%**	**32%**	**31%**	**28%**
Institutionalized	**65%**	**61%**	**65%**	**55%**	**55%**
Time since diagnosis of Alzheimer's (months), Mean	**36.7**	**31.3**	**32.3**	**28.2**	**32.1**
Time since onset of current agitation episode (months), Mean	**7.0**	**9.3**	**4.7**	**5.2**	**4.5**

Studies 283 and 284: Similar Completion Rates

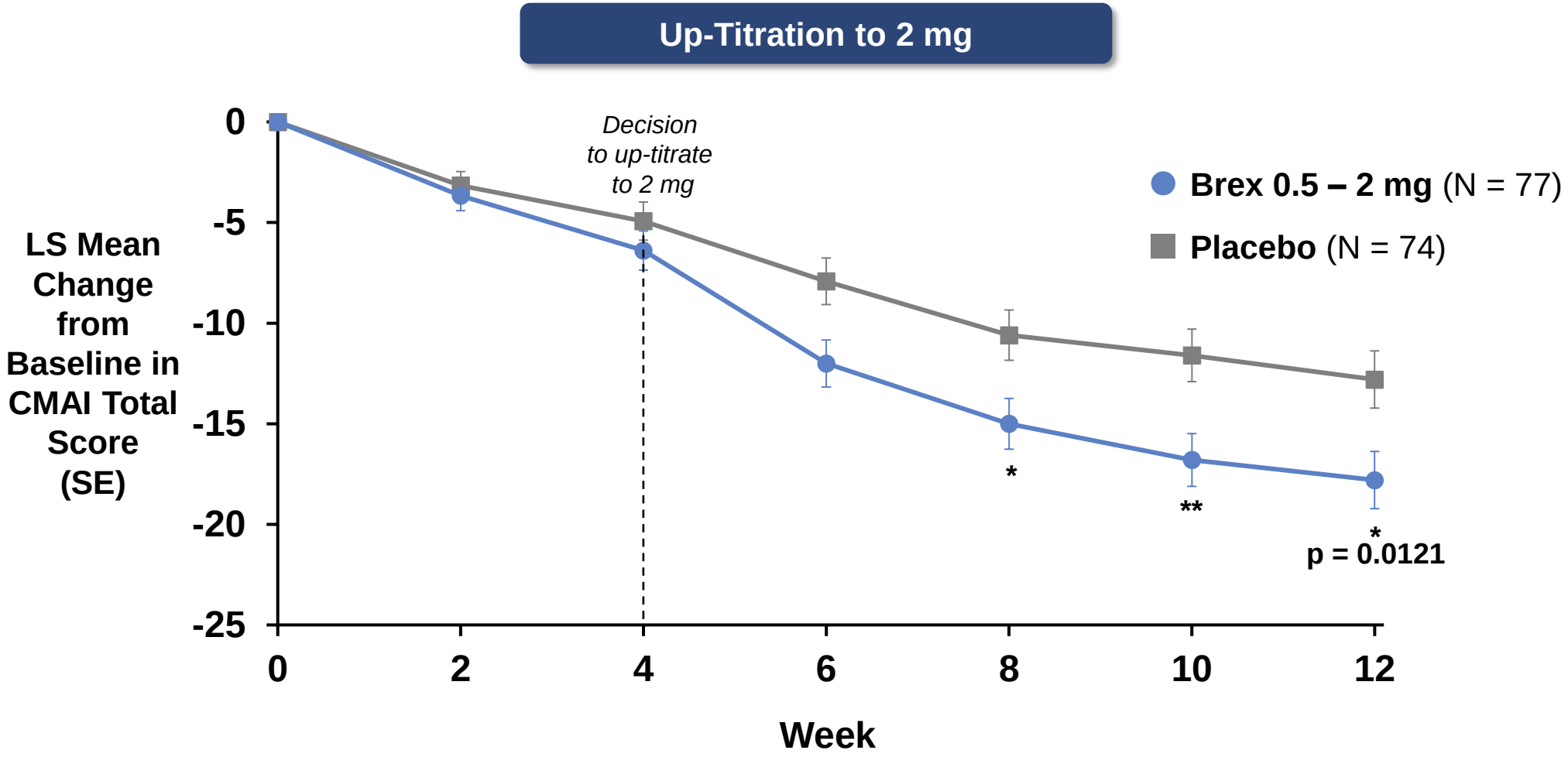


Studies 283 and 284: Primary CMAI Results Show Improvements with Brexpiprazole



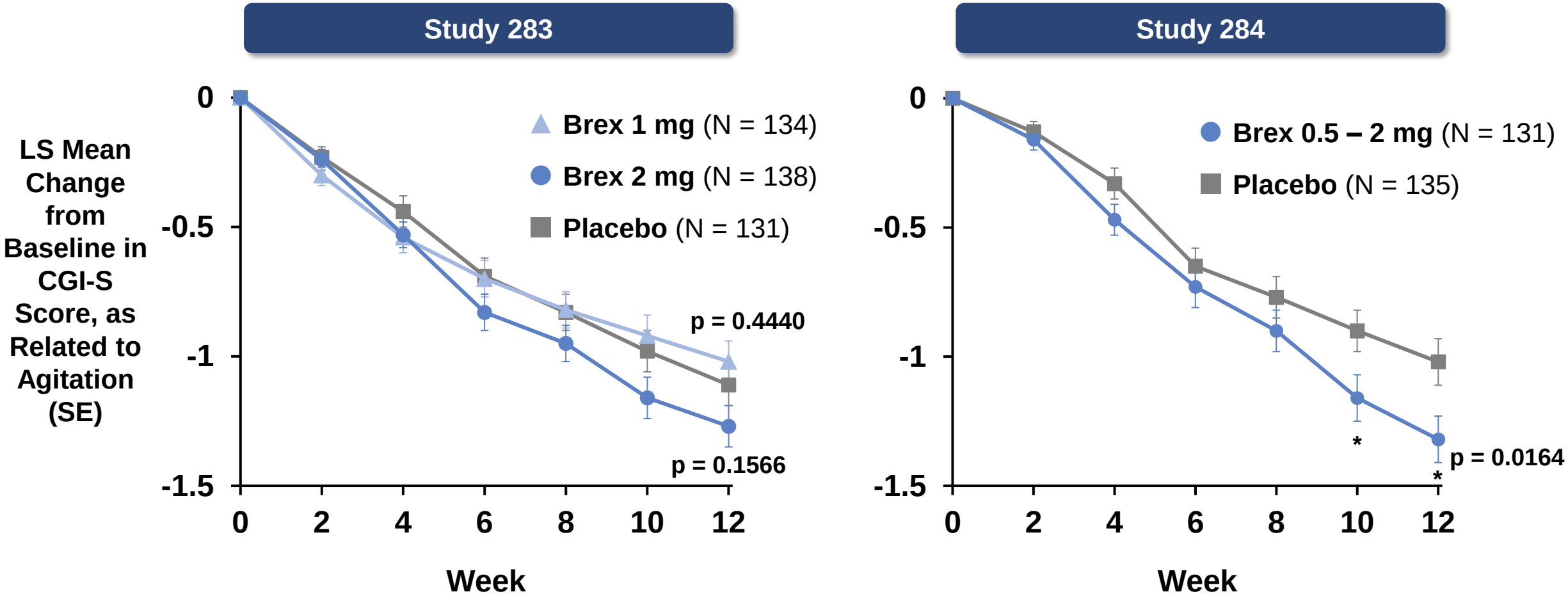
*p<0.05, **p<0.01 versus placebo; MMRM

Study 284: Patients Up-Titrated to Brexpiprazole 2 mg Demonstrated Efficacy on CMAI Total Score (Post-Hoc)



*p<0.05, **p<0.01 versus placebo; nominal p-values presented; MMRM

Studies 283 and 284: Improvement on Key Secondary (CGI-S) Endpoint with Brexpiprazole



*p<0.05 versus placebo; MMRM

Studies 283 and 284: Key Conclusions

- Study 283 met primary endpoint; Study 284 did not
- Data supports efficacy of brexpiprazole 2 mg
  - 2 mg identified as minimum effective dose

Studies 283 and 284: Enrollment of Some Patients with Insufficient Agitation May Have Impacted Results

Agitation inclusion criterion in 283 and 284 based on NPI-NH Agitation/Aggression item score of ≥ 4[1] not on CMAI

Focused on behaviors that are more prominent and more impactful on patient's and caregiver's quality of life

- **CMAI Factor 1* encompasses physical and verbal aggressive behaviors[2]**

Post-hoc analyses of patients meeting criteria for Factor 1 demonstrated greater baseline frequency and greater effect of treatment over placebo

- **~ 86% met criteria for CMAI Factor 1 with baseline of 71-75 points**
- **Those who did not meet Factor 1 criteria had baseline of 55-59 points**

*To meet criterion, one of following must be displayed: i. ≥ 1 aggressive behaviors occurring several times per week; ii. ≥ 2 aggressive behaviors occurring once or twice per week; iii. ≥ 3 aggressive behaviors occurring less than once per week

1. Grossberg et al. 2020; 2. Rabinowitz et al. 2005

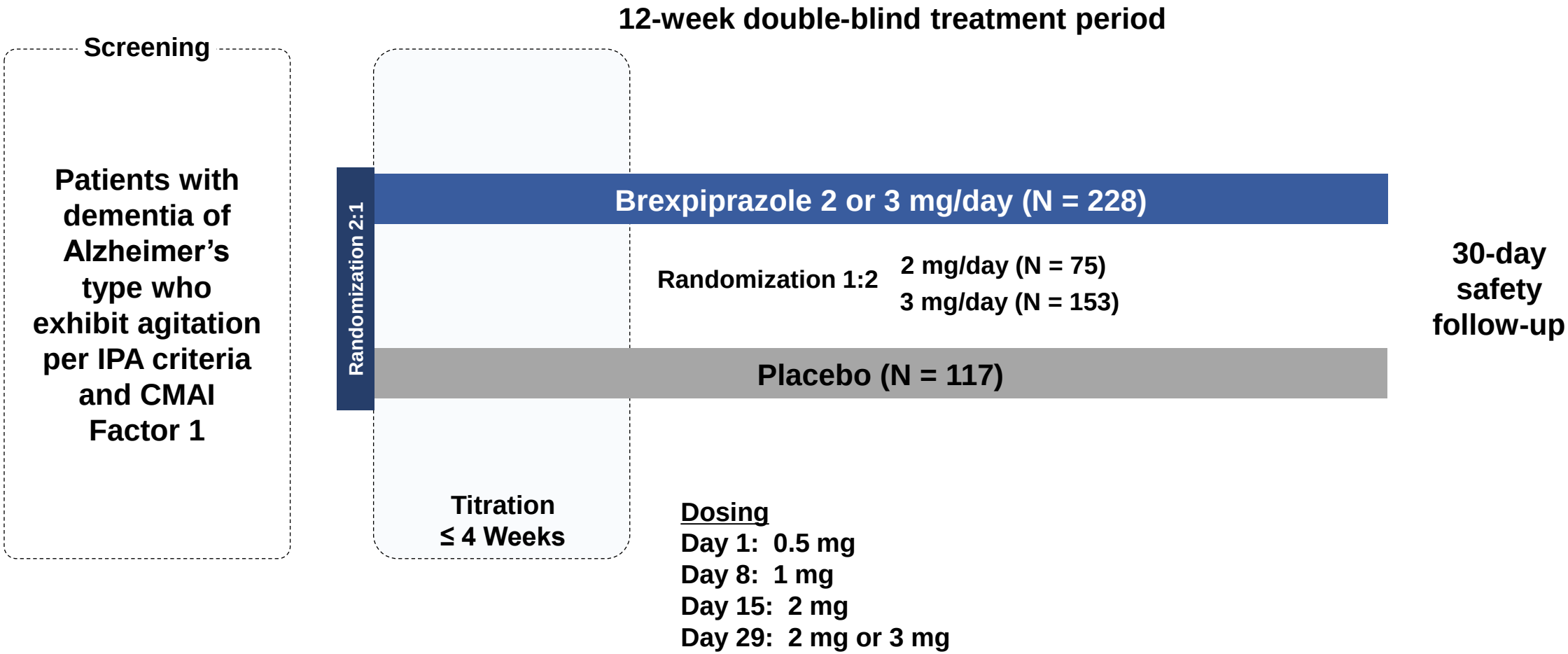
Three Phase 3 Studies Support Efficacy of Brexpiprazole 2 and 3 mg

Study 283
Fixed-dose
1 or 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 284
Flexible-dose
0.5 to 2 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 213
Fixed-dose
2 or 3 mg/day
Randomized, double-blind, placebo-controlled
12 Weeks

Study 213: Clinical Design Based on FDA Feedback



The study had an interim analysis at 255 patients. Decision to move to full sample of 330. Alpha level for final analysis is 0.035.
For all patients who terminated early from the study, a mortality assessment was obtained from the patient's caregiver by telephone contact at Week 16

Study 213: Key Enrollment Criteria Included Enrichment for More Prominent Agitated Behaviors

Inclusion Criteria

- Adults 55-90 years old
- Diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA criteria and MMSE score 5-22
- Diagnosis of agitation **meeting IPA provisional definition** and onset of symptoms ≥ 2 weeks prior to screening
- NPI-NH or NPI/NPI-NH Agitation/Aggression Score ≥ 4 at screening and baseline
- **Meet criteria for CMAI Factor 1 at baseline**

Exclusion Criteria

- Dementia or memory impairment not due to Alzheimer's disease
- Axis-1 disorders (schizophrenia, BD, current MDE)
- History of stroke, transient ischemic attack, or pulmonary or cerebral embolism
- Delirium or history of delirium within 30 days of screening
- Serious risk of suicide (Sheehan-STS scale)

Study 213: Endpoint Selection Same as 283 and 284

Primary Endpoint	**Mean change in Cohen-Mansfield Agitation Inventory (CMAI) Total Score at Week 12**
Key Secondary Endpoint	**Mean change on Clinical Global Impression of Severity (CGI-S) score as related to agitation at Week 12**

Study 213: Demographics Consistent Across Arms

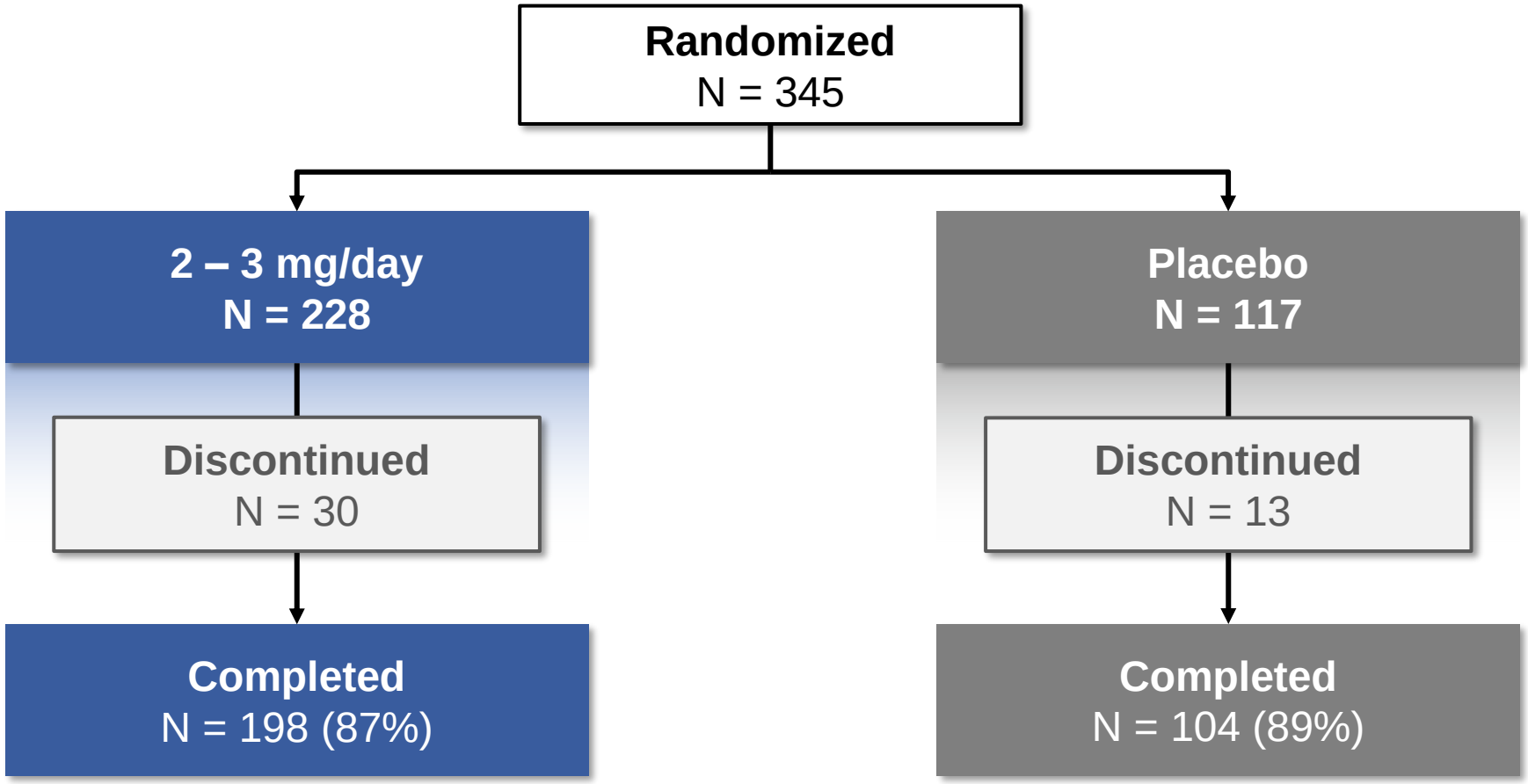
Characteristic	2 mg/day N = 75	3 mg/day N = 153	Placebo N = 117
Age (years), Mean	74	75	73
Female	57%	60%	51%
Race			
White	93%	94%	98%
Black / African-American*	7%	4%	1%
Other	0%	2%	0.9%
Hispanic or Latino	33%	30%	32%

* Black / African American patients represented 8% of randomized US patients

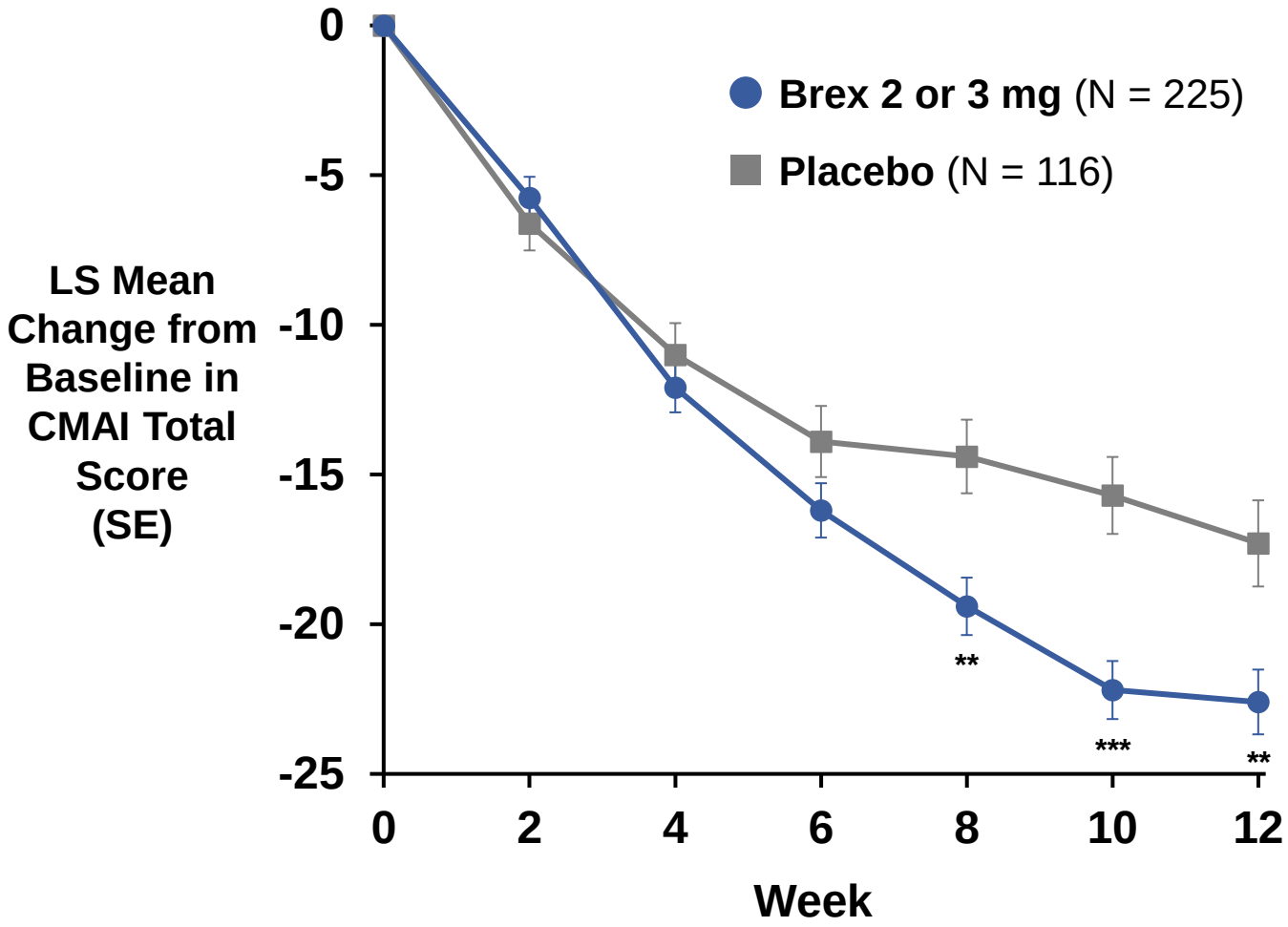
Study 213: Disease Characteristics Similar Across Arms

Characteristic	2 mg/day N = 75	3 mg/day N = 153	Placebo N = 117
CMAI total score, Mean	**78.6**	**81.2**	**79.4**
CGI severity score, Mean	**4.6**	**4.7**	**4.7**
Dementia severity (MMSE)			
Mild (> 18)	**21%**	**24%**	**24%**
Moderate (13 – 18)	**64%**	**52%**	**56%**
Severe (≤ 12)	**15%**	**24%**	**20%**
Institutionalized	**43%**	**42%**	**46%**
Time since diagnosis of Alzheimer's (months), Mean	**34.5**	**37.8**	**34.1**
Time since onset of current agitation episode (months), Mean	**9.0**	**10.5**	**8.9**

Study 213: Most Patients Completed Study



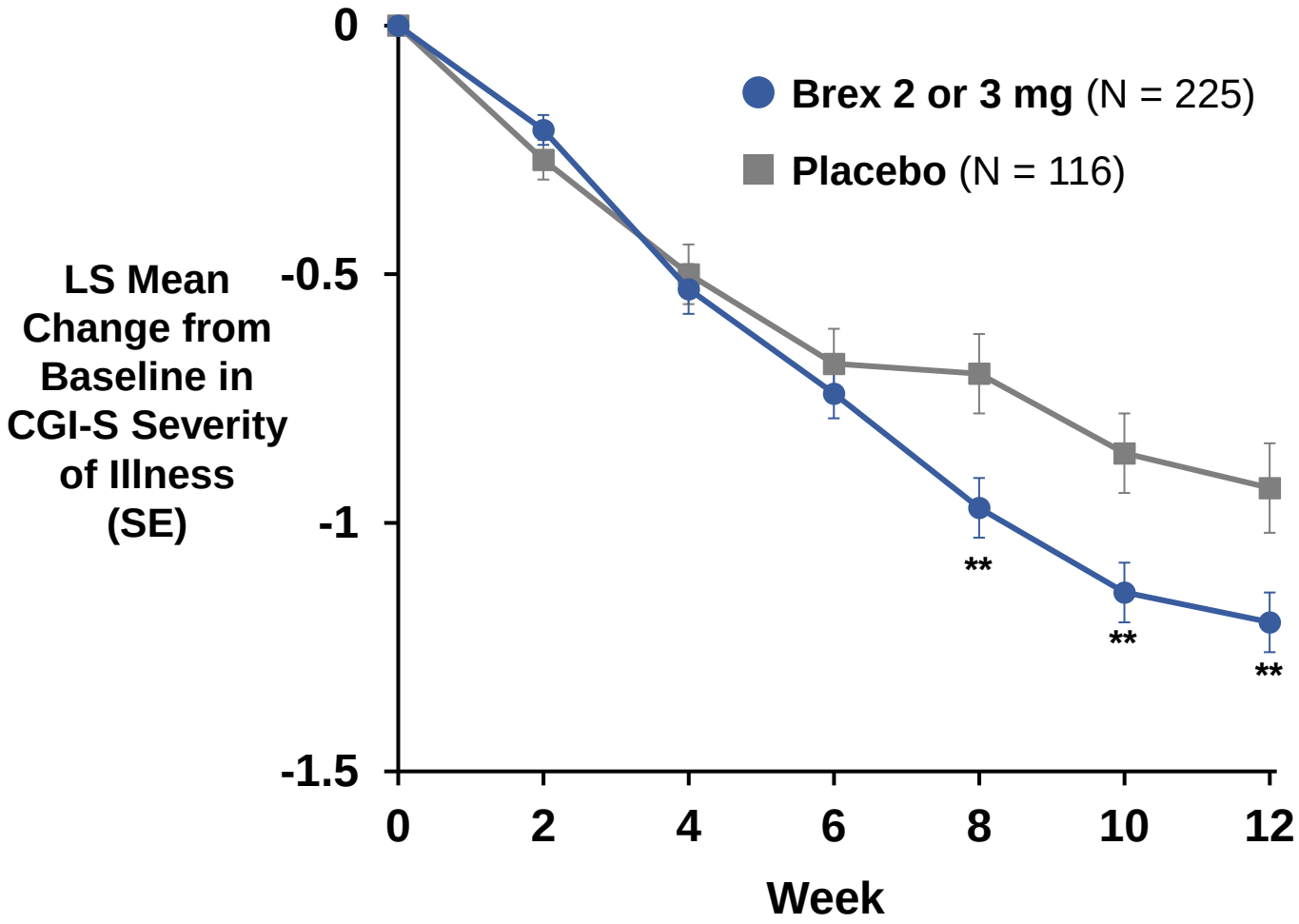
Study 213: Brexpiprazole 2 or 3 mg Significant Improvement vs Placebo in Primary Endpoint CMAI



	Brexpiprazole N = 225	Placebo N = 116
CMAI Total score at baseline, Mean (SD)	80.6 (16.6)	79.2 (17.5)
Mean Change in CMAI Total score at Week 12, LS Mean (SE)	-22.6 (1.08)	-17.3 (1.44)
Treatment Difference at Week 12 (95% CI)	-5.32 (-8.77, -1.87) p = 0.0026	

**p<0.01, ***p<0.001 versus placebo; MMRM

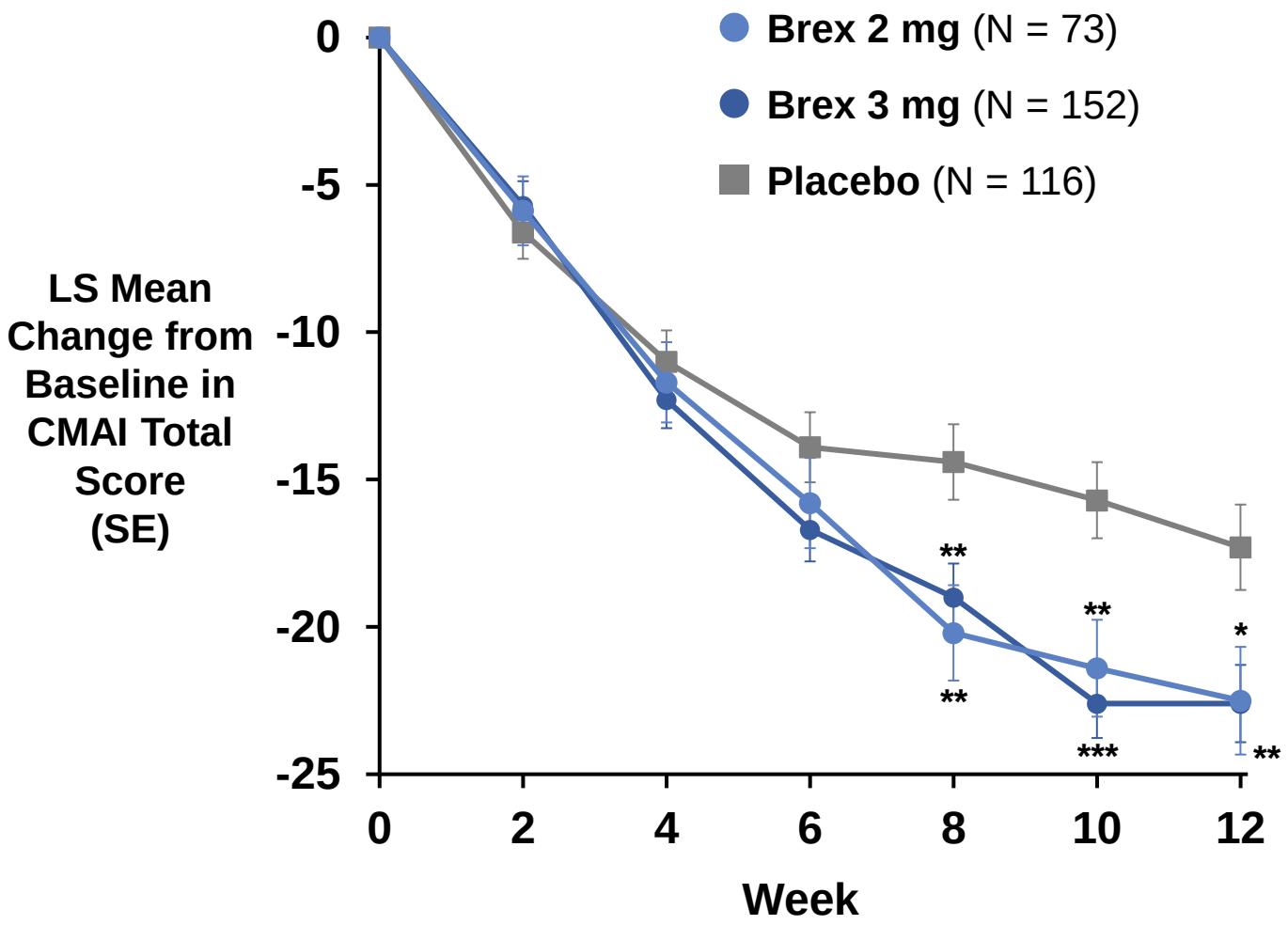
Study 213: Brexpiprazole 2 or 3 mg Significant Improvement vs Placebo in Key Secondary Endpoint CGI-S



	Brexpiprazole N = 225	Placebo N = 116
CGI-S score at baseline, Mean (SD)	4.71 (0.66)	4.71 (0.69)
Mean Change in CGI-S score at Week 12, LS Mean (SE)	-1.20 (0.06)	-0.93 (0.08)
Treatment Difference at Week 12 (95% CI)	-0.27 (-0.47, -0.07) p = 0.0078	

**p<0.01 versus placebo; MMRM

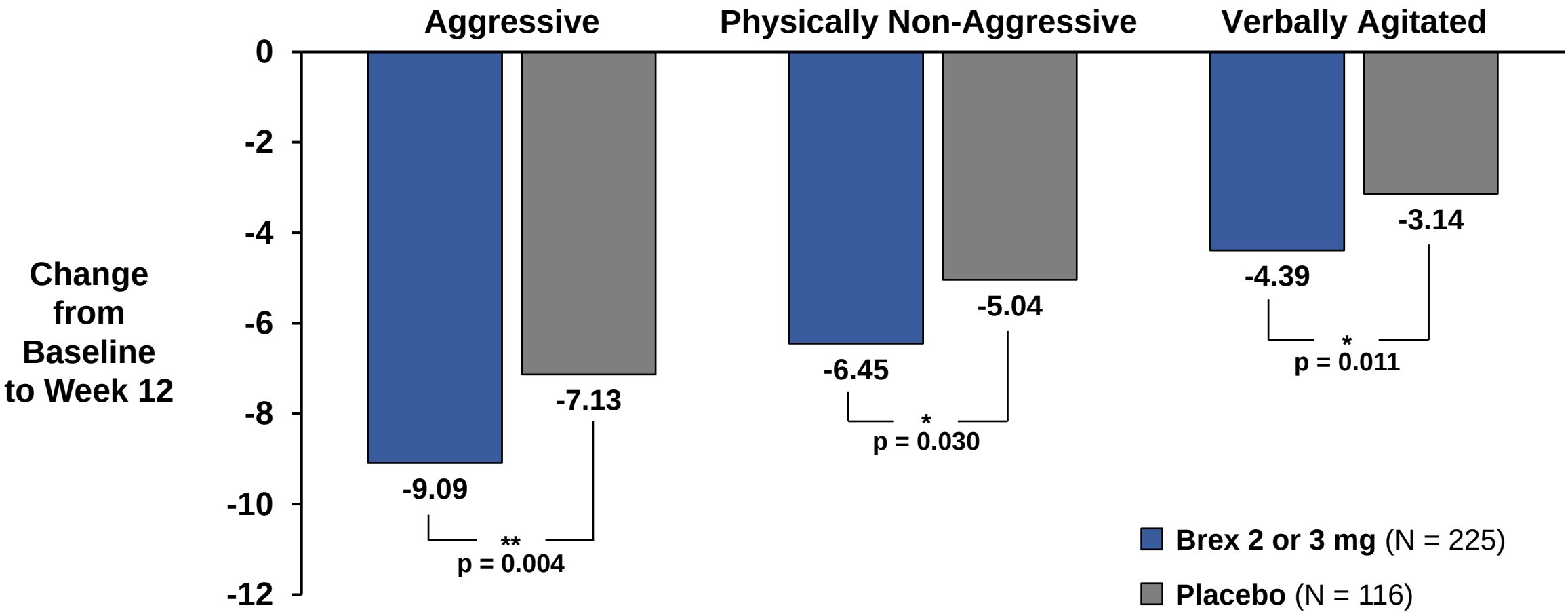
Study 213: CMAI Endpoint Demonstrates Improvement vs Placebo for Both Brexpiprazole 2 and 3 mg



	Brex 2 mg N = 73	Brex 3 mg N = 152	Placebo N = 116
CMAI Total score at baseline, Mean (SD)	79.1 (15.2)	81.3 (17.3)	79.2 (17.5)
Mean Change in CMAI Total score at Week 12, LS Mean (SE)	-22.5 (1.83)	-22.6 (1.31)	-17.3 (1.45)
Treatment Difference at Week 12 (95% CI)	-5.28 (-9.77, -0.78) p = 0.0216	-5.35 (-9.09, -1.60) p = 0.0053	---

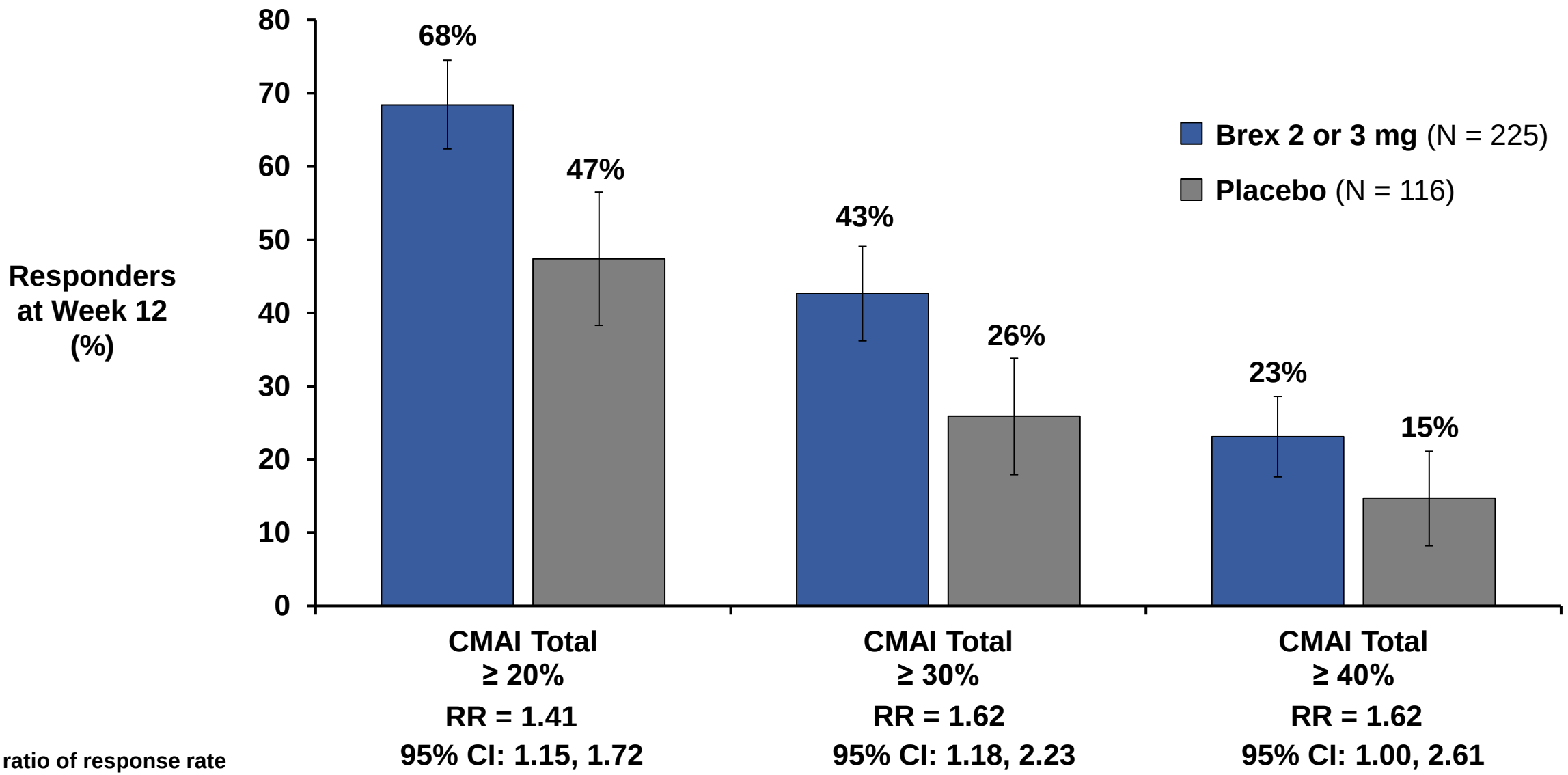
*p<0.05, **p<0.01, ***p<0.001 versus placebo; nominal p-values presented; MMRM

Study 213: Brexpiprazole Separated from Placebo Across 3 Key Factors of Agitation



*p<0.05, **p<0.01 versus placebo; nominal p-values presented; MMRM

Study 213: Higher Percentage of Responders with Brexpiprazole vs Placebo on CMAI Total Score

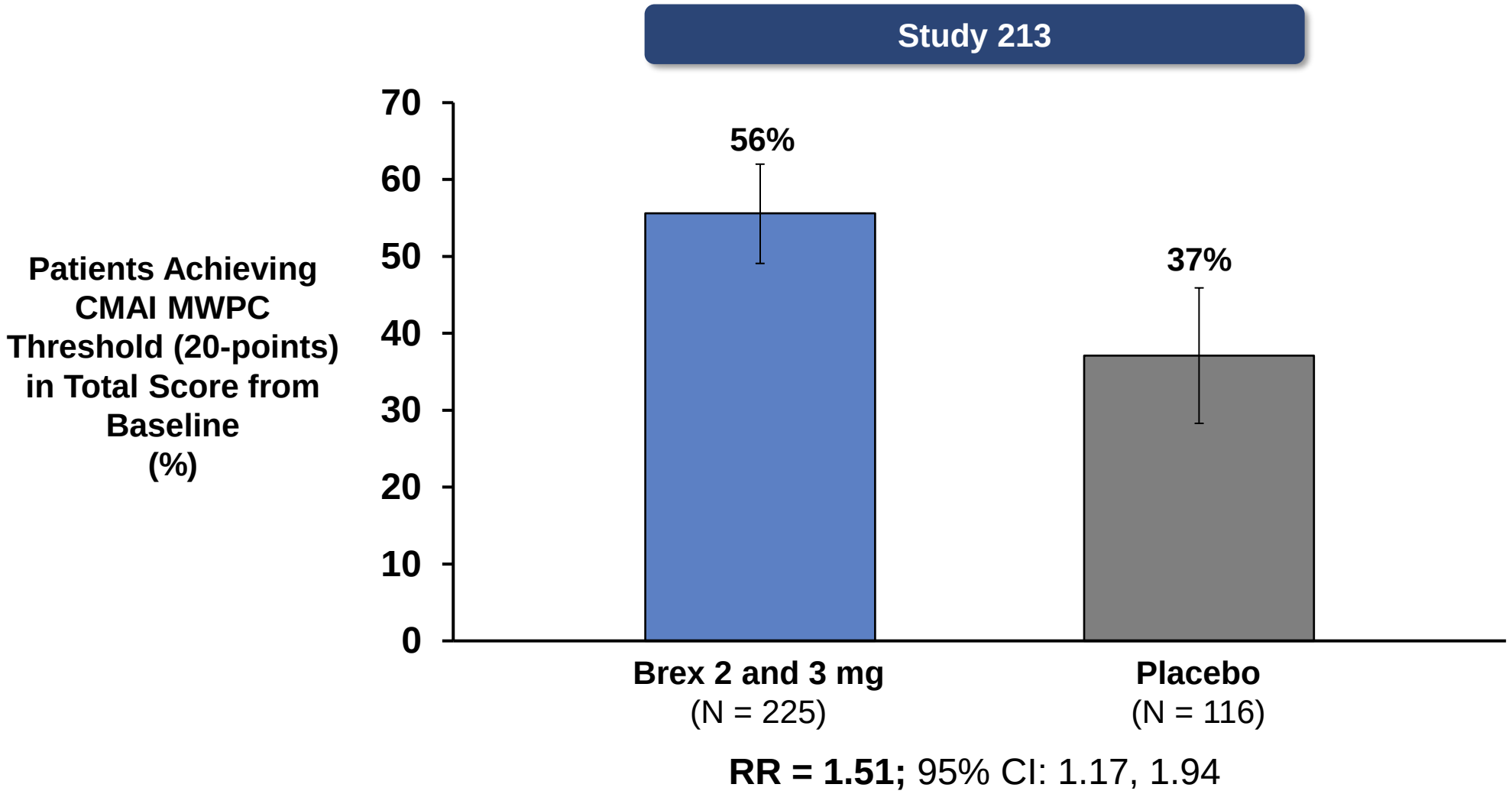


RR: ratio of response rate

CMAI Reduction Strongly Correlated with Improvement on CGI-S

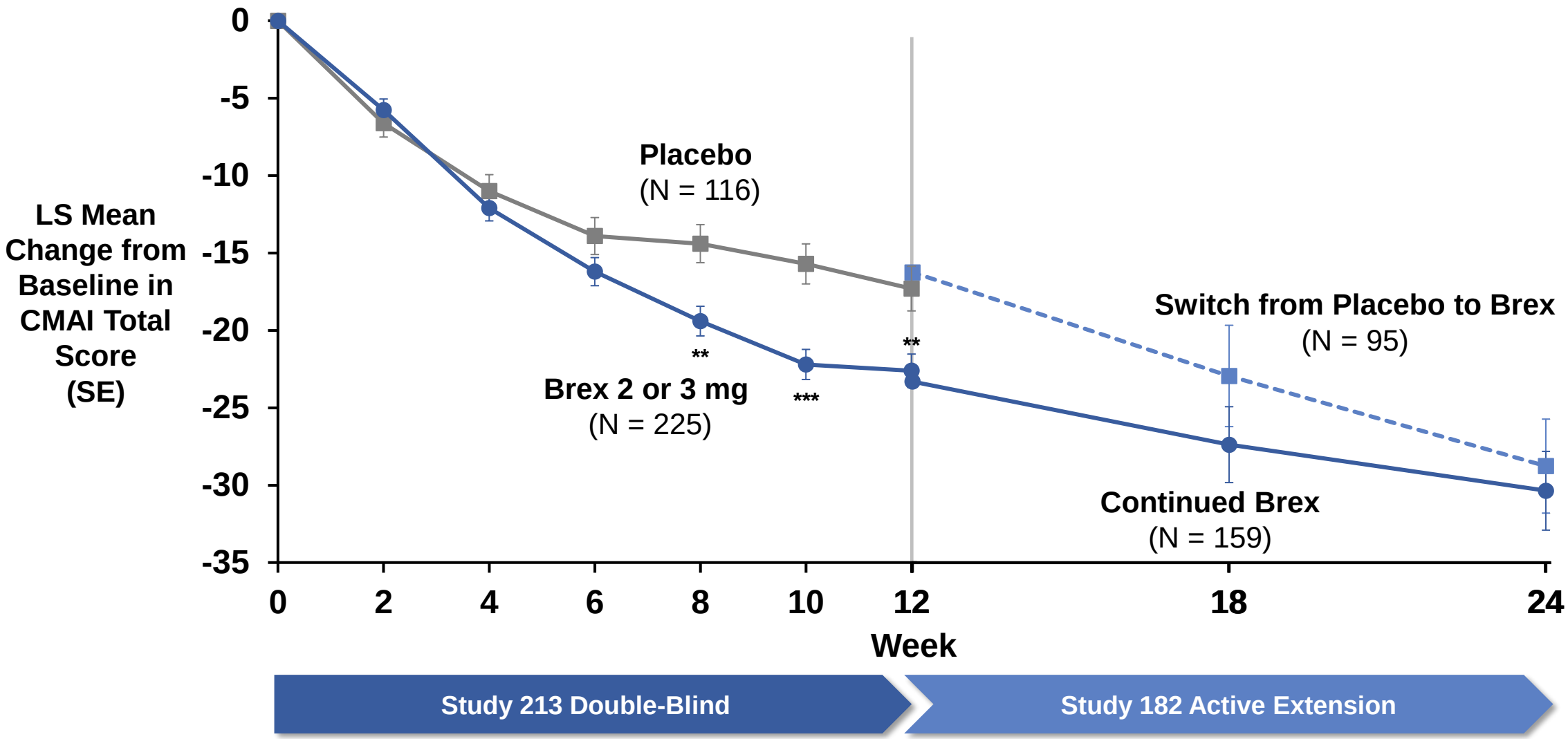
- Strong correlation between reductions in CMAI Total Score and CGI-S
- Meaningful within patient change threshold in CMAI (20-point reduction) correlated to improvement of CGI-S (2-point reduction)

Higher Percentage of Brexpiprazole-Treated Patients Achieve Meaningful Within Patient Change Threshold



MWPC: meaningful within patient change; RR: ratio of response rate

Study 182: Continued Improvements Observed in 12-Week Extension Trial with Brexpiprazole Treatment



**p<0.01, ***p<0.001 versus placebo; MMRM

Brexpiprazole Shows Consistent Efficacy Across 3 Trials Supporting Meaningful Benefit to Patients with AAD

Trial Number and Analysis	Daily Dose	CMAI Result	CMAI p-value	CGI-S Result	CGI-S p-value
Pre-specified Analyses					
Study 283 ITT	**2 mg**	-3.77	**0.0404**	-0.16	0.1566
Study 213 ITT	**2 or 3 mg**	-5.32	**0.0026**	-0.27	**0.0078**
Study 284 ITT	**0.5 – 2 mg** (Mean dose 1.54 mg)	-2.34	0.1454	-0.31	**0.0164***

***Nominal p-values not adjusted for multiple comparisons**
Bolded text indicates p-values or nominal p-values < 0.05, and Cohen's-D Effect size of 0.25 to 0.35

Safety

John Kraus, MD, PhD

Executive Vice President and Chief Medical Officer
Otsuka Pharmaceutical

Brexpiprazole AAD Safety Population

Three Phase 3 Studies

N = 432	**Study 283** Fixed-dose (1 or 2 mg/day)
N = 269	**Study 284** Flexible-dose (0.5 to 2 mg/day)
N = 342	**Study 213** Fixed-dose (2 or 3 mg/day)

N = 655	All Brexpiprazole	Placebo	N = 388

In AAD short-term controlled trials, completion rate was 88%

Brexpiprazole Generally Safe and Well-Tolerated in Patients with AAD, Similar with Established Safety Profile

N (%)	Brexpiprazole Fixed ≤ 1 mg N = 157	Brexpiprazole Fixed 2 mg N = 213	Brexpiprazole Fixed 3 mg N = 153	All Brexpiprazole N = 655	Placebo N = 388
≥ 1 AE	77 **(49%)**	119 **(56%)**	64 **(42%)**	335 **(51%)**	178 **(46%)**
AEs leading to discontinuation	14 **(9%)**	7 **(3%)**	11 **(7%)**	41 **(6%)**	13 **(3%)**
Serious AEs	16 **(10%)**	13 **(6%)**	6 **(4%)**	42 **(6%)**	16 **(4%)**
Deaths	4 **(2.5%)**	1 **(0.5%)**	1 **(0.7%)**	6 **(0.9%)**	1 **(0.3%)**

Brexpiprazole flexible dose 0.5 – 2 mg group from Study 284 not included in this table

AEs Generally Consistent Across Groups

Three Phase 3 Studies

MedDRA Preferred Term ≥ 2%, N (%)	Brexpiprazole Fixed 2 to 3 mg N = 366	All Brexpiprazole N = 655	Placebo N = 388
Headache	28 **(8%)**	50 **(8%)**	36 **(9%)**
Dizziness	14 **(4%)**	21 **(3%)**	13 **(3%)**
Insomnia	12 **(3%)**	24 **(4%)**	11 **(3%)**
Somnolence	12 **(3%)**	22 **(3%)**	7 **(2%)**
Urinary tract infection	12 **(3%)**	17 **(3%)**	6 **(2%)**
Nasopharyngitis	9 **(2%)**	18 **(3%)**	10 **(3%)**
Asthenia	8 **(2%)**	11 **(2%)**	5 **(1%)**
Fall	7 **(2%)**	11 **(2%)**	10 **(3%)**
Decreased appetite	6 **(2%)**	10 **(2%)**	10 **(3%)**
Agitation	6 **(2%)**	16 **(2%)**	10 **(3%)**

Serious Adverse Events Generally Low in Frequency

Three Phase 3 Studies

MedDRA Preferred Term ≥ 2 Events in All Brexpiprazole or Placebo, N (%)	Brexpiprazole Fixed 2 to 3 mg N = 366	All Brexpiprazole N = 655	Placebo N = 388
Any SAE	19 **(5%)**	42 **(6%)**	16 **(4%)**
Urinary tract infection	6 **(2%)**	6 **(0.9%)**	1 **(0.3%)**
Agitation	1 **(0.3%)**	3 **(0.5%)**	**0**
Pneumonia	1 **(0.3%)**	2 **(0.3%)**	2 **(0.5%)**
Hip fracture	1 **(0.3%)**	1 **(0.2%)**	2 **(0.5%)**
Chronic obstructive pulmonary disease	1 **(0.3%)**	2 **(0.3%)**	**0**
Dementia Alzheimer's type	1 **(0.3%)**	2 **(0.3%)**	**0**
Fall	1 **(0.3%)**	2 **(0.3%)**	**0**
Syncope	**0**	1 **(0.2%)**	2 **(0.5%)**
Seizure	**0**	2 **(0.3%)**	1 **(0.3%)**

Safety Topics of Special Interest Expected and Balanced Across Treatment Groups

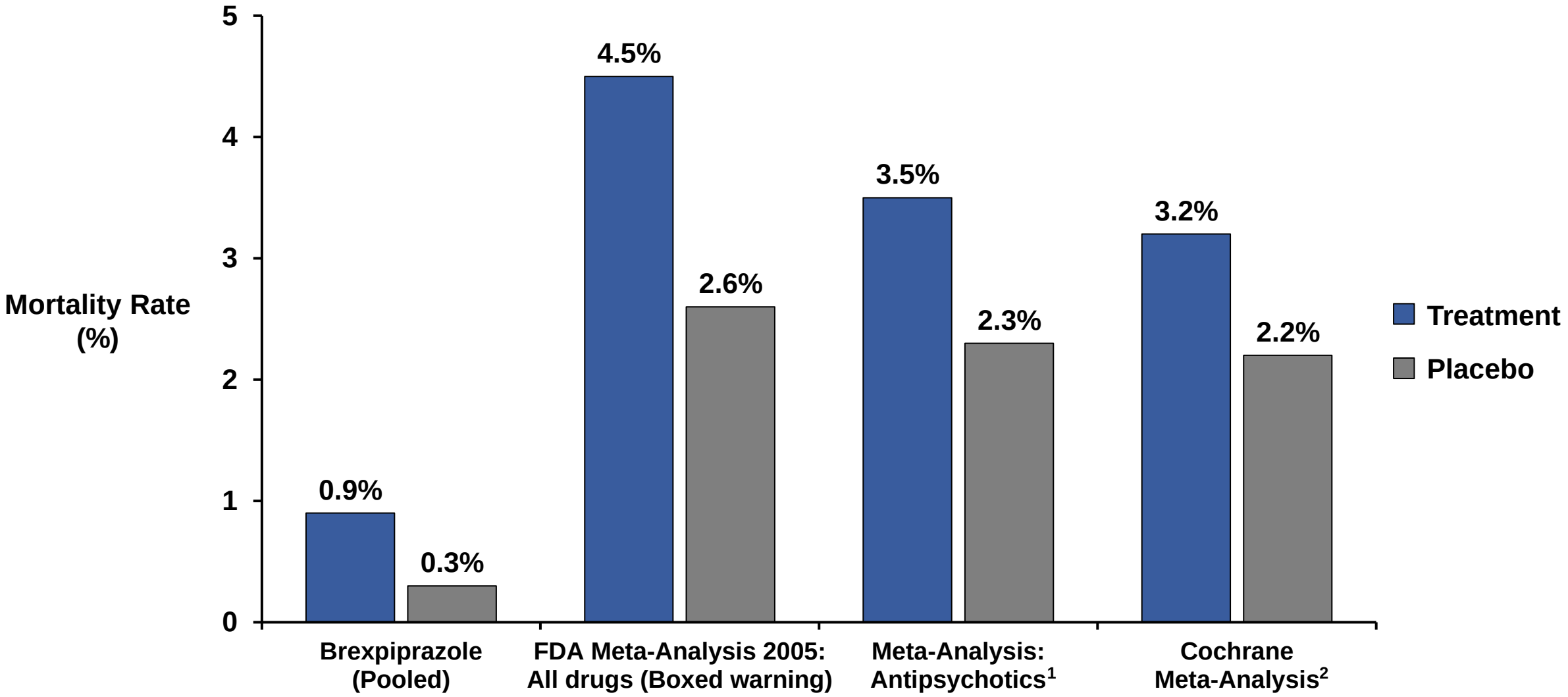
Three Phase 3 Studies

System Organ Class / Preferred Term, N (%)	Brexpiprazole Fixed 2 to 3 mg N = 366	All Brexpiprazole N = 655	Placebo N = 388
Orthostatic hypotension, dizziness and syncope	17 **(5%)**	30 **(5%)**	19 **(5%)**
Extrapyramidal symptoms (EPS)[1]	17 **(5%)**	35 **(5%)**	12 **(3%)**
Somnolence, sedation	13 **(4%)**	24 **(4%)**	7 **(2%)**
Cardiovascular events[1]	10 **(3%)**	24 **(4%)**	9 **(2%)**
Cerebrovascular events[1]	**0**	3 **(0.5%)**	1 **(0.3%)**
Accidents and injuries[1]	8 **(2%)**	15 **(2%)**	16 **(4%)**
Falls	7 **(2%)**	11 **(2%)**	10 **(3%)**

- No worsening in cognition as assessed by MMSE change from baseline compared to placebo

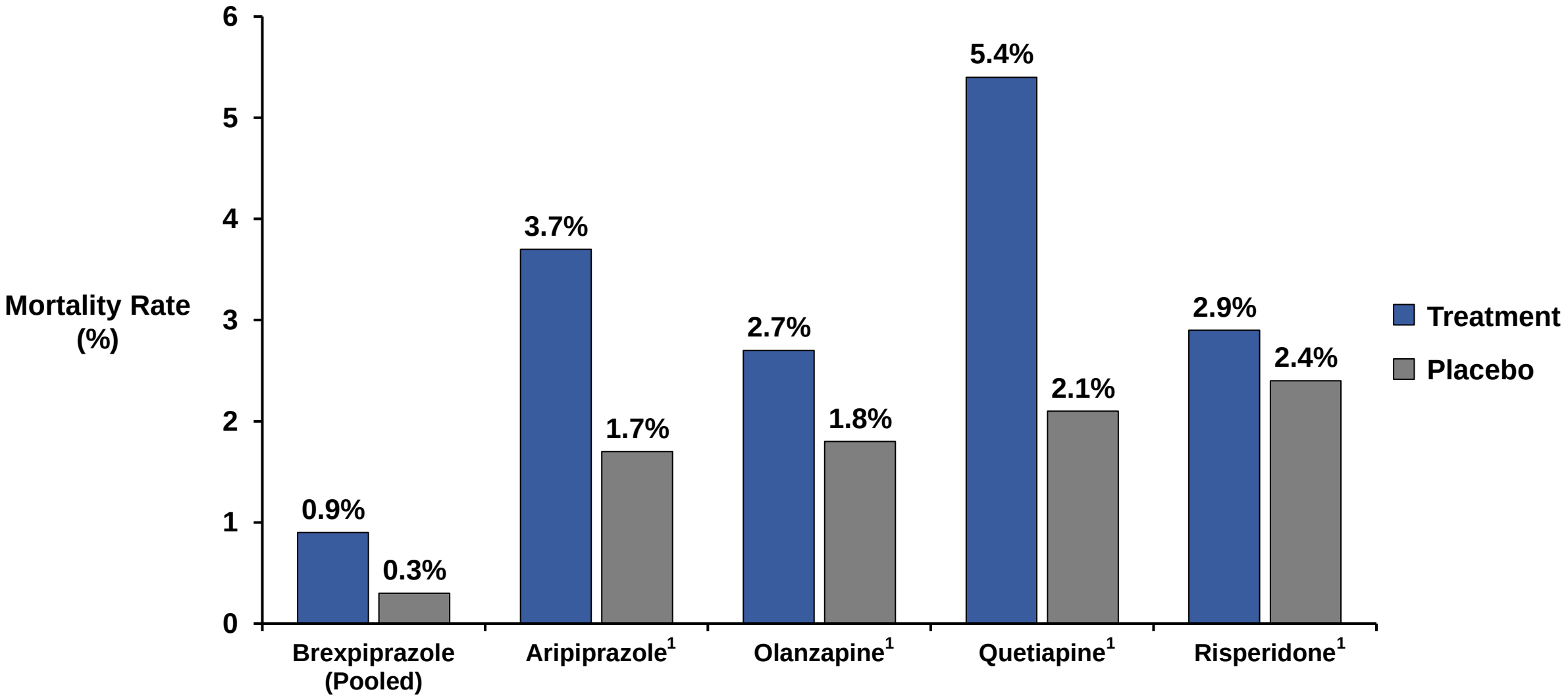
1. Grouped terms
MMSE = Mini-Mental State Examination

< 1% Mortality Rate Observed in Brexpiprazole AAD Program Lower than Meta-Analyses for Other Antipsychotics



1. Schneider et al. 2005; 2. Mühlbauer et al. 2021 (Data presented exclude brexpiprazole studies)

Lower Mortality Rates with Brexpiprazole Compared to Other Antipsychotics in Elderly Population with Dementia



1. Mühlbauer et al. 2021 – Included majority of studies with AD population, similar age range and study duration with Brexpiprazole AAD program

Events Within Study or 30-Day Follow-Up Period that Led to Death from Three Phase 3 Studies

Study	Dose	Age	Sex	Study Treatment Duration (days)	Days Since Last Dose Prior to Death	Fatal Event Verbatim	Treatment Completion	Relevant Details
283	0.5 mg	87	F	8	27	Intracranial hemorrhage	Withdrew – Fall	History of subarachnoid hemorrhage and recent initiation of clopidogrel
283	0.5 mg	76	M	50	2	Acute purulent meningoencephalitis	Withdrew – Personal reason	Multiple significant medical conditions, incidental infection-related event
283	1 mg	78	M	65	13	Aspiration pneumonia	Withdrew – Aspiration pneumonia	History of COPD, gastritis, oesophagitis and encephalopathy
283	1 mg	66	F	85	67	Airway obstruction	Completed	Choked on an orange
283	2 mg	86	F	86	9	End stage Alzheimer's dementia	Completed	Transferred to hospice, disease progression
213	3 mg	78	M	28	23	Heart failure	Withdrew – Hallucinations	Concurrent pneumonia, autopsy showed cerebral and coronary atherosclerosis
284	Placebo	86	M	74	2	Pneumonia	Completed	Bed bound, lived in nursing home

2 additional deaths not included. One patient in Study 284 died from vascular encephalopathy and brain edema 2 days after 30-day protocol specified safety follow-up period. One patient in Study 284 died from pancreatic cancer > 100 days after last dose

Study 182 Open-Label Extension Study: Use of Brexpiprazole Long-Term Is Safe and Well-Tolerated

- Patients (N = 259) who completed Study 213 rolled over into Brexpiprazole extension trial (Study 182) for 12 weeks of brexpiprazole
  - Of these, 163 patients were exposed to brexpiprazole up to 24 weeks
- Long-term use generally safe and well-tolerated in patients with AAD
  - No new safety signals
  - No deaths
- Safety profile similar to double-blind placebo-controlled studies

Brexpiprazole 2 and 3 mg Safe and Well-Tolerated in Patients with AAD

- AEs comparable between brexpiprazole and placebo
  - Consistent with established safety profile
  - Consistent with events observed from extensive clinical experience
- High tolerability to brexpiprazole with low incidence of discontinuations
- Deaths numerically higher in all brexipiprazole group (0.9%) vs placebo (0.3%)
  - No pattern of time after first administration or time since last dose
  - No consistent cause of death
  - No deaths considered by investigator as related to treatment

Clinical Perspective

Alireza Atri, MD, PhD

Director

Banner Sun Health Research Institute

Dire Need for Approved and Safe Options to Treat AAD

- Clinically meaningful benefits for patients and families
- Favorable benefit/risk profile
- Many patients with AD suffer from severe agitation behaviors
  - Agitated behaviors negatively impact QoL and health of dyads
- Current off-label options are problematic and lacking evidence
  - Limited clinical benefit must be balanced with safety, tolerability, and serious side effects
  - Leads to pharmacological yo-yo

Need better treatment options

Examples of Agitation-Related Behaviors that Increased Dyad Burden

Patient Example 1

- 62-year-old male, physically healthy, 6’2’’ 220 lbs
  - Early onset AD, significant receptive aphasia
- Constant humming and pacing
- Separation anxiety
- Weekly and unprovoked episodes of grabbing, glaring, or pushing

Patient Example 2

- 56-year-old female
  - Early onset AD
  - Good communication but substantial difficulties with visuospatial cognition and praxis
- Repeatedly resistant to hygiene
- Hitting family and caregivers
- Crying and screaming

Pattern of agitated behaviors varies by patient and their impact also dyad specific

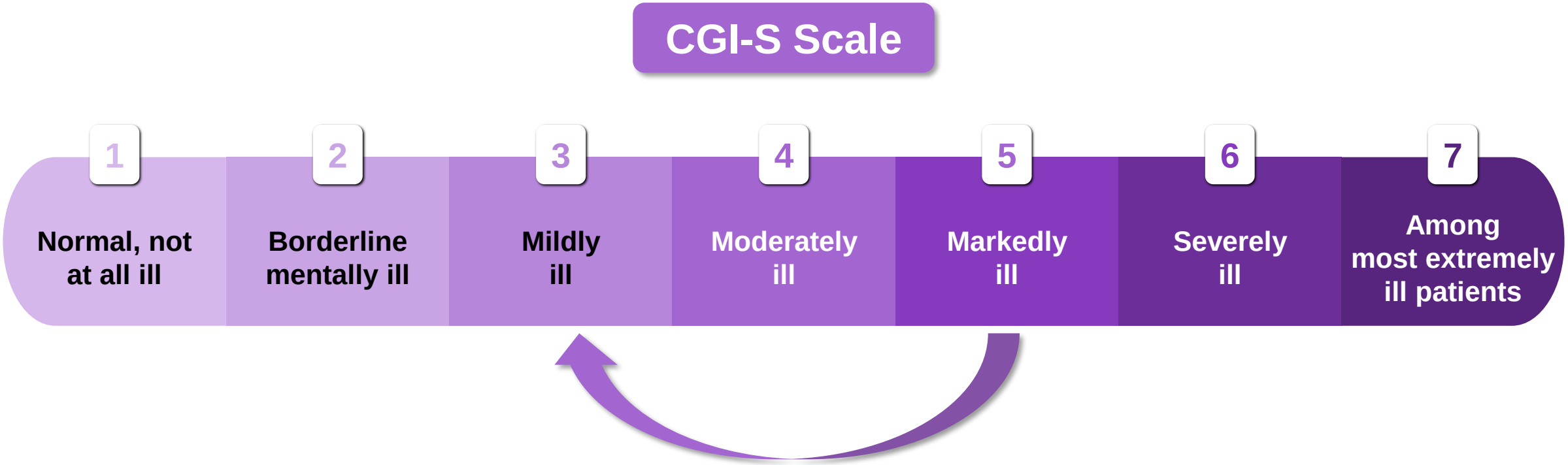
Relevant Assessment in Evaluation of Treatment

1. **What is overall acuity of condition?**
   What factors could be triggering or exacerbating it?

2. **What is frequency, severity, duration, timing, triggers, and impact of relevant behavioral disturbances?**
   Commonly evaluated using holistic observations and scales

3. **Could intervention meaningfully help my patient?**

20-Point CMAI Reductions Associated with Clinically Meaningful Decreases of 2 Points on CGI-S



CGI-S improvement could prevent downward spiral and clinical / psychosocial tipping point

Reducing Impact of Agitation-Related Behaviors Reduces Burden

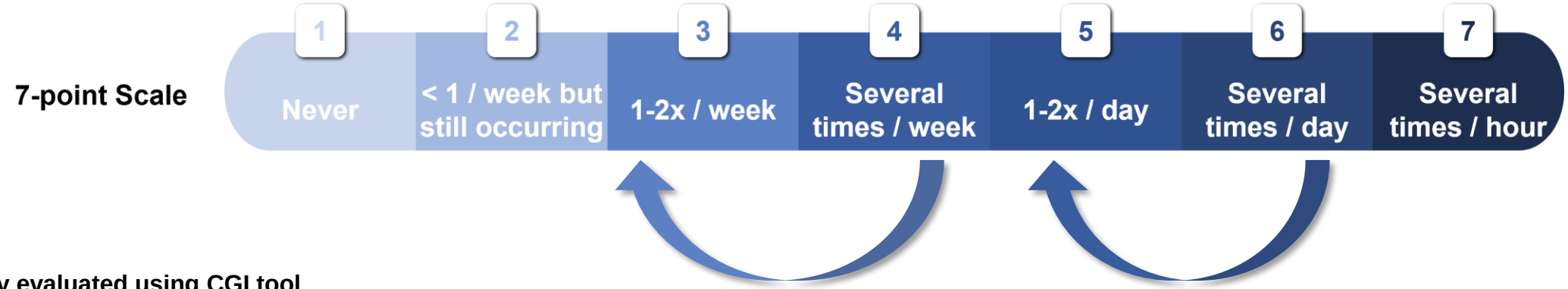
- Reduce frequency, severity, duration or “diffusibility” of troubling and volatile symptoms*

62-Year-Old Male

- Reducing glaring and grabbing episodes could have kept at home (e.g., 1-point CGI change)
- Shorter or less-intense episodes easier to diffuse

56-Year-Old Female

- Reducing resistance, combativeness, to hygiene might lessen medical issues (e.g., 1-point CGI change)
- Preventing escalation to refusal to take medication and food needed to allow patient management



*Commonly evaluated using CGI tool

Brexpiprazole Is A Needed Treatment Option for Care of AAD
Efficacy with Favorable Tolerability and Benefit-Risk Profile

- Effect size point estimates range between 0.25 – 0.35 for group-level differences
- Clinically meaningful and beneficial within patient changes for individual-level differences
  - 50% greater likelihood that any given patient may benefit from large 2-point CGI improvement
- Tolerability and safety profile allows patients to remain on treatment sufficiently to have opportunity to receive benefit
- Need to stop solely relying on off-label treatment options
  - Need FDA-approved products with favorable and well-defined efficacy and safety profiles, clear dosing directions, and defined appropriate use

Meaningful effectiveness to provide better options for positive impact on patients, families, and caregivers

Benefit / Risk Summary

Mary Hobart, PhD

Vice President, Global Regulatory Affairs

Otsuka Pharmaceutical

Brexpiprazole Has Favorable Benefit/Risk Profile for Treatment of Agitation in Patients with AD

EFFICACY

- Substantial evidence of efficacy in multiple measures of agitation
  - Demonstrated across 3 main factors on CMAI scale
  - Improvement in aggressive and non-aggressive behaviors
  - Clinically meaningful benefit

SAFETY

- Safety profile in AAD consistent with known safety profile in other indications
- Well-tolerated with no new safety events
- Low mortality overall (< 1%) but greater number of events with brexpiprazole than placebo

Appropriate labelling will guide prescribers on appropriate use of brexpiprazole in elderly patients with dementia

BREXPIPRAZOLE sNDA for Agitation Associated with Alzheimer's Dementia (AAD)

April 14, 2023

Psychopharmacologic Drugs Advisory Committee and Peripheral and Central Nervous System Drugs Advisory Committee

Otsuka Pharmaceutical Co.

Lundbeck Inc.

Back-up Slides

5-Point Reduction in CMAI Total Score is Associated with Improved Patient and Caregiver Outcomes

Outcome		Percent Reduction in Likelihood of Outcome	Odds Ratio (95% CI)
Patient Outcomes	Hospital Admissions	19%	**1.19** (1.12, 1.25)
	Emergency Room Visits	17%	**1.17** (1.10, 1.23)
	Falls	15%	**1.15** (1.08, 1.21)
Caregiver Outcomes	High Level of Caregiver Burden *(Zarit Burden Interview)*	19%	**1.19** (1.14, 1.25)
	Caregiver Depression *(PHQ-2 subscale of PHQ-4)*	11%	**1.11** (1.07, 1.16)
	Caregiver Generalized Anxiety Disorder *(GAD-2 subscale of PHQ-4)*	7%	**1.07** (1.03, 1.10)

Odds ratios were obtained from logistic regression adjusted for care recipient's and caregiver's age and gender, AD severity, and time since AD diagnosis. An Odds Ratio > 1 indicates that the variable is associated with a higher risk of the care recipient having the event in the year prior to the data collection

1. Caregiver Burden Study, 2022 (data on file)

Deaths in Patients Exposed to Brexpiprazole in Clinical Program Was Low, Without Trend Observed Among Specific Fatal Events

	AAD N = 751	Schizophrenia N = 3,170	MDD N = 5,265	Placebo N = 2,259
Incidence of Deaths	6 **(0.8%)**	9 **(0.3%)**	6 **(0.1%)**	**1 (0.04%)**
Fatal Events				
	▪ Haemorrhage intracranial (1) ▪ Obstructive airways disorder (1) ▪ Dementia alzheimer's type (1) ▪ Cardiac failure (1) ▪ Encephalitis (1) ▪ Pneumonia aspiration (1)	▪ Gun shot wound (1) ▪ Uterine cancer (1) ▪ Completed suicide (1) ▪ Asphyxia (1) ▪ Cardiac failure (1) ▪ Coronary artery disease (1) ▪ Gastric ulcer perforation (1) ▪ Death (1) ▪ Peritonitis (1) ▪ Septic shock (1)	▪ Acute myocardial infarction (1) ▪ Metastatic malignant melanoma (1) ▪ Completed suicide (2) ▪ Pulmonary embolism (1) ▪ Myocardial rupture (1) ▪ Gastric ulcer perforation (1) ▪ Peritonitis (1)	▪ Pneumonia

Deaths in completed clinical trials

Rexulti Dosing Adjustments for Drug Interactions

Factors	Dose Adjustment for REXULTI
Strong CYP2D6 or CYP3A4 inhibitors	Administer half the usual dose
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the usual dose
Strong CYP3A4 inducers	Double the usual dose and further adjust based on clinical response

Low Incidence of AEs Leading to Discontinuations

Pooled Studies

System Organ Class / Preferred Term ≥ 1%	Brexpiprazole ≤ 1 mg N = 157	Brexpiprazole Fixed 2 to 3 mg N = 366	Brexpiprazole 0.5 – 2 mg N = 132	All Brexpiprazole N = 655	Placebo N = 388
AEs leading to discontinuation	9%	5%	7%	6%	4%
Psychiatric disorders	4%	1%	0	2%	2%
Nervous system disorders	3%	1%	2%	2%	0.3%
Infections and Infestations	1%	0.8%	0.8%	0.9%	0
Investigations	1%	0.5%	2%	0.9%	0.8%

AEs Leading to Discontinuation Were Low in Three Phase 3 Studies

Pooled Studies

Preferred Term > 1 AE	All Brexpiprazole N = 655	Placebo N = 388
AEs leading to discontinuation	6%	3%
Agitation	0.6%	0.8%
Pneumonia	0.5%	0
Seizure	0.5%	0
Asthenia	0.3%	0
Insomnia	0.3%	0
Fall	0.3%	0
Alanine aminotransferase increased	0.3%	0
Aspartate aminotransferase increased	0.3%	0
Electrocardiogram QT prolonged	0.3%	0
Positive COVID-19 test	0	0.5%

Categorical Changes in QTcB/QTcF Were Higher in Placebo Than Brexpiprazole in Three Phase 3 Studies

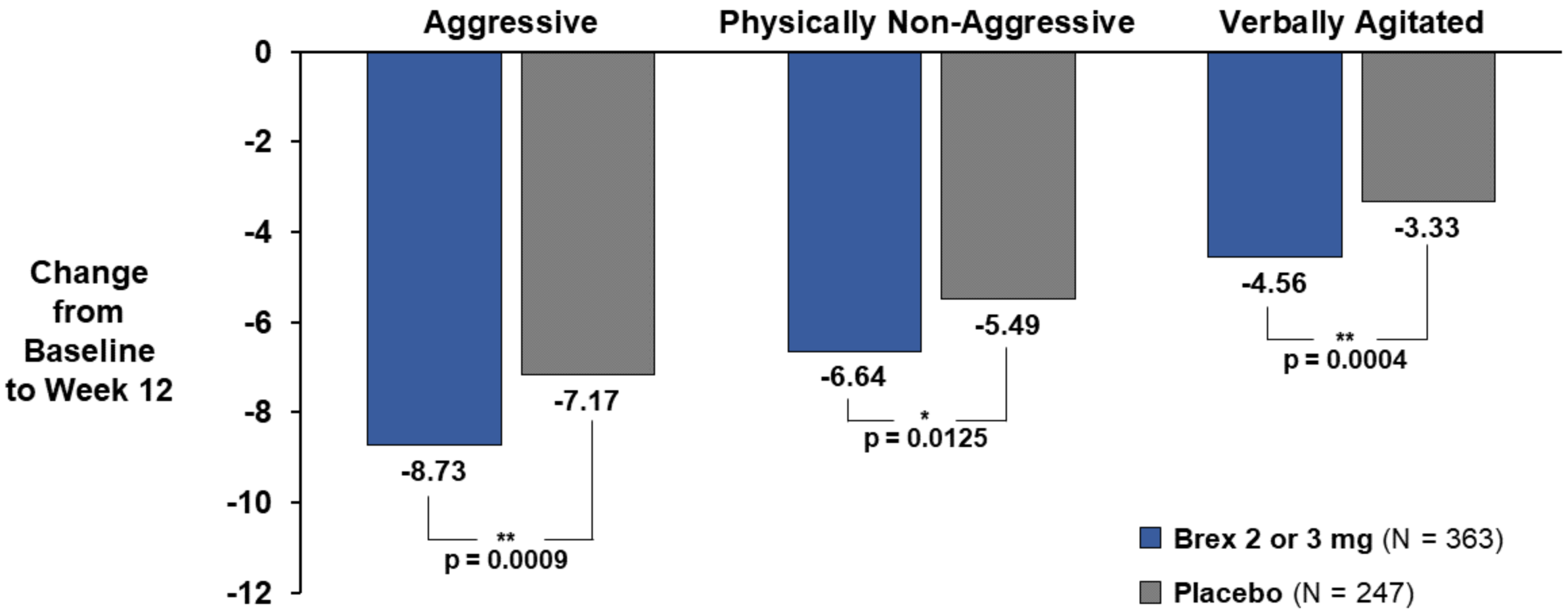
Pooled Studies

Classification	Category	All Brexpiprazole N = 645	Placebo N = 382
QTcB	New Onset (> 500 MSEC)	0	4 (1%)
	30 – 60 MSEC	96 (15%)	58 (15%)
	≥ 60 MSEC	5 (0.8%)	11 (3%)
QTcF	New Onset (> 500 MSEC)	0	0
	30 – 60 MSEC	66 (10%)	44 (12%)
	≥ 60 MSEC	2 (0.3%)	6 (2%)

Study 283 and 284: Quality of Life

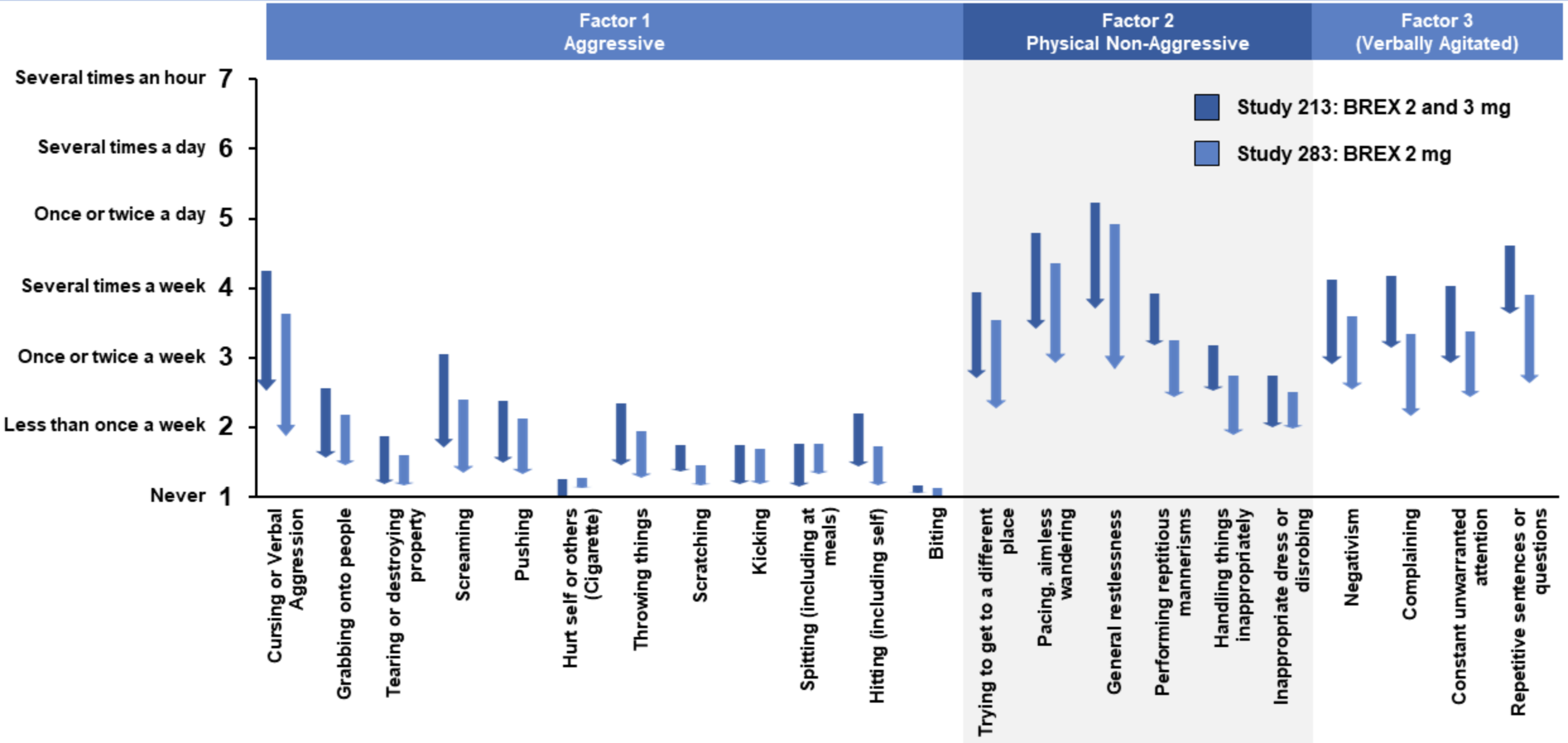
Endpoint/Variable	Placebo		Brexpiprazole		Treatment Difference (95% CI)	p-value
	Baseline Mean	LS Mean Change	Baseline Mean	LS Mean Change		
Study 283						
QoL Alzheimer's Disease Score – Patient	28.96	1.41	28.96	1.20	-0.21 (-1.31, 0.88)	0.7026
QoL Alzheimer's Disease Score – Family Member or Caregiver	26.05	1.78	24.89	1.39	-0.39 (-1.35, 0.58)	0.4331
Study 284						
QoL Alzheimer's Disease Score – Patient	30.36	1.18	29.35	1.64	0.45 (-0.53, 1.44)	0.3634
QoL Alzheimer's Disease Score – Family Member or Caregiver	26.65	1.52	25.97	2.21	0.69 (-0.29, 1.67)	0.1668

Pooled: Brexpiprazole Separated from Placebo Across 3 Key Factors of Agitation

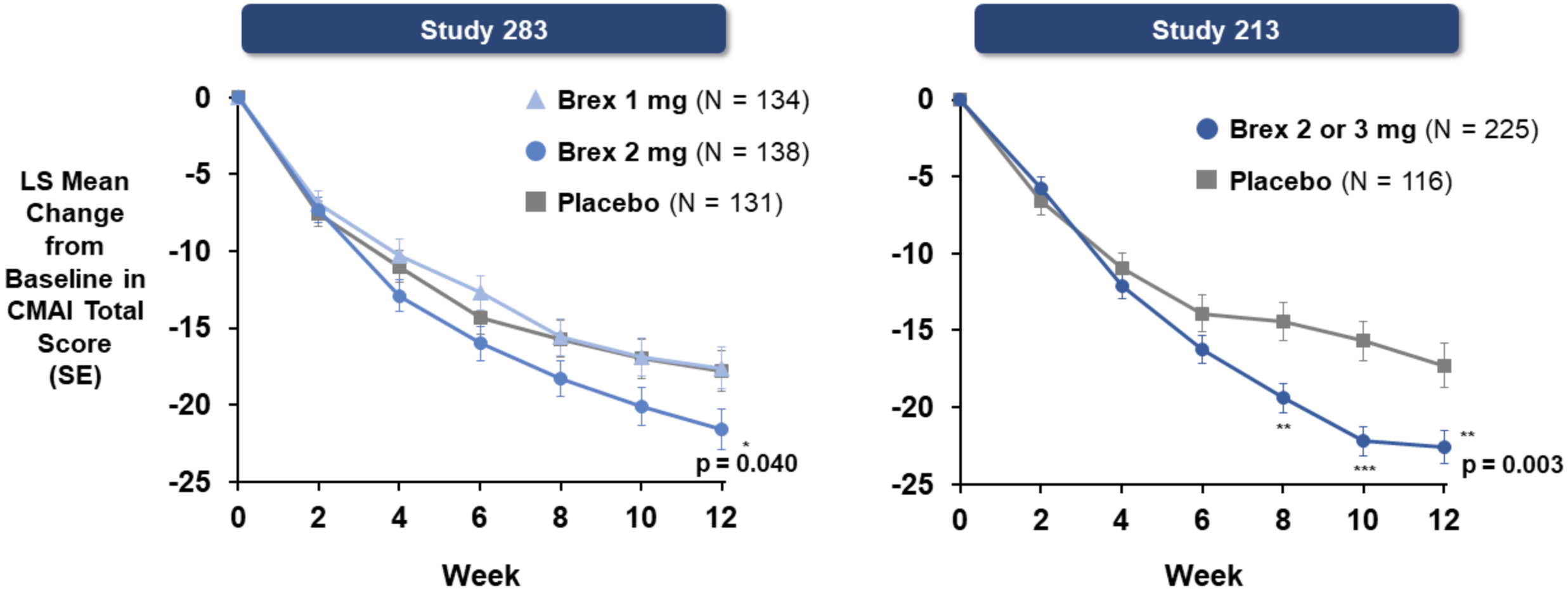


*p<0.05, **p<0.01 versus placebo; nominal p-values presented; MMRM

Study 213 and 283: Brexpiprazole Demonstrates Reduction in Mean Frequency Across Aggressive, Physically Non-Aggressive, and Verbally Agitated Behaviors



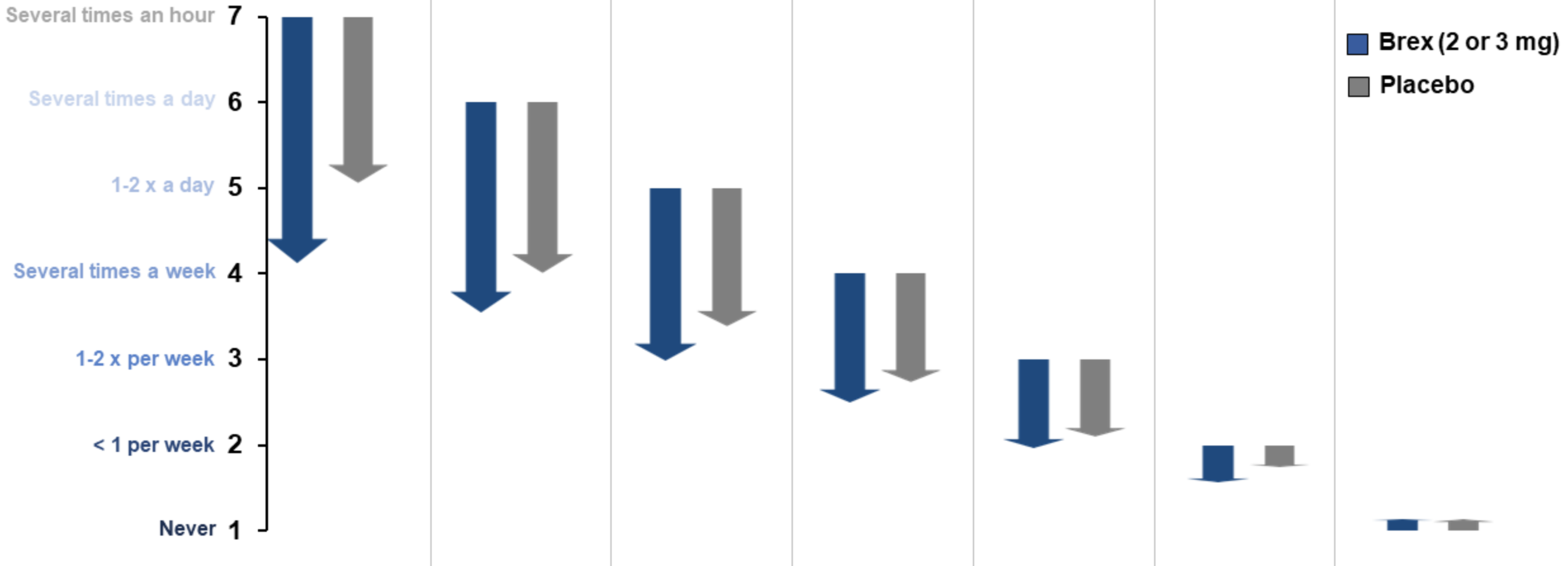
Brexpiprazole Efficacy Results Across 2 Phase 3 Trials Support Meaningful Benefit to Patients with AAD



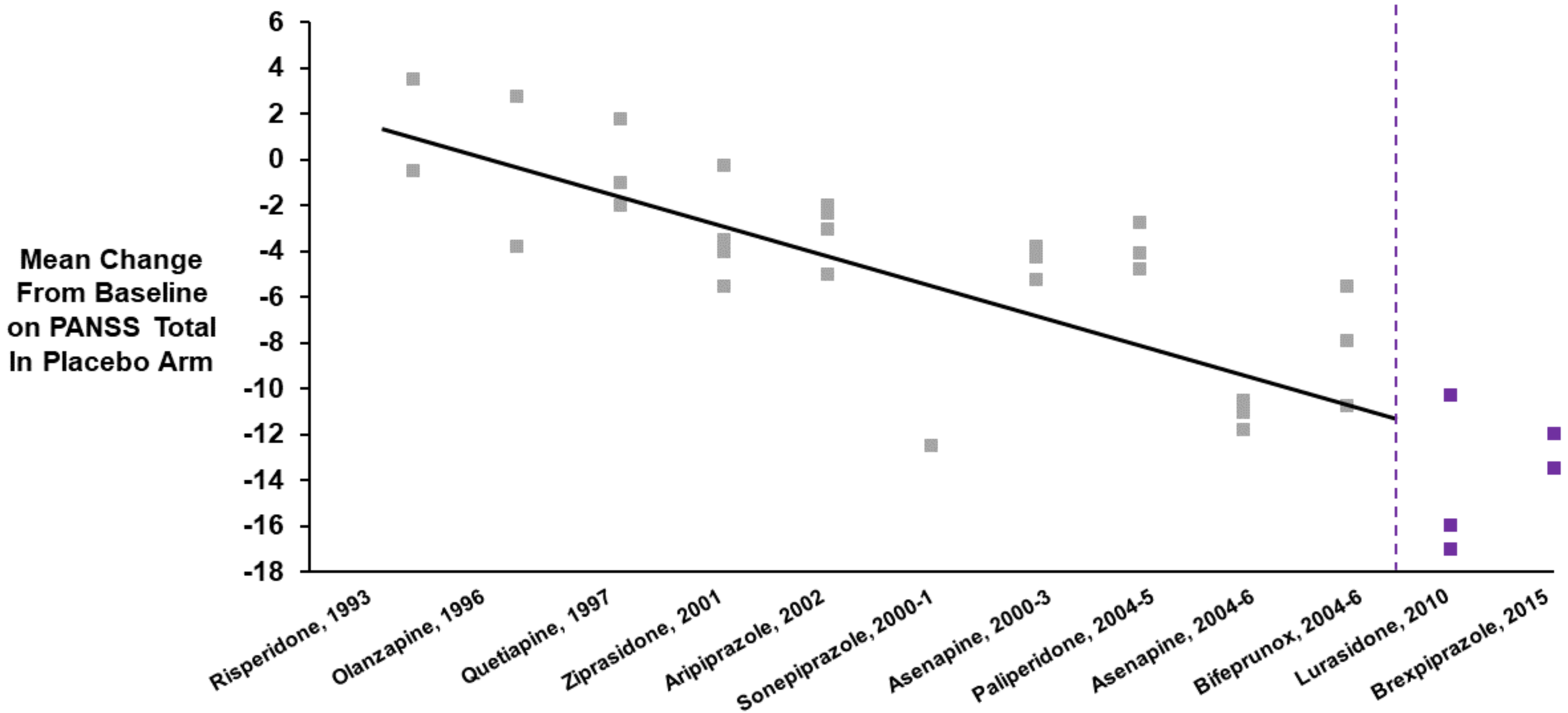
*p<0.05, **p<0.01, ***p<0.001 versus placebo; MMRM

Pooled: Agitated Behaviors Are Reduced to Lower Frequencies in Brexpiprazole-Treated Patients Compared to Placebo

Baseline Frequency	Several times an hour		Several times a day		1-2 x a day		Several times a week		1-2 x per week		< 1 per week		Never	
n:	191	119	941	597	873	587	1159	809	854	689	464	403	4566	3205
Mean Pt Reduction:	-2.87	-1.94	-2.45	-2.00	-2.01	-1.61	-1.50	-1.26	-1.04	-0.90	-0.44	-0.26	+0.13	+0.14



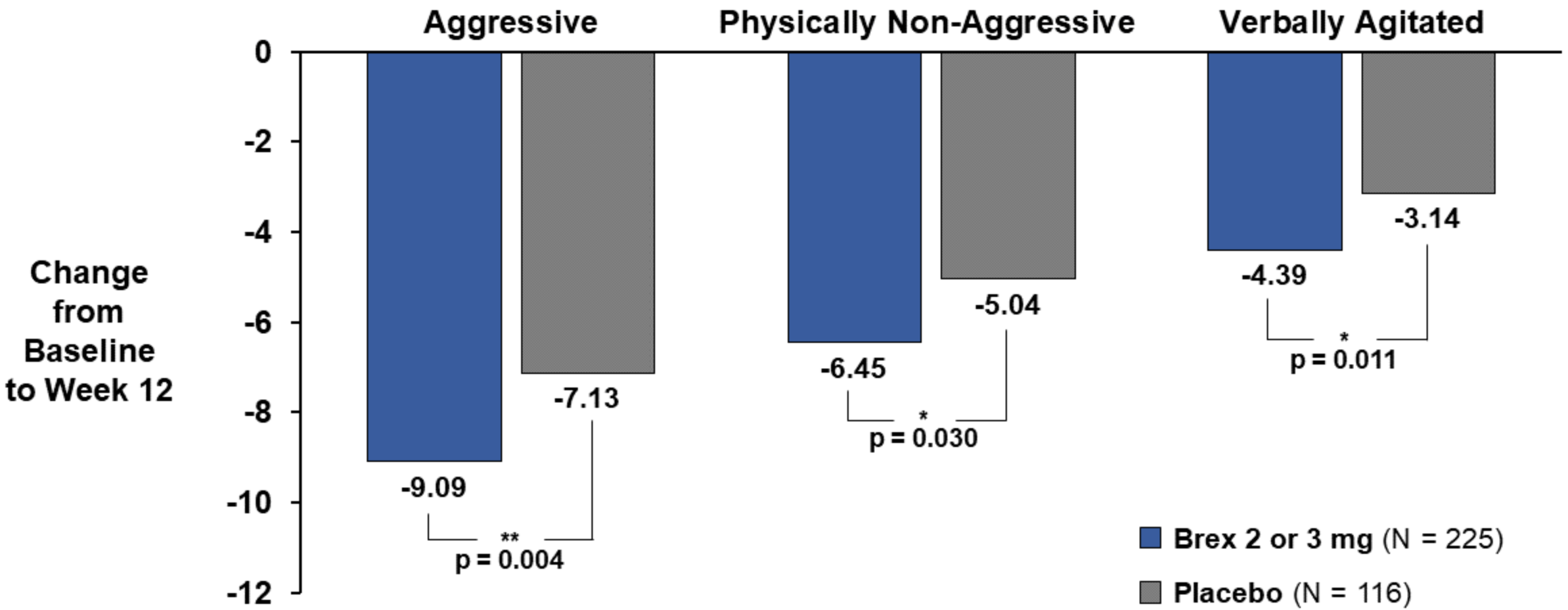
Increased Response in the Placebo Group Over Time in Acute Schizophrenia Trials



Note: Latuda and Brex data was not part of the original paper and has been added in based on the package insert

Kemp et al. 2010

Study 213: Brexpiprazole Separated from Placebo Across 3 Key Factors of Agitation



*p<0.05, **p<0.01 versus placebo; nominal p-values presented; MMRM