Dextromethorphan/Quinidine for Treatment of Pseudobulbar Affect in Patients with Dementia: Treatment Effects by Concomitant Antidepressant Use in a 12-week Open-Label Trial (PRISM II)

Rachelle S. Doody, MD, PhD; Stephen D'Amico, MD; Andrew J. Cutler, MD; Paul Shin; Fred Ledon; Charles Yonan, PharmD; Joao Siffert, MD

Disclosure

- Dr. Doody has consulted AC Immune, AZ Therapies, Biogen, Biotie, Cerespir, Forum, GlaxoSmithKline, Hoffman LaRoche, Merck, Nutricia, Riovant, Shanghai Green Valley, Suven, Takeda and Transition. She has served as a Principal Investigator in Clinical Trials (BCM) for Accera, Avanir, Genentech, Lilly, Merck, Pfizer and Takeda and holds stock options with AZ Therapies, QR Pharma, Sonexa and Transition.

- Other: Hoffman LaRoche (DSMB), Lilly/UCSD (ADCS-DAPC)

Introduction

- Pseudobulbar affect (PBA)
  - Occurs in a variety of neurological conditions [1-3]
  - Characterized by uncontrollable episodes of crying/laughing
  - Contextually inappropriate/exaggerated to mood or situation[1,2]
  - Episodes can be disruptive, distressing and impair social function [1,2,4]
- Dextromethorphan hydrobromide/quinidine sulfate
  - FDA- and EMEA-approved (NUEDEXTA®) for treatment of PBA based on trials in patients with ALS or MS[6-8]
  - Dextromethorphan (DM) is CNS-active component; low-dose quinidine (Q), substantially increases DM bioavailabity[5]
- PRISM II study provides additional DM/Q effectiveness, safety, & tolerability data for PBA secondary to stroke, traumatic brain injury (TBI), or dementia

1. Schiffer R, Pope LE. *J Neuropsychiatry Clin Neurosci* 2005;17:447-454; **2.** Wortzel HS, et al. *CNS Drugs* 2008;22:531-545; **3.** Work SS, et al. *Adv Ther* 2011;28:586-601; **4.** Colamonico J, et al. *Adv Ther* 2012;29:775-798; **5.** Pope LE, et al. *J Clin Pharmacol* 2004;44:1132-1142; **6.** Brooks BR, et al. *Neurology* 2004;63:1364-1370; **7.** Panitch HS, et al. *Ann Neurol* 2006;59:780-787; **8.** Pioro EP, et al. *Ann Neurol* 2010;68:693-702.

ALS=amyotrophic lateral sclerosis; DM/Q=dextromethorphan hydrobromide/quinidine sulfate; MS=multiple sclerosis; PBA=pseudobulbar affect.

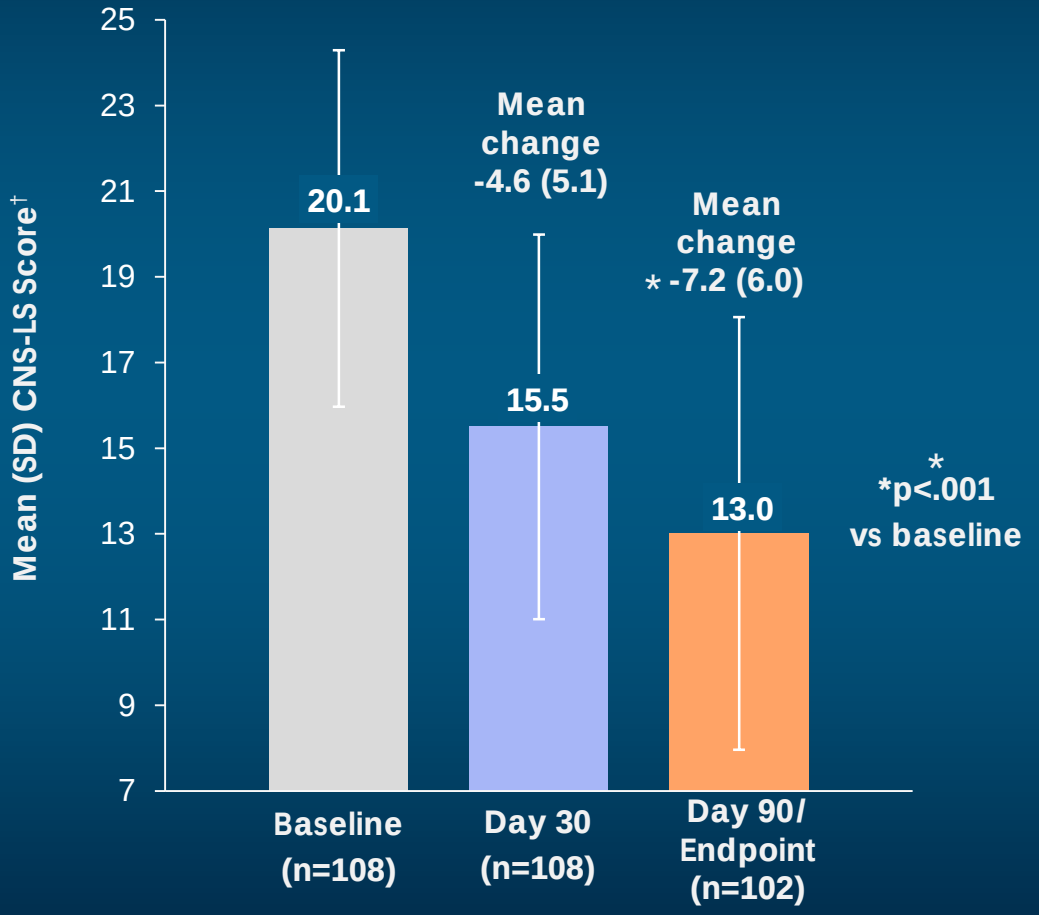
CNS-LS

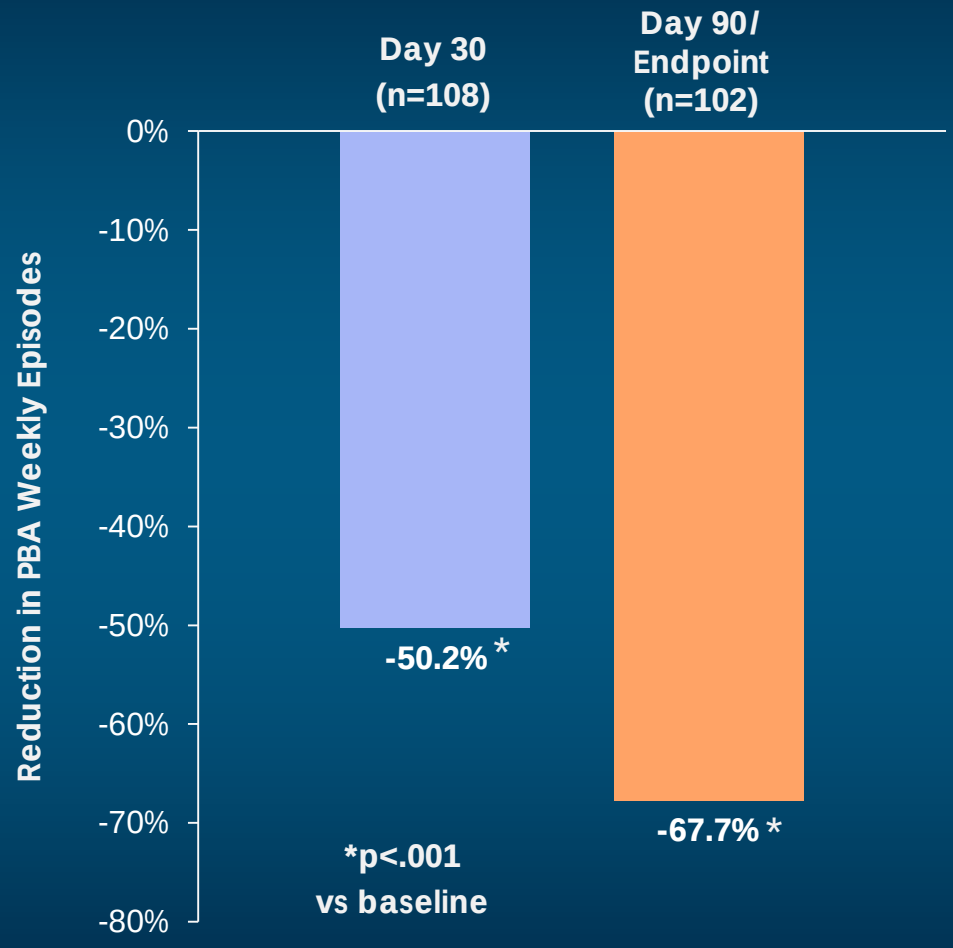
Instructions: Using the scale below, please write the number that describes the degree to which each item applies to you *DURING THE PAST WEEK*. Write only one number for each item.

	Applies never	Applies rarely	Applies occasionally	Applies frequently	Applies most of the time	
	1	2	3	4	5	
Assessment questions						**Answers**
1. There are times when I feel fine one minute and then I'll become tearful the next over something small or for no reason at all.						
2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren't funny.						
3. I find myself crying very easily.						
4. I find that even when I try to control my laughter, I am often unable to do so.						
5. There are times when I won't be thinking of anything happy or funny at all, but then I'll suddenly be overcome by funny or happy thoughts.						
6. I find that even when I try to control my crying, I am often unable to do so.						
7. I find that I am easily overcome by laughter.						
					Total Score:	_____

Moore SR, Gresham LS, Bromberg MB, et al. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry*. 1997; 63:89-93.

PRISM II Dementia Cohort
CNS-LS Score and PBA Episode Reduction (mITT)





†The CNS-LS is a patient-reported quantitative measure of the perceived frequency and severity of PBA episodes. There are 7 items with each item scored 1 (applies never) to 5 (applies most of the time). CNS-LS scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes; CNS-LS scores were not normalized.

Avanir Study 12-AVR-401 (Unpublished Data).

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PRISM II Analysis of Antidepressant Impact

- **Overview/Objective**
  - Evaluate the effect of concomitant antidepressant use on PRISM II outcomes for the dementia cohort
- **Study Design**
  - Open-label, multicenter (~120 US sites), 12-week trial (NCT01799941)
  - Treatment: DM/Q 20/10 mg BID; (QD during Week 1)
  - Dementia cohort completed July 2014
  - Effectiveness outcomes for antidepressant “users” vs “non-users” were compared using student’s t-tests

Patient Eligibility

- Adults (age ≥ 18)
- Clinically diagnosed PBA[1] and baseline CNS-LS[2,3] ≥13*
- Clinical diagnosis of dementia with baseline MMSE ≥ 10
- No contraindications to DM/Q use
- No history or current psychosis or delirium
- Medical/neurological condition stable and not rapidly changing
- Memantine or AChEIs allowed if stable doses (≥6 weeks)
- Antidepressants/neuropsychiatric meds allowed if stable doses (≥2 months)

1. Cummings JL, et al. *CNS Spectr* 2006;11:1-7; **2.** Smith RA, et al. *Mult Scler* 2004;10:679-685; **3.** Moore SR, et al. *J Neurol Neurosurg Psychiatry* 1997;63:89-93.
CNS-LS=Center for Neurologic Study–Lability Scale; MMSE=Mini Mental State Examination.
*The CNS-LS was validated as a measure of PBA episode frequency and severity tool in ALS and MS populations.

Study Visits and Outcome Measures

Baseline
Day 1

Effectiveness
- CNS-LS
- PBA episode count
- MMSE
- QOL VAS

Safety
- Medical history
- Concomitant meds
- Vital signs

Other
- PHQ-9

Visit 1
Day 30

Effectiveness
- CNS-LS
- PBA episode count

Safety
- AEs
- Concomitant Meds
- Vital signs

Other
- PHQ-9
- Compliance inquiry

Visit 2
Day 60

Effectiveness
- None

Safety
- AEs
- Concomitant meds

Other
- Compliance inquiry

Final Visit
Day 90/Endpoint

Effectiveness
- CNS-LS
- PBA episode count
- MMSE
- QOL VAS
- PGIC/CGIC
- Treatment Satisfaction

Safety
- AEs
- Concomitant meds
- Vital signs

Other
- PHQ-9
- Compliance inquiry

Caregivers completed ratings as proxies for patients who were unable (except for MMSE)

AEs=adverse events; CGIC=Clinical Global Impression of Change; CNS-LS=Center for Neurologic Study–Lability Scale; MMSE=Mini Mental State Examination; PBA=pseudobulbar affect; PGIC=Patient Global Impression of Change; PHQ-9=patient health questionnaire; QOL=quality of life; VAS=visual analog scale.

Patient Disposition

Enrolled (Safety Population)[a]
N=134

Early Term: n=28 (20.9%)

Completed
n=106 (79.1%)

No post-baseline CNS-LS measurement (16)
Failure to meet all inclusion criteria (10)

Effective Analysis Population[b]
n=108 (74.5%)

Discontinued, n(%)	"Users" (n=76)	"Non- Users" (n=58)
Adverse event	9 (11.8%)	5 (8.6%)
Consent withdrawn	3 (3.9%)	4 (6.9%)
Death	1 (1.3%)	1 (1.7%)
Lack of efficacy	1 (1.3%)	1 (1.7%)
Lost to follow-up	2 (2.6%)	0 (0.0%)
Other	0 (0.0%)	1 (1.7%)

[a]Safety population consisted of all enrolled patients who received ≥1 dose of DM/Q.
[b]Effective Analysis Population=modified intent-to-treat population (patients who received ≥1 dose of DM/Q, had ≥1 post-baseline CNS-LS measurement, and met all eligibility criteria).
CNS-LS=Center for Neurologic Study–Lability Scale.

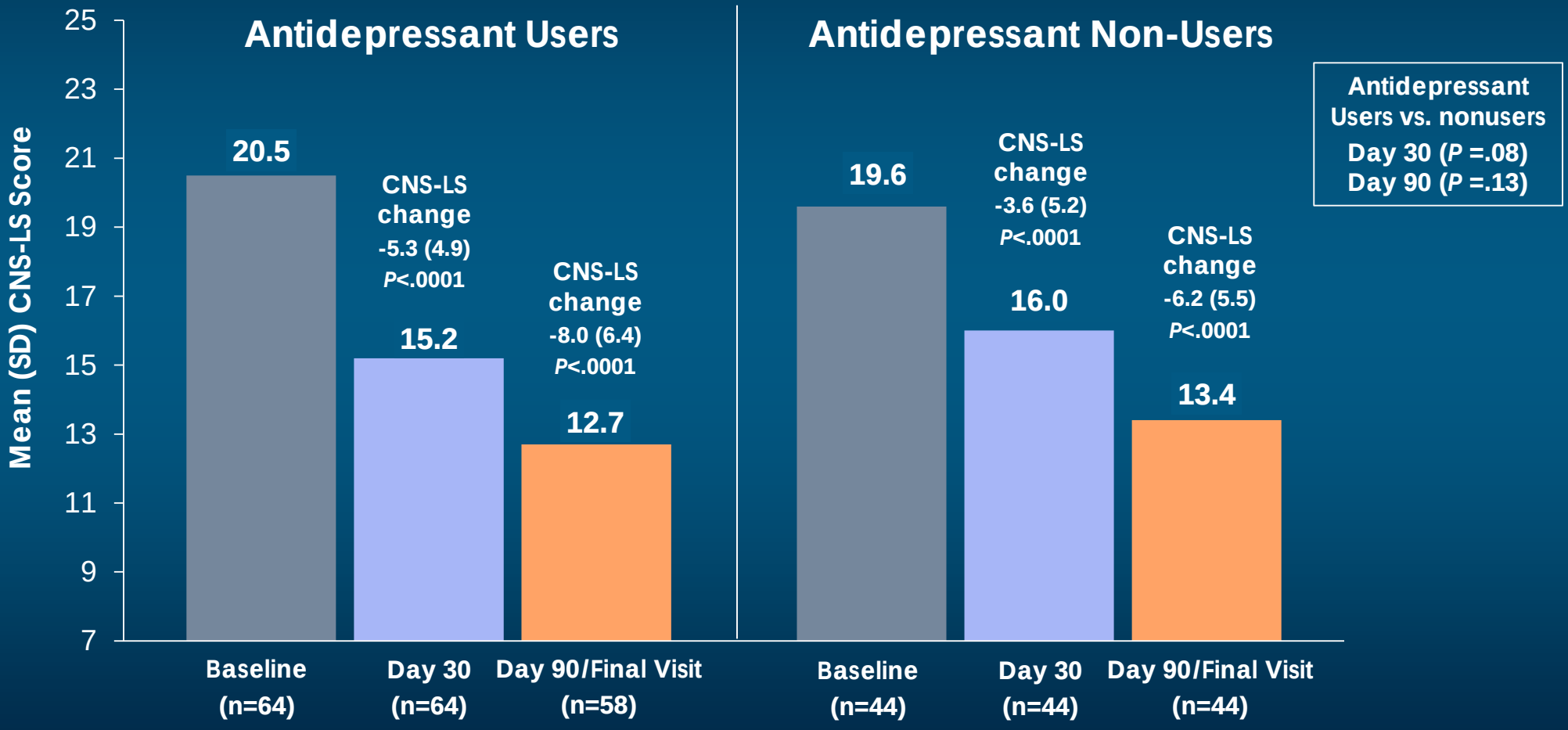
Patient Characteristics

	Antidepressant Users (N=76)	Antidepressant Non-Users (N=58)
Sex		
Male	37%	47 %
Female	63 %	53 %
Age, (years)		
Mean, (SD)	69 (11.8)	73 (12.3)
Race		
Asian	1 %	0 %
Black/African American	8 %	10 %
White/Caucasian	90 %	86 %
Unknown	1 %	3 %
Ethnicity		
Hispanic/Latino	22 %	29 %
Patient has a caregiver	73 %	72 %
Patient lives at home	62 %	69 %
Psychopharmacologic Med Use		
Anticonvulsants	26 %	19 %
Antipsychotics	32 %	26 %
Axiolytics	40 %	31 %
Memantine	29 %	28 %
AChEI	49 %	43 %

Percentages may not add to 100 due to rounding

Primary Outcome: Change in CNS-LS Score

- Significant improvement in PBA symptoms vs. baseline in both groups
- No significant difference in CNS-LS change between antidepressant users vs. non-users

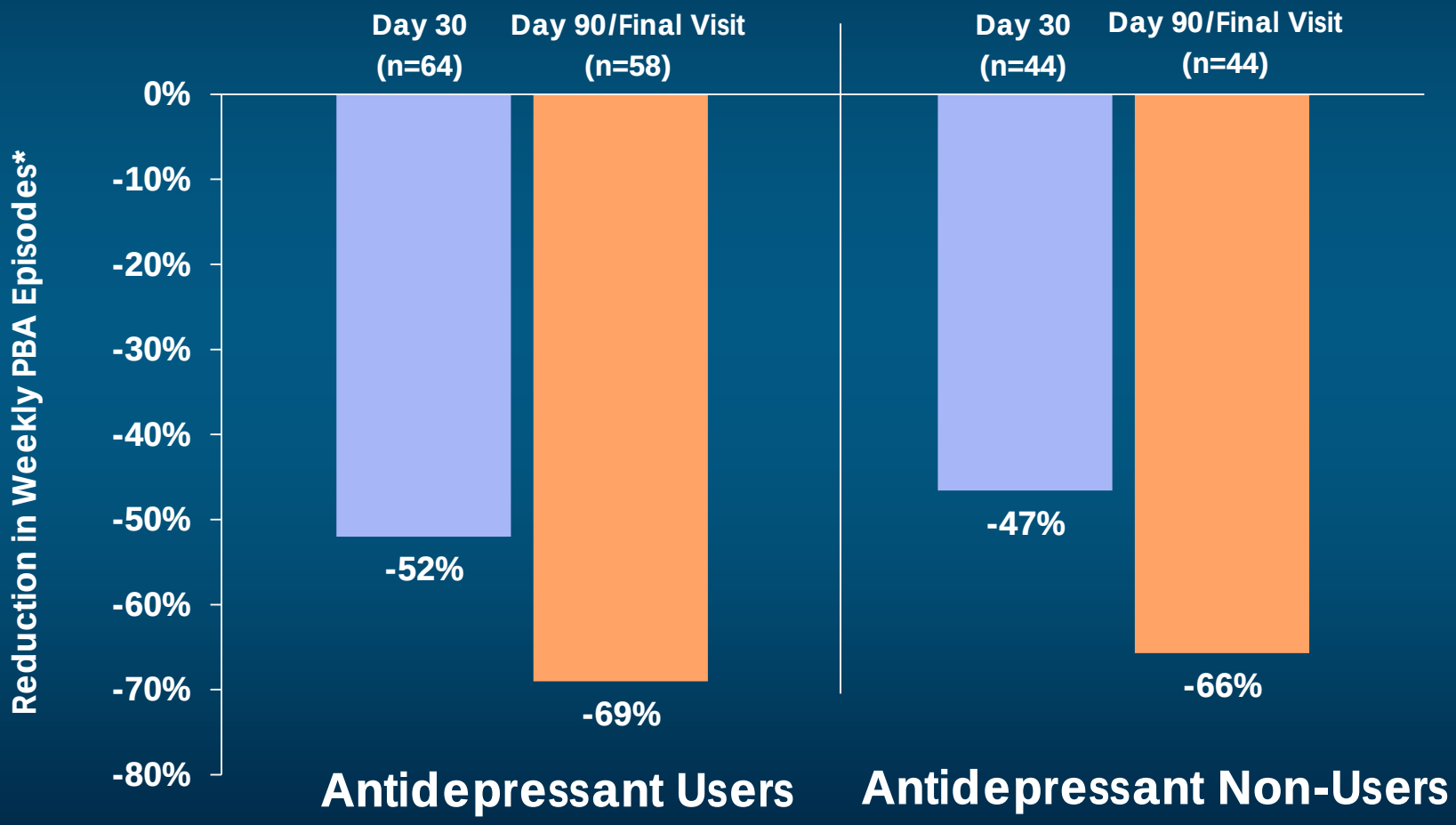


1-sample t-test of absolute change in CNS-LS; between group comparison: two-sample t-test of absolute change for baseline

CNS-LS scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes; mITT=modified intent-to-treat; Change score expressed as mean (standard deviation)

Reduction in PBA Weekly Episode Count

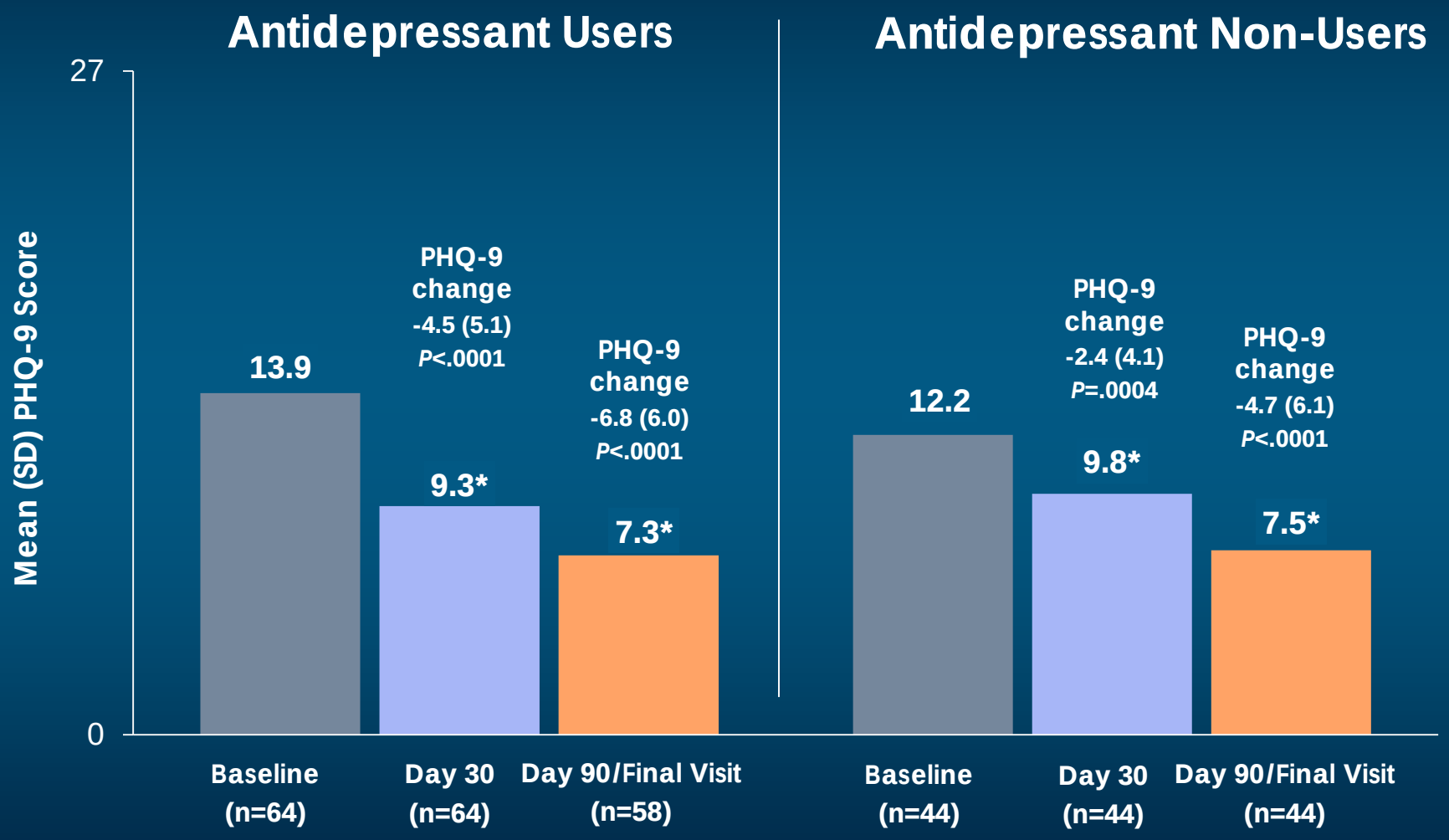
- Significant PBA episode reduction vs. baseline in both groups at Days 30 and 90; *P*<.001 for all
- No difference in episode reduction between antidepressant users vs. non-users; *P*=.42**



*Estimated percent change from baseline for PBA episode count was evaluated via mixed-effects Poisson regression model for the effectiveness analysis population.
PBA=pseudobulbar affect.

** 2-sample t-test

Other Secondary Outcomes: Patient Health Questionnaire-9 (PHQ-9)

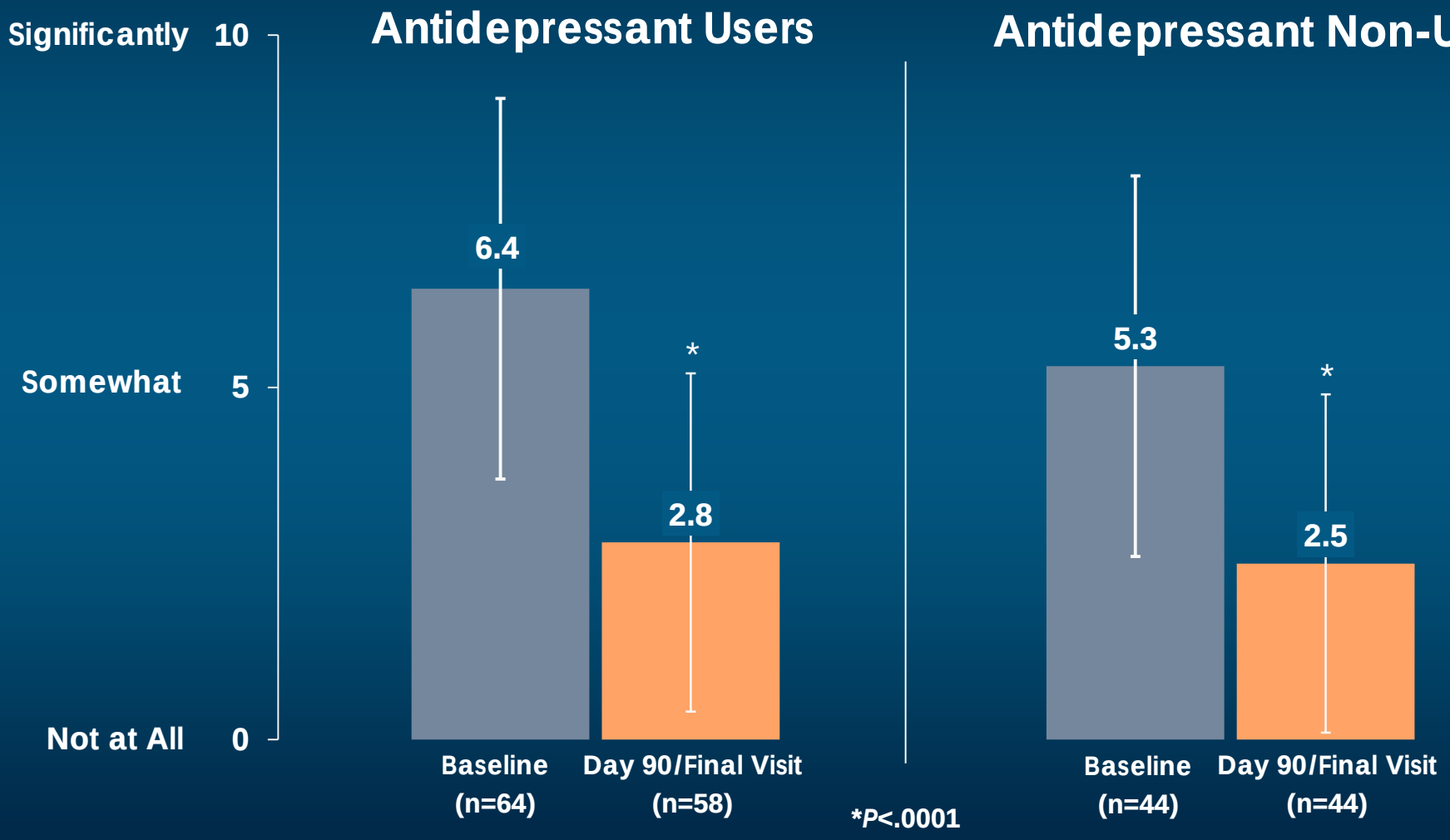


*P<.001, 1-sample t-test of absolute change in score from baseline

PHQ-9 scores range from 0 to 27, with higher scores indicating increased severity of depression.

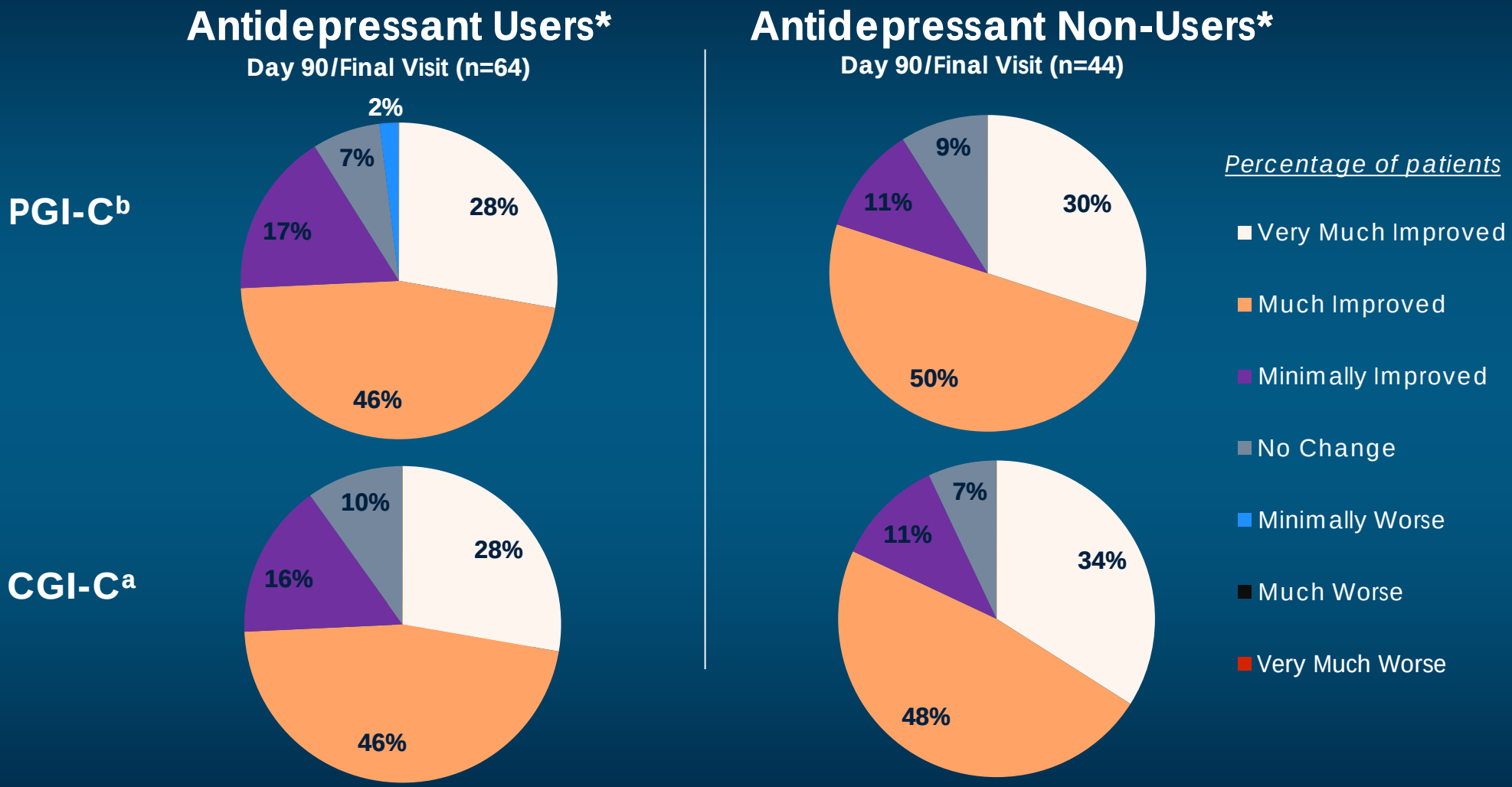
Other Secondary Outcomes: QoL VAS

In both groups, QOL-VAS scores improved significantly from baseline (*P*<.0001)



QOL=quality of life; SD=standard deviation; VAS=visual analog scale.

Clinical and Patient Global Impression of Change (with respect to PBA)



[a]CGI-C is a 7-point investigator-rated scale that assessed overall treatment response (with respect to PBA) from baseline to day 90/Final Visit, rated as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.
[b]PGI-C is a 7-point patient/patient's caregiver rated scale that assessed overall treatment response (with respect to PBA) from baseline to day 90/Final Visit, rated as very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse.
CGI-C=Clinical Global Impression of Change; PGI-C=Patients' Global Impression of Change.

Adverse Events Occurring in ≥2 Patients Overall

Adverse Event, Preferred Term	Safety Population (n=134)	Antidepressant Users (n=76)	Antidepressant Non-Users (n=58)
Headache	10 (7.5%)	6 (7.9%)	4 (6.9%)
Urinary tract infection	6 (4.5%)	2 (2.6%)	4 (6.9%)
Diarrhea	5 (3.7%)	2 (2.6%)	3 (5.2%)
Nausea	4 (3.0%)	2 (2.6%)	2 (3.4%)
Fall	3 (2.2%)	1 (1.3%)	2 (3.4%)
Dizziness	3 (2.2%)	0 (0.0%)	3 (5.2%)
Somnolence	3 (2.2%)	3 (3.9%)	0 (0.0%)

Serious AEs: 6 (7.9%) antidepressant users vs. 8 (13.9% nonusers); none were considered treatment-related; no SAE occurred in >1 patient

Conclusions

- PRISM II is the first trial to systematically evaluate PBA treatment in patients with dementia
- The majority of enrolled patients were taking psychopharmacologic medications, most commonly antidepressants (57%)
- Patients taking DM/Q showed significant PBA symptom reduction; PGI-C, CGI-C and QoL improvement suggests clinically meaningful response
- Concomitant antidepressant use did not appear to influence magnitude of treatment effect
- Despite open-label limitation, CNS-LS reduction was consistent with that seen in DM/Q phase 3 trials, supporting labeled indication for treatment of PBA (without regard to causative etiology)
- DM/Q appeared well tolerated in this largely elderly population