Poster # P1-300

Alzheimer's Association International Conference

July 18-23, 2015 • Washington, DC, USA

Dextromethorphan/Quinidine for Treatment of Pseudobulbar Affect in Patients With Dementia: Comparison of Patient-Reported Ratings to Those of Caregiver Proxies in a 12-Week Open-Label Trial (PRISM II)

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Introduction

- Pseudobulbar affect (PBA) is characterized by frequent, uncontrollable episodes of crying and/or laughing that are exaggerated or incongruous with mood or social context[1,2]
- PBA occurs when certain neurologic diseases or brain injury damages neuronal pathways coordinating expression of affect[1–3]
- PBA episodes are disruptive, are often distressing, impair social function, can have considerable negative impact on patients' lives and may contribute to nursing home placement[1,2,4]
- Prevalence data suggest that up to 10% of patients with dementia have moderate to severe PBA symptoms (Center for Neurologic Study–Lability Scale [CNS-LS[5,6]] score ≥21); however, the condition is frequently not diagnosed and its symptoms may be mistaken for depression or another dementia-related neuropsychiatric disturbance[2,3,7]
- Dextromethorphan hydrobromide and quinidine sulfate (DM/Q; NUEDEXTA®) is the only approved treatment for PBA (FDA and EMA) based on well-controlled trials in patients with PBA secondary to amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS)[8–10]
- This study (PRISM II) was conducted to provide additional DM/Q effectiveness, safety, and tolerability data in patient cohorts with PBA secondary to stroke, traumatic brain injury, or dementia
- Patient-rated outcomes were completed by caregivers for patients who were unable to do so. To assess potential differences in patient-completed vs caregiver-completed ratings, we evaluated PRISM II dementia cohort results stratified by rater type

Methods

Study Design

- Open-label, multicenter (~120 US sites), 12-week trial (NCT01799941)

Eligibility

- Adults with a clinical diagnosis of PBA[11] and baseline CNS-LS[5,6] score ≥13
- Clinical dementia diagnosis (Mini Mental State Examination [MMSE] score ≥10)
- Stable doses (≥6 weeks) of dementia medications (memantine/cholinesterase inhibitors) or other neuropsychiatric medications (≥2 months) were allowed
- No history of psychosis or delirium; no contraindications to DM/Q; medical/neurologic condition stable and not rapidly changing

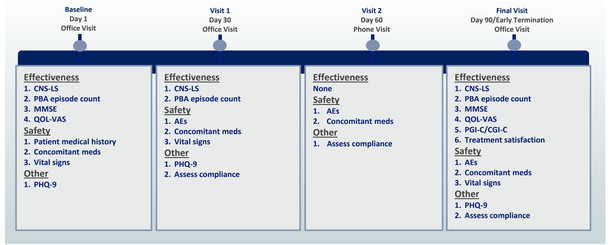
Treatment

- All patients received DM/Q 20/10 mg twice daily (once daily during Week 1)

Assessments

- Study visits and measures are shown in **Figure 1**. Caregivers completed ratings as proxies for patients who were unable to do so (except for MMSE)
  - Caregivers were required to spend 3 to 4 days of waking hours with the patient for the week prior to the visit to ensure knowledgeability about PBA episodes

Figure 1. Study Visits and Outcome Measures



AE=adverse event; CGI-C=Clinical Global Impression of Change; CNS-LS=Center for Neurologic Study-Lability Scale; MMSE=Mini Mental State Examination; PBA=pseudobulbar affect; PGI-C=Patient Global Impression of Change; PHQ-9=Patient Health Questionnaire-9; QOL-VAS=quality-of-life visual analog scale.

Statistical Analysis

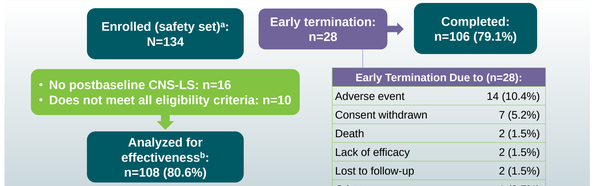
- Primary analysis: Change from baseline to Day 90/Final Visit in CNS-LS (1-sample *t*-test)
- The CNS-LS is an established PBA rating scale (range, 7–35) validated in patients with MS and ALS[5,6] and used as an outcome measure in DM/Q phase 3 trials[8-10]
- Results were stratified by respondent type (patient or caregiver) and compared for the primary and all additional effectiveness ratings that were completed by the same rater at baseline and follow-up points

Results

Patient Disposition and Baseline Characteristics

- 134 patients with dementia were evaluated for safety; 108 (81%) met all eligibility criteria, had a post-baseline CNS-LS and qualified for effectiveness analyses; 106 (79%) completed the trial (**Figure 2**)
- Approximately 40% (small variations by outcome assessed) of ratings were completed by caregivers on behalf of patients; the rater (patient or caregiver) did not change in ~90% of cases
- Patient characteristics are shown in **Table 1**

Figure 2. PRISM II Patient Disposition



Early Termination Due to (n=28):	
Adverse event	14 (10.4%)
Consent withdrawn	7 (5.2%)
Death	2 (1.5%)
Lack of efficacy	2 (1.5%)
Lost to follow-up	2 (1.5%)
Other	1 (0.7%)

[a]Safety analysis set consisted of all enrolled patients who received ≥1 dose of DM/Q.
[b]The effectiveness analysis set includes patients who received ≥1 dose of DM/Q, had ≥1 postbaseline CNS-LS measurement, and met all eligibility criteria.
CNS-LS=Center for Neurologic Study-Lability Scale.

Table 1. Patient Characteristics—Safety Population (N=134)

Characteristic	n (%)	Characteristic	n (%)
Age			
Mean, years (SD)	71 (12)	Patient has a caregiver[a]	98 (73)
≥75 years, n (%)	58 (43)		
Gender		Patient residence	
Male	55 (41)	Home	87 (65)
Female	79 (59)	Assisted living	31 (23)
		Skilled nursing facility	16 (12)
Race		Type of dementia	
White/Caucasian	118 (88)	Alzheimer's disease	86 (64)
Black/African American	12 (9)	Vascular dementia	21 (16)
Asian	1 (1)	Frontotemporal lobe dementia	12 (9)
Unknown	3 (2)	Lewy body dementia	5 (4)
		Other[b]	10 (7)
Ethnicity		Anti-dementia drugs	73 (54)
Hispanic/Latino	34 (25)	Psychotropic medication use[c]	
Non-Hispanic/non-Latino	92 (69)	At least 1 psychotropic medication	109 (81)
Unknown	8 (6)	Antipsychotics	39 (29)
		Antidepressants	76 (57)
		Sedative/hypnotics or anxiolytics	48 (36)

[a]Although most patients had a caregiver, the caregivers completed ratings only if the patient was unable.
[b]Other dementia included dementia due to multiple sclerosis (n=4), Parkinson's disease (n=1), alcohol-induced (n=1), brain cell deterioration (n=1), subcortical (n=1), unspecified (n=1), and mild cognitive impairment (n=1).
[c]Reported at screening. SD=standard deviation.

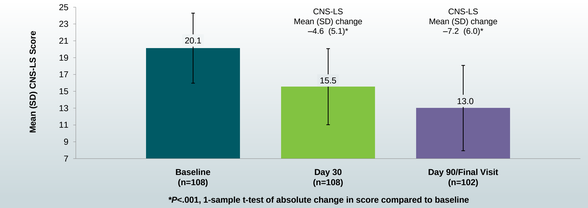
Primary Outcome

- Overall mean CNS-LS scores showed significant PBA symptom reduction at both Day 30 and Day 90/Final Visit (*P*<.001 for both; **Figure 3**) vs baseline
- There was no significant difference in CNS-LS results by respondent (caregiver vs patient respondent, -8.2 [4.9] vs -6.2 [6.2] at Day 90/Final Visit; *P*=.11; **Figure 4**

Secondary Outcomes

- PBA episode counts decreased during the study from a median (range) of 21 per week (0, 90) at baseline to 6 per week (0, 77) at Day 30 and 3 per week (0, 80) at Day 90/Final Visit
- Estimated weekly episode reductions corresponded to an overall 50.2% reduction at Day 30 and 67.7% reduction at Day 90/Final Visit vs baseline (*P*<.001; mixed-effects Poisson regression model; **Figure 5A**)
  - Estimated weekly PBA episode count did not differ significantly by respondent at baseline *P*=.36; however, caregivers reported significantly larger episode reductions than patients at both Day 30 and Day 90/Final visit (*P*<.001; **Figure 5B)**
- The impact of PBA episodes on quality of life was evaluated using a 10-point visual analog scale (QOL-VAS). Scores improved significantly from a mean (SD) of 5.95 (2.8) at baseline to 2.7 (2.4) at Day 90/Final Visit (change -3.2 [3.0]; *P*<.001)
  - Although baseline ratings were larger (greater impact of PBA on QOL) for caregiver vs patient respondents (6.7 [2.5] vs 5.3 [2.9]; *P*=.01 caregiver vs patient); similar improvements were seen between these groups at Day 90/Final Visit (-3.8 [2.8] vs -2.7 [3.1]; *P*=.08 caregiver vs patient)

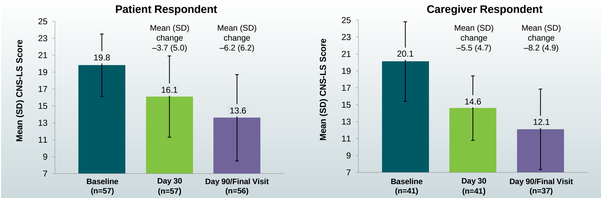
Figure 3. Primary Outcome, Change in CNS-LS Score



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

CNS-LS scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes.
CNS-LS=Center for Neurologic Study–Lability Scale; SD=standard deviation.

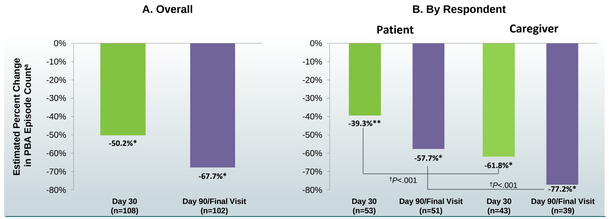
Figure 4. Change From Baseline in CNS-LS Score by Respondent Type (Patient or Caregiver)



P=NS (.074 at Day 30, .108 at Day 90/Final Visit), Patient vs. Caregiver respondent, 2-sample independent *t*-test

CNS-LS scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes.
CNS-LS=Center for Neurologic Study–Lability Scale; NS=nonsignificant; SD=standard deviation.

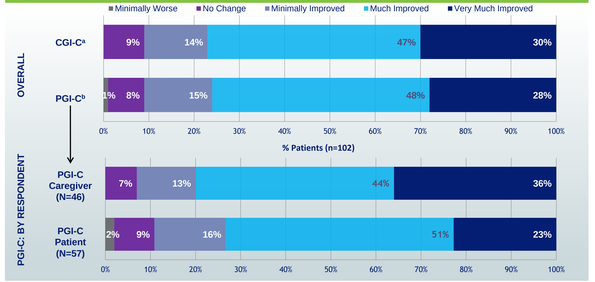
Figure 5. Estimated Weekly PBA Episode Count Reduction



[a]Estimated percent change from baseline for PBA episode count was evaluated via mixed-effects Poisson regression model for the effectiveness analysis set.
*P<.001 vs baseline (Poisson regression); **P=.002 vs baseline (Poisson regression); †P<.001, caregiver vs patient respondent, Wald chi-square test.
PBA=pseudobulbar affect.

- Symptoms of depression were measured using the Patient Health Questionnaire-9 (PHQ-9)
  - Overall, symptoms of depression improved from baseline to Day 90/Final Visit (mean [SD] PHQ-9 scores, 13.2 [5.3] to 7.4 [5.2]; *P*<.001)
  - PHQ-9 ratings did not differ significantly by respondent (caregiver vs patient, -5.4 [6.8] vs -6.2 [6.0]; *P*=.58)
- Clinical and Patient/Caregiver Global Impression of Change (CGI-C and PGI-C) ratings showed 77% and 76% of patients, respectively, were much or very much improved at Day 90/Final Visit (**Figure 6**)
  - PGI-C ratings did not differ significantly by respondent; 80% of patients were rated by caregivers as much/very much improved vs 74% of patients who rated themselves (*P*=.65; Figure **6**)
- Patient satisfaction with treatment also did not differ by respondent; 76% of caregiver respondents vs 74% of patient respondents (*P*=.22) were "somewhat" or "very satisfied" with treatment
- Mean (SD) MMSE score improved by 0.5 (3.1) points, from 20.2 (5.6) at baseline to 21.0 (6.4) at Day 90/Final Visit (*P*=.08)

Figure 6. CGI-C and PGI-C at Day90/Final Visit



[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.

Safety

- 49 (36.6%) patients reported ≥1 AE (**Table 2**); most Aes were mild to moderate in intensity
- AEs were considered at least possibly related to DM/Q treatment in 16 (11.9%) patients
- Serious AEs occurred in 14 (10.4%) patients; none were considered treatment related by clinical investigators
- AEs led to study discontinuation in 16 (11.9%) patients

Table 2. AEs Occurring in ≥2% Patients

AE Category, n (%)	Safety Population (n=134)
Headache	10 (7.5)
Urinary tract infection	6 (4.5)
Diarrhea	5 (3.7)
Nausea	3 (2.2)
Fall	3 (2.2)
Dizziness	3 (2.2)
Somnolence	3 (2.2)

AE=adverse event.

Conclusions

- PRISM II is the first clinical trial of PBA treatment in patients with dementia
- DM/Q effectively reduced PBA symptoms in patients with dementia over this 12-week open-label uncontrolled trial
- PBA symptom improvement was clinically meaningful, to patients and caregivers, as demonstrated by significant improvement in PGI-C, CGI-C, and QOL scores
- Caregiver-proxy versus patient-completed ratings did not differ significantly, except for PBA episode counts requiring patients/caregivers to estimate the number of PBA episodes occurring during the past week
  - -Respondent-based differences in PBA episode reduction may have been influenced by patient's memory deficits, lack of awareness of PBA symptoms, or both
- DM/Q appeared well tolerated in this largely elderly population with dementia; AEs experienced were consistent with DM/Q prescribing information

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Support This study and presentation were funded by Avanir Pharmaceuticals, Inc. Editorial assistance was provided by Peloton Advantage, LLC, and was supported by Avanir Pharmaceuticals, Inc.

Disclosures Rachelle Doody has consulted within the past 12 months for AbbVie, AC Immune, Avanir Pharmaceuticals, Inc., AZ Therapies, Baxter, Biote, Ceresipr, Chiesi, GlaxoSmithKline, Hoffmann-La Roche, Neurocog, Novartis, and Pfizer; has stock options in AZ Therapies, QR Pharma, Sonexa, and Transition; receives funding from the NIH-Alzheimer's Disease Cooperative Study and from the Texas Alzheimer's Research and Care Consortium; serves as principal investigator on clinical trials funded by Accera, Avanir Pharmaceuticals, Inc., Genentech, Janssen Alzheimer Immunotherapy, NIH, Pfizer, and Takeda; and serves on the editorial boards of *Alzheimer's Research & Therapy* and *Dementia and Geriatric Cognitive Disorders*. Stephen D'Amico has received honoraria as a consultant and speaker for Avanir Pharmaceuticals, Inc.; has been a consultant and received research grants from AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, Sanofi, and Takeda. Andrew Cutler has served as a consultant for, received research grants from, and served as a speaker for Abbott, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Lilly, Merck, Novartis, Ortho-McNeil-Janssen, Otsuka, Pamlab, Pfizer, Shire, Sunovion, Takeda, and Vanda. Paul Shin, Fred Ledon, Charles Yonan, and Joao Siffert are employees of Avanir Pharmaceuticals, Inc.