P3-288

Presented at the
2013 Alzheimer's Association International Conference
July 13–18, 2013 • Boston, MA

A Study to Assess the Safety, Tolerability, and Effectiveness of NUEDEXTA (Dextromethorphan 20 mg/Quinidine 10 mg) in the Treatment of Pseudobulbar Affect (PBA) [PRISM II]

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Background

- Pseudobulbar affect (PBA) is a neurological condition characterized by sudden, frequent, and uncontrollable episodes of laughing and/or crying that are excessive or inappropriate to the situation and independent of the underlying mood[1-3]
  - PBA episodes are disruptive, embarrassing, and distressing to patients and others[2,4]
  - PBA may lead to social isolation and even contribute to nursing home placement[2,4]
- PBA occurs secondary to a variety of neurological conditions, including dementia,[5] and is hypothesized to be caused by injury to, or presence of brain lesions in, the neurological pathways that regulate and coordinate affect[3]
- Prevalence studies estimate 10% to 29% of patients with dementia have PBA symptoms[5-8]; however, the condition remains under-recognized and may be misdiagnosed as depression or other behavioral disturbance[2,9]
- Dextromethorphan 20 mg/quinidine 10 mg (DMQ) is currently the only FDA-approved treatment for PBA[10]
- Safety and efficacy studies of DMQ for treatment of PBA were conducted in patients with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS)[11,12]
- An open-label study (N=553) of patients with PBA due to a variety of neurological conditions (including dementia; n=17) provided additional safety data; however, effectiveness was not studied[13]
- This poster reports the study design for an ongoing study called PRISM II

Study Objective

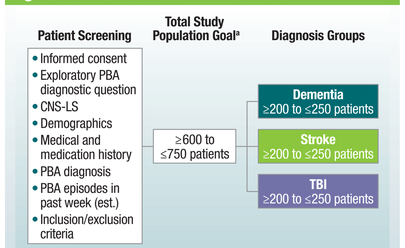
- PRISM II is a clinical trial evaluating the effectiveness, safety, and tolerability of DMQ for PBA in patients with dementia, stroke, or traumatic brain injury (TBI)

Methods

Study Design

- Open-label, 12-week study enrolling up to 750 adults with PBA secondary to dementia, stroke, or TBI (minimum 200 each) at ~150 centers nationwide (Figure 1)
- Conducted according to Good Clinical Practice and the Declaration of Helsinki

Figure 1. PRISM II: Patient Enrollment

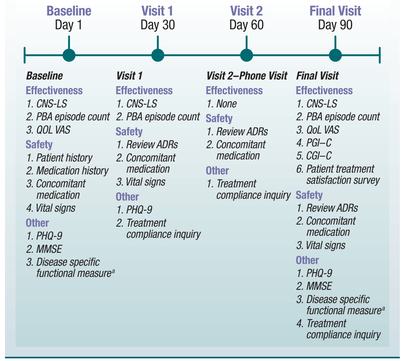


[a]Based on data from a previous randomized, controlled trial of DMQ for treatment of PBA;[4] a sample size of 200 patients in each of the 3 diagnosis groups will provide 90% power to detect an increase of 1.4 points over the assumed true placebo mean change (ie, a mean change of –7.1 points): this sample size will also provide a 95% interval for the true rate of adverse events, with a half wide of ≤3 percentage points.

CNS-LS, Center for Neurologic Study–Lability Scale; PBA, pseudobulbar affect; TBI, traumatic brain injury.

- Patients will be treated with DMQ 20/10 mg twice daily (once daily during Week 1; Figure 2)
- Study visits occur at baseline, 30 and 90 days, or early termination, with a phone visit at Day 60 (Figure 2)

Figure 2. PRISM II: Study Design



[a]For stroke: Stroke Impact Scale; for traumatic brain injury: TBI-Neurobehavioral Functioning Inventory.

ADRs, adverse drug reactions; 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 item; QOL, quality of life; VAS, visual analogue scale.

Study Population

- Eligibility criteria include (Table 1)
  - Clinical diagnosis of dementia (Alzheimer's, vascular, Lewy body, or frontotemporal), stroke (ischemic or hemorrhagic), or TBI (non-penetrating)

Table 1. Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age ≥18 years	• Severe dementia (MMSE <10)
• Diagnosis of dementia (vascular, Alzheimer's, Lewy body, frontotemporal), stroke (ischemic, hemorrhagic), or TBI (nonpenetrating, mild, moderate, or severe)	• Penetrating TBI
• Clinical diagnosis of PBA	• Residing in a mental health facility
• Neurological condition stable for ≥3 months (not rapidly changing or progressing)	• Myasthenia gravis
• Residing at home or assisted-living facility/skilled nursing home	• History of complete heart block, QTc prolongation, or torsade de pointes
• Memantine or cholinesterase inhibitors allowed if stable dose for ≥6 weeks	• Family history of congenital QT prolongation syndrome
• Antidepressants allowed if stable dose for ≥2 months	• Dextromethorphan quinidine (NUEDEXTA®) use in past 6 months
• Medications for affective/behavioral or emotional symptoms allowed if stable dose for ≥2 months	• Severe depressive disorder
• Patient (or authorized individual) must consent to study participation	• History/current psychosis or bipolar disorder
• Caregiver (if present) willing to comply with study procedures	• Unstable systemic disease*
	• MAOI or drugs that both significantly prolong QT interval and are primarily metabolized by CYP2D6 (eg, thioridazine) within past 2 weeks
	• Very short life expectancy (≤6 months)
	• Pregnant or planning pregnancy
	• Participated in interventional clinical study within 30 days
	• Substance/alcohol abuse in past 3 years

*For example, certain malignancies; poorly controlled diabetes or hypertension; unstable pulmonary, renal, hepatic, or cardiac disease; unstable ischemic cardiac disease).

MAOI, monoamine oxidase inhibitors; MMSE, Mini-Mental State Examination; PBA, pseudobulbar affect; TBI, traumatic brain injury.

  - Diagnosis of PBA, based on published clinical criteria (Table 2)[9,11]
  - A baseline visit score ≥13 on the Center for Neurologic Study-Lability Scale (CNS-LS), an established PBA rating instrument validated in patients with MS and ALS[14,15] (Figure 3)
- Exclusion criteria include (Table 1)
  - Severe dementia (Mini-Mental State Examination score [MMSE]) <10)
  - Penetrating TBI
  - Stroke diagnosis within 3 months of study entry

Table 2. Clinical Criteria for Pseudobulbar Affect

• Episodes of involuntary or exaggerated emotional expression that result from a brain disorder; including episodes of laughing, crying, or related emotional displays
• Episodes represent a change from the person's usual emotional reactivity
• Episodes are incongruent with the person's mood or in excess of the corresponding mood state
• Episodes are independent or in excess of any provoking stimulus
• The symptoms are not better accounted for by another neurologic or psychiatric disorder (eg, gelastic or dacrystic epilepsyl, facial dystonia, facial or vocal tics, facial dyskinesias, mania, depression, panic disorder, psychosis)
• The symptoms are not the direct physiological effect of a substance (eg, drug abuse or medication)

Adapted from Cummings et al.[9]

Figure 3. Center for Neurologic Study–Lability Scale (CNS-LS) for Pseudobulbar Affect (PBA)[14,15]

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 1 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 1 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:	

References: Moore SR, Gresham LS, Bromberg MB, et al. A self report measure of affective lability. *J Neurol Neurosurg Psychiatry* 1997;63:89–93. Smith RA, Berg JE, Pope LE, et al. Validation of the CNS emotional lability scale for pseudobulbar affect (pathological laughing and crying) in multiple sclerosis patients. *Multiple Sclerosis* 2004;10:679–685.

- Secondary measures include the change from baseline to Day 90 in
  - Estimated PBA episode counts
  - Visual analogue scale for impact of PBA episodes on quality of life
- Other measures include (administered at Day 90 only)
  - Clinical Global Impression-Change of PBA symptoms
  - Patient Global Impression-Change of PBA symptoms
  - Patient Satisfaction with Treatment Survey
- Safety and tolerability measures include
  - Treatment-related adverse events
  - Serious adverse events
  - Total discontinuations and discontinuations for adverse events
  - Concomitant medication usage and changes in usage
  - Vital signs
- Exploratory analyses include the change from baseline to Day 90 in
  - MMSE: evaluation of cognitive changes
  - 9-item Patient Health Questionnaire: evaluation of mood changes
  - Disease-specific functional measures
    - TBI: Neurobehavioral Functioning Inventory
    - Stroke: Stroke Impact Scale
  - Predictive utility of a single question to screen for PBA diagnosis: "In the last week, have you/the patient you care for experienced involuntary episodes of crying and/or laughing that were exaggerated or even contrary to how you/they felt at the time?"

Statistical Analysis

- For each diagnosis group, the primary analysis will test the null hypothesis that the mean change in CNS-LS from baseline to Week 12 is equal to 0 using paired *t*-tests
- The 95% confidence interval for the mean change from baseline will also be reported

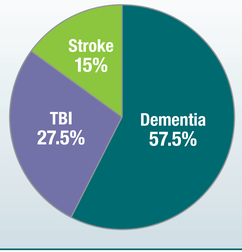
Assessments

- Primary endpoint: mean CNS-LS change from baseline to Day 90 (or early withdrawal)
  - Analyzed for all patients and for each diagnosis group separately
  - Results will be compared with mean CNS-LS change in previous phase 3, double-blind DMQ trials

Results

- This US study is currently underway, with initial sites activated in February 2013
- As of July 1, 2013, 40 patients have enrolled (Figure 4)

Figure 4. PRISM II: Enrollment by Neurological Condition as of July 1, 2013



Total current enrollment=40
TBI, traumatic brain injury.

Conclusions

- PRISM II will provide a prospective, systematic assessment of DMQ effectiveness and safety as treatment for PBA in patients with dementia, stroke, or TBI

References **1.** Schiffer R, et al. *J Neuropsychiatry Clin Neurosci.* 2005;17:447–454. **2.** Wortzel HS, et al. *CNS Drugs.* 2008;22:531–545. **3.** Parvizi J, et al. *J Neuropsychiatry Clin Neurosci.* 2009;21:75–87. **4.** Colamonico J, et al. *Adv Ther.* 2012;29:775–798. **5.** Work S, et al. *Adv Ther.* 2011;28:586–601. **6.** Lopez OL, et al. *J Neuropsychiatry Clin Neurosci.* 2003;15:346–353. **7.** Starkstein SE, et al. *J Neurol Neurosurg Psychiatry.* 1995;59:55–60. **8.** Brooks B, et al. Presented at the 65th Annual Meeting of the American Academy of Neurology. March 16–23, 2013; San Diego, CA. Poster P03.215. **9.** Cummings JL, et al. *CNS Spectr.* 2006;11:1–7. **10.** Nuedexta (dextromethorphan hydrobromide/quinidine sulfate) capsules [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc.; August 2011. **11.** Brooks BR, et al. *Neurology.* 2004;63:1364–1370. **12.** Pioro EP, et al. *Ann Neurol.* 2010;68:693–702. **13.** Pope LE, et al. Presented at the 164th Annual Meeting of the American Psychiatric Association. May 14–18, 2011; Honolulu, HI. Poster NR9-70. **14.** Moore SR, et al. *J Neurol Neurosurg Psychiatry.* 1997;63:89–93. **15.** Smith RA, et al. *Mult Scler.* 2004;10:679–685.

Support This study and presentation were funded by Avanir Pharmaceuticals, Inc. Editorial assistance was provided by The Curry Rockefeller Group, LLC, and was supported by Avanir Pharmaceuticals, Inc.

Disclosures Dr. Alexander has served as an advisor for Avanir Pharmaceuticals, Inc. Dr. 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. Dr. D'Amico has received honoraria as a consultant for Avanir Pharmaceuticals, Inc. Dr. Doody has consulted for Accera, AC Immune, Allon, Avanir Pharmaceuticals, Inc., AZ Therapies, Banner Health, BioTE, Chiesi, Hoffman LaRoche, Merck, Suven, Takeda, and Toyama; 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 PI on clinical trials funded by Avanir, Genentech, Janssen Alzheimer Immunotherapy, Pfizer, and Takeda; and serves on the editorial boards of Alzheimer's Research and Therapy and Dementia and Geriatric Cognitive Disorders. Dr. Hammond has served as an advisor for Avanir Pharmaceuticals, Inc. Dr. Sauve has served as an advisor for Avanir Pharmaceuticals, Inc. and as a speaker for Sunovion. Dr. Yonan is an employee of Avanir Pharmaceuticals, Inc. Dr. Zorowitz has served on advisory boards for Avanir Pharmaceuticals, Inc.