

**Safety, Tolerability, and Effectiveness of Dextromethorphan/Quinidine for
Pseudobulbar Affect among Study participants with Traumatic Brain Injury:
Results from the PRISM-II Open Label Study**

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ABSTRACT (Currently 300/300)

Background. Dextromethorphan 20mg /quinidine 10mg (DM/Q) was approved to treat pseudobulbar affect (PBA) based upon phase 3 trials conducted in participants with amyotrophic lateral sclerosis or multiple sclerosis. PRISM II evaluated DM/Q effectiveness, safety and tolerability for PBA following stroke, dementia or traumatic brain injury (TBI). **Objective.** To report results from the TBI cohort of PRISM II, including a TBI-specific functional scale. **Design.** Open-label trial evaluating twice daily DM/Q over 90 days. **Study participants.** Adults (n=120) with a clinical diagnosis of PBA secondary to non-penetrating TBI; stable psychiatric medications were allowed. **Methods. Main Outcome Measurements.** Primary endpoint was change in Center for Neurologic Study-Lability Scale (CNS-LS) score from baseline to day 90. Secondary outcomes included PBA episode count, Clinical and Patient Global Impression of Change (CGI-C; PGI-C), Quality of Life-Visual Analog Scale (QOL-VAS), treatment satisfaction, Neurobehavioral Functioning Inventory (NFI), Patient Health Questionnaire (PHQ-9), and Mini Mental State Examination (MMSE). **Results.** DM/Q-treated participants showed significant mean (SD) reductions in CNS-LS from baseline (day 30, -5.6 [5.2]; day 90, -8.5 [5.2]; both, $P<.001$). Compared with baseline, PBA episodes were reduced by 61.3% and 78.5% at days 30 and 90 (both, $P<.001$). At day 90, 78% and 73% of study participants had “much improved” or “very much improved” on the CGI-C and PGI-C. QOL-VAS scores were significantly reduced from baseline (-3.7 [3.3]; $P<.001$). Mean (SD) PHQ-9 scores improved compared to baseline at day 30 (-3.2 [5.3], $P<.001$) and 90 (-5.2 [6.4], $P<.001$). NFI T-scores were significantly improved ($P<.001$), while MMSE scores were unchanged. Adverse events (AEs) were consistent with the known DM/Q safety profile; the most common AE was diarrhea (8.3%). **Conclusions.** DM/Q was well tolerated and significantly reduced PBA episodes in study participants with TBI. Changes in CNS-LS and PBA episode count were similar to changes with DM/Q in phase 3 trials.

INTRODUCTION

Traumatic brain injury (TBI) is associated with a broad range of emotional and behavioral disturbances that are often distressing for affected individuals, their family members and caregivers.[1] Pseudobulbar affect (PBA) is among the disorders of emotion regulation affecting people with TBI and is characterized by sudden, uncontrollable outbursts of laughing and/or crying that are independent of mood and out of proportion or incongruous to social context.[2,3,4] PBA episodes tend to be stereotypical and can last for seconds to several minutes, occur multiple times per day, and cause clinically significant distress.[2] PBA episodes can result in embarrassment, social isolation, and occupational disability.[3] The pathophysiology of PBA is incompletely understood, but brain lesions of various etiologies (inflammatory, ischemic, hemorrhagic, or neurodegenerative) involving the corticobulbar tracts, extrapyramidal region, or subcortical areas, particularly subcortical white matter, have been associated with the uncontrollable laughing or crying episodes of PBA.[5,6]

The diagnosis of PBA is based on patient history and neurological examination, but PBA is generally under-recognized due to lack of routine screening, limited awareness of the condition, and confusion with other neuropsychiatric conditions.[4,7,8] In the absence of specific questioning, patients may fail to describe PBA episodes to their physicians or may describe them non-specifically, leading to lack of identification or misattribution to mood or other disorders. These factors may play a role in the wide range of estimated prevalence rates for PBA in people with TBI. Based on patient interviews, PBA has an estimated prevalence of 5 to 30% within the first year following TBI,[9,10,11] but other

studies have reported some degree of uncontrollable crying or laughing in up to 48% and even 66% with mild TBI as measured using the self-reported Center for Neurologic Study–Lability Scale (CNS-LS).[7,12,13] The CNS-LS is a tool to measure laughing and crying episode frequency and severity; it was developed and validated using patient samples with amyotrophic lateral sclerosis (ALS) or multiple sclerosis (MS).[14,15] A CNS-LS score of ≥ 13 in these studies was found to predict a neurologist diagnosis of PBA for 82% of study participants with ALS and 78% with MS, and CNS-LS scores correlated well with PBA episode frequency.

Currently, the only drug approved by the US Food and Drug Administration for the treatment of PBA is the fixed combination of dextromethorphan (DM) and quinidine (Q) (Nuedexta[®] [DM/Q]; Avanir Pharmaceuticals, Inc., Aliso Viejo, CA, USA).[16,17] Limited evidence also suggests efficacy for some antidepressants; however these are not FDA-approved for PBA.[3,18,19,20,21,22,23]

In the United States, the approved DM/Q dose for PBA is 20mg/10 mg twice daily.[16] DM is a weak, uncompetitive *N*-methyl-D-aspartate receptor antagonist, a moderate affinity sigma-1 receptor agonist, a serotonin and norepinephrine reuptake inhibitor, and an $\alpha 3\beta 4$ neuronal nicotinic receptor antagonist.[24,25,26,27] Due to its rapid metabolism to dextrophan by cytochrome P450 2D6 (CYP2D6), DM typically has poor central nervous system bioavailability. However, in the presence of low-dose quinidine (Q), a potent CYP2D6 inhibitor, systemic exposure to DM is increased approximately 20-fold, without undesirably high concentrations of dextrophan, resulting in an improved

therapeutic profile.[28] DM/Q was approved for the treatment of PBA based on clinical trials enrolling study participants with PBA secondary to ALS or MS that showed efficacy over placebo or similar doses of DM or Q given alone.[29,30,31] In addition, a large (N=553), 1-year safety study enrolled participants with PBA secondary to any neurologic condition, but included only a small number of study participants with traumatic brain injury (TBI; n=23).[32]

The Pseudobulbar Affect Registry Investigating Symptom Management II (PRISM II) trial was conducted to provide expanded DM/Q clinical data for PBA in patient populations with Alzheimer's disease and other dementias, stroke or TBI, three neurological conditions commonly associated with PBA. Results from the aggregate study and dementia cohort have been reported elsewhere.[33,34] The objective of the present article is to specifically report results from the TBI cohort of PRISM II, including a functional scale specific to this cohort.

METHODS

Study Design

PRISM II was an open-label, 12-week, multicenter trial enrolling adults with PBA secondary to dementia, stroke, or TBI and conducted from February 26, 2013 to April 20, 2015. All study participants received DM/Q 20/10 mg twice daily (once daily in week 1). Study visits occurred at baseline and at day 30 and day 90 (or early termination), with a telephone consultation at day 60. The study was registered on www.clinicaltrials.gov (NCT01799941) and conducted according to Good Clinical Practice and the Declaration

of Helsinki at 74 enrolling sites (36 enrolled patients with TBI) across the United States. Each site received institutional review board approval.

Study participants

Study participants were included in the TBI cohort of PRISM II if they were aged ≥ 18 years and had a clinical diagnosis of PBA secondary to a non-penetrating TBI of any severity. For the purposes of this study, mild TBI was defined as: a loss of consciousness (if any) lasting for less than 30 minutes; post-traumatic amnesia lasting less than 24 hours; or a Glasgow Coma Score of 13 to 15. Moderate TBI was defined as: a loss of consciousness lasting for more than 30 minutes but less than 24 hours; post-traumatic amnesia lasting from 24 hours to less than 7 days; or a Glasgow Coma Score of 9 to 12. Severe TBI was defined as: a loss of consciousness lasting more than 24 hours; post-traumatic amnesia lasting 7 days or longer; or a Glasgow Coma Score of 8 or less, which indicates that the patient is in a coma.

PBA was defined as: involuntary or exaggerated episodes of emotional expression (specifically laughing or crying) that result from a brain disorder; episodes represent a change from the person's usual emotional reactivity and are incongruent or in excess to the corresponding mood state or provoking stimulus; and the episodes are not better accounted for by another disease state or the direct physiological effect of a substance (drug of abuse or medication). A Center for Neurologic Study-Lability Scale (CNS-LS) score ≥ 13 at baseline also was required. Antidepressants and medications for the treatment of affective/behavioral or emotional issues secondary to or TBI were allowed

provided doses were stable dose for at least 2 months prior to enrollment (6 weeks prior to enrollment for memantine and cholinesterase inhibitors). All other medications were allowed to the extent that they were not prohibited in the approved prescribing information. Study exclusion criteria were: Mini-Mental State Examination (MMSE) score <10, neurologically unstable or stroke within 3 months of screening, history of penetrating TBI, severe depressive disorder, active or a history of schizophrenia, psychosis, schizoaffective disorder, or bipolar disorder, residence in a mental health facility, substance abuse in the 3 years preceding, unstable medical illness, life expectation <6 months, contraindication to DM/Q, use of DM/Q within 6 months, or participation in an interventional study within 30 days. All study participants (or authorized individuals) provided written informed consent. Study participants who were unable to complete study measures were required to have a caregiver who could complete the study measures on their behalf; a caregiver was defined as a person who spent ≥ 3 to 4 days of waking hours with the patient for the week prior to clinic visits (to be knowledgeable about PBA episodes).

Outcome Measures

The primary endpoint was change in CNS-LS score from baseline to day 90 (or final visit if early withdrawal). The CNS-LS is a 7-item measure of affective lability of laughing and crying [14,15] with scores ranging from 7 to 35 (higher scores indicating higher frequency and/or severity of PBA episodes).

Secondary measures included the number of PBA episodes (estimated for the 7 days prior to each clinic visit), Quality of Life-Visual Analog Scale (QOL-VAS), Clinical and Patient Global Impression of Change with respect to PBA (CGI-C and PGI-C, respectively),^[35] Neurobehavioral Functioning Inventory (NFI), MMSE, Patient Health Questionnaire (PHQ-9), and a question assessing treatment satisfaction, and adverse events (AEs).

The QOL-VAS is an anchored, continuous line scale that assesses the impact of PBA episodes on the participant's global subjective well-being (0 = not at all affected to 10 = significantly affected) during the past week. CGI-C and PGI-C^[35] are completed by the investigator and the participant (or caregiver), respectively, and assess overall change in condition and treatment response on a Likert-type scale (1 = very much improved to 7 = very much worse). The NFI is a standardized self-reported rating scale for TBI, composed of 76 items organized into 6 independent scales (depression, somatic, memory/attention, communication, aggression, and motor).^[36] The MMSE^[37] comprises 11 questions or simple tasks assessing orientation, memory, attention, and language to evaluate the patient's cognitive state (scored from 0 to 30). The PHQ-9 is a 9-item scale that assesses depressive symptoms, scored from 0 to 27 (with higher scores indicating greater severity). The treatment satisfaction question is completed by the patient (or caregiver) and rates satisfaction with DM/Q treatment as very dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied, and very satisfied. All scales were completed at day 90; the CNS-LS, PBA episode count and

PHQ-9 were also completed at day 30. AEs occurring any time from enrollment to 30 days after the last dose of DM/Q were recorded.

Statistical Analysis

The safety population included all study participants who received at least one dose of DM/Q. For the effectiveness analysis, a modified intent-to-treat (mITT) population was utilized in which study participants were included if they met all study eligibility criteria, received at least one dose of DM/Q, had at least one post-baseline CNS-LS score, and were without significant site non-compliance. Unless otherwise specified, statistical tests were two-tailed and carried out at the $\alpha = 0.05$ level of significance; all analyses were completed using either SAS v9.2 (SAS Institute Inc, Cary, NC) or Stata v12 (StataCorp, College Station, TX). Missing data were not imputed; however, if the patient had a final visit, it was included as the day 90 Visit. If there was no final visit, data from the day 30 visit were not carried forward as the final visit.

The primary analysis tested the null hypothesis that the mean change in CNS-LS score from baseline to the day 90 visit was equal to zero; the 95% confidence interval (CI) also was calculated to enable a pre-specified descriptive comparison with the CNS-LS change observed in the 12-week, phase 3, pivotal registration trial (the STAR trial) conducted in study participants with PBA secondary to ALS or MS that led to the US approval of DM/Q for PBA.[31]

Changes from baseline were analyzed inferentially using one-sample t-tests for rating scale measures (CNS-LS, QOL, NFI, MMSE, and PHQ-9). To estimate change in PBA episode counts, a mixed-effects Poisson regression model was used, with number of PBA episodes in the past seven days as the dependent variable and age, gender, and time (day 30 and day 90) as fixed effects, while allowing for individual differences in baseline rate (a random subject effect). The percentage change in episode rate from baseline to a given visit is $1 - e^{-\lambda}$.

An a priori power calculation was performed, based on CNS-LS data from the pivotal STAR trial.[31] While caution must be exercised in drawing statistical comparisons across trials, the change from baseline values for study participants treated with placebo provide a basis for comparison of results for this open-label trial where all study participants received DM/Q. The mean (SD) CNS-LS change was -5.7 (5.3) points for placebo-treated study participants in the STAR trial. It was determined that a sample size of 100 study participants with TBI would provide 80% power to detect a CNS-LS mean change of -7.45 points (increase of 1.75 points over assumed true placebo mean change of -5.7), or 90% power to detect a CNS-LS mean change of -7.7 points (increase of 2.0 points over assumed true placebo mean change).

Associations between variables were estimated using the Pearson correlation coefficient and the null hypothesis that the true correlation was equal to zero was assessed using two-sided tests. AEs were categorized via Medical Dictionary for Regulatory Activities (MedDRA version 15.1) coding and reported descriptively.

RESULTS

Participants

Patient disposition is summarized in **Figure 1**. Of the 130 study participants screened, 120 were enrolled and received at least one dose of DM/Q (safety population). A total of 74 (61.7%) study participants completed the study through day 90. Early discontinuations were most commonly due to AEs (11.7%) and loss to follow up (8.3%). A total of 33 study participants were excluded from the effectiveness analysis set due to any or all: lack of post-baseline CNS-LS score (n = 19), failure to meet all inclusion criteria (n = 9), or site non-compliance (n = 9). The day 30 mITT analysis population included 87 study participants, and 67 study participants with available assessments at day 90.

Baseline demographics and clinical characteristics of the safety population are described in **Table 1**. Mean (SD) patient age was 45.7 (14.1) years, and 95.8% lived at home.

Based on protocol criteria described above, 48 (40%) study participants were classified as having mild TBI, 48 (40%) moderate, and 24 (20%) severe. The most common injury mechanism was due to motor vehicle accident (55.8%). A large proportion of study participants were taking one or more concomitant psychiatric medications at baseline (70.0%), most commonly antidepressants (42.5%), followed by anxiolytics or sedatives (38.3%). The mean (SD) CNS-LS score for the mITT population at baseline was 20.5 (4.3), with mean (SD) PBA episode count for the 7 days prior to baseline of 17.9 (20.3) and median of 10 (range: 0, 80; **Table 1**).

Primary Effectiveness Endpoint

The mean (SD) changes from baseline in CNS-LS score at day 30 and day 90/final visit were -5.6 (5.2) and -8.5 (5.2) respectively, which represent significant improvements compared to baseline ($P < .001$, both; **Figure 2**). The mean (95% CI) improvement of -8.5 (-9.8, -7.3) from baseline to day 90 in CNS-LS score was consistent with results for the same DM/Q dose in the 12-week pivotal STAR trial (mean [95% CI], -8.2 [-9.4, -7.0]) and was larger than with placebo (-5.7 [-6.8, -4.7]).[31] The percentage of study participants achieving CNS-LS < 13 was 38.4% by day 30 and 67.2% by day 90/final visit.

Secondary Analyses

Mean (SD) 7-day PBA episode counts decreased from 17.9 (20.3) at baseline to 6.9 (12.6) at day 30 (mean change [SD], -11.0 [19.2], $P < .0001$) and 4.2 (8.0) at day 90 (mean change [SD], -15.7 [18.9], $P < .0001$). Median 7-day episode counts were 10 at baseline, 2 at day 30, and 1 at day 90. PBA episodes were reduced by 61.3% at day 30 and 78.5% at day 90 compared with baseline ($P < .001$, both). By day 30, 53.7% of study participants achieved a $\geq 75\%$ reduction in PBA episode counts; by day 90, 69.8% of study participants achieved a $\geq 75\%$ reduction in PBA episodes. Complete remission (no reported episodes in the week before assessment) was reported by 26.7% at day 30 and 42.4% at day 90, among study participants with reported episodes in the week before baseline.

Global impression of change, with respect to PBA, as measured by CGI-C and PGI-C, indicated the majority of study participants experienced substantial overall improvement (**Figure 3**). Mean (SD) change in NFI T-score from baseline to day 90/final visit improved significantly across all six subscales (**Figure 4**). The QOL-VAS rating of PBA impact on quality of life improved significantly from a baseline mean (SD) of 6.1 (2.6) to 2.3 (2.8) at day 90/final visit (mean change (SD), -3.7 (3.3); $P < .001$). At baseline, PHQ-9 scores were indicative of moderate depression, but improved by day 30 and further improved by day 90/final visit to scores indicative of mild depression (**Figure 5a**). Mean (SD) MMSE scores did not change significantly from baseline (27.3 [3.6]) to day 90/final visit (27.0 [4.2]; mean change -0.1[3.0] $P = .74$). A majority of study participants indicated they were very satisfied or somewhat satisfied with DM/Q treatment; less than 10% were dissatisfied. (**Figure 5b**). Correlation analysis demonstrated that CNS-LS score reduction from baseline to day 90 was significantly correlated with improvements on QOL-VAS, PGIC, CGIC, and the PHQ-9, but not with patient satisfaction, weekly PBA episode count, and MMSE scores (Table 2). Despite the lack of association of change scores between CNS-LS and PBA episode count, absolute CNS-LS score did show significant correlation with PBA episode counts at both day 30 and day 90 (Table 2).

Safety

Among the 120 study participants who received DM/Q (the safety population), 43 (35.8%) reported at least one AE, including 23 (19.2%) with any AE classified as at least possibly related to DM/Q treatment. The most frequently reported AE was diarrhea (n=10 [8.3%]) followed by dizziness, urinary tract infection, and gastroesophageal reflux

disease (each, n=3 [2.5%]). Most AEs were mild or moderate in intensity. Serious AEs occurred in 4 (3.3%) study participants, with none considered treatment-related by study investigators. These included one study participant with urinary tract infection; one with urinary tract infection, prostate infection and sepsis; one study participant with myocardial infarction (MI); and one with depression and suicidal ideation. The study participant with MI had a family history of cardiac disease on both parental sides (father died before age of 50 from cardiac disease), multiple cardiac risk factors, and was also receiving taking venlafaxine, gabapentin, estradiol, dextroamphetamine/amphetamine and atorvastatin. An EKG obtained during hospitalization revealed ischemia and a non-ST segment elevation myocardial infarction; however, there was no QT prolongation, and the QT interval appeared normal. Cardiac catheterization showed stenosis. Based on the above, the investigator assessed the event as not related to DM/Q treatment, and DM/Q was restarted after discharge. The patient with suicidal ideation exhibited symptoms of wanting to harm himself during the final study visit; although he later retracted the statement, he was hospitalized and treatment with DM/Q continued. The patient had a history of depression and current social stressors that the investigator considered as the likely cause of these symptoms. In total, 14 (11.7%) study participants withdrew from the trial due to AEs, most commonly diarrhea (6 [5.0%]), dizziness, nausea, and labile affect (2 [1.7%] each).

DISCUSSION

PRISM II was the first prospectively conducted study to systematically evaluate DM/Q effectiveness, including safety and tolerability, for PBA in people with TBI. The trial

inclusion and exclusion criteria allowed for a study population that closely resembled actual clinical conditions. The main efficacy measure, CNS-LS score, which measures the frequency and severity of PBA, improved significantly after both 30 days and 90 days of open-label DM/Q treatment, and was consistent with significant reductions in PBA episodes. The measured reduction in PBA episodes in this trial appeared clinically meaningful, as demonstrated by corresponding improvements in clinician and patient or caregiver reported global impression of change with respect to PBA (PGI-C and CGI-C), a quality of life assessment (QOL-VAS), and measures of depressive symptoms (PHQ-9) and neurobehavioral problems (NFI). Correlation analysis showed that CNS-LS improvement was significantly correlated with improvement in each of these secondary outcome measures, except for NFI where correlation analysis was not performed. DM/Q was generally well tolerated; most AEs were of mild to moderate severity and do not represent new or different safety concerns. The purpose of quinidine in DM/Q is to inhibit CYP2D6 enzymatic metabolism. As most study participants were receiving concomitant neuropsychiatric medications, including some that are metabolized by CYP2D6, the safety findings in this population are reassuring in that no new safety concerns were identified. Taken together, the use of DM/Q in study participants with TBI resulted in effective PBA episode reduction.

The findings in this open-label trial are consistent with three prior randomized, controlled trials assessing DM/Q treatment for PBA in study participants with MS or ALS, and with results for the stroke and dementia cohorts from this study. These trials, across 5 distinct patient populations, demonstrate that DM/Q efficacy is not dependent on the neurologic

condition that gives rise to PBA.[29,30,31,33,34] A pre-specified analysis calculated the 95% CI for mean CNS-LS change at day 90, to allow evaluation relative to CNS-LS change in the prior 12-week (84 day), phase 3 pivotal trial. Although treatment effectiveness from different trials cannot be directly compared, improvement in mean CNS-LS scores in the PRISM II TBI cohort was similar to that seen for the same dose of DM/Q in the pivotal trial and greater than the change with placebo in that trial.[31] The CNS-LS change in PRISM II also compares favorably to that seen in two earlier randomized, controlled trials of DM/Q for PBA that used higher DM/Q doses than this trial (range: -7.4 to -7.7).[12,30] The results here are also consistent with PBA improvement observed overall in the PRISM II trial, as well as the improvement seen in the other individual disease cohorts included in the PRISM II trial [34] and dementia[33]). Across the three cohorts, the improvements in CNS-LS and PBA episode counts were statistically significant and similar in magnitude. Similarly, results for secondary outcomes, including CGI-C and PGI-C, QOL-VAS, and PHQ-9, were generally similar across cohorts.[34] The NFI is only administered to persons with TBI in this study, and therefore, performance cannot be compared with other cohorts (ie, stroke, dementia); however, NFI T-score changes here appear better than those reported previously on one study with a similar time frame.[38] Subscales of the NFI likely have differences in the maximal performance, or ceiling, that can be achieved. For example, a previous analysis identified that motor scores may drop as low as 16 to 8 to represent the ceiling improvement, whereas memory/attention scores reach ceiling between 38 to 19[39] The variance in improvements observed here across subscales seems to align with

variance in the reasonable maximal improvement that can be measured on NFI-T subscales.

Further, over 40% of study participants here were receiving concomitant antidepressant and antiepileptic medications, which may be used off-label to treat PBA. As such, further reductions in PBA episodes and symptoms are in addition to any benefit study participants may have been receiving from other medications. Taken together, these results show a consistent effectiveness of DM/Q for PBA secondary to distinct neurological diseases, including ALS, MS, stroke, dementia and TBI.

The limitations of this study are principally the potential subjective bias related to the open-label design and use of self-reported measures based on observations by study participant, caregiver, or clinician. Although the CNS-LS was validated as a PBA measure in studies of people with ALS and MS,[29,30] the scale has not been specifically validated in people with TBI. However, the improvements in CNS-LS scores were consistent with other outcome measures, including the number of PBA episodes and the global measures of change with respect to PBA. As is typical with any clinical trial, inclusion and exclusion criteria may have limited the generalizability of the current results; however, inclusion criteria in this trial were broader (and exclusion criteria more limited) than those traditionally employed in clinical trials, allowing a broader, more clinically applicable, range of study participants to enroll. Therefore, generalizability should be improved compared with traditional phase 3 trials.

CONCLUSIONS

Open-label DM/Q 20/10mg twice daily resulted in significant improvements in CNS-LS scores and significant reduction of PBA episodes and was well tolerated in people with PBA secondary to TBI. These findings are consistent with prior well-controlled studies of DM/Q for PBA secondary to ALS or MS, and with the results from the other disease cohorts of the PRISM II study, and support DM/Q effectiveness for PBA regardless of neurologic etiology.

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AUTHOR CONTRIBUTIONS

FMH, WS, and AEF participated in study design and interpretation. FL and AEF participated in data review and analysis. FL participated in study execution and data management. CD directed statistical analysis. FMH wrote the first draft of the manuscript. All authors had full access to study data and provided direction on manuscript content and data presentation. All authors approved the final manuscript for submission.

AUTHOR DISCLOSURES

FMH

WS

FL and AEF are employees of Avanir Pharmaceuticals, Inc.

CD served as a consultant for Avanir Pharmaceuticals, Inc.

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Table 1. Baseline Demographics and Clinical Characteristics, Safety Population

	Safety Population (N=120)
Age, mean (SD), y	45.7 (14.1)
Gender, n (%)	
Male	63 (52.5)
Female	57 (47.5)
Race, n (%)	
White/Caucasian	98 (81.7)
Black/African American	17 (14.2)
Native Hawaiian or other Pacific Islander	2 (1.7)
Unknown	3 (2.5)
Ethnicity, n (%)	
Hispanic/Latino	11 (9.2)
Place of residence, n (%)	
Home	115 (95.8)
Skilled nursing facility	5 (4.2)
Injury mechanism, n (%)	
Fall	29 (24.2)
Motor vehicle accident	67 (55.8)
Assault	5 (4.2)
Struck by/against	8 (6.7)
Recreation injury	2 (1.7)
Other	9 (7.5)
TBI severity, n (%)	
Mild	48 (40)
Moderate	48 (40)
Severe	24 (20)
Concomitant medications at baseline	

Number of Medications, Mean (SD)	6.5 (4.9)
Number of Medications, Median (range)	5.5 (0, 23)
Psychotropic medications,^a n (%)	
≥1 Psychotropic Medication ^a	84 (70.0)
Antiepileptics	35 (29.2)
Antipsychotics	17 (14.2)
Antidepressants	51 (42.5)
Sedatives or anxiolytics	46 (38.3)
Any Benzodiazepines ^b	37 (30.8)
Psychostimulants	19 (15.8)
Anti-dementia drugs	10 (8.3)
Baseline measurements, Mean, (SD)	Effectiveness Analysis Population n = 87
CNS-LS ^c	20.5 (4.3)
PBA episodes/per week	
Mean (SD)	17.9 (20.3)
Median (range) ^d	10 (0, 80)
QOL-VAS	6.1 (2.6)
PHQ-9	13.9 (6.5)
MMSE	27.3 (3.6)

^aPsychotropic medications included anticonvulsants, antipsychotics, antidepressants, sedative/hypnotics, or anxiolytics, and benzodiazepines.

^bBenzodiazepines included benzodiazepines used as sedatives/hypnotics, anxiolytics and clonazepam as an anticonvulsant.

^cCNS-LS scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes.

^dMedian reported because data are skewed.

CNS-LS, Center for Neurologic Study–Lability Scale; MMSE, Mini Mental State Examination; PBA, pseudobulbar affect; PHQ-9, Patient Health Questionnaire; QOL-VAS, Quality of Life Visual Analog Scale; SD, standard deviation.

Table 2. Correlation between CNS-LS and Other Efficacy Outcomes at Day 90

First Variable	Second Variable	Pearson Correlation	Observations	P-Value
CNS-LS	Patient satisfaction score ^a	-0.0290	67	0.8157
CNS-LS	Weekly episode rate	0.4381	66	0.0002
CNS-LS	QoL VAS	0.6080	67	<.0001
CNS-LS	PGIC ^b	0.5155	67	<.0001
CNS-LS	CGIC ^b	0.4619	67	<.0001
CNS-LS	MMSE	-0.1218	66	0.3298
CNS-LS	PHQ-9	0.6480	67	<.0001
Weekly episode rate	Patient satisfaction score ^a	-0.1940	66	0.1186
Weekly episode rate	QoL VAS	0.5787	66	<.0001
Weekly episode rate	PGIC ^b	0.4703	66	<.0001
Weekly episode rate	CGIC ^b	0.4791	66	<.0001
Weekly episode rate	MMSE	-0.3805	66	0.0016
Weekly episode rate	PHQ-9	0.3534	66	0.0036

^aPatient satisfaction is scored on a Likert-type scale, with higher scores representing greater satisfaction (ie, 1, “very dissatisfied” to 5, “very satisfied”).

^bLower scores on the Global Impression of Change are representative of improvement (ie, 1, “very much improved” to 7 “very much worse”).

CGIC, Clinician’s Global Impression of Change; CNS-LS, Center for Neurologic Study–Lability Scale; MMSE, Mini Mental State Examination; PHQ-9, Patient Health Questionnaire; PGIC, Patient’s/Caregiver’s Global Impression of Change; QOL-VAS, Quality of Life Visual Analog Scale.

FIGURE LEGENDS

Figure 1. CONSORT Diagram for the PRISM II TBI Cohort

CNS-LS, Center for Neurologic Study–Lability Scale

^aCategories are not mutually exclusive; a patient may be counted in more than one category.

Figure 2. Mean CNS-LS Scores at Baseline, Day 30, and Day 90 in PRISM II TBI Cohort (Effectiveness Analysis Set)

CNS-LS is a patient-reported quantitative measure of the perceived frequency and severity of PBA episodes. Scores range from 7 to 35, with higher scores indicating increased frequency and severity of PBA episodes. *P* values were based on the one sample t-test and represent comparison with baseline.

**P*<.001 vs. baseline.

CNS-LS, Center for Neurologic Study–Lability Scale; CI, confidence interval; PBA, pseudobulbar affect; SD, standard deviation.

Figure 3. Percent Reduction in Mean PBA Episode Count in PRISM II TBI Cohort (Effectiveness Analysis Set)

Estimated percent change from baseline for PBA episode count was evaluated via a mixed-effects Poisson regression model for each time point, based upon patient/caregiver estimates of the number of PBA episodes experienced in the 7 days prior to each clinic visit.

**P*<.001 vs. baseline.

PBA, pseudobulbar affect.

Figure 4. 90-day Clinical and Patient Global Impression of Change in PRISM II TBI Cohort (Effectiveness Analysis Set)

CGI-C is a 7-point investigator-rated scale that assess overall treatment response with respect to PBA from baseline to day 90/final visit; 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. Percentages use the count of study participants with non-missing data as the denominator (CGI-C, n=68; PGI-C, n=67) and may not sum to 100.0 due to rounding.

CGI-C, Clinical Global Impression of Change; PGI-C, Patient/Caregiver Global Impression of Change.

Figure 5. Mean NFI Subscales Scores in PRISM II TBI Cohort (Effectiveness Analysis Set)

NFI T-scores are standardized across six independent subscales; scores range from 1 to 99 with higher scores indicating greater neurologic disability.

**P*<.001 vs. baseline.

NFI, Neurobehavioral Functioning Inventory; SD, standard deviation.

Figure 6. (a) Mean PHQ-9 Score and (b) Patient Treatment Satisfaction in PRISM II TBI Cohort (Effectiveness Analysis Set)

PHQ-9 is a 9-item scale that assesses depressive symptoms, scored from 0 to 27 with higher scores indicating greater severity. Treatment satisfaction was assessed with the following question: how satisfied are you with NUEDEXTA as a treatment for your pseudobulbar affect? Results were scored from 1 (very dissatisfied) to 5 (very satisfied). * $P < .001$.

PHQ-9, Patient Health Questionnaire; SD, standard deviation.

Screened Patients
n=130

Screen Fails
n=10

Enrolled Patients/Safety Population
n=120

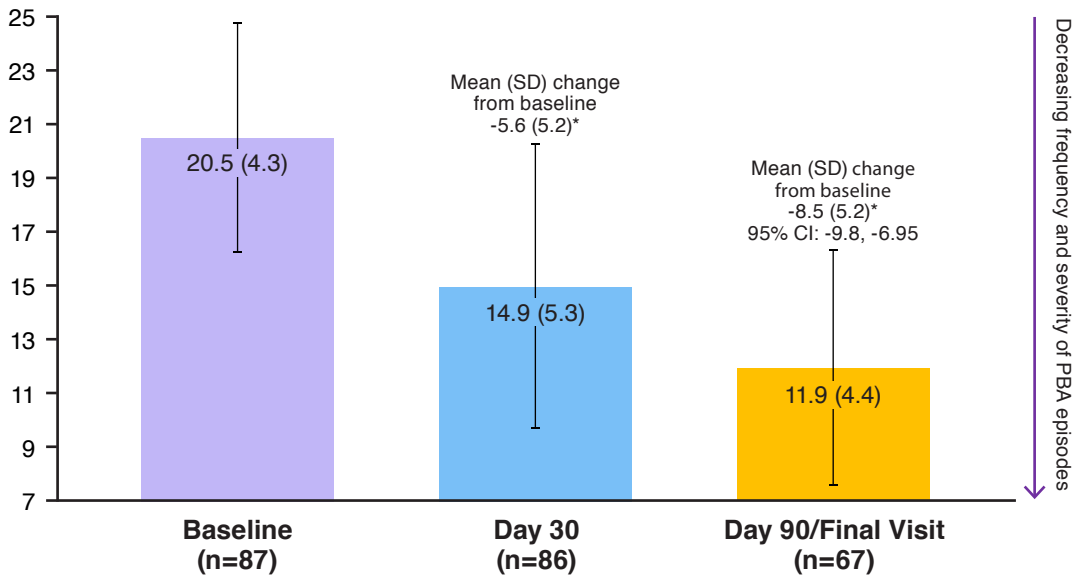
Discontinued, n (%)	46 (38.3)
Adverse event	14 (11.7)
Lost to follow up	10 (8.3)
Consent withdrawn	7 (5.8)
Investigator decision	3 (2.5)
Lack of efficacy	1 (0.8)
Other	11 (9.2)

Completed Study
n=74 (61.7%)

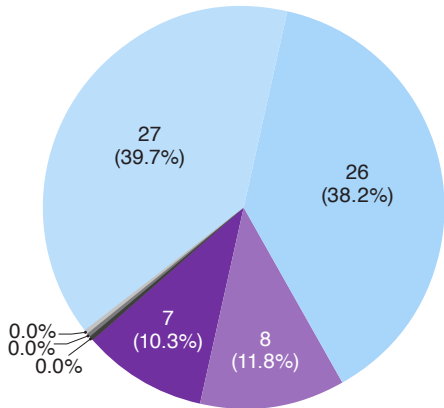
Excluded From Effectiveness, n (%)^a	33 (27.5)
No post-baseline CNS-LS	19 (15.8)
Failure to meet all eligibility criteria	9 (7.5)
Site non-compliance	9 (7.5)

Effectiveness Analysis Population
n=87 (72.5%)

Mean (SD) CNS-LS Score

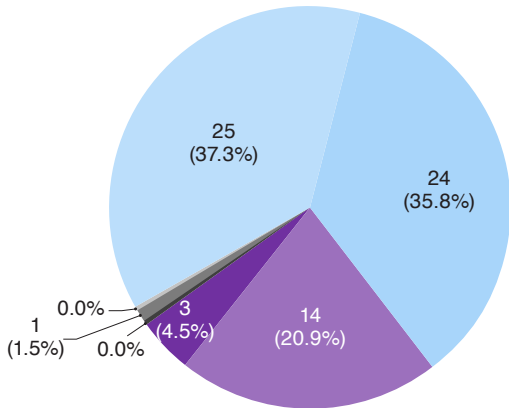


CGI-C



Effectiveness Set, N=87; Missing, n=0;
No Day 90 Visit, n=19; Valid, n=68

PGI-C



Effectiveness Set, N=87; Missing, n=1;
No Day 90 Visit, n=19; Valid, n=67

Very much improved Much improved Minimally improved No change Minimally worse Much worse Very much worse

