Table 2. ORs From Final Regression Models

Parameter	MADRS Model		EWB Model	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
ESL 1200 mg vs PBO	2.68 (1.94 to 3.69)	< .001	2.64 (1.92 to 3.64)	< .001
ESL 800 mg vs PBO	1.89 (1.37 to 2.62)	< .001	1.89 (1.37 to 2.61)	< .001

ESL, eslicarbazepine acetate; EWB, Emotional Well-Being subscale; MADRS, Montgomery-Åsberg Depression Rating Scale; PBO, placebo.

Reproduced with permission from TC Bond, PhD.

Levodopa-Carbidopa Intestinal Gel Shows Promise in Advanced Parkinson Disease

Written by Maria Vinall

Interim data from an ongoing phase 3b trial, presented in a poster by Jordan Dubow, MD, AbbVie, Inc., North Chicago, Illinois, USA, indicated that treatment with levodopa-carbidopa intestinal gel (LCIG) significantly improved nonmotor symptoms (NMSs) in patients with advanced Parkinson disease (PD).

NMSs play an important role, clearly affecting health-related quality of life (HRQOL) of patients with PD. LCIG (carbidopa-levodopa enteral suspension) is an effective treatment option for motor fluctuations in advanced refractory PD [Olanow CW et al. *Lancet Neurol.* 2014]. Open-label studies have shown that LCIG is associated with significant improvements in NMSs and HRQOL in patients with advanced PD [Fasano A et al. *Eur Rev Med Pharmacol Sci.* 2012; Reddy P et al. *Clin Neuropharmacol.* 2012].

This phase 3b, open-label, multicenter study [NCT01736176] included patients aged ≥30 years with levodopa-responsive idiopathic PD and severe motor fluctuations with ≥3 hours of "off" time/day (despite individually optimized therapy). After conversion to oral levodopa-carbidopa, all patients underwent a percutaneous endoscopic gastrostomy-jejunostomy placement procedure. The study included an initial 12-week LCIG treatment period and a 48-week long-term treatment period. The primary end point was the change in NMSs from baseline to week 12 as measured by the Non-Motor Symptoms Scale (NMSS) total score. Secondary end points included the change from baseline to week 12 in the 9 NMSS domains. Adverse events (AEs) were recorded. Interim analysis was completed for the first 17 of 36 participants.

Patients had a mean age of 64 years (range, 45-76), 65% were men, and 94% were white. Mean exposure to LCIG was 180 days (range, 5-368 days). Fourteen of 17 patients had a reduction in NMSS total score between baseline and final evaluation; the mean reduction was 38.3% (–20.7; $P = .001$).

Significant decreases were noted in 3 of the 9 NMSS domains: sleep/fatigue (–6.7; $P = .008$), sexual function (–2.5; $P = .011$), and miscellaneous (–4.9; $P = .002$).

At least 1 treatment-emergent AE was reported for 16 patients, and 2 patients discontinued due to AEs. The most frequently reported AEs were procedural pain (65%) and anxiety (24%). Serious AEs were reported for 2 patients; neither was considered related to LCIG.

This study provides additional evidence that LCIG can be a safe and effective treatment for NMSs in patients with advanced PD.

Brivaracetam Reduces Seizure Frequency in Patients With Partial-Onset Seizures

Written by Maria Vinall

Pavel Klein, MD, Mid-Atlantic Epilepsy and Sleep Center, Bethesda, Maryland, USA, presented the results of a phase 3 trial [NCT01261325] showing that adjunctive treatment with brivaracetam is associated with a significant reduction in the frequency of partial-onset seizures (POS) and improved response.

Brivaracetam is a selective high-affinity synaptic vesicle protein 2A ligand in clinical development for the treatment of epilepsy. The objective of this multicountry phase 3 study was to evaluate the efficacy, safety, and tolerability of brivaracetam compared with placebo as an adjunctive therapy in adult patients with focal epilepsy. Patients enrolled in this study had POS not fully controlled, despite treatment with 1 or 2 concomitant antiepileptic drugs. The study consisted of an 8-week baseline observational period and a 12-week treatment period, after which patients could undergo a 4-week down titration or enter into an open-label follow-up study. The co–primary efficacy outcomes were percentage reduction over placebo in 28-day adjusted seizure frequency and ≥50% responder rate based on percentage reduction in seizure frequency from baseline to the treatment period.

Patients aged ≥16 to 80 years with refractory POS who experienced ≥8 POS during the 8-week baseline period and ≥2 POS per month, with or without secondary generalization, during the 3 months prior to screening were recruited. Eligible patients were randomized 1:1:1 to placebo or brivaracetam 100 or 200 mg/d BID. During the 12 weeks of treatment, the rate of discontinuation was low and mostly due to adverse events (AEs; 3.8% in the placebo group and 8.3% and 6.8% among patients in the

100- and 200-mg/d brivaracetam groups, respectively). The majority of participants completed the study and entered the follow-up study. Patient disposition is shown in Table 1.

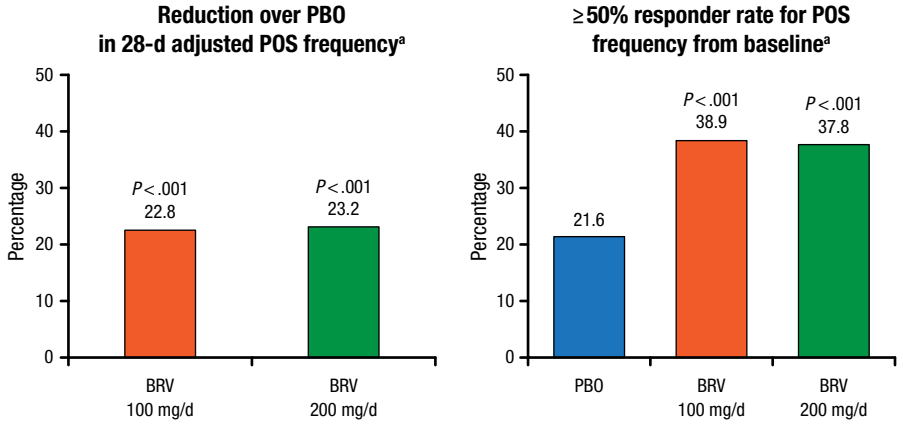
Both doses of brivaracetam significantly ($P < .001$) improved the co–primary outcomes of percentage reduction in POS and ≥ 50% responder rate adjusted to a 28-day duration compared with placebo (Figure 1). Patients receiving brivaracetam also had significantly higher median percentage reduction in seizures compared with baseline and significantly higher rates of seizure freedom (all types) during treatment (Figure 2).

Table 1. Patient Disposition

Adjunctive Treatment	Randomized	ITT Population	Completed 12-wk Study	Entered Follow-up
Brivaracetam 100 mg/d	254	252	225 (88.6)	219 (86.2)
Brivaracetam 200 mg/d	251	249	225 (89.6)	220 (87.6)
Placebo	263	259	246 (93.5)	237 (90.1)

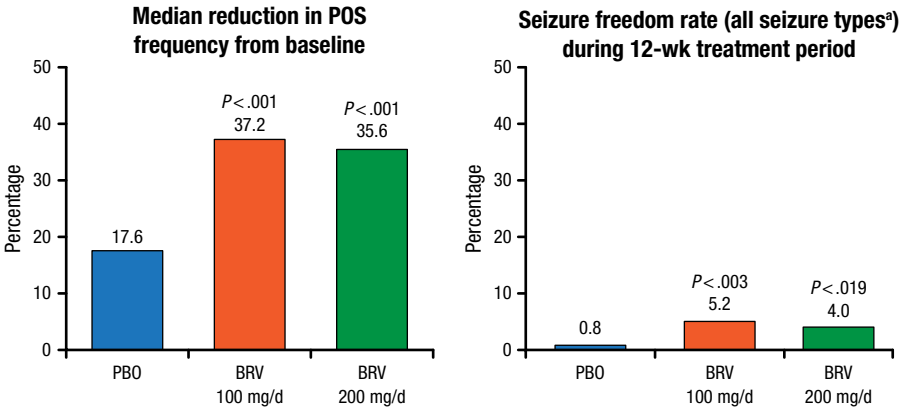
Data are expressed in n (%).
ITT, intention-to-treat.

Figure 1. Co–primary Efficacy Outcomes (Intention-to-Treat Population)



BRV, brivaracetam; PBO, placebo; POS, partial-onset seizures.
[a]During the treatment period.
Reproduced with permission from P Klein, MD.

Figure 2. Secondary Efficacy Outcome (Intention-to-Treat Population)



BRV, brivaracetam; PBO, placebo; POS, partial-onset seizures.
[a]Partial-onset, generalized, and unclassified seizures.
Reproduced with permission from P Klein, MD.

Treatment-emergent AEs occurred in 59.4% of placebo patients and 68.4% and 66.8% of patients in the 100- and 200-mg/d brivaracetam groups, respectively. The most common AEs (≥5%) were somnolence, followed by dizziness, fatigue, headache, and urinary tract infection; however, the latter 2 occurred with similar frequency in briviracetam- and placebo-treated patients. Serious treatment-emergent AEs occurred in <3.5% of participants, without difference between the briviracetam and placebo treatment groups. There were 2 deaths, both in the brivaracetam 200-mg/d group; neither was considered related to the study drug.

This study confirms the results of 2 previous fixed-dose phase 3 trials that used 5- to 100-mg/d doses of brivaracetam [Biton V et al. *Epilepsia.* 2014; Ryvlin P et al. *Epilepsia.* 2014].

A2NTX an Effective Substitute for OnabotulinumtoxinA in Poststroke Spasticity

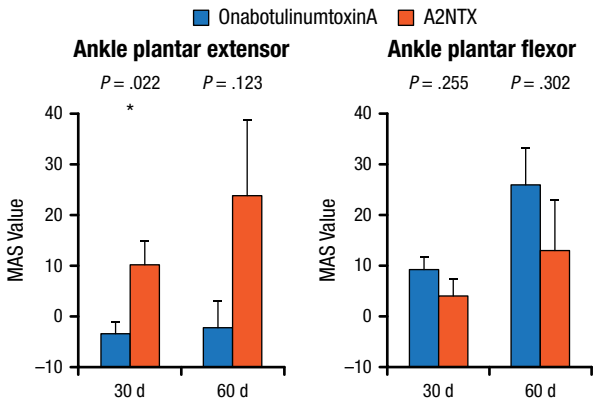
Written by Maria Vinall

In a poster presentation, Ryuji Kaji, MD, University of Tokushima, Tokushima, Japan, reported that A2NTX, a new botulinum toxin preparation derived from botulinum toxin serotype A (BoNT/A), is more effective for treating poststroke lower limb spasticity compared with the A1 subtype of BoNT (onabotulinumtoxinA).

In this phase 2/3 proof-of-concept study [NCT01910363], patients were not prescribed any rehabilitation posttreatment, to reduce the influence of varying rehabilitation intensiveness. Men and women, aged 40 to 79 years, with poststroke lower limb spasticity of >6 months' duration were included. Participants had a Modified Ashworth Scale (MAS) score for either flexion or extension ankle joint ≥2 and both flexion and extension >0.

Guided by electromyography, either onabotulinumtoxinA or A2NTX was first injected into the tibialis posterior (150 Units), then into the medial gastrocnemius (150 Units) using the same needle tract on the affected side. Ninety days later, this procedure was repeated. MAS was measured at baseline, 30 (27-33) days, and 60 (56-63) days after injection. Areas under the curve of MAS changes at day 30 and day 60 after injection were compared between treatments. Secondary outcome measures included changes in functional independence measure (FIM) and changes in handgrip measured in kg units. As injections were made in the lower limbs, any decrease of grasp power was assessed as a measure of unwanted spread of the toxin action, and thus a measure of safety and toxin spread.

Figure 1. Changes in Extensor and Flexor MAS Values at 30 and 60 Days



Mean±standard error of AUC, Student t.

AUC, area under the curve; MAS, Modified Ashworth Scale.

*Paired-t analysis.

Reproduced with permission from R Kaji, MD.

The men-to-women ratio was higher in the onabotulinumtoxinA group (15:1) compared with the A2NTX group (10:5). Mean age was 65.6 years; duration of illness was 93 months; side of paresis favored the left in the onabotulinumtoxinA group and the right in the A2NTX group; MAS for ankle plantar extension was 2.53 and flexion 0.97; hand grip power was 30 kg; and mean FIM was 26.1 (on a scale of 18-126, with higher scores indicating more independence).

At 30 days, A2NTX significantly improved ankle plantar extensor compared with onabotulinumtoxinA ($P = .022$), although the same was not true at 60 days. There were no significant differences in flexor values at either 30 or 60 days (Figure 1).

FIM was significantly improved at 60 days for patients treated with A2NTX ($P = .006$) but not onabotulinumtoxinA. Patients in the onabotulinumtoxinA-treated group had a significant reduction of handgrip at 60 days ($P = .002$), whereas patients in the A2NTX group did not, likely indicating that A2NTX had less distant spread than onabotulinumtoxinA.

The investigators concluded that A2NTX is an effective substitute for onabotulinumtoxinA, with less distant spread.