CNS Drugs

Rapidity of CNS Effect on Photoparoxysmal Response for Brivaracetam vs Levetiracetam: A Randomized, Double-blind, Crossover Trial in Photosensitive Epilepsy Patients

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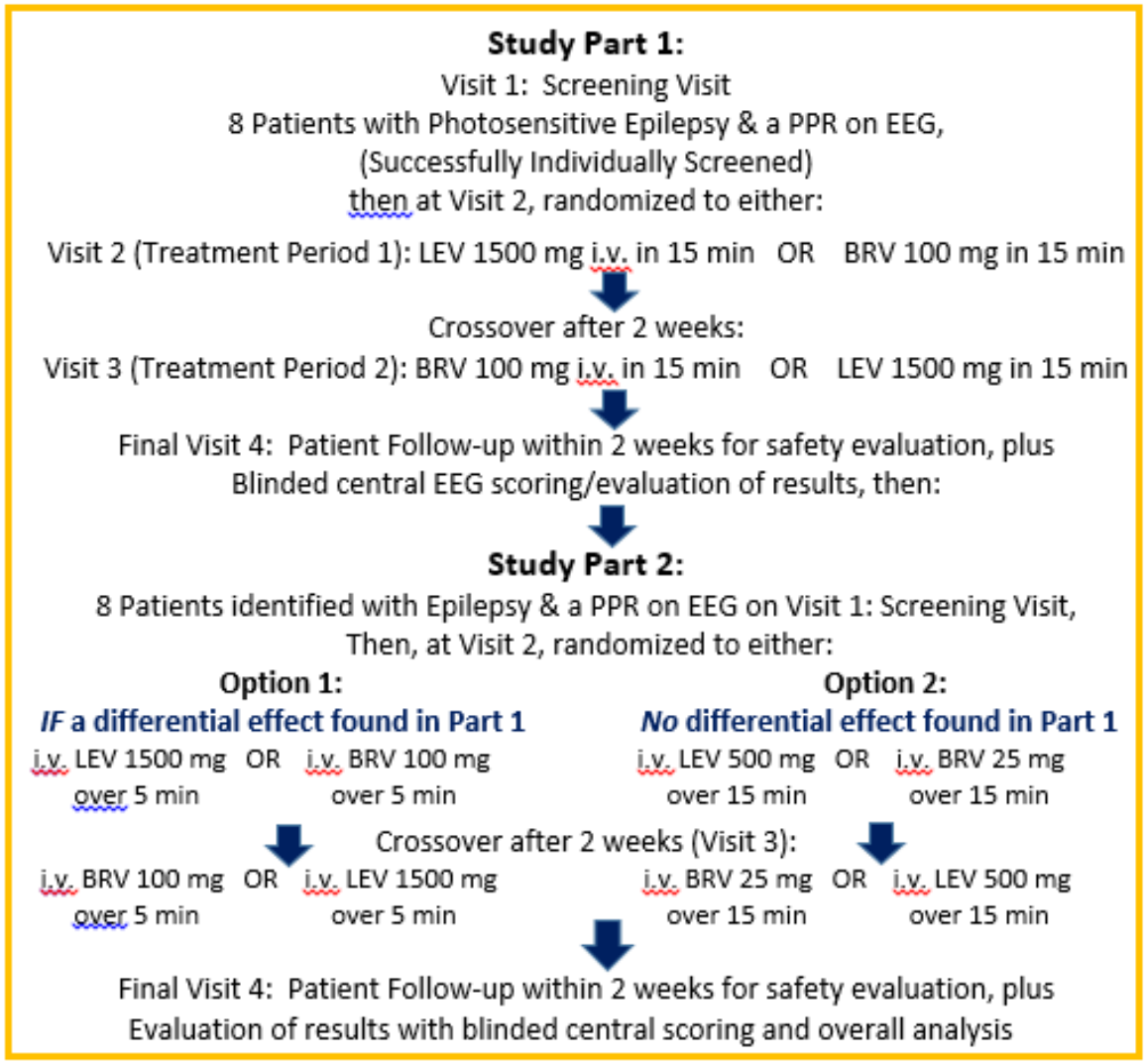
Supplementary Materials

Figures and Tables appear in the order presented in the manuscript text.

Supplementary Figure 1: Study Design Flow Chart, Parts 1 & 2[a]



[a] **The reader is referred to 'Expanded Descriptions of Select Items from Manuscript Text, Methods, 2.1 Protocol' for more information regarding the only patient (blinding code AAA) who was placed into Option 2, Part 2.**

Supplementary Table 1: Flowchart of Study Procedures / Events for Patient Visits--

For a 15-minute i.v. ASM infusion with crossover to 2nd ASM infusion (Part 1, Visits 2 then 3), then separately, a 5-min. ASM i.v. infusion with crossover to 2nd ASM infusion (Part 2, Visits 2&3). (A minimum of 14 days occurred between Visit 2 = Treatment Period 1, and Visit 3 = Treatment Period 2).

DAY	-21 to -1 Visit 1 (Screening)	0	1 and 15 (+14 days) Visit 2 and 3										Up to two weeks post visit 3
	Screening	Admitted	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	IPS + blood	Final visit Day
Time min from baseline	Morning	-60	0	+1	+ 2	+5	+10	+15	+20	+30	+60	+120	
Signed informed consent	✖												
Inclusion/exclusion criteria	✖		✖										
Pregnancy Test	✖		✖										✖
Medical history	✖												✖
Demography	✖												
Physical examination	✖												✖
Vital Signs	✖		✖						✖	✖	✖	✖	✖
EEG-IPS Assessment	✖		✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	
Biochem, hematology	✖		✖										✖
Drug levels LEV /BRV			✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	
Levels Co-ASMs	✖		✖									✖	
Administration LEV/BRV			✖										
Concomitant medication if applicable and as prescribed	✖	✖											✖
Adverse events monitoring	✖		✖	✖	✖	✖	✖	✖	✖	✖	✖	✖	✖

Supplementary Table 2: Physical & Clinical Characteristics, including Seizure Types, Co-morbidities, Concomitant ASMs with Total Daily milligram Dose, plus EEG PPR Baseline Conditions, for All Patients

Patient:	AAA	BBB	CCC	GGG	HHH	KKK	NNN	OOO[a]	PPP[a]
Sex	M	M	M	F	F	F	F	F	F
Age (yr) at Study Start	34	34	25	23	36	36	38	18	42
Wgt (kg)[b]	82.4	84.8	63.6	82.4	74.3	108.6	52.2	85.9	105.6
Co-ASM(s) Generic Name & Total mg Daily Dose	LTG-XR: 800 LZP: 1 (prn)	VPA-ER: 1750 LCM: 400 ZNS: 400 CBD: 1.32 (in Part 2)	ZNS: 600 LCM: 500 PER: 8 CBD: 33	ZNS: 400 LTG: 450	LTG: 700	TPM: 400	none	none	VPA: 500 PGB: 150
Seizure (Sz) types	GTC, MYO ABS drop attacks	GTC MYO ABS drop attacks	GTC MYO ABS	GTC MYO ABS	MYO ABS	GTC MYO ABS	GTC MYO ABS	GTC MYO ABS	GTC MYO
Visually induced szs / type	Yes: GTC MYO	Yes: MYO	Yes: MYO	Yes: GTC MYO	Yes: MYO	Yes: GTC MYO	Yes: MYO	Yes: GTC MYO	Yes: MYO
Sz Frequency previous 6 months	GTC:1-2/mo MYO:qd ABS:infreq Drops:qd	MYO: periodic ABS: qd Drops:1/yr	GTC:2/mo	GTC:2/6 mo MYO: qd	MYO: occas	MYO: occas	MYO: occas	None	MYO: occasional ,if tired, with flash-ing lights
Epilepsy type	1° gen	1° gen	1° gen	1° gen	1° gen	1° gen	1°gen	1°gen	1° gen
Co-morbidities	ADD	No	No	ADD	Cervical cancer, SLE, DM	Mild dev delay, Hx colon/thyroid Ca, hyperlip-idemia, fatty liver	No	Anx, Dep	Obesity, Gastric sleeve, AODM
Neurologi-cal exam	wnl	wnl	wnl	wnl	wnl	Abn[c]	wnl	wnl	wnl

EEG PPR Baseline Conditions[d,e]

Part 1 PPR[f] (Hz)	V2	60	50	60	60	25	30	30	30	---
	V3	20[g]	25	40	40	25	50	30	60	---
Part 1 Eye condi-tion	V2	during closure	during closure or closed	during closure	during closure or closed	during closure	during closure	during closure	during closure	---
	V3	during closure	during closure or closed	during closure	during closure or closed	during closure	during closure	during closure	during closure	---
Part 2 PPR[f] (Hz)	V2	50[h]	40	50	20	25	50	30	---	30
	V3	18[h]	25	40	30	20	40	30	---	60
Part 2		closure	closed	during	closed	during	during	during	---	during

Eye condi-tion	V2 V3	closure	during closure	closure during closure	during closure	closure during closure	closure during closure	closure during closure	---	closure during closure

Abbreviations used: M = male, F = female, Hgt = height, Wgt = weight; BMI = body mass index; Co-ASMs = concomitant Anti-Seizure Medicines (ASMs); Sz = seizure; wnl = within normal limits; Abn = abnormal; LTG = lamotrigine, LTG-XR = lamotrigine extended-release, LZP = lorazepam, VPA-ER = valproic acid extended-release, LCM = lacosamide, ZNS = zonisamide, CBD = cannabidiol, PER = perampanel, TPM = topiramate, PGB = pregabaline; GTC = generalized tonic-clonic seizure; MYO = myoclonic; ABS = absence; Drops = drop attacks; 1° gen = Primary generalized; mo. = month, qd = daily, occas = occasionally; ADD = attention deficit disorder; SLE = systemic lupus erythematosus, DM = diabetes mellitus; AODM = adult onset DM; Ca = cancer, de = developmental; Anx = anxiety; dep = depression.

a Patient OOO only participated in Part 1; patient PPP only in Part 2.

b Weight was only calculated for each patient at the Screening Visit, V1, in Part 1 and at Screening V1, Part 2, for PPP.

c Abn = Abnormal neurological exam for Patient KKK, at baseline, included mild cognitive dysfunction, moderate tremor and mild wide-based gait.

d IPS was performed by the neurologist/epileptologist (WER), with the EEG technologist assistance, for 5 sec or less with 5 sec intervals at 0 (baseline), 1, 2, 5, 10, 15, 20, 30, 60 and 120 minutes from start of intravenous ASM administration. Counting of the 5-second intervals was performed out-loud by neurologist/epileptologist (SML), assisted with a metronome. Procedures and observations for PPR were continuously followed on video EEG screen on a Nihon Kohden digital machine. The lamp was placed 11 inches from the nasion. Patients were checked for spontaneous epileptiform discharges (2.5 minutes EEG with eyes open and 2.5 minutes with eyes closed) at baseline. Patients were continuously observed clinically.

e Prior to any patient recruitment, the entire investigative team performed a multiple-hour simulation of photic stimulation, EEG recording, and blood sampling/processing on a staff volunteer until the protocol-defined precise timing of the procedures was performed efficiently and correctly.

f Upper limit threshold starting point (determined at baseline).

g Patient AAA's testing started 3 hrs post-GTCS.

h AAA received lower mg dose at the same infusion rate in Part 2 (Protocol Option 2).

Supplementary Table 3: Concomitant ASM Plasma Concentrations [ASM, mg/L][a] for Participating Patients, AAA through GGG

Patient:	AAA	BBB		CCC		GGG	
Co-AED(s) Generic Name & Total mg Daily Dose	LTG-XR: 800 LZP: 1 (prn)		VPA-ER: 1750 LCM: 400 ZNS: 400 CBD: 1.32 (in Part 2)		ZNS: 600 LCM: 500 PER: 8 CBD: 33		ZNS: 400 LTG: 450
Date:	06-01-18		06-01-18		06-06-18		06-26-18
AAA Date,Part 1 time,visit #	[LTG]	BBB Date,Part 1 time,visit #	[VPA] [LCM]	CCC Date,Part 1 time,visit #	[LCM]	GGG Date,Part 1 time,visit #	[LTG]
06-01-18, 08:43, V1	8.5	06-01-18, 12:38p, V1	118.2 9.6	06-06-18, 11:00, V1	n.d.	06-26-18, 15:27p, V1	10.0
06-02-18, 08:12, V2	5.1	06-05-18, 14:09p, V2	105.5[b] 9.2[b] [b]2 hr post-start LEV or BRV intravenous	06-11-18, V2	- - -	07-10-18, 09:10, V2	9.3
06-19-18, 08:08, V3	14.3	06-21-18, 08:11, V3	95.0 9.7	06-25-18, 09:09, V3	2.1	07-10-18, 12:11p, V2	9.6[b]
06-19-18, 10:58, V3	9.4[b]	06-21-18, 11:12, V3	88.4[b] 9.1[b]	06-25-18, 12:35p, V3	2.0[b]	07-31-18, 09:15, V3	8.9
06-19-18, 12:52p, V3	14.9[b]	-	-			07-31-18, 11:58, V3	10.8[b]
Date,Part 2 time,visit #	[LTG]	Date,Part 2 time,visit #	[VPA] [LCM]	Date,Part 2 time,visit #	[LCM]	Date,Part 2 time,visit #	[LTG]
11-08-18, 09:09, V2	14.9	12-05-18, 09:14, V2	97.7 13.8	11-06-18, 09:05, V2	6.3	11-26-18, 18:39p, V2	9.0
11-08-18, 13:01p, V2	18.0	12-05-18, 11:57, V2	90.1[b] 12.5[b]	11-20-18, 09:00, V3	3.0	12-12-18, 14:05, V3	9.8
11-28-18, 08:32, V3	9.4	12-19-18, 09:27, V3	110.0 10.5	11-20-18, 11:45, V3	2.7[b]	12-12-18, 16:46p, V3	8.1[b]
11-28-18, 10:58, V3	9.4	12-19-18, 12:51p, V3	92.3[b] 9.6[b]				

Abbreviations used: LTG = lamotrigine, LEV = levetiracetam, BRV = brivaracetam, LTG-XR = lamotrigine extended-release, LZP = lorazepam, VPA-ER = valproic acid extended-release, LCM = lacosamide, ZNS = zonisamide, CBD = cannabidiol, PER = perampanel, TPM = topiramate, PGB = pregabaline, n.d. not detected.

[a] *All* Plasma [ASM] concentration measurements are given as mg/L = mcg/ml. Samples for [ASMs] were taken where assays for clinical care existed commercially, including LTG, VPA, LCM and TPM. Plasma concentrations were not taken, nor available for: LZP, ZNS, CBD, PER and PGB.

[b] Plasma [ASM] result obtained at 2 hrs post-start of LEV or BRV intravenous.

Supplementary Table 3 (con't): Concomitant ASM Plasma Concentrations [ASM, mg/L][a] for Participating Patients, HHH through PPP

Patient:	HHH	KKK		NNN	OOO	PPP
Co-AED(s) Generic Name & Total mg Daily Dose	LTG: 700		TPM: 400	None	None	VPA: 500 PGB: 150
Date:	06-26-18		09-05-18	09-17-18	09-20-18	11-19-18
HHH Date,Part 1 time,visit #	[LTG]	KKK Date,Part 1 time,visit #	[TPM]			
06-26-18, 18:03p, V1	4.8	09-05-18, 11:56, V1	8.6			
07-09-18, 17:00, V2	3.9	09-06-18, 09:10, V2	8.9			
07-09-18, 19:46p, V2	3.7	09-06-18, 12:44p, V2	9.5[b] 2 hr post-start intravenous LEV or BRV			
07-30-18, 17:12p, V3	6.9	09-20-18, 08:58, V3	10.5			
07-30-18, 19:58p, V3	8.6[b]	09-20-18, 12:53p, V3	8.7[b]			
Date,Part 2 time,visit #	[LTG]	Date,Part 2 time,visit #	[TPM]		For PPP, Date,Part 2 time,visit #	PPP [VPA]
11-06-18, 17:29p, V2	4.0	12-05-18, 14:58p, V2	8.1		11-19-18, 18:12p, V1	13.3
11-06-18, 20:08p, V2	3.8	12-05-18, 17:57, V2	8.0[b]		11-26-18, 09:29, V2	20.9
11-20-18, 17:25p, V3	4.7	12-19-18, 15:34, V3	16.5		12-12-18, 09:10, V3	25.8
11-20-18, 19:59p, V3	4.4	12-19-18, 18:51p, V3	13.4[b]			

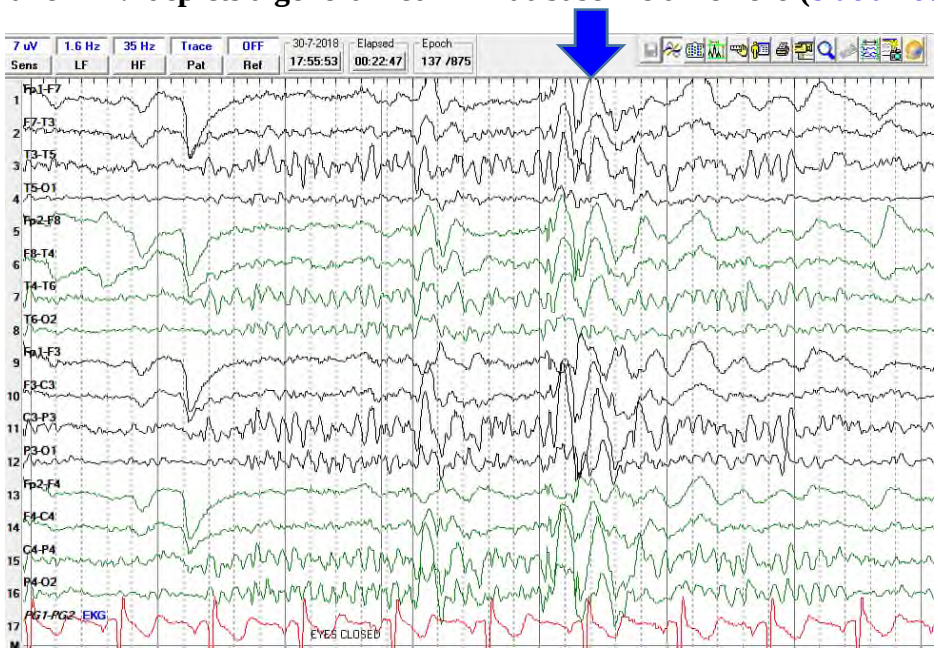
Abbreviations used: LTG = lamotrigine, LEV = levetiracetam, BRV = brivaracetam, LTG-XR = lamotrigine extended-release, LZP = lorazepam, VPA-ER = valproic acid extended-release, LCM = lacosamide, ZNS = zonisamide, CBD = cannabidiol, PER = perampanel, TPM = topiramate, PGB = pregabaline, n.d. not detected.

[a] *All* Plasma [AED] concentration measurements are given as mcg/ml. Samples for [AEDs] were taken where assays for clinical care existed commercially, including LTG, VPA, LCM and TPM. Plasma concentrations were not taken, nor available for: LZP, ZNS, CBD, PER and PGB.

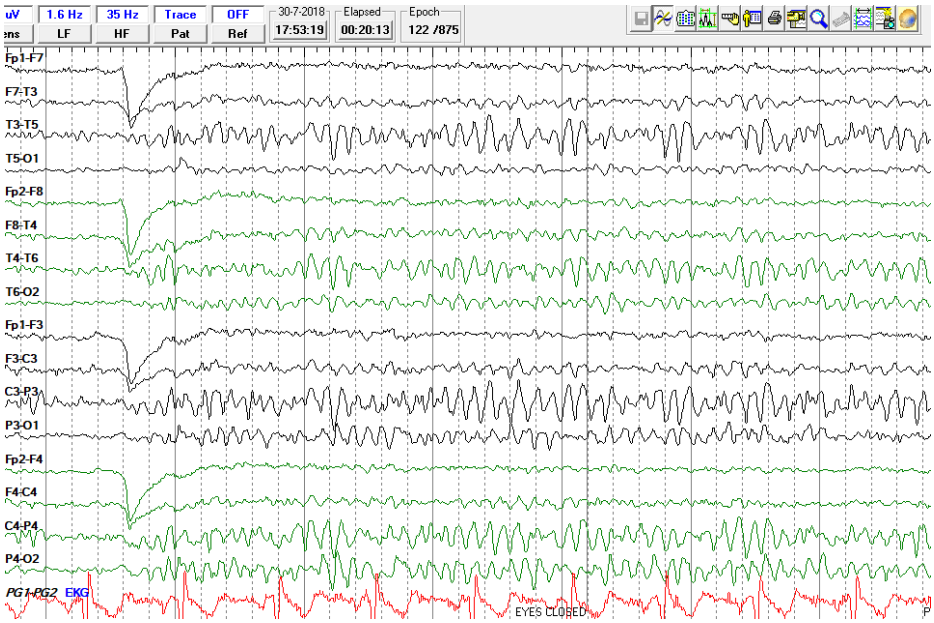
[b] Plasma [AED] result obtained 2 hrs post-start of intravenous LEV or BRV.

Supplementary Figure 2: Example of a select patient's EEG- (patient 'HHH', 07-30-18, Part 1, at 20 Hz)

Panel 'A': depicts a generalized PPR at baseline time-zero (blue arrow)



Panel 'B': PPR abolition in 'HHH' occurring at 1-min after the start of a 15-min i.v. BRV infusion.



Note: Complete PPR suppression continued for 'HHH' at 20 min. post-start of an i.v. infusion (EEG segment not shown, since it looks

similar to panel 'B').

Expanded Descriptions of Select Items from Manuscript Text

Methods

2.1 Protocol

We conducted a prospective, computer-randomized, double-blind, two-period crossover study at a single site in patients with identified photosensitive epilepsy. Our protocol (**Supplementary Fig. 1**, Study Design Flow Chart) had two Parts: i. Part 1, a single i.v. infusion of LEV 1,500 mg OR an equipotent mg dose of i.v. BRV 100 mg, administered *over 15 minutes* (eight patients, crossed-over to the other treatment arm no earlier than one week later); ii. Part 2 (Option 1), the same single, fixed mg dose of LEV and BRV, as in Part 1, given on separate occasions, randomly, by i.v. infusion *over 5 minutes.* However, Part 2 had two options: patients entered Part 2-Option 1 if they had a *different* time to EEG response to ASM administration on the two occasions in Part 1 (study blind was maintained); patients entered Part 2, Option 2, if they had *no differential* response to the two ASMs in Part 1. In Option 2, a reduced dose of LEV=500 mg ($1/3^{rd}$ of that given in Part 1) and equivalent dose of BRV=25 mg ($1/4^{th}$ of that given in Part 1) was administered i.v. over 15 minutes. We surmised that a lower mg LEV or BRV dose might be able to "tease out" a differential effect between the time to peak EEG effect for the two ASMs, if it existed, if no difference in time to effect on EEG had been detected between LEV and BRV in Part 1. Our protocol had a mandatory 14-day washout period between Visit 2 and Visit 3. The same patients participating in Part 1 were allowed to enter Part 2, but each patient had to wait a minimum of two weeks after their last drug infusion (*i.e.*, >14 days post-Part 1, Visit 3 (2^{nd} ASM infusion) before entering Part 2, Visit 2 (1^{st} ASM infusion). Part 1 and Part 2 each had two treatment periods, as per the balanced-crossover design, with four patients randomized either to BRV first, then to LEV (or four patients to LEV first, then to BRV). For both Parts, Visits #2 and #3 were separated by a mandatory 14-days to allow for an adequate ASM washout period. Our protocol and concordant consent forms (one each, Parts 1&2) were approved for the site by Schulman & Associates IRB on 04-27-18, according to the Declaration of Helsinki. The schedule/flowchart for all procedures / events required for patients in our study protocol can be seen in **Supplementary Table 1**.

LEV/BRV intravenous injection preparation/administration

All staff were blinded to LEV/BRV randomization except for RCR plus the unblinded physician-SML-who prepared the injections of assigned ASMs (SML maintained blinding sequence via sealed envelope, marked-SML-only-access, in a locked safe). Commercial LEV/BRV was admixed with 0.9% normal saline per package insert. Levetiracetam ([Keppra®], containing 500 mg/5 ml, single-unit vials x3) were removed

by syringe and placed into a 100ml intravenous sodium chloride bag (0.9%NaCL, 115ml). Brivaracetam [Briviact®], 50 mg/5 ml, single-unit vials x2) were removed by syringe, placed into a 100ml intravenous 0.9%Nacl bag, plus an additional 5 ml (unit-dose) 0.9%NaCl, so that equivalent fluid was present in each bag (115 ml), allowing for blinding. The medication was administered with a Baxter-6201 intravenous pump, delivering up to 1,999 ml/hr. For the 15-min. infusion rate (Part 1), only one patient, AAA, displayed a BRV:LEV time ratio for PPR abolition = 1, *i.e.*, no difference between LEV and BRV. AAA volunteered for Part 2. Thus, according to protocol, he was place into Option 2, receiving a lower dosage of LEV or BRV over 15 min. The following procedure was followed: 500 mg LEV (5 ml/vial x1) along with 10ml 0.9%NaCl was added to 100ml of 0.9%NaCl (115ml total) and administered over 15 min (460 ml/hr). For BRV, 25 mg/2.5 ml (½ vial) along with 12.5 ml of 0.9%NaCl was added to 100ml of 0.9%NaCl (115ml total) and administered over 15 min (460 ml/hr) – again, so as to maintain the blind. The medication was administered with a Baxter 6201 intravenous pump, delivering up to 1,999 mls/hr.

Blood sample acquisition

Prior to starting IPS, 18-gauge indwelling catheters were placed into an antecubital vein (one, each arm). One catheter was used for administration of intravenous LEV or BRV; the contralateral arm for blood sample acquisition. For each protocol-designated sampling time, 0.5-1.0 ml blood was initially drawn via syringe and discarded; the next 4 mls were collected in a green-top lithium-heparin tube, then immediately centrifuged at room temperature. Harvested plasma was placed into appropriately-labelled, patient de-identified polypropylene tubes and frozen at an average of $\leq$ -20 degrees Celsius until analysis. Prior to starting IPS, 18-gauge indwelling catheters were placed into an antecubital vein (one, each arm). One catheter was used for administration of i.v. LEV or BRV; the contralateral arm for blood sample acquisition. Multiple blood samples for LEV, BRV determination were obtained concurrent with IPS testing.

Plasma [LEV] and [BRV] concentration analysis

Liquid chromatography-mass spectrometry/mass spectrometry was used for determining plasma [LEV] and [BRV] concentrations. The internal standards for this proprietary methodology were deuterated levetiracetam (LEV-d6) and brivaracetam-2H5. All LEV samples were run in-batch by ClinLab, Inc. (763 S New Ballas Rd #160, St. Louis, MO 63141). The lower limit of LEV detection (LLoD) was 1.0 mcg/ml, with a % coefficient of variation (%CV) = 10% at LLoD; 6.9% at the upper LoD; the intra-day assay %CV = 8%. All BRV samples were run in-batch by NMS Labs (200 Welsh Rd, Horsham, PA 19044). The LLoD was 0.1 mcg/ml (=100 nanog/ml, ng/ml), with a 3.1% within-day %CV.