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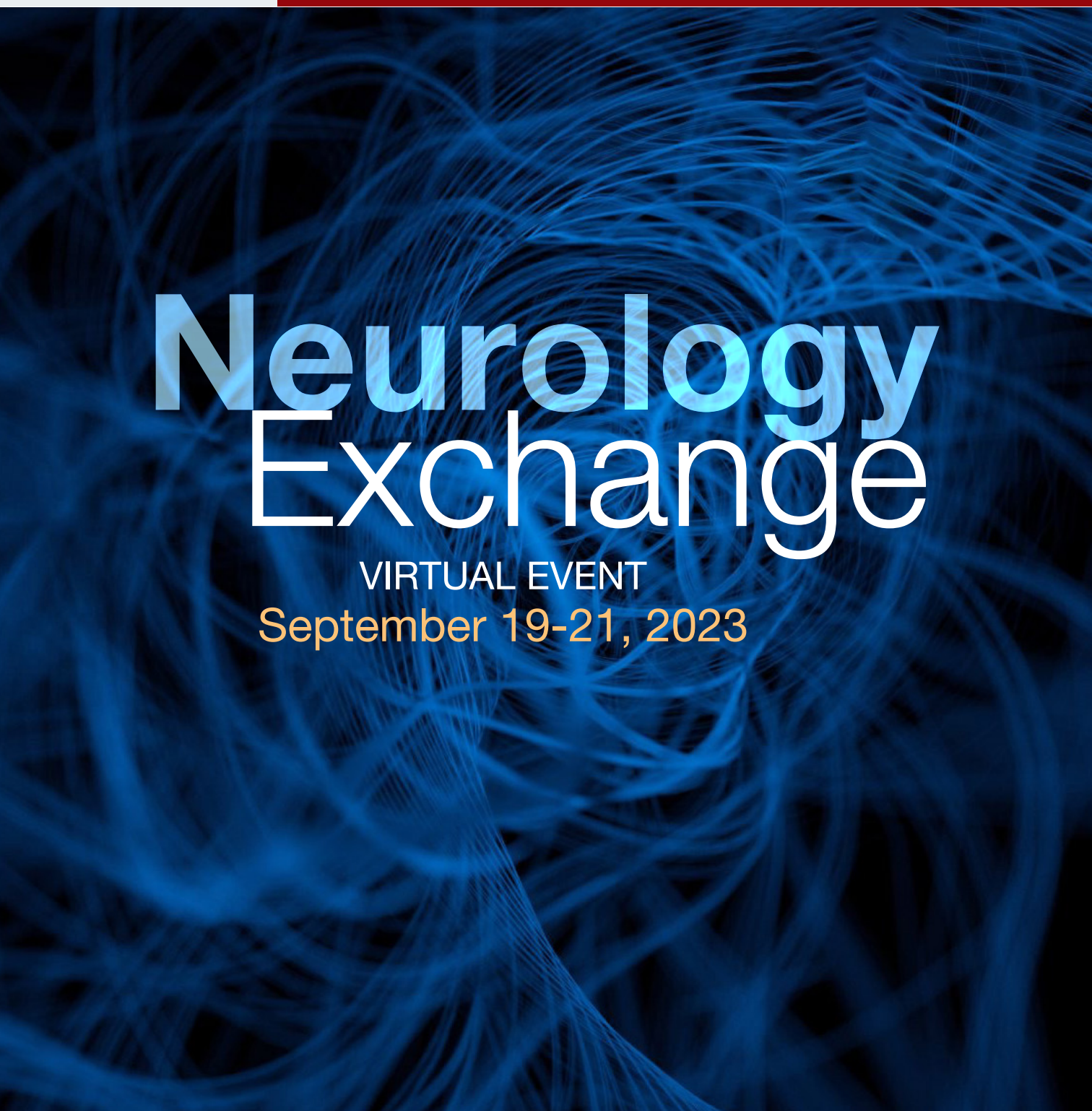


Abstract 1

Acute Motor Axonal Neuropathy and Transient Sensorineural Deficits After Acute Mononucleosis Infection and Acute-Onset Initial Systemic Lupus Erythematosus Flare

Wottrich, Stephanie, MD[1]

[1]Department of Neurology, Dell Seton Medical Center at the University of Texas at Austin,1500 Red River St, Austin, TX, 78701

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune condition that impacts several organ systems, including the nervous system. There are a handful of case reports presenting acute motor axonal neuropathy (AMAN) associated with SLE. This case presents a patient with AMAN as well as acute sensorineural deficits in the setting of a severe first-time SLE flare also following acute infectious mononucleosis (IM).

Case: A 45-year-old healthy woman presented to a small hospital emergency department (ED) with a sore throat, decreased oral intake, generalized weakness, and several months of "increasingly sporadic behavior" per her family. She was febrile and tachycardic and was found to have IM and an *Escherichia coli* urinary tract infection (UTI). She was discharged with antibiotics and return precautions but returned a few days later for persistent fevers and malaise. She then had pancytopenia, transaminitis, hypoxic respiratory failure, and acute pancreatitis. Her abnormal vitals, symptoms and labs persisted during admission despite receiving appropriate therapy, so she was transferred to a larger hospital for infectious disease consultation, and eventually transferred again for rheumatology evaluation given no improvement.

Results: At the final hospital, in addition to flu-like symptoms, she had bilateral upper and lower extremity weakness and tenderness (most severe in the lower extremities) with sensory loss of the bilateral lower extremities (most severe in the left extremity). She exhibited hypophonia, drowsiness, and delayed responses consistent with abulia. Neurology was consulted for these deficits. Imaging studies showed diffuse muscular edema suspicious for myositis. An array of labs for autoimmune pathologies returned positive (Table 1). Her lumbar puncture was unremarkable, and her bone marrow biopsy was undiagnostic. She was started on IV methylprednisolone for a leading diagnosis of SLE. On day four of therapy she complained of an "echo sound" and bilateral hearing loss prominent on the left. After initiating IVIg, her hearing and sensation improved, but her motor deficits persisted. She underwent EMG (Table 2) showing reduced motor but normal sensory amplitudes consistent with AMAN. She continued steroids and cyclophosphamide and was eventually discharged to a neurological rehabilitation facility.

TABLE 1. Relevant Abnormal Lab Results

Relevant Abnormal Labs: (High Unless "L" = low)	Positive Antibodies:
WBC 1.8 (L), hgb 6.7 (L), plts 58K (L)	EBV IgG 145
Ferritin >10000, abs retic 186.6, haptoglobin 183	EBV early antigen 26.9
Lipase 924	EBV nuclear antigen 112
AST 345	anti-dsDNA
ALT 133	anti-Histone
GGT 158	anti-Chromatin
Alkaline phosphatase 231	anti-Fibrallarin (U3 RNP)
ANA >1:1280	Myeloperoxidase IgG 20
C3 44 (L); C4 10 (L)	TSH receptor 2.40
ESR 80	
BNP 1040	
Alpha 1 antitrypsin 230	

Conclusions: This case is novel in describing the clinical progression of an adult patient that developed the Guillain-Barre variant AMAN in the context of both a first time SLE flare, and acute IM. While there is a well-established association between IM and SLE in the literature,[1,2] the association between AMAN and SLE is scarce,[3,4] and there is a paucity of literature describing an association between AMAN and IM, particularly in the adult population.

References:

1. Draborg AH, et al. Epstein-Barr virus and systemic lupus erythematosus. *Clinical and Developmental Immunology*. 2012;2012:1-10.
2. Lee M, et al. Second-Order Peer Reviews of Clinically Relevant Articles for the Physiatrist: Is Shockwave Therapy With Eccentric Strengthening Superior to Eccentric Rehabilitation Alone for Treatment of Insertional Achilles Tendinopathy? *Am J Phys Med Rehabil*. 2022;101(5):e69-e71.
3. Santiago-Casas Y, et al. Efficacy of low-dose intravenous cyclophosphamide in systemic lupus erythematosus presenting with Guillain-Barré syndrome-like acute axonal neuropathies: report of two cases. *Lupus*. 2013;22:324-327.
4. Wallace LA, et al. Acute Epstein-Barr virus infection presenting as Guillain-Barre syndrome. *IDCases*. 2021;25:e01196.

Disclosures: The author has nothing to disclose.

TABLE 2. EMG Results

Sensory and Mixed Nerve Conduction:							
Nerve and Site	**Onset Lat ms**	**Peak Lat ms**	**Amp µV**	**Segment**	**Lat Diff ms**	**Dist mm**	**CV m/s**
Sural.R to Ankle.R							
Lower leg			**NR**	Ankle-Lower leg		140	
Median.R to Digit II (index finger).R							
Wrist	2.4	3.2	49	Digit II (index finger)-Wrist	2.4	130	54
Ulnar.R to Digit V (little finger).R							
Wrist	2.0	2.7	44	Digit V (little finger)-Wrist	2.0	110	55
Radial.R to Anatomical snuff box.R							
Forearm	1.5	2.1	49	Anatomical snuff box-Forearm	1.5	100	67

Motor Nerve Conduction:						
Nerve and Site	**Lat ms**	**Amp µV**	**Segment**	**Dist mm**	**Lat Diff ms**	**CV m/s**
Peroneal.R to Extensor digitorum brevis.R						
Ankle	3.3	**0.1**	Extensor digitorum brevis-Ankle	90	3.3	
Fibula (head)		**NR**	Ankle-Fibula (head)			
Peroneal.R to Tibialis anterior.R						
Fibula (head)	4.7	**0.1**	Tibialis anterior-Tibialis anterior		0.0	
Popliteal fossa	8.7	**0.0**	Fibula (head)-Popliteal fossa	90	4.0	23
Tibial.R to Abductor hallucis.R						
Ankle	3.6	**0.3**	Abductor hallucis-Ankle	90	3.6	
Popliteal fossa		**NR**	Ankle-Popliteal fossa			
Median.R to Abductor pollicis brevis.R						
Wrist	3.2	**4.5**	Abductor pollicis brevis-Wrist	70	3.2	
Elbow	7.2	3.3	Wrist-Elbow	210	4.0	53
Ulnar.R to Abductor digiti minimi (manus).R						
Wrist	2.9	**2.9**	Abductor digiti minimi (manus)-Wrist	70	2.9	
Below elbow	6.0	2.7	Wrist-Below elbow	147	3.1	47
Above elbow	8.1	2.8	Below elbow-Above elbow	127	2.1	60

Abstract 2

Next Generation Prodrug Troriluzole: Increased Bioavailability of Riluzole with No Food Effect in Healthy Subjects

Sevinsky, Heather, MS[1]; Rozakis, Rachel, PharmD[2]; Nepomuceno, Tracy, BS, RPh[1]; Malatesta, Jo Ann, BA[3]; Awsare, Bharat, MD[1]; Ashbrenner, Eric, MS[1]; Kaplita, Stephen, MS[1]; Gentile, Kim, BS[1]; Hussey, Elizabeth, PharmD[2]; Qureshi, Irfan, MD, PhD[1]; Coric, Vlad, MD[1]; Bertz, Richard, PhD[1]

[1]Biohaven Pharmaceuticals; [2]Allucent; [3]Certara, Inc.

Background: Riluzole, a glutamate-modulator with neuroprotective effects, is FDA approved for the treatment of amyotrophic lateral sclerosis. Oral riluzole is subject to significant first pass metabolism and high PK variability and the absolute oral bioavailability (BA) is approximately 60%.[1] Another major limitation of oral riluzole is its negative food effect (FE) as food may limit the drug's effectiveness by decreasing riluzole concentrations. Troriluzole, a third-generation prodrug, has been designed to optimize riluzole delivery and overcome oral riluzole's negative FE. Troriluzole is actively absorbed in the gut via the peptide transporter 1 (PepT1), which is expected to result in increased BA and less variability of riluzole. Clinical studies have investigated FE and BA of troriluzole and its active metabolite riluzole.

Objectives: The objectives were to evaluate 1) FE on riluzole after oral administration of troriluzole (BHV4157-101, BHV4157-105) and 2) oral BA of riluzole from troriluzole relative to oral riluzole (BHV4157-107).

Methods: All three studies were single-center, Phase 1, randomized, and single dose in healthy subjects. BHV4157-101 (N=6) and BHV4157-105 (N=20) included assessments of FE on riluzole administered as troriluzole (200 and 280 mg, respectively, under fasting conditions and with a high-fat meal). BHV4157-107 (N=24) assessed relative BA of riluzole from troriluzole under fasting conditions (equimolar dose of 100 and therapeutic dose of 280 mg) compared to oral riluzole 50 mg. Riluzole PK parameters were calculated by noncompartmental analysis.

Results: In BHV4157-101 and BHV4157-105, riluzole median T_{max} was delayed by 1.25-1.4 hours and correspondingly C_{max} was reduced; however overall riluzole absorption (AUC) was unaffected by food (Table 1). In Study BHV4157-107, riluzole AUC_{0inf} values were 40% higher after troriluzole 100 mg and 50% higher after troriluzole 280 mg than following oral riluzole 50 mg (Table 2). The absolute oral BA of riluzole from troriluzole is estimated to be 80-90%. Additionally, the C_{max} of riluzole was similar after troriluzole with T_{max} delayed by 1 hour compared to riluzole (median T_{max} 1.99 vs 0.824 hours). Riluzole variability represented by AUC CV% was consistently lower after troriluzole (~40% vs 54%).

Conclusions: Troriluzole administered with a high-fat meal had no impact on the extent of riluzole absorption relative to fasting. Troriluzole resulted in a delayed appearance of riluzole in plasma and lower variability, representing an optimized riluzole profile suitable for once daily administration. Troriluzole also displayed higher riluzole BA (80-90%) when compared to oral riluzole (60%), suggesting that administration of troriluzole bypasses first pass metabolism and lowers the initial liver burden of riluzole. The lack of a negative FE, higher oral BA and once daily dosing associated with troriluzole confer important PK enhancements compared to generic riluzole.

Reference:

1. Riluzole (prescribing information). Clovis Pharma, US, Inc. Zug, Switzerland. 1995. Revised 2022.

Disclosures: Sevinsky, Heather, MS; Nepomuceno, Tracy, BS, RPh; Awsare, Bharat, MD; Ashbrenner, Eric, MS; Kaplita, Stephen, MS; Gentile, Kim, BS;Qureshi, Irfan, MD, PhD1; Coric, Vlad, MD; Bertz, Richard, PhD are employees and hold stock/stock options at Biohaven.

TABLE 1. Ratios (Fed/Fasting) and 90% Geometric Confidence Intervals for Plasma PK Parameters (AUC_{0-inf} and C_{max}) for Riluzole (Studies BHV4157-101 and BHV4157-105)

Study	N	Parameter	Ratio Fed/Fasting,[a] %	90% Geometric CP[b]	
				Lower, %	Upper, %
BHV4157-101	6	AUC_{0-inf}	90.01	77.84	104.08
	6	C_{max}	62.24	44.96	86.17
BHV4157-105	20	AUC_{0-inf}	98.39	91.57	105.72
	20	C_{max}	77.56	68.83	87.39

AUC_{0-inf} = area under the concentration vs time curve from time zero to infinity; C_{max} = maximum observed concentration; CI = confidence interval

[a]Calculated using least squares means on ln-transformed data according to the formula: $\exp^{(DIFFERENCE)} * 100$

[b]90% Geometric CI calculated according to the formula: $\exp(_{DIFFERENCE} \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$

TABLE 2. Bioavailability Summary of Riluzole PK, Ratios, 90% Geometric Confidence Intervals, and *P* Values for $AUC_{0\text{-inf}}$ and C_{max} for Study BHV4157-107

Parameter	N	Treatment A	Treatment C	Ratio A/C[a], %	90% Geometric CI[b]	
		Geometric Mean, CV%	Geometric Mean, CV%		Lower, %	Upper, %
$AUC_{0\text{-inf}}$	24	798.98 (43.34)	570.83 (53.78)	139.97	130.78	149.80
C_{max}	24	130.19 (35.60)	128.95 (55.12)	100.96	86.25	118.18
Parameter	**N**	**Treatment B**	**Treatment C**	**Ratio B/C[a], %**	**90% Geometric CI[b]**	
		Geometric Mean, CV%	Geometric Mean, CV%		Lower, %	Upper, %
$AUC_{0\text{-inf}}$	24	856.54 (39.84)	570.83 (53.78)	150.05	140.36	160.41
C_{max}	24	131.14 (41.67)	128.95 (55.12)	101.70	87.09	118.76

$AUC_{0\text{-inf}}$ = area under the concentration vs time curve from time zero to infinity; C_{max} = maximum observed concentration; CI = confidence interval; CV = coefficient of variation

[a]Calculated using least squares means on ln-transformed data according to the formula: $\exp^{(DIFFERENCE)} * 100$

[b]90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$

Treatment A (Test 1): 1 x 100 mg troriluzole capsule administered orally under fasted conditions

Treatment B (Test 2): 2 x 140 mg troriluzole capsule administered orally under fasted conditions

Treatment C (Reference): 1 x 50 mg riluzole tablet administered orally under fasted conditions

Rozakis Rachel, PharmD; Hussey, Elizabeth, PharmD are employees at Allucent, the company contracted by Biohaven to do this work on behalf of Biohaven.

Malatesta, Jo Ann, BA is an employee at Certara, the company contracted by Biohaven to do this work on behalf of Biohaven.

Abstract 3

No Clinically Relevant Effects of Hepatic Impairment on the Pharmacokinetics of a Next Generation Prodrug Troriluzole

Rozakis, Rachel, PharmD[1]; Donohue, Mary, MS[2]; Sevinsky, Heather, MS[2]; Awsare, Bharat, MD[2]; Kaplita, Stephen, MS[2]; Hussey, Elizabeth, PharmD[1]; Qureshi, Irfan, MD, PhD[2]; Coric, Vlad, MD[2]; Bertz, Richard, PhD[2]

[1]Allucent; [2]Biohaven Pharmaceuticals

Background: Troriluzole is a third-generation prodrug of the glutamate-modulating agent riluzole. Riluzole is a member of the benzothiazole class and was approved by the FDA in 1995 for the treatment of amyotrophic lateral sclerosis (ALS).[1,2] Oral riluzole has a number of limitations including pharmacokinetic (PK) variability, dose dependent elevations in liver function tests, relatively low oral bioavailability and twice-daily dosing to maintain therapeutic exposures. Approximately 8% of riluzole-treated patients will experience elevations in serum alanine aminotransferase (ALT) levels three times above the upper limit of normal (ULN) (Covis, Riluzole USPI 2022). In contrast, clinical trials for troriluzole showed a lower incidence (2.6%) of 3 times ULN ALT elevations in over 1,300 subjects. Following oral riluzole, subjects with mild or moderate hepatic impairment (HI) displayed 1.7- and 3-fold higher total riluzole exposures, respectively, compared to normal hepatic function.3 Troriluzole may reduce riluzole burden on the liver, due to troriluzole's ability to bypass first pass hepatic metabolism.

Objective: The objective of Study BHV4157-104 was to determine the effect of moderate HI on the PK of riluzole after administration of troriluzole.

Methods: BHV4157-104 was a Phase 1, single-dose, open-label study conducted in 8 subjects with moderate HI (Group 1, Child-Pugh score 7 - 9 points), and 8 healthy subjects (Group 2). All subjects received a single oral 100 mg dose of troriluzole under fasted conditions. Subjects with normal hepatic function were matched to those with HI by age (± 10 years, but ≤80 years), body mass index (± 15%), and gender utilizing a mean matching strategy.

PK samples were collected predose and through 144 hours (Group 1) and 72 hours (Group 2) postdose. Riluzole PK parameters (total and unbound) were calculated by noncompartmental analysis.

Results: No clinically meaningful differences were observed between groups in mean total riluzole exposure following administration of troriluzole, with total riluzole AUC and C_{max} in subjects with moderate HI within ~10% of those observed in subjects with normal hepatic function (Table 1).

TABLE 1. Ratios (Moderate Hepatic Impairment/Normal) and 90% Geometric Confidence Intervals for Plasma PK Parameters for Total Tiluzole (BHV4157-104)

Parameter, unit	Ratio Moderate/Normal[a], %	90% Geometric CI[b]	
		Lower, %	Upper, %
$AUC_{0\text{-}inf}$ (h*ng/mL)	111.33	80.45	154.08
C_{max} (ng/mL)	91.74	63.88	131.74

$AUC_{0\text{-}inf}$ = area under the concentration vs time curve from time zero to infinity; C_{max} = maximum observed concentration; CI = confidence interval

[a]Calculated using least squares means on ln-transformed data according to the formula: $\exp(^{DIFFERENCE}) * 100$

[b]90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(df_{Residual})} * SE_{DIFFERENCE}) * 100$

TABLE 2. Ratios (Moderate Hepatic Impairment/Normal) and 90% Geometric Confidence Intervals for Plasma PK Parameters for Unbound Riluzole (BHV4157-104)

Parameter, unit	Ratio Moderate/Normal[a], %	90% Geometric CI[b]	
		Lower, %	Upper, %
$AUC_{0\text{-}inf}$ (h*ng/mL)	171.47	117.16	250.96
C_{max} (ng/mL)	141.29	88.89	224.58

$AUC_{0\text{-}inf}$ = area under the concentration vs time curve from time zero to infinity; C_{max} = maximum observed concentration; CI = confidence interval

[a]Calculated using least squares means on ln-transformed data according to the formula: $\exp(^{DIFFERENCE}) * 100$

[b]90% Geometric CI calculated according to the formula: $\exp(DIFFERENCE \pm t_{(df_{Residual})} * SE_{DIFFERENCE}) * 100$

Unbound riluzole exposure was approximately 1.7-fold ($AUC_{0\text{-}inf}$) and 1.4-fold (C_{max}) greater in subjects with moderate HI compared to subjects with normal hepatic function (Table 2).

Single dose troriluzole was well tolerated in both groups. There were no clinically meaningful trends in laboratory values, nor any incidence of liver enzyme values greater than three times the ULN.

Conclusions: No clinically meaningful differences in mean total riluzole exposure were observed between subjects with moderate HI and healthy subjects following troriluzole administration.

References:

1. Lacomblez L, et al. A confirmatory dose-ranging study of riluzole in ALS. ALS/Riluzole Study Group-II. *Neurology*. 1996;47 (6 Suppl 4):S242-S250.
2. Nightingale SL, et al. From the Food and Drug Administration. *JAMA*. 1995;273:982.
3. Riluzole (prescribing information). Clovis Pharma, US, Inc. Zug, Switzerland. 1995. Revised 2022.

Disclosures: Rozakis, Rachel, PharmD; Hussey, Elizabeth, PharmD are employees at Allucent, the company contracted by Biohaven to do this work on behalf of Biohaven. Donohue, Mary, MS; Sevinsky, Heather, MS; Awsare, Bharat, MD; Kaplita, Stephen, MS; Qureshi, Irfan, MD, PhD; Coric, Vlad, MD; Bertz, Richard, PhD are employees and hold stock/stock options at Biohaven.

Abstract 4

Population Pharmacokinetic Modeling of Riluzole After Administration of a Next Generation Prodrug Troriluzole

Pene Dumitrescu, Teodora, MS, PhD[1]; Wu, Yi Shuan, PharmD[1]; Jeong, Angela, PharmD, PhD[1]; Sevinsky, Heather, MS[2]; Qureshi, Irfan, MD, PhD[2]; Coric, Vlad, MD[2]; Bertz, Richard, PhD[2]

[1]Allucent; [2]Biohaven Pharmaceuticals

Background: Troriluzole, a third-generation tripeptide prodrug, was designed to improve the bioavailability (BA), delivery, and safety of the glutamate modulator riluzole. Riluzole is approved

by the FDA for the treatment of amyotrophic lateral sclerosis (ALS),[1,2] but its use in other indications have been limited due to a number of factors including high pharmacokinetic (PK) variability, elevated liver function tests, negative food effect, relatively low BA, and requirement for twice-daily dosing.

Objectives: The primary objective of the population PK (popPK) analysis was to characterize riluzole's PK following troriluzole administration while assessing the statistical and clinical relevance of covariates on the variability of riluzole PK. The secondary objective was to compare riluzole's PK after riluzole vs troriluzole administration, using the popPK model.

Methods: The analysis included eight Phase 1 studies in healthy subjects (HS), five Phase 2 or 3 studies in patients, all receiving troriluzole, and one Phase 1 study in HS receiving

TABLE. Final PopPK Model Parameter Estimates

Fixed Effect Parameter	Estimate (RSE)	Random Effect Parameter	Estimate (RSE) [Shrinkage]
Absorption Parameters for Riluzole	Interindividual Variability		
Ka (h^{-1})	3.15 (6.7%)	IIV on CL/F of Phase 1 subjects (CV%)	19.2 (6.6%) [48.6%]
D1, duration of zero-order release (h)	0.512 (3.3%)	IIV on F1 of Phase 1 subjects on riluzole (CV%)	34.8 (6.7%) [64.5%]
Absorption Parameters for Troriluzole		IIV on Ka of Phase 1 subjects on riluzole (CV%)	88.0 (8.2%) [67.4%]
Ka (h^{-1})	0.8 (12.3%)	IIV on D1 of Phase 1 subjects on riluzole	44.6 (7.7%) [73.3%]
Ka, Fractional effect of food or evening dose	-0.308 (26.4%)	IIV on F1 of Phase 1 subjects on troriluzole (CV%)	17.9 (17.1%) [71.2%]
D1, duration of zero-order release (h)	1.4 (3.9%)	IIV on Ka of Phase 1 subjects on troriluzole (CV%)	34.6 (15.4%) [75.6%]
F1, Fractional effect of troriluzole[a]	0.538 (13.7%)	IIV on CL/F of patients (CV%)	64.6 (11.8%) [25.7%]
Systemic PK Parameters		IOV on Ka of Phase 1 subjects on troriluzole	47.9 (9.5%)
CL/F (Uh)	67.9 (3.5%)	IOV on D1 of Phase 1 subjects on troriluzole	62.7 (4.2%)
CL/F, Fractional effect of male sex	0.223 (12.8%)	IOV on F1 of Phase 1 subjects on troriluzole	17.8 (13.3%)
CL/F, Fractional effect of fluvoxamine	-0.556 (5.8%)	Residual variability	
CL/F, Fractional effect of aqe	-0.00728 (12.7%)	Proportional error on riluzole (%)	30.1 (2.0%)
Vc/F (L)	285 (4.6%)	Proportional error on Phase 1 subjects taking troriluzole	31.3 (2.0%)
Vp/F (L)	457 (3.5%)	Proportional error on patients taking troriluzole (%)	52.2 (2.9%)
Q/F (L/h)	49.2 (4.8%)		

CI = confidence interval; CV – coefficient of variation; IIV = inter-individual; IOV = inter-occasion variability; RSE = relative standard error

[a]Fractional effect of troriluzole to riluzole administration, transformed from the NONMEM estimate of -0.24 to account for molecular weight difference in dose (dose of troriluzole is expressed as troriluzole chloride monohydrate salt [molecular weight 473.85 g/mol] while dose of riluzole is expressed as riluzole base [molecular weight 234.2 g/mol])

riluzole. Quantifiable plasma concentrations of riluzole were available for 169 HS and 810 patients receiving troriluzole and for 134 HS receiving riluzole. Data analysis, popPK model evaluation, and postprocessing were conducted in NONMEM Version 7.4.4 and in R Version 4.1.3.

Results: Riluzole PK was best described by a two-compartment model after riluzole or troriluzole administration. The model included separate zero-order followed by first-order absorption kinetics for each drug, linked together by relative BA (F). Parameter estimates are given in Table 1. The covariate model included effects of sex, fluvoxamine use, and age on apparent clearance CL/F, and food or evening dose on the absorption rate constant (Ka).

In Phase 1 HS, troriluzole led to 53.8% higher F, 75.6% lower Ka, ~2.7-fold increase in the duration of zero-order release, and ~50% lower interindividual variability (IIV) in F and Ka, overall resulting in improved absorption and reduction in the PK variability compared to riluzole. Administration with food resulted in a ≤10% change in AUC; a 30.8% slower Ka was noted. Furthermore, concomitant fluvoxamine use was associated with 55.6% decrease in CL/F. Lastly, sex and age were statistically significant, with modest decreases in CL/F (~22.3% for female sex and ~13.9% for 65 vs 45 years of age), which were not considered clinically relevant.

Conclusions: The results indicate improved PK of riluzole after troriluzole administration, with higher BA, longer absorption duration, and lower variability in absorption compared to riluzole. Food does not have a significant effect on the extent of riluzole BA after troriluzole administration. The model revealed a significant interaction with strong CYP1A2 inhibitor, fluvoxamine. Overall, the results demonstrate distinct PK advantages of troriluzole and support once daily dosing.

References:

1. Lacomblez L, et al. A confirmatory dose-ranging study of riluzole in ALS. ALS/Riluzole Study Group-II. *Neurology.* 1996;47 (6 Suppl 4):S242-S250.
2. Nightingale SL, et al. From the Food and Drug Administration. *JAMA.* 1995;273:982.

Disclosures: Pene Dumitrescu, Teodora, MS, PhD; Wu, Yi Shuan, PharmD; Jeong, Angela, PharmD, PhD are employees at Allucent, the company contracted by Biohaven to do this work on behalf of Biohaven.

Sevinsky, Heather, MS; Qureshi, Irfan, MD, PhD; Coric, Vlad, MD; Bertz, Richard, PhD, are employees and hold stock/stock options at Biohaven.

Abstract 5

Safety, Tolerability, and Pharmacokinetics of Single and Multiple Rising Doses of a Next Generation Prodrug Troriluzole in Healthy Subjects

Sevinsky, Heather, MS[1]; Awsare, Bharat, MD[1]; Rozakis, Rachel, PharmD[2]; Gentile, Kim, BS[1]; Mydlow, Patricia, BS[2]; Ashbrenner, Eric MS[1]; Ham, Rachel, MS[2]; Stock, David, PhD[1]; Qureshi, Irfan, MD, PhD[1]; Coric, Vlad, MD[1]; Bertz, Richard, PhD[1]

[1]Biohaven Pharmaceuticals; [2]Allucent

Background: Riluzole, a glutamate modulator with neuroprotective effects, is approved by the Food and Drug Administration for the treatment of amyotrophic lateral sclerosis but its clinical use in other neurological disorders has been limited by pharmacokinetic (PK) variability (coefficient of variation [CV] ~70% has previously been reported in the clearance of oral riluzole), dose dependent elevations in liver function tests, relatively low oral bioavailability and twice-daily dosing to maintain therapeutic exposures.[1-4] Troriluzole is a third-generation prodrug rationally designed to improve the PK and pharmacodynamic profile to deliver its active metabolite.

FIGURE 1. Concentration-Time Profiles of Riluzole and Troriluzole After Multiple Dose Troriluzole 280 mg Administration on Days 1 and 5 as Measured in Plasma (Study BHV4157-103)

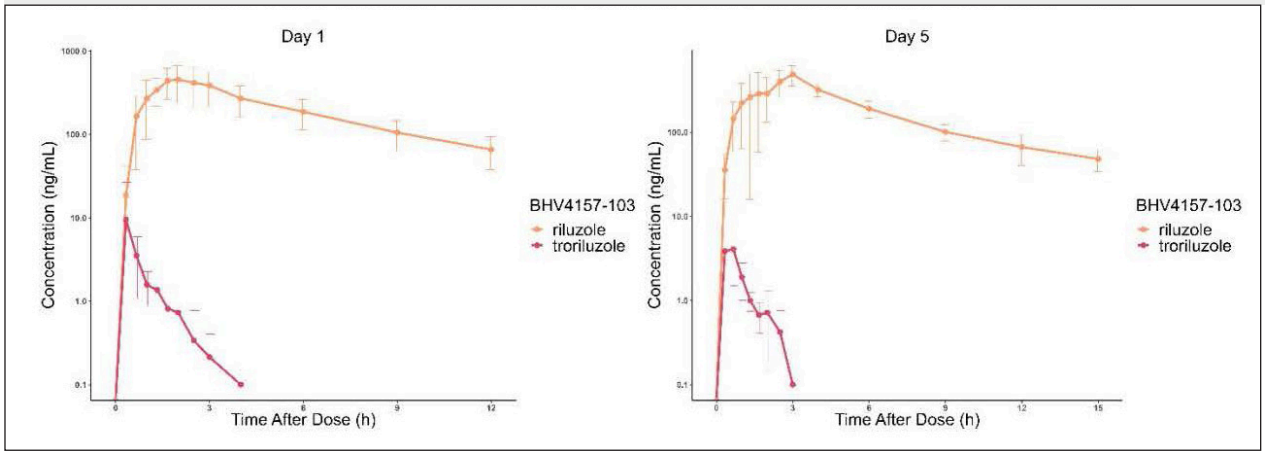
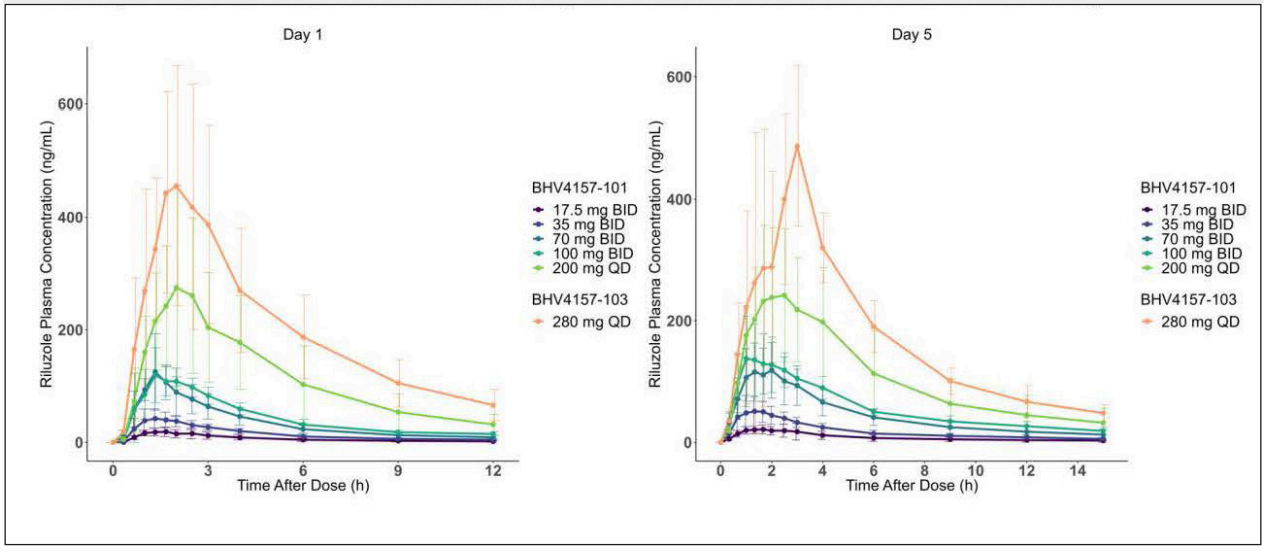


FIGURE 2. Concentration-Time Profiles of Riluzole After Multiple Dose Troriluzole Administration on Days 1 and 5 as Measured in Plasma (Studies BHV4157-101 and BHV4157-103)



Objectives: Evaluate the safety, tolerability, and PK of troriluzole when administered orally in healthy subjects.

Methods: BHV4157-101 was a first in human, single and multiple ascending dose study, BHV4157-103 was a multiple dose study, and BHV4157-108 included an assessment of single escalating doses of troriluzole. In BHV4157-101, 58 subjects received single or multiple troriluzole doses of 17.5 to 200 mg while in BHV4157-103, 8 subjects received troriluzole 280 mg once daily for 5 days. Single doses of troriluzole from 280 to 840 mg were evaluated in 30 subjects in BHV4157-108. For all results described, doses were administered under fasting conditions.

Results: Troriluzole was readily absorbed and rapidly converted to its active metabolite riluzole (Figure 1). Riluzole $AUC_{0\text{-inf}}$ and C_{max} were approximately dose proportional across the studied dose range. Within the troriluzole therapeutic dosage range of 200 to 280 mg/day, T_{max} of riluzole was approximately 2-3 hours, with a half-life of 9-12 hours. Riluzole steady state was achieved by Day 5 of troriluzole daily dosing (BHV4157-101, BHV4157-103; concentration time profiles are in Figure 2). Repeat dose administration of troriluzole was associated with riluzole C_{max} CVs from 31.6% to 41.2% and AUC CVs from 31.5% to 49.4%. No clinically meaningful accumulation of riluzole was observed with once daily dosing. Troriluzole was well tolerated up to the highest studied dose (840 mg), and the incidence of adverse events (AEs) did not increase with dose escalation. AEs were mostly mild and transient, with the most frequent across studies being headache and somnolence.

References:

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Disclosures: Sevinsky, Heather, MS; Awsare, Bharat, MD; Rozakis, Gentile, Kim, BS; Ashbrenner, Eric MS; Stock, David, PhD; Qureshi, Irfan, MD, PhD; Coric, Vlad, MD; Bertz, Richard, PhD are employees and hold stock/stock options at Biohaven.

Rozakis, Rachel, PharmD; Mydlow, Patricia, BS; Ham, Rachel, MS are employees at Allucent, the company contracted by Biohaven to do this work on behalf of Biohaven.

Abstract 6

Therapeutic Implications of Transcutaneous Vagal Nerve Stimulation on PTSD

Akwuole, Ihechi, BA[1]; Imtiaz, Ayyub, MD[1]; Wadhawan, Abhishek, MD[2]

[1]Ross University School of Medicine; [2]Saint Elizabeth's Hospital Department of Behavioral Health

Introduction: Posttraumatic stress disorder (PTSD) is a debilitating condition that has been linked to dysregulation of autonomic function and disruption of the neurobiological pathways modulated by the vagus nerve. Transcutaneous vagal nerve stimulation (tVNS) is a noninvasive form of neuromodulation

that utilizes electrical current to stimulate the vagus nerve. The use of tVNS has shown efficacy in treating several disorders such as epilepsy and depression. However, research on the effects of tVNS on PTSD is significantly limited. We tried to consolidate current knowledge on the use of tVNS in treating PTSD.

Methods: A literature search was performed using relevant keywords on PubMed, PsycInfo, and Google Scholar, limiting the results to the past 10 years. The search yielded a total of four randomized controlled studies that evaluated the effects of vagal nerve stimulation in patients with PTSD.

Results: The 4 studies were double-blinded & placebo-controlled RCTs that assessed the effects of tVNS on PTSD patients through sympathetic response parameters. The RCTs concluded that there was a statistically significant reduction in sympathetic responses to traumatic stress in individuals who received tVNS as compared to the control group. One RCT also found that there was a 31% reduction [d = 0.79, p = 0.013], in PTSD symptoms, and a 21% reduction [d = 1.0, p = 0.008] in hyperarousal symptoms after three months of active tVNS compared to placebo treatment, as measured by the PTSD Checklist.

Conclusion: The data currently accessible suggests that tVNS could alleviate heightened sympathetic nerve activity with a mostly medium effect size, which is associated with hyperarousal symptoms in individuals with PTSD. However, additional research is necessary to evaluate its effectiveness and potentially deepen our understanding of the mechanisms underlying PTSD.

Disclosures: All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this abstract. The authors did not receive funding from any organization for the submitted work.

Abstract 7

Troriluzole Exhibits Favorable Hepatic Safety Profile Across a Diverse Range of Disorders

Qureshi, Irfan, MD, PhD[1]; Beiner, Melissa, MD[1]; Bertz, Richard, PhD[1]; Kaplita, Stephen, MS[1]; Yang, Rong, PhD[1]; Munivar, Azim, MD[1]; Stock, David, PhD[1]; Wirtz, Victoria, MS[1]; Coric, Vlad, MD[1]

[1]Biohaven Pharmaceuticals

Background: Troriluzole is a novel, optimized, third-generation prodrug of the glutamate modulating agent riluzole, which is approved for amyotrophic lateral sclerosis. Troriluzole was rationally designed to overcome the liabilities of riluzole, including significant first-pass effects in the liver, dose-dependent transaminase elevations, relatively low oral bioavailability, high PK variability and a negative food effect requiring fasting around dosing. Approximately 50% of riluzole-treated patients experience ALT levels above the upper limit of normal (ULN), 8% > 3xULN and 2% > 5xULN.[1] Elevated ALT is one of the most common adverse events leading to discontinuation; and fatal hepatic injury has been reported with riluzole.[1] Troriluzole bypasses first-pass metabolism reducing riluzole burden on the liver and is expected to have a superior hepatic safety profile.

Objectives: Characterize the hepatic safety profile of troriluzole from an extensive clinical program in a diverse range of disorders.

Methods: Available hepatic safety data were analyzed from participants treated with troriluzole across 6 completed and ongoing phase 2/3 clinical trials in spinocerebellar

TABLE. Hepatic Safety Profile of Troriluzole

Liver function test: n (%)	SCA N = 337	OCD N = 397	GAD N = 335	AD N = 276	Total N = 1,345
ALT					
> 3xULN	6 (1.8)	11 (2.8)	11 (3.3)	7 (2.5)	35 (2.6)
> 5xULN	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.4)	8 (0.6)
AST					
> 3xULN	2 (0.6)	7 (1.8)	4 (1.2)	3 (1.1)	16 (1.2)
> 3xULN	1 (0.3)	3 (0.8)	2 (0.6)	0	6 (0.4)
TBL					
> 2xULN	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.7)	5 (0.4)

ALT= alanine transaminase, AST= Aspartate transferase, TBL= total bilirubin, ULN= upper limit normal

ataxia (SCA; 2 studies, n=337), obsessive-compulsive disorder (OCD; 2 studies, n=397), generalized anxiety disorder (GAD; 1 study, n=335) and Alzheimer's disease (AD; 1 study, n=276). Doses studied ranged from 140-280mg QD for SCA/AD/OCD and 100mg BID for GAD. Alanine transferase (ALT), aspartate transferase (AST) and total bilirubin (TBL) were measured and expressed as ULN.

Result: A total of 1,345 participants received troriluzole 140, 200 or 280mg QD or 100mg BID and had >=1 on-treatment liver function test data. Mean (SD) average daily dose across indications was 205 mg (45) and mean (SD) treatment duration was 323 days (343). A total of 35 (2.6%) subjects had ALT > 3xULN and 8 (0.6%) subjects had ALT > 5xULN (Table). No participants experienced ALT or AST elevation > 3xULN concurrent with TBL > 2xULN. Liver enzyme increases generally occurred within the first 12 weeks of treatment and resolved fully with continued treatment or with treatment discontinuation. No signal of severe drug-induced liver injury was reported.

Conclusion: Troriluzole exhibited a favorable hepatic safety profile in a large clinical trial safety database, including elderly trial participants with AD. The cumulative frequencies of ALT increases of > 3xULN (2.6%) and > 5xULN (0.6%) for troriluzole were substantially lower than those reported in the USPI for riluzole (8% and 2%, respectively), confirming troriluzole's hepatic safety advantages over riluzole.

Reference:

1. Riluzole (prescribing information). Clovis Pharma, US, Inc. Zug, Switzerland. 1995. Revised 2022.

Disclosures: All authors are employees and hold stock/stock options at Biohaven.

Abstract 8

Imaging CO2 Reactivity in Migraine

Govindan, Srini, MD

Wheeling Hospital, Wheeling West Virginia

Background: Intra and extracranial vasomotor reactivity (VMR) has been studied using induced hypercarbia in migraine research, primarily intracranial.[1] Intracranial and extracranial arteries have differences in receptors and response to hypercarbia[2] and humoral agents.[3-5]

Objective: To present a methodology for imaging external carotid artery/face, blood flow by visualizing CO2 induced temperature changes in the forehead microvasculature using infrared technology and migraine case report.

Methodology: It is compliant with CARE and TISEM.[6] AGA Model 782, AGEMA infrared system was used.

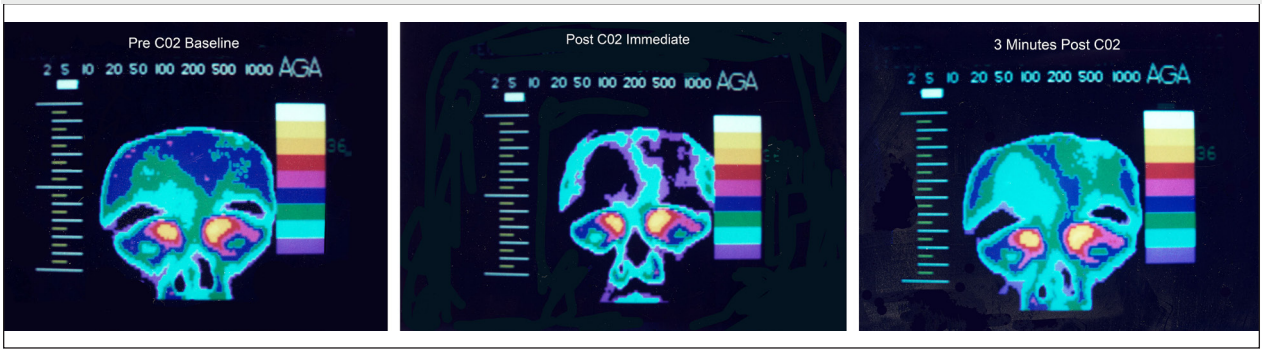
Imaging was done in a temperature/humidity controlled, draft free, 21°C laboratory following 20 minutes of monitored equilibrium. The end-tidal CO2 mmHg was monitored. 5% CO2 inhalation for 3 minutes. Images were done at baseline, immediately after and 3 minutes post disconnection of CO2. Temperature changes of 0.5°C were recorded.

Case report: 32 YO WF Migraine without aura. Rt handed, 5'5", BMI 23.3. Nonsmoker. Propranolol 200 mg daily, moderate relief of migraines. Physical/neurological exam, lab work, brain imaging were normal. No migraine during imaging. Not taken betablocker for 24 hours.

Results: Top of color scale "White" 37°C. Each color change is 0.5°C. Temperatures are taken at the lateral two thirds of the forehead. 0.5°C change is significant.

	Right Forehead	Left Forehead
Baseline	33.5-34.0°C	33.5-34.5°C
Post CO2 Immediate	32.5°C	32.5°C-33.0°C
Post CO2 3 minutes	33.5°C	33.5°C-34.0°C

FIGURE. Pre and Post CO_2



Pre CO2. Right side colder by 0.5°C compared to Left. Figure 2: In the immediate image, forehead temperature decrease of 1°C. Figure 3: In the 3 minutes images, temperature pattern returns to baseline.

Normal response to induced hypercarbia is vasodilation.

Immediate post CO2 images shows 1°C decrease, ie, vasoconstriction (paradoxical response) to induced hypercarbia. Altered VMR.

Discussion: Per Heyck's hypothesis,[7] the opening of AVAs generated the "steal." When D.H.E.45 was given the AVDO2, value on the symptomatic side improved significantly. He concluded that the action of D.H.E.45 in migraine must involve a shunt-closing mechanism. Spierings EL, et al. revisited the action of ergotamine and antimigraine drugs. They called for further clinical assessment of Heyck's shunt hypothesis.[8,9]

Report of effect of methysergide maleate in cluster.[10]

Conclusion: Hypercarbia induced changes in temperature in the images indicates visualization of changes in microvasculature. This may be due to opening of AVAs- shunting. Additional studies using hypercarbia in migraine/cluster patients will help us revisit shunt hypothesis clinically.

Disclosures: Srini Govindan, MD has nothing to disclose. No financial or other help was obtained from equipment manufacturers, drug companies, pharmacies, or others with regard to this research project.

References:

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2. Welch KM, et al. Effects of prostaglandins on the internal and external carotid blood flow in the monkey. *Neurology.* 1974;24:705-710.
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Abstract 9

Impact of the Highly Selective D1/D5 Partial Dopamine Agonist Tavapadon on Daytime Sleepiness: Evidence From a Phase 2 Clinical Trial

Leoni, Matthew[1]; Chang, Ih[1]; Combs, Cari[1]; Gangadharan, Amy[1]; Pastino Gina[1]; Duvvuri Sridhar[1]

[1]Cerevel Therapeutics, Cambridge, MA

Background: D2-like receptors are expressed in sleep-regulating dopaminergic pathways, and dopamine agonists (DAs) targeting D2/D3 receptors (eg, pramipexole, ropinirole, rotigotine) can be associated with increased somnolence, excessive daytime sleepiness, and sudden-onset sleep, presenting challenges for daytime activities, including driving.[1] For example, in 2 previous clinical trials in early Parkinson's disease (PD), pramipexole monotherapy was associated with Epworth Sleepiness Scale (ESS) score increases from baseline of 1.2 to 1.8 points compared with -0.6 and 0.3-point changes from baseline for placebo, respectively.[2,3] Tavapadon, a new, highly selective partial agonist for D1/D5 receptors in development for PD, may ameliorate daytime sleepiness effects and sudden-onset sleep by avoiding D2/D3 receptor agonism. Herein, we report daytime sleepiness data from a phase 2 proof-of-concept trial investigating tavapadon in early-stage PD.

Methods: This randomized, double-blind, placebo-controlled phase 2 trial of tavapadon monotherapy flexible dosing up to 15 mg once daily enrolled participants with early-stage PD (Hoen and Yahr Stage I-III) who were treatment naïve or had received dopaminergic agents for ≤28 days (NCT02847650). The change from baseline in daytime sleepiness was investigated as an exploratory endpoint using the ESS (range, 0-24).

Results: Mean (SD) baseline ESS scores were 5.1 (3.02) and 4.3 (2.95) for tavapadon (flexible dosing up to 15 mg; n=26) and placebo (n=22), respectively. The mean change from baseline (SD) ESS score at Week 15 was -1.1 (3.01) for tavapadon flexible dosing and 0.3 (2.71) for placebo.

Conclusions: Preliminary results indicate that unlike D2/D3 DAs, the unique mechanism of action of tavapadon may impart avoidance of increase in daytime sleepiness effects. Larger ongoing phase 3 trials will further characterize daytime sleepiness with tavapadon.

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Disclosures: Hubert H Fernandez has received research support from Biogen, Cerevel, Michael J. Fox Foundation, NIH/NINDS, Parkinson Study Group, Parkinson's Foundation, Roche but has

no owner interest in any pharmaceutical company; has received honoraria from, Cleveland Clinic as a speaker in CME events; has received honoraria from Amneal, AbbVie, Cerevel, Neurocrine, Parkinson Study Group as a consultant. Elsevier as the Editor-In-Chief of *Parkinsonism and Related Disorders* journal; has received royalty payments from Springer for serving as a book author/editor.

David Gray is a former employee of Cerevel Therapeutics.

Abstract 10

Remote Scoring of a Low-Cost Quantitative Continuous Measurement of Movements in the Extremities of People with Parkinson's Disease

Elshourbagy, Abdelwahab[1]; Eltaras, Mennatullah Mohamed[2]; Abdalshafy, Hassan[3]; Javed, Samrah[4]; Sadaney, Ahmed O.[5]; Harrigan, Timothy P.[5]; Mills, Kelly Alexander[6]; Hernandez, Manuel Enrique[7]; Brašlć, James Robert[8]

[1]MISR University for Science and Technology, Al Motamayez District-6th of October, Giza Governorate 3236101, Egypt; [2]Faculty of Medicine for Girls, Al-Azhar University, Cairo Governorate 4434003, Egypt; [3]Faculty of Medicine, Cairo University, Giza Governorate 12613, Egypt; [4]Jinnah Sindh Medical University, Karachi, Sindh 75510, Pakistan; [5]Research and Exploratory Development, Applied Physics Laboratory, The Johns Hopkins University, Laurel, MD 20723, United States; [6]Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States; [7]Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL 61801, United States; [8]Section of High Resolution Brain Positron Emission Tomography Imaging, Division of Nuclear Medicine and Molecular Imaging, The Russell H. Morgan Department of Radiology and Radiological Science, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, United States

Objective: To develop a procedure for trained raters to remotely score videotaped motor assessments.

Method: Five participants aged 66.2 ± 9.2 (55, 76) years including four men and two people with Parkinson's disease (PD) underwent a low-cost quantitative continuous measurement of movements in the extremities of people with PD[1] administered in person by an examiner certified in the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS).[2] The procedure was conducted with the participant on a straight-back chair without wheels and recorded by a videographer. A technologist recorded the output of instrumentation.

Two trained raters edited the original videotapes to extract each of the 12 tasks for individual video clips. The coordinator

TABLE. Demographic Traits and Consensus Scores of 6 Independent Raters of Videos of Motor Tasks of 5 Participants[1]

Age	PD	Male	Ht	Wt	3.17UR	3.17UL	3.17UCR	3.17UCL	3.15R	3.15L	3.4R	3.4L	3.5R	3.5L	3.6R	3.6L	3.9U
76	1	1	72	178	0	.	0	0	1	.	.	.	.	.	.	.	1
70	0	1	61	122	0	0	0	0	.	.	.	.	.	.	.	.	0
72	1	0	64	177	1	1	1	1	1	1	.	3	.	.	.	.	0
58	0	1	71	215	0	0	0	0	2	2	.	.	3	3	3	3	0
55	0	1	67	159	.	.	.	.	.	.	1	.	.	.	1	1	.

Age	3.17LR	3.17LL	3.17LCR	3.17LCL	3.7R	3.7L	3.8R	3.8L	3.9L
76	.	.	0	.	.	.	.	.	1
70	0	0	0	0	.	.	2	2	0
72	1	0	1	0	.	.	.	.	0
58	0	0	0	0	3	3	.	.	0
55	.	.	.	.	.		.	.	.

Age: Age in years; PD: Parkinson's disease 1 = present, 0 = absent (healthy control with typical development); Male: Male 1 = present, 0 = absent (female); Ht: Height in inches; Wt: Weight in pounds; 3.17UR: 3.17 Rest tremor amplitude upper limbs right; 3.17UL: 3.17 Rest tremor amplitude upper limbs left; 3.17URC: 3.17 Rest tremor amplitude upper limbs right counting; 3.17ULC: 3.17 Rest tremor amplitude upper limbs left counting; 3.15R: 3.15 Postural tremor of the hands right; 3.15L: 3.15 Postural tremor of the hands left; 3.4R: 3.4 Finger tapping right; 3.4L: 3.4 Finger tapping left; 3.5R: 3.5 Hand movements right; 3.5L: 3.5 Hand movements left; 3.6R: 3.6 Pronation-supination movements of the hands right; 3.6L: 3.6 Pronation-supination movements of the hands left; 3.9U: 3.9 Arising from chair upper limbs; 3.17LR: 3.17 Rest tremor amplitude lower limbs right; 3.17LL: 3.17 Rest tremor amplitude lower limbs left; 3.17LRC: 3.17 Rest tremor amplitude lower limbs right counting; 3.17LLC: 3.17 Rest tremor amplitude lower limbs left counting; 3.7R: 3.7 Toe tapping right; 3.7L: 3.7 Toe tapping left; 3.8R: 3.8 Leg agility right; 3.8L: 3.8 Leg agility left; 3.9L: 3.9 Arising from chair lower limbs; period (.): absence of consensus agreement.

then presented the edited videos once on his shared computer screen to six trained raters for independent scoring without knowledge of the age, sex, or diagnosis of the participants. After independently scoring each task, raters sent theirs to the coordinator, who then conducted a consensus conference with the raters to agree on a score for each task. Lack of agreement was recorded by a period (.).

Results: Altogether 110 consensus conferences were conducted among the six raters of the 22 video clips of the protocol conducted on five participants. Raters on three continents agreed on 28 scores of 0, 14 scores of 1, 4 scores of 2, and 7 scores of 3. The raters did not agree on scores for 57 video clips indicated by periods (.) on the Table. Interruptions and blurring of video images presented challenges for rating using the techniques of visual observation for live rating. Internet disconnections prevented some ratings during the experimental sessions.

Conclusion: The proposed protocol provides the means for trained raters in different locations to conduct ratings of structured motor assessments of videos. Future assessments may be improved with improved remote video collection and display.

References:

1. McKay GN, et al. A low-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's disease. *MethodsX*. 2019;6:169-189.
2. Goetz CG, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* 2008;23:2129-2170.

Disclosures: The authors have nothing to disclose.

Abstract 11

Setting the TEMPO: A Phase 3 Program to Investigate Tavapadon, a Selective D1/D5 Partial Agonist, for Parkinson's Disease

Fernandez, Hubert H.[1]; Pfister, Stephanie[2]; Leoni, Matthew[2]; Gray, David[3]; Berry Mark[2]; Gangadharan, Amy[2]; Duvvuri, Sridhar[2]; Parker, Jonathon[2]; Wang, Shuai[2]; Briscoe, Richard[2]; Sanchez, Raymond[2]

[1]Cleveland Clinic, Cleveland, OH; [2]Cerevel Therapeutics, Cambridge, MA; [3]Inscopix, Cambridge, MA

Background: Tavapadon is a first-in-class, highly selective partial agonist at dopamine D1 and D5 receptors. By selectively targeting D1/D5 receptors, tavapadon may improve motor symptoms while minimizing adverse events generally associated with traditional D2/D3 receptor agonists. Previous phase 1b/2 studies support phase 3 investigation of tavapadon. The phase 3 TEMPO program will evaluate the efficacy, safety, and tolerability of once-daily (QD) tavapadon in Parkinson's disease (PD).

Methods: TEMPO-1 and TEMPO-2 are phase 3, randomized, placebo-controlled, 27-week studies of tavapadon monotherapy as fixed doses (5 and 15 mg QD) and flexible doses (5-15 mg QD), respectively, in patients with early-stage PD (Movement Disorder Society – Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part II score ≥2 and Part III score ≥10; modified Hoehn and Yahr stage 1, 1.5, or 2). TEMPO-3 is a randomized, placebo-controlled, 27-week study of tavapadon (flexible dose: 5-15 mg QD) adjunctive to levodopa in patients experiencing motor fluctuations (modified Hoehn and Yahr stage 2, 2.5, or 3 in the "ON" state, minimum 2.5 h of "OFF" time on 2 consecutive days). Participants who complete TEMPO-1/-2/-3 will be eligible for the open-label, 58-week TEMPO-4 study. COVID-19 mitigation for TEMPO studies includes home health visits, telemedicine, and direct-to-patient delivery of study drug.

Results: Detailed study designs will be presented. Primary endpoints include change from baseline in the MDS-UPDRS Parts II and III combined score (TEMPO-1/-2) and change from baseline in total "ON" time without troublesome dyskinesia based on Hauser diary 2-day average (TEMPO-3). TEMPO-4 will investigate long-term safety, tolerability, and efficacy (change from baseline in MDS-UPDRS Parts I-III, Hauser diary).

Conclusions: There has been no FDA-approved levodopa-adjunct and monotherapy drug in over a decade. The TEMPO program will establish the efficacy and safety profile of tavapadon as a promising next-generation PD treatment.

Abstract 12

Virtual Low-Cost Quantitative Continuous Measurement of Movements in the Extremities of People with Parkinson's Disease

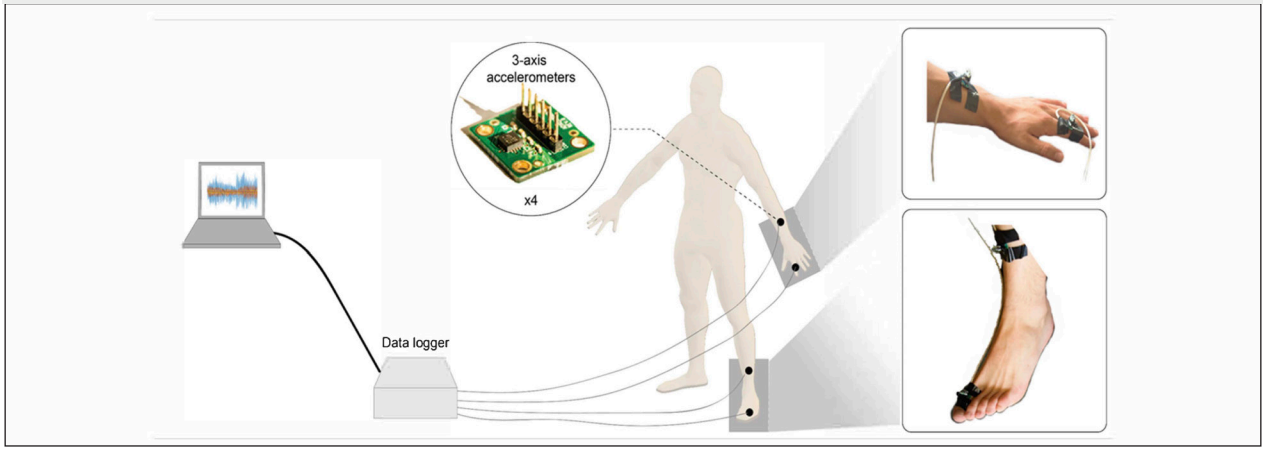
Brasic, James[1]; Elshourbagy, Abdelwahab[2]; Eltaras, Mennatullah[3]; Abdalshafy Hassan[4]; Javed, Samrah[5]; Sadaney, Ahmed O.[6]; Harrigan, Timothy[7]; Mills, Kelly[8]; Hernandez, Manuel[9]

[1]Johns Hopkins University, Baltimore, MD, United States; [2]MISR University of Science and Technology, Cairo, Cairo Governorate, Egypt; [3]Al-Azhar University, Cairo, Cairo Governorate, Egypt; [4]Cairo University, Giza, Giza Governorate, Egypt; [5]Jinnah Sindh Medical University, Karachi, Sindh, P akistan; [6]Faculty of Medicine, Cairo University, Giza, Giza Governorate, Egypt; [7]Research and Exploratory Development, Applied Physics Laboratory, The Johns Hopkins University, Laurel, MD, United States; [8]Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD, United States; [9]Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL, United States

Background: Structured assessments of motor impairments common in people with Parkinson's disease (PD) were developed to be performed in person to utilize human observation by trained examiners. However, risks of infections, lack of transportation, and other environmental influences may prevent the conduct of live ratings. For these reasons we developed procedures for conducting motor assessments online.

Method: A low-cost quantitative continuous measurement of movements in the extremities of people with Parkinson's

FIGURE. Schematic Diagram of Procedure to Generate Output From Accelerometers on the Extremities to Record on a Data Logger to Connect to a Laptop Computer for Conversion to Signals for Further Analysis[1]



Courtesy of Jenny-Ann Phan, MD, PhD

disease[1] (Figure) was performed in person by an examiner certified in the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[2] on cohorts of participants with PD (N=20) and healthy controls with typical development (TD) [N=8]. The original clinical scores were recorded by the trained examiner immediately after the administration of the protocol in person. Rating of the videos of the original assessments was conducted by a team of six trained raters who were all in different physical locations. Rating sessions were hosted by the coordinator (AE) who presented the video clips of the individual tasks performed by participants for viewing providing only the code number of the participant without name, age, sex, diagnosis, or other identifying characteristics. After all protocol items were scored independently by the raters, the coordinator asked all raters to send him electronic copies of their score sheets. Then the coordinator conducted a consensus conference with all raters to attain agreement for the score for each item.

Results: Six trained raters on three continents provided the scores for each of the 22 tasks performed by five participants (Parkinson's disease aged 72 and 76 years and typical development aged 55, 58, and 70 years) including repeat administrations by two participants. Ratings were obtained by viewing on individual monitors the videos shown through screen sharing by the coordinator.

Conclusion: The proposed protocol provides the foundations for colleagues to expand the motor evaluation of people with PD throughout the globe. The proposed protocol will generate an optimal framework for clinical trials.

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Abstract 13

Cytotoxic Lesions of the Corpus Callosum (CLOCC) Secondary to COVID-19: A Review of Pathophysiology and Treatment

Rangoonwala, Saqib, MS3[1]; Imtiaz, Ayyub, MD[2]; Levin, Yuval, MS4[3]; Borja, Benedicto, MD[4]

[1]American University of Antigua College of Medicine, Antigua and Barbuda; [2]Saint Elizabeths Hospital - Department of Behavioral Health, Washington, DC; [3]George Washington University School of Medicine and Health Sciences, Washington, DC; [4]Department of Psychiatry and Behavioral Sciences, George Washington University, Washington, DC

Background: Cytotoxic lesions of the corpus callosum (CLOCC) represent a collection of disparate conditions that can cause signal change in the corpus callosum, usually involving the splenium. CLOCC has multiple causes, including but not limited to, antiepileptic drugs, post-seizure, encephalitis, subarachnoid hemorrhage, trauma, and COVID-19. Correction of the underlying cause usually reverses the symptoms and lesions seen on imaging of the brain, as seen in Figure 1. However, CLOCC has potentially been increasing due to COVID-19, and it's often misdiagnosed on radiology as an acute ischemic stroke. Thus, CLOCC can be difficult to diagnose acutely and treat.

Objectives: Review and discuss pathophysiology of COVID-19-induced CLOCC. Review symptoms of COVID-19-induced CLOCC

FIGURE 1. DWI-MRI Showing CLOCC (Restricted Diffusion)

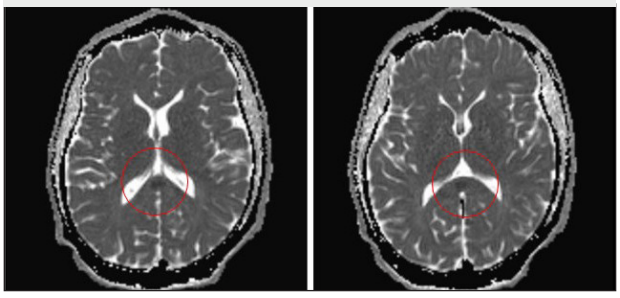
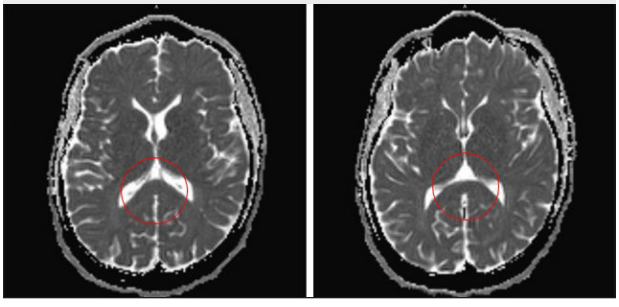


FIGURE 2. DWI-MRI Showing CLOCC Resolution After Treatment



Methods: Articles were chosen from multiple databases via a comprehensive but nonsystematic search to gather supporting evidence about the anatomy, pathophysiology, and treatment of CLOCC. Specific keywords, such as "Corpus Callosum," "Cytotoxic Lesions," "COVID-19," and "Splenium," were used.

Results: COVID-19-induced CLOCCs can occur anywhere but are primarily associated with lesions in the splenium. Although the mechanism of COVID-19-induced CLOCC is widely unknown, it is thought to be a result of a pro-inflammatory state due to cytokine release into the bloodstream after alveolar viral infection.[1] These cytokines enter the central nervous system and increase white matter microglial activity resulting in an inflammatory cascade of changes manifested as cytotoxic edema secondary to an increased influx of water molecules in astrocytes and neurons caused by the release of interleukin-1 and 6, which in turn cause an increase in extracellular glutamate levels. The excess glutamate results in neurotoxicity and neuronal dysfunction resulting in the symptoms of CLOCC.[2] This pathophysiological pathway is visualized in Figure 2.

Symptoms of COVID-19-induced CLOCC differ in the pediatric population versus the adult population. Symptoms often seen in children and adolescents with CLOCC are primarily psychiatric, such as hallucinations, delirium and behavioral disturbances, while symptoms in adults are often neurological, such as ataxia, dysarthria, vertigo, headaches, tremor, and psychomotor retardation.[3] The symptoms usually resolve with supportive care and with clearance of the COVID-19 infection.

Conclusion: For a long time, CLOCC has been misunderstood and misdiagnosed. Although there are many causes of CLOCC, we have seen a significant increase in the amount of cases due to COVID-19. The symptoms of CLOCC due to COVID-19 differ in children and adults. The prognosis of CLOCC usually depends on the cause, and the treatment focuses on treating the underlying condition.

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