

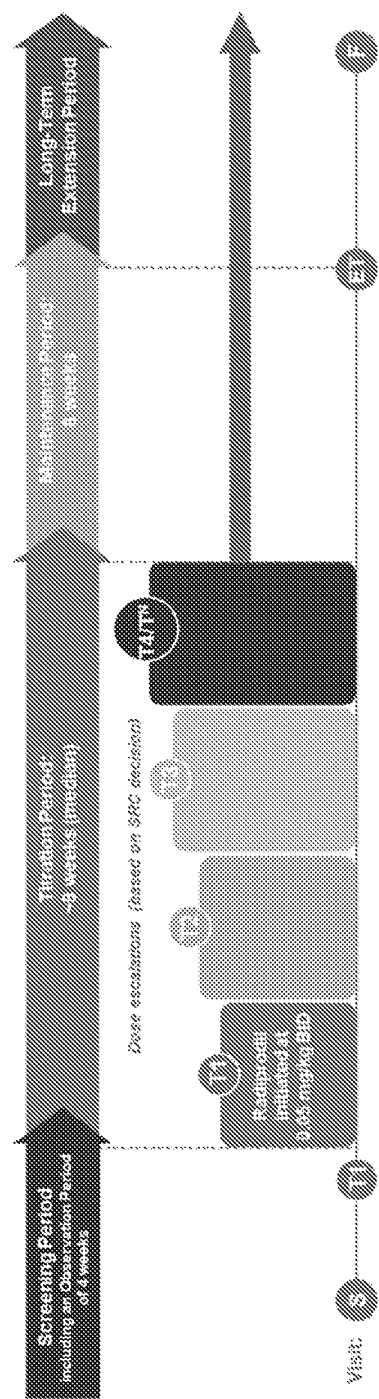


FIG. 1

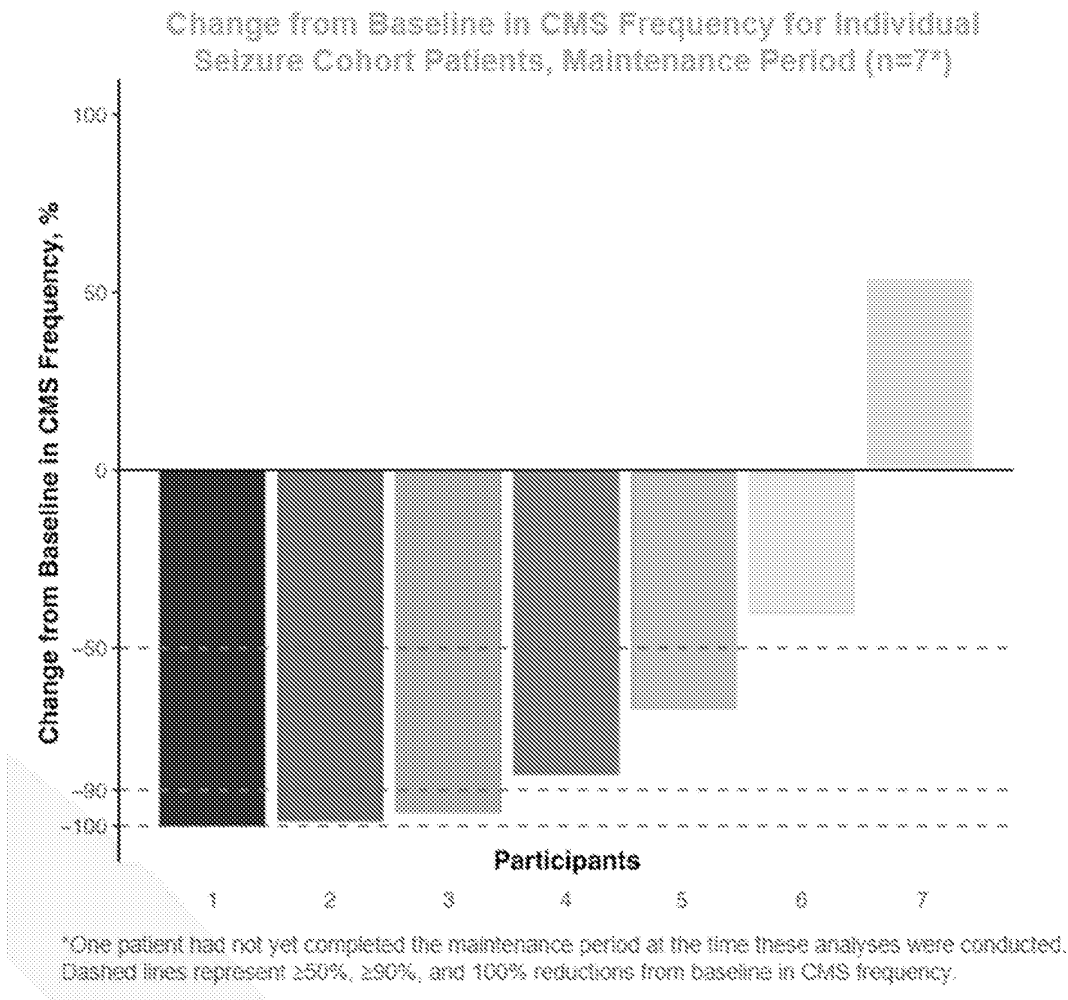
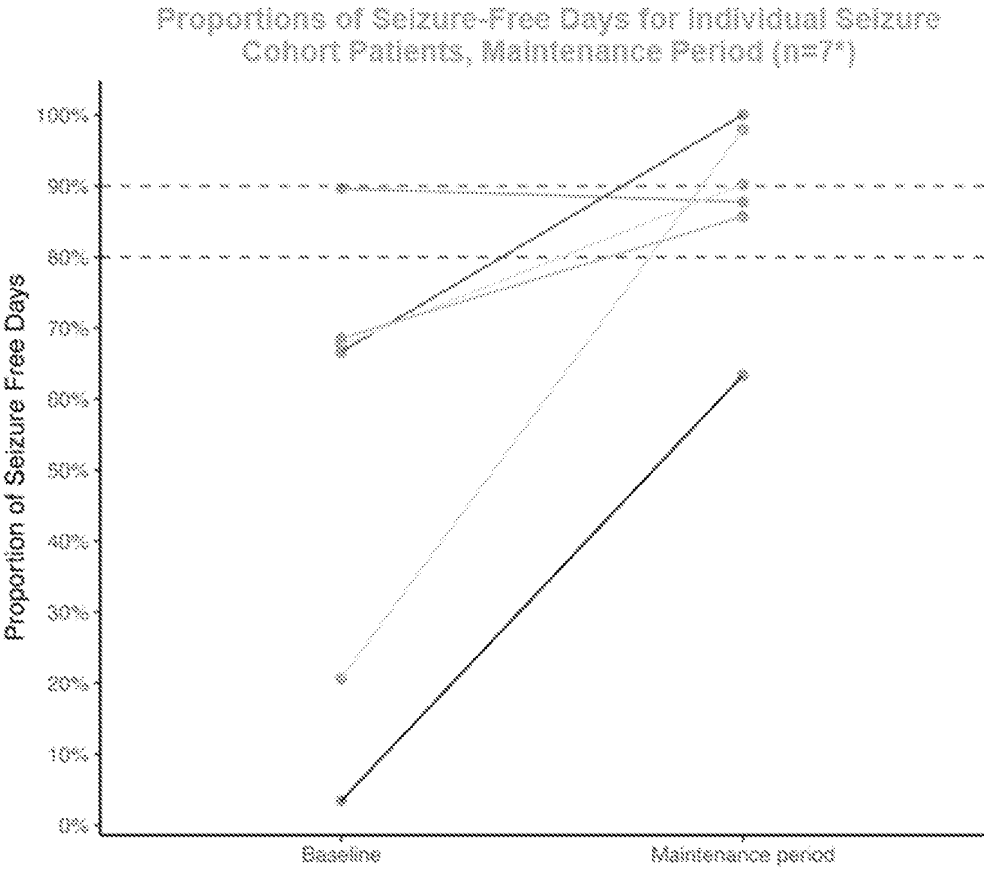


FIG. 2



*One patient had not yet completed the maintenance period at the time these analyses were conducted. Dashed lines represent 80% and 90% seizure-free days.

FIG. 3

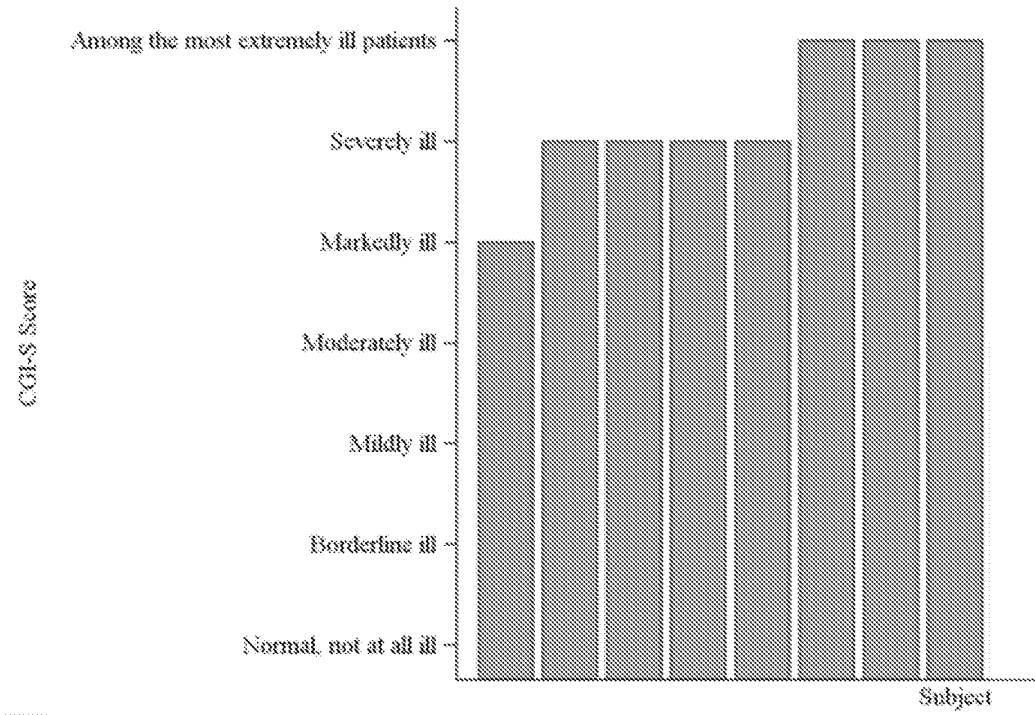
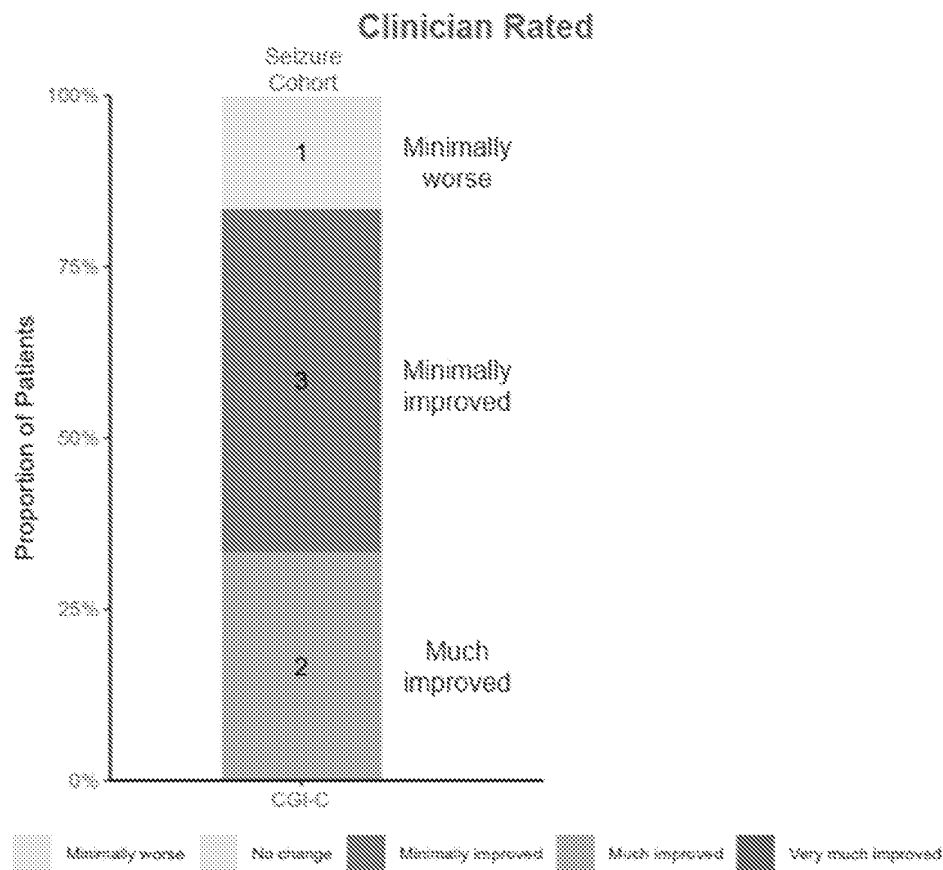


FIG. 4

Clinical Global Impression of Change, 8-week Maintenance Period*

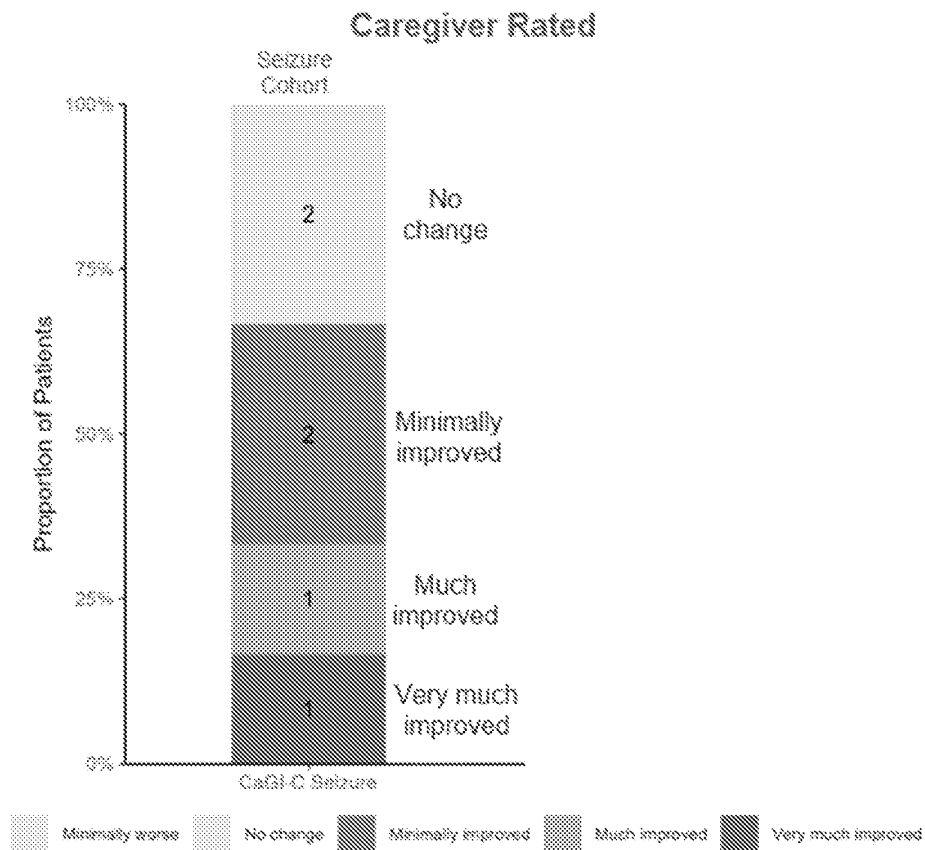


*Six patients completed CGI baseline and end of maintenance period assessments at the time these analyses were conducted.

FIG. 5

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Caregiver Global Impression of Change, 8-week Maintenance Period*



*Six patients completed CaGI baseline and end of maintenance period assessments at the time these analyses were conducted.

FIG. 6

Visit/Week	Screening Period with 4-week observation)	Titration Period ^a					Maintenance Period				UNS Visit / EOS ^a	Follow-up Visit ^c
		T1/Week 1	T2 / Week 2	T3 / Week 3	T4 ^d / Week 4	M1 ^e / Week 1	M2 Week 2	M3 / Week 6	M4 ^e / Week 12 or EOS ^e			
Timeframe [days]	Days -35 to -2	-1	T1 (-7) +3	T2 (+7) +3	T3 (+7) +3	M1 (+3)	M2 ±3	M3 ±3	M4 ±3		14 (+7) post last dose	
(Telemedicine or (Home Health Visit Allowed			I	I	I		I				H	
Written informed consent	X											
Inclusion/exclusion criteria	X	X										
Sponsor eligibility review	X											
Feedback interview / questionnaire ^b	X ^a								X ^c (M4 only)			
Demographics	X											
Medical/neurological history, including medications and procedures	X											
Physical / neurological examination ¹	X	X				X			X			
Vital signs (blood pressure and pulse rate) ^a	X	X	X			X		X	X		X	
Height and weight ^c	X	X	X			X			X			
ECG ^a		X							X ^a			
V-EEG ^b		X							X		X	
Clinical laboratory tests ^a	X	X ^b				X			X			
Pregnancy test ^a	X	X				X			X			
Distribute eDiary / instruct caregivers	X											
Check eDiary / records, retrain if needed		X	X	X	X	X	X	X	X			
Randomization ¹		X										
Daily study drug dosing ^b												
Blood sampling for PK ^c		X				X			X ^c			

FIG. 7A

Visit/Week	Screening Period with 4-week observation Screening	Titration Period ^a				Maintenance Period				UNS Visit / EOT ^b	Follow-up Visit ^c
		T1/Week 1	T2 / Week 2	T3 / Week 3	T4 / Week 4	M1 ^d Week 1	M2 Week 2	M3 / Week 6	M4 ^{max} Week 12 or EOS ^e		
Timeframe [days]	Days -35 to -2	-1	T1 (T1+7) +3	(T2+7) +3	(T3+7) +3	m1 +3	m15 ±3	m45 ±3	m85 ±3		14 (+7) post last dose
(Telemedicine or Home Health Visit Allowed			T	T	T		T				H
Blood sampling for metabolites ^f									X		
VABS-3 ^g		X							X		
ORCA ^h		X							X		
CGI-S	X	X				X		X	X		
CGI-C		X				X		X	X		
ABC-2C ^g		X							X		
PedsQL ^g		X							X		
Suicidality assessments ²	X	X							X		
Submission of sIF to ESCI (if applicable) ³	X	X							X		
Concomitant medications ²	X	X							X		
AEs	X	X							X		

Abbreviations: ABC-2C = aberrant behavior checklist-community AE = adverse event BID = twice daily (hs in the) CGI-C = Clinical Global Impression of Change scale
CGI-S = Clinical Global Impression - Severity scale C-SRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form
eDiary = electronic diary EOS = End of Study; EOT = End of Treatment; ESCI = Epilepsy Study Consortium; m = Maintenance Period study day; M = Maintenance Period Visit;
ORCA = Observer-Reported Communication Ability; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; SIF = seizure identification form; t = Titration Period
study day; T = Titration Period Visit; UNS = unscheduled; V-EEG = video electroencephalogram; VABS-3 = Vineland Adaptive Behavior Scale, Third Edition
Note 1: Telemedicine visits must be led by the investigator or sub-investigator, conducted as per local regulations, and documented in the participant's medical record. Details
regarding the coordination and conduct of Home Health visits will be provided.
Note 2: Participants who discontinue treatment early will be encouraged to remain in study to complete visits and assessments in per the study schedule until they choose to
withdraw or otherwise meet criteria to discontinue from study (see Section 5.3.2)
a. For the first dose, participants will stay at the site for a minimum of 1 day with the potential for overnight stays up to 3 days. For Visits T2, T3, and T4, if visits occur on-
site, an overnight stay (as noted say) before and after the titration day is allowed as deemed necessary based on practical considerations and taking into account
participant and caregiver preference.
b. Unscheduled visits may be conducted as needed with the option to use telemedicine visit technology if medically indicated. If the participant discontinues treatment
early, an unscheduled visit will be conducted at the site with assessments selected by the investigator as clinically appropriate. The unscheduled end of treatment visit
must include a V-EEG assessment if the participant stopped treatment during the Maintenance Period though this is not required if treatment is discontinued prior to Visit
M1. If possible with consideration to participant safety, the unscheduled visit and V-EEG (if required) should be conducted before beginning paper of study drugs

FIG. 7B

- (recommendations in Section 7.1.5). A feedback interview will be conducted within ~5 days of the unscheduled end of treatment visit. If a participant will continue with study visits and assessments after discontinuation of treatment, V-EEGs and interviews beyond the unscheduled end of treatment visit are NOT required.
- c. The ECG visit should be conducted at the same visit where the decision to discontinue the participant from study is made or as early as possible following the decision. The Follow-up Visit is only applicable for those participants who discontinue from study (e.g., will not continue into Part B). The Follow-up visit should be conducted 14 days after the last dose of the tapes or 14 days after the decision to discontinue from study, whichever is later.
- d. It is anticipated that there will be up to 4 dose levels starting with 0.125 mg/kg or reaching placebo with the target dose level of 0.75 mg/kg at Termination visit T4. If a participant is unable to escalate to 0.75 mg/kg, they will be discontinued from study treatment.
- e. Visit M1 will be scheduled 7 days (~3 days) after T4 (last dose titration visit).
- f. For Visit M4, an overnight stay at the site or at suitable accommodation close to the site will be required for all participants on the day prior to the visit. This is to accommodate the overnight V-EEG.
- g. The first Transition Termination visit (TT1, Table 2-5) should be scheduled on the same day as Visit M4.
- h. The baseline feedback interview / questionnaire is required and will be conducted during Screening. It must be conducted within 5 days prior to Visit T-1 (including the T-1 visit).
- i. The Visit M4 Feedback interview should be conducted within ~5 days of the visit.
- j. A complete physical and neurological examination according to standard of care excluding the genitourinary examination will be performed at Screening and Visit M4 ECGs. At all other site visits, a neurological examination and observation of symptom directed physical examination will be performed.
- k. Vital signs will be measured after the participant has been in a sitting position for 5 minutes, using an age-appropriate cuff for blood pressure measurements.
- l. Height will be measured at the Screening Visit and Visit M4-EOS Visit only. Weight will be measured at the noted visits.
- m. Standard 12-lead ECGs will be performed in triplicate after the participant has been supine for at least 5 minutes. The M1 and M4 ECGs will be done pre-dose and 2.5 hours (~30min) after dosing.
- n. V-EEG applicable to Visit M4 and unscheduled visit upon early treatment discontinuation (if applicable). The M4 V-EEG will be conducted the evening PRIOR to Visit M4. An EOS V-EEG is needed only if the participant will discontinue treatment and study at the same time. See footnote b regarding timing of the V-EEG in this case.
- o. Laboratory assessments will include hematology, serum chemistry, and coagulation (see Section 10.2.2.1.1). Screening central laboratory results must be available and assessed by the investigator before a participant is randomized. Local lab results may be used to evaluate entry criteria and/or any other key lab parameter during the course of the study in certain circumstances. In place of central laboratory results, please consult the medical monitor.
- p. Clinical laboratory tests at Visit T-1 should be done locally and are only needed if Screening laboratory results indicate additional assessment or follow-up is required, per investigator judgement, or if the Screening laboratory test is test (e.g., sample was hemolyzed). If needed, this Visit T-1 laboratory assessment can be done at any time prior to and including at Visit T-1. This sample may also be collected as a home visit.
- q. For participants of childbearing potential only, a serum pregnancy test will be conducted at Screening and a serum or urine test at all applicable subsequent visits. A positive urine test will be confirmed with a serum pregnancy test.
- r. Participants will be randomized prior to initial receipt of study drug.
- s. Resupply of the study drug will occur to the participants home as needed. If a participant's weight changes by >10%, their dose will be adjusted for the new weight.
- t. For PK and metabolite samples, blood will be collected at the timepoints specified in Table 2-5. On site-visit days, participants will take IP at the site in conjunction with the PK sampling schedule. If the participant is discontinued from treatment and study at the same time, the EOT PK sample will be collected at the combined unscheduled EOT/EOS visit. In the case of participant discontinuing from treatment before discontinuing from study, the EOT PK sample is required only at the unscheduled EOT visit.

FIG. 7C

- u. The VABS-3 will be centrally and virtually administered up to 5 days before the scheduled visit day or on the day of the visit if not done before hand, preferably early during the visit. The rater will be blinded to the participant's treatment assignment and cohort.
- v. The ORCA assessment may be completed up to 5 days before the scheduled visit day or on the day of the visit if not completed before hand, preferably early during the visit. It will only be conducted if the appropriate translation is available
- w. The indicated assessments may be completed up to 5 days before the scheduled visit day or on the day of the visit if not completed before hand, preferably early during the visit.
- x. Participants who are assessed as being capable of understanding the concepts of suicidality and death will be administered the adult C-SSRS version. All other participants will be assessed by the investigator (in discussion with the caregiver) for any indications of potential suicidal ideation or behavior, and the conclusion will be recorded in the eCRF.
- y. Each site will be required to complete a SIF for each participant. This information will be submitted to ESCI after the Screening Visit for review and confirmation. The SIF will be used to ensure that the seizures are classified accurately. If a new seizure type occurs during the study that was not previously confirmed by ESCI, a past seizure type (from >1 year prior to screening) reoccurred, or a seizure type was inadvertently omitted, the site will be required to complete a New Seizure Form and submit to ESCI for review and confirmation.
- z. At Screening, all current and historic ASMs must be recorded. For all other medications, only active concomitant medications need to be recorded (e.g., medications discontinued prior to Screening do not need to be recorded).

FIG. 7D

Visit/Week Timeframe [days]	Screening Period Days -35 to -2	Titration Period ^a				End of Study (EOS) ^e	UNS Visit / EOI ^c	Follow-up Visit ^d 14 (+/-) post last dose H
		T1/ Week 1	T2/ Week 2	T3 / Week 3	T4 ^b / Week 4			
		-1	(T1-7) +3	(T2-7) +3	(T3-7) +3			
(T)elemedicine or (H)ome Health Visit Allowed		I	I	I	I			
Written informed consent	X							
Inclusion/exclusion criteria	X	X						
Sponsor eligibility review	X							
Feedback interview / questionnaire ^c	X ^f							
Demographics	X							
Medical / neurological history, including medications / procedures	X						X	
Physical / neurological examination ^g	X	X					X	
Vital signs (blood pressure and pulse rate) ^h	X	X	X				X	X
Height and weight ⁱ	X	X					X	
ECG ^j		X					X	
N-EEG ^c		X					X	
Clinical laboratory tests ^k	X	X ^l					X	
Pregnancy test ^m	X	X					X	
Distribute eDiary / instruct caregivers	X							
Check eDiary / records; retain if needed		X	X	X	X		X	
Randomization ⁿ		X						
Daily study drug dosing ^o								
Blood sampling for PK ^p		X					X ^q	
VABS-3 ⁴		X					X	
ORCA ^r		X					X	
CGI-S	X	X					X	
CGI-C							X	

Unscheduled visits may be done at any time with assessments conducted as needed as clinically indicated. See Table 2-8 for associated PK sample.

FIG. 8A

Visit/Week	Screening Period	Titration Period ^a				End of Study (EOS) ^d	UNS Visit / EOI ^c	Follow-up Visit ^d
		T1/Week 1	T2/Week 2	T3/Week 3	T4/Week 4			
Timeframe (days)	Days -35 to -2	-1	0	(T2+7) +3	(T3+7) +3	(T4+7) +3		14 (-7) post last dose
(T)elemedicine or (H)ome Health Visit Allowed			I	I	I	I		H
ABC-2C ^b		X					X	
PedsQL ^b		X					X	
Suicidality assessment ^b	X	X					X	
Submission of SIF to ESCI (if applicable) ^e	X							
Concomitant medications ^b	X							
AEs	X							

Abbreviations: ABC-2C = aberrant behavior checklist-community; AE = adverse event; BID = twice daily (b.i.d.); CGI-C = Clinical Global Impression of Change scale; CGI-S = Clinical Global Impression - Severity scale; C-SRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; EOS = End of Study; EOI = End of Treatment; ESCI = Epilepsy Study Consortium; m = Maintenance Period study day; M = Maintenance Period Visit; ORCA = Observer-reported Communication Ability; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; SIF = seizure identification form; t = Titration Period study day; T = Titration Period Visit; V-EEG = video electroencephalogram; VABS-3 = Vineland Adaptive Behavior Scale, Third Edition

Note 1: Telemedicine visits must be led by the investigator or sub-investigator, conducted as per local regulations, and documented in the participant's medical record. Details regarding the coordination and conduct of Home Health visits will be provided.

Note 2: Participants who discontinue treatment early will be encouraged to remain on study to complete visits and assessments as per the study schedule until they choose to withdraw or otherwise meet criteria to discontinue from study (see Section 3.3.3).

- a. For the first dose, participants will stay at the site for a minimum of 1 day with the potential for overnight stays up to 3 days. For Visits T1, T3, and T4, if visits occur on-site, an overnight stay (or hotel stay) before and after the titration day is allowed as deemed necessary based on practical considerations and taking into account participant and caregiver preference.
- b. Visit M1 (see Table 2-4) will be scheduled 7 days (+3 days) after T4 (last dose titration visit).
- c. Unscheduled visits may be conducted as needed with the option to use telemedicine visit technology if medically indicated. If the participant discontinues treatment early, an unscheduled visit will be conducted at the site with assessments selected by the investigator as clinically appropriate. The unscheduled visit for end of treatment will NOT include a V-EEG since treatment was discontinued prior to start of Maintenance. A feedback interview will be conducted within -5 days of the unscheduled end of treatment visit. If a participant will continue with study visits and assessments after discontinuation of treatment, V-EEGs and interviews beyond the unscheduled end of treatment visit are NOT required.
- d. The EOS visit should be conducted at the same visit where the decision to discontinue the participant from study is made or as early as possible following the decision. The Follow-up Visit is only applicable for those participants who discontinue from study (e.g., will not continue into Part B). The Follow-up visit should be conducted 14 days after the last dose of the taper or 14 days after the decision to discontinue from study, whichever is later.
- e. It is anticipated that there will be up to 4 dose levels starting with 0.175 mg/kg or matching placebo with the target dose level of 0.75 mg/kg at Titration visit T4. If a participant is unable to escalate to 0.75 mg/kg, they will be discontinued from study treatment.

FIG. 8B

- f. The baseline feedback interview / questionnaire is required and will be conducted during Screening. It must be conducted within 5 days prior to Visit T-1 (including the T-1 visit).
- g. A complete physical and neurological examination according to standard of care excluding the genitourinary examination will be performed at Screening and EOS. At all other site visits, a neurological examination and abbreviated or symptom directed physical examination will be performed.
- h. Vital signs will be measured after the participant has been in a sitting position for 5 minutes, using an age-appropriate cuff for blood pressure measurement.
- i. Height will be measured at the Screening Visit and EOS Visit only. Weight will be measured at the noted visits.
- j. Standard 12-lead ECGs will be performed in triplicate after the participant has been supine for at least 5 minutes.
- k. Laboratory assessments will include hematology and serum chemistry (see Section 10.3.1.1). Screening central laboratory results must be available and assessed by the Investigator before a participant is randomized. Local lab results may be used to evaluate entry criteria and/or any other key lab parameter during the course of the study in certain circumstances. In place of central laboratory results, please consult the medical monitor.
- l. Clinical laboratory tests at Visit T-1 should be done locally and are only needed if Screening laboratory results indicate additional assessment or follow-up is required, per investigator judgement, or if the Screening laboratory test is lost (e.g., sample was hemolyzed). If needed, this Visit T-1 laboratory assessment can be done at any time prior to and including at Visit T-1. This sample may also be collected as a future visit.
- m. For participants of childbearing potential only, a serum pregnancy test will be conducted at Screening and a serum or urine test at all applicable subsequent visits. A positive urine test will be confirmed with a serum pregnancy test.
- n. Participants will be randomized prior to initial receipt of study drug.
- o. Resupply of the study drug will occur to the participants home as needed. If a participant's weight changes by >10%, their dose will be adjusted for the new weight.
- p. For PK samples, blood will be collected at the timepoints specified in Table 2-4. On site-visit days, participants will take IP at the site in conjunction with the PK sampling schedule. If the participant is discontinued from treatment and study at the same time, the EOT PK sample will be collected at the combined unscheduled EOT/EOS visit; in the case of participant discontinuing from treatment before discontinuing from study, the EOT PK sample is required only at the unscheduled EOT visit.
- q. The VARS-3 will be orally and virtually administered up to 5 days before the scheduled visit day or on the day of the visit if not done before hand, preferably early during the visit. The rater will be blinded to the participant's treatment assignment and cohort.
- r. The ORCA assessment may be completed up to 5 days before the scheduled visit day or on the day of the visit if not completed before hand, preferably early during the visit. It will only be conducted if the appropriate translation is available.
- s. The indicated assessments may be completed up to 5 days before the scheduled visit day or on the day of the visit if not completed before hand, preferably early during the visit.
- t. Participants who are assessed as being capable of understanding the concepts of suicidality and death will be administered the adult C-SSRS version. All other participants will be assessed by the investigator (in discussion with the caregiver) for any indications of potential suicidal ideation or behavior, and the conclusion will be recorded in the eCRF.
- u. If seizures develop after starting study drug, each one will be required to complete a SIF for each participant. The SIF will be submitted after the Screening Visit to ensure that the seizures are classified accurately. If a new seizure type occurs during the study that was not previously confirmed by ESCI, a past seizure type from >1 year prior to screening) reoccurred, or a seizure type was inadvertently omitted, the site will be required to complete a New Seizure Form and submit to ESCI for review and confirmation. If seizures develop after starting study drug for Randomized Auxiliary Cohort in Participants Without Qualifying Seizures participants who did not previously submit a SIF after the screening visit for review and confirmation, a SIF will be required to be submitted at that time.
- v. At Screening, only active concomitant medications need to be recorded (e.g., medications discontinued prior to Screening do not need to be recorded).

FIG. 8C

Visit/Week Timeframe [days]	Maintenance Period ^a										Follow-up Period ^b
	M1 ^c / Week 1	M2 ^d / Week 2	M3 ^d / Week 4	M4 ^a / Week 8	M5/ Week 2	M6 ^d / Week 16	M7 ^d / Week 20	M8 ^{e, f} / Week 24 or ET ^g	m169±14		14 (+/-7) post last dose
Participant feedback interview / questionnaire									X		X
Demographics											
Physical / neurological examination ^h					X				X		
Vital signs (blood pressure and pulse rate) ^h	X		X		X				X		X
Height and weight ⁱ	X		X		X				X		
ECG ^j	X				X				X		
V-EEG									X		
Clinical laboratory tests ^k	X				X				X		X
Pregnancy test ^l	X		X		X				X		
Check participant's eDiary and records and provide eDiary retraining if necessary	X	X	X	X	X	X	X		X		
Daily study drug administration ^m											
Blood sampling for PK ⁿ	X								X		
Vineland-3 ^o					X				X		
CGI-C					X				X		
ABC-C					X				X		
PedsQL					X				X		
Cach-C					X				X		
Suicidality assessment ^p					X				X		
Submission of SIF to ESCI (if applicable) ^q											
Concomitant medications											
AEs											

FIG. 9A

- Abbreviations: ABC-C = aberrant behavior checklist-community; AE = adverse event; bid = twice daily (bis in die); CaGI-C = Caregiver Global Impression of Change; CGI-C = Clinical Global Impression of Change scale; CGI-S = Clinical Global Impression - Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; ET = early termination; M = Maintenance Period study day; M = Maintenance Period Visit; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; SIF = seizure identification form; T = Titration Period study day; T = Titration Period Visit; V-EEG = video electroencephalogram.
- a. Unscheduled visits could be conducted as needed with the option to use telemedicine visit technology.
- b. The ET visit should be conducted at the same visit where the decision to discontinue treatment is made or as early as possible following the decision. The participant should be encouraged to remain in the study. The Safety Follow-up Visit will only be applicable for those participants who are not eligible or do not agree to participate in Part B. Before entering the Safety Follow-up Period, participants should undergo a tapering regimen reflecting the schedule recommended by the sponsor, namely ~ the dose of ratirodiol should be reduced by 25% of the full dose for each of three 5-day steps (i.e., to 75%, 50%, and then 25% before stopping entirely).
- c. Visit M1 will be scheduled 7 days (± 3 days) after T5 (last dose titration visit).
- d. The noted visits may be performed as telephone/home visits.
- e. For Visit M5, an overnight stay at the site or in suitable accommodation close to the site will be required for all participants.
- f. The first Transition Titration visit (TT1, Table 2) should be scheduled on the same day as Visit M8.
- g. A complete physical and neurological examination according to standard of care excluding the genitourinary examination will be performed at Visit M5 and M8/early termination. At all other site visits, a neurological examination and abbreviated or symptom directed physical examination will be performed.
- h. Vital signs will be measured after the participant has been in a sitting position for 5 minutes, using an age-appropriate cuff for blood pressure measurements.
- i. Height will be measured at the Visit M1 and Visit M8/Early Termination Visit only. Weight will be measured at all indicated visits.
- j. A standard 12-lead ECG will be performed in triplicate after the participant has been supine for at least 5 minutes pre-dose and 2.5 hours (± 30 min) after dosing at M1 and M5 visits.
- k. Laboratory assessments will include hematology, serum chemistry, and coagulation.
- l. For participants of childbearing potential only, a serum or urine test at all noted visits. A positive urine test will be confirmed with a serum pregnancy test.
- m. Resupply of the study drug will occur to the participants home as needed.
- n. For PK samples, blood will be collected at the timepoints specified in Table 7. On the days on which participants will visit the site, participants will take their doses at the site in conjunction with the PK sampling schedule.
- o. The Visit end-3 will be centrally and virtually administered ± 3 days from the scheduled visit day. The rater will be blinded to the participant's cohort and treatment assignment.
- p. Participants who are assessed as being capable of understanding the concepts of suicidality and death will be administered either the pediatric or the adult C-SSRS version at the investigator's discretion. All other participants will be assessed by the investigator (in discussion with the caregiver) for any indications of potential suicidal ideation or behavior, and the conclusion will be recorded in the eCRF.
- q. If seizures develop after starting study drug, each site will be required to complete a SIF for each participant. This information will be submitted to the ESCI after the Screening Visit for review and approval. The SIF will be used to ensure that the seizures are classified accurately. If a new seizure type occurs during the study that was not previously confirmed by ESCI, a past seizure type (from >1 year prior to screening) reoccurred, or a seizure type was inadvertently omitted, the site will be required to complete a new SIF and submit to ESCI for review and confirmation.

FIG. 9B

Timeframe ^d	Transition Titration	Baseline ^a Day 1	Screening/ Baseline Phase 1b ^b Day 1 ^c	Treatment Period ^{d,e} (to be Repeated for Each Further Year of Study Participation)							Follow-up Period (EOSE I) ^a 14 Days After Last Dose
				Phone Calls (Months 1 and 2) ^f	Month 3 ^g	Phone Calls (Months 4 and 5) ^f	Month 6 ^g	Phone Calls (Months 7 and 8) ^f	Month 9 ^g	Phone Calls (Months 10 and 11) ^f	Month 12 ^g etc.
Visit window [days]		-	-	±14	±14	±14	±14	±14	±14	±14	±7
Eligibility reconfirmation		X	X								
Participant feedback interview / questionnaire					X						X
Demographics											
Medical / neurological history, including indications and procedures		X ^h	X								
Physical / neurological examination		X ^h	X		X		X		X		X
Vital signs (blood pressure and pulse rate) ^a		X ^h	X		X		X		X		X
Height, weight, and BMI		X ^h	X		X		X		X		X
ECG		X ^h	X		X		X		X		X
V-EEG ¹			X		X		X		X		X
Clinical laboratory tests ¹		X ^h	X		X		X		X		X
Pregnancy test ^a		X ^h	X		X		X		X		X
Distribute eDiary		X	X		X		X		X		X
Check eDiary records / return if necessary ^a				X	X		X		X		X
Return of eDiary											
Daily study drug dosing ^c	Table 6										
Vineland-3 ^h		X ^h			X ^h		X				X
CGI-C		X ^h	X		X ^h		X				X
ABC-C		X ^h	X		X ^h		X				X
PulsQ		X ^h	X		X ^h		X				X
CsQI-C		X ^h	X		X ^h		X				X
Survivability measurement ^h		X ^h	X		X ^h		X				X
Submission of SIF to ESCI (if applicable) ^c											

FIG. 10A

Timeframe ^d	Transition	Baseline ^a	Screening/ Baseline Phase 1b ^c	Treatment Period ^{c,d} (to be Repeated for Each Further Year of Study Participation)								Follow-up Period (EOS/ED) ^d
				Phone Calls (Months 1 and 2) ^f	Month 3 ^e	Phone Calls (Months 4 and 5) ^f	Month 6 ^e	Phone Calls (Months 7 and 8) ^f	Month 9 ^e	Phone Calls (Months 10 and 11) ^f	Month 12 ^e etc.	
Visit window (days)		-	-	±14	±14	±14	±14	±14	±14	±14	±14	14 Days After Last Dose ±7
Concomitant medications		N ₂										
		N ₃										

FIG. 10B

- Abbreviations: ABC-C = Aberrant Behavior Checklist-Community; AE = adverse event; bid = twice daily (as in the); BMI = body mass index; CaCl-C = Caregiver Global Impression of Change; CCL-C = Clinical Global Impression – Change scale; CGI-S = Clinical Global Impression – Severity scale; C-SSRS = Columbia Suicide Severity Rating Scale; eDiary = electronic diary; ECG = electrocardiogram; eCRF = electronic case report form; EOS = End of Study; ESCI = Epilepsy Study Consortium; ET = Early Termination; PedsQL = Pediatric Quality of Life Inventory; SIF = seizure identification form; V-EEG = video electroencephalogram
- a. Visit applicable for those participants who directly rolled over from either of the Phase 3 Randomized Cohorts. The Baseline Visit of Part B should be scheduled 7 days (± 3 days) after the last visit of the preceding period.
- b. Optional visit for Part A – Phase 1b only: Participants, not immediately rolling over into Part B due to exceptional circumstances will need to attend a new screening visit for Part B. On-site visits could be conducted remotely; (e.g., as telemedicine visits) in exceptional circumstances with approval of the medical monitor. Unscheduled visits could be conducted as needed with the option to use telemedicine visit technology. The tests and assessments to be performed during an unscheduled visit will be the same as for the regular 3-monthly visits, except that V-EEG, ECG, and completion of the scales are optional.
- c. Before entering the Follow-up Period, participants should undergo a tapering regimen reflecting the schedule recommended by the sponsor, namely – the dose of ratiopril should be reduced by 25% of the full dose for each of three 5-day steps i.e., to 75%, 50%, and then 25% before stopping entirely. Participants will then attend an End-of-Study Visit approximately 14 days after the last dose. Participants terminating early will taper off ratiopril and should attend an early termination visit as soon as possible after the last full dose.
- d. The visit timing (day or month) will be calculated from the last visit of the preceding period.
- e. Site visits required on Day 1 and then every 3 months (except in exceptional circumstances with approval of the medical monitor) for completion of study-related assessments
- f. Monthly telephone calls will be conducted by the sites at those months that do not have a visit to the site to assess caregivers' eDiary entries (seizure data, daily study drug administration volume, participant's usual or prescribed regimen and frequency of rescue therapy for seizures, and data reported by the caregivers based on the integrated scales), any AEs, and changes to concomitant medications.
- g. Assessments performed at the last visit of the preceding period will be carried forward and used as the baseline evaluations for Part B.
- h. Vital signs will be measured after the participant has been in a sitting position for 5 minutes, using an age-appropriate cuff for blood pressure measurements.
- i. If any clinically relevant changes in weight are observed, the dose should be adjusted as needed.
- j. A standard 12-lead ECG will be performed after the participant has been supine for at least 5 minutes
- k. First year only
- l. Laboratory assessments will include hematology, chemistry, and coagulation.
- m. For participants of childbearing potential only, a serum pregnancy test will be conducted at the Baseline Visit and a serum or urine test at each subsequent visit to the site. A positive urine test will be confirmed with a serum pregnancy test. For participants who become of childbearing potential (defined as starting periods) during the course of the study, a serum or urine pregnancy test will be conducted at each subsequent visit to the site.
- n. eDiary to be checked at site visit.
- o. Resupply of the study drug will be provided to the participant's home as needed.
- p. Vineland-3 assessed for former Part A – Phase 3 cohort participants only. The Vineland-3 will be centrally and virtually administered 43 days from the scheduled visit day. The ruler will be blinded to the participant's cohort and treatment assignment.
- q. Participants who are assessed as being capable of understanding the concepts of suicidality and death will be administered either the pediatric or the adult C-SSRS version at the investigator's discretion. All other participants will be assessed by the investigator (in discussion with the caregiver) for any indicators of potential suicidal ideation or behavior, and the conclusion will be recorded in the eCRF.
- r. If a new seizure type occurs during the study that was not previously confirmed by ESCI, a past seizure type (from >1 year prior to screening) reoccurred, or a seizure type was inadvertently omitted, the site will be required to complete a new SIF and submit to ESCI for review and confirmation.

FIG. 10C

Visit/Week Timeframe [days]	Transition Titration Period ^{ac}					Early Termination or ET ³	Follow-up Period ⁴ 14 (+7) days post last dose
	TT1 ^a /Week 1	TT2 ^a /Week 2	TT3 ^a /Week 3 (tt2+7) +3	TT4 ^{a,d} /Week 4 (tt3+7) +3	TT5 ^{a,b} /Week 5 (tt4+7) +3		
Eligibility reconfirmation	tt1 ^a	(tt1+7) +3					
Participant feedback interview / questionnaire	X					X	X
Physical and neurological examination ¹	X					X	
Vital signs (blood pressure and pulse rate) ¹							⋈
Height and weight ¹	X		X			X	
V-EEG	X					X	
Clinical laboratory tests ¹							⋈
Pregnancy test ¹	X					X	
Check eDiary / records; retain if necessary	X	X	X	X	X	X	
Daily study drug administration ⁶					⋈		
Blood sampling for PK ^a	X						
Vineland-3 ^o	X					X	
CGI-C	X					X	
ABC-C	X					X	
PedsQL	X					X	
CaGI-C	X					X	
Suicidality assessment ¹	X					X	
Submission of SIF to ESCI (if applicable) ⁹							⋈
Concomitant medications							⋈
AEs							⋈

FIG. 11A

- Abbreviations: ABC-C = aberrant behavior checklist-community; AE = adverse event; b.i.d. = twice daily (in in Latin); CAGI-C = Caregiver Global Impression of Change; CAGI-S = Clinical Global Impression of Change scale; CAGI-S = Clinical Global Impression - Severity scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eCRF = electronic case report form; eDiary = electronic diary; ET = early termination; m = Maintenance Period; Visit: PedaQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; SIF = seizure identification form; u = Titration Titration Visit; V-EEG = video electroencephalogram.
- a. For the first dose (T1 visit), participants will stay at the site for a minimum of 1 day with the potential for overnight stays up to 3 days. For Visits T1, T2, T3, T4 and T5, if there occur on-site, an overnight stay (or hotel stay) before and after the titration day is allowed as deemed necessary based on practical considerations and taking into account participant and caregiver preference.
- b. Seven to 14 days after T5 will be Day 1 of Part B (see Table 5).
- c. Unscheduled visits could be conducted as needed with the option to use telemedicine visit technology.
- d. The ET visit should be conducted at the same visit where the decision to discontinue treatment is made or as early as possible following the decision. The Safety Follow-up Visit will only be applicable for those participants who terminate early. Before entering the Safety Follow-up Period, participants should undergo a tapering regimen reflecting the schedule recommended by the sponsor, namely - the dose of ractiprolol should be reduced by 25% of the full dose for each of three 5-day steps i.e., to 75%, 50%, and then 25% before stopping entirely.
- e. It is anticipated that there will be up to 5 dose levels starting with 0.125 mg/kg or matching placebo with the target dose level of 0.75 mg/kg at Transition Titration visit T14.
- f. Titration visits (except T1 and T5) may be performed as telemedicine visits.
- g. T1 should be scheduled on the same day as the last visit of the maintenance period (Visit M5 for the Randomized Seizure Cohort or Visit M8 for the Randomized Auxiliary Cohort visit). Any assessments already done at this visit do NOT need to be repeated.
- h. A complete physical and neurological examination according to standard of care including the penitentiary examination will be performed at T1 and Early Termination. At all other site visits, a neurological examination and abbreviated or symptom directed physical examination will be performed.
- i. Vital signs will be measured after the participant has been in a sitting position for 5 minutes, using an age-appropriate cuff for blood pressure measurements.
- j. Height will be measured at the T1 Visit and Early Termination Visit only. Weight will be measured at the noted visits. If Visit T3 is performed as a telephone home visit, weight measurement is not mandatory.
- k. Laboratory assessments will include hematology, serum chemistry, and coagulation.
- l. For participants of childbearing potential only, a serum pregnancy test will be conducted at T1 and a serum or urine test at all applicable subsequent visits. A positive urine test will be confirmed with a serum pregnancy test.
- m. Resupply of the study drug will occur to the participants home as needed.
- n. For PK samples, blood will be collected at the timepoints specified in Table 7. On the days on which participants will visit the site, participants will take their doses at the site in conjunction with the PK sampling schedule. For T1, the participant should receive the highest tolerated dose from the Maintenance Period for the first daily dose and begin the titration dose with the second daily dose.
- o. The Viasland-3 will be centrally and virtually administered ± 3 days from the scheduled visit day. The rater will be blinded to the participant's cohort and treatment assignment.
- p. Participants who are assessed as being capable of understanding the concepts of suicidality and death will be administered either the pediatric or the adult C-SSRS version at the investigator's discretion. All other participants will be assessed by the investigator (in discussion with the caregiver) for any indications of potential suicidal ideation or behavior, and the conclusion will be recorded in the eCRF.
- q. If seizures develop after starting study drug, each site will be required to complete a SIF for each participant. This information will be submitted to the ESCI after the Screening Visit for review and approval. The SIF will be used to ensure that the seizures are classified accurately. If a new seizure type occurs during the study that was not previously confirmed by ESCI, a post seizure type (from >1 year prior to screening) reoccurred, or a seizure type was inadvertently omitted, the site will be required to complete a new SIF and submit to ESCI for review and confirmation.

FIG. 11B

FIG. 12

Visit	Timepoint (Hours After First Dose)	Time Window (+ Minutes)
Part A – Phase 1b		
T1 predose	Predose	NA
T1 after first dose	1	15
	2	15
	4	60
	6	60
	8	60
	10	60
T1 immediately before second dose	12	60
T2, T3, T4, and T ^N (first dose)	Predose	NA
	1	15
	2	15
	5	60
M1, M2, and M3 ^a	Predose	NA
M4 (first dose)	Predose	NA
	1	15
	2	15
	5	60
Phase 3 Randomized Cohorts		
T1	Predose	NA
	2	15
M1	Predose	NA
	1	15
	2	15
M5 (first dose)	Predose	NA
	1	15
	2	15
	4	60
	6	60
	8	60
	10	60
	12 (prior to 2 nd dose)	60

Abbreviations: M = Maintenance Period Visit; NA = not applicable; T = Titration Period Visit

- a. Samples for analysis of metabolites are collected predose.
- b. The Day 1 Visit will only be applicable for those participants who do not immediately roll over into Part B. For participants who immediately roll over into Part B, the PK evaluations performed at the last visit of the preceding period will be carried forward and used as baseline evaluations for Part B if the data were collected within 7 days prior to Day 1 of Part B.

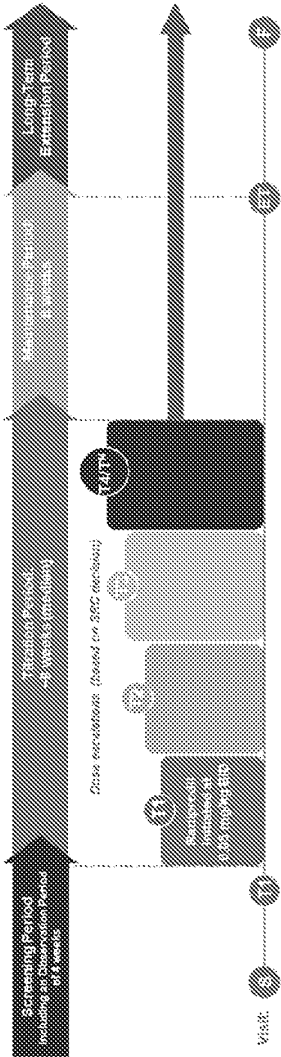


FIG. 13

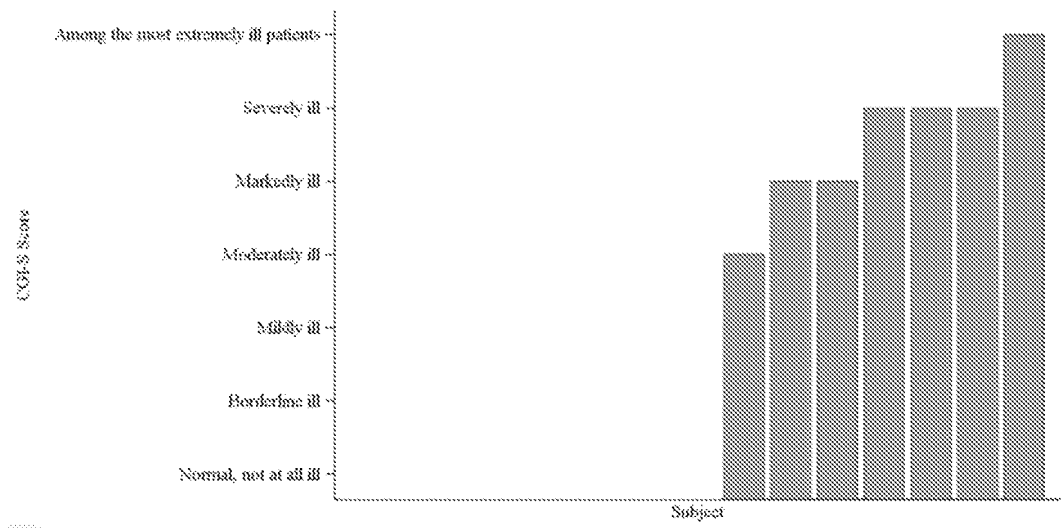
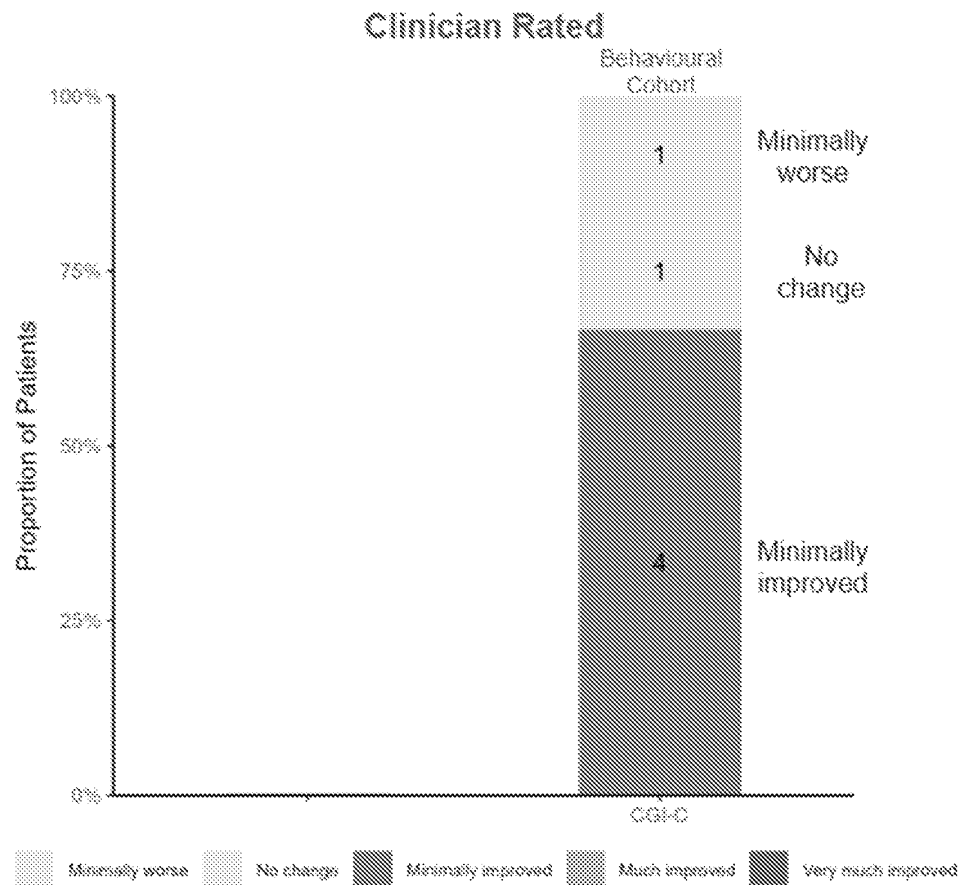


FIG. 14

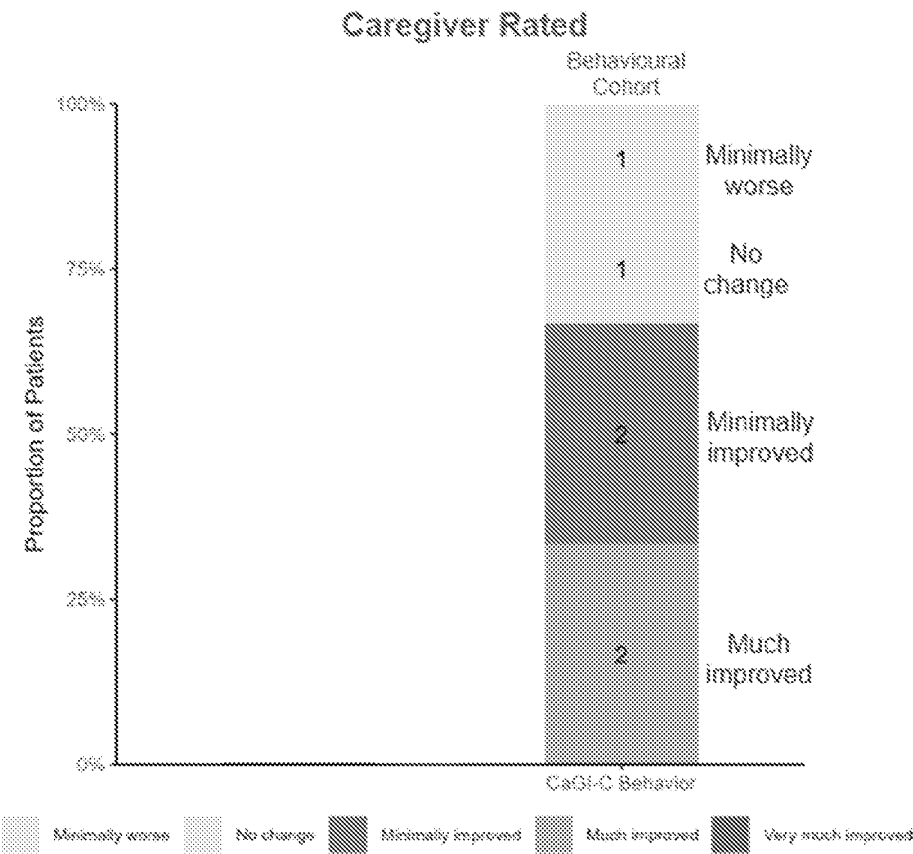
Clinical Global Impression of Change, 8-week Maintenance Period*



*Six patients completed CGI baseline and end of maintenance period assessments at the time these analyses were conducted.

FIG. 15

Caregiver Global Impression of Change, 8-week Maintenance Period*



*Six patients completed CaGI baseline and end of maintenance period assessments at the time these analyses were conducted.

FIG. 16

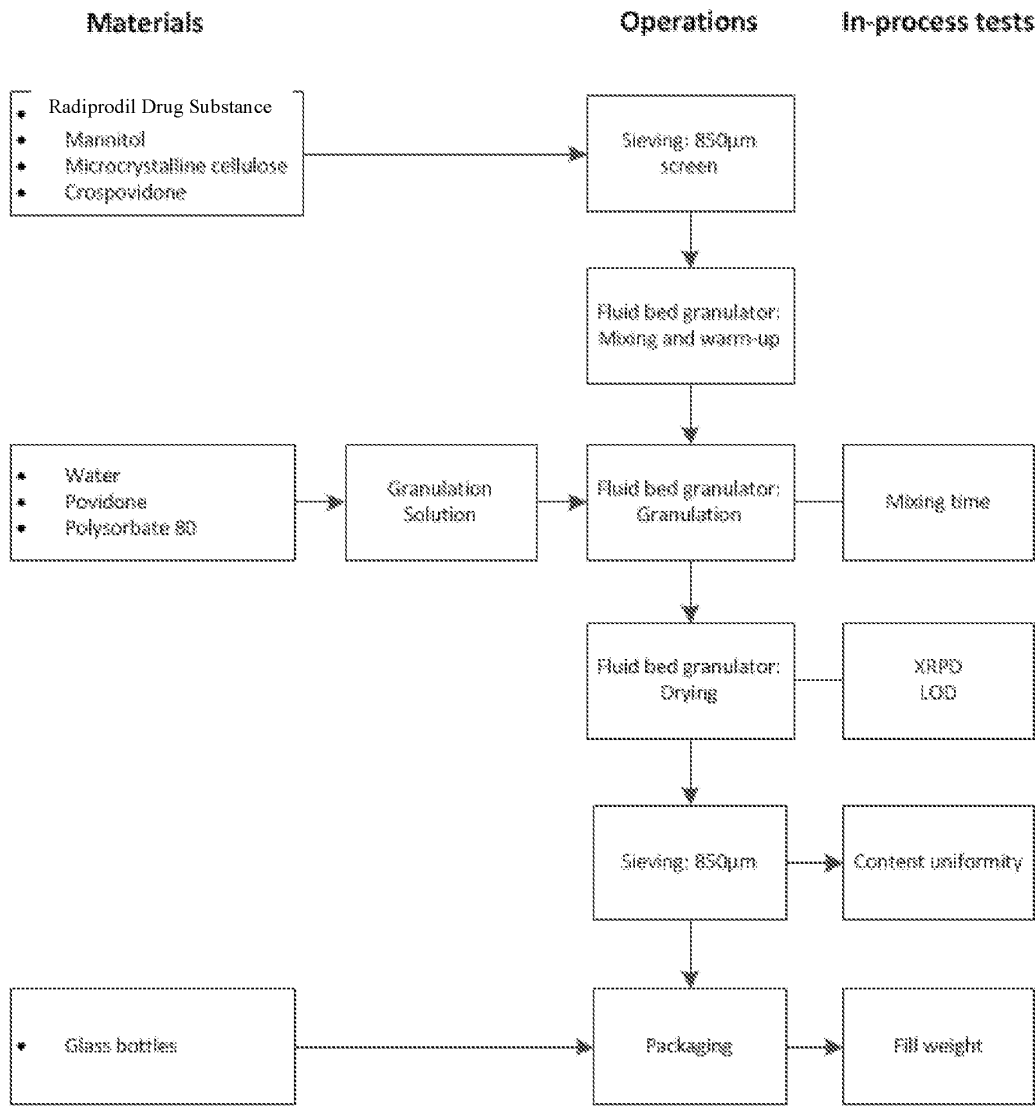
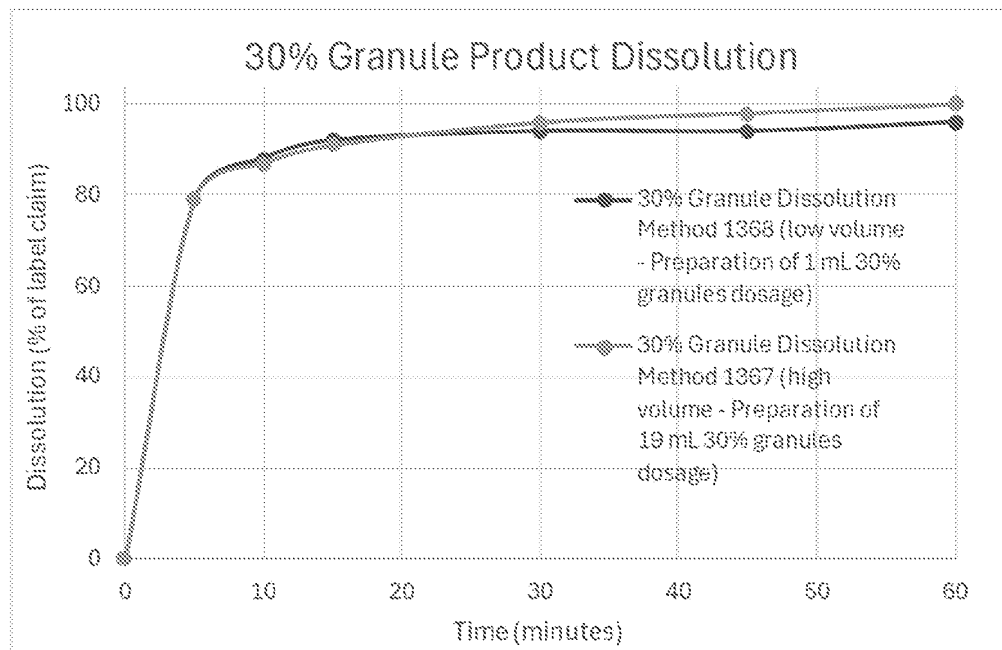


FIG. 17

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**FIG. 18**