Clinical Study Protocol

NCT Number: NCT04940624

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects With Dravet Syndrome (DS)

Study Number: TAK-935-3001

Document Version and Date: Amendment 2.0, 22 April 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects With Dravet Syndrome (DS)

Study of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects With Dravet Syndrome

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421		
Study Number:	TAK-935-3001		
IND Number:	133627	**EudraCT Number:**	2021-002480-22
Compound:	Soticlestat		
Date:	22 April 2022	**Version/Amendment Number:**	Amendment 2

Amendment History:

Date	Amendment Number	Amendment Type	Region
22 April 2022	Amendment 2	Substantial	Global
03 November 2021	Amendment 1 FR-IT-RS v1	Substantial	France, Italy, Serbia
23 March 2021	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided in the study manual.

Takeda Development Center (TDC)-sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

The names and contact information for the medical monitor and responsible medical officer are in the study contact list.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual subjects in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic signatures are provided on the last page of this document.

[redacted], MD, MMSc	Date
[redacted], Clinical Science	
Neuroscience	
Takeda	

[redacted], PhD	Date
[redacted], Statistical and Quantitative Sciences	
Takeda	

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix D).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix F of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 2 Summary of Changes

Protocol Amendment 2 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 2, including those previously submitted in France, Italy, and Serbia. The primary reasons for Amendment 2 are to make slight changes to entry criteria to avoid unnecessary screen failures. The following table summarizes these changes.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only and are not captured in the following table.

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
Changes originally provided in Amendment 1 FR-IT-RS v1 for France, Italy. Serbia now apply to all countries unless affected by "Additional changes" below.			
1	Section 1.2 Approval	Changed personnel for signatures.	New assignments.
2	Section 2.0 STUDY SUMMARY, Study Design, Exploratory Objectives Section 5.1.3 Exploratory Objectives Section 6.2.2 Endpoints Section 9.1.15.6 [redacted]	[redacted]	Clarification.
3	Section 6.1.5 End of Study	Added definition of end of study.	Health authority request.
4	Section 9.1.11.3 Procedures for Clinical Laboratory Samples	Indicated the maximum volume of blood collected at any single visit and the total volume of blood collected in the study.	Health authority request.
5	Section 9.3.5.1 [redacted] Section 9.3.5.2 [redacted] Section 9.3.5.3 [redacted]	[redacted]	Clarification.
6	Appendix B Strong CYP3A Inducers Strong CYP3A Inducers and CYP3A4 Inhibitors	Updated table with additional examples of CYP3A inducers/CYP3A4 inhibitors.	Correction to maintain consistency with protocols TAK-935-3002 and TAK-935-3003.
7	Appendix C Virtual Visits and Trial Management During COVID-19	Revised language regarding conditions under which virtual	Clarification.

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
	Pandemic and Other Extenuating Circumstances	visits are allowed.	
Additional changes in global Amendment 2.			
8	Section 1.2 Approval	Changed personnel for signature.	New assignment.
9	Section 2.0 STUDY SUMMARY	Changed "TAK-935/OV935" to "TAK-935" [redacted]	Corrections.
10	Section 2.0 STUDY SUMMARY	Changed number of estimated sites from 65 to 100.	Increases patient recruitment rate.
11	Section 2.0 STUDY SUMMARY Section 5.1.3 Exploratory Objectives Section 5.2.3 Exploratory Endpoints Section 9.1.15.6 [redacted]	[redacted]	[redacted]
12	Section 2.0 STUDY SUMMARY Section 5.1.4 Safety Objectives Section 5.2.4 Safety Endpoints	Separated incidence and change from baseline into separate safety objectives for laboratory values and electrocardiograms (ECGs).	Clarification.
13	Section 2.0 STUDY SUMMARY Section 5.2.2 Secondary Endpoints	Reordered secondary endpoints to follow the order of secondary objectives.	Consistency.
14	Section 2.0 STUDY SUMMARY Section 5.2.4 Safety Endpoints	Removed ophthalmological evaluations from safety endpoints.	Cataract as an adverse event of special interest is covered in the treatment-emergent adverse event (TEAE) endpoint, so no need to include this as a separate endpoint; ophthalmological evaluations will occur as scheduled; results will still be available and will be presented in safety analysis tables.
15	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Appendix A Schedule of Study Procedures	Clarified minimum time between screening and randomization visits.	Minimum window of 28 days of screening data to establish baseline seizure frequency.
16	Section 6.1 Study Design	Made study day and dose day	Clarifies the numbering.

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
	Appendix A Schedule of Study Procedures	numbers the same and added a Day 0: randomization = Visit 2 = Day 0; first dose is taken the next day on Day 1 (or first day after study medication is received).	
17	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 8.1.3 Dose and Regimen	Low-profile gastric tube (MIC-KEY button) used instead of percutaneous endoscopic gastrostomy.	Percutaneous endoscopic gastrostomy is a surgical procedure; MIC-KEY button is a device.
18	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Appendix A Schedule of Study Procedures Appendix C Virtual Visits and Trial Management During COVID-19 Pandemic and Other Extenuating Circumstances	Broadened option to have virtual visits to allow more flexibility for subjects/parents or caregivers who may have difficulties with travel for clinic visits, such as COVID-19 restrictions or other extenuating circumstances. Also allowed virtual visits to be done as clinic visits.	Allows more flexibility for subjects/parents or caregivers.
19	Section 2.0 STUDY SUMMARY Section 6.1.1 Dose Titration Period (4 Weeks) Appendix A Schedule of Study Procedures	Clarified timing and procedures of dose titration period.	Clarification.
20	Section 2.0 STUDY SUMMARY Section 6.1.3 Study Discontinuation/Completion Appendix A Schedule of Study Procedures	Clarified procedures and timing of dose taper period and final dose.	Clarification.
21	Section 6.1.5 End of Study Section 6.1.5 End of Study Overall	Clarified overall end of study versus end of study for an individual subject.	Corrected inadvertent omission of the definition for individuals; definition for study overall was simplified based on the individuals' definitions.
22	Section 6.2.2 Endpoints	Clarified that QI-disability measurement is for subjects [redacted]	Clarifies the purpose of scales.
23	Section 7.1 Inclusion Criteria No. 1	Allowed inclusion of subjects living in a residential facility.	Allows subject population that might otherwise be excluded.
24	Section 7.1 Inclusion Criteria No. 2	All electronic (e)consent	Subjects/parents or caregivers

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
	Section 9.1.1 Informed Consent Procedure Section 12.1 eCRFs Section 12.2 Record Retention Section 14.1 Study-Site Monitoring Visits Section 15.1 IRB and/or IEC Approval Section 15.2 Subject Information, Informed Consent, and Subject Authorization Section 15.3 Subject Confidentiality Appendix D Responsibilities of the Investigator Appendix E Elements of the Subject Informed Consent	changed to consent.	prefer written consent and signatures.
25	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria, No. 4	Clarified that clinical diagnosis should be supported by variable combinations of typical clinical features (listed) and these are guidance only; final eligibility is confirmed by TESC. [redacted]	Clarifies that the bullets are not a mandatory checklist of diagnostic criteria. Chinese health authority request.
26	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria No. 5	Clarified primary outcome seizure types used in calculating the number of seizures.	Clarifies that not all seizures will be used for calculations for eligibility.
27	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria, No. 45	Increased number of convulsive seizures from ≥4 to ≥12 over 12 weeks before screening.	Mitigates potential heterogeneity in recollection of number of seizures during the prescreening period.
28	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria No. 7	Required prior treatment failure of 1 ASM rather than 2.	Allows enrollment of subjects who were being unnecessarily excluded.
29	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria, No. 8 Section 9.1.12 Documentation of Concomitant (Including ASM and Rescue) Medications	Added new criterion: Artisanal cannabidiols are allowed (at consistent dose and from the same manufacturer) and do not count as an ASM. (Subsequent numbering of inclusion criteria shift by +1 relative to Amendment 1 FR-IT-RS v1.)	More representative of the patient population.

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
30	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria No. 9	Allowed fenfluramine and cannabidiol (Epidiolex) as ASMs where available and counted as an ASM (formerly No. 8).	Some countries have these medications available as ASMs.
31	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria, No. 13 Section 9.1.3 Seizure Identification and Diagnostic Review Forms (TESC)	Added that TESC review may include review of electroencephalogram and magnetic resonance imaging results (if available and permitted by local regulations), and that sponsor may be consulted if needed (formerly No. 12).	Makes additional information available to TESC.
32	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria No. 14	Clarified allowed contraceptive methods (formerly No. 13).	Clarifies that highly effective contraception is acceptable, in addition to effective contraception.
33	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria, No. 3	Clarified the exclusion around participation in other clinical studies.	Clarifies that only trials related to treatment devices are excluded.
34	Section 7.2 Exclusion Criteria, No. 11 Section 9.1.11.3 Procedures for Clinical Laboratory Samples, Table 9.a	Clarified exclusion based on hepatitis history. Added hepatitis screening to clinical laboratory tests.	Clarification. Correction of omission.
35	Section 7.2 Exclusion Criteria, No. 14. Section 7.2 Exclusion Criteria, originally No. 15 Section 7.3 Excluded Medications Section 7.4 Diet, Fluid, Activity Control Appendix B Strong CYP3A Inducers	Removed inhibitors of CYP3A from the exclusion criteria, prohibited medications, and from the appendix. Allowed topical CYP3A inducers. Deleted original criterion No. 15, "Unwilling to withhold the fruit and juice of grapefruit, Seville oranges, and starfruit from their diet during the entire clinical trial." (Subsequent numbering of exclusion criteria shift by -1 relative to Amendment 1 FR-IT-RS v1.) Deleted same prohibition from Section 7.4.	Per recent interim PK results from a phase 1 study, TAK-935-1007, the effect of a strong CYP3A4 inhibitor, itraconazole, on the PK exposure measures of soticlestat is small (<25% on maximum concentration and area under the plasma concentration-time curves). Therefore, strong CYP3A4 inhibitors will be allowed in the study.
36	Section 8.4 Accountability and	Allowed drug supplies to be destroyed at the site rather than	Allows flexibility in

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
	Destruction of Study Drugs	being returned to the sponsor or designee.	destruction of study drug.
37	Section 9.1.6 Height and Weight	If unable to obtain height or weight, other sources (specified) may be used for these data, which may be used to determine the weight-based starting dose.	Allows flexibility (eg, for subject in a wheelchair).
38	Section 9.1.11.1 Ophthalmological Evaluation Procedure	Added preference to obtain a picture of the fundus from ophthalmoscopy. Clarified that discontinued subjects should have ophthalmological evaluation at the ET visit.	Provides visual record of results. Corrects omission of these subjects.
39	Section 9.1.11.3 Procedures for Clinical Laboratory Samples Appendix A Schedule of Study Procedures Appendix G Blood Volumes	Details on blood volumes added in prior local amendment corrected and moved to a new appendix. [redacted]	Main text focuses on blood volume maximums; details available in appendix. Sampling changes allow more flexibility (allows Visit 2 to be a virtual visit).
40	Section 9.1.11.3 Procedures for Clinical Laboratory Samples, Table 9.a.	Added nitrite, urobilinogen, and microscopy to urinalysis. Added footnote that urinalysis is the primary method. Urine dipstick may be used as a backup only. In text, clarified that local laboratories are allowed before randomization only if a screening laboratory value is missing, and after randomization only for emergent reasons, including	Corrects omission of tests. Clarification.

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
		pregnancy tests.	
41	Section 9.1.14 Clinical Assessment of Suicidal Ideation and Behavior	Clarified that children under age 6 at the start of the study will be evaluated with C-SSRS if and when they turn 6 during the study.	Allows C-SSRS assessment of this additional group of children.
42	Section 9.1.15.3 CGI-I Seizure Intensity and Duration	Changed "convulsive seizures" to "the most impactful seizures."	Correction.
43	Section 9.1.15.5 QI-Disability (Parent/Caregiver Version)	Removed reference to translation and validation.	Translation and validation are completed for all countries.
44	Section 9.1.16.1 Male Subjects and Their Female Partners	Clarified that sperm donation by subjects is not allowed.	It is difficult to track and report pregnancy resulting from donated sperm. Sponsor does request that pregnancy of the subject's partner be reported.
45	Section 9.1.16.2 Female Subjects and Their Male Partners Appendix A Schedule of Study Procedures	Clarified definitions of nonfertile subjects. Clarified timing of pregnancy tests.	Adds definition of nonfertile subjects per Takeda template. Clarifies timing of pregnancy test to allow virtual visit flexibility at Visit 2.
46	Section 9.1.17 Pregnancy	Added requirement to report pregnancy of female partners of male subjects.	There is no evidence suggesting any risk in pregnancy of female partners of male subjects. To be conservative, the sponsor will follow up on such pregnancy and newborn information.
47	Section 9.2 Monitoring Subject Treatment Compliance	Additional instructions regarding the electronic daily seizure and medication diary.	Provides more clarification in regards the use of the electronic diary.
48	Section 9.3.5.1 [redacted] Appendix A Schedule of Study Procedures	[redacted]	[redacted]
49	Section 9.4 Biological Sample Retention and Destruction	Added provision for storage of leftover blood samples for further research.	Potential future research related to soticlestat and/or seizure disorders.
50	Section 9.5.1 Unscheduled Visits	Clarified types of and reasons for unscheduled visits.	Clarification.
51	Section 10.1 Definitions	Clarified definitions to distinguish AEs and TEAEs.	Makes terminology consistent. Applies change

Protocol Amendment 2			
Summary of Changes Since the Original Approved Protocol			
No.	**Sections Affected by Change**	**Description**	**Rationale**
			throughout protocol.
52	Section 10.1.4 AEs of Special Interest	Removed instruction that an AE of special interest and clinical significance be recorded as a serious adverse event (SAE).	Correction.
53	Section 10.2.1.1 AE Collection Period	TEAE collection period was clarified.	Clarification.
54	Section 10.2.2 Collection and Reporting of SAEs	Indicated that contacts for SAE reporting are provided in the study manual.	Correction.
55	Section 13.2.1.2 mITT Analysis Set	Clarified that the mITT analysis set only includes subjects who have been assessed for seizures during the treatment period.	Clarification.
56	Section 2.0 STUDY SUMMARY Section 13.2.4 Efficacy Analysis Section 13.2.6 Exploratory/Additional Analyses	Corrected analysis description, including planned statistical tests.	Correction.
57	Section 13.3.3 Interim Analyses	Indicated that a blinded interim analysis may be performed to allow for sample size re-estimation.	Corrects inadvertent omission.
58	Section 14.1 Study-Site Monitoring Visits	With the exception of visits in China, monitoring visits can be virtual or on site, as indicated in the clinical monitoring plan.	Clarification.
59	Appendix H Protocol History	Added history of Amendment 1 FR-IT-RS v1 to this new appendix.	Template requirement.

TABLE OF CONTENTS

1.0 ADMINISTRATIVE INFORMATION 2
1.1 Contacts 2
1.2 Approval 3
1.3 Protocol Amendment 2 Summary of Changes 5
2.0 STUDY SUMMARY 19
3.0 STUDY REFERENCE INFORMATION 27
3.1 Study-Related Responsibilities 27
3.2 Coordinating Investigator 27
3.3 List of Abbreviations 28
3.4 Corporate Identification 29
4.0 INTRODUCTION 30
4.1 Background 30
4.2 Rationale for the Proposed Study 31
4.3 Benefit/Risk Profile 31
5.0 STUDY OBJECTIVES AND ENDPOINTS 32
5.1 Objectives 32
5.1.1 Primary Objectives 32
5.1.2 Secondary Objectives 32
5.1.3 Exploratory Objectives 33
5.1.4 Safety Objectives 33
5.2 Endpoints 34
5.2.1 Primary Endpoints 34
5.2.2 Secondary Endpoints 34
5.2.3 Exploratory Endpoints 34
5.2.4 Safety Endpoints 35
6.0 STUDY DESIGN AND DESCRIPTION 35
6.1 Study Design 35
6.1.1 Dose Titration Period (4 Weeks) 39
6.1.2 Maintenance Period (12 Weeks) 39
6.1.3 Study Discontinuation/Completion 39
6.1.4 End of Study for Individual Subject 40
6.1.5 End of Study Overall 40
6.2 Justification for Study Design, Dose, and Endpoints 40
6.2.1 Study Design 40

6.2.2 Endpoints 41
6.2.3 Dose 41
6.3 Premature Termination or Suspension of Study or Study Site 43
6.3.1 Criteria for Premature Termination or Suspension of the Study 43
6.3.2 Criteria for Premature Termination or Suspension of Study Sites 43
6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s) 43
7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS 43
7.1 Inclusion Criteria 44
7.2 Exclusion Criteria 47
7.3 Excluded Medications 48
7.4 Diet, Fluid, Activity Control 49
7.5 Criteria for Discontinuation or Withdrawal of a Subject 49
7.6 Procedures for Discontinuation or Withdrawal of a Subject 51
8.0 CLINICAL STUDY MATERIAL MANAGEMENT 51
8.1 Study Drug and Materials 51
8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling 51
8.1.1.1 Study Drug 51
8.1.1.2 Rescue Medication 52
8.1.2 Storage 52
8.1.3 Dose and Regimen 52
8.1.4 Overdose 54
8.2 Study Drug Assignment and Dispensing Procedures 54
8.3 Unblinding Procedures 54
8.4 Accountability and Destruction of Study Drugs 55
9.0 STUDY PLAN 56
9.1 Study Procedures 56
9.1.1 Informed Consent Procedure 56
9.1.2 Historical Seizure Diary Review 56
9.1.3 Seizure Identification and Diagnostic Review Forms (TESC) 56
9.1.4 Seizure Frequency 57
9.1.5 Demographics, Medical History, and Medication History Procedure 58
9.1.6 Height and Weight 58
9.1.7 Concomitant Medications and Nonpharmacologic Therapies and Procedures 58
9.1.8 Vital Sign Procedure 58
9.1.9 Physical Examination Procedure 59

9.1.10 Neurological Examination Procedure 59
9.1.11 Safety Evaluations 59
9.1.11.1 Ophthalmological Evaluation Procedure 60
9.1.11.2 ECG Procedure 60
9.1.11.3 Procedures for Clinical Laboratory Samples 61
9.1.12 Documentation of Concomitant (Including ASM and Rescue) Medications 63
9.1.13 Documentation of Concurrent Medical Conditions 63
9.1.14 Clinical Assessment of Suicidal Ideation and Behavior 63
9.1.15 Health Outcome/Quality of Life Measures 64
9.1.15.1 CGI-I (Clinician) 64
9.1.15.2 Care GI-I (Caregiver) 64
9.1.15.3 CGI-I Seizure Intensity and Duration 64
9.1.15.4 CGI-I Nonseizure Symptoms 64
9.1.15.5 QI-Disability (Parent/Caregiver Version) 65
9.1.15.6 [redacted] 65
9.1.16 Contraception and Pregnancy Avoidance Procedure 65
9.1.16.1 Male Subjects and Their Female Partners 65
9.1.16.2 Female Subjects and Their Male Partners 65
9.1.16.3 General Guidance With Respect to the Avoidance of Pregnancy 66
9.1.17 Pregnancy 67
9.1.18 Documentation of Screen Failure 67
9.1.19 Documentation of Study Entrance 68
9.2 Monitoring Subject Treatment Compliance 68
9.3 Safety Monitoring 69
9.3.1 Reporting of Abnormal LFTs 69
9.3.2 Reporting of QTcF Interval Increase 69
9.3.3 Reporting of Perampanel Drug-Drug Interaction 70
9.3.4 Reporting of Cataracts 70
9.3.5 [redacted] 70
9.3.5.1 [redacted] 70
9.3.5.2 [redacted] 71
9.3.5.3 [redacted] 71
9.3.5.4 [redacted] 71
9.4 Biological Sample Retention and Destruction 72
9.5 Schedule of Study Procedures 72

9.5.1 Unscheduled Visits 72
9.5.2 Poststudy Care 72
10.0 COLLECTION AND REPORTING OF ADVERSE EVENTS 73
10.1 Definitions 73
10.1.1 AEs 73
10.1.2 Additional Points to Consider for AEs 73
10.1.3 SAEs 75
10.1.4 AEs of Special Interest 75
10.1.5 Intensity of AEs 76
10.1.6 Causality of AEs 76
10.1.7 Relationship to Study Procedures 76
10.1.8 Start Date 77
10.1.9 Stop Date 77
10.1.10 Frequency 77
10.1.11 Action Concerning Study Drug 77
10.1.12 Outcome 77
10.2 Procedures 78
10.2.1 Collection and Reporting of AEs 78
10.2.1.1 AE Collection Period 78
10.2.1.2 AE Reporting 78
10.2.2 Collection and Reporting of SAEs 79
10.3 Follow-up of SAEs 79
10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities 80
11.0 STUDY-SPECIFIC COMMITTEES 80
12.0 DATA HANDLING AND RECORDKEEPING 80
12.1 eCRFs 80
12.2 Record Retention 81
13.0 STATISTICAL METHODS 82
13.1 Statistical and Analytical Plans 82
13.2 Determination of Sample Size 82
13.2.1 Analysis Sets 82
13.2.1.1 ITT Analysis Set 82
13.2.1.2 mITT Analysis Set 83
13.2.1.3 Safety Analysis Set 83
13.2.2 Analysis of Demographics and Baseline Characteristics 83

13.2.3 Subject Disposition 83
13.2.4 Efficacy Analysis 83
13.2.5 Safety Analysis 84
13.2.6 Exploratory/Additional Analyses 84
13.3 Other Statistical Issues 85
13.3.1 Significance Levels 85
13.3.2 Missing or Invalid Data 85
13.3.3 Interim Analyses 85
14.0 QUALITY CONTROL AND QUALITY ASSURANCE 85
14.1 Study-Site Monitoring Visits 85
14.2 Protocol Deviations 85
14.3 Quality Assurance Audits and Regulatory Agency Inspections 86
15.0 ETHICAL ASPECTS OF THE STUDY 86
15.1 IRB and/or IEC Approval 87
15.2 Subject Information, Informed Consent, and Subject Authorization 87
15.3 Subject Confidentiality 88
15.4 Publication, Disclosure, and Clinical Trial Registration Policy 89
15.4.1 Publication and Disclosure 89
15.4.2 Clinical Trial Registration 89
15.4.3 Clinical Trial Results Disclosure 89
15.5 Insurance and Compensation for Injury 89
16.0 REFERENCES 91

LIST OF IN-TEXT TABLES

Table 6.a Dosing Schedules by Weight, 10 to <15 kg 37
Table 6.b Dosing Schedules by Weight, 15 to <30 kg 37
Table 6.c Dosing Schedules by Weight, 30 to <45 kg 38
Table 6.d Dosing Schedules by Weight, ≥45 kg 38
Table 9.a Clinical Laboratory Tests 62

LIST OF IN-TEXT FIGURES

Figure 6.a Schematic of Study Design 36

LIST OF APPENDICES

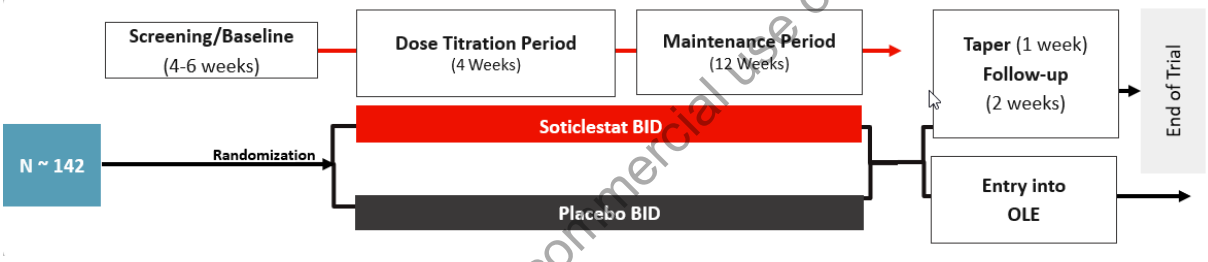
Appendix A Schedule of Study Procedures 92
Appendix B Strong CYP3A Inducers 98
Appendix C Virtual Visits and Trial Management During COVID-19 Pandemic and Other Extenuating Circumstances 99
Appendix D Responsibilities of the Investigator 101
Appendix E Elements of the Subject Informed Consent 103
Appendix F Investigator Consent to Use of Personal Information 106
Appendix G Blood Volumes 107
Appendix H Protocol History 108

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** Soticlestat (also known as TAK-935)	
Title of Protocol: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, and Tolerability of Soticlestat as Adjunctive Therapy in Pediatric and Young Adult Subjects With Dravet Syndrome (DS)	**IND No.:** 133627	**EudraCT No.:** 2021-002480-22
Study Number: TAK-935-3001 Amendment 2	**Phase:** 3	

Study Design:

This is a phase 3, global, multicenter, 1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and young adult subjects with DS. The treatment period is 16 weeks. The total duration of the study is approximately 25 weeks for subjects who complete the study and choose not to roll over to the open-label extension (OLE) study. For those who roll over to the OLE study, the study duration is 3 weeks shorter.



Approximately 142 male and female pediatric and young adult subjects will be randomized.

The study will consist of the following periods:

- 4- to 6-week screening/baseline period. The minimum visit window for screening is 28 days (ie, Visit 2/Day 0 cannot occur earlier than 29 days after screening).
- 16-week full treatment period:
  - 4-week titration period.
  - 12-week maintenance period.
- 1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit or a phone call.

This is a 2-arm study. All subjects will be randomized at a 1:1 ratio to receive standard of care (SOC) plus one of the following adjunctive therapies: soticlestat or placebo.

Soticlestat or matching placebo added to current antiseizure therapy will be administered orally twice daily (BID) with or without food or via gastrostomy tube (G-tube) or low-profile gastric tube (MIC-KEY button). A jejunostomy tube (J-tube) may be considered following written approval by the medical monitor or sponsor. Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.

All doses will be blinded and will undergo the same titration scheme, with the same number and type of tablets/mini-tabs. Subjects randomized to placebo will undergo a mock titration to ensure the blind is maintained (see tables below).

The total daily dose of study drug (either placebo or soticlestat) will be calculated based on body weight at Visit 1 (screening visit) and given BID starting on the morning after Visit 2/Day 0 (ie, on study Day 1) (see tables below). The 100 mg BID dose (or 100 mg BID equivalent weight-based dosing for weight <45 kg) is the minimum dose allowed during the study. Subjects who cannot tolerate the minimal dose will be discontinued from the study. Subjects weighing <45 kg will be dispensed 20 mg mini-tablets or matching placebo. Subjects weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets or matching placebo.

Dosing Schedules by Weight, 10 to <15 kg

	10 to <15 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		**Dose 2 (Days 8-14): Adult Reference 200 mg BID**		**Dose 3 (Days 15-28): Adult Reference 300 mg BID**	
Treatment Arm	**(mg/dose)**	**No. Tablets/ Mini-tablets**	**(mg/dose)**	**No. Tablets/ Mini-tablets**	**(mg/dose)**	**No. Tablets/ Mini- tablets**
Soticlestat	40 mg BID	2 mini tabs soticlestat BID	60 mg BID	3 mini tabs soticlestat BID	100 mg BID	5 mini tabs soticlestat BID
PBO	---	2 mini tabs PBO BID	---	3 mini tabs PBO BID	---	5 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

Dosing Schedules by Weight, 15 to <30 kg

	15 to <30 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		**Dose 2 (Days 8-14): Adult Reference 200 mg BID**		**Dose 3 (Days 15-28): Adult Reference 300 mg BID**	
Treatment Arm	**(mg/dose)**	**No. Tablets/ Mini-tablets**	**(mg/dose)**	**No. Tablets/ Mini-tablets**	**(mg/dose)**	**No. Tablets/ Mini- tablets**
Soticlestat	60 mg BID	3 mini tabs soticlestat BID	120 mg BID	6 mini tabs soticlestat BID	200 mg BID	10 mini tabs soticlestat BID
PBO	---	3 mini tabs PBO BID	---	6 mini tabs PBO BID	---	10 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

Dosing Schedules by Weight, 30 to <45 kg

	30 to <45 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		**Dose 2 (Days 8-14): Adult Reference 200 mg BID**		**Dose 3 (Days 15-28): Adult Reference 300 mg BID**	
Treatment Arm	**(mg/dose)**	**No. Tablets/ Mini-tablets**	**(mg/dose)**	**No. Tablets/ Mini-tablets**	**(mg/dose)**	**No. Tablets/ Mini- tablets**
Soticlestat	80 mg BID	4 mini tabs soticlestat BID	140 mg BID	7 mini tabs soticlestat BID	200 mg BID	10 mini tabs soticlestat BID
PBO	---	4 mini tabs PBO BID	---	7 mini tabs PBO BID	---	10 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

Dosing Schedules by Weight, ≥45 kg

Treatment Arm	≥45 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
Soticlestat	100 mg BID	1 tab soticlestat BID OR 5 mini tabs soticlestat BID	200 mg BID	2 tabs soticlestat BID OR 10 mini tabs soticlestat BID	300 mg BID	3 tabs soticlestat BID OR 15 mini tabs soticlestat BID
PBO	---	1 tab PBO BID OR 5 mini tabs PBO BID	---	2 tabs PBO BID OR 10 mini tabs PBO BID	---	3 tabs PBO BID OR 15 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

The study design allows virtual visits if aligned with institutional or local guidelines, via phone or via any platforms approved by local regulations, in addition to the communication platform offered through the study. Screening (Visit 1) and Visit 11 (Day 113)/early termination must be conducted in person; Visit 9 is to be conducted in person if possible but may be conducted virtually (via video or phone) in response to the coronavirus disease 2019 (COVID-19) pandemic and/or based on sponsor approval and if permitted by local regulations. In extenuating circumstances, the randomization visit (Visit 2) and Visit 11 (Day 113)/early termination can be virtual visits (only via video, not phone), with sponsor approval and if permitted by local regulations. In addition, any visit identified as a virtual visit in this protocol may be conducted in clinic and in person if requested by the subject/parent or guardian and/or at the investigator's discretion.

Dose Titration Period (4 Weeks):

Subjects will take the first dose of study drug (Dose 1) the day after the study medication is received. Approximately 7 days after initiating study medication, if there are no tolerability issues, study drug dose will be increased to Dose 2. After approximately 7 days on Dose 2, if there are no tolerability issues, study drug dose will be increased to Dose 3. If the subjects do not experience any tolerability issues, they will continue on Dose 3 for the remainder of the titration period. Subjects will only be allowed to increase their dose within the 4-week titration period before entering the 12-week maintenance period. Decrease in dose level is allowed during the titration period if required for safety and tolerability. Subjects who cannot tolerate the minimum dose of 100 mg BID (or weight-based equivalent dosing <45 kg) will be discontinued from treatment. The maximum allowed dose is 300 mg BID. The subjects/parents or caregivers will be contacted by phone within approximately 2 days following each dose escalation to assess safety and tolerability of the study drug. The final dose tolerated by the end of the 4-week titration period should be maintained until the end of the maintenance period, unless tolerability issues arise.

Maintenance Period (12 Weeks):

The dose level at the end of the titration period will be maintained until the end of the maintenance; period (dose increases are not permitted); however, during the maintenance period, the dose may be decreased by 1 dose level to the previous lower dose, for safety and tolerability issues. For example, Dose 3 may be reduced to Dose 2, and Dose 2 may be reduced to Dose 1. The minimum dose is Dose 1 (100 mg BID adult reference dose; or weight-based equivalent dosing for <45 kg); subjects who cannot tolerate the minimum dose of 100 mg BID will be discontinued from treatment. Dose changes during the maintenance period are allowed for safety or tolerability reasons as assessed by the investigator; however, if possible, dose changes will need to be discussed with the medical monitor and/or the sponsor.

Study Discontinuation/Completion:

At Visit 11/early termination, subjects will have the option to enroll in the OLE study as per that study's inclusion/exclusion criteria.

Subjects who enroll in the OLE study on the same day as Visit 11/early termination will take their final dose of double-blind study drug in the evening of the day of Visit 11/early termination and should continue to record seizures in the seizure diary until midnight of the day of Visit 11/early termination, at which time they will exit the study.

Subjects who do not roll over to the OLE study on the same day as Visit 11/early termination will take their final dose of double-blind study drug in the morning of Visit 11/early termination, followed by a taper period. The study drug dose will be tapered down to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) approximately every 3 days until the study drug dose is discontinued. The subject/parent or caregiver should continue to record seizures in the seizure diary until the safety follow-up phone call, which will occur approximately 14 days after the last dose of study drug. After completion of the safety follow-up phone call, the subject will exit the study.

Subjects/parents or caregivers who choose to enroll in the OLE study after Visit 11/early termination will continue the taper procedure until the investigator confirms eligibility for the OLE study; the subject will then exit the study and roll over to the OLE study.

Primary Objectives:

- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC as compared with placebo during the full treatment period (titration + maintenance).

For European Medicines Agency (EMA) registration:

- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.

Secondary Objectives:

To assess the following in subjects taking soticlestat as compared with placebo during the full treatment period, unless otherwise noted:

- Proportion of treatment responders defined as those with ≥50% reduction in convulsive seizures from baseline during the maintenance period and the full treatment period.
- Effect on total seizure frequency of all seizure types during the maintenance period and the full treatment period.
- Change from baseline in proportion of convulsive seizure–free days.
- Longest convulsive seizure–free interval.
- Number of days when rescue antiseizure medications (ASMs) are used.
- Effect on the Clinical Global Impression of Improvement (CGI-I) (clinician) and Caregiver Global Impression of Improvement (Care GI-I).
- Effect on CGI-I Seizure Intensity and Duration.
- Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregivers.
- Effect on Quality of Life Inventory-Disability (QI-Disability).

Exploratory Objectives:

[redacted]

Safety Objectives:

- To assess the incidence of treatment-emergent adverse events (TEAEs).
- To assess the incidence of abnormal values and change for clinical laboratory evaluations, vital signs, electrocardiogram (ECG) parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS) parameters.
- To assess the incidence of new seizure types arising during soticlestat treatment that are not identified at the time of screening (by history) or during prospective baseline.

Subject Population: Pediatric and young adult DS subjects aged ≥2 and ≤21 years, inclusive, with treatment-resistant seizures (defined as having seizures despite appropriate trials of 1 or more ASMs), and are currently on stable antiseizure therapy, including 0 to 4 concomitant ASMs.

Number of Subjects:	**Number of Sites:**
Approximately 142 male and female pediatric and young adult subjects will be randomized in a 1:1 ratio to receive soticlestat or placebo, resulting in approximately 71 subjects per arm. A minimum of 20 pediatric subjects aged 2 through 6 years will be enrolled.	Global, multicenter study to be conducted at approximately 100 sites.
Dose Level(s):	**Route of Administration:**
300 mg BID (300 mg BID equivalent dose; weight-based dosing for <45 kg) soticlestat or matching placebo	Oral or via G-tube or MIC-KEY button.
Duration of Treatment:	**Period of Evaluation:**
16 weeks (titration and maintenance)	~25 weeks (including up to 6-week screening/baseline period, 16-week double-blind treatment period [4-week titration and 12-week maintenance periods], 1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit)

Main Criteria for Inclusion:

Male or female and aged 2 to 21 years, inclusive, at the time of informed consent.

Documented clinical diagnosis of DS supported by variable combinations of typical clinical features such as those noted below. (Note: These criteria are for guidance only as the final diagnostic eligibility decision is made by TESC.)

- Onset of seizures usually in the first year of life.
- History of fever-induced prolonged seizure as determined by the investigator:
  - May include prolonged (approximately 15 minutes or longer) hemi-clonic seizures
  - Multiple seizure types, which may include:
    - Generalized tonic-clonic.
    - Focal to bilateral tonic-clonic.
    - Clonic.
    - Myoclonic seizures.
- History of developmental delay/intellectual disability presenting after onset of seizures and usually presenting after 12 months of age.
- Documented genetic mutations consistent with DS is not required, but results of genetic test will be collected if available. [redacted]

Has had ≥12 convulsive seizures over 12 weeks before screening based on the historical information and has had ≥4 convulsive seizures per 28 days during the 4- to 6-week prospective baseline period.

Weighs ≥10 kg at the screening visit (Visit 1).

Failure to control seizures despite appropriate trials of at least 1 ASM based on historical information and is currently

on an antiseizure therapy (eg, ASMs, vagus nerve stimulation, ketogenic/modified Atkins diet) or other treatment options considered as SOC.

Artisanal cannabidiols are allowed at a stable dose for at least 4 weeks before the screening visit (Visit 1); the dosing regimen and manufacturer should remain constant throughout the study. (Artisanal cannabidiols will not be counted as ASMs.)

Currently taking 0 to 4 ASMs at stable doses for at least 4 weeks before the screening visit (Visit 1); benzodiazepines used chronically (daily) to treat seizures are considered ASMs. Fenfluramine and cannabidiol (Epidiolex) are allowed where available and should be counted as an ASM. ASM dosing regimen must remain constant throughout the study.

Female subjects of childbearing potential (defined as first menarche) must have a negative pregnancy test and agree to use an effective or highly effective method of birth control during the study and for 30 days following the last dose of study drug.

Main Criteria for Exclusion:

Currently enrolled in a clinical study involving an investigational product (ie, not approved in that country, other than soticlestat) or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Note: Compatibility will be determined based on consultation with the medical monitor or the sponsor.

Participated in a clinical study involving another study drug in the last 30 days (or 5 half-lives of the study drug, whichever is longer) before screening (Visit 1).

Received soticlestat in a previous clinical study.

Known hypersensitivity to any component of the soticlestat formulation.

Admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately before screening (Visit 1). For the purpose of this exclusion criterion, status epilepticus is defined as continuous seizure activity lasting longer than 5 minutes or repeated seizures without return to baseline in between seizures.

Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality that may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the medical monitor may be warranted.

Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, within the 2 years immediately before screening (Visit 1).

Abnormal and clinically significant ECG abnormality at screening (Visit 1) or before randomization (Visit 2), including QT interval with Fridericia correction method (QTcF) >450 ms, confirmed with a repeat ECG using manual measurement of QTcF. Clinically significant ECG abnormalities should be discussed with the medical monitor.

Abnormal clinical laboratory test results at screening (Visit 1) that suggest a clinically significant underlying disease that would compromise the well-being of the subject. If the subject has a serum alanine aminotransferase and/or aspartate aminotransferase level >2.5 times the upper limit of normal (ULN), the medical monitor should be consulted.

Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug.

Criteria for Evaluation and Analyses:

Primary Endpoint:

- Percent change from baseline in convulsive seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the full treatment period.

For EMA registration:

- Percent change from baseline in convulsive seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the maintenance period.

Secondary Endpoints:

To assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period, unless otherwise noted:

- Proportion of responders, defined as those with ≥50% reduction from baseline in convulsive seizures during the maintenance period and the full treatment period.
- Responder analysis of the proportion of subjects with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, and >75% to ≤100% reduction in convulsive seizures in a cumulative response curve.
- Care GI-I (caregiver).
- CGI-I (clinician).
- CGI-I Nonseizure Symptoms.
- Change in QI-Disability score.
- CGI-I Seizure Intensity and Duration.
- Percent change from baseline in frequency of all seizures per 28 days during the maintenance period and the full treatment period.
- Percent change from baseline in convulsive seizure frequency per 28 days during the maintenance period.
- Change from baseline in proportion of convulsive seizure-free days.
- Longest convulsive seizure–free interval.
- Number of days when rescue ASM is used.

Exploratory Endpoints:

[redacted]

Safety Endpoints:

- Incidence of TEAEs.
- Incidence of abnormal values for clinical laboratory values and ECG evaluations.
- Change from baseline in clinical laboratory evaluations, vital signs, C-SSRS, and ECG parameters.
- Incidence of new seizure types arising post–study treatment initiation.

Statistical Considerations:

Efficacy Analyses

The seizure frequency will be calculated based on all data collected during the baseline and treatment periods. For all efficacy analyses on seizure frequency, baseline refers to the prospective 4- to 6-week baseline period. The efficacy endpoints will be summarized for each treatment group, and comparisons will be made between soticlestat and placebo groups. Percent change from baseline in convulsive seizure frequency per 28 days will be analyzed using rank analysis of covariance (ANCOVA) with treatment group as the main effect; age group (≤6 years, >6 years) and baseline seizure frequency will be covariates. [redacted]

Percent change from baseline in frequency of all seizures per 28 days will be compared between soticlestat and placebo using rank ANCOVA, adjusting for baseline seizure frequency and age stratum. The Hodges-Lehmann estimator and the corresponding 95% CI comparing soticlestat and placebo will also be displayed.

The proportion of responders will be analyzed using a Cochran-Mantel-Haenszel test stratified by age group (≤6 years, >6 years).

The main analysis for CGI-I (clinician), Care GI-I, CGI-I Seizure Severity and Duration, CGI-I Nonseizure Symptoms, and QI-Disability scores will be based on the responses at each subject's last visit during which these instruments were utilized. The QI-Disability scores will be analyzed with a mixed model for repeated measures, and the other scores will be analyzed using ordinal logistic regression. [redacted]

The global type I error will be controlled using a hierarchical gatekeeping procedure on the primary and secondary endpoints. The order of testing will be soticlestat versus placebo for the primary endpoint, responder rate, Care GI-I, CGI-I (clinician), CGI-I Nonseizure Symptoms, QI-Disability, and CGI-I Seizure Intensity and Duration. All statistical tests will be 2-sided at the 5% significance level. Techniques for handling missing information with respect to reporting of seizures in the treatment period and with respect to subjects who discontinue early will be specified in detail in the statistical analysis plan (SAP).

Safety Analyses

Descriptive statistics will be used to summarize all safety endpoints for each of the 2 treatment groups. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight, and ECG parameters, as appropriate.

Exploratory/Additional Analyses

[redacted]

Sample Size Justification: The study will randomize a total of approximately 142 subjects at a 1:1 ratio to receive soticlestat, or placebo, resulting in approximately 71 subjects per arm. A minimum of 20 pediatric subjects aged 2 through 6 years will be enrolled. The sample size calculation is based on the results from the ELEKTRA study (TAK-935-2002) and other similar studies on seizure frequency reduction in Dravet syndrome subjects and under the assumption of using the Wilcoxon rank-sum test. The pooled SD of the percent change from baseline in convulsive seizure frequency is 55%. It is assumed that subjects in the placebo group will experience a mean reduction from baseline in convulsive seizure frequency of 5%. A sample size of 71 subjects per treatment arm will provide at least 80% power at a 2-tailed significance level of 5% to detect a 27% difference in mean percent reduction in convulsive seizure frequency per 28 days during the 16-week treatment period between treatments (assuming subjects receiving soticlestat will experience at least a 32% mean reduction in convulsive seizure frequency).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

24HC	24*S*-hydroxycholesterol
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ASM	antiseizure medication
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
AUC	area under the plasma concentration-time curve
BID	twice daily
Care GI-C	Caregiver Global Impression of Change
Care GI-I	Caregiver Global Impression of Improvement
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CH24H	cholesterol-24-hydroxylase
COVID-19	coronavirus disease 2019
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEE	developmental epileptic encephalopathy
DMC	Data Monitoring Committee
DRF	diagnostic review form
DS	Dravet syndrome
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
EO	enzyme occupancy
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
G-tube	gastrostomy tube
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee

INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
J-tube	jejunostomy tube
LFT	liver function test
LGS	Lennox-Gastaut syndrome
MMD	major motor drop
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
OLE	open-label extension
PD	pharmacodynamic(s)
PK	pharmacokinetics
PTE	pretreatment event
QI-Disability	Quality of Life Inventory-Disability
QTc	corrected QT interval
QTcF	QT interval with Fridericia correction method
rSDV	remote Source Data Verification
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESC	The Epilepsy Study Consortium
ULN	upper limit of normal
US	United States
VNS	vagus nerve stimulation
WHO	World Health Organization

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Dravet syndrome (DS) or severe myoclonic epilepsy in infancy is one of the most well-described disorders of epileptic encephalopathies. Clinically, DS is characterized at onset by frequent convulsive febrile seizures, followed later by frequent status epilepticus and nonfebrile seizures that are mainly clonic, unilateral, and of long duration (Dravet 2011).

Soticlestat is a first-in-class small molecule inhibitor of cholesterol-24-hydroxylase (CH24H) in the brain. It is hypothesized that soticlestat treatment will decrease the levels of 24*S*-hydroxycholesterol (24HC) and improve convulsive seizure control in DS subjects. Nonclinical studies have demonstrated that soticlestat modulates the glutamatergic signaling and significantly reduces spontaneous seizure in a murine model of DS. Clinical Study TAK-935-2002 (ELEKTRA) showed efficacy of soticlestat in subjects with DS or Lennox-Gastaut syndrome (LGS).

ELEKTRA was a phase 2, multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of soticlestat as adjunctive therapy in pediatric subjects aged ≥2 and ≤17 years with LGS or DS. A total of 141 subjects were enrolled (51 with DS and 90 with LGS), and 126 completed the study. Subjects were eligible for enrollment if they demonstrated ≥3 convulsive seizures (in the DS cohort) or ≥4 drop seizures (in the LGS cohort) during a minimum of 4 weeks during the prospective baseline period (based on the seizure diary records), and they were currently on a stable regimen of 1 to 4 concomitant antiseizure medications (ASMs). This study consisted of 2 main periods, a 4- to 6-week screening/baseline period followed by a 20-week treatment period (8-week titration and dose optimization period and a 12-week maintenance period). Subjects who met the entry criteria were stratified by syndrome and randomized in a 1:1 ratio to soticlestat or matching placebo within each cohort. Subjects were dosed with oral 20 mg or 100 mg soticlestat tablets or matching placebo at 100 mg twice daily (BID) for 1 week, followed by 200 mg BID for another week, before titrating up to 300 mg BID, the maximum allowable dose. Subjects weighing <60 kg were dosed by weight.

In the DS cohort (n = 51), subjects treated with soticlestat demonstrated a 33.8% median reduction in convulsive seizure frequency compared with a 7.0% median increase seen in subjects taking placebo during the 20-week treatment period (median placebo-adjusted reduction in convulsive seizure frequency was 46.0%; p = 0.0007). The responder rate (≥50% reduction in convulsive seizure frequency compared with baseline) for subjects taking soticlestat in the DS cohort was 30.8% while for placebo was 0%. In the LGS cohort (n = 88), soticlestat decreased drop seizures by a median of 20.6% as compared with a median decrease of 6% in the placebo group (median placebo-adjusted reduction in drop seizure frequency was 14.8%; p = 0.1279) during the 20-week treatment period. Other secondary endpoints included the Clinical Global Impression of Change (CGI-C) and the Caregiver Global Impression of Change (Care GI-C). For the CGI-C, more soticlestat-treated DS and LGS subjects showed improvement than those receiving placebo (26.9% versus 8% and 27.9% versus 11.1%, respectively) as deemed by the investigator.

Caregivers also rated greater improvement in 57.7% and 51.2% of soticlestat-treated DS and LGS subjects compared with 32% and 28.9% of those receiving placebo, respectively, as assessed by the Care GI-C.

In ELEKTRA, soticlestat was generally well tolerated, and safety data were consistent with findings in previous studies. The incidence of treatment-emergent adverse events (TEAEs) was similar in the treatment and placebo groups, with 57 (80.3%) of soticlestat subjects experiencing at least 1 TEAE compared with 52 (74.3%) of placebo subjects. The most common TEAEs in the soticlestat group were upper respiratory tract infection, pyrexia, seizure, nasopharyngitis, decreased appetite, and vomiting. The most frequent TEAEs reported in soticlestat-treated subjects with ≥5% difference from placebo were lethargy and constipation. The incidence of serious TEAEs was similar in both soticlestat and placebo groups, with 11 (15.5%) in the soticlestat group experiencing at least 1 serious TEAE compared with 13 (18.6%) in the placebo group. Four soticlestat (5.6%) subjects discontinued the study compared with 3 in the placebo group (4.3%) due to TEAEs.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of soticlestat may be found in the current edition of the Investigator's Brochure (IB).

4.2 Rationale for the Proposed Study

Soticlestat has shown antiseizure efficacy in nonclinical studies, including models relevant to the rare developmental epileptic encephalopathies (DEEs) that are inadequately treated by current adjunctive antiepileptic drugs. In phase 1 studies in healthy adult subjects and in phase 1b/2a (TAK-935-2001) and phase 2 (ELEKTRA) studies in adult and pediatric subjects with DEEs, acceptable PK and safety characteristics have been observed.

Based on the efficacy, safety, and tolerability data collected in the phase 2 ELEKTRA study, combined with the safety and tolerability data from phase 1 and other completed or ongoing studies (please see the IB), soticlestat is being proposed as adjunctive therapy in pediatric and young adult subjects with DS, a highly impacted population with great unmet need. This phase 3 study will evaluate the efficacy, safety, and tolerability of soticlestat in this population. The current study is designed to further characterize the effects of soticlestat on convulsive seizure frequency by using a seizure diary in subjects with DS. Additional aims are to assess efficacy by the investigator (characterized by Clinical Global Impression of Improvement [CGI-I]) as well as by the caregivers, CGI-I in nonseizure-related symptoms, impact on quality of life, and the safety, tolerability, [redacted] of soticlestat administration in pediatric and young adult subjects with DS.

4.3 Benefit/Risk Profile

In the phase 1b/2a TAK-935-2001, phase 2 TAK-935-2002 (ELEKTRA), and open-label pilot TAK-935-18-002 (ARCADE) studies, the safety and tolerability data indicate that soticlestat was generally well tolerated in subjects with DEEs at doses up to 300 mg BID (weight-based dosing for <60 kg).

The following have been identified as important potential risks and are being closely monitored during the clinical development program:

- Neurological and psychiatric effects (clinical safety data and risks associated with compounds affecting glutamate excitotoxicity).
- Cognitive effects (soticlestat inhibition of neuronal CH24H and clinical safety data).
- Suicidal ideation or behaviors (class effect of ASMs).
- Cataracts (nonclinical data).
- Corrected QT interval (QTc) prolongation (nonclinical data).

More information about the known and expected benefits and reasonably anticipated AEs of soticlestat may be found in the current edition of the IB. This study will further examine risk and establish benefit in DS. This study will enroll subjects aged 2 to 21 years, inclusive.

DS is characterized by treatment-resistant seizures, presenting at a very young age. In addition, mortality is especially high in DS (up to 21%) (Shmuely et al. 2016), even compared with other chronic epilepsies, with a 30-fold higher rate of sudden unexpected death in epilepsy that accounts for up to 60% of deaths in these patients (Richards et al. 2018). Given the severe, profound, and chronic nature of DS and its associated signs and symptoms and their impact on quality of life, and considering the potential benefits that soticlestat treatment can confer to patients affected by DS, the benefit-risk profile is acceptable for this population.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to standard of care (SOC) as compared with placebo during the full treatment period (titration + maintenance).

For European Medicines Agency (EMA) registration:

- To assess the efficacy of soticlestat in reducing convulsive seizure frequency as add-on therapy to SOC compared with placebo during the maintenance period only.

5.1.2 Secondary Objectives

To assess the following in subjects taking soticlestat as compared with placebo during the full treatment period, unless otherwise noted:

- Proportion of treatment responders defined as those with ≥50% reduction in convulsive seizures from baseline during the maintenance period and the full treatment period.

- Effect on total seizure frequency of all seizure types during the maintenance period and the full treatment period.
- Change from baseline in proportion of convulsive seizure–free days.
- Longest convulsive seizure–free interval.
- Number of days when rescue ASMs are used.
- Effect on the Clinical Global Impression of Improvement (CGI-I) (clinician) and Caregiver Global Impression of Improvement (Care GI-I).
- Effect on CGI-I Seizure Intensity and Duration.
- Effect on the CGI-I Nonseizure Symptoms completed by clinician with input from the caregiver.
- Effect on Quality of Life Inventory-Disability (QI-Disability).

5.1.3 Exploratory Objectives

[redacted]

5.1.4 Safety Objectives

- To assess the incidence of TEAEs.
- To assess the incidence of abnormal clinical laboratory values and electrocardiogram (ECG) evaluations.
- To assess change from baseline in clinical laboratory values, vital signs, ECG parameters, and Columbia-Suicide Severity Rating Scale (C-SSRS) responses.
- To assess the incidence of new seizure types arising during soticlestat treatment that are not identified at the time of screening (by history) or during prospective baseline.

5.2 Endpoints

5.2.1 Primary Endpoints

- Percent change from baseline in convulsive seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the full treatment period.

For EMA registration:

- Percent change from baseline in convulsive seizure frequency per 28 days in subjects receiving soticlestat as compared with placebo during the maintenance period.

5.2.2 Secondary Endpoints

To assess the following in subjects receiving soticlestat as compared with placebo during the full treatment period, unless otherwise noted:

- Proportion of responders defined as those with ≥50% reduction from baseline in convulsive seizures during the maintenance period and the full treatment period.
- Responder analysis of the proportion of subjects with ≤0%, >0% to ≤25%, >25% to ≤50%, >50% to ≤75%, and >75% to ≤100% reduction from baseline in convulsive seizures in a cumulative response curve.
- Care GI-I (caregiver).
- CGI-I (clinician).
- CGI-I Nonseizure Symptoms.
- Change in QI-Disability score.
- CGI-I Seizure Intensity and Duration.
- Percent change from baseline in frequency of all seizures per 28 days during the maintenance period and the full treatment period.
- Percent change from baseline in convulsive seizure frequency per 28 days during the maintenance period.
- Change from baseline in proportion of convulsive seizure–free days.
- Longest convulsive seizure–free interval.
- Number of days when rescue ASM is used.

5.2.3 Exploratory Endpoints

[redacted]

5.2.4 Safety Endpoints

- Incidence of TEAEs.
- Incidence of abnormal clinical laboratory values and ECG evaluations.
- Change from baseline in clinical laboratory values, vital signs, ECG parameters, and C-SSRS responses.
- Incidence of new seizure types arising post–study treatment initiation.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, global, multicenter, 1:1 randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of soticlestat as an adjunctive therapy in pediatric and young adult subjects with DS. The treatment period is approximately 16 weeks. The total duration of the study is approximately 25 weeks for subjects who complete the study and choose not to roll over to the open-label extension (OLE) study. For those who roll over to the OLE study, the study duration is 3 weeks shorter.

Approximately 142 male and female pediatric and young adult subjects will be randomized.

This study consists of the following periods:

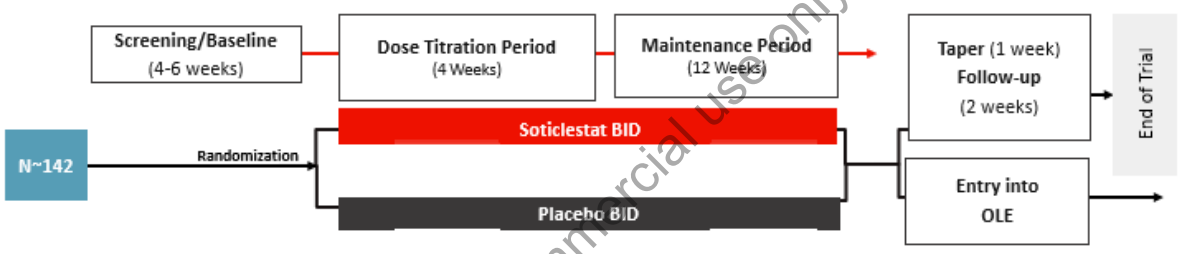
- 4- to 6-week screening/baseline period. The minimum duration for screening is 28 days (ie, Visit 2/Day 0 cannot occur earlier than 29 days after screening).
- 16-week treatment period.
  - 4-week titration period.
  - 12-week maintenance period.
- 1-week taper period for those discontinuing study drug, followed by a 2-week safety follow-up visit or phone call.

This is a 2-arm study. All subjects meeting entry criteria will be randomized at a 1:1 ratio to receive SOC plus 1 of the following adjunctive therapies: soticlestat or placebo.

Soticlestat or matching placebo added to current antiseizure therapy will be administered orally BID with or without food or via gastrostomy tube (G-tube) or low-profile gastric tube (MIC-KEY button). A jejunostomy tube (J-tube) may be considered following approval by the medical monitor or sponsor. Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.

A schematic of the study design is shown in Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



BID: twice daily; OLE: open-label extension.

All doses will be blinded; subjects on soticlestat or placebo will undergo the same titration scheme, with the same number and type of tablets (mini-tablets or tablets). Subjects randomized to placebo will undergo a mock titration to ensure the blind is maintained (see Table 6.a through Table 6.d).

The total daily dose of study drug (either placebo or soticlestat) will be calculated based on body weight at screening (Visit 1) and given BID starting on the morning after Visit 2/Day 0 (ie, on study Day 1) or on the day after receiving study medication. The dosing schedules by weight are shown in Table 6.a through Table 6.d. The minimum dose allowed during the study is 100 mg BID (weight-based dosing <45 kg). Subjects who cannot tolerate the minimum dose will be discontinued from the study. Subjects weighing <45 kg will be dispensed 20 mg mini-tablets or matching placebo. Subjects weighing ≥45 kg may be dispensed 20 mg mini-tablets or 100 mg tablets, or matching placebo.

Table 6.a Dosing Schedules by Weight, 10 to <15 kg

Treatment Arm	10 to <15 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
Soticlestat	40 mg BID	2 mini tabs soticlestat BID	60 mg BID	3 mini tabs soticlestat BID	100 mg BID	5 mini tabs soticlestat BID
PBO	---	2 mini tabs PBO BID	---	3 mini tabs PBO BID	---	5 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

Table 6.b Dosing Schedules by Weight, 15 to <30 kg

Treatment Arm	15 to <30 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
Soticlestat	60 mg BID	3 mini tabs soticlestat BID	120 mg BID	6 mini tabs soticlestat BID	200 mg BID	10 mini tabs soticlestat BID
PBO	---	3 mini tabs PBO BID	---	6 mini tabs PBO BID	---	10 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

Table 6.c Dosing Schedules by Weight, 30 to <45 kg

Treatment Arm	30 to <45 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
Soticlestat	80 mg BID	4 mini tabs soticlestat BID	140 mg BID	7 mini tabs soticlestat BID	200 mg BID	10 mini tabs soticlestat BID
PBO	---	4 mini tabs PBO BID	---	7 mini tabs PBO BID	---	10 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

Table 6.d Dosing Schedules by Weight, ≥45 kg

Treatment Arm	≥45 kg Weight Reference Dose					
	Dose 1 (Days 1-7): Adult Reference 100 mg BID		Dose 2 (Days 8-14): Adult Reference 200 mg BID		Dose 3 (Days 15-28): Adult Reference 300 mg BID	
	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini-tablets	(mg/dose)	No. Tablets/ Mini- tablets
Soticlestat	100 mg BID	1 tab soticlestat BID OR 5 mini tabs soticlestat BID	200 mg BID	2 tabs soticlestat BID OR 10 mini tabs soticlestat BID	300 mg BID	3 tabs soticlestat BID OR 15 mini tabs soticlestat BID
PBO	---	1 tab PBO BID OR 5 mini tabs PBO BID	---	2 tabs PBO BID OR 10 mini tabs PBO BID	---	3 tabs PBO BID OR 15 mini tabs PBO BID

BID: twice daily; No.: number; PBO: placebo.

The study design allows virtual visits if aligned with institutional or local guidelines, via phone or via any platforms approved by local regulations, in addition to the communication platform offered through the study. Screening (Visit 1) and Visit 11/early termination must be conducted in person; Visit 9 is to be conducted in person if possible, but may be conducted virtually (via video or phone) in response to the coronavirus disease 2019 (COVID-19) pandemic and/or based on sponsor approval and if permitted by local regulations. In extenuating circumstances, the randomization visit (Visit 2), and Visit 11/early termination can be virtual visits (only via video, not phone), with sponsor approval and if permitted by local regulations. In addition, any visit identified as a virtual visit in this protocol may be conducted in clinic and in person if requested by the subject/parent or guardian and/or at the investigator's discretion. Appendix C has additional information on virtual visits.

In the event of rescreening, the subject may not need to repeat all assessments for the screening visit (Visit 1); this will need to be discussed with the medical monitor and/or sponsor.

6.1.1 Dose Titration Period (4 Weeks)

Subjects will take the first dose of study drug (Dose 1) the day after the study medication is received. Approximately 7 days after initiating study medication, if there are no tolerability issues, study drug dose will be increased to Dose 2. After approximately 7 days on Dose 2, if there are no tolerability issues, study drug dose will be increased to Dose 3. If the subjects do not experience any tolerability issues, they will continue on Dose 3 for the remainder of the titration period. Subjects will only be allowed to increase their dose within the 4-week titration period before entering the 12-week maintenance period. Decrease in dose level is allowed during the titration period if required for safety and tolerability. Subjects who cannot tolerate the minimum dose of 100 mg BID (or weight-based equivalent dosing <45 kg) will be discontinued from treatment. The maximum allowed dose is 300 mg BID. The subjects/parents or caregivers will be contacted by phone within approximately 2 days following each dose escalation to assess safety and tolerability of the study drug. The final dose tolerated by the end of the 4-week titration period should be maintained until the end of the maintenance period, unless tolerability issues arise.

6.1.2 Maintenance Period (12 Weeks)

The dose level at the end of the titration period will be maintained until the end of the maintenance period (dose increases are not permitted); however, during the maintenance period, the dose may be decreased by 1 dose level to the previous lower dose, for safety and tolerability issues. For example, Dose 3 may be reduced to Dose 2, and Dose 2 may be reduced to Dose 1. The minimum dose is Dose 1 (100 mg BID adult reference dose; or weight-based equivalent dosing for <45 kg); subjects who cannot tolerate the minimum dose of 100 mg BID will be discontinued from treatment. Dose changes during the maintenance period are allowed for safety or tolerability reasons as assessed by the investigator; however, if possible, dose changes will need to be discussed with the medical monitor and/or the sponsor.

6.1.3 Study Discontinuation/Completion

At Visit 11/early termination, subjects will have the option to enroll in the OLE study as per that study's inclusion/exclusion criteria.

Subjects who enroll in the OLE study on the same day as Visit 11/early termination will take their final dose of double-blind study drug in the evening of the day of Visit 11/early termination and should continue to record seizures in the seizure diary until midnight of the day of Visit 11/early termination, at which time they will exit the study.

Subjects who do not roll over to the OLE study on the same day as Visit 11/early termination will take their final dose of double-blind study drug in the morning of Visit 11/early termination, followed by a taper period. The study drug dose will be tapered down to a lower dose (taper Dose 3 to Dose 2, taper Dose 2 to Dose 1) approximately every 3 days until the study drug dose is discontinued. The subject/parent or caregiver should continue to record seizures in the seizure

diary until the safety follow-up phone call, which will occur approximately 14 days after the last dose of study drug. After completion of the safety follow-up phone call, the subject will exit the study.

Subjects/parents or caregivers who choose to enroll in the OLE study after Visit 11/early termination will continue the taper procedure until the investigator confirms eligibility for the OLE study; the subject will then exit the study and roll over to the OLE study.

6.1.4 End of Study for Individual Subject

The end of study for an individual subject who does not enroll in the OLE study on the same day as Visit 11/early termination is either:

- The day of the scheduled safety follow-up phone call or visit.

OR

- Midnight of the day after Visit 11/early termination but before the scheduled safety follow-up phone call, if, in agreement with the investigator, the subject/parent or caregiver decides on that day to enroll in the OLE study.

The end of study for an individual subject who enrolls in the OLE study on the same day as Visit 11/early termination is midnight of that same day.

6.1.5 End of Study Overall

The overall end of the study is defined as the date of the last individual subject's end of study (as defined in Section 6.1.4).

6.2 Justification for Study Design, Dose, and Endpoints

6.2.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group study to further evaluate the safety, tolerability, and efficacy of soticlestat as adjunctive therapy in pediatric and young adult subjects with DS.

Randomization of subjects in the study will be stratified by age group and country. The strata for stratification by age group will be: ≤6 years and >6 years; these age-group randomization strata will be included as a fixed effect factor in the statistical model for the analysis of the primary endpoint.

The strata for stratification by country will be: China, Japan, and the rest of the world. This country stratification is planned to be implemented for an administrative reason and therefore will not be included in the primary analysis model.

During this study, subjects will continue their current ASMs; therefore, placebo was chosen as the control group to provide maximum difference between the treatment and control arms.

6.2.2 Endpoints

An ideal outcome measure for assessment of seizures should be clinically relevant, easily identifiable, and reliably counted by the parent or caregiver. The primary endpoint is percent change from baseline in convulsive seizure frequency per 28 days for those subjects on soticlestat compared with placebo during the 16-week treatment period (for EMA regions, analysis will only include convulsive seizure frequency during the 12-week maintenance period). In close cooperation with researchers in the epilepsy field and epileptologists, and in consent with The Epilepsy Study Consortium (TESC) and consistent with the International League Against Epilepsy seizure classification, the sponsor will evaluate soticlestat's effect in the percent change from baseline in convulsive seizures compared with placebo during the full treatment period (or maintenance period for EMA registration regions) as the primary efficacy endpoint using the modified intent-to-treat (mITT) analysis set.

The secondary [redacted] endpoints defined are clinically meaningful and consistent with seizure studies in similar populations. The secondary efficacy endpoints [redacted] endpoints could elucidate benefits outside of seizure reduction to demonstrate soticlestat's potential impact on overall quality of life for the subjects (QI-Disability) [redacted]

The safety-related endpoints of TEAEs, clinical laboratory test results, vital sign measurements, C-SSRS measurements, and ECG parameters selected for this study are standard methods for assessing safety and tolerability in clinical studies as well as the potential risks for soticlestat.

6.2.3 Dose

Dose selection is based on a comprehensive analysis of the safety, tolerability, PK, and PD data from 4 completed single- and multiple-dose phase 1 studies in healthy subjects; the safety, tolerability, and PK data from the phase 1b/2a study of soticlestat as adjunctive therapy in adult subjects with DEEs; and the efficacy, safety, PK, and PD data in the ELEKTRA study in pediatric subjects with DS or LGS, where the same target dose of 300 mg BID (weight-based equivalent in pediatrics) demonstrated statistically significant and clinically meaningful seizure reduction in DS subjects while maintaining a favorable safety and tolerability profile. Numerical reduction in seizure frequency was also noted in subjects with LGS.

The efficacy of soticlestat is related to CH24H inhibition and a decrease in 24HC levels in humans. The extent of CH24H inhibition required for efficacy was estimated in an animal model of epilepsy. In a mouse pentylenetetrazol-induced kindling development model, effects of soticlestat on seizure severity were associated with the degree of CH24H inhibition (Nishi et al. 2020). A 75% reduction in the severity score was associated with 90% reduction in brain 24HC levels. The minimum required 24HC lowering for efficacy was approximately 60%, yielding 40% decrease in the severity score. The 24HC lowering effect was then converted into 65% of the CH24H enzyme occupancy (EO) rate, using a model established in mice (Target occupancy evaluation for

cholesterol 24-hydroxylase (CH24H) inhibitor, soticlestat, with liquid chromatography/tandem mass spectrometry. Report number:16354). In summary, these preclinical pharmacology studies suggest that high degree of target occupancy (≥65%) and 24HC reduction (≥60%) are considered to be related to the efficacy in the nonclinical animal model.

The target dose of 300 mg BID (weight-based equivalent in pediatrics) will achieve the degree target occupancy and 24HC reduction required for efficacy. Based on a population PK/PD/EO model using data from 4 phase 1 studies in healthy subjects, the phase 1b/2a study in adult subjects with DEEs, and the TAK-935-2002 (ELEKTRA) study in pediatric subjects with DS or LGS, the 300 mg BID dose (weight-based equivalent in pediatrics) is estimated to achieve approximately 90% EO with approximately 82% decrease in 24HC level and potentially resulting in efficacy.

In addition, the same soticlestat target dose of 300 mg BID (adult reference dose; weight-based equivalent dosing for <60 kg) was administered in ELEKTRA and demonstrated clinically meaningful seizure reduction in DS subjects while maintaining a favorable safety and tolerability profile. Approximately 79% of subjects in the double-blind, randomized, placebo-controlled ELEKTRA study were able to be titrated up to and maintained on 300 mg BID (or adult weight-based equivalent) until the end of the maintenance period. Soticlestat-treated subjects with DS reported a 33.8% median reduction in convulsive seizures while those subjects receiving placebo experienced a median increase of 7.0% in convulsive seizures (median placebo-adjusted reduction in seizure frequency was 46.0%; p = 0.0007) over the 20-week treatment period. Responder rates (≥50% reduction in convulsive seizure frequency compared with baseline) for soticlestat-treated subjects with DS were 30.8% versus 0% in placebo, respectively. Soticlestat was generally safe and well tolerated at this dose in this study, and safety was consistent with previous studies with no new signals identified. The incidence of TEAEs was similar between the DS and LGS strata compared with placebo with 57 soticlestat subjects (80.3%) experiencing at least 1 TEAE compared with 52 placebo subjects (74.3%). The most frequent TEAEs reported in soticlestat-treated subjects with ≥5% difference from placebo were lethargy and constipation. The incidence of serious adverse events (SAEs) was similar in both soticlestat and placebo groups, with 11 (15.5%) in the soticlestat group experiencing at least 1 treatment-emergent SAE compared with 13 (18.6%) in the placebo group. There were no deaths reported. The combination of clinically meaningful convulsive seizure reduction and favorable tolerability and safety profile in ELEKTRA support the selection of 300 mg BID as the soticlestat target dose (adult reference dose; weight-based equivalent dosing for <45 kg BID).

Before reaching the target dose in the current study, subjects will receive the minimum soticlestat dose (ie, 100 mg BID adult equivalent dose for 1 week, followed by 200 mg BID adult equivalent dose for 1 week) in the titration phase. The goal of titration is to reach the target final dose of 300 mg BID adult equivalent dose after a 14-day titration period; the same titration regimen was evaluated in study ELEKTRA and demonstrated a favorable safety and tolerability profile in addition to clinically meaningful and statistically significant efficacy.

The weight-based equivalent dosing in pediatrics was determined using the population PK model. Simulations were conducted using body weight intervals of 1 kg, dose strengths from 40 to 300 mg using 20 mg mini-tablets and 100 mg tablets, and a BID dosing regimen. A total of 10,000

simulations of steady-state exposure (median area under the plasma concentration-time curve [AUC]) were performed. A threshold for the fraction of subjects at or above the reference value was set to 35%. Setting the percentage threshold at "35%" ensures the safety of pediatric subjects as the reference AUC values are median steady-state AUC values in adults, ie, 50% of the adult population has AUCs above the reference AUC values while no more than 35% of pediatric population will have AUCs above the reference AUC values). Furthermore, an effort has been made to keep pediatric exposure from exceeding the 90th percentile of the adult exposure. The resulting weight-based equivalent dosing in pediatrics is provided in Table 6.a through Table 6.d.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for soticlestat, such that the benefit-risk is no longer acceptable for subjects participating in the study.
- The Data Monitoring Committee (DMC) recommends that the study should be suspended or terminated.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or is otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization or first dose. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, based on discussions and approval by the medical monitor and sponsor.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject or the subject's parent or legal guardian or caregiver is capable of understanding and complying with protocol requirements including the use of digital tools, complete appropriate assessments, maintain an accurate and complete daily seizure diary and take study drug for the duration of the study.

   If the subject is living in a residential facility, a minimally possible number of staff member(s) at the facility who are the subject's primary caretaker(s) may be identified as caregivers who (per investigator's judgment) are capable of complying with protocol requirements as indicated above.

2. The subject or the subject's parent or legal guardian is willing and able to read, understand, and sign and date an informed consent form (ICF), assent form (if applicable), and any required privacy authorization before the initiation of any study procedures.

3. The subject is male or female and aged 2 to 21 years, inclusive, at the time of informed consent.

4. Documented clinical diagnosis of DS supported by variable combinations of typical clinical features, such as those noted below. (Note: These criteria are for guidance only because the final diagnostic eligibility is adjudicated by TESC.)

   - Onset of seizures usually in the first year of life.
   - History of fever-induced prolonged seizure as determined by the investigator:
     - May include prolonged (approximately 15 minutes or longer) hemi-clonic seizures.
     - Multiple seizure types, which may include:
       - Generalized tonic-clonic.
       - Focal to bilateral tonic-clonic.
       - Clonic.
       - Myoclonic.
     - History of developmental delay/intellectual disability presenting after onset of seizures and usually presenting after 12 months of age.
   - Documented genetic mutation consistent with DS is not required, but results of genetic testing will be collected if available [redacted]

5. Has had ≥12 convulsive seizures over 12 weeks before screening based on the historical information and has had ≥4 convulsive seizures per 28 days during the 4- to 6-week prospective baseline period. The seizure frequency will be calculated as:

   (total number of seizures) / (total number of days seizures were assessed) × 28.

   The total number of seizures includes only primary outcome seizure types with documentation TESC approval:

   - Hemi-clonic or focal clonic.
   - Focal to bilateral tonic-clonic.
   - Generalized tonic-clonic.
   - Bilateral clonic.
   - Convulsive status.
6. Weighs ≥10 kg at the screening visit (Visit 1).
7. Failure to control seizures despite appropriate trials of at least 1 ASM based on historical information and is currently on an antiseizure therapy (eg, ASMs, vagus nerve stimulation [VNS], ketogenic/modified Atkins diet) or other treatment options considered as SOC.
8. Artisanal cannabidiols are allowed at a stable dose for at least 4 weeks before the screening visit (Visit 1); the dosing regimen and manufacturer should remain constant throughout the study. (Artisanal cannabidiols will not be counted as ASMs.)
9. Currently taking 0 to 4 ASMs at stable doses for at least 4 weeks before the screening visit (Visit 1); benzodiazepines used chronically (daily) to treat seizures are considered ASMs. Fenfluramine and cannabidiol (Epidiolex) are allowed where available and should be counted as an ASM. ASM dosing regimen must remain constant throughout the study.
10. If using a VNS, the subject must have had VNS placed at least 3 months before the screening visit (Visit 1) with stable settings for 4 weeks; VNS parameters must remain constant throughout the study (VNS will not be counted as an ASM).
11. If on ketogenic diet (or any other diet used for treatment of epilepsy, such as modified Atkins diet), the subject must have started the diet at least 3 months before the screening visit (Visit 1), and the subject's diet should be stable for 4 weeks before the screening visit (Visit 1); the subject should continue this diet throughout the duration of the study (ketogenic diet, or any other diet for the treatment of epilepsy will not be counted as an ASM).
12. The use of felbamate is allowed provided that the subject does not meet the liver function test (LFT) exclusion criteria, the dose has been stable for at least 6 months before screening (Visit 1), and the subject has had stable liver function (as determined by serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels) and hematology laboratory tests during the course of treatment.

13. Approved to participate by the sponsor's designee (ie, TESC) based on the review of medical history and seizure classification, as well as review of electroencephalogram (EEG) and imaging results (if available and permitted by local regulations). The sponsor may be consulted if needed.
14. Female subjects of childbearing potential (defined as first menarche) must have a negative pregnancy test and agree to use an effective or highly effective method of birth control during the study and for 30 days following the last dose of study drug.

    Effective contraceptive methods include the following:

    - Double-barrier method (contraceptive sponge, diaphragm, or cervical cap with spermicidal jellies or creams PLUS male condom).
    - Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action, PLUS condom with or without spermicide.

    Highly effective contraceptive methods include the following:

    - Nonhormonal methods:
      - Intrauterine device (IUD).
      - Bilateral tubal occlusion.
      - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
      - Sexual abstinence:

        Sexual abstinence may be considered as a method only if defined as refraining from heterosexual intercourse and determined to be the usual lifestyle before entering the study with reliability of abstinence for the duration of the study participation and for 30 days after last dose of study drug.
    - Hormonal methods:
      - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months.
      - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter until she has been on the contraceptive for 3 months.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Investigator site personnel directly affiliated with this study and/or their immediate family.

   Note: Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

2. Takeda employees or immediate family members.
3. Currently enrolled in a clinical study involving an investigational product or treatment device (ie, not approved in that country, other than soticlestat), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

   Note: Compatibility will be determined based on consultation with the medical monitor or the sponsor.

4. Participated in a clinical study involving another study drug in the last 30 days (or 5 half-lives of the study drug, whichever is longer) before screening (Visit 1).
5. Received soticlestat in a previous clinical study.
6. Known hypersensitivity to any component of the soticlestat formulation.
7. Admitted to a medical facility and intubated for treatment of status epilepticus 2 or more times in the 3 months immediately before screening (Visit 1). For the purpose of this exclusion criterion, status epilepticus is defined as continuous seizure activity lasting longer than 5 minutes or repeated seizures without return to baseline in between seizures.
8. Unstable, clinically significant neurologic (other than the disease being studied), psychiatric, cardiovascular, ophthalmologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, hematopoietic, endocrine disease, malignancy including progressive tumors, or other abnormality that may impact the ability to participate in the study or that may potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the medical monitor may be warranted.
9. Any history of alcohol, opioid, or other drug use disorder, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), within the 2 years immediately before the screening visit (Visit 1).
10. Considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within 12 months before the screening visit (Visit 1). Subjects who have positive answers on item numbers 4 or 5 on the C-SSRS before dosing (Visit 2) are excluded. This scale will only be administered to subjects aged ≥6 years.
11. The following medical histories:

    a) History of HIV infection (subject who has tested positive for HIV-1/2 antibodies).

b) History of hepatitis B infection or current active infection.
Note: Subjects who have been vaccinated against hepatitis B (hepatitis B surface antibody-positive) and who test negative for other markers of prior hepatitis B infection (eg, negative for hepatitis B core antibody) are eligible.

c) History of hepatitis C infection or current active infection.
Note: Subjects who test positive for hepatitis C antibody are eligible if they have a negative hepatitis C viral load by quantitative polymerase chain reaction.

12. Abnormal and clinically significant ECG abnormality at screening (Visit 1) or before dosing (Visit 2), including QT interval with Fridericia correction method (QTcF) >450 ms confirmed with a repeat ECG using manual measurement of QTcF. Clinically significant ECG abnormalities should be discussed with the medical monitor.
13. Abnormal clinical laboratory test results at screening (Visit 1) that suggest a clinically significant underlying disease that would compromise the well-being of the subject. If the subject has serum ALT and/or AST level >2.5 times the upper limit of normal (ULN), the medical monitor should be consulted.
14. Unable to withhold the use of strong inducers of cytochrome P450 (CYP) 3A during the entire clinical trial, except for ASMs (eg, carbamazepine, phenobarbital, phenytoin) and topical preparations.
15. Use of herbal preparations (when used as an ASM) during the entire clinical trial.
16. Currently pregnant or breastfeeding or is planning to become pregnant within 30 days of the last dose of study drug.

7.3 Excluded Medications

Strong CYP3A inducers are excluded from screening (Visit 1) until the end of the follow-up visit, except for ASMs (eg, carbamazepine, phenobarbital, phenytoin) and topical preparations; refer to Appendix B for examples.

The use of herbal preparations (when used as an ASM) are not permitted.

Vaccinations are allowed; however, the medical monitor and sponsor should be informed about changes in the subject's vaccination status and document it under the concomitant medication section of the electronic case report form (eCRF).

The use of felbamate is allowed provided that the subject meets the relevant inclusion and exclusion criteria.

If the subject is using VNS, the device must have been placed at least 3 months before the screening visit with stable settings for >1 month; VNS parameters must remain constant throughout the study (VNS will not be counted as an ASM).

All medications, including vitamin supplements and over-the-counter medications, will be documented throughout the study.

Subjects are instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

7.4 Diet, Fluid, Activity Control

If the subject is on a ketogenic diet (or other diet used as antiseizure therapy, such as modified Atkins diet), they must have started the ketogenic diet at least 3 months before the screening visit (Visit 1), and their diet should be stable for 1 month before the screening visit (Visit 1); the diet should be continued throughout the duration of the study.

As the effect of a strong CYP3A4 inhibitor on the PK of soticlestat is small (<25%), consumption of the fruit and juice of grapefruit, Seville oranges, and starfruit is permitted.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the eCRF using the categories detailed in this section. For screen failure subjects, refer to Section 9.1.18.

Study subjects will be withdrawn from the study/study drug for the following reasons:

1. Failure to meet continuation criteria: Enrollment in any other clinical study involving an investigational product or enrollment in any other type of clinical trial judged not to be scientifically or medically compatible with this study.
2. Withdrawal by investigator (Note: The specific reason for discontinuation must be recorded in the eCRF, and is only to be used if no other pertinent reason for discontinuation is applicable):
   a) The investigator decides that the subject should be discontinued from the study.
   b) If the subject, for any reason, requires treatment with another therapeutic agent, discontinuation from the study occurs before introduction of the new agent.
3. Withdrawal by subject/parent or legal guardian (Note: The specific reason for discontinuation should be recorded in the eCRF and is only to be used if no other pertinent reason for discontinuation is applicable). All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded; ie, withdrawal due to a TEAE should not be recorded in this category. Similarly, lack of efficacy should not be recorded in this category.
4. Sponsor decision:
   a) The sponsor or its designee discontinues the study.
   b) The sponsor or its designee discontinues the subject's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.
   c) The sponsor or its designee stops the clinical study at a particular site.

5. Discontinuation due to AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the AE.

   If the investigator decides that the subject should be withdrawn because of an AE or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The sponsor or its designee is to be alerted immediately.

   a) LFT abnormalities: Study drug should be discontinued immediately (withdrawal of the subject from the study should be discussed with the sponsor/medical monitor) with appropriate clinical follow-up, including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status (see Section 9.3.1) if the following circumstances occur at any time during study drug treatment:

      i. Serum ALT or AST >8 times the ULN, or

      ii. Serum ALT or AST persistently >5 times the ULN that persists for more than 2 weeks, or

      iii. Serum ALT or AST >3 times the ULN in conjunction with elevated total bilirubin >2 times the ULN or international normalized ratio (INR) >1.5, or

      iv. Serum ALT or AST >3 times the ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

   b) QTcF >500 ms or an increase of QTcF >60 msec above baseline.

      Note: Study drug should be discontinued immediately (withdrawal of the subject from the study should be discussed with the sponsor/medical monitor) with appropriate clinical follow-up and confirmation by repeat ECG with manual measurement of the QTcF interval if the QTcF is >500 ms or if there is an increase of QTcF >60 msec above baseline.

   c) Greater than a 100% increase in 28-day seizure frequency from the 4- to 6-week prospective baseline period and considered by the investigator to be clinically significant worsening of the seizure frequency that is related to the study drug.

   d) Not tolerating the lowest dose of the study drug.

   e) Suicidal ideation: Subjects who experience suicidal ideation or who attempt suicide will be immediately withdrawn from the study.

6. Lost to follow-up: The subject did not attend visits, and multiple attempts to contact the subjects were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.

7. Pregnancy: Female subject of childbearing potential is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.17.

8. Other: The specific reason should be recorded in the eCRF.

9. COVID-19/pandemic: If, in the opinion of the investigator, the safety of a trial subject is at risk because the subject cannot complete key evaluations or adhere to critical mitigation steps, then the investigator should consider discontinuing that subject. In addition, for any such subject with COVID-19 diagnosis or in a pandemic circumstance, GCP for AE reporting processes will apply.
10. Noncompliance with study drug.
11. Significant protocol deviation: The discovery following randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and/or continued participation poses an unacceptable risk to the subject's health.

Subjects who discontinue the study drug and/or study early will have end-of-study procedures/early termination visit performed as shown in the schedule of assessments (Appendix A). Precise reason for discontinuation will be recorded in the eCRF; for example, instead of "withdrawal by the subject/parent or legal guardian" or "withdrawal by the investigator," a more accurate reason will need to be recorded in the eCRF if applicable (eg, discontinuation due to AEs, discontinuation due to lack of efficacy).

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to a TEAE should not be recorded in the "withdrawal by subject/parent or legal guardian" category).

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term "study drug" refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

The sponsor will supply the study sites with soticlestat 20 mg mini-tablets, soticlestat 100 mg tablets, matching placebo mini-tablets, and matching placebo tablets. Study drug will be supplied

in high-density polyethylene bottles with induction seal and child-resistant caps. Each bottle will contain a label that includes pertinent study information and caution statements.

Clinical study materials will be labeled according to the country's regulatory requirements.

All subjects will continue on SOC antiseizure therapies throughout the study.

8.1.1.2 Rescue Medication

Rescue ASMs as per SOC will be allowed throughout the study and their use recorded in the daily electronic seizure and medication diary. Rescue medication will not be supplied by the sponsor.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is dispensed or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

Please refer to the pharmacy manual for additional information related to the study drug. In instances where the protocol and pharmacy manual text conflict, the pharmacy manual text shall supersede the text in the protocol.

8.1.3 Dose and Regimen

This study involves a comparison of soticlestat to matching placebo.

The investigator or his/her designee is responsible for the following:

- Explaining the correct use of the study drug to the subject/parent or caregiver.
- Verifying that instructions are followed properly.
- Maintaining accurate records of study drug dispensing and collection.
- Returning or destroying all unused study drugs to the sponsor or its designee at the end of the study after the monitor completes final accountability and reconciliation.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical study materials. Clinical supply manager review and approval are required before proceeding.

Subject/parent or caregiver will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug so that the situation can be assessed.

All study drug provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained persons. The allocation and dispensing of the study drug will be fully documented and verified by a second person. Detailed records of the amounts of the study drug received, dispensed, and remaining at the end of the study will be maintained.

All subjects will receive study drug BID orally with or without food or via G-tube or MIC-KEY button. A J-tube may be considered following written approval by the sponsor and medical monitor.

Note: Study drug will be administered only orally for subjects enrolled in sites in jurisdictions where alternative means are not permitted.

The study site personnel will indicate how many tablets/mini-tablets should be taken per day in a separate dosing instruction. All doses will be blinded; placebo and soticlestat-treated subjects will undergo the same titration scheme with the same number/type of tablets. See Section 6.1.1 for a detailed description of the titration scheme.

Tablets/mini-tablets may be crushed and mixed well in applesauce, yogurt, or other liquid of similar consistency before dosing. The amount of applesauce, yogurt, or other liquid of similar consistency needed is dependent upon the number of tablets/mini-tablets the subject is taking. Approximately one-half teaspoon or 2.5 mL of applesauce or yogurt or other liquid of similar consistency is needed for each mini-tablet taken, and 2 teaspoons or 10 mL is needed for each tablet taken.

For subjects receiving study drug via G-tube or MIC-KEY button, study drug will be crushed and suspended in water, and the suspension will be administered via the G-tube or MIC-KEY button (or J-tube using a syringe if approved by the sponsor and medical monitor). Complete instructions for the G-tube, MIC-KEY button, or J-tube will be provided to the subject/parent or caregiver. Other medications or enteral feeds should not be given concurrently with the study drug.

Soticlestat or placebo tablets should be administered at approximately the same times each day.

[redacted]

If a subject misses a dose, the missed dose should be skipped, and the subject should continue with his/her normal dosing schedule. The scheduled dose can be administered or taken up to 4 hours after the scheduled time of dosing. If the subject/parent or caregiver remembers after 4 hours of the scheduled time of dosing, the dosing should be skipped and reported as a missed dose in their electronic daily seizure and medication diary and on the next clinic visit.

The planned daily dose and tablet count to be administered to subjects during the titration period is shown in Section 6.1. During the titration period, 2 days after each dose escalation or taper, the subject/parent or caregiver will be contacted by phone (safety check phone call) to monitor study drug compliance, to assess the tolerability and safety of the study drug, and to monitor concomitant medication use and TEAEs.

The subject or the subject's parent or caregiver should return unused study drug at each study visit to allow the investigator or designee to evaluate subject's compliance with the dosing instructions.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at doses above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated TEAEs) will be documented on an Overdose page of the eCRF to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered TEAEs. TEAEs associated with an overdose will be documented on TEAE eCRFs according to Section 10.2.1.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically, as determined by the investigator.

8.2 Study Drug Assignment and Dispensing Procedures

Sites should refer to the interactive web response system (IWRS) manual for specific instructions. The subjects will be assigned to receive their treatment according to the randomization schedule. The investigator or investigator's designee will access the IWRS at the Visit 1 (screening/baseline) to obtain the subject number. At Visit 2 (randomization), the investigator or the investigator's designee will use the IWRS to randomize eligible subjects into the study. During this visit, the investigator or designee will provide the necessary subject identifying information, including the subject number assigned at screening. The medication identification number of the study drug to be dispensed will then be provided by the IWRS. If study drug supplied is lost or damaged, the site can request a replacement from IWRS (refer to the IWRS manual provided separately). At subsequent drug-dispensing visits, the investigator or designee will again access the IWRS to request additional study drug for a subject. The medication identification number of the study drug to be dispensed will be provided by the IWRS.

8.3 Unblinding Procedures

Unblinding should only be considered for the safety of the subject. The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor or sponsor should be contacted before the study drug blind is broken to discuss the need for unblinding. If unblinding is deemed necessary by the investigator, the investigator can unblind the subject's treatment allocation using IWRS. The investigator must note the date, time, and reason for unblinding in subject's source documents.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study. The investigator should inform the sponsor that the subject was unblinded; however, they are not required to reveal to the sponsor the subject's treatment allocation.

In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from the sponsor's medical monitor for the subject to continue in the study.

When a TEAE is an unexpected, related SAE, the blind will be broken by the sponsor only for that specific subject for reporting purposes and to adhere to regional regulatory requirements for unblinding investigators. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the monitors, investigators, etc.) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to health authorities, ethics committees, and/or IRBs.

Investigators will receive only blinded information unless unblinded information is judged necessary for regulatory requirements or safety reasons.

8.4 Accountability and Destruction of Study Drugs

Drug supplies, including the number of returned tablets to sites, will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed at the site.

The investigator or designee must ensure that the study drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. The investigator or designee is responsible for ensuring that the study drug provided to the subject and returned from the subject is accounted for and noted in source documents. To document appropriate use of study drug, the investigator or designee must maintain records of all study drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee. If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Periodically, throughout and at the conclusion of the study, the monitor or a sponsor representative will conduct an inventory of unused study drug. At the completion of the study, a final study drug accountability review will be conducted before the unused study drugs are returned to the sponsor or its designee for destruction. All study drug not returned to the site by a subject must be investigated by the site and appropriately documented.

Destruction at the site, where applicable, must be in accordance with local standard practice with prior approval from the sponsor/CRO.

Please refer to the pharmacy manual for additional information related to the study drug. In instances where the protocol and pharmacy manual text conflict, the pharmacy manual text shall supersede the text in the protocol.

The site must have destruction procedures in place and be able to supply a Certificate of Destruction (COD) or similar document once destruction is completed. Sites shall also document the event in the IWRS.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of study procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

The investigational site is responsible for the consenting process. The requirements of informed consent are described in Section 15.2.

9.1.2 Historical Seizure Diary Review

Per inclusion criteria, historical seizure information will be used to support study entry. It is very common for caregivers of subjects with DS to maintain daily seizure diaries that capture both seizure type and frequency and days when no seizures occur as part of their SOC treatment regimen. A 3-month (12-week) daily historical seizure diary will be reviewed at screening (Visit 1) to determine eligibility. In the event that daily seizure diaries are not routinely maintained as part of the SOC, the investigator will be asked to review in detail with the subject/caregiver the number of seizures over the last 3 months for each seizure type and attest eligibility to the study at screening (Visit 1).

9.1.3 Seizure Identification and Diagnostic Review Forms (TESC)

Per inclusion criteria, enrollment into the study is based on a subject having ≥12 convulsive seizures during the 12 weeks preceding screening based on the historical information and having ≥4 convulsive seizures per 28 days during the 4- to 6-week prospective baseline period (Day -42 to Day -1). To confirm diagnosis, standardize seizure identification and classification, and approve seizures that will be recorded by the parent or caregiver in the electronic daily seizure and medication diary, a Seizure Identification Form (SIF)/Diagnostic Review Form (DRF) will be submitted to, reviewed by, and approved by TESC. In addition, previously prepared documents (including, but not limited to, EEG and imaging results and summary reports) may be sent to TESC as part of the SIF/DRF for diagnosis evaluation, if allowed by local regulations. Submission of these materials is expected shortly after the screening visit and needs to be approved before randomization.

All new reports of seizures (parent or caregiver descriptions) identified by the parent or caregiver after screening (Visit 1) must also be reviewed by the investigator and approved by TESC to confirm seizure classification. A new DRF must be submitted to TESC for review and approval for all new seizures and/or recurrence of past (>1 year) identified seizures throughout the course of the

study. Only seizure classification/descriptions approved by TESC will be collected in the electronic seizure and medication diary for this study.

9.1.4 Seizure Frequency

The primary efficacy measure is the percent change from baseline in convulsive seizure frequency per 28 days in subjects on soticlestat as compared with placebo during the treatment period (or during the 12-week maintenance period only for EMA registration regions). Secondary efficacy measures include the proportion of responders defined as those with a ≥50% reduction in convulsive seizures from baseline.

Seizure frequency will be collected via an electronic daily seizure and medication diary. The electronic diary will allow a 7-day window for data entry/correction by the subject/parent or caregiver. In the event of a device malfunction, the subject/parent or caregiver should contact the site as soon as possible for the back-up solution (access to web back-up) to record daily seizures and medications. The backup paper daily seizure and medication diary will be utilized to ensure compliance and reduce the incidence of missed entries only in cases when the web backup is not available. The electronic daily seizure and medication diary is an observer-reported clinical outcome assessment measure that captures seizures noted as occurring as individual seizures and seizures occurring in a cluster. Countable and uncountable seizures occurring within a cluster will be captured. Subject/parent or caregiver will be the observers and reporters in the current study. Subject/parent or caregiver will be educated on the importance to record seizures throughout the day to ensure that the daily diary assessment is completed each evening, even if no seizures occurred.

Convulsive seizures include hemi-clonic or focal clonic, focal to bilateral tonic-clonic, generalized tonic-clonic, bilateral clonic seizures, and convulsive status epilepticus.

At the screening visit (Visit 1), the subject/parent or caregiver will be provided with the electronic daily seizure and medication diary and specific instructions to ensure compliance with the seizure recording. In addition, a corresponding web backup solution and paper daily seizure and medication diary will be provided in the case of an electronic diary device malfunction. All seizure events will be recorded starting at the screening/baseline period up until the follow-up visit. At each visit, the electronic diary will be reviewed, and paper diary collected, if applicable. All entries will be reviewed by the investigator with the subject/parent or caregiver at the time of each visit to ensure proper recording. Any new seizures that may have occurred since the last visit must be reviewed by the investigator and approved by TESC via submission of a DRF. Only seizure classification/descriptions approved by TESC will be collected in the electronic daily seizure and medication diary for this study.

For the prospective baseline period, the seizure frequency will be calculated as:

(total number of seizures) / (total number of days seizures were assessed) × 28.

Seizure frequency calculated through this method will be used to confirm the eligibility.

9.1.5 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth or age, sex, Hispanic ethnicity, and race as described by the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.13).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 6 months before signing of informed consent.

All ASMs stopped prior to signing of informed consent should be recorded.

9.1.6 Height and Weight

Weight and height are to be measured while the subject is wearing indoor clothing and with shoes off. If unable to obtain height or weight, data that was obtained ≤30 days before the screening visit may be collected from other sources (eg, medical records or the subject's caregiver). The investigator must record in the source document the reason for not obtaining height or weight (eg, the subject is in a wheelchair). These data may be used to determine the weight-based starting dose.

9.1.7 Concomitant Medications and Nonpharmacologic Therapies and Procedures

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. A by-subject listing of concomitant medications will include all medications (including vaccinations) taken during the study regardless of the timing for the start of the medication. All medications started before the administration of the study drug will be included in the data but will be identified as "prior" in the listing. Only the concomitant medication use will be summarized.

The number and percentage of subjects who took at least 1 medication during the double-blind period as well as the number and percentage of subjects who took each type of medication will be presented for each treatment group. Medications will be listed according to their WHO Drug Dictionary Anatomic Therapeutic Chemical (ATC) class level 4 and preferred drug name within ATC class level 4 by decreasing frequency of incidence for all active treatment groups combined.

The list of excluded medications is provided in Appendix B.

9.1.8 Vital Sign Procedure

The following vital signs will be recorded at the times specified in Appendix A: height (cm), weight (kg), systolic and diastolic blood pressure (mm Hg), heart rate (beats/min), respiratory rate (breaths/min), and temperature (°C or °F). If clinically significant vital sign changes from screening/baseline are noted, the changes will be documented as TEAEs in the TEAE eCRF. Screening/baseline events will be documented in the Medical History eCRF. Clinical significance

is defined as any variation in vital signs that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

9.1.9 Physical Examination Procedure

A physical examination will be performed at the times specified in Appendix A. Each examination will include the following assessments: eyes; ears; nose; throat; cardiovascular system; respiratory system; gastrointestinal system; dermatologic system; musculoskeletal system; extremities; nervous system; lymph nodes; and other.

If clinically significant changes from screening/baseline are noted, the changes will be documented as TEAEs in the TEAE eCRF. Screening/baseline events will be documented in the medical history eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance and may result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

9.1.10 Neurological Examination Procedure

A separate neurological examination will be performed and results collected in the eCRF. This will include testing mental status, gait, cerebellar function, cranial nerves, motor function (including strength and reflexes), and sensation.

9.1.11 Safety Evaluations

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

The investigator remains responsible for following, through an appropriate health care option, TEAEs that are serious, considered related to the study treatment or the study, or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The following additional clinical safety monitoring and expanded evaluation by the previously established DMC for soticlestat phase 3 clinical studies to utilize the following:

- Electronic data capture (EDC) will have a specific flag that will be checked at enrollment for subjects on concomitant perampanel.
- Electronic daily seizure and medication diary will be used for the phase 3 studies. This will enable review of blinded seizure count data for subjects on concomitant perampanel (and all subjects included in phase 3).

- The contract research organization (CRO) and sponsor medical monitors will closely monitor the seizure frequency counts entered in the electronic daily seizure and medication diary for subjects on concomitant perampanel and will have a standing agenda item to review data for subjects on perampanel in the medical monitor review meetings.
- If there is a significant increase in seizure frequency rate noted for the subjects on concomitant perampanel (blinded review), an ad hoc DMC meeting will be called for an unblinded review and recommendation by the independent DMC members.
- There will be a standing agenda item for review of seizure frequency rate and safety data for all subjects on concomitant perampanel in the DMC meetings.

9.1.11.1 Ophthalmological Evaluation Procedure

An ophthalmologic evaluation will be conducted by a pediatric ophthalmologist or neuro-ophthalmologist preferably, although an adult ophthalmologist or an optometrist experienced with examining children may be allowed following discussion with the medical monitor. The ophthalmologic evaluation may include:

1. Age and developmentally appropriate quantitative visual acuity.
   a) If the subject is unable to perform quantitative visual acuity assessment due to age or developmental ability, a qualitative assessment should be attempted.
2. Bilateral red reflex test (also known as Bruckner transillumination test), to assess for lens abnormalities.
3. Postinstillation of mydriatic eye drop (cyclopentylate is contraindicated in this population with epilepsy), slit lamp (portable acceptable) examination for anterior or posterior lens opacities concerning for cataracts after adequate pupil dilation. For subjects unable to cooperate with slit lamp examination due to age or developmental ability, use of a 20-D double aspheric binocular indirect ophthalmoscopy lens or penlight is acceptable.
4. Indirect and or direct ophthalmoscopy of the optic nerve and retina after adequate pupillary dilation, preferably with a picture of the fundus.

These evaluations are to be collected at baseline (between the screening and randomization visits) and end of the study (before the last visit) for subjects who complete the 16 weeks of double-blind treatment or at the early termination visit for those subjects who do not complete (please see Appendix A).

9.1.11.2 ECG Procedure

For each subject, 12-lead digital electrocardiograms (ECGs) will be collected according to the schedule of study procedures (Appendix A). Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed when needed to ensure high-quality recordings.

ECGs will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present at the site, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the subject will be assessed by the investigator for symptoms (eg, palpitations, near syncope, syncope) and to determine whether the subject can continue in the study, and the medical monitor or the sponsor should be contacted. The investigator or qualified designee is responsible for determining if any change in subject's management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Any clinically significant finding that was not present at screening/baseline will be reported and discussed with the medical monitor or the sponsor. When there are differences in ECG interpretation between the investigator (or qualified designee) and the site/local cardiologist, the investigator (or qualified designee's) interpretation will be used for study entry and immediate subject management. The investigator (or qualified designee) must document his/her review of the ECGs printed at the time of collection.

9.1.11.3 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and specimen handling will be given in the laboratory manual.

The details for amounts of blood collected per visit and for the study are provided in Appendix G. The volumes do not exceed 3 mL/kg of body weight during any 8-week period or at any visit.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis [a]
Erythrocytes	Sodium	pH [a]
Hemoglobin	Potassium	Protein [a]
Hematocrit	Total bilirubin	Glucose [a]
	Direct bilirubin	Ketones [a]
Red blood cell indices	Indirect bilirubin	Bilirubin [a]
Mean corpuscular volume	Alkaline phosphatase	Nitrite [a]
Mean corpuscular hemoglobin	Alanine aminotransferase (ALT)	Urobilinogen [a]
Mean corpuscular hemoglobin concentration	Aspartate aminotransferase (AST)	Erythrocytes
Red cell distribution width	Gamma glutamyl transferase (GGT)	Leukocyte esterase
	Blood urea nitrogen (BUN)	
White blood cell count and differential	Creatinine	Microscopy
Neutrophils, segmented	Urea	
Lymphocytes	Calcium	
Monocytes	Phosphate	
Eosinophils	Glucose	
Basophils	Albumin	
	Protein	
Platelets	Carbon dioxide	
Mean platelet volume	Magnesium	
	Chloride	
	[redacted]	

Other Serum
Hepatitis B virus surface antigen
Hepatitis B core antibody
Hepatitis C virus antibody
Parathyroid hormone, intact
Vitamin D
Pregnancy test (female subjects only)—choriogonadotropin beta

[a] Urinalysis is the primary method. Urine dipstick may be used as a backup only. If sufficient volume of urine cannot be obtained for either central urinalysis testing or dipstick testing in clinic, per investigator's discretion, dipstick tests can be provided to parents/caregivers for home urine testing and results reported to the site for interpretation.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Local laboratories are allowed before randomization only if a screening laboratory value is missing, and after randomization only for emergent reasons, including pregnancy tests.

It is anticipated that some laboratory values may be outside of the normal value range due to the underlying disease. As in routine practice, the investigators should use their medical judgment when assessing clinical significance. Clinical significance is defined as any variation in laboratory measurements which has medical relevance, and which results in a change in medical care. If clinically significant laboratory changes from baseline are noted, the changes will be documented as TEAEs in the eCRF. The investigator will also assess the relationship to study treatment for all

clinically significant out of range values. The investigator will continue to monitor the subject with additional laboratory assessments until (1) values have reached normal range and/or baseline, or (2) in the judgment of the investigator, out of range values are not related to the administration of study drug or other protocol-specific procedures.

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase [GGT], and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 9.3.1 for the appropriate guidance on reporting abnormal liver function tests.)

If ALT or AST remains elevated >3 times the ULN on these 2 consecutive occasions the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as a TEAE (please refer to Section 9.3.1).

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.12 Documentation of Concomitant (Including ASM and Rescue) Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject/parent or caregiver over the counter. Concomitant medication is not provided by the sponsor. At each study visit, the subject/parent or caregiver will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medications including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF. Documentation will include generic or trade medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

ASMs treatments, artisanal cannabidiol use, VNS settings, and ketogenic diet should not be altered during the study.

9.1.13 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. These include clinically significant laboratory, ECG, or physical examination abnormalities noted at screening (Visit 1), according to the judgment of the investigator. The condition (ie, diagnosis) should be described and recorded in the eCRF.

9.1.14 Clinical Assessment of Suicidal Ideation and Behavior

Suicidal ideation and behavior will be assessed in children aged ≥6 years by use of the C-SSRS. The C-SSRS is a 3-part scale that measures suicidal ideation (eg, subject endorses thoughts about a wish to be dead or has other thoughts of suicide), intensity of ideation (frequency), and suicidal behavior (actually, interrupted, and aborted attempts at suicide) (Posner et al. 2011).

Two versions of the C-SSRS will be used in this study for all subjects ages 6 through 21 years: the C-SSRS Children's Screening/Baseline (recall period lifetime/12 months) and the C-SSRS Children's Since-Last-Visit.

Children who are <6 years old at the start of the study will have an unscheduled visit after turning age 6, at which time the C-SSRS Children's Screening/Baseline version will be completed. The C-SSRS Children's Since-Last-Visit version will be completed at the end of the study.

Study staff trained in the administration of the C-SSRS will assess subject suicidality using the C-SSRS, eliciting answers from the subject/parent or caregiver. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the clinical judgment of the investigator.

If a subject exhibits signs of suicidal ideation or behavior, the subject will be withdrawn as described in Section 7.5.

9.1.15 Health Outcome/Quality of Life Measures

9.1.15.1 CGI-I (Clinician)

The CGI-I Clinician) is a 7-point Likert scale that the investigator uses to rate a subject's change (improvement) in overall seizure control, behavior, safety and tolerability, after the initiation of study drug relative to baseline (before treatment with the study drug). The subject will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The investigator or designee will complete the CGI-I at the timepoints specified in Appendix A.

9.1.15.2 Care GI-I (Caregiver)

The Care GI-I is a 7-point Likert scale that the caregiver uses to rate improvement in overall seizure control, behavior, safety and tolerability after the initiation of study drug relative to baseline (before treatment with the study drug). The subject will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The parent/caregiver will complete the Care GI-I via interview at the timepoints specified in Appendix A.

9.1.15.3 CGI-I Seizure Intensity and Duration

The CGI-I Seizure Intensity and Duration instrument is used by the parent/caregiver to rate changes in intensity and/or duration of the most impactful seizures from the first assessment. The subject's symptoms will be rated as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). The parent/caregiver will complete the CGI-I seizure intensity and duration at the timepoints specified in Appendix A.

9.1.15.4 CGI-I Nonseizure Symptoms

The CGI-I nonseizure symptoms instrument is a series of single-item assessments that the investigator uses to rate improvement in the symptoms and impacts in select nonseizure domains

(including communication, alertness, and disruptive behaviors) since initiating the study drug. The subject will be rated by the investigator as follows: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), and 7 (very much worse). At baseline, a symptoms form is completed by the clinician in collaboration with the primary caregiver to assess the subject's status based on the presence of any nonseizure symptoms. The baseline form is intended to serve as a reference for the investigator and caregiver during subsequent visits when assessing change in the subject's condition pertaining to these symptoms.

The investigator or designee will complete the CGI-I Nonseizure Symptoms instrument in consultation with the primary caregiver at the timepoints specified in Appendix A.

9.1.15.5 QI-Disability (Parent/Caregiver Version)

The QI-Disability tool is a parent/caregiver-reported questionnaire that evaluates quality of life in children with intellectual disabilities (Downs et al. 2019). It contains 32 items covering 6 domains of quality of life: physical health, positive emotions, negative emotions, social interaction, leisure and the outdoors, and independence.

The parent/caregiver-reported questionnaires will be administered according to the schedule of assessments (Appendix A).

9.1.15.6 [redacted]

[redacted]

9.1.16 Contraception and Pregnancy Avoidance Procedure

9.1.16.1 Male Subjects and Their Female Partners

Male subjects are not required to use barrier contraception. Donation of sperm is not allowed during the study and within 90 days following the last administration of the study drug.

9.1.16.2 Female Subjects and Their Male Partners

Plasma pregnancy testing at screening and the subject's last clinic visit will be processed using the central laboratory. Additional pregnancy tests (serum or urine) may be performed by a local laboratory throughout the study at the investigator's discretion.

Please refer to Section 7.1 for inclusion criteria for detailed contraception requirements.

The following definitions apply for contraception and pregnancy avoidance procedures.

- A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For sterilized male partners, at least 1 year should have passed since bilateral vasectomy, and they must confirm they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy. Subjects and parents/legal guardians will be provided with information regarding acceptable methods of contraception as part of the informed consent process and will be asked to sign a consent form stating that there is clear understanding (including by the parents/legal guardian) of the requirements for avoidance of pregnancy and donation of ova during the course of the study and for 30 days after the last dose of study drug. This consent may be signed by the legally authorized representative of the subject.

Female subjects of childbearing potential must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening (Visit 1). A pregnancy test at randomization (Visit 2) is not required for eligibility if performed and confirmed negative at Visit 1 and if the investigator does not deem it necessary to repeat pregnancy test at Visit 2.

During the course of the study, subjects will receive continued guidance with respect to the avoidance of pregnancy and ova donation as part of the study procedures. A serum or urine hCG pregnancy test will also be performed at Visit 11 (Day 113)/early termination. Additional pregnancy tests (serum or urine) may be performed throughout the study at the investigator's discretion.

9.1.16.3 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study.
- Assessment of subject compliance through such questions as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late? (Even in women with irregular or infrequent menstrual cycles, a pregnancy test must be performed if the answer is "yes.")
  - Is there a chance you could be pregnant?

9.1.17 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn immediately, and the study drug should be immediately discontinued.

For female subjects, if the pregnancy occurs during administration of active study drug, eg, after Visit 2 or within 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1. For partners of male subjects, if the pregnancy occurs during the study or within 90 days after the last dose, it should be reported following authorization from the subject's partner.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.18 Documentation of Screen Failure

Investigators must account for all subjects with a signed informed consent. If the subject is found to be ineligible for the study before randomization, the investigator should record the primary reason for screen failure in the eCRF. The IWRS should be contacted as a notification of screen failure.

The primary reason for screen failure is to be recorded in the IWRS. Subjects may be rescreened after consultation with the medical monitor or sponsor.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Pretreatment event (PTE).
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Withdrawal by subject/parent or legal guardian (specify reason).
- Study terminated by sponsor.

- Other (specify reason).

Subjects may be rescreened after consultation with the medical monitor or sponsor.

9.1.19 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the study.

If the subject is found to be ineligible, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

The subject/parent or caregiver will record the study drug taken by subject daily, in the morning and evening. This module in the electronic daily seizure and medication diary is only available to the subject/parent or caregiver for entry each day, and retroactive entries are not allowed using the handheld device or web portal.

Confirmation of study drug intake and dosing will be recorded in the electronic daily seizure and medication diary on a daily basis. Any missed doses will be recorded in the electronic daily seizure and medication diary by the subject/parent or caregiver and reviewed by the site personnel. The subject/parent or caregiver will be required to bring used/unused study drug and the electronic daily seizure and medication diary device to each site visit. All subject/parent or caregiver should be re-instructed about the dosing requirements during study contacts. The authorized site personnel conducting the re-education must document the process in the subject's source records.

Missed or discrepant entries must be reconciled at the site level and must be accurately reflected in the eCRF. Sites will be asked to submit data correction request forms to correct any discrepancies regarding study medication that may pose a potential safety concern for the participant. This includes potential typographical and/or data entry errors indicating study drug overdose or underdose, etc. Sites must ensure the eCRF accurately reflects study drug administration in accordance with eCRF completion guidelines.

Subject compliance with study drug will be assessed at each visit.

Compliance will be tracked through the subject electronic daily seizure and medication diary and all entries will be reviewed by site personnel, reconciled against returned study medication with queries, as necessary.

Subjects who are significantly noncompliant will be discontinued from the study. A subject will be considered significantly noncompliant if he or she misses more than 20% of study medication during the study duration unless there is a valid reason for interruption in the study medication such as hospitalization. These cases should be discussed with the study monitor. Similarly, a subject will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

9.3 Safety Monitoring

The sponsor's medical monitor and/or pharmacovigilance physician will monitor safety data throughout the course of the study.

9.3.1 Reporting of Abnormal LFTs

If subjects experience ALT or AST >3 times the ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.1 for the appropriate guidance on reporting abnormal liver function tests.)

If a subject is noted to have elevated ALT or AST >3 times the ULN on 2 consecutive occasions, the abnormality should be recorded as a TEAE or SAE. In addition, eCRFs must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed. The investigator must contact the medical monitor for discussion of the relevant subject details. and possible alternative etiologies. The abnormality should be recorded as a TEAE (please refer to Section 10.2.1).

If a subject is noted to have ALT or AST >3 times the ULN and total bilirubin >2 times the ULN for which an alternative etiology has not been identified, a CRF must be completed and transmitted with the SAE Report form (as per Section 10.2.2). The investigator must contact the medical monitor for discussion of the relevant subject details, possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions, and continued participation in the study. Follow-up laboratory tests as described in Table 9.a must also be performed.

A consultation with a hepatologist may be considered as per investigator judgement or consultation with the medical monitor/sponsor.

9.3.2 Reporting of QTcF Interval Increase

As noted in Section 7.5, if the QTcF is >500 ms or if there is an increase of QTcF >60 msec above baseline, study drug should be discontinued immediately, and the subject should be provided with appropriate clinical follow-up. The subject's ECG findings should be confirmed by repeat ECG with manual measurement of the QTcF interval.

The investigator must contact the medical monitor for discussion of the relevant subject details, possible alternative etiologies, such as medical history/concurrent medical conditions, and continued participation in the study.

In addition, the eCRF must be completed and transmitted with the SAE Report form (as per Section 10.2.2).

If safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the DMC (see Section 11.0) can conduct additional analyses of the safety data.

9.3.3 Reporting of Perampanel Drug-Drug Interaction

To assess the potential interaction of soticlestat with perampanel, the following clinical safety monitoring and expanded evaluation will be performed:

- Investigators will perform close monitoring of the seizure frequency counts entered into the electronic daily seizure and medication diary for all subjects, including those on concomitant perampanel.
- The medical monitor and sponsor will provide blinded reviews of the electronic daily seizure and medication diary for subjects on concomitant perampanel including at the regular medical monitoring review meetings. If a significant increase in the blinded review of seizures frequency is detected, an ad hoc DMC meeting will be called for an unblinded review (see Section 11.0).

9.3.4 Reporting of Cataracts

To assess the potential for developing cataracts (see Sections 4.3 and 10.1.4), an ophthalmological evaluation will be performed (see Section 9.1.11.1). If there is a potential finding of cataract, the eCRF must be completed and the abnormality should be recorded as an TEAE/SAE of special interest following Section 10.2.2. An SAE must be transmitted with the SAE Report form (as per Section 10.2.2).

9.3.5 [redacted]

9.3.5.1 [redacted]

9.3.5.2 [redacted]

[redacted]

9.3.5.3 [redacted]

[redacted]

9.3.5.4 [redacted]

[redacted]

[redacted]

9.4 Biological Sample Retention and Destruction

If permitted by local regulations and with written consent of the subject/parent or legal guardian, the sponsor will store blood left from clinical laboratory tests for potential future research related to soticlestat and/or seizure disorders. The samples will be held for up to 15 years after the end of the study. The samples will be stored securely at sample storage facilities at the expense of the sponsor and only be identified by a unique code such that no one will be able to link the sample to a subject.

Subjects who consented to stored samples for future research can withdraw their consent and request disposal of a stored sample at any time. The site will notify sponsor of consent withdrawal. If samples have been analyzed, results may not be able to be removed from the study.

9.5 Schedule of Study Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.5.1 Unscheduled Visits

Subjects may return to the study center for unscheduled visits as needed. Unscheduled study visits can be performed when the subject has a study-related issue in between regular study visits as per investigator discretion.

The following should be performed during this visit:

- Documentation of concomitant medications.
- TEAE assessment.
- Other procedures, including dose adjustments, as deemed appropriate by the investigator.

These visits can also be performed as virtual visits, depending on the planned assessments and per the investigator's judgment (as allowed by local regulations).

9.5.2 Poststudy Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies initiated or resumed as required. However, following completion of the study, subjects will have the option to enroll in an OLE study, as per the OLE study's inclusion/exclusion criteria.

10.0 COLLECTION AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

In this study, AE refers to both PTEs and TEAEs. PTEs are AEs that started after the signing of informed consent but before receiving any study drug. TEAEs are AEs that started after the first dose of study drug.

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has been administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as AEs.

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required, or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased serum creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, radiographs) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or a TEAE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the event term recorded captures the change in the condition from baseline (eg, "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as a TEAE. Investigators should ensure that the event term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of a TEAE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs but instead will be documented on an Overdose page of the (e)CRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.1.4 AEs of Special Interest

An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

- Potential drug-drug interaction between soticlestat and perampanel leading to increased seizure frequency:

A potential drug-drug interaction with perampanel and soticlestat resulting in increased seizure frequency was noted in 3 subjects in the TAK-935-2001 study of adult subjects with DEEs. To assess this potential interaction, the following clinical safety monitoring and expanded evaluation will be performed to closely monitor seizure frequency in these subjects. (Please see Section 9.3.3.)

- Cataracts:

  During nonclinical studies, incipient posterior cortical, subcapsular lenticular cataracts of moderate grade were seen in 1 male rat at 300 mg/kg/d and in 1 female rat at 100 mg/kg/d. To assess these potential changes, a detailed ophthalmological monitoring and evaluation will be performed. (Please see Section 9.1.11.1 and Section 9.3.4.)

- Psychosis:

  During the phase 1 multiple rising dose study in healthy subjects, episodes of confusion, euphoria, and psychosis were seen at the highest dose of 600 mg/d. However, in this study subjects were not up-titrated to the target dose. Psychiatric AEs should be monitored closely by the investigator and reported based on AE/SAE criteria described in Section 10.1.3.

AEs of special interest must be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.1.5 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.9 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE (eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE).
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Dose interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or sign/symptom has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, sign/symptom, or laboratory value on the last day of the observed study period is worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "not recovered/not resolved."
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).

- Fatal – the AE is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of PTEs will commence from the time the subject/parent or legal guardian signs the informed consent to participate in the study and will continue until the subject is first administered study drug (Day 1) or until screen failure. For subjects who discontinue before study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of TEAEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection of TEAEs will continue until Visit 12 for those who do not roll over to the OLE study. For those who do roll over, routine collection of TEAEs will continue to midnight on the day of Visit 11.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing TEAEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until a satisfactory explanation for the changes is observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not applicable for PTEs).

6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

Subject diary and/or health outcome/quality of life measures will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up, if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

- A sponsor SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event.
- Regardless of causality, SAEs must be reported to the sponsor Global Pharmacovigilance department or designee, to the attention of the individual identified in the contact information list, which will be provided in the study manual, within 24 hours of becoming aware of the event. This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible within 24 hours, then a facsimile of the completed paper-based SAE form should be sent. If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of serious PTEs will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC.

11.0 STUDY-SPECIFIC COMMITTEES

Details of the DMC are captured in a DMC charter written before the start of the study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent form.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After submission of the CRFs to the sponsor, any change of, modification of or addition to the data on eCRFs should be made by the investigator with use of change and modification records of eCRFs (data clarification form) provided by the sponsor. The principal investigator must review the data clarification form for completeness and accuracy and must sign and date the form.

After the lock of the study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with the approval from the sponsor. The principal investigator must review the data change for completeness and accuracy and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The following procedure is applicable for all countries except Japan.

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), including consent to use digital tools and applications, if applicable, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The following procedure is applicable for Japanese sites only.

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in

the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator and the head of the study site to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and/or the head of the study site and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.2 Determination of Sample Size

The study will randomize a total of approximately142 subjects at a 1:1 ratio to receive soticlestat or placebo, resulting in approximately 71 subjects per arm. A minimum of 20 pediatric subjects aged 2 through 6 years will be enrolled. The sample size calculation is based on the results from the ELEKTRA study and other studies on seizure frequency reduction in subjects with DS and under the assumption of using the Wilcoxon rank-sum test. The pooled SD of the percent change from baseline in convulsive seizure frequency is 55%. It is assumed that subjects in the placebo group will experience a mean reduction from baseline in convulsive seizure frequency of 5%. A sample size of 71 subjects per treatment arm will provide at least 80% power at a 2-tailed significance level of 5% to detect a 27% difference in mean percent reduction in convulsive seizure frequency per 28 days during the 16-week treatment period between treatments (assuming subjects receiving soticlestat will experience at least a 32% mean reduction in convulsive seizure frequency).

13.2.1 Analysis Sets

13.2.1.1 ITT Analysis Set

All randomized subjects will be included in the intent-to-treat (ITT) analysis set. All ITT analyses will be based on each subject's randomized treatment assignment.

13.2.1.2 mITT Analysis Set

All randomized subjects who have received at least 1 dose of study drug and have been assessed for seizures for at least 1 day in the treatment period will be included in the mITT analysis set. All mITT analyses will be based on each subject's randomized treatment assignment.

13.2.1.3 Safety Analysis Set

All subjects who take at least 1 dose of study drug will be included in the safety analysis set. Safety analyses will be based on the medication that was administered to each subject.

13.2.2 Analysis of Demographics and Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed for enrolled subjects by treatment group and overall. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (eg, number of subjects, mean, median, SD, and range) and for such categorical variables as sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.

13.2.3 Subject Disposition

All subjects who discontinue from the study will be identified. If known, a reason for their discontinuation will be given.

13.2.4 Efficacy Analysis

The primary efficacy analysis will be performed on the mITT analysis set. The seizure frequency will be calculated based on all data collected during the baseline and treatment periods. For all efficacy analyses on seizure frequency, baseline refers to the prospective 4- to 6-week baseline period. The efficacy endpoints will be summarized for each treatment group, and comparisons will be made between the soticlestat and placebo groups. The primary objective of the study is to demonstrate that soticlestat is superior to placebo. The primary endpoint (percent change from baseline in convulsive seizure frequency per 28 days) will be analyzed using rank analysis of covariance (ANCOVA) with treatment group as the main effect; age group (≤6 years, >6 years), and baseline seizure frequency will be covariates. [redacted]

Percent change from baseline in frequency of all seizures per 28 days will be compared between soticlestat and placebo using rank ANCOVA, adjusting for baseline seizure frequency and age stratum. The Hodges-Lehmann estimator and the corresponding 95% CI comparing soticlestat and placebo will also be displayed.

The proportion of responders will be analyzed using a Cochran-Mantel-Haenszel test stratified by age group (≤6 years, >6 years).

The main analysis for CGI-I (clinician), Care GI-I, CGI-I Seizure Intensity and Duration, CGI-I Nonseizure Symptoms, and QI-Disability scores will be based on the responses at each subject's

last visit where these instruments were utilized. The QI-Disability scores will be analyzed with a mixed model for repeated measures, and the other scores will be analyzed using ordinal logistic regression. [redacted]

The global type I error will be controlled using a hierarchical gatekeeping procedure on the primary and key secondary endpoints. The order of testing will be soticlestat versus placebo for the primary endpoint, responder rate, Care GI-I, CGI-I (clinician), CGI-I Nonseizure Symptoms, QI-Disability, and CGI-I Seizure Intensity and Duration. All statistical tests will be 2-sided at the 5% significance level. Techniques for handling missing information with respect to reporting of seizures in the treatment period and with respect to subjects who discontinue early will be specified in detail in the SAP.

13.2.5 Safety Analysis

Descriptive statistics will be used to summarize all safety endpoints for each of the treatment groups. AEs will be summarized using the safety analysis set. All AEs will be coded using MedDRA. Data will be summarized using Preferred Terms and primary System Organ Classes.

Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight, and ECG parameters as appropriate.

13.2.6 Exploratory/Additional Analyses

[redacted]

13.3 Other Statistical Issues

13.3.1 Significance Levels

All statistical analyses will be 2-sided and will be tested at the 0.05 level of significance.

13.3.2 Missing or Invalid Data

Techniques for handling missing information with respect to reporting of seizures in the treatment period and with respect to subjects who discontinue early will be specified in detail in the SAP.

13.3.3 Interim Analyses

A blinded interim analysis may be performed to allow for sample re-estimation based on the pooled standard deviation of the percent change from baseline in convulsive seizure frequency per 28 days. Details will be provided in the SAP.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. With the exception of visits in China, monitoring visits can be virtual or on site, as indicated in the clinical monitoring plan. The investigator guarantees access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In case of prolonged access restrictions to external visits (study monitors) to an investigative site due to COVID-19 pandemic and wherever possible by local regulations, remote Source Data Verification (rSDV) may be considered for critical data related to subject's safety and any key variables to ensure data accuracy and integrity.

If rSDV is required, full details of the process will be included the Clinical Monitoring Plan following any applicable local guidance for secure access to remote source documents and data security provisions to protect personal data.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require

deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A protocol deviation form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

The following procedure applies to Japanese sites only:

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the United States [US] Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site (or in Japan, the head of the study site) guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix D. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the US Department of Health and Human Services (for studies including TDC Americas).

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written and electronic consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject

and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ballpoint ink in the case of written consent. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent or after the receipt of subject signature (in the case of consent) and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable.

Once signed, the original informed consent form or certified copy (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) will be maintained by the study site. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be provided to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As

permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials, may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 9.1.1).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's

designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

[redacted]

Downs, J., Jacoby, P., Leonard, H., Epstein, A., Murphy, N., Davis, E., et al. 2019. Psychometric properties of the Quality of Life Inventory-Disability (QI-Disability) measure. *Qual Life Res,* 28(3), 783-94.

Dravet, C. 2011. Dravet syndrome history. *Dev Med Child Neurol,* 53 Suppl 2, 1-6.

[redacted]

Nishi, T., Kondo, S., Miyamoto, M., Watanabe, S., Hasegawa, S., Kondo, S., et al. 2020. Soticlestat, a novel cholesterol 24-hydroxylase inhibitor shows a therapeutic potential for neural hyperexcitation in mice. *Sci Rep,* 10(1), 17081.

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., et al. 2011. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry,* 168(12), 1266-77.

Richards, K. L., Milligan, C. J., Richardson, R. J., Jancovski, N., Grunnet, M., Jacobson, L. H., et al. 2018. Selective NaV1.1 activation rescues Dravet syndrome mice from seizures and premature death. *Proc Natl Acad Sci U S A,* 115(34), E8077-E85.

Shmuely, S., Sisodiya, S. M., Gunning, W. B., Sander, J. W. and Thijs, R. D. 2016. Mortality in Dravet syndrome: a review. *Epilepsy Behav,* 64(Pt A), 69-74.

[redacted]

Appendix A Schedule of Study Procedures

Study Procedure	Screening/ Baseline Period	Double-Blind Treatment Period													Follow-up Period
		Ran-dom-izatio n	Start Dose 1	Safety Check	Dose Ti-trati on	Start Dose 2	Safety Check	Dose Ti-trati on	Start Dose 3	Safety Check					
Visit Number (Type) [a]	V1 (CV)	V2 [b] (CV)	NA [c]	V3 [d] (SCP)	V4 [c,e] (VV)	NA[c]	V5 [d] (SCP)	V6 [c,e] (VV)	NA[c]	V7 [d] (SCP)	V8 [f] (VV)	V9 [f] (CV)	V10 [f] (VV)	V11 [f] (CV)	V12 (VV or CV)
Study Day	Days -42 to -1	Day 0	Day 1	Day 3	Day 8	Day 8	Day 10	Day 15	Day 15	Day 17	Day 29	Day 57	Day 85	Day 113/ET [g,h,j,k]	Day 134 Follow-up [l]
Visit Window (days)					±2			±2			±7	±7	±7	±7	-7
Informed consent and assent (if applicable)	X														
Historical seizure calendar review	X														
Inclusion/exclusion criteria	X	X													
Randomization		X													
Demographics, medical history, medication history	X														
Seizure identification and diagnostic review form (TESC)	X														
Height, weight	X	Weight only												X	
Serum/urine pregnancy test [m]	X	X												X	
Vital signs	X	X										X		X	
Physical examination	X	X										X		X	
Neurological examination	X	X										X		X	
Ophthalmological examination [n]	X													X [n]	
12-lead ECG [j]	X	X										X		X	

Study Procedure	Screening/ Baseline Period	Double-Blind Treatment Period													Follow-up Period
		Ran-dom-ization	Start Dose 1	Safety Check	Dose Ti-tration	Start Dose 2	Safety Check	Dose Ti-tration	Start Dose 3	Safety Check					
Visit Number (Type) [a]	V1 (CV)	V2 [b] (CV)	NA [c]	V3 [d] (SCP)	V4 [c,e] (VV)	NA[c]	V5 [d] (SCP)	V6 [c,e] (VV)	NA[c]	V7 [d] (SCP)	V8 [f] (VV)	V9 [f] (CV)	V10 [f] (VV)	V11 [f] (CV)	V12 (VV or CV)
Study Day	Days -42 to -1	Day 0	Day 1	Day 3	Day 8	Day 8	Day 10	Day 15	Day 15	Day 17	Day 29	Day 57	Day 85	Day 113/ET [g,h,j,k]	Day 134 Follow-up [l]
Visit Window (days)					±2			±2			±7	±7	±7	±7	-7
Clinical laboratory tests (chemistry, hematology, and urinalysis)	X	X										X		X	
Hepatitis B virus surface antigen Hepatitis B core antibody Hepatitis C virus antibody	X														
[redacted]															
Concomitant medications review [o]	X	X		X	X		X	X		X	X	X	X	X	X
Prior ASM review	X	X													
Concomitant ASM and rescue medications	X	X		X	X		X	X		X	X	X	X	X	X
C-SSRS [p]	X	X										X		X	
Electronic daily seizure and medication diary review	X	X		X	X		X	X		X	X	X	X	X	X
CGI-I (clinician)		X									X			X	
Care GI-I		X									X			X	
CGI-I Nonseizure Symptoms		X									X			X	
CGI-I Seizure Intensity and Duration		X									X			X	

Study Procedure	**Screening/ Baseline Period**	**Double-Blind Treatment Period**													**Follow-up Period**
		Ran-dom-ization	**Start Dose 1**	**Safety Check**	**Dose Ti-tration**	**Start Dose 2**	**Safety Check**	**Dose Ti-tration**	**Start Dose 3**	**Safety Check**					
Visit Number (Type) [a]	**V1 (CV)**	**V2** [b] **(CV)**	**NA** [c]	**V3** [d] **(SCP)**	**V4** [c,e] **(VV)**	**NA**[c]	**V5** [d] **(SCP)**	**V6** [c,e] **(VV)**	**NA**[c]	**V7** [d] **(SCP)**	**V8** [f] **(VV)**	**V9** [f] **(CV)**	**V10** [f] **(VV)**	**V11** [f] **(CV)**	**V12 (VV or CV)**
Study Day	**Days -42 to -1**	**Day 0**	**Day 1**	**Day 3**	**Day 8**	**Day 8**	**Day 10**	**Day 15**	**Day 15**	**Day 17**	**Day 29**	**Day 57**	**Day 85**	**Day 113/ET** [g,h,j,k]	**Day 134 Follow-up** [l]
Visit Window (days)					**±2**			**±2**			**±7**	**±7**	**±7**	**±7**	**-7**
QI-Disability		X									X			X	
[redacted]															
Contact IWRS to obtain subject ID/medication ID/subject status [s]	X	X										X		X	
Dispense study drug		X										X		X[k]	
At-home administration of first dose of study drug (Dose 1) in the morning (continue Dose 1 through morning dose of Day 8)			X												
At-home dose adjustment to Dose 2 (continue Dose 2 through morning dose of Day 15)						X[t]									

Study Procedure	Screening/ Baseline Period	Double-Blind Treatment Period													Follow-up Period
		Ran-dom-ization	Start Dose 1	Safety Check	Dose Ti-tration	Start Dose 2	Safety Check	Dose Ti-tration	Start Dose 3	Safety Check					
Visit Number (Type) [a]	V1 (CV)	V2 [b] (CV)	NA [c]	V3 [d] (SCP)	V4 [c,e] (VV)	NA[c]	V5 [d] (SCP)	V6 [c,e] (VV)	NA[c]	V7 [d] (SCP)	V8 [f] (VV)	V9 [f] (CV)	V10 [f] (VV)	V11 [f] (CV)	V12 (VV or CV)
Study Day	Days -42 to -1	Day 0	Day 1	Day 3	Day 8	Day 8	Day 10	Day 15	Day 15	Day 17	Day 29	Day 57	Day 85	Day 113/ET [g,h,j,k]	Day 134 Follow-up [l]
Visit Window (days)					±2			±2			±7	±7	±7	±7	-7
At-home dose adjustment to Dose 3 (all subjects continue Dose 3 through morning dose of V11/ET; subjects rolling over to OLE study on same day also take Dose 3 in the evening of that day)									X [u]						
Optional in-clinic administration of study drug												X		X	
Study drug return												X		X	
Study drug accountability/ compliance				X	X		X	X		X	X	X	X	X	X
AEs	X	X		X	X		X	X		X	X	X	X	X	X

24HC: 24S-hydroxycholesterol; AE: adverse event; ASM: antiseizure medication; Care GI-I: Caregiver Global Impression of Improvement; CGI-I: Clinical Global Impression of Improvement; COVID-19: coronavirus disease 2019; C-SSRS: Columbia-Suicide Severity Rating Scale; CV: clinical visit; ECG: electrocardiogram; ET: early termination; [redacted]; hCG: human chorionic gonadotropin; ID: identification; IWRS: interactive web response system; OLE: open-label extension; [redacted] QI-Disability: Quality of Life Inventory-Disability; SCP: safety check phone call; TESC: The Epilepsy Study Consortium; V#: Visit number; VV: virtual visit.

[a] VVs are allowed if aligned with institutional or local guidelines, via phone or via any platforms approved by local regulations, in addition to the communication platform offered through the study. V1 (screening) and V11 (Day 113)/ET must be conducted in person; V9 (Day 57) is to be conducted in person if possible, but may be conducted virtually (via video or phone) in response to the COVID-19 pandemic and/or based on sponsor approval and if permitted by local regulations. In extenuating circumstances, V2 (Day 0/randomization) and V11 (Day 113)/ET can be virtual visits (only via video, not phone), with sponsor approval and if permitted by local regulations. In addition, any visit identified as VV in this table may be conducted in clinic and in person if requested by the subject/parent or guardian and/or at the investigator's discretion.

[b] The minimum duration for screening is 28 days (ie, V2 [Day 0/randomization] cannot occur earlier than 29 days after V1 [screening]). All efforts shall be made to complete all procedures at randomization visit (V2 [Day 0/randomization]). If unable to complete, reason should be captured and subject can proceed to randomization if there are no clinically significant abnormalities in screening procedures and it is thought appropriate, in the investigator's judgment. For female subjects of childbearing potential, pregnancy test at V2 (Day 0/randomization) is not required for eligibility if performed and confirmed negative at V1 (screening) and if the investigator does not deem it necessary to repeat pregnancy test at V2 (Day 0/randomization).

[c] Dose 1 is started the morning after V2 (Day 0/randomization) or the day after study medication is received. Dose 2 and Dose 3 are started the evening of dose titration (V4 [Day 8] and V6 [Day 15], respectively).

[d] Approximately 2 days after starting Dose 1 and after each dose escalation or taper and before the next visit, subjects will be contacted by phone to monitor study drug compliance, to assess the tolerability and safety of the study drug, and to monitor concomitant medication use and treatment-emergent AEs. These safety checks at V3 (Day 3), V5 (Day 10), and V7 (Day 17) are calculated as approximately 2 days after starting Dose 1, Dose 2, and Dose 3, respectively.

[e] Dates of V4 [Day 8] and V6 [Day 15] are calculated from the date of the first dose (Day 1) and the date of titration to Dose 2 (V6 [Day 15]), respectively.

[f] Dates calculated from V2 (Day 0/randomization).

[g] Subjects who do not continue into the OLE study will undergo the dose taper procedures and will then proceed to the follow-up period.

[h] Subjects who withdraw early from the study should complete all final visit procedures at V11 (Day 113)/ET.

(For legibility considerations, footnote [i] is not used.)

[j] A 12-lead ECG will be recorded at V1 (Day -42 to -1/screening), V2 (Day 0/randomization), V9 (Day 57), and V11 (Day 113)/ET and will be read locally. ECG at V1 needs to be recorded before randomization to evaluate subject's eligibility.

[k] At V11 (Day 113)/ET, subjects who do not enroll in the OLE study that day will be dispensed study drug to taper down. Subjects who enroll in the OLE study that day should take their final dose of double-blind study drug in the evening of the day of V11 (Day 113)/ET.

[l] The timing of the follow-up phone call, follow-up period, or follow-up visit will depend on the dose taper procedures followed. Visit will be eliminated for subjects enrolled in OLE.

[m] For female subjects of childbearing potential, pregnancy test at V2 (Day 0/randomization) is not required for eligibility if performed and confirmed negative at V1 (screening) and if the investigator does not deem it necessary to repeat pregnancy test at V2 (Day 0/randomization). A serum or urine hCG pregnancy test will also be performed at V11 (Day 113)/ET. Additional pregnancy tests (serum or urine) may be performed throughout the study at the investigator's discretion.

[n] Ophthalmological examination at V11 (Day 113)/ET may be conducted within a 14-day window (-14 days) before V11 (Day 113)/ET.

[o] Subjects on concomitant perampanel will undergo additional safety monitoring as per Section 9.3.3.

[p] Two versions of the C-SSRS will be used for all participants ages 6 through 21 years: the C-SSRS Children's Screening/Baseline (recall period lifetime/12 months) and the C-SSRS Children's Since-Last-Visit. Children who are <6 years old at the start of the study will have an unscheduled visit after turning age 6, at which the C-SSRS Children's Screening/Baseline version will be completed. The C-SSRS Children's Since-Last-Visit version will be completed at the end of the study.

[redacted]

[s] If additional study drug needs to be dispensed, contact IWRS and enter as an unscheduled visit.

[t] Subject takes the last dose of Dose 1 on the morning of V4 (Day 8) and the first dose of Dose 2 in the evening.

[u] Subject takes the last dose of Dose 2 on the morning of V6 (Day 15) and the first dose of Dose 3 in the evening.

Appendix B Strong CYP3A Inducers

Strong inducers of CYP3A are prohibited, except antiseizure medication. Examples of prohibited inducers are listed below. (Source: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers, Table 3-3 [inducers], accessed 06 March 2022.)

Strong CYP3A Inducers (examples)
Apalutamide
Enzalutamide
Mitotane
Rifampin
St. John's wort

Appendix C Virtual Visits and Trial Management During COVID-19 Pandemic and Other Extenuating Circumstances

The purpose of this section is to safeguard the safety of study subjects, ensure continuation of study conduct and uninterrupted maintenance of treatment, and preserve the integrity of the study, in case of a general public health crisis or pandemic, such as COVID-19, or other extenuating circumstances, such as war or natural disaster. This section addresses situations in which scheduled in-person clinic visits are not feasible due to local, regional, or national restrictions.

COVID-19 vaccination of subjects is allowed during the study.

The principal investigator holds the ultimate responsibility for the safety and well-being of study subjects and shall maintain compliance with the current local and health authority guidelines and recommendations pertaining to the pandemic. The study procedures outlined in this protocol may be modified subsequently according to any emerging or revised health authority guidelines during conduct of the trial due to the ongoing COVID-19 pandemic.

Due to the COVID-19 pandemic or other extenuating circumstances, such as war or natural disaster, study subjects may not be able to attend scheduled in-person clinic visits as per protocol. All investigational sites should follow local and country health and government authorities' restrictions and recommendations on conduct of clinical trials during the event. Sites are encouraged to discuss subjects and their continued virtual participation with the medical monitor.

In the event an in-person visit is not possible for the planned clinic visits and in alignment with institutional or local guidelines, comfort level of site staff, and caregiver/family willingness to travel, virtual visits are allowed to monitor subject safety. Additional details around such virtual visits are provided in Appendix A.

The virtual visits identified in Appendix A, if aligned with institutional or local guidelines, to ensure a point of contact between subjects/parents/caregivers and site staff, can be conducted via phone or via any platforms approved by local regulations, besides the communication platform offered through the study. This flexibility of communication is not expected to negatively affect subject safety or study data integrity.

In addition, the virtual visits included in the study, if aligned with institutional or local guidelines, can be converted into clinic visits at the request of subjects or parents/caregivers or at investigators' discretion to lessen the burden of the study and support investigators, subjects, and parents/caregivers, particularly during the COVID-19 pandemic or other extenuating circumstances, such as war or natural disaster. This conversion is not expected to negatively affect subjects' safety or study data integrity.

A decentralized clinical trial platform may be used to conduct the virtual visits, if permitted by local regulations. The site will ensure that any related subject data privacy aspects are appropriately managed and will obtain subjects' consent for the use of the platform for virtual visits.

If necessary and in alignment with institutional or local guidelines and as allowed by local regulations, a virtual visit can be conducted as a phone visit instead. Likewise, if necessary, the site can use the site's own platform or phone/tablet social media apps in place of virtual visits.

In case subjects are not able to attend the planned clinic visits, Direct to Patient (DTP) study drug shipment may be considered using a specialized courier vendor, if in alignment with institutional or local guidelines and as allowed by local regulations. A process has been put in place to ensure shipment traceability, proper temperature control conditions, study drug return and accountability should be properly managed to ensure that any related subject data privacy aspects are appropriately covered. The investigator will obtain subject's consent to DTP study drug shipment and the use of their personal data to that effect.

Any protocol deviations, missing visits, or missing assessments related to COVID-19 restrictions will be recorded and reported in the clinical study report.

In case of prolonged access restrictions to external visits (study monitors) to an investigative site due to COVID-19 pandemic and wherever possible by local regulations, remote Source Data Verification (rSDV) may be considered for critical data related to subject's safety and any key variables to ensure data accuracy / integrity.

If rSDV is required, full details of the process will be included the Clinical Monitoring Plan following any applicable local guidance for secure access to remote source documents and data security provisions to protect personal data.

Appendix D Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If a consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including (e)CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix E Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written ICF, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative (parent or legal guardian) may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative (parent or legal guardian) will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the ICF or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for subjects, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use effective or highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study, and for 30 days following the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued, and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male partners of female subjects must use effective or highly effective contraception (as defined in the informed consent) if required as part of the method (eg, double-barrier, vasectomized partner) from signing the informed consent throughout the duration of the study, and for a minimum of 30 days following the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix F Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix G Blood Volumes

The amount of blood collected from subjects at any single visit and at all scheduled visits during the study (including screening and post randomization treatment period) will be the volumes as shown in the table for the respective weight categories. Additional blood may be drawn for retests or unscheduled visits, if any, and will not exceed the volume indicated for each weight group. Additional blood may be drawn for retests or unscheduled visits, if any, and will not exceed 30 mL per visit.

Blood Sample Volumes (mL) by Visit and Subject Weight

Subject Weight	Screening, Visit 1 [a]	Randomization, Day 0, Visit 2	Day 57, Visit 9 [a]	ET, Visit 11 (Day 113) [a]	Total, Scheduled Visits	Unscheduled/ Retest [b]
10-15 kg	21.5	5.3	14.6	14.6	56.0	21.5
>15-45 kg	26.1	7.0	18.3	20.0	71.4	26.1
>45 kg	30.0	9.0	22.0	23.5	84.5	30.0

See the laboratory manual for details.

ET = early termination.

[a] Blood volumes may vary slightly if performed by a local laboratory or by central antiseizure medication testing laboratory in China.

[b] Unscheduled retests are allowed at investigator discretion. Scheduled and unscheduled blood sample volumes must not exceed 3 mL/kg of body weight during any 8-week period or in any single day.

Weight is measured to 1 decimal place for determining dosing bands. Thus, 44.9 kg would be in the 30 to <45 mg band.

These volumes represent the approximate maximum for visit and weight. [redacted] These volumes do not exceed 3 mL/kg of body weight during any 8-week period or in any single day.

Appendix H Protocol History

Date	Amendment Number	Amendment Type	Region
22 April 2022	Amendment	Substantial	Global
03 November 2021	Amendment 1 FR-IT-RS v1	Substantial	France, Italy, Serbia
23 March 2021	Initial protocol	Not applicable	Global

Protocol Amendment 1 FR-IT-RS v1 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment FR-IT-RS v1. The primary reason for this amendment is to indicate approximate blood volumes during the study.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only and are not captured in the following table. The following table summarizes the changes.

Protocol Amendment FR-IT-RS v1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 1.2 Approval	Changed personnel for signatures.	New assignments.
2	Section 2.0 STUDY SUMMARY, Study Design, Exploratory Objectives Section 5.1.3 Exploratory Objectives Section 6.2.2 Endpoints Section 9.1.15.6 [redacted]	[redacted]	Clarification.
3	Section 6.1.4 End-of-Study	Added definition of end-of-study.	Health authority request.
4	Section 9.1.11.3 Procedures for Clinical Laboratory Samples	Indicated the maximum volume of blood collected at any single visit and the total volume of blood collected in the study.	Health authority request.
5	Section 9.3.5.1 [redacted] Section 9.3.5.2 [redacted] Section 9.3.5.3 [redacted]	[redacted]	Clarification.
6	Appendix B Strong CYP3A Inducers and CYP3A4 Inhibitors	Updated table with additional examples of CYP3A inducers/CYP3A4 inhibitors.	Correction to maintain consistency with protocols TAK-935-3001 and TAK-935-3003.

Protocol Amendment FR-IT-RS v1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
7	Appendix C Trial Management During COVID-19 Pandemic	Revised language regarding conditions under which virtual visits are allowed.	Clarification.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	27-Apr-2022 13:49 UTC
[redacted]	Clinical Science Approval	27-Apr-2022 17:46 UTC