Janssen Research & Development *

Clinical Protocol

A Randomized, Active-Controlled, Open-Label, Flexible-Dose Study to Assess the Safety and Tolerability of Topiramate as Monotherapy Compared with Levetiracetam as Monotherapy in Pediatric Subjects with New or Recent-Onset Epilepsy

Protocol TOPMATEPY4067; Phase 3

Amendment INT-6

RWJ-17021-000 (topiramate)

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EudraCT NUMBER: 2012-001552-19

Status: Approved
Date: 3 November 2017
Prepared by: Janssen Research & Development, LLC
EDMS No & Version: EDMS-ERI-21111756, 14.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	21 November 2013
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Amendment INT-3	15 October 2014
Amendment INT-4	10 July 2015
Amendment INT-5	24 August 2017
Amendment INT-6	3 November 2017

Amendments are listed beginning with the most recent amendment.

Amendment INT-6 (03 November 2017)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall objective of this amendment is to include minor changes and corrections for consistency within the protocol, and to align the protocol with the sponsor's current protocol template.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that tapering off of treatment after study completion or at early withdrawal is not mandatory linked to the use of study drug but is also possible with commercially available product.	
6. Dosage and Administration; 9.1.1. Overview	The term "study drug" was replaced by the generic drug name "topiramate or levetiracetam" to allow the use of commercially available drug for tapering off.
Rationale: To clarify that the decision regarding subects' eligibility to participate in the optional Post Study Follow-up phase is based on local dual energy x-ray absorptiometry (DEXA) scan results (change in Z-score of -0.5 or greater). This is because the central DEXA scan results are available only with delay, and the decision should be made on the day of the regular M12 visit.	
3.1 Overview of Study Design; 9.1.1. Overview	The statement "… based on local DEXA scan results …" was added.
Rationale: Changes were made to align the protocol text per the sponsor's current protocol template.	
17.11. Use of Information and Publication	Outdated text regarding Authorship of publications resulting from this study was updated to reflect changes to the International Committee of Medical Journal Editors (ICMJE) Recommendations.
Rationale: Minor errors were noted.	
Throughout the protocol	Abbreviations were updated per the sponsor's style guide

Applicable Section(s)	Description of Change(s)
Protocol amendment table, Amendment INT-5 (24 August 2017)	The 24-hour urine collection was moved from Baseline/W1 visit to Screening period. This change in timing of urine collection was made in the synopsis (safety evaluations), but, it was not captured in amendment table of Amendment INT-5.

Amendment INT-5 (24 August 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does impact the scientific value of the trial.

The overall reason for the amendment: The overall objective of this amendment is to improve a slower-than-expected study enrollment. At the current rate of subject randomization, the previously agreed-upon milestone for the study completion will not be met. Two major revisions, which should lead to a higher enrollment rate without impacting the overall study objectives and data analysis, will be implemented in this amendment:

- The inclusion criterion # 2 will be expanded to allow a higher number of seizures within a longer period prior to subject enrollment – from "up to 2 seizures within the last 3 months" to "up to 10 seizures within the last 5 months" – and
- An optional use of local laboratory evaluations as basis for randomization (in addition to the mandatory central laboratory evaluation), although the central laboratory evaluation results will be used for change-from-baseline analyses. The optional use of a local lab for the evaluation of 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Parathyroid hormone (intact) and IGF-1 might significantly reduce the duration of the screening period and consequently might increase the enrollment rate. Investigators have objected that a screening period of up to 28 days before initiating a drug treatment for new-onset, pediatric seizure disorder is not a reasonable waiting period for the subjects, their parents, and treating/referring physicians. It is expected that a shorter minimum screening period will improve the enrollment rate.

In addition, minor changes were included to specify the use of local DEXA scan results for deciding about the subject's eligibility to participate in the optional Follow-Up phase, and a clarification that the screening period should start no more than 35 days before baseline, instead of "28 ± 7 days", and may be as short as possible if all appropriate screening assessments will have been completed.

Applicable Section(s)	Description of Change(s)
Synopsis, Study Population; 3.1 Overview of Study Design; 4.1 Inclusion Criteria, Criterion #2	Inclusion criterion #2 was revised to specify that subjects should have at least 1, but no more than 10, unprovoked seizures during the 5 months prior to screening.

Rationale: The expansion of inclusion criterion #2 increases the number of eligible study participants and might lead to an increased enrollment rate without hazarding the study objectives. By allowing subjects to have at least 1 seizure, but no more than 10 seizures in 5 months (that is, a seizure frequency of approximately no greater than 2 seizure episodes per month), the loss of prospective subjects will be reduced, while the expected efficacy of monotherapy, using either of the two study drugs, would not be adversely affected. Moreover, this revision is expected not to change the treatment that each patient would otherwise receive if the patient were to receive treatment outside of the study.

Rationale: To reduce the duration of the screening period and, in consequence, a potential reduction of the time before the study drug treatment can be initiated.

Applicable Section(s)	Description of Change(s)
Time and Events Schedule, footnote " k"; 9.1.1 Study Procedures, Overview, Table 2, footnote "a", footnote "c"; 9.3 Safety Evaluations, Clinical Laboratory Tests	An optional use of a local laboratory is allowed at screening for the decision regarding subject randomization for the following parameters: 25-hydroxy-vitamin D; 1,25-dihydroxy-vitamin D; Parathyroid hormone (intact); and IGF-1. To reduce the duration of the screening phase, one or more of these laboratory parameters may be evaluated at the local laboratory, at the discretion of the investigator. In such instance, the local laboratory instructions should be followed and local reference ranges should be applied. The local laboratory results should be used for decision regarding randomization. The central laboratory evaluation results will still be obtained and will be used for change-from-baseline analyses. The additional use of a local laboratory might lead to an increase in blood volume to be drawn from the subject at screening.

Rationale: To ensure that the initial 24-hour urine collection will be completed before initiation of study drug therapy and the 24-hour urine collection at Month-12 during study drug therapy.	
Time and Events Schedule, footnote "m"; 9.3 Safety Evaluations, Clinical Laboratory Tests	The 24-hour urine collection was moved from Baseline/W1 visit to Screening period. It should be ensured that the initial 24-hour urine collection is completed before study drug therapy is initiated. Additionally, it is clarified that the 24-hour urine collection at Month 12 should be completed before the Month-12 visit as this evaluation should be obtained during study-drug therapy.

Rationale: To clarify that tapering off of treatment after study completion or at early withdrawal is not mandatory linked to the use of study drug but is also possible with commercially available product.	
3.1 Overview of Study Design, Posttreatment Phase; 9.1.4 Posttreatment Phase (Follow Up)	The term "study drug" was replaced by the generic drug name "topiramate or levetiracetam" to allow the use of commercially available drug for tapering off.

Rationale: To clarify that the screening phase is any period up to 35 days. The previous Time and Event Schedule described a screening phase of 21 to 35 days (28 ±7days). A screening phase of less than 21 days is desirable and this is reflected in the updated Time and Event Schedule.	
Time and Events Schedule Synopsis, Overview of Design; 3.1 Overview of Study Design; 9.1.1 Overview; 9.1.2 Screening Phase	The screening phase with study day -28 including a study day window of ±7days was changed to study day ≤-28 including a study day window of -7 days (ie, day -35).

Rationale: To clarify that the decision regarding subects' eligibility to participate in the optional Post Study Follow-up phase is based on local DEXA scan results (change in Z-score of -0.5 or greater). This is because the central DEXA scan results are available only with delay, and the decision should be made on the day of the regular M12 visit.

Applicable Section(s)	Description of Change(s)
Synopsis, Overview of Study Design; Time and Events Schedule, footnote "b"; 3.1 Overview of Study Design, Post Study Phase (Follow Up); Figure 1: Study Diagram, footnote "a"; 9.1.5 Post Study Phase (Follow Up).	The statement "… based on local DEXA scan results …" was added.

Amendment INT-4 (10 July 2015)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to respond to health authority feedback requesting a more specific definition of age at which to conduct Tanner staging. Also the eligibility criterion for vitamin D level at screening was revised, and text was clarified for other study eligibility criteria and procedures.

Applicable Section(s)	Description of Change(s)
Rationale: Systematically conducting Tanner staging at a sufficiently early age ensures that all children who may be exhibiting pubertal changes earlier than expected will be identified. This change was requested by the US health authority.	
Synopsis, Safety Evaluations; Time and Events Schedule footnote "n"; Sec. 9.3. Safety Evaluations, Physical Examination	Text was added to clarify that Tanner staging is to be conducted uniformly in subjects of age 8 years and above.
Rationale: To ensure consistency of seizure counting for determination of study eligibility.	
Sec. 4.1., Inclusion Criteria	Inclusion criterion #2 was revised to specify that unprovoked seizure clustering that occurs within a 24 hour period is to be considered as a single unprovoked seizure. This is in accordance with International League Against Epilepsy (ILAE) clinical definitions.[16]
Rationale: To ensure correct units are applied to the collection of WBC and neutrophil counts for determination of study eligibility.	
Sec. 4.2., Exclusion Criteria	Exclusion criterion #17 was corrected to show the units for WBC count and neutrophil count to be per μL.

Applicable Section(s)	Description of Change(s)
Rationale: The threshold of clinical concern for 25-hydroxy-vitamin D is the deficiency threshold (<12ng/mL [<30 nmol/L]).[19,42]	
Sec. 4.2., Exclusion Criteria	Exclusion criterion #17 was revised to define the threshold of clinical concern for 25-hydroxy-vitamin D.
Rationale: To clarify that the 7-day window allowed for scheduling study visits applies to all visits.	
Time and Events Schedule	A row was added to depict that the "± 7day" window applies to all study visits.
Rationale: To ensure that source data is collected correctly and, with regard to height, to clarify the blinded manner in which it is to be obtained.	
Sec. 5., Treatment Allocation and Blinding; Sec 9.3., Safety Evaluations, Physical Examination; Sec. 17.4., Source Documentation	Text was edited to state that the specified parameters would be recorded in source documents first and then entered into the CRF, and text was added to clarify how how height measurements is to be obtained so as to remain blinded.
Rationale: To clarify that venous ammonia is to be analyzed by the central laboratory in countries where local testing is not available.	
Sec. 9.1.1., Table 2, footnote "b"; Sec. 9.3., Safety Evaluations, Clinical Laboratory Tests	The clinical laboratory tests will be performed by the central laboratory, except venous ammonia, which will be evaluated locally (except in select countries where local testing is not possible, in which case the central laboratory will also evaluate venous ammonia).
Rationale: To clarify and maintain consistency within the protocol regarding the timing and volume of blood collection for venous ammonia.	
Sec. 9.1.1., Table 2	Table 2 (Volume of Blood to be Collected From Each Subject (mL)) was revised to reflect a blood draw volume of 1.2 mL for venous ammonia at Month 1 for a corresponding total blood volume of 7.2 mL collected during the study. Accordingly, also in Table 2, total blood volumes were revised at Month 1 and during the study to 4.7 mL and 45.8 mL, respectively. Text in Sec. 9.1.1. was revised to reflect a total blood volume of 44.7 mL collected during the study. For adolescent girls who require serum pregnancy test at screening, text was revised to reflect a total blood volume of 45.8 mL collected during the study.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify and maintain consistency within the protocol regarding the timing of serum biochemical assessments of bone metabolism and DEXA scans.	
Sec. 9.3., Safety Evaluations, Bone Mineralization	Text was revised to reflect that serum biochemical assessments of bone metabolism are to be obtained at *screening*, Month 6 and Month 12/early withdrawal, and DEXA scans are to be obtained at *baseline*, Month 6 and Month 12/early withdrawal.
Rationale: To clarify that C-SSRS is to be administered for subjects 6 to 15 years of age.	
Time and Events Schedule, footnote “x”; Sec. 9.3., Safety Evaluations, Suicidality	Text was revised in Sec. 9.3 to state that C-SSRS will be administered for subjects 6 to 15 years of age and a footnote was added to the Time and Events Schedule to clarify the ages for which to administer C-SSRS.
Rationale: Concern that, in certain countries, the current protocol language would disagree with local product handling instructions on the study drug label.	
Sec. 14.4., Preparation, Handling and Storage	Revised language to delete specific storage parameters and add *"All study drug should be stored and handled per the labelled storage conditions."*
Rationale: To clarify that ECG data would not be transmitted directly to the sponsor's database from a central laboratory.	
Sec. 17.6, Data Quality Assurance/Quality Control and Sec. 17.11., Use of Information and Publication	Text was revised to remove that ECG data would be transmitted directly to the sponsor's database from a central laboratory.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-3 (15 October 2014)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to change the phase of the study from Phase 4 to Phase 3, due to investigational monotherapy dosing for study medications in some countries, and to add a subspecialty referral for clinically important reductions in bone mineral density Z-score.

Applicable Section(s)	Description of Change(s)
Rationale: Since topiramate and levetiracetam are not approved in all pediatric age groups as monotherapy in all countries in which the study is being conducted, the study is being changed from Phase 4 to Phase 3.	

Applicable Section(s)	Description of Change(s)
Title page	Phase of the study changed from Phase 4 to Phase 3.

Rationale: For subjects with a clinically relevant drop in bone mineral density Z-score, a consultation may be recommended at the discretion of the investigator to assess the subject and guide potential management of the case.	
Sec. 9.3, Safety Evaluations, Bone Mineralization	Language added for the investigator to make an appropriate referral (ie, subspecialty consult) for further evaluation of subjects who develop treatment-emergent clinically significant bone mineral density Z-scores (at 6 month or 12 month measurement).

Rationale: To provide consistent interpretation of all renal ultrasound results (ie, screening, 6- and 12-month results) in all patients across sites, central rather than local readings will be performed.	
Time and Events Schedule; Sec. 9.3, Safety Evaluations, Renal Stone Evaluation	Text changed to indicate that renal ultrasounds will be read and interpreted centrally rather than locally (local reading at the screening visit is acceptable to determine eligibility for study enrollment), and that both the technician administering the text and the central and local readers are blinded to study drug treatment.

Rationale: Clarified that subjects will not be discontinued from the study for exceeding currently labeled, maximum recommended doses if higher doses are required for optimal clinical effect, as judged by the investigator. In the event a subject takes a higher-than-recommended dose, their data collected while receiving higher doses may be analyzed separately. Higher doses could possibly confound safety evaluations including DEXA scans, laboratory tests (eg, bicarbonate), and renal ultrasounds (eg, increased nephrolithiasis).

Synopsis; Section 6, Dosage and Administration	Added language that subjects will not be discontinued from the study if recommended maximum doses of study medication are exceeded. For any subject that exceeds the maximum recommended daily dose, data collected subsequent to the use of higher doses may be analyzed in a secondary analysis for each safety outcome of interest.

Rationale: Evaluation of concomitant medications at screening visit is needed to determine if subjects meet inclusion/ exclusion criteria regarding whether they are treatment naïve or have previous treatment with AEDs.	
Time and Events Schedule	Added evaluation of concomitant medications at screening visit.

Rationale: To provide flexibility in the Data Monitoring Committee (DMC) meeting frequency according to the needs of the study.	
Sec. 11.5 Data Monitoring Committee	Change DMC meetings from minimally on a quarterly basis to minimally on a semiannual basis.

Rationale: Updated versions of Habitual Activity Estimation Scale (HAES) and Child Behavior Checklist (CBCL) scales added to protocol.	
Attachment 1	Replaced HAES with updated version available from vendor.
Attachments 6 and 7	Replaced CBCL-Preschool and CBCL-School Age with updated versions (scales were edited to meet the needs of this study - revised to remove irrelevant sections and open-ended questions).

Applicable Section(s)	Description of Change(s)
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-2 (23 April 2014)

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to revise the blood draw volume to accommodate a larger volume required for 1,25-dihydroxy-vitamin D; HIV and hepatitis serology at screening have been removed to keep blood volume at a minimum.

Applicable Section(s)	Description of Change(s)
Rationale: Blood draw volume revised to accommodate a larger volume required for 1,25-dihydroxy-vitamin D; HIV and hepatitis serology at screening have been removed to keep blood volume at a minimum.	
Time and Events Schedule; 4.2. Exclusion Criteria; 9.3. Safety Evaluations	HIV and hepatitis serology at screening removed.
9.1.1. Overview	Blood volume revised.
Rationale: Added description of visual field defects reported with topiramate.	
1. Introduction, Safety Issues of Clinical Concern, Vision Abnormalities	Added description of visual field defects reported with topiramate.
Rationale: Study procedures clarified.	
Time and Events Schedule; 3.1. Overview of Study Design, Screening Phase; 9.1.3. Open-Label Treatment Phase; 9.3. Safety Evaluations	Parents of each subject will record the description, rather than the type, of seizure in the seizure diary.
3.2.Study Design Rationale	Description of approved uses for levetiracetam revised for consistency with Section 1.1, Comparator Agent.
5. Treatment Allocation and Blinding; 15. Study-Specific Materials	Interactive system will be web-based (IWRS), rather than IVRS.
9.1.1. Overview	Clarification added that higher blood volume will be required for adolescent girls who require serum pregnancy test at screening.
9.1.1. Overview; 9.3. Safety Evaluations	Clarification added that venous ammonia will be evaluated locally.
9.1.3. Open-Label Treatment Phase	Deleted statement that investigator or study personnel will describe the different types of seizures to be recorded in the seizure diary; this is no longer applicable with the current setup of the diary.
15. Study-Specific Materials	Worksheet for NEPSY II and other scales added.

Applicable Section(s)	Description of Change(s)
16.2.3. Informed Consent	Language added that assent will be obtained from subjects typically 7 years and older, for consistency with language later in the section.
16.2.5. Country Selection	Clarification that the study will only be conducted in those countries where topiramate and levetiracetam are commercially available for the treatment of epilepsy.
17.4. Source Documentation	Added C-SSRS to assessments that will be recorded separately from the CRF and be considered source data.

Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (11 March 2014)

The overall reason for the amendment: The overall reason for the amendment is to clarify exclusion and withdrawal criteria for subjects with a history of or significant risk of suicidal or violent behavior.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify exclusion and withdrawal criteria for subjects with a history of or significant risk of suicidal or violent behavior.	
4.2. Exclusion Criteria	Added exclusion criterion for subjects with a history of any suicidal behavior (attempt, interrupted, aborted, or preparatory) in the past 6 months prior to the screening visit.
10.2. Withdrawal From the Study	Added withdrawal criterion if the investigator believes the subject to be at significant risk of suicidal or violent behavior.
Rationale: Study procedures clarified.	
Synopsis Overview of Study Design; Time and Events Schedule; 3.1. Overview of Study Design; 3.2.1. Blinding; 5. Treatment Allocation and Blinding; 9.3. Safety Evaluations; 16.1. Study-Specific Design Considerations	Renal ultrasound will be obtained under blinded conditions after randomization; screening ultrasound will not be blinded.
Synopsis Dosage and Administration; 6. Dosage and Administration	Maximum recommended daily dosage for levetiracetam added, for consistency with approved labeling.
Synopsis Safety Evaluations; Time and Events Schedule;	Renal ultrasound changed from baseline to screening, for consistency with Section 9.3, Safety Evaluations, to ensure results are available prior to randomization.
Synopsis Safety Evaluations; Time and Events Schedule; 9.3. Safety Evaluations	BMI will not be obtained by the site, but will be calculated during statistical analysis.
Time and Events Schedule	Clarification added that seizure counts will be recorded in the seizure diary (in addition to the date and type of seizure)
9.3. Safety Evaluations	Statement added that for all evaluations, if possible, the same individual should evaluate the subject at all visits. Statement regarding shipment of ammonia samples deleted, since testing will be done locally. "Bone Age Scan" changed to "Bone Age Radiograph" for accuracy; clarification added that this will be obtained in the nondominant hand/wrist.

Applicable Section(s)	Description of Change(s)
	Number of questions for CBCL-Preschool and CBCL-School Age revised to 99 questions and 112 questions, respectively, for consistency with Attachments 6 and 7.
	Clarification added for who can administer the Columbia Suicide Severity Rating Scale (C-SSRS), and that subjects themselves will respond if cooperative, in all subjects 6 years of age and older.
9.3. Safety Evaluations; 11.4. Safety Analyses	Reference to vital signs obtained in a seated position deleted, since orthostatic vital signs will be measured supine then standing.
15. Study-Specific Materials	Added “refrigerated centrifuge, if not available locally”.

Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Active-Controlled, Open-Label, Flexible-Dose Study to Assess the Safety and Tolerability of Topiramate as Monotherapy Compared With Levetiracetam as Monotherapy in Pediatric Subjects With New or Recent-Onset Epilepsy

TOPAMAX® (topiramate) (2,3:4,5-Di-*O*-isopropylidene-ß-D-fructopyranose sulfamate) is a structurally unique compound that is effective and well tolerated as an anticonvulsant after oral administration in animals and humans. Topiramate is approved as adjunctive treatment in adults and in pediatric patients (2 to 16 years of age) with partial-onset seizures (POS), primary generalized tonic-clonic seizures (PGTCS), or seizures associated with Lennox-Gastaut syndrome. It is also approved for monotherapy treatment in adult and pediatric patients down to 2 years of age with newly or recently diagnosed POS or PGTCS, and for the prophylaxis of migraine in adults and adolescents 12 years of age and older.

The effects of topiramate on growth, bone mineralization, and kidney stone formation have not been fully and systematically evaluated or well characterized in pediatric populations. This study will systematically assess the long-term safety of topiramate monotherapy compared with levetiracetam monotherapy; specific emphasis will be on metabolic acidosis related to topiramate therapy and its association with nephrolithiasis, bone mineral density (BMD) abnormalities, and delayed growth in children (2 to 15 years of age). Levetiracetam is an appropriate comparator because of its established efficacy for target seizure types, relatively low toxicity, and lack of significant known risk of kidney stones or possible deleterious effects on bone or growth.

EudraCT NUMBER: 2012-001552-19

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to evaluate the effects of topiramate monotherapy compared with levetiracetam, another standard antiepileptic drug (AED), as monotherapy for new-onset or recent-onset epilepsy on pediatric growth and maturation, bone mineralization, and kidney stone formation in children 2 to 15 years of age.

Secondary Objective

Overall safety will be assessed.

Hypothesis

The study will test the hypothesis that flexible dosages of topiramate monotherapy have the same effect as flexible dosages of levetiracetam monotherapy on pediatric growth, bone mineralization, and kidney stone formation in children 2 to 15 years of age with new-onset or recent-onset epilepsy, versus the alternative hypothesis that the effect of topiramate is different from that of levetiracetam.

OVERVIEW OF STUDY DESIGN

This is a 1-year, active-controlled, randomized, outpatient, multicenter, open-label, 2-arm flexible-dose monotherapy study of topiramate compared with 1 other AED (levetiracetam) in pediatric subjects with epilepsy. Subjects will be required to have newly or recently diagnosed epilepsy characterized by POS with or without secondary generalized tonic-clonic seizures or PGTCS.

The study will include the following 3 phases: a screening phase of up to 35 days, an open-label treatment phase of 1 year's duration, and a posttreatment phase of 30 days' duration. There may be an optional post-study follow-up phase to obtain dual energy x-ray absorptiometry (DEXA) measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or

greater) in BMD, based on local DEXA scan results, after 1 year of treatment with topiramate, to determine whether a decrease in BMD after or during 1 year of treatment with topiramate is reversible. These subjects will have a repeat DEXA scan 6 months after discontinuation of study drug.

To minimize any bias in measurement, after randomization 3 of the safety assessments will be obtained in a blinded fashion, including the DEXA scan, renal ultrasound, and height.

An external, independent Data Monitoring Committee will be commissioned for this study and will evaluate safety data periodically throughout the study.

SUBJECT POPULATION

Approximately 282 male and female subjects, 2 to 15 years of age with newly or recently diagnosed epilepsy, will be randomly assigned to either the topiramate or levetiracetam arm, in a 1:1 ratio. The randomization will be balanced using randomly permuted blocks and will be stratified by country and age group (2 to 5 years of age, 6 to 9 years of age, 10 to 12 years of age, and 13 to 15 years of age). The enrollment will be monitored throughout the study to ensure that subjects are enrolled for each integer year in each treatment group.

Subjects will be required to have newly or recently diagnosed epilepsy characterized by POS with or without secondary generalization or PGTCS. The epilepsy diagnosis must be within the previous 2 years before screening and the subject must have at least 1, but not more than 10, unprovoked seizures during the 5 months prior to screening. Subjects must have evidence of appropriate physical development (height and weight), including weight and height values within the 5th to 95th percentile for chronological age at study entry. Previous AED exposure is limited to no more than 31 days immediately preceding study enrollment or to a total of 6 months of previous AED exposure in the past if the AED has been discontinued for at least 1 year prior to study enrollment. If the subject is currently treated with an AED, inadequacy of current epilepsy treatment must be documented.

Subjects must not have nephrocalcinosis, renal stones of any type, hydronephrosis, a history of long bone fractures, indwelling hardware, or abnormalities of the skeleton or spine. Subjects must not have congenital glaucoma, known ocular deficits, or clinically relevant abnormalities on renal ultrasound or DEXA scans. Subjects must not have a known history of disturbances of autonomic function, inborn errors of metabolism, mitochondrial dysfunction, or prior evidence of hyperammonemia. Subjects must not have any clinically significant abnormality in laboratory tests at screening, including a bicarbonate level <20 mEq/L, have a diagnosis of metabolic acidosis, or be on alkali therapy.

Caregivers of the subjects must be able to accurately maintain the subject take-home record and seizure diary.

DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned to receive unblinded, flexible dosages of topiramate or levetiracetam as follows:

- Topiramate: weight-based dosing for subjects 2 to <10 years of age, not to exceed 350 mg/day, as tolerated; dosage for subjects 10 to 15 years of age not to exceed 400 mg/day, as tolerated
- Levetiracetam: weight-based dosing for all subjects 2 to 15 years of age, not to exceed 60 mg/kg/day, as tolerated. The maximum recommended daily dosage is 3,000 mg (1,500 mg BID).

Subjects will receive study drug in a twice-a-day regimen. After randomization, subjects will be titrated as tolerated to the maximum recommended dosage for optimal clinical effect over 6 to 8 weeks and will be maintained on that dosage through the open-label treatment phase, with the option for dosage adjustment as required for optimal clinical effect. Changes to this schedule will be based on a risk-benefit

assessment of the subject's clinical condition by the investigator. All study drugs will be provided in child-resistant packaging during the study.

Subjects are recommended not to exceed maximum recommended maintenance dosages; however, subjects will not be discontinued from the study if higher dosages are required for optimal clinical effect as judged by the investigator. Data collected while on dosages that exceed maximal recommendations may be analyzed separately, as appropriate.

Only AED monotherapy will be used for both treatment groups. However, subjects will not be discontinued from the study if 1 or more concomitant AEDs are added after initiating treatment with study drug. Data will be collected prior to the use of the concomitant AED(s) for the primary analysis. Data subsequently collected while on the concomitant AED(s) will be analyzed in a secondary analysis for each safety outcome of interest.

PHARMACOKINETIC EVALUATIONS

Blood samples (1 mL per sample) for the determination of plasma topiramate and levetiracetam concentrations will be obtained during clinic visits according to the Time and Events schedule. If possible, blood samples for pharmacokinetic (PK) evaluations should be trough samples (ie, taken immediately before the morning dose) and coincide with samples drawn for clinical laboratory tests. During each PK assessment, the dosing regimen, dose administered, time and date of dose administration, time of sample collection, and concomitant medications will be recorded in the case report form.

Pharmacokinetic parameters will not be estimated. Topiramate and levetiracetam plasma concentration data will be summarized.

SAFETY EVALUATIONS

Safety evaluations will include:

- 12-lead electrocardiogram (screening only)
- Vital signs (including orthostatic vital signs), body weight, and height (all visits except Month 2)
- Neurologic and physical examinations (all visits except Month 2)
- Physical activity evaluation (screening)
- Clinical laboratory tests (screening, Month 1, Month 3, Month 6, Month 9, and Month 12/early withdrawal)
- Pregnancy testing (for girls of childbearing potential; serum at screening only; urine at all other visits)
- 24-hour urine collection (Screening, Month 6, and Month 12/early withdrawal)
- Adverse event monitoring, concomitant medication monitoring (throughout)
- Suicidality, as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS; all visits except screening)
- DEXA scan (baseline, Month 6, and Month 12/early withdrawal)
- Renal ultrasound, biochemical bone markers (screening, Month 6, and Month 12/early withdrawal)
- Bone age, as determined by hand/wrist x-ray (baseline and Month 12/early withdrawal)
- Tanner staging of subjects of age 8 years and above (baseline, Month 6, and Month 12 or early withdrawal)
- Seizure counts recorded by parent/guardian in take-home seizure diary (all visits beginning at baseline)

- Cognitive, developmental, and behavioral assessments, conducted as follows:
    - ◊ Cogstate Battery (2 practice sessions, 1 at screening and 1 at baseline prior to the baseline assessment; assessed at baseline, Month 6, and Month 12/early withdrawal):
        - o For subjects 6 to 15 years of age, the Detection Test, Identification Test, One Card Learning Test, One Back Test, and Groton Maze Learning Test will be administered.
        - o For cooperative subjects 4 to 5 years of age, the Detection Test and the Identification Test will be administered.
    - ◊ Language function test (Animal Fluency NEPSY-II (A Developmental NEuroPSYchological Assessment); 1 practice session at screening; assessed at baseline, Month 6, and Month 12/early withdrawal for subjects 6 to 15 years of age)
    - ◊ Vineland Adaptive Behavior Scale (to be completed by a parent or guardian for subjects 2 to 5 years of age, assessed at baseline, Month 3, Month 6, and Month 12/early withdrawal)
    - ◊ Child Behavior Checklist (CBCL; assessed at baseline, Month 3, Month 6, and Month 12/early withdrawal) - Parent version (Achenbach System of Empirically Based Assessment)
        - o Preschool version – subjects 2 to 5 years of age
        - o School-age version - subjects 6 to 15 years of age

      Note: For subjects who turn 6 years of age during the study, the Vineland Adaptive Behavior Scale and the preschool version of the CBCL will continue to be administered throughout the study.

STATISTICAL METHODS

Sample Size Determination

A total of 282 randomized subjects, 141 in each treatment group, will be enrolled in the study. The sample size takes into account a 1-year dropout rate of 29%, which is a conservative estimate based on the dropout rates was observed in a previous monotherapy study in the 6- to 15-year-old age group, Study TOPMAT-EPMN-106, including a dropout rate of 22% in the study overall (both double-blind and open-label phases) and a dropout rate of 35% for the double-blind phase. The sample size was estimated in order to achieve a sufficient precision for the estimates of the treatment effect on the key endpoints. The precision of the confidence interval (CI) estimates for the key safety parameters are shown below:

- *Annual change in BMD (L1-L4) Z-score:* In the Bone Mineral Density in Childhood Study (BMDCS), mean annual change in BMD (L1-L4) Z-score in 6- to 15-year-old healthy subjects was, as expected, minimal (0.01-0.07). The standard deviation (SD) varied from 0.3 to 0.48 across sex and age groups. Assuming an SD of 0.4, with 100 completed subjects per group, the 95% CI for the treatment difference will have a precision of 0.12.
- *Annual change in height Z-score in the 2- to 9-year-old age group:* In the monotherapy epilepsy study TOPMAT-EPMN-106, the observed change from baseline in mean height Z-score at 1 year among the 2- to 9-year-old subjects treated with topiramate 400 mg/day was -0.18, with an SD of 0.28. Assuming that 53% of the subjects will be recruited in the 2 to 9-year-old age group, ie, 53 completed subjects per treatment group, the 95% CI for the treatment difference will have a precision of 0.11.
- *Incidence of kidney stone formation:* In the studies TOPMAT-PEP-3001 and TOPMAT-PEP-1002 in infants (1 month to 2 years of age), a 7% incidence of kidney stones was observed during the 1-year topiramate adjunctive treatment period. A sample size of 100 completed subjects per treatment group will provide a 95% CI (Wilson score CI) for the treatment difference with a width of 0.12, assuming that the incidence of kidney stone formation is 7% and near zero in the topiramate group and the levetiracetam group, respectively.

- *Change in weight Z-score in the 2- to 15-year-old age group:* In the monotherapy epilepsy study TOPMAT-EPMN-106, a -0.59 decrease from baseline in weight Z-score, with an SD of 0.43, was observed after 1 year of treatment with topiramate 400 mg/day. Assuming an SD of 0.43, a sample size of 100 completed subjects per treatment group will provide a 95% CI with a precision of 0.12.

Safety Analyses

The key safety endpoints will include:

- Percentage of subjects with kidney stones
- Change from baseline in weight Z-score over time
- The following height analyses will be conducted for prepubertal subjects 2 to 9 years of age, subjects 10 to 15 years of age, and subjects 2 to 15 years of age:
    - ◊ Height at 1 year postbaseline
    - ◊ Height change from baseline over time
    - ◊ Height Z-score at 1 year postbaseline
    - ◊ Change from baseline in height Z-score over time
    - ◊ Height velocity at 1 year postbaseline
    - ◊ Height velocity Z-score at 1 year postbaseline
    - ◊ Percentage of outlier subjects with height Z-score decrease of >0.5, >1.0, and >2.0 over time
- The following BMD and bone mineral content (BMC) endpoints:
    - ◊ BMD and BMC over time
    - ◊ BMD and BMC change from baseline over time
    - ◊ Z-score for BMD and BMC over time
    - ◊ Change from baseline in Z-score for BMD and BMC over time
    - ◊ Percent change from baseline in BMD and BMC over time
    - ◊ Percentage of outlier subjects with BMD Z-score decrease of >0.5, >1.0, and >2.0 over time
- Change from baseline in biochemical markers of bone mineralization including: serum levels of calcium, phosphorus, alkaline phosphatase, 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, insulin-like growth factor 1 (IGF-1), and parathyroid hormone.
- Change from baseline in serum and urine laboratory tests, eg, bicarbonate, ammonia, renal function tests, and liver function tests
- Change from baseline in bone age

Longitudinal endpoints will be analyzed using a mixed-model repeated measures (MMRM) analysis. The MMRM model will include treatment group, age group, visit, treatment-by-visit interaction, baseline measure, and baseline-by-visit interaction. An unstructured covariance will be used. Other appropriate covariance structures will be explored as needed. Confidence intervals with 95% confidence for the estimated treatment differences will be provided at each time point as appropriate. For proportion endpoints, 95% confidence intervals will be provided for the treatment difference. Each of the endpoints will also be summarized by age group.

Seizure counts and cognitive, developmental, and behavioral assessments will be summarized by treatment group and age group. The incidence of suicide-related thoughts and behaviors as determined by the C-SSRS will be summarized by treatment group and age group.

In addition to the above endpoints, other safety-related endpoints may be included in the analyses if deemed necessary.

TIME AND EVENTS SCHEDULE

Phase	Screening	Open-Label Treatment[a]						Posttreatment[b]	
								End-of-Study/Early Withdrawal	Follow-up Telephone Contact
Week (W)/Month (M)		**Baseline/ W1**	**M1**	**M2**	**M3**	**M6**	**M9**	**M12**	**M13**
Study Day	≤-28	**1[c]**	**30**	**60**	**90**	**180**	**270**	**360**	**390[d]**
Study Day Window	-7days	±7days	±7days	±7days	±7days	±7days	±7days	±7days	±7days
Visit[e]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**NA**
Screening/Administrative									
Informed consent and assent	X								
Inclusion/exclusion criteria	X	X							
Medical/seizure history	X	X							
Physical activity evaluation[f]	X								
Prestudy AED and other therapy[g]	X								
Randomization		X							
Study Drug									
Dispense study drug		X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	
Pharmacokinetics									
Blood sample collection for quantitation of study drug[h]			X		X	X		X	
Safety									
Physical examination	X	X	X		X	X	X	X	
Neurologic examination	X	X	X		X	X	X	X	
12-lead ECG	X								
Height/weight[i]	X	X	X		X	X	X	X	
Vital signs (temperature, HR, RR, BP)[j]	X	X	X		X	X	X	X	
Clinical laboratory tests[k]	X		X		X	X	X	X	
Pregnancy test[l]	X	X	X	X	X	X	X	X	
24-hour urine collection[m]	X					X		X	
Tanner staging[n]		X				X		X	

Phase	Screening	Open-Label Treatment[a]						Posttreatment[b]	
								End-of-Study/Early Withdrawal	Follow-up Telephone Contact
Week (W)/Month (M)		**Baseline/ W1**	**M1**	**M2**	**M3**	**M6**	**M9**	**M12**	**M13**
Study Day	≤-28	**1[c]**	**30**	**60**	**90**	**180**	**270**	**360**	**390[d]**
Study Day Window	-7days	±7days	±7days	±7days	±7days	±7days	±7days	±7days	±7days
Visit[e]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**NA**
Renal ultrasound[o]	X					X		X	
Biochemical bone markers[p]	X					X		X	
DEXA scan[b,q]		X				X		X	
Bone age x-ray[r]		X						X	
Dispense seizure diary and take-home record[s]		X	X	X	X	X	X		
Review seizure diary and take-home record			X	X	X	X	X	X	
Cogstate Battery[t]	X	X				X		X	
Animal Fluency Test NEPSY-II[u]	X	X				X		X	
Vineland Adaptive Behavior Scale[v]		X			X	X		X	
CBCL–Parent Version[w]		X			X	X		X	
C-SSRS[x]		X	X	X	X	X	X	X	
Ongoing Review									
Concomitant therapy	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X

Footnotes appear on the following page.

[a] Includes a titration period of approximately 6 to 8 weeks, followed by a maintenance period.

[b] There may be an optional post-study follow-up phase to obtain DEXA measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or greater) in BMD, based on local DEXA scan results, after 1 year of treatment with topiramate; these subjects will have a repeat DEXA scan 6 months after discontinuation of study drug.

[c] The Day 1 visit will serve as the baseline visit. All procedures on Day 1 (except dispensing of study drug) should be completed before randomization.

[d] The site will contact the subject via telephone at Month 13, to collect data on adverse events and concomitant medications.

[e] Window for all visits will be ±7 days.

[f] Adequacy of physical activity will be assessed with the Habitual Activity Estimation Scale.

[g] Investigator will document inadequacy of any epilepsy treatment that the subject is receiving at the time of screening. Information regarding AED use and other medications within 2 years prior to the study will also be collected.

[h] If possible, blood samples for determination of plasma topiramate and levetiracetam concentrations should be trough samples (taken immediately before the morning dose) and should coincide with samples drawn for clinical laboratory tests.

[i] Subjects will be weighed in examination gowns or in lightweight clothing and without shoes.
Height will be assessed using a wall-mounted stadiometer.
All study site personnel measuring height will be blinded to treatment to avoid/minimize bias.

[j] Orthostatic vital signs will be obtained for all subjects pending cooperation of subjects. A set of 3 measurements will be obtained at baseline only at intervals of 10 minutes. Thereafter, only 1 orthostatic vital sign measurement will be taken at all subsequent visits. The method for obtaining orthostatic vital signs will be as follows: subject will be supine for 5 minutes prior to measurement, and standing for 2 minutes prior to measurement.

[k] Clinical laboratory tests (nonfasting) include serum chemistry, hematology, venous ammonia and urinalysis. Insulin-like growth factor 1, 1,25-dihydroxy-vitamin D, 25-hydroxy-vitamin D, and parathyroid hormone will be measured at screening and at Months 6 and 12/early withdrawal. The laboratory tests for 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Parathyroid hormone (intact) and IGF-1 at screening will be evaluated centrally, but additional evaluation at a local laboratory is allowed in order to reduce the duration of the screening phase.

[l] Serum pregnancy test at screening; urine pregnancy test at all other visits.

[m] A 24-hour urine collection will be analyzed for pH, calcium, citrate, phosphorus, and creatinine levels. Collection instructions and storage conditions will be specified in the laboratory manual. A 14-day window on either side of the scheduled Month 6 visit will be allowed for 24-hour urine collection. The collection at Month 12 should be completed before the Month–12 visit as this evaluation should be obtained while the subject is still receiving study–drug therapy.

[n] Tanner staging of subjects of age 8 years and above will be conducted by a qualified pediatric endocrinologist or by a physician trained in the method.

[o] Renal ultrasound will be obtained under blinded conditions after randomization and will be read/interpreted centrally (local reading at the screening visit is acceptable to determine eligibility for randomization). Both the technicians administering the renal ultrasound scans and the local and central readers will be blinded to the study treatment group.

[p] Biochemical bone markers will include serum calcium, phosphorus, parathyroid hormone [intact], 25-hydroxy-vitamin D, and 1,25-dihydroxy-vitamin D.

[q] DEXA measurements will include posterior-anterior spine (lumbar) and total body less head areal BMD and BMC. Short-term precision testing will be performed for DEXA measurements according to standard protocols. The same DEXA machine will be used at each site for all subjects and all measurements; only clinical sites using recent-generation Hologic or General Electric Lunar systems will participate in the study; the GE/Lunar systems will only be used for subjects ≥5 years of age. If possible, the same technician should acquire all scans for any particular subject.
Both the technicians administering the DEXA scans and the central reader will be blinded to the treatment group.
For each time point, up to 3 scan attempts will be performed all on the same day (with repositioning between each scan), with the goal of obtaining 2 complete, movement-free scans of both the spine and whole body at screening.

[r] A hand/wrist x-ray (in the nondominant hand/wrist) will be used to determine bone age.

[s] Subjects will be given a take-home record, to capture data on study drug administration, concomitant medications, and items of general health, and a seizure diary with instructions to record seizure counts and the date and description of each seizure.

[t] The computerized Cogstate Battery will be administered by non-expert (non-psychologist) study site personnel trained in the Cogstate administration method, with 2 practice sessions, 1 at screening and 1 at baseline prior to the baseline assessment. For subjects 6 to 15 years of age, the Detection Test, Identification Test, One Card Learning Test, One Back Test, and Groton Maze Learning Test will be administered. For cooperative subjects 4 to 5 years of age, the Detection Test and Identification Test will be administered.

[u] The Animal Fluency Test NEPSY-II will be administered for subjects 6 to 15 years of age, with 1 practice session at screening.

[v] The Vineland Adaptive Behavior Checklist will be completed by a parent or guardian for subjects 2 to 5 years of age.

[w] The CBCL-Parent version will be used for all subjects. For subjects 2 to 5 years of age, the preschool version will be administered. For subjects 6 to 15 years of age, the school-age version will be administered.

[x] The C-SSRS will be administered for subjects 6 to 15 years of age and will not be administered for subjects 2 to 5 years of age.

AED=antiepileptic drug; BMC=bone mineral content; BMD=bone mineral density; BP=blood pressure; CBCL=Child Behavior Checklist; C-SSRS=Columbia Suicide Severity Rating Scale; DEXA=dual energy x-ray absorptiometry; ECG=electrocardiogram; HR=heart rate; IGF-1=insulin-like growth factor 1; NEPSY =A Developmental NEuroPSYchological Assessment; RR=respiratory rate.

ABBREVIATIONS

AED	antiepileptic drug
ALT	alanine aminotransferase
ASEBA	Achenbach System of Empirically Based Assessment
AST	aspartate aminotransferase
BID	twice a day
BMC	bone mineral content
BMD	bone mineral density
BMDCS	Bone Mineral Density in Childhood Study
BMI	body mass index
CBCL	Child Behavior Checklist
CDC	Centers for Disease Control
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DEXA	dual energy x-ray absorptiometry
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EEG	electroencephalogram
GABA	γ-aminobutyrate
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HAES	Habitual Activity Estimation Scale
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor 1
IRB	Institutional Review Board
IWRS	interactive web-based response system
JME	juvenile myoclonic epilepsy
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-model repeated measures
NEPSY	A Developmental NEuroPSYchological Assessment
NSAIDs	nonsteroidal anti-inflammatory drugs
PGTCS	primary generalized tonic-clonic seizures
PK	pharmacokinetic(s)
POS	partial-onset seizures
PQC	product quality complaint
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

TOPAMAX® (topiramate) (2,3:4,5-Di-*O*-isopropylidene-ß-D-fructopyranose sulfamate) is a structurally unique compound that is effective and well tolerated as an anticonvulsant after oral administration in animals and humans. Topiramate is approved as adjunctive treatment in adults and in pediatric patients (2 to 16 years of age) with partial-onset seizures (POS), primary generalized tonic-clonic seizures (PGTCS), or seizures associated with Lennox-Gastaut syndrome. It is also approved for monotherapy treatment in adult and pediatric patients down to 2 years of age with newly or recently diagnosed POS or PGTCS, and for the prophylaxis of migraine in adults and adolescents 12 years of age and older.

Background information on nonclinical and clinical studies with topiramate is provided below.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of topiramate, refer to the latest version of the Investigator's Brochure for topiramate.[33]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

Nonclinical Studies

Pharmacologic Profile

Pharmacologic effects that may contribute to the anticonvulsant activity of topiramate include inhibition of some voltage-activated sodium channels; potentiation of the ability of γ-aminobutyrate (GABA) to activate some $GABA_A$ receptors; inhibition of the kainate or ∝-amino-3-hydroxy-5-methylisoxazole-4-propionic acid subtype but not the N-methyl-D-aspartate subtype of glutamate receptors; and a modest negative modulatory effect on L-type and R-type voltage-activated calcium channels. Some studies suggest topiramate has an activating effect on some types of potassium channels, but this may be secondary to effects on calcium channels. These pharmacodynamic properties are observed at therapeutically relevant concentrations (1 to 100 μM) and may have a common molecular mechanism that affects the phosphorylation state of these complex membrane proteins. Topiramate also inhibits some carbonic anhydrase isozymes, particularly carbonic anhydrase-II and carbonic anhydrase-IV (Ki ~1 μM). The possible role of carbonic anhydrase inhibitory activity in the AED efficacy of topiramate is not definitively established, but there is clear evidence that carbonic anhydrase inhibition causes or contributes to metabolic acidosis and nephrolithiasis.[33]

Toxicology

Acute and long-term oral exposure to topiramate is generally well tolerated. Topiramate is teratogenic in animals, does not affect the fertility of male or female rats, and exhibits no genotoxic potential.[33]

In juvenile rats, findings were similar to those in adults, with no unique toxicities and no effect on memory and learning, mating and fertility, or hysterotomy parameters (numbers of corpora lutea, implantations, conceptuses or implantation losses). Males had decreased serum inorganic phosphate levels, and both males and females had increased urine inorganic phosphate levels at dosages of 300 mg/kg/day. There were no effects on mean long bone (tibia) growth; global left femoral bone mineral density (BMD) was minimally lower in juvenile rats given 300 mg/kg/day compared with controls. Lower (around -20%) mean total height (thickness) of the growth plate and mean height of the proliferative or hypertrophic zones taken separately were observed in males given 300 mg/kg/day in comparison with controls. Individual values were below or within the lower part of the control range. However, there was an opposite trend in females given the same dosage, where marginally higher (+3%) mean total height was noted. Individual values in females were within the control range.[28]

Pharmacokinetic Profile

In studies evaluating the pharmacokinetic (PK) profile and metabolism of topiramate in animals, oral doses of topiramate were rapidly and almost completely absorbed, rapidly distributed to the tissues, poorly bound to plasma protein, and eliminated primarily via the kidneys. The metabolic pathways for topiramate are qualitatively similar in the mouse, rat, rabbit, dog, and human.[33]

Clinical Studies

Human Pharmacokinetics

Topiramate exhibits linear PK, with no evidence of auto-induction or inhibition of metabolism. It is rapidly absorbed and not extensively metabolized. Its absolute bioavailability is 81% to 95% and its metabolism is not affected significantly by food. The major elimination route of unchanged topiramate and its metabolites is renal.

The PK of topiramate were evaluated in pediatric subjects with epilepsy (4 to 17 years of age) receiving 1 or 2 other AEDs.[32] Pharmacokinetic profiles were obtained after 1 week, at dosages of 1, 3, and 9 mg/kg/day. The PK of topiramate were linear, with clearance independent of dosage and steady-state plasma concentrations increasing in proportion to dosage. Pediatric subjects (4 to 17 years of age) had a 50% higher clearance, and consequently a shorter elimination half-life, compared with adults. Consequently, the plasma concentration for the same milligram-per-kilogram dosage may be lower in pediatric subjects than in adults. As in adults, hepatic enzyme-inducing AEDs decreased the steady-state plasma concentrations of topiramate.

In a separate study, unchanged topiramate and 6 metabolites were quantified from the urine of children with infantile spasms who were between the ages of 9 and 43 months and receiving topiramate dosages of 7 to 10 mg/kg/day.[14] The relative amounts of topiramate and its metabolites found in the urine of subjects with infantile spasms were similar to those observed in

adults.[14] Both infants and adults receiving topiramate adjunctive to hepatic enzyme-inducing AEDs had a higher proportion of metabolites than of parent topiramate in the urine. Two metabolites, topiramate-N-glucuronide and hydroxytopiramate sulfate, were identified in trace amounts (≤8%) in infants but were not detected in adults. The results of this study indicate that topiramate does not appear to be metabolized significantly differently in infants or young children compared with adults.

Efficacy/Safety Studies

Clinical studies have shown that topiramate is effective as an adjunctive treatment in adults and in pediatric subjects (2 to 16 years of age) with POS or PGTCS, and in pediatric subjects (≥2 years of age) with seizures associated with Lennox-Gastaut syndrome. In the controlled adjunctive therapy studies, which included pediatric subjects, target topiramate dosages were based on weight and ranged from approximately 5 to 9 mg/kg/day, administered in 2 divided doses. Topiramate was superior to placebo with regard to percent reduction in average monthly seizure rate, percentage of treatment responders, and global assessments made by investigators and subjects. Dosages above 400 mg/day (600, 800, or 1,000 mg/day) have not been shown to improve responses in dose-response studies in adults with POS.[33]

Topiramate has also been shown to be effective as monotherapy in adult and pediatric subjects with refractory epilepsy or newly or recently diagnosed epilepsy. In monotherapy studies, topiramate was administered at dosages ranging from 25 to 400 mg/day in children (≥6 years of age) and 50 to 500 mg/day in adults (≥16 years of age), and was effective in reducing the number of seizures experienced.[7,8,9] In particular, comparison of Kaplan-Meier survival curves for time to first seizure (primary efficacy endpoint) in the double-blind monotherapy study TOPMAT-EPMN-106 (n=487; age ranging from 6 to 83 years) favored a higher dosage of topiramate over a lower dosage (400 mg/day vs. 50 mg/day; p=0.0002 [log-rank test]). The separation between the groups in favor of the high-dosage group occurred early in the titration phase and was statistically significant as early as 2 weeks after randomization (p=0.046), when, by following the weekly titration schedule, subjects in the high-dosage group achieved a maximum topiramate dosage of 100 mg/day. The high-dosage group was also superior to the low-dosage group with respect to proportion of subjects remaining seizure-free, based on the Kaplan-Meier estimates, for at least 6 months (82.9% vs. 71.4%; p=0.005) and for at least 1 year (75.7% vs. 58.8%; p=0.001). The treatment effects, with respect to time to first seizure, were consistent across subgroups defined by age, sex, geographic region, baseline body weight, baseline seizure type, time since diagnosis, and baseline AED use.[33]

Pharmacokinetic-pharmacodynamic modeling and simulation bridging was used to identify and validate the efficacious monotherapy dosing regimen for topiramate in children 2 to <10 years of age with newly diagnosed epilepsy.[17]

Topiramate appears to be well tolerated; neuropsychiatric events of mild or moderate severity are the most common treatment-emergent adverse events across subject populations. In general, there were no noteworthy changes in clinical laboratory analytes other than the expected decreases in serum bicarbonate/CO_2 levels in topiramate clinical studies. Metabolic acidosis, considered to be possibly related to the carbonic anhydrase-inhibiting effect of topiramate, has been reported less frequently in adults compared with children but was most common in infants (1 to 24 months of age). In adolescents with migraine, there was no clinically significant effect on serum CO_2. Overall, the incidence of adverse events and abnormal laboratory findings are not notably different for pediatric and adult subjects.

Several issues of special interest have emerged during the development of topiramate, including effects on liver function; metabolic acidosis; effects on growth and maturation; vision abnormalities (acute myopia and secondary angle-closure glaucoma); oligohidrosis, hyperthermia, and secondary rash; hyperammonemia and encephalopathy, and kidney stones. These are discussed in brief below, and are described in further detail in the Investigator's Brochure.

Safety Issues of Clinical Concern

Effects on Liver Function

Comprehensive review of clinical study and postmarketing data revealed no evidence of direct or cumulative hepatotoxicity by topiramate. Across study populations (adjunctive epilepsy, monotherapy epilepsy, and migraine), hepatic event rates and laboratory liver function test (LFT) values for topiramate-treated subjects were similar to those of placebo-treated subjects and, generally, better than those of subjects treated with comparator medications (carbamazepine, valproate, and lithium). Spontaneously reported hepatic events are very rare (<1/10,000 patient-years). Based collectively on clinical study and postmarketing data, the majority of hepatic events are transient and mild to moderate in severity. Moreover, hepatic adverse events that were considered serious, led to discontinuation, or involved markedly abnormal LFT values often were confounded by concomitant medications or intercurrent illness.[33]

Metabolic Acidosis

Hyperchloremic, non-anion gap, metabolic acidosis (ie, decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate treatment. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Such electrolyte imbalance has been

observed with the use of topiramate in placebo-controlled clinical studies and in the post-marketing period. Generally, topiramate-induced metabolic acidosis occurs early in treatment, although cases can occur at any time during treatment. Bicarbonate decreases are usually mild to moderate (average decrease of 4 mEq/L at daily dosages of 400 mg/day in adults and at approximately 6 mg/kg/day in children); rarely, subjects can experience severe decreases, to values <10 mEq/L.[33]

Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae, including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteopenia or osteoporosis, with an increased risk for fractures. Chronic metabolic acidosis in pediatric subjects may also reduce growth rates. A reduction in growth rate may eventually decrease the maximum height achieved. The effect of topiramate on growth and bone-related sequelae has not been systematically investigated.

Growth and Maturation

Reports have suggested that certain AEDs may adversely affect growth and maturation in some children. Body weight was evaluated among pediatric subjects 6 to 15 years of age in clinical studies with topiramate monotherapy, and in 1 of these studies (study TOPMAT-EPMN-106) body mass index (BMI) was evaluated according to Centers for Disease Control (CDC) criteria. Among pediatric subjects administered topiramate monotherapy in studies TOPMAT-EPMN-104, TOPMAT-EPMN-105, and TOPMAT-EPMN-106, mean body weight increased in the double-blind treatment phase; most subjects experienced an increase or no change in body weight. Of those with weight loss, most exhibited decreases of 1% to 9%. Adverse events of weight loss were reported in 21% of pediatric subjects but none was serious or treatment-limiting. In the open-label extension of monotherapy treatment studies TOPMAT-EPMN-104 and TOPMAT-EPMN-106, mean body weight of pediatric subjects also increased.

During the double-blind phase of study TOPMAT-EPMN-106, mean BMI decreases were observed for approximately half of the pediatric subjects in the topiramate 50-/400-mg/day group and topiramate 400-/400-mg/day group, with most of the remaining subjects showing no change in BMI. Larger BMI decreases followed 400 mg/day topiramate than followed 50 mg/day. Based on CDC criteria, topiramate treatment rarely resulted in underweight BMI among pediatric subjects with normal BMI values at baseline. Mean BMI decreases (-1.3 kg/m^2) were observed at 6 months among pediatric subjects whose dosage increased from 50 to 400 mg/day during this study's open-label extension.[39]

Weight, height, and BMI Z-scores decreased from baseline to endpoint in pediatric subjects in monotherapy studies. These results indicate that, in general, children continue to grow while receiving topiramate monotherapy treatment, although at a rate slower than their normal healthy counterparts.[33]

Vision Abnormalities (Acute Myopia and Secondary Angle-Closure Glaucoma)

A medical condition consisting of sudden worsening of vision and an elevation of fluid pressure in the eyes (secondary glaucoma) has been described in clinical studies and post-marketing reports in subjects taking topiramate, usually at the beginning of their treatment. In contrast to primary narrow-angle glaucoma, which is rare under 40 years of age, secondary angle-closure glaucoma associated with topiramate has been reported in pediatric as well as adult subjects. Symptoms include acute onset (within 1 month of initiating topiramate therapy) of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. The primary treatment to reverse symptoms is discontinuation of topiramate as rapidly as possible according to the judgment of the treating physician.[33]

Visual field defects have been reported in subjects receiving topiramate independent of elevated intraocular pressure. In clinical studies, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.

Oligohidrosis, Hyperthermia, and Secondary Rash

Oligohidrosis (decreased sweating) and hyperthermia, infrequently resulting in hospitalization, has been reported in clinical studies and post-marketing reports in association with the use of topiramate. These cases were characterized by decreased sweating and an elevation in body temperature above normal. Some of the cases were reported after exposure to elevated environmental temperatures. The majority of the reports have been in children. Skin erythema has been reported secondary to the hyperthermia and oligohidrosis and should be monitored; adequate hydration is encouraged.

Hyperammonemia and Encephalopathy

In clinical studies and post-marketing reports, concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in subjects who have tolerated either drug alone. In most cases, symptoms and signs abated with discontinuation of either drug. This adverse event is not due to a PK interaction.

Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical studies in adolescents (12-16 years of age) who were treated with topiramate monotherapy for migraine prophylaxis and in very young pediatric subjects (1-24 months of age) who were

treated with adjunctive topiramate for POS. In some subjects, ammonia was markedly increased (defined in the clinical study report as >50% increase from baseline and absolute value >2x upper limit of normal [ULN]). In the adolescent subjects, the incidence of markedly increased hyperammonemia was 3% (1 subject), 0%, and 9% (3 subjects) for the placebo, 50 mg/day, and 100 mg/day groups, respectively.[10]

The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy in placebo-controlled studies, and in an open-label extension study in infants. Dose-related hyperammonemia was also observed in the open-label extension study in pediatric subjects 1 month to 2 years of age. Clinical symptoms of hyperammonemic encephalopathy may include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Hyperammonemia with and without encephalopathy has also been observed in post-marketing reports in patients who were taking topiramate without concomitant valproic acid.[38]

Kidney Stones

The occurrence of renal calculi (1.5% to 1.9% incidence) was observed in clinical studies and post-marketing reports of topiramate in adult and pediatric subjects ≥2 years of age with epilepsy. The majority of cases did not require surgical intervention. Kidney stones have also been reported in infant subjects during long-term (up to 1 year) topiramate treatment. In an open-label extension study (TOPMAT-PEP-1002_3001 OLE) of 284 pediatric subjects 1 to 24 months old with epilepsy, 7% developed kidney or bladder stones, which were primarily asymptomatic and were assessed systematically by renal ultrasound. Topiramate is not approved for pediatric patients less than 2 years of age.[38]

The mechanism is believed to be associated with the carbonic anhydrase inhibitory activity of topiramate. Carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH.[33]

1.1. Comparator Agent

Levetiracetam

Levetiracetam is indicated for use as an adjunctive therapy for POS (adults and children ≥1 month of age with epilepsy), PGTCS (adults and children ≥6 years of age with idiopathic generalized epilepsy), and myoclonic seizures (adults and children ≥12 years of age with juvenile myoclonic epilepsy [JME]).[24] The safety profile in pediatric subjects with epilepsy is summarized below.

Subjects With Partial-Onset Seizures

In pediatric subjects experiencing POS, levetiracetam is associated with somnolence, fatigue, and behavioral abnormalities.[24]

In a double-blind, controlled study in children with epilepsy experiencing POS, 22.8% of levetiracetam-treated subjects experienced somnolence, compared with 11.3% of placebo subjects. The design of the study prevented accurately assessing dose-response effects. No subject discontinued treatment for somnolence. In about 3.0% of levetiracetam-treated subjects and in 3.1% of placebo subjects, the dosage was reduced as a result of somnolence.[24]

Asthenia was reported in 8.9% of levetiracetam-treated subjects, compared with 3.1% of placebo subjects. No subject discontinued treatment for asthenia, but asthenia led to a dosage reduction in 3.0% of levetiracetam-treated subjects compared with 0% of placebo subjects.[24]

A total of 37.6% of the levetiracetam-treated subjects experienced behavioral symptoms (reported as agitation, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, nervousness, neurosis, and personality disorder), compared with 18.6% of placebo subjects. Hostility was reported in 11.9% of levetiracetam-treated subjects, compared with 6.2% of placebo subjects. Nervousness was reported in 9.9% of levetiracetam-treated subjects, compared with 2.1% of placebo subjects. Depression was reported in 3.0% of levetiracetam-treated subjects, compared with 1.0% of placebo subjects.[24]

A total of 3.0% of levetiracetam-treated subjects discontinued treatment due to psychotic and nonpsychotic adverse events, compared with 4.1% of placebo subjects. Overall, 10.9% of levetiracetam-treated subjects experienced behavioral symptoms associated with discontinuation or dosage reduction, compared with 6.2% of placebo subjects.[24]

Subjects With Myoclonic Seizures

During clinical development, the number of subjects with myoclonic seizures exposed to levetiracetam was considerably smaller than the number with partial seizures. Therefore, underreporting of certain adverse events was more likely to occur in the myoclonic seizure population. In adult and adolescent subjects experiencing myoclonic seizures, levetiracetam is associated with somnolence and behavioral abnormalities. It is expected that the events seen in POS subjects would occur in patients with JME. In a double-blind, controlled study in adults and adolescents with JME experiencing myoclonic seizures, 11.7% of levetiracetam-treated subjects experienced somnolence compared with 1.7% of placebo subjects. In 1.7% of levetiracetam-treated subjects and in 0% of placebo subjects, the dosage was reduced as a result of somnolence.

Non-psychotic behavioral disorders (reported as aggression and irritability) occurred in 5% of the levetiracetam-treated JME subjects compared with 0% of placebo subjects. Non-psychotic mood disorders (reported as depressed mood, depression, and mood swings) occurred in 6.7% of levetiracetam-treated JME subjects compared with 3.3% of placebo subjects. A total of 5.0% of levetiracetam-treated subjects had a reduction in dosage or discontinued treatment due to behavioral or psychiatric events (reported as anxiety, depressed mood, depression, irritability, and nervousness), compared with 1.7% of placebo subjects.

In a well-controlled clinical study that included both adolescent (12 to 16 years of age) and adult subjects with myoclonic seizures, the most frequently reported adverse events associated with the use of adjunctive levetiracetam, not seen at an equivalent frequency among placebo-treated subjects, were somnolence, neck pain, and pharyngitis. The different pattern of adverse events, as compared with subjects with POS, is likely due to the much smaller number of subjects in the JME study.[24]

Subjects With Primary Generalized Tonic-Clonic Seizures

During clinical development, the number of subjects 4 years of age and older with PGTCS exposed to levetiracetam was considerably smaller than the number with POS. As in the POS subjects, behavioral symptoms appeared to be associated with levetiracetam treatment. Gait disorders and somnolence were also described in the study in PGTCS, but with no difference between placebo and levetiracetam treatment groups and no appreciable discontinuations. Although it may be expected that drug-related events seen in POS subjects would be seen in PGTCS subjects (eg, somnolence and gait disturbance), these events may not have been observed because of the smaller sample size.[24]

Discontinuation or Dosage Reduction in Well-Controlled Clinical Studies

The adverse events most commonly associated (≥3% in subjects receiving levetiracetam) with discontinuation or dosage reduction in the well-controlled pediatric POS study were asthenia, hostility, and somnolence. The adverse event most commonly associated (≥3% in subjects receiving levetiracetam) with discontinuation or dosage reduction in the well-controlled pediatric JME study was anxiety (2 subjects, 3.3%), but the small study size (a total of 113 subjects enrolled with JME) limits the conclusions that can be drawn. The PGTCS study was too small to adequately characterize the adverse events leading to discontinuation or dosage reduction.[24]

Hematologic Abnormalities

Levetiracetam-treated pediatric subjects with POS experienced small, but statistically significant, decreases in white blood cell (WBC) and neutrophil counts and increases in lymphocyte counts, as compared with placebo. In a well-controlled study, more levetiracetam-treated pediatric subjects with POS had a possibly clinically significant abnormally low total WBC value (3.0%

levetiracetam-treated versus 0% placebo); however, there was no apparent difference between treatment groups with respect to neutrophil count. No subject was discontinued secondary to low WBC or neutrophil counts. Although there were no obvious hematologic abnormalities observed in subjects with JME, the limited number of subjects limits the conclusions that can be drawn.[24]

Liver Function Test Abnormalities

There were no meaningful changes in mean LFT values in controlled studies in adult or pediatric subjects; LFT abnormalities were similar in drug- and placebo-treated subjects in controlled studies (1.4%). No pediatric subjects were discontinued from controlled studies due to LFT abnormalities.[24]

Impaired Renal Function

Levetiracetam is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.[24]

Post-Marketing Experience With Adjunctive Therapy

The following have been reported in patients receiving marketed levetiracetam worldwide (alphabetical order): abnormal LFT values, choreoathetosis, dyskinesia, erythema multiforme, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), Stevens-Johnson syndrome, thrombocytopenia, toxic epidermal necrolysis, and weight loss. Alopecia has been reported with levetiracetam use; recovery was observed in the majority of cases where levetiracetam was discontinued.

Levetiracetam Monotherapy

Levetiracetam is not approved as monotherapy for epilepsy; however, investigator-initiated studies of children with epilepsy support its use in this indication. These monotherapy studies used the same titration and maintenance dosing as pivotal adjunctive studies; overall efficacy and safety outcomes were similar in both treatment settings.[21,24,29,43]

1.2. Overall Rationale for the Study

Among its various pharmacologic actions, topiramate is a carbonic anhydrase inhibitor and may induce metabolic acidosis, and other changes (eg, hypocitraturia, hypercalciuria, and elevated urine pH) that may be associated with an increased tendency for kidney stone formation.[41] Chronic metabolic acidosis may be associated with abnormal bone mineralization and/or homeostasis of vitamin D, calcium, or phosphorus. Childhood is a critical period for bone mineralization and growth. The effects of topiramate on growth, bone mineralization, and kidney stone formation have not been fully and systematically evaluated or well characterized in pediatric populations.

Preclinical juvenile rat studies demonstrated various clinical chemistry and bone findings (eg, changes in serum and urinary phosphate, decreased global BMD, decreased growth plate thickness) with topiramate treatment that raise concerns about long-term toxicities in pediatric patients.

This study will systematically assess the long-term safety of topiramate monotherapy compared with levetiracetam monotherapy; specific emphasis will be on metabolic acidosis related to topiramate therapy and its association with nephrolithiasis, BMD abnormalities, and delayed growth in children (2 to 15 years of age).

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to evaluate the effects of topiramate monotherapy compared with levetiracetam, another standard AED, as monotherapy for new-onset or recent-onset epilepsy on pediatric growth and maturation, bone mineralization, and kidney stone formation in children 2 to 15 years of age.

Secondary Objective

Overall safety will be assessed.

2.2. Hypothesis

The study will test the hypothesis that flexible dosages of topiramate monotherapy have the same effect as flexible dosages of levetiracetam monotherapy on pediatric growth, bone mineralization, and kidney stone formation in children 2 to 15 years of age with new-onset or recent-onset epilepsy, versus the alternative hypothesis that the effect of topiramate is different from that of levetiracetam.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a 1-year, randomized, active-controlled, outpatient, multicenter, open-label, 2-arm flexible-dose monotherapy study of topiramate compared with 1 other AED (levetiracetam) in pediatric subjects with epilepsy. Subjects will be required to have newly or recently diagnosed epilepsy (within the previous 2 years, with at least 1, but no more than 10, unprovoked seizures during the 5 months prior to screening) characterized by POS with or without secondary generalization or PGTCS.

Approximately 282 male and female subjects, 2 to 15 years of age, with newly or recently diagnosed epilepsy, who meet the inclusion/exclusion criteria will be randomly assigned to either the topiramate or levetiracetam arm, in a 1:1 ratio. The randomization will be balanced using randomly permuted blocks and will be stratified by country and age group (2 to 5 years of age, 6 to 9 years of age, 10 to 12 years of age, and 13 to 15 years of age). The enrollment will be monitored throughout the study to ensure that subjects are enrolled for each integer year in each treatment group.

For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related activity. Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent from parents or a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided informed assent/consent refers to the subject (assent as applicable) and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw their assent should not be maintained in the study against their will, even if their parents still want them to participate.

The study will include the following 3 phases: a screening phase of up to 28 days, an open-label treatment phase of 1 year's duration, and a posttreatment phase of 30 days' duration. There may be an optional post-study follow-up phase to obtain dual energy x-ray absorptiometry (DEXA) measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or greater) in BMD, based on local DEXA scan results, after 1 year of treatment with topiramate, to determine whether a decrease in BMD after or during 1 year of treatment with topiramate is reversible. These subjects will have a repeat DEXA scan 6 months after discontinuation of study drug.

To minimize any bias in measurement, after randomization 3 of the safety assessments will be obtained in a blinded fashion, including the DEXA scan, renal ultrasound, and height.

Screening Phase:

Subjects meeting the inclusion/exclusion criteria (see Section 4, Subject Selection) will be eligible to enter into the study. They (and/or their parents or legally acceptable representatives) will sign an informed consent/assent form as appropriate (see Section 16.2.3, Informed Consent) and enter a screening phase of up to 35 days. During the screening phase, subjects will be assessed for study

qualifications. Subjects (or their parents/guardians) will keep a seizure diary (date of seizure and description). Information will be transcribed onto the case report form (CRF). Seizure diaries will be maintained with the source documents.

Open-Label Treatment Phase:

Immediately following the Screening Phase, qualified subjects, based on inclusion/exclusion criteria, will be randomly assigned to 1 of 2 treatment groups during the open-label treatment phase: topiramate (up to 350 mg/day in subjects 2 to <10 years of age, and up to 400 mg/day in subjects 10 to 15 years of age) or levetiracetam (up to 60 mg/kg/day). Antiepileptic drug dosages may be adjusted for clinical effect (efficacy and safety) during the open-label treatment phase but may not exceed these maximum dosages.

Only AED monotherapy will be used for both treatment groups. However, subjects will not be discontinued from the study if 1 or more concomitant AEDs are added after initiating treatment with study drug. Data will be collected prior to the use of the concomitant AED(s) for the primary analysis. Data subsequently collected while on the concomitant AED(s) will be analyzed in a secondary analysis for each safety outcome of interest.

All subjects will enter a 30-day posttreatment phase after completing the open-label treatment phase.

The open-label treatment phase has 2 periods, titration and maintenance.

Titration Period

Randomization will take place on Day 1 (Visit 2). The Day 1 visit will serve as the baseline visit. All procedures on Day 1 (except dispensing of study drug) should be completed before randomization.

Study drug will be titrated as tolerated to the maximum recommended dosage for optimal clinical effect over approximately 6 to 8 weeks, based on titration guidelines according to clinical response (see Section 6, Dosage and Administration). For all subjects, at any time, up-titration of open-label study drug may be slowed down if clinically indicated for tolerability, and may be accelerated if clinically indicated for seizure control.

Subjects will return for a clinic visit at Month 1 and Month 2 for dispensing of study medication.

Maintenance Period

Subjects should be maintained on the dosage achieved at the end of the titration period through the remainder of the open-label treatment phase, with the option for dosage adjustment as required for optimal clinical effect. Changes to this schedule will be based on a risk-benefit assessment of the subject's clinical condition by the investigator.

Clinic visits will be scheduled at Months 1, 2, 3, 6, 9, and 12/early withdrawal. Extra visits may be scheduled at the discretion of the investigator. Blood samples for PK evaluations will be taken at Months 1, 3, 6, and 12/early withdrawal.

Posttreatment Phase

Subjects will be contacted by telephone 30 days after the last dose of study drug to monitor adverse events and concomitant medications. Subjects who complete the study or discontinue early from the study may, at the discretion of the investigator, either continue on commercially available topiramate or levetiracetam or taper off topiramate or levetiracetam over a period of up to 2 weeks during the posttreatment phase.

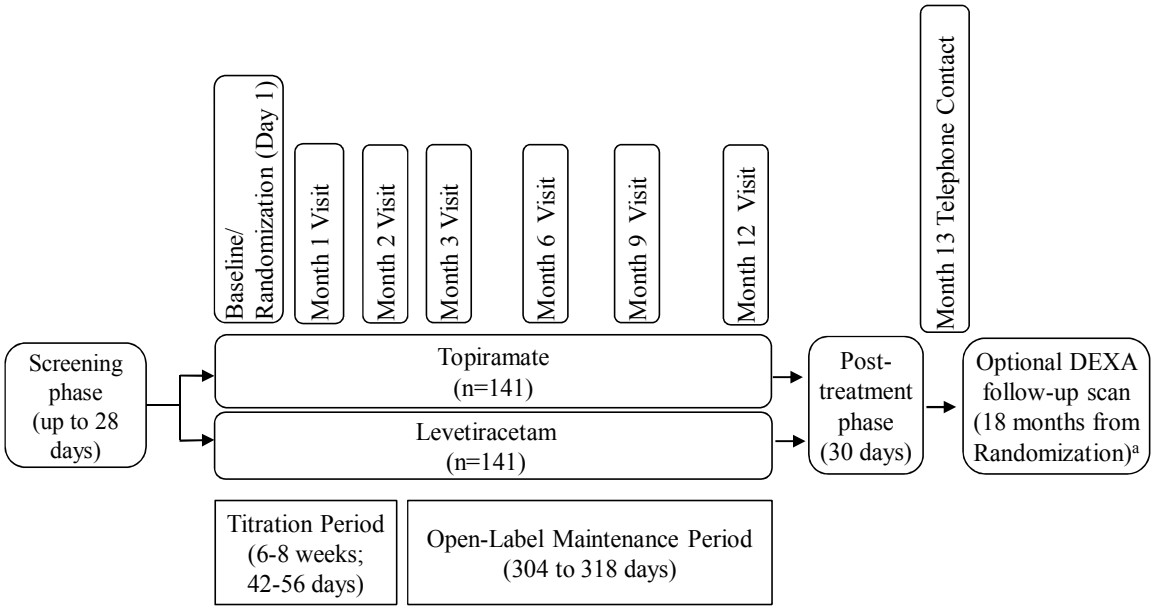
Post-Study Follow-up Phase

There may be an optional post-study follow-up phase to obtain DEXA measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or greater) in BMD, based on local DEXA scan results, after 1 year of treatment with topiramate, to determine whether a decrease in BMD after or during 1 year of treatment with topiramate is reversible. These subjects will have a repeat DEXA scan 6 months after discontinuation of study drug. During study conduct, the sponsor will assess site/investigator interest for participation in this phase to determine if the follow-up phase will be included. An additional consent/assent will be required for this phase.

An external, independent Data Monitoring Committee (DMC) will be commissioned for this study. See Section 11.5, Data Monitoring Committee, for details.

A diagram of the study design is provided in Figure 1.

Figure 1: Study Diagram



[a] Optional post-study follow-up phase to obtain DEXA measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or greater) in BMD , based on local DEXA scan results, after 1 year of treatment with topiramate; these subjects will have a repeat DEXA scan 6 months after discontinuation of study drug.

3.2. Study Design Rationale

A study population from 2 to 15 years of age is appropriate for this study because this is the approved pediatric age group for topiramate monotherapy. Levetiracetam is indicated as adjunctive therapy for POS in adults and children ≥1 month of age with epilepsy), PGTCS (adults and children ≥6 years of age with idiopathic generalized epilepsy), and myoclonic seizures (adults and children ≥12 years of age with JME). It has been studied as monotherapy in pediatric subjects down to neonates and has been demonstrated to be effective and safe in all treatment settings. Evaluation of this target age group will provide long-term systematic assessments of important safety issues, eg, chronic metabolic acidosis and effects on growth, bone mineralization, and nephrolithiasis. Subjects will be stratified by country and by age (2 to 5 years of age, 6 to 9 years of age, 10 to 12 years of age, and 13 to 15 years of age) in order to examine any differences in the safety profile between prepubescent children and postpubescent adolescents. A study duration of 1 year is appropriate in order to detect clinically important treatment-related effects on key safety parameters (growth retardation, bone mineralization, or kidney stone formation). See also Section 16.1, Study-Specific Design Considerations.

3.2.1. Blinding

The study is designed as an open-label study to enhance subject participation and completion and to simulate a naturalistic treatment setting. Given the technical challenges regarding blinding of study drug, along with the prolonged blinding required in young children and possible consequent impact on study conduct and results (eg, difficult regimens requiring too many tablets may result in poor compliance, protocol violations, or subjects prematurely dropping out of the study), a double-blind approach is not optimal. An open-label study is considered to be optimal given that the study population will include pediatric subjects down to 2 years of age and the study duration will be 1 year. An open-label design allows flexibility in dosing regimens.

To minimize any bias in measurement, after randomization 3 of the safety assessments will be obtained in a blinded fashion, including the DEXA scan, renal ultrasound, and height. These are the key assessments that are being evaluated on the basis of the biological effects associated with topiramate, and are necessary for achieving the primary objective.

3.2.2. Active Control

An active control will be used as opposed to a placebo control because of obvious ethical concerns of placebo treatment in a long-term monotherapy treatment setting for epilepsy, a chronic and potentially life-threatening disorder. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Levetiracetam is an appropriate comparator because of its established efficacy for target seizure types, relatively low toxicity, and lack of significant known risk of kidney stones or possible deleterious effects on bone or growth. Levetiracetam is not approved as monotherapy for epilepsy; however, studies of children with epilepsy support its use in this indication. Notably, these monotherapy studies used the same titration and maintenance dosing as pivotal adjunctive studies; overall efficacy and safety outcomes were similar in both treatment settings.[21,24,29,43] On this basis, the FDA-approved dosing recommendations for levetiracetam (titration schedule, dosing frequency) will be used in this study.

Study drug will be given as monotherapy only, since use of any concomitant AED may potentially confound results. However, subjects will not be discontinued from the study if 1 or more concomitant AEDs are added after initiating treatment with study drug. Data will be collected prior to the use of the concomitant AED(s) for the primary analysis. Data subsequently collected while on the concomitant AED(s) will be analyzed in a secondary analysis for each safety outcome of interest.

4. SUBJECT SELECTION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. Subject must be a child or adolescent (male or female) 2 to 15 years of age with a clinical diagnosis of new-onset or recent-onset epilepsy characterized by POS (with or without secondary generalization) or PGTCS in accordance with criteria of the International League Against Epilepsy.[12] The epilepsy diagnosis must be within the previous 2 years before screening.

2. Subject must have clinical or electroencephalogram (EEG) evidence of POS (simple or complex), with or without secondary generalization, or PGTCS within 5 months prior to the first day of screening. Subjects should have at least 1, but no more than 10, unprovoked seizures during the 5 months prior to screening. Unprovoked seizure clustering within a 24-hour period will be considered as a single unprovoked seizure for the purposes of counting seizures to determine eligibility.[16]

   Acceptable evidence of POS includes 1 of the following:

   - Documented recurrent clinical seizures with asymmetric motor features or characteristic behavioral alterations. The interictal EEGs may be negative or inconclusive, provided that the clinical criterion for POS is met.
   - A routine EEG or video EEG showing focal or asymmetric EEG findings (epileptiform discharges, focal slowing, focal attenuation, or a combination), with or without secondary generalization. Clinical seizures with symmetric or behavioral features are acceptable in the presence of EEG evidence of an asymmetric origin.

   Acceptable evidence of PGTCS includes 1 of the following:

   - Documented recurrent clinical seizures with seizures that are initially generalized, associated with tonic contractions and clonic movements
   - EEG expression that is a generalized, synchronous, symmetrical discharge
   - Interictal EEGs may be normal or show generalized discharges such as spikes, polyspike, spike-wave, and polyspike wave.

3. At screening, subject must have weight and height values within the 5th to 95th percentile for chronological age (based on standard Child Height and Weight Charts from the CDC).[25]

4. Subject must never have been treated for epilepsy (treatment-naïve) or have been treated with no more than 1 standard AED if temporary or urgent AED use was necessary. Previous AED exposure must not exceed either of the following:

   - Thirty-one days immediately preceding enrollment, or
   - A total of 6 months of previous AED exposure in the past if the AED has been discontinued for at least 1 year prior to enrollment

5. If subject is currently treated with an AED, inadequacy of current epilepsy treatment must be documented on a worksheet provided to the investigator. Criteria for inadequacy include:

   - AED dosage is considered optimized (including, if clinically appropriate, recent demonstration of adequate blood levels) in the opinion of the investigator and unchanged for at least 5 half-lives prior to the first day of screening and found to be:
     - ◊ Inadequate in controlling seizures in the opinion of the investigator, as shown in part by a retrospective history of at least 1 seizure in the 3 months prior to screening, or
     - ◊ Not well tolerated

6. Parents (or legally acceptable representatives) of the subject must sign an informed consent/permission document, indicating that they understand the purpose of and procedures required for the study and are willing to give permission for their child to participate in the study. Subjects 7 years of age and older, capable of understanding the nature of the study, must provide assent for their participation.

7. Caregivers (parents or legally acceptable representatives) of the subject must be able to accurately maintain the subject take-home record and seizure diary.

8. Subject must have had a computerized tomography or magnetic resonance imaging scan within 2 years prior to study entry, to confirm the absence of a progressive lesion, such as a tumor, with the exception of lesions of tuberous sclerosis and Sturge-Weber syndrome, which are allowed. The report must be included in the source documents.

9. Subject must have an electrocardiogram (ECG) at screening with no “abnormal, clinically significant” interpretations by a local cardiologist.

10. Subject must be otherwise healthy on the basis of physical examination, medical history, vital signs, clinical laboratory tests, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population. This determination must be recorded in the subject's source documents and initialed by the investigator.

11. Subject must be ambulatory and must have normal activity levels based on the Habitual Activity Estimation Scale (HAES; see Attachment 1) at screening, according to recommended levels.

12. Before randomization, a girl must be either:

- Not of childbearing potential: premenarchal; permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy
- Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies, eg, established use of oral, injected, or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject).

  Note: Male partners must use a barrier method, such as a condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

  Note: If the childbearing potential changes after start of the study (eg, girl who is not heterosexually active becomes active, premenarchal girl experiences menarche), the subject must begin a highly effective method of birth control, as described above.

13. A girl of childbearing potential must have a negative serum β-human chorionic gonadotropin pregnancy test at screening, and a negative urine pregnancy test at randomization/baseline and at all subsequent visits of the open-label treatment phase.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Subject has a surgically implanted and functioning vagus nerve stimulator.

2. Subject has a history of seizures as a result of a correctable medical condition, such as metabolic disturbance, toxic exposure, neoplasm, or active infection within 2 weeks prior to the first day of screening.

3. Subject has had uncontrolled seizures while previously taking either topiramate or levetiracetam.

4. Subject has a history of nonepileptic seizures within 2 weeks prior to the first day of screening.

5. Subject has myoclonic or absence seizures.

6. Subject has a history of status epilepticus within 2 weeks prior to first day of screening. Status epilepticus is defined as 30 minutes of continuous motor seizures.

7. Subject has had epilepsy surgery within 3 months prior to the first day of screening.

8. Subject has any progressive neurologic disorder, including malignancy, brain tumor, active central nervous system infection, demyelinating disease, or degenerative or progressive central nervous system disease, with the exception of tuberous sclerosis and Sturge Weber syndrome.

9. Subject has any clinically significant uncontrolled medical illness, including hepatic or renal failure, ischemic cardiac disease, bone disorders, growth and maturation disorders of any type, malignancy, physical impairments that prevent normal ambulation, or any disorder that, in the opinion of the investigator, places the subject at risk through participation in a clinical study.

10. Subject has nephrocalcinosis, renal stones of any type, or hydronephrosis, as evidenced by medical history or screening examination.

11. Subject has a history of ≥2 long bone fractures if the subject is ≤10 years old; ≥3 long bone fractures if the subject is >10 years old, where at least 1 of the fractures was a low-impact fracture, defined as slight trauma that may include:

    - Falling to the ground from <0.5 m (standing height)
    - Falling to a resilient surface (rubber or sand) from 0.5 to 3 m
    - Falling from a bed or cot
    - Playing injuries, including playground scuffles

12. Subject has indwelling hardware, or has an abnormality of the skeleton or spine, such as scoliosis of 20 degrees or more, kyphosis, or skeletal dysplasia.

13. Subject has clinically relevant abnormalities noted on renal ultrasound or DEXA scans. Subjects with baseline BMD Z-scores ≤-2, for either posterior-anterior lumbar spine (L1-L4) or total body less head, will not be enrolled.

14. Subject has congenital glaucoma or known ocular deficits, or is receiving any ocular medications except lubricating eye drops or topical antibiotics.

15. Subject has a known history of central hyperthermia, dysautonomia, or other disturbances of autonomic function.

16. Subject has a known history of inborn errors of metabolism, mitochondrial dysfunction, or prior evidence of hyperammonemia.

17. Subject has any clinically significant abnormality in laboratory tests at screening, including but not limited to:

    - WBC count <3,000/μL or absolute neutrophil count <1,000/μL in the last 6 months
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or gamma-glutamyltransferase (GGT) ≥3 times the ULN
    - Total bilirubin ≥1.5 mg/dL or conjugated bilirubin ≥20% of total
    - Venous ammonia ≥2 times the ULN
    - 25-hydroxy-vitamin D (level for clinically significant vitamin D deficiency is <12.0 ng/mL, conventional units [<30 nmol/L, SI units])[19,42]
    - Parathyroid hormone (normal reference range is 14.0 to 72.0 pg/mL)
    - 1,25-dihydroxy-vitamin D, as determined by the age-dependent reference ranges (see lab manual)
    - Insulin-like growth factor 1 (IGF-1), as determined by the age-dependent reference ranges (see lab manual)

18. Subject has a bicarbonate level <20 mEq/L, has a diagnosis of metabolic acidosis, or is on alkali therapy.

19. Subject has refractory epilepsy and requires adjunctive AED therapy or is receiving >1 concurrent AED (including benzodiazepines, regardless of the reason for prescription).

20. Subject is being treated with furosemide, hydrochlorothiazide, vigabatrin, vitamin B_6 therapy for epilepsy, monoamine oxidase (A or B) inhibitors, felbamate, zonisamide, or any other medication that is a potent carbonic anhydrase inhibitor (eg, acetazolamide). Past treatment with furosemide for more than 2 weeks must be discussed with the sponsor and the discussion documented.

21. Subject is being treated with other drugs that may affect bone metabolism, eg, steroids (intravenous or oral steroids), growth hormone, antacids, or nonsteroidal anti-inflammatory drugs (NSAIDs) for chronic or underlying disorders for more than 7 consecutive days at least 1 month prior to the first day of screening.

22. Subject has been treated with an investigational drug within 5 half-lives prior to the first day of screening.

23. Subject has used topiramate or levetiracetam within 1 month prior to the first day of screening.

24. Subject has a known allergy or hypersensitivity to formulations for either topiramate or levetiracetam.

25. Subject is on a ketogenic diet to control epilepsy (eg, the ketogenic diet, the Atkins diet, the South Beach diet, or another low-carbohydrate diet).

26. Subjects with history of poor dietary intakes including requirements for special diets, inadequate caloric intake, inadequate nutrient intake, failure to thrive, growth abnormalities, poor weight gain, etc.

27. For subjects with at least 2 previous measurements available prior to the first day of screening, if the subject's length or weight has crossed (in a decreasing direction) 2 major percentile lines on the standard CDC growth charts, enrollment must be discussed with the sponsor and the discussion must be documented.

28. For all subjects, if the weight-versus-length plot at screening is lower than the 3rd percentile on the standard CDC chart, enrollment must be discussed with the sponsor and the discussion must be documented.

29. Subject has a history of noncompliance with AEDs or clinic attendance that is sufficient, in the judgment of the investigator, to interfere with participation in this study.

30. Subject is not reasonably expected to complete the study.

31. Subject is a child or other family member of the investigator or of an employee of the study center, with direct involvement in the proposed study or other studies under the direction of that investigator or study center.

32. Subject is pregnant, breast-feeding, or planning to become pregnant while enrolled in this study or within 4 weeks after the last dose of study drug.

33. Subject has a history of any suicidal behavior (attempt, interrupted, aborted, or preparatory) in the past 6 months prior to the screening visit.

NOTE: Investigators should ensure that all randomization criteria have been met prior to baseline. If a subject's status changes (including clinical laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. A girl of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (see Section 4.1, Inclusion Criteria).

2. Subjects must refrain from using any of the prohibited medications, including:

    - Ocular medications, except lubricating eye drops or topical antibiotics

- Furosemide, hydrochlorothiazide, vigabatrin, vitamin B_6 therapy for epilepsy, monoamine oxidase (A or B) inhibitors
- Any other medication that is a potent carbonic anhydrase inhibitor (eg, acetazolamide, furosemide, zonisamide)
- Citrate treatment
- Medications that may affect bone metabolism if taken for more than a 10-day treatment course, including intravenous or oral steroids, growth hormone, NSAIDs, or antacids

5. TREATMENT ALLOCATION AND BLINDING

Procedures for Randomization and Stratification

Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced using randomly permuted blocks and will be stratified by country and age group (2 to 5 years of age, 6 to 9 years of age, 10 to 12 years of age, and 13 to 15 years of age). The enrollment will be monitored throughout the study to ensure that subjects are enrolled for each integer year in each treatment group.

Based on this information, the interactive web-based response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. As subjects are randomly assigned to treatment, the IWRS will assign a study drug kit to be dispensed at that visit. New study drug kits will be assigned each time the IWRS is accessed for dispensing additional study drug.

Blinding

As this is an open-label study, blinding procedures are not applicable for treatment assignment.

To minimize any bias in measurement, after randomization 3 of the safety assessments will be obtained in a blinded fashion, including the DEXA scan, renal ultrasound, and height. The location for these data should be kept separate from the rest of the study data. Procedures for maintaining the blind will include the following (further details will be provided in a separate Blinding Plan for this study):

- Separate secure locations for blinded and unblinded study documents
- A separate office or physical space for obtaining the height measurements
- Blinded staff will not be permitted access to areas where unblinded activities are performed.
- Measures will be required to ensure no overlap of equipment. Height will be measured by a trained individual who is blinded (unaware of the treatment); blinded height measures are not to overlap assessments of unblinded assessments (weight and vital signs). The same blinded

person should obtain height measurements using the same technique on the same stadiometer at a given center. It is also recommended that the stadiometer be calibrated at least monthly and that this be documented.

- Blinded height measures are to be recorded in the source documents, or provided to the unblinded study coordinator for entry into the source documents. The unblinded study coordinator will then enter this data, along with other visit data, into the CRF.
- Documented measures will be required to ensure that no communication of blinded vs. unblinded data takes place in the same office suite.

6. DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned to receive unblinded, flexible dosages of topiramate or levetiracetam as follows:

- Topiramate: weight-based dosing for subjects 2 to <10 years of age, not to exceed 350 mg/day, as tolerated; not to exceed 400 mg/day in subjects 10 to 15 years of age, as tolerated
- Levetiracetam: weight-based dosing for all subjects 2 to 15 years of age, not to exceed 60 mg/kg/day, as tolerated

Subjects will receive study drug in a twice-a-day regimen (BID). The first dose of study drug on Day 1 will be taken in the evening. After randomization, subjects will be titrated as tolerated to the maximum recommended dosage for optimal clinical effect over 6 to 8 weeks and will be maintained on that dosage through the open-label treatment phase, with the option for dosage adjustment as required for optimal clinical effect. Changes to this schedule will be based on a risk-benefit assessment of the subject's clinical condition by the investigator.

Topiramate Titration in Subjects 2 to <10 Years of Age

Dosing in subjects 2 to <10 years of age is based on weight. During the titration period, the initial dosage of topiramate should be 25 mg/day, administered nightly for the first week. Based upon tolerability, the dosage can be increased to 50 mg/day (25 mg BID) in the second week (see Tables 1 to 3 in the titration schedules in Attachment 2). Dosage can be increased by 25 to 50 mg/day each subsequent week as tolerated. Titration to the maximum recommended dosage should be attempted over 6 to 8 weeks. Based upon tolerability and seizure control, the rate of titration may be adjusted to achieve optimal clinical response. The total daily dosage should not exceed the maximum maintenance dosage for each range of body weight (Table 1). Subjects with a body weight >38 kg will be assigned to the titration schedule for subjects 10 to 15 years of age, as described below.

Table 1: Topiramate Monotherapy Target Total Daily Maintenance Dosing for Subjects 2 to <10 Years of Age

Weight (kg)	Total Daily Dosage (mg/day)[a] Minimum Maintenance Dosage	Total Daily Dosage (mg/day)[a] Maximum Maintenance Dosage
Up to 11	150	250
12 – 22	200	300
23 – 31	200	350
32 – 38	250	350

[a] Administered in 2 equally divided doses.

The topiramate sprinkle formulation will be provided for those subjects who cannot swallow tablets. Sprinkle capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use.

Topiramate Titration in Subjects 10 to 15 Years of Age

The recommended dosage for topiramate monotherapy in adults and pediatric patients 10 years of age and older is 400 mg/day in 2 divided doses. The dosage should be achieved by titration according to the schedule shown in Table 4 in the titration schedules in Attachment 2.

Levetiracetam Titration in Subjects 2 to 15 Years of Age

Treatment should be initiated with a daily dosage of 20 mg/kg/day in 2 divided doses (10 mg/kg BID). The daily dosage may be increased every 2 weeks by increments of 20 mg/kg/day to the recommended daily dosage of 60 mg/kg/day (30 mg/kg BID). The maximum recommended daily dosage is 3,000 mg (1,500 mg BID). Subjects with a body weight ≤20 kg should be dosed with oral solution. Subjects with body weight above 20 kg can be dosed with either tablets or oral solution. See Tables 5, 6, and 7 in the titration schedules in Attachment 2 for dosing for oral solution for subjects with a body weight ≤20 kg, and Table 8 in the titration schedules in Attachment 2 for dosing for tablets for subjects with a body weight >20 kg.

The following calculation should be used to determine the appropriate daily dosage of oral levetiracetam solution for pediatric subjects based on a daily dosage of 20 mg/kg/day, 40 mg/kg/day, or 60 mg/kg/day:

$$\text{Total daily dosage (mL/day)} = \frac{\text{Daily dosage (mg/kg/day) x subject weight (kg)}}{\text{100 mg/mL}}$$

All study drugs will be provided in child-resistant packaging during the study. It is recommended that tablets not be broken. Both topiramate and levetiracetam can be taken without regard to

meals. Study staff will instruct subjects and/or parents/caregivers on how to store medication for at-home use as indicated for this study. If a subject vomits within 30 minutes of receiving a dose, the dose will be repeated. If a subject vomits a second time or more than 1 hour later, the dose will not be repeated. All cases of vomited doses and action taken must be recorded in the subject's take-home record. Subjects will be instructed to take any missed doses of study drug as soon as possible. However, if the subject is within 6 hours of taking the next scheduled dose, he or she should wait until then to take the usual dose of study drug and skip the missed dose. Subjects should not take a double dose in case of a missed dose.

Subjects should be titrated and maintained according to clinical response, eg, titration may be slowed on the basis of tolerability and may be accelerated for the purposes of seizure control. Maintenance dosages should be based on optimal clinical response and may be adjusted at any time during the open-label treatment phase. Subjects are recommended not to exceed maximum recommended maintenance dosages; however, subjects will not be discontinued from the study if higher doses are required for optimal clinical effect as judged by the investigator. Data collected while on dosages that exceed maximal recommendations may be analyzed separately, as appropriate.

Once a subject completes the study or discontinues early from the study, at the discretion of the investigator, he or she will either continue on commercially available topiramate or levetiracetam or be tapered off of topiramate or levetiracetam over a period of up to 2 weeks.

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of all drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study (at each visit). Subjects will receive instructions on compliance with study treatment at the screening visit (eg, subject take-home record). During the course of the study, the investigator or designated study research staff will be responsible for providing additional instruction to reeducate any subject who is not compliant with taking the study drug.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy AEDs and other medications taken within 2 years prior to the study must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with the start of the first dose of study drug. Concomitant therapies should also be recorded beyond 30 days after the last dose of study drug, but only in conjunction with new or worsening adverse events or serious adverse events that meet the criteria outlined in Section 12.3.2, Serious Adverse Events.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

For subjects receiving an AED at baseline, this AED should be tapered down and discontinued during the titration period. Concomitant AEDs at baseline used for any purpose will be withdrawn in one-third decrements during the 6- to 8-week titration period.

Only AED monotherapy will be used for both treatment groups. In the event of insufficient seizure control or intolerability, it should be explored first if a dosage adjustment of the study drug might be useful before adding another AED. However, subjects will not be discontinued from the study if 1 or more concomitant AEDs are added after initiating treatment with study drug. Data will be collected prior to the use of the concomitant AED(s) for the primary analysis. Data subsequently collected while on the concomitant AED(s) will be analyzed in a secondary analysis for each safety outcome of interest.

Other prohibited concomitant medications include:

- Ocular medications, except lubricating eye drops or topical antibiotics
- Furosemide, hydrochlorothiazide, vigabatrin, vitamin B_6 therapy for epilepsy, monoamine oxidase (A or B) inhibitors, or felbamate
- Any other medication that is a potent carbonic anhydrase inhibitor (eg, acetazolamide, furosemide, zonisamide)
- Citrate treatment
- Medications that may affect bone metabolism taken for more than a 10-day treatment course, including intravenous or oral steroids, growth hormone, NSAIDs, antacids, calcium, vitamin D, or multivitamins

Subjects will be allowed to take calcium, vitamin D, and multivitamins as concomitant therapy provided the dosages fall within the range of recommended daily allowances for the age of the subject. These agents will only be allowed as prophylaxis against a deficiency, and not as a treatment for a previously diagnosed deficiency.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule that follows the synopsis summarizes the frequency and timing of safety, PK, and other measurements applicable to this study.

The study includes 3 phases: a screening phase of up to 35 days, an open-label treatment phase of 1 year's duration (including titration and maintenance), and a posttreatment phase of 30 days, during which subjects will either continue on commercially available topiramate or levetiracetam or will be tapered off of topiramate or levetiracetam over a period of up to 2 weeks. There may be an optional post-study follow-up phase to obtain DEXA measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or greater) in BMD, based on local DEXA scan results, after 1 year of treatment with topiramate, to determine whether a decrease in BMD after or during 1 year of treatment with topiramate is reversible. These subjects will have a repeat DEXA scan 6 months after discontinuation of study drug.

The total blood volume to be collected from each subject will be approximately 44.7 mL (45.8 mL for adolescent girls who require serum pregnancy test at screening; Table 2). Blood samples for testing specific analytes are listed in order of priority, in the event of difficulties in obtaining the desired volume of blood for any reason at a specific visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 2: Volume of Blood to be Collected From Each Subject (mL)

Visits	Screening[a]	Month 1	Month 3	Month 6	Month 9	Month 12	Total Volume of Blood[b]
Blood chemistry profile, including electrolytes	1.1	1.1	1.1	1.1	1.1	1.1	6.6
CBC (EDTA whole blood)	1.2	1.2	1.2	1.2	1.2	1.2	7.2
25-hydroxy-vitamin D[c]	1.1			1.1		1.1	3.3
IGF-1[c]	1.1			1.1		1.1	3.3
Parathyroid hormone (intact)[c]	1.1			1.1		1.1	3.3
1,25-dihydroxy-vitamin D[c]	3.0			3.0		3.0	9.0
Ammonia, venous[c]	1.2	1.2	1.2	1.2	1.2	1.2	7.2

Table 2: Volume of Blood to be Collected From Each Subject (mL)

Visits	Screening[a]	Month 1	Month 3	Month 6	Month 9	Month 12	Total Volume of Blood[b]
Pharmacokinetic samples (plasma; AED levels)		1.2	1.2	1.2		1.2	4.8
Serum pregnancy test	1.1						1.1
Total	10.9 mL	4.7 mL	4.7 mL	11.0 mL	3.5 mL	11.0 mL	45.8 mL

a The optional use, during the screening period, of local laboratory evaluations for 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Parathyroid hormone (intact) and IGF-1 might lead to an increase in blood volume for the subject concerned. The total volume is dependent on the local laboratory requirements and on the number and type of individual assays.

b Calculated as number of samples multiplied by amount of blood per sample.

c All laboratory tests will be evaluated centrally except for venous ammonia, which will be evaluated locally (except in select countries where local testing is not possible, in which case the central laboratory will also evaluate venous ammonia). The laboratory tests for 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Parathyroid hormone (intact) and IGF-1 at screening will be evaluated centrally but additional evaluation at local laboratory is allowed to reduce the duration of the screening phase. At the discretion of the investigator, one, or more of these laboratory parameters may be evaluated at the local laboratory. The volume of blood is based on reference laboratory minimal volumes.

AED=antiepileptic drug; CBC=complete blood count; EDTA= ethylene diamine tetra-acetic acid; IGF-1=insulin-like growth factor 1.

9.1.2. Screening Phase

The screening phase will last up to 35 days, during which subjects will be assessed for study qualifications and other measures as listed in the Time and Events Schedule following the synopsis.

9.1.3. Open-Label Treatment Phase

The open-label treatment phase includes randomization and distribution of study drug and titration instructions (Visit 2; Day 1), a 6- to 8-week titration period, and a maintenance period, during which subjects will remain in the study until they either complete 1 year of open-label treatment or withdraw from the study.

Subject take-home records and seizure diaries will be given to parents/guardians at Visit 1 and at each subsequent visit. Each subject's parent will record in the seizure diary the date, description, and number of seizures. The investigator or designated study personnel will review the data to be recorded in the subject take-home record with the subject’s parents/legally acceptable representatives at the beginning of the study. At each visit, the investigator will review the seizure data, and then transcribe the data onto the appropriate page of the CRF.

Titration intervals and dosages may be adjusted for individual subjects to achieve their optimal dosage. Subjects receiving 1 concomitant AED at baseline for any purpose will have their AED tapered down and discontinued in one-third decrements during the 6- to 8-week titration period.

At the end of the titration period, the dosage of study drug should be maintained but may be adjusted at the investigator's discretion for optimal clinical effect.

Subjects will return for a clinic visit at Months 2 and 3, with subsequent visits to occur every 3 months.

9.1.4. Posttreatment Phase (Follow-Up)

Subjects who complete the study or discontinue early from the study may at the discretion of the investigator either continue on commercially available topiramate or levetiracetam or be tapered off of topiramate or levetiracetam over a period of up to 2 weeks during the posttreatment phase. A final visit will be performed at the end of the 1-year open-label treatment period or upon early withdrawal, including review of seizure frequencies from the subject seizure diary and review of safety and adverse events.

Telephone contact will be made to assess adverse events and concomitant medications 30 days after the last dose of study drug, unless the subject has died, is lost to follow-up, or has withdrawn consent/assent. If the information on adverse events and concomitant medications is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the subject has died, the date and cause of death must be collected and documented on the CRF.

9.1.5. Post-Study Phase (Follow-Up)

There may be an optional post-study follow-up phase to obtain DEXA measurements in a subgroup of subjects who experience a clinically important reduction (change in Z-score of -0.5 or greater) in BMD, based on local DEXA scan results, after 1 year of treatment with topiramate, to determine whether a decrease in BMD after or during 1 year of treatment with topiramate is reversible. These subjects will have a repeat DEXA scan 6 months after discontinuation of study drug.

9.2. Pharmacokinetics

9.2.1. Sample Collection and Handling

Blood samples (1 mL per sample) for the determination of plasma topiramate and levetiracetam concentrations will be obtained during clinic visits according to the Time and Events schedule. If possible, blood samples for PK evaluations should be trough samples (ie, taken immediately before the morning dose) and coincide with samples drawn for clinical laboratory tests. During each PK assessment, the dosing regimen, dose administered, time and date of dose administration, time of sample collection, and concomitant medications will be recorded in the CRF.

Attachment 3, Attachment 4, and Attachment 5 detail further information regarding handling and shipment of plasma samples.

9.2.2. Analytical Procedures

Pharmacokinetics

All PK samples will be analyzed under the supervision of the sponsor's Department of Bioanalysis. Plasma samples will be analyzed to determine concentrations of topiramate and levetiracetam using validated, specific and sensitive liquid chromatography-tandem mass spectrometry methods.

9.2.3. Pharmacokinetic Parameters

Pharmacokinetic parameters will not be estimated. Topiramate and levetiracetam plasma concentration data will be determined by a validated bioanalytical method(s) and summarized.

9.3. Safety Evaluations

Details regarding the DMC are provided in Section 11.5.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedule. For all evaluations, if possible, the same individual should evaluate the subject at all visits.

Take-Home Record/Seizure Diary

Throughout the study, caregivers (parents or legally acceptable representatives) of the subjects must maintain a subject take-home record and a seizure diary. The take-home record will include data on study drug administration, concomitant medications, and items of general health. The seizure diary contains instructions to record the date and description of each seizure and will be reviewed by the investigator at each study visit during the open-label treatment phase and at the end-of-study/early withdrawal visit. The information from the take-home record and seizure diary will be reviewed by the investigator and transcribed into the electronic case report form (eCRF).

Adverse Events

Adverse events will be reported by the parent (or his or her legally acceptable representative) for the duration of the study, from the time of signing the consent/assent. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. Subjects will be monitored for signs of suicidal ideation and behavior with both adverse event reports and the C-SSRS (see below), and they (or their caregivers, as appropriate) will be advised to seek immediate medical attention should signs of suicidal ideation or behavior emerge.

Clinical Laboratory Tests

Blood samples for serum chemistry (nonfasting) and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The following tests will be performed by the central laboratory except for venous ammonia, which will be evaluated locally (except in select countries where local testing is not possible, in which case the central laboratory will also evaluate venous ammonia). The laboratory tests for 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Parathyroid hormone (intact) and IGF-1 at screening will be performed at a central laboratory, but additional evaluation at local laboratory is allowed in order to reduce the duration of the screening phase:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell count
  -WBC count with differential
  -platelet count

- Serum Chemistry Panel

-sodium	-creatine phosphokinase
-potassium	-lactic acid dehydrogenase
-chloride	-uric acid
-bicarbonate	-calcium
-blood urea nitrogen (BUN)	-phosphorus
-creatinine	-albumin
-glucose	-total protein
-AST	-cholesterol
-ALT	-triglycerides
-GGT	-magnesium
-total bilirubin	-25-hydroxy-vitamin D*
-ammonia	-1,25-dihydroxy-vitamin D*
-serum pregnancy test (at screening, for girls of childbearing potential)	-parathyroid hormone*
-alkaline phosphatase	-IGF-1*

* Only measured at visits for screening, Month 6, and Month 12/early withdrawal (see Bone Mineralization section below).

  - Special instructions for ammonia sample collection: Collect blood on ice, separate plasma from cells, and freeze ASAP (within 15 minutes of draw time). Specimens need to be spun in a refrigerated centrifuge and are unstable if thawed and refrozen.
  - In addition to its routine assessment, free-flowing venous ammonia will be obtained on an immediate basis in the event of:
    - Clinical evidence of change in mental status consistent with a hyperammonemic encephalopathy (not seizures or post-ictal state)
    - Elevated hepatic enzymes as follows, unless a routine ammonia done at the same time was normal:
      - ALT, AST, or GGT ≥3 times the ULN (or ≥2 times the ULN for subjects taking valproic acid)
      - Total bilirubin ≥1.5 mg/dL
      - Conjugated bilirubin ≥20% of the total
      - Any other appropriate clinical indication

- 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, Parathyroid hormone (intact) and IGF-1:

  At the discretion of the investigator, one or more of these laboratory parameters may be evaluated at the local laboratory to reduce the duration of the screening phase. In such instances, the local laboratory instructions should be followed and local reference ranges should be applied. The local laboratory results would be used for decision regarding randomization. The central laboratory evaluation results will be used for study data analysis. The additional use of a local laboratory might lead to an additional amount of blood volume to be drawn from the subject at screening.

- Urinalysis will be performed by the central laboratory, and will include dipstick and sediment as noted below. If dipstick result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

Dipstick	**Sediment**
-specific gravity	-RBCs
-pH	-WBCs
-glucose	-epithelial cells
-protein	-crystals
-blood	-casts
-ketones	-bacteria
-nitrite	

- Urine Pregnancy Testing (for girls of childbearing potential only) to be obtained at all visits after screening during the open-label treatment phase. If a girl starts menstruating and becomes of childbearing potential during the study, urine pregnancy tests should be obtained at all subsequent visits during the open-label treatment phase.
- 24-Hour Urine Collection: A 24-hour urine collection will be analyzed for pH, calcium, citrate, phosphorus, and creatinine levels. Collection instructions and storage conditions will be specified in the laboratory manual. A 14-day window on either side of the scheduled Month 6 visit will be allowed for 24-hour urine collection. The collection at Month 12 should be completed before the Month–12 visit as this evaluation should be obtained while the subject is still receiving study–drug therapy.

Additional use of local laboratories is allowed in cases where safety follow-up is time-critical and the central laboratory results are not expected before the need to take actions for safety reasons.

After consultation with the medical monitor, investigators may obtain additional laboratory assessments and/or advice from local medical consultants in the event of any clinically important safety concern.

Bone Age Radiograph

A hand/wrist x-ray will be obtained in the nondominant hand/wrist to determine bone age at baseline and at Month 12 (or final study visit if a subject discontinues prematurely).[20] This will be read and interpreted locally.

Electrocardiogram

A single 12-lead ECG will be collected at screening only. To be enrolled, subjects must have an ECG at screening with no "abnormal, clinically significant" interpretations by a local cardiologist.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG, vital signs, blood draw.

Vital Signs

Vital signs will be recorded at the times given in the Time and Events Schedule. Measurement of vital signs includes axillary temperature, heart rate, respiratory rate, and blood pressure. Temperature will be assessed using an axillary thermometer; if temperature is ≥38.0°C, the temperature should be repeated immediately and both values recorded in the CRF. Respiration measurements will be assessed over at least 30 seconds. Blood pressure and heart rate measurements should be assessed with a completely automated device (if available) consisting of an inflatable cuff and an oscillatory detection system. All values will be registered on a built-in recorder so that measurements are observer-independent. If an automated device is not available, all manual heart rate measurements will be measured each time for a full minute to minimize the effects of heart rate variability. Blood pressure will be measured with the cuff placed on the right arm. An appropriate size cuff has 1) an inflatable cuff bladder width that is at least 40% of the arm circumference (at a point midway between the olecranon and the acromion) and 2) a cuff bladder length that covers 80% to 100% of the circumference of the arm.

Orthostatic vital signs will be obtained for all subjects pending cooperation of subjects. A set of 3 measurements will be obtained at baseline only, separated by intervals of 10 minutes. Thereafter, only 1 orthostatic vital sign measurement will be taken at all subsequent visits. The method for obtaining orthostatic vital signs will be as follows: subject will be supine for 5 minutes prior to measurement, and standing for 2 minutes prior to measurement.

Physical Examination

Physical examinations and anthropometric measurements, including weight, height, and pubertal stage according to Tanner's classification,[37] will be performed at the times specified in the Time and Events Schedule.

- Height will be assessed using a wall-mounted stadiometer. Height will be read to the nearest 0.1 cm; measures are to be repeated at least 3 times. Based on previous measurements and

clinical judgment, the healthcare professional should discard any extreme results and make additional measurements until 3 approximately consistent measurements are obtained. All 3 final measurements will be recorded in the CRF; all measurements will be recorded into the source documents. To obtain accurate measures, shoes and hair adornments should be removed and the child should be positioned with heels, buttocks, and back of head against the stadiometer.

The healthcare professionals who measure height at each visit must be trained in the standardized procedure. If possible, the same individual and the same equipment should collect all height measurements at each study site, to help ensure consistency of measurements.

All study site personnel performing the height assessment must be blinded to study treatment assignment and the rest of the subjects' data to avoid/minimize bias. A blinded study nurse or other staff will measure the height of the subject and record it in the source documents, or provide it to the unblinded study coordinator for entry into the source documents. The unblinded study coordinator will then enter this data, along with other visit data, into the CRF. The location for the height measurement data should be kept separate from the rest of the study data, and procedures must be in place to ensure maintenance of the blind.

- Body weight will be measured using digital electronic or beam balance scale to the nearest 0.1 kg. Prior to weight measurements, the scale should be set to zero to avoid drift in equipment functioning. Subjects will be weighed in examination gowns or in lightweight clothing and without shoes. If possible, weight measurements should be taken at the same time of day after the bladder is emptied so subjects are always evaluated in the same physiologic state.
- Tanner staging of subjects of age 8 years and above will be conducted by a qualified pediatric endocrinologist or by a physician trained in the method.[27]

Any abnormalities present at baseline, or subsequent changes, will be documented in the appropriate sections of the eCRF. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Neurologic Examination

Neurologic examinations (including mental status, cranial nerves, motor examination [muscle tone, strength, deep tendon reflexes], cerebellar functions, and gait) will be performed by the investigators at all visits except Month 2.

Any abnormalities present at baseline, or subsequent changes from baseline, will be documented in the appropriate sections of the eCRF. Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Bone Mineralization

Monitoring changes in bone mineralization will include: DEXA scans of the posterior-anterior lumbar spine (L1-L4) and total body less head area BMD and bone mineral content (BMC), and serum biochemical parameters of bone metabolism, including serum levels of alkaline phosphatase, calcium, phosphorus, parathyroid hormone (intact), 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin D, and IGF-1. Biochemical assessments will be obtained at screening, Month 6, and Month 12/early withdrawal. DEXA scans (without sedation) will be obtained at baseline, Month 6, and Month 12/early withdrawal. For all scans, up to 3 DEXA scan attempts will be performed all on the same day with the goal of obtaining 2 complete, movement-free scans, recognizing that it might not be possible to obtain 2 adequate scans in some younger children.

All scans will be centrally analyzed; central analysis will be performed by one highly trained technologist at the DEXA reading center with International Society for Clinical Densitometry (ISCD) certification, a license to operate a DEXA scanner, and 3 to 5 years of experience with whole body and spine scans. In addition, the baseline and M12 scans will be read locally to determine eligibility for randomization and for the Post-Study Follow-Up phase.

If any subject shows a clinically important reduction (change in Z-score of -0.5 or greater) at 6 months or 12 months, the central reader will reassess the scan for quality and to determine the presence of any artifacts, and will provide recommendations based on the Z-score and BMD. Abnormalities will be reported to parents and primary-care physicians, and appropriate referrals for further evaluation will be made by the investigator, if needed.

Short-term precision testing will be performed for DEXA measurements according to standard protocols. The same DEXA machine will be used at each site for all subjects and all measurements; only clinical sites using recent-generation Hologic systems (Discovery and Delphi systems) or General Electric Lunar systems will participate in the study; the GE/Lunar systems will only be used for subjects ≥5 years of age. The same technician should acquire all scans for any particular subject. All technicians should be certified by the ISCD or have similar competency training with specific knowledge of the DEXA system, including a degree program in radiologic technology. Technicians must also pass a written competency test and undergo specific training for this study, either online or in person, for scanning of young children. Further details regarding the DEXA measurements, including the reference databases to be used, will be provided in the DEXA Manual for this study.

Both the technicians administering the DEXA scans and the central reader will be blinded to the treatment group.

Physical Activity Evaluation

Information regarding physical activity will be obtained at screening from the HAES (see Attachment 1 for an example). Parents/caregivers will be asked how many hours their children spent in a 24-hour day in 1 of 4 categories of activity/inactivity to assess physical activity levels on the basis of the standardized and validated activity questionnaire. The total number of hours each subject spends in each category will be processed to determine the activity score on a scale of -100 (100% inactive) to +100 (100% active). A value of 0 indicates that the subject spent 12 hours of the day active and an equal number of hours inactive.[22]

Renal Stone Evaluation

Renal ultrasounds (at screening, Month 6, and Month 12/early withdrawal; without sedation and after a 3-hour period during which only water, juice, or electrolyte solution will be permitted, as clinically indicated) will be performed under blinded conditions (after randomization) by a qualified radiologist or nephrologist at each site with age-appropriate inducers. The ultrasounds will be read/interpreted centrally (local reading at the screening visit is acceptable to determine eligibility for randomization; both the local and central readers will be blinded to the study treatment group). If possible, examinations should be done by the same individual at any given site.

Subjects with definite renal stones, nephrocalcinosis, or hydronephrosis at screening will be excluded from the study. Other abnormalities will be followed in subsequent examinations, which may occur more frequently at the discretion of the investigator in collaboration with the sponsor's medical monitor. Abnormalities will be reported to parents and primary-care physicians, and appropriate referrals will be made by the investigator if needed.

Cognitive, Developmental, and Behavioral Assessments

Cognitive, developmental, and behavioral assessments will be conducted as follows:

- Cogstate Battery (2 practice sessions, 1 at screening and 1 baseline prior to the baseline assessment; assessed at baseline, Month 6, and Month 12/early withdrawal):
    - ◊ For subjects 6 to 15 years of age, the Detection Test, Identification Test, One Card Learning Test, One Back Test, and Groton Maze Learning Test will be administered.
    - ◊ For cooperative subjects 4 to 5 years of age, the Detection Test and the Identification Test will be administered.
- Language function test (Animal Fluency NEPSY-II (A Developmental NEuroPSYchological Assessment) Test - subjects 6 to 15 years of age; 1 practice session at screening; assessed at baseline, Month 6, and Month 12/early withdrawal)
- Vineland Adaptive Behavior Scale (to be completed by a parent or guardian for subjects 2 to 5 years of age, assessed at baseline, Month 3, Month 6, and Month 12/early withdrawal)

- Child Behavior Checklist (CBCL)-Parent version (Achenbach System of Empirically Based Assessment [ASEBA]) (assessed at baseline, Month 3, Month 6, and Month 12/early withdrawal)
    - ◊ Preschool version - subjects 2 to 5 years of age
    - ◊ School-age version - subjects 6 to 15 years of age

Note: For subjects who turn 6 years of age during the study, the Vineland Adaptive Behavior Scale, the preschool version of the CBCL, and only the Detection Test and Identification Test of the Cogstate Battery will continue to be administered throughout the study.

Cognitive Assessments

The Cogstate Computerized Test Battery[15,26,30] requires less than 30 minutes to administer, and will be administered by non-expert (non-psychologist) study site personnel trained in the Cogstate administration method. All tests will be managed and scored centrally by Cogstate. The Battery includes tests that assess information processing speed and fine motor skills, attention, learning and memory, working memory, and executive functions. The tests were designed for multiple assessments over a short time period, with virtually no practice effects in adults and children. The pediatric version of the card tests (Detection Test, Identification Test, One Card Learning Test, and One Back Test) use cards with age-appropriate designs (ie, colors, shapes, and numbers) rather than using cards from a French playing card deck. However, the paradigms are the same.

- The Detection Test is a measure of information processing speed and fine motor skills, and uses a well-validated simple reaction time paradigm with card stimuli. In this test, the playing cards are all red and black. The subject is asked to press the Yes key as soon as the card in the center of the screen flips over.
- The Identification Test is a measure of visual attention and uses a well-validated choice reaction time paradigm with card stimuli. In this test, the playing cards are all either red or black. The subject is asked whether the card currently being presented in the center of the screen is red. The subject responds by pressing the Yes key when the card is red and the No key when it is black.
- The One Card Learning Test is a measure of visual recognition memory and uses a well-validated pattern separation paradigm using card stimuli. In this test, the cards are similar to those found in a deck of playing cards. The subject is asked whether the card currently being presented in the center of the screen was seen previously in this test. The subject responds by pressing the Yes or No key. Because no card has been presented yet, the first response is always No.
- The One Back Test is a measure of working memory and uses a well-validated n-back paradigm using card stimuli. In this test, the cards are similar to those found in a deck of playing cards. The subject is asked whether the card currently being presented is the same as the one presented immediately previously. The subject responds by pressing the Yes or No key. Because no card has been presented yet, the first response is always No.

- The Groton Maze Learning Test is a measure of problem solving and reasoning and uses a well-validated maze learning paradigm. In this test, the subject is shown a grid of boxes on a computer screen. A pathway is hidden among these possible locations. Each box represents move locations, and the grid refers to the box array (eg, 10 × 10). Subjects are required to find the hidden pathway guided by search rules. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. There are a specific number of well-matched alternative pathways available. The software records each move as an error or as a correct move.

The Cogstate pediatric normative database consists of cognitive tests from over 55,000 healthy children. The majority of the data are from select test scales (One Card Learning Test, One Back Test, Detection Test, Identification Test) in 10- to 18-year-old children, but there are data on the Groton Maze Learning Test in younger children. Furthermore, the Cogstate tests have been shown to have demonstrated utility in pediatric clinical studies in oncology, and in the treatment of disorders such as attention-deficit/hyperactivity disorder, HIV, neurodevelopmental disorders, and sickle cell disease.

The semantic item "Animals" from the Word Generation subtest of the NEPSY-II (A Developmental NEuroPSYchological Assessment) will be included in this study. This test measures verbal productivity through the ability to generate words within specific categories and is a commonly used and standardized measure of language and executive functioning in children and adolescents. This will be administered by study site personnel who are trained according to a study-specific rater training plan. The test will be scored by the site rater and the data will be transferred to Cogstate.

Developmental Assessments in Subjects 2 to 5 Years of Age

The Vineland Adaptive Behavior Scale will be administered for subjects 2 to 5 years of age, to assess developmental level and adaptive functioning. For very young children, the behaviors assessed are closely correlated with developmental milestones.

The Vineland Adaptive Behavior Scale, version II focuses on behaviors needed to operate in an age-appropriate manner in the individual's environment. It is age-specific and provides an assessment of function in the domains of communication, daily living, socialization, and motor skills, as well as a composite scale. The Vineland scores have a mean of 100 and a standard deviation of 15, based on a normative population sample.[6,36]

The interview will be completed by the parent/guardian and will be scored by a trained rater at screening, at Month 3, Month 6, and Month 12/early withdrawal.

Behavioral Assessments

The CBCL is a widely used method of identifying problem behavior in children.[1,2] It is a component in the ASEBA. It is a detailed, specific measure of competencies, adaptive functioning, and behavioral/emotional problems in children, split into competencies and problems. The CBCL has been shown to have good reliability and validity,[2] and has been used in many pediatric populations with different disorders, including epilepsy.[5,13,34]

Problems are identified by a respondent who knows the child well, usually a parent. There are two versions of the CBCL-Parent version. The preschool checklist (CBCL/1½-5) is intended for use with children 18 months to 5 years of age (see Attachment 6 for an example). The school-age version (CBCL/6-18) is for children 6 to 18 years of age (see Attachment 7 for an example).

The checklists consist of a number of statements about the child's behavior, eg, "Acts too young for his/her age." Responses are recorded on a Likert scale: 0=not true, 1=somewhat or sometimes true, 2=very true or often true. The preschool checklist contains 99 questions and the school-age checklist contains 112 questions.

Similar questions are grouped into a number of syndromes, eg, Aggressive behavior, and their scores are summed to produce a score for that syndrome. Some syndromes are further summed to provide scores for Internalizing (Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints) and Externalizing problem scales (Rule-Breaking Behavior and Aggressive Behavior). A total score from all questions is also derived. For each syndrome, problem scale, and the total score, tables are given that determine whether the score represents normal, borderline, or clinical behavior. These categorizations are based on quantiles from a normative sample.

Suicidality

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and will be administered at every visit, to assess suicidal ideation, intent, and behavior.[31] The scale will be administered by study personnel (either non-expert, eg, study coordinator, or clinical expert, eg, MD or PhD psychologist), asking questions of the subjects (preferable, if cooperative) or parents/caregivers for subjects who are not cooperative. If possible, the same individual should evaluate the subject at all visits. The assessment will be administered for subjects 6 to 15 years of age and will not be administered for subjects 2 to 5 years of age. Examples of the scales are provided in Attachment 8 (Baseline) and Attachment 9 (Since Last Visit).

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has completed 1 year of open-label treatment. Subjects who prematurely discontinue study treatment for any reason before completion of the 1-year open-label treatment phase will not be considered to have completed the study. Subjects who require a concomitant AED(s) after initiating treatment with study drug and continue in the study until Month 12 will also not be considered to have completed the study.

10.2. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- The investigator or sponsor believes (eg, that for safety or tolerability reasons such as an adverse event) it is in the best interest of the subject to discontinue treatment.
- Death
- Other reasons
- If a female subject becomes pregnant during the study, she must be discontinued from the study and the pregnancy followed to term, if applicable.

During the study, subjects will also be withdrawn if:

- Subject develops status epilepticus not controlled by a single rescue agent.
- At the discretion of the investigator, subject develops any new seizure types or any clinically relevant safety issue.
- Subject requires greater than a 10-day course of medications that may impact bone metabolism, including intravenous or oral steroids, furosemide, growth hormone, NSAIDs, antacids, or calcium/vitamin D supplements.
- Subject develops nephrocalcinosis (diagnosed in any way) or develops a significant clinical adverse event (eg, serious event, treatment-limiting event, or other consideration) diagnosed as being related to a new kidney stone. Ultrasound results that suggest an asymptomatic kidney stone will not necessarily serve as a reason for withdrawal from the study.
- The investigator believes the subject to be at significant risk of suicidal or violent behavior.

If a subject discontinues treatment before the end of the open-label treatment phase, the end-of-study assessments should be obtained.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the study data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

All subjects who are randomized will be included in the analysis population.

11.2. Sample Size Determination

A total of 282 randomized subjects, 141 in each treatment group, will be recruited to the study. The sample size takes into account a 1-year dropout rate of 29%, which is a conservative estimate based on the dropout rates observed in a previous monotherapy study in the 6- to 15-year-old age group, Study TOPMAT-EPMN-106, including a dropout rate of 22% in the study overall (both double-blind and open-label phases) and a dropout rate of 35% for the double-blind phase. The sample size was estimated in order to achieve a sufficient precision for the estimates of the treatment effect on the key endpoints. The precision of the confidence interval (CI) estimates for the key safety parameters are shown below:

- *Annual change in BMD (L1-L4) Z-score:* In the Bone Mineral Density in Childhood Study (BMDCS), mean annual change in BMD (L1-L4) Z-score in 6- to 15-year-old healthy subjects was, as expected, minimal (0.01-0.07).[35] The standard deviation (SD) varied from 0.3 to 0.48 across sex and age groups.[35] Assuming an SD of 0.4, with 100 completed subjects per group, the 95% CI for the treatment difference will have a precision of 0.12.
- *Annual change in height Z-score in the 2- to 9-year-old age group:* In the monotherapy epilepsy study TOPMAT-EPMN-106, the observed change from baseline in mean height Z-score at 1 year among the 2- to 9-year-old subjects treated with topiramate 400 mg/day was -0.18, with an SD of 0.28.[40] Assuming that 53% of the subjects will be recruited in the 2- to 9-year-old age group, ie, 53 completed subjects per treatment group, the 95% CI for the treatment difference will have a precision of 0.11.
- *Incidence of kidney stone formation:* In the studies TOPMAT-PEP-3001 and TOPMAT-PEP-1002 in infants (1 month to 2 years of age), a 7% incidence of kidney stones was observed during the 1-year topiramate adjunctive treatment period.[11,38] A sample size of 100 completed subjects per treatment group will provide a 95% CI (Wilson score CI) for the

treatment difference with a width of 0.12, assuming that the incidence of kidney stone formation is 7% and near zero in the topiramate group and the levetiracetam group, respectively.

- *Change in weight Z-score in the 2- to 15-year-old age group:* In the monotherapy epilepsy study TOPMAT-EPMN-106, a -0.59 decrease from baseline in weight Z-score, with an SD of 0.43, was observed after 1 year of treatment with topiramate 400 mg/day. Assuming an SD of 0.43, a sample size of 100 completed subjects per treatment group will provide a 95% CI with a precision of 0.12.

11.3. Pharmacokinetic Analyses

Data will be listed for all subjects with available plasma concentrations per treatment group.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each treatment group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum will be calculated for the topiramate or levetiracetam plasma concentrations at each sampling time.

Topiramate and levetiracetam plasma concentrations will be provided as listings.

11.4. Safety Analyses

The key safety endpoints will include:

- Percentage of subjects with kidney stones
- Change from baseline in weight Z-score over time
- The following height analyses will be conducted for prepubertal subjects (2 to 9 years of age), subjects 10 to 15 years of age, and subjects 2 to 15 years of age:
    - Height at 1 year postbaseline
    - Height change from baseline over time
    - Height Z-score at 1 year postbaseline
    - Change from baseline in height Z-score over time
    - Height velocity at 1 year postbaseline
    - Height velocity Z-score at 1 year postbaseline
    - Percentage of outlier subjects with height Z-score decrease of >0.5, >1.0, and >2.0 over time
- The following BMD and BMC endpoints:

  - BMD and BMC over time
  - BMD and BMC change from baseline over time
  - Z-score for BMD and BMC over time
  - Change from baseline in Z-score for BMD and BMC over time
  - Percent change from baseline in BMD and BMC over time
  - Percentage of outlier subjects with BMD Z-score decrease of >0.5, >1.0, and >2.0 over time
- Change from baseline in biochemical markers of bone mineralization including: serum levels of alkaline phosphatase, calcium, phosphorus, parathyroid hormone (intact), 25-hydroxy-vitamin D, 1,25-dihyroxy vitamin D, and IGF-1
- Change from baseline in serum and urine laboratory tests, eg, bicarbonate, ammonia, renal function tests, and LFTs
- Change from baseline in bone age

Z-scores for the DEXA scans will be calculated locally at baseline and at M12 to determine eligibility for the study and the Post-Study Follow-Up phase, and centrally for all statistical analyses. The Z-score calculation will take the DEXA machine and the subject's age, sex, height, and ethnicity into consideration. The reference databases for calculating the Z-scores are provided in the DEXA Manual for this study.

Longitudinal endpoints will be analyzed using a mixed-model repeated measures (MMRM) analysis. The MMRM model will include treatment group, age group, visit, treatment-by-visit interaction, baseline measure, and baseline-by-visit interaction. An unstructured covariance will be used. Other appropriate covariance structures will be explored as needed. Confidence intervals with 95% confidence for the estimated treatment differences will be provided at each time point as appropriate. For proportion endpoints, 95% confidence intervals will be provided for the treatment difference. Each of the endpoints will also be summarized by age group.

Seizure counts, cognitive, developmental level, and behavioral assessments will be summarized by treatment group and age group. The incidence of suicide-related thoughts and behaviors as determined by the C-SSRS will be summarized by treatment group and age group.

For the cognitive assessments, standardized change from baseline scores will be calculated by computing the change for each postdose assessment score from the baseline assessment score, relative to the expected within-subject standard deviations for each Cogstate task. For the tasks for which lower scores indicate improvement (eg, Detection Test and Identification Test), the score will be multiplied by (-1), so that negative standardized scores represent a decline in cognitive performance consistently across all tasks.

A meaningful decline in cognition has been defined as a standardized change of less than -1.65 from the baseline assessment. These calculations will indicate meaningful decline at the subject level. For each individual score assessment, standardized change scores that meet the definition of a meaningful decline will be identified using a binary flag, where 1 represents a meaningful decline from baseline and 0 otherwise.

Group-based summary data (frequency distribution of the binary flags) will also be presented by computing the proportion of subjects who meet the criteria for meaningful decline at each postdose assessment.

In addition to the above endpoints, other safety-related endpoints may be included in the analyses and summarized if deemed necessary.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the treatment phase (ie, treatment-emergent adverse events, and adverse events that have worsened since baseline) will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group and by age group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Adverse events of clinical interest for topiramate are: effects on liver function; metabolic acidosis; effects on growth and maturation; vision abnormalities; oligohidrosis with hyperthermia and rash; hyperammonemia and encephalopathy; kidney stones; cognitive disorders; and suicidality.

Adverse events of clinical interest for levetiracetam are as listed previously, notably somnolence, asthenia, and behavior disturbances (especially hostility and nervousness).

Subjects with adverse events of special interest may be counted or listed.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in pre- versus

posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Vital Signs

Descriptive statistics of temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits (using age-appropriate ranges) will be summarized.

Physical Examination/Neurologic Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

11.5. Data Monitoring Committee

An external, independent DMC will be established to review safety data on at least a semiannual basis (or more frequently, if necessary) and ensure the continuing safety of the subjects enrolled in this study. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

The DMC will include experts from pediatric subspecialties and one statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not

related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the informed consent/assent form (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dosage:

- Results in death
- Is life-threatening
  (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.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For topiramate, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.[33] For levetiracetam, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.[24]

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor medicinal product that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor medicinal product
- Suspected abuse/misuse of a sponsor medicinal product
- Inadvertent or accidental exposure to a sponsor medicinal product
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor medicinal product, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, subjects or parents/caregivers must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study, indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF)

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the investigational agent, is considered a serious adverse event.

12.3.3. Pregnancy

All initial reports of pregnancy must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth, congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drugs

TOPAMAX® tablets and sprinkle capsules will be supplied for topiramate; KEPPRA® tablets and solution will be supplied for levetiracetam.

The topiramate tablets supplied for this study are debossed, round, coated tablets in the following strengths and colors: 25 mg white or cream, 50 mg light yellow, 100 mg yellow. The tablets are imprinted as follows:

- 25 mg - “OMN” on one side, “25” on the other
- 50 mg - “OMN” on one side, “50” on the other
- 100 mg - “OMN” on one side, “100” on the other

Topiramate sprinkle capsules are provided as small, white to off-white spheres in gelatin capsules consisting of white bodies with clear caps. The capsules are printed with black pharmaceutical ink as follows:

- 25 mg - “TOP” on the cap and “25 mg” on the capsule body

Refer to the topiramate prescribing information for a list of excipients.[38]

Levetiracetam tablets are provided as oblong-shaped, scored, film-coated tablets in the following strengths and colors: 250 mg blue, 500 mg yellow, 750 mg orange. The tablets are imprinted as follows:

- 250 mg - "ucb 250" on one side
- 500 mg - "ucb 500" on one side
- 750 mg - "ucb 750" on one side

Levetiracetam oral solution is a clear, colorless, grape-flavored liquid (100 mg/mL).

Refer to the levetiracetam prescribing information for a list of excipients.[24]

14.2. Packaging

Topiramate tablets and sprinkle capsules will be packaged in high-density polyethylene bottles. Levetiracetam tablets will be supplied in blister cards packed in cartons; levetiracetam (100 mg/mL) oral solution will be provided in glass bottles.

All study drugs will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug should be stored and handled per the labelled storage conditions. Both formulations should be stored in tightly closed containers and protected from moisture. Topiramate drug product formulations are not sterile. While topiramate sprinkle capsules are designed for use by subjects who require that the administered drug be dispensed with food, neither this formulation nor tablets are intended for storage in food mixtures, as this practice may create the risk of bacterial contamination. This particular risk is relevant to subjects whose comorbidities make them susceptible to infections (systemic or enteral) by pathogens capable of growing in food mixtures such as enteric or infant formulas. To prevent the possibility for bacterial contamination, the topiramate sprinkle capsules drug/food mixture should be used immediately and not stored for later use.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. The subjects must return unused study drug to the site.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the site is an authorized destruction unit and study drug supplies are destroyed on site, this must also be documented on the drug return form.

Potentially hazardous materials, such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Topiramate Investigator's Brochure
- Topiramate Prescribing Information
- Levetiracetam Prescribing Information
- Laboratory manual
- IWRS manual
- Electronic data capture (eDC) manual
- Blinding Plan for TOPMATEPY4067
- DEXA Manual for TOPMATEPY4067
- CDC growth charts
- Subject take-home records
- Seizure diaries
- Subject recruitment materials
- Subject information materials
- Sample scale, instructions and workbook (if applicable) for the following outcome assessments: Tanner scale; CBCL; HAES; Vineland Adaptive Behavior Scale, version II; C-SSRS, NEPSY-II
- Worksheet for inadequacy of current epilepsy treatment
- Preprinted labels for blood samples
- Computers, software, and thumb drives for the Cogstate battery
- Refrigerated centrifuge, if not available locally

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This study is a postmarketing requirement that is being conducted to evaluate long-term safety issues associated with topiramate monotherapy in children 2 to 15 years of age with newly or recently diagnosed epilepsy. Of particular concern is the potential for chronic metabolic acidosis and the potential impact on growth, bone mineralization, and kidney stone formation. The study is designed to assess these issues in comparison with levetiracetam monotherapy. The study is designed as a randomized, active-controlled, open-label study; however, to eliminate bias, after randomization the key safety outcomes (DEXA scan, renal ultrasound, and height) will be obtained in a blinded fashion.

Ethical concerns include the enrollment of pediatric subjects and the requirement for them to taper off their current AED. Performing this study in children is justified because it remains unclear how long term AED may impact normal bone mineralization and development. Overall, an extensive clinical database that included children from age 1 month and above in different clinical settings has not demonstrated bone-related adverse clinical outcomes, but more quantitative and systemic safety data are desirable in this population. The concern of tapering off an existing AED is mitigated by the requirement that investigators document the inadequacy of the subject's current AED treatment.

Levetiracetam is an appropriate comparator because it has demonstrated efficacy and safety in a number of investigator-initiated studies when used as monotherapy in dosages similar to those used in the current study. It also has relatively low toxicity, and specifically a lack of significant concerns for risks for kidney stones or possible deleterious effects on bone or growth. Other AEDs that might be considered as a comparator beside levetiracetam include carbamazepine, lamotrigine, or valproic acid. However, there are possible concerns with all of these AEDs. There are many publications in the literature that suggest carbamazepine may decrease BMD, increase serum alkaline phosphatase and decrease serum calcium and phosphorus, which might suggest problems with bone development. Lamotrigine has potentially serious toxicity especially serious rash (eg, Stevens-Johnson syndrome or toxic epidermal necrolysis) and there are various publications that suggest that valproic acid may also have deleterious effects on decreasing BMD.

A 1-year study duration is justified based on the following:

- The American Academy Pediatrics Clinical Report Bone Densitometry in children and adolescents states that the recommended interval between repeat DEXA scans depends on progression of bone disorder, with a minimal interval between scans of 6 months, but often 1 year or more may be appropriate to allow measurable change to occur.[3] The Position

statement on DEXA scans in children and adolescents from ISCD states that in pediatric patients, repeat scans should generally be obtained within 1 to 2 years for clinical purposes and in some settings, such as a patient in a research study and/or receiving a therapeutic skeletal agent, every 6 months.[18] The shorter 6-month interval may reveal trends in skeletal losses and gains, reflecting variations in bone turnover from either a chronic disease or intervention, but ones not yet clinically significant. The ISCD suggests a minimum monitoring time interval of 6 months for repeating BMD measurement.[4]

- Abnormalities in height have been detected during 1 year of treatment in children treated with topiramate monotherapy. Topiramate as monotherapy for newly or recently diagnosed POS has been evaluated in 3 double-blind Phase 3 studies, each of which included subjects between the ages of 6 and 15 years of age at enrollment.[33] One of these 3 studies included post-baseline height or BMI data and also included an open-label extension phase.[9] During the combined double-blind and open-label extension, there was a small percentage of children who met height criteria for growth delay.
- Renal stones as documented by renal ultrasound have been demonstrated within a 1-year treatment duration with topiramate. Results from the open-label extension study performed in 284 infants with epilepsy 1 to 24 months of age treated with topiramate for 1 year showed that 18 of 284 subjects (6.3%) had nephrolithiasis detected by sonogram approximately 4 to 5 months into the study.[11]

Additional ethical concerns relate to consent/assent and ensuring that ethical principles related to pediatric subjects as vulnerable subjects are in effect, primarily to ensure that total allowable blood volumes are not exceeded during study conduct.

Potential subjects and their guardians will be fully informed of the risks and requirements of the study and, during the study, they will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Enrollment will only be allowed if parents/legally acceptable representatives or subjects are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent/assent voluntarily.

When referring to the signing of the informed consent form, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent/assent refers to the subjects (assent as applicable) and his or her parent(s) or the subject's legal guardian(s) or legally acceptable

representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw their assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected during the study is less than 3 mL/kg body weight per 8-week period (approximately 11.0 mL or less at each visit), consistent with the guidelines for total allowable blood volumes drawn from pediatric subjects from multiple sources, including NIH IRB, US Department of Health and Human Services, Alliance Laboratory Services, and Harvard's Massachusetts General Hospital (Boston, Massachusetts).[23]

Although a subject could be exposed to as many as 18 DEXA scans over the 12-month course of the study, the additional amount of radiation is less than the yearly natural background radiation in the United States (3 mSV), and involves minimal risk. Further details, including the radiation dose by machine, scan, and age, are provided in the DEXA Manual for this study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the clinical study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form and assent forms (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any), the informed consent form, assent forms, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments
- Revision(s) to informed consent form, assent forms, and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the investigational drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Annual Safety Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct), the amendment and applicable informed consent/assent form revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Parents (or a legally acceptable representative) and pediatric subjects must give written consent and assent, respectively, according to local requirements, after the nature of the study has been fully explained. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies, as described below. The consent and assent forms must be signed before performance of any study-related activity. The consent form and assent forms that are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the parents or legally acceptable representative and subject can read and understand. The informed consent and assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects and their parents or legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent and assent forms the subject and parents or legally acceptable representative is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent and assent for additional safety evaluations, if needed.

The subject and parents or legally acceptable representative will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent and assent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature.

After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject and parents or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the informed consent and assent forms after the oral consent of the subject and parents or legally acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent from parents or a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent and/or legally acceptable representative.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

The informed consent and assent obtained from the subject or parent (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject or parent has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Country Selection

This study will only be conducted in those countries where the 2 study drugs are commercially available for the treatment of epilepsy.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, informed consent form, assent forms, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all clinical subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All

reports and communications relating to the study will identify subjects by dummy initials and assigned number only.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent and assent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly in the source documents and then entered into the CRF:

- Race
- Blood pressure and heart rate
- Height – A blinded study nurse or other staff will measure the height of the subject and record it in the source documents, or provide it to the unblinded study coordinator for entry into the source documents. The unblinded study coordinator will then enter this data, along with other visit data, into the CRF.
- Weight
- Details of physical examination

Subject- and investigator-completed scales and assessments designated by the sponsor below will be recorded separately from the CRF and will be considered source data:

- Vineland Adaptive Behavior Scale
- CBCL - Parent version (preschool and school-age versions)
- Seizure diary

- C-SSRS

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic data capture will be used for this study. The study data will be transcribed by study personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

Every effort should be made to ensure that all subjective measurements (eg, pain scale information or other questionnaires) to be recorded in the CRF are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Site manager can generate a query for resolution by the investigational staff.
- Clinical data manager can generate a query for resolution by the investigational staff.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of DEXA, and clinical laboratory data from a central laboratory into the sponsor's

database. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source

documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final subject assessment at that site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding topiramate or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the clinical study will be used by the sponsor in connection with the continued development of topiramate, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all investigational sites that participate in the study and data from DEXA, and clinical laboratory tests, which will be directly transmitted from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

The sponsor shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Achenbach TM, Rescorla LA. Manual for the ASEBA Preschool Forms and Profiles. 1991;Burlington, VT: University of Vermont Department of Psychiatry.
2. Achenbach TM, Rescorla LA. Manual for the ASEBA School-Age Forms and Profiles. 1991;Burlington, VT: University of Vermont, Research Center for Children, Youth, and Families.
3. Bachrach LK, Sills IN; Section on Endocrinology. Clinical report—bone densitometry in children and adolescents. Pediatrics. 2011;127(1):189-194.
4. Bishop N, Braillon P, Burnham J, et al. Dual-energy X-ray absorptiometry assessment in children and adolescents with diseases that may affect the skeleton: the 2007 ISCD Pediatric Official Positions. J Clin Densitom. 2008;11(1):29-42.
5. Caplan R, Sagun J, Siddarth P, et al. Social competence in pediatric epilepsy: Insights on underlying mechanisms. Epilepsy Behav. 2005;6:218-228.
6. Ciochetti DV, Sparrow SS, Carter A. Development and validation of the Vineland Adaptive Behavior screening instruments. 1991;San Francisco, CA: American Psychological Association.
7. Clinical Study Report TOPMAT-EPMN-104. Topiramate monotherapy clinical trial in subjects with recently diagnosed partial onset seizures. RWJPRI (22 Apr 1999).
8. Clinical Study Report TOPMAT-EPMN-105. Topamax (Topiramate) monotherapy comparison trial to standard monotherapy in the treatment of newly diagnosed epilepsy. RWJPRI (26 Oct 2000).
9. Clinical Study Report TOPMAT-EPMN-106. A randomized, double blind, parallel group, monotherapy study to compare the safety and efficacy of two doses of topiramate in the treatment of newly diagnosed or recurrent epilepsy. J&JPRD (20 Aug 2002).
10. Clinical Study Report TOPMAT-MIG-3006. A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for the prophylaxis of migraine in pediatric subjects 12 to 17 years of age. J&JPRD (20 Aug 2007).
11. Clinical Study Report TOPMAT-PEP-1002 and TOPMAT-PEP-3001. Long-term safety of topiramate administered as the oral liquid and sprinkle capsule formulations as an adjunct to concurrent anticonvulsant therapy in infants (aged 1 to 24 months, inclusive) with refractory partial-onset seizures (Interim Report Based on Available Data as of 15 June 2007). J&JPRD (14 Jan 2008).
12. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of the epilepsies and epileptic syndromes. Epilepsia. 1989;30:389-399.
13. Connolly AM, Northcott E, Cairns DR, et al. Quality of life of children with benign rolandic epilepsy. Ped Neurol. 2006;35:240-245.
14. Drug Metabolism Research Report DM97328. Topiramate metabolite profiling and identification in infant subjects. RWJPRI. (20 Jan 1998).
15. Falleti MG, Maruff P, Collie A, Darby DG. Practice effects associated with the repeated assessment of cognitive function using the Cogstate Battery at 10-minute, one week and one month test-retest intervals. J Clin Exp Neuropsychol. 2006;28(7):1095-1112.
16. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report A practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475-482.
17. Girgis IG, Nandy P, Nye JS, et al. Pharmacokinetic–pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to <10 years of age. Epilepsia. 2010;51:1954–1962.
18. Gordon CM, Bachrach LK, Carpenter TO, et al. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: The 2007 ISCD Pediatric Official Positions. J Clin Densitometry: Assessment of Skeletal Health. 2008;11:43-58.

19. Greer FR. Defining vitamin D deficiency in children: beyond 25-OH vitamin D serum concentrations. Pediatrics. 2009;124(5):1471-3.

20. Greulich W, Pyle S. Radiographic Atlas of Skeletal Development of the Hand and Wrist. 2nd edition. (1959) Stanford, CA: Stanford University Press.

21. Grosso S, Cordelli DM, Franzoni E, et al. Efficacy and safety of levetiracetam in infants and young children with refractory epilepsy. Seizure. 2007;16:345—350.

22. Hay JA. Development and testing of the Habitual Activity Estimation Scale. In Armstrong N, Welsman J, Kirby B (eds). Children and Exercise. XIX: Promoting Health and Well-being. XIXth International Symposium of Pediatric Work Physiology, Exeter, London: E&FN Spon, 1997;II:125–129.

23. Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011;89(1):46-53.

24. Keppra® (levetiracetam) Package Insert. UCB, Inc. Apr 2009.

25. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Adv Data. 2000;314:1-27.

26. Maruff P, Thomas E, Cysique L, et al. Validity of the Cogstate brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol. 2009;24(2):165-178.

27. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. J Youth Adolesc. 1980;9:271-280.

28. Nonclinical Safety Study Report TOX6898. Oral toxicity study in juvenile rats. CIT Study No. 29067 RSR. J&JPRD (22 Dec 2006).

29. Opp J, Tuxhorn I, May T, et al. Levetiracetam in children with refractory epilepsy: a multicenter open label study in Germany. Seizure. 2005;14:476-484.

30. Pietrzak RH, Olver J, Norman T, Piskulic D, Maruff P, Snyder PJ. A comparison of the Cogstate schizophrenia battery and the measurement and treatment Research to improve cognition in Schizophrenia (MATRICS) battery in assessing cognitive impairment in chronic schizophrenia. J Clin Exp Neuropsychol. 2009;31(7): 848-859. doi:10.1080/13803390802592458.

31. Posner K, Oquendo M, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.

32. Rosenfeld WE, Doose, DR, Walker SA, Baldassarre JS, Reife RA. A study of topiramate pharmacokinetics and tolerability in children with epilepsy. Pediatr Neurol. 1999;20:339-344.

33. RWJ-17021-000 (topiramate) Investigator's Brochure Edition 15. Janssen R&D (15 March 2017).

34. Sabaz M, Cairns DR, Bleasel AF, et al. The health-related quality of life of childhood epilepsy syndromes. J Paediatr Child Health. 2003;39:690-696.

35. Shepherd JA, Wang L, Fan B, et al. Optimal monitoring time interval between DXA measures in children. J Bone Miner Res. 2011;26:2745-2752.

36. Sparrow SS, Balla DA, Cicchetti DV. Vineland Adaptive Behavior Scales: Interview Edition Survey Forms Manual. Circle Pines, MN. American Guidance Service 1984.

37. Tanner JM. Growth at Adolescence, 2nd ed. (1962). London, England Oxford: Blackwell Scientific.

38. TOPAMAX® (topiramate) Prescribing Information. Janssen Pharmaceuticals, Inc., Jul 2011.

39. Topiramate Integrated Summary of Safety. Topiramate as monotherapy for pediatric and adult subjects with newly diagnosed epilepsy. J&JPRD (30 Sep 2002).

40. Topiramate Pediatric Monotherapy sNDA Integrated Summary of Safety. J&JPRD (9 Dec 2009).

41. Vega D, Maalouf NM, Sakhaee K. Increased propensity for calcium phosphate kidney stones with topiramate use. Expert Opinion Drug Safety. 2007;6(5):547-557.

42. Vitamin D fact sheet for health professionals. http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional. Accessed 08 Jun 2015.

43. von Stuelpnagel C, Holthausen H, Kluger G. Long-term use of levetiracetam in patients with severe childhood-onset epilepsy. Eur J Paed Neur. 2007;11:341–345.

ATTACHMENTS

Attachment 1: Habitual Activity Estimation Scale

Janssen Research and Development
Protocol TOPMATEPY4067

SUBJECT NUMBER: | | | | | | | | |

VISIT: Screening

DATE: | | | | | | | | | | (d d m m m y y y y)

TIME: | | : | | (24 hour clock)

Two Days in the Life of My Child

This questionnaire will ask you about your child's daily activity levels. Please read all the instructions carefully and answer each question as truthfully as you can.

INSTRUCTIONS (Please Read!)

This form will ask you to think about ***a typical weekday*** (Tuesday, Wednesday, or Thursday) and ***one typical Saturday in the past two weeks***. For each part of the day you will be asked to estimate the percentage of time that your child spent in four different activity levels. In each section, the time spent in all activity levels must add up to 100%.
The four activity levels are described below:

ACTIVITY LEVEL DESCRIPTIONS

Here are some examples of activities that are typical of each activity level. Please refer back to these descriptions as often as you need when completing this form.

a) ***Inactive*** – lying down, sleeping, resting, napping

b) ***Somewhat inactive*** – sitting, reading, watching television, playing video games, time in front of the computer, playing games or activities that are mostly done sitting down.

c) ***Somewhat active*** – walking, shopping, light household chores – washing dishes

d) ***Very active*** – running, jumping, skipping, bicycling, skating, swimming, or games that require lots of movement and make you breathe hard

Following is a sample of a completed time period with examples of activities:

SAMPLE

From when your child finished supper until bed-time, please estimate the percentage of time that they spent in each of the following activity levels:

a)	**Inactive**	5 %	(e.g., having a nap)
b)	**Somewhat inactive**	60 %	(e.g., watching TV, talking with friends)
c)	**Somewhat active**	25 %	(e.g., going for a walk, helping with meals)
d)	**Very Active**	10 %	(e.g., riding a bike fast, running)
	TOTAL	**100 %**	

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Janssen Research and Development
Protocol TOPMATEPY4067
VISIT: Screening

SUBJECT NUMBER: ☐☐☐☐☐☐☐☐

WEEKDAY ACTIVITY

For a *typical weekday in the past 2 weeks* (think about a Tuesday, Wednesday or Thursday), please answer the following questions as accurately as possible in the spaces provided. If your child misses a meal just put down the time they would normally eat and put in a zero (0) for the time spent eating!

When did your child get out of bed in the morning? ___:___ **A.M.**

When did your child start eating breakfast? ___:___ **A.M.**

How long did your child spend eating breakfast? _____ **min.**

When did your child start eating lunch? ___:___ **P.M.**

How long did your child spend eating lunch? _____ **min.**

When did your child start eating supper? ___:___ **P.M.**

How long did your child spend eating supper? _____ **min.**

At what time did your child go to bed? ___:___ **P.M.**

Janssen Research and Development
Protocol TOPMATEPY4067
VISIT: Screening

SUBJECT NUMBER: ☐☐☐☐☐☐☐☐

For the *typical weekday* you are describing, please estimate the percentage of time your child spent in each activity level.

After getting out of bed until starting breakfast:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**

INACTIVE

After finishing breakfast until lunch

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**


SOMEWHAT INACTIVE

After finishing lunch until starting supper:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**


SOMEWHAT ACTIVE

After finishing supper until bedtime:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**


VERY ACTIVE

Janssen Research and Development
Protocol TOPMATEPY4067
VISIT: Screening

SUBJECT NUMBER: ☐☐☐☐☐☐☐☐

For the *typical weekday you are describing* please rate your child's *overall* level of activity *(circle your choice)*

a) Very inactive
b) Inactive
c) Somewhat inactive
d) Somewhat active
e) Active
f) Very active

The *weekday* I described in this form is: *(circle your choice)*

a) Very much like most weekdays in the last six months
b) A little bit like most weekdays in the last six months
c) A little bit different from most weekdays in the last six months
d) Very different from most weekdays in the last six months

In the last six months has your child become: *(circle your choice)*

a) Much less active on weekdays than six months ago
b) Somewhat less active on weekdays than six months ago
c) No real change in activity on weekdays from six months ago
d) Somewhat more active on weekdays than six months ago
e) Much more active on weekdays than six months ago

Janssen Research and Development
Protocol TOPMATEPY4067
VISIT: Screening

SUBJECT NUMBER: ☐☐☐☐☐☐☐☐

SATURDAY ACTIVITY

For a *typical Saturday in the past 2 weeks*, please answer the following questions as accurately as possible in the spaces provided. If your child misses a meal just put down the time they would normally eat and put in a zero (0) for the time spent eating!

When did your child get out of bed in the morning? ___:___ **A.M.**

When did your child start eating breakfast? ___:___ **A.M.**

How long did your child spend eating breakfast? _____ **min.**

When did your child start eating lunch? ___:___ **P.M.**

How long did your child spend eating lunch? _____ **min.**

When did your child start eating supper? ___:___ **P.M.**

How long did your child spend eating supper? _____ **min.**

At what time did your child go to bed? ___:___ **P.M.**

Janssen Research and Development
Protocol TOPMATEPY4067
VISIT: Screening

SUBJECT NUMBER: ☐☐☐☐☐☐☐☐

For the *typical Saturday* you are describing, please estimate the percentage of time your child spent in each activity level.

After getting out of bed until starting breakfast:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**

INACTIVE

After finishing breakfast until starting lunch:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**

SOMEWHAT INACTIVE

After finishing lunch until starting supper:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**

SOMEWHAT ACTIVE

After finishing supper until bedtime:

a)	Inactive	_____%
b)	Somewhat inactive	_____%
c)	Somewhat active	_____%
d)	Very Active	_____%
	TOTAL	**100 %**

VERY ACTIVE

Janssen Research and Development
Protocol TOPMATEPY4067
VISIT: Screening

SUBJECT NUMBER: ☐☐☐☐☐☐☐☐

For the *typical Saturday you are describing* please rate your child's *overall* level of activity *(circle your choice)*

a) Very inactive
b) Inactive
c) Somewhat inactive
e) Somewhat active
f) Active
g) Very active

The Saturday I described in this form is: *(circle your choice)*

a) Very much like most Saturdays in the last six months
b) A little bit like most Saturdays in the last six months
c) A little bit different from most Saturdays in the last six months
d) Very different from most Saturdays in the last six months

In the last six months has your child become: *(circle your choice)*

a) Much less active on weekends than six months ago
b) Somewhat less active on weekends than six months ago
c) No real change in activity on weekends from six months ago
d) Somewhat more active on weekends than six months ago
e) Much more active on weekends than six months ago

You are finished now - Thank you for completing this form!

Attachment 2: Titration Schedules for Topiramate and Levetiracetam

Topiramate Monotherapy Titration Schedule for Subjects 2 to <10 Years of Age

Table 1: Topiramate Monotherapy Titration Schedule for Subjects 2 to <10 Years of Age – Body Weight up to 11 kg (Maximum Recommended Maintenance Dosage 250 mg/day)

	Total Daily Dosage (mg)	Morning Dose (mg)	Evening Dose (mg)
Week 1	25	0	25
Week 2	50	25	25
Week 3	75	25	50
Week 4	100	50	50
Week 5	125	50	75
Week 6	150	75	75
Week 7	200	100	100
Week 8	250	100	150

Table 2: Topiramate Monotherapy Titration Schedule for Subjects 2 to <10 Years of Age – Body Weight 12 to 22 kg (Maximum Recommended Maintenance Dosage 300 mg/day)

	Total Daily Dosage (mg)	Morning Dose (mg)	Evening Dose (mg)
Week 1	25	0	25
Week 2	50	25	25
Week 3	75	25	50
Week 4	100	50	50
Week 5	150	75	75
Week 6	200	100	100
Week 7	250	125	125
Week 8	300	150	150

Table 3: Topiramate Monotherapy Titration Schedule for Subjects 2 to <10 Years of Age – Body Weight 23 to 38 kg (Maximum Recommended Maintenance Dosage 350 mg/day)

	Total Daily Dosage (mg)	Morning Dose (mg)	Evening Dose (mg)
Week 1	25	0	25
Week 2	50	25	25
Week 3	75	25	50
Week 4	100	50	50
Week 5	200	100	100
Week 6	250	125	125
Week 7	300	150	150
Week 8	350	175	175

Topiramate Monotherapy Titration Schedule for Subjects 10 to 15 Years of Age

Table 4: Topiramate Monotherapy Titration Schedule for Subjects 10 to 15 Years of Age

	Morning Dose (mg)	Evening Dose (mg)
Week 1	25	25
Week 2	50	50
Week 3	75	75
Week 4	100	100
Week 5	150	150
Week 6	200	200

Levetiracetam Weight-Based Titration Dosing Guide (Oral Solution, 100 mg/mL) for Subjects With a Body Weight ≤20 kg

Table 5: Levetiracetam Weight-Based Titration Dosing Guide (Oral Solution; 100 mg/mL) for Subjects With a Body Weight ≤20 kg – Weeks 1 to 2 (20 mg/kg/day)

Body Weight (kg)	Total Daily Dosage (mg)	Morning Dose (mg)	Evening Dose (mg)	Dosage Regimen
10	200	100	100	1.0 mL BID
11	220	110	110	1.1 mL BID
12	240	120	120	1.2 mL BID
13	260	130	130	1.3 mL BID
14	280	140	140	1.4 mL BID
15	300	150	150	1.5 mL BID
16	320	160	160	1.6 mL BID
17	340	170	170	1.7 mL BID
18	360	180	180	1.8 mL BID
19	380	190	190	1.9 mL BID
20	400	200	200	2.0 mL BID

Table 6: Levetiracetam Weight-Based Titration Dosing Guide (Oral Solution; 100 mg/mL) for Subjects With a Body Weight ≤20 kg – Weeks 3 to 4 (40 mg/kg/day)

Body Weight (kg)	Total Daily Dosage (mg)	Morning Dose (mg)	Evening Dose (mg)	Dosage Regimen
10	400	200	200	2.0 mL BID
11	440	220	220	2.2 mL BID
12	480	240	240	2.4 mL BID
13	520	260	260	2.6 mL BID
14	560	280	280	2.8 mL BID
15	600	300	300	3.0 mL BID
16	640	320	320	3.2 mL BID
17	680	340	340	3.4 mL BID
18	720	360	360	3.6 mL BID
19	760	380	380	3.8 mL BID
20	800	400	400	4.0 mL BID

Table 7: Levetiracetam Weight-Based Titration Dosing Guide (Oral Solution; 100 mg/mL) for Subjects With a Body Weight ≤20 kg – Weeks 5 to 8 and Maintenance (60 mg/kg/day)

Body Weight (kg)	Total Daily Dosage (mg)	Morning Dose (mg)	Evening Dose (mg)	Dosage Regimen
10	600	300	300	3.0 mL BID
11	660	330	330	3.3 mL BID
12	720	360	360	3.6 mL BID
13	780	390	390	3.9 mL BID
14	840	420	420	4.2 mL BID
15	900	450	450	4.5 mL BID
16	960	480	480	4.8 mL BID
17	1,020	510	510	5.1 mL BID
18	1,080	540	540	5.4 mL BID
19	1,140	570	570	5.7 mL BID
20	1,200	600	600	6.0 mL BID

Levetiracetam Weight-Based Titration Dosing Guide (Tablets) for Subjects With a Body Weight >20 kg

Table 8: Levetiracetam Weight-Based Titration Dosing Guide (Tablets) for Subjects With a Body Weight >20 kg

	Morning Dose (mg)		Evening Dose (mg)	
	20.1 to 40 kg	>40 kg	20.1 to 40 kg	>40 kg
Week 1	250	500	250	500
Week 2	250	500	250	500
Week 3	500	500	500	1,000
Week 4	500	500	500	1,000
Week 5	750	1,000	750	1,500
Week 6	750	1,000	750	1,500

Attachment 3: Pharmacokinetic Collection and Handling Procedure

Materials and Labeling

The central laboratory will provide the investigational site with blood collection tubes, storage tubes, preprinted labels (or tubes labeled with preprinted labels), and related supplies for the collection and shipment of PK samples. Labels should be attached to the storage tubes at least 12 hours before being frozen to ensure proper adherence.

Use of alternative materials will not result in a protocol amendment if preapproved by the Bioanalysis Scientist.

Detailed information regarding the collection and storage containers will be provided in the laboratory manual from the central laboratory.

Preparation of Plasma Pharmacokinetic Samples for Topiramate

- Collect 1 mL of blood into the appropriate K_2-EDTA-containing collection tube (eg, Vacutainer®) at each time point.
- Record the exact date and time of sampling in the CRF or laboratory requisition form, as appropriate.
- Gently invert the tubes 8 to 10 times to afford mixing, before processing.
- Centrifuge blood samples at room temperature within 1 hour(s) of collection at 1,300 g for 10 minutes, unless otherwise specified by the supplier, to yield approximately 0.4 mL of plasma from each 1 mL whole blood sample.
- Transfer all separated plasma immediately with a clean, disposable glass or polyethylene pipette (use 1 new pipette per sample) to a pre-labeled storage tube (3.6-mL NUNC™ Cryotube™, Cat. No. 366524 or 379189).
- Store plasma samples in an upright position in a freezer, at a set temperature of –20°C until transfer to the central laboratory.
- The time between blood collection and freezing the plasma should not exceed 2 hours.
- Ship specimens to the central laboratory according to the instructions provided.
- Questions regarding handling the plasma PK specimens should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

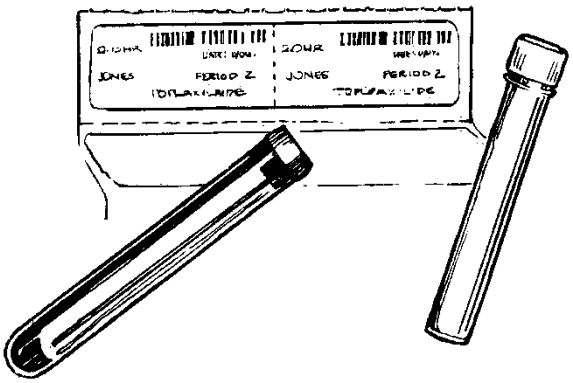
Preparation of Plasma Pharmacokinetic Samples for Levetiracetam

- Collect 1 mL of blood into the appropriate K_3-EDTA-containing collection tube (eg, Vacutainer®) at each time point.
- Record the exact date and time of sampling in the CRF or laboratory requisition form, as appropriate.
- Gently invert the tubes 8 to 10 times to afford mixing, before processing.
- Centrifuge blood samples at room temperature within 1 hour(s) of collection at 1,300 g for 10 minutes, unless otherwise specified by the supplier, to yield approximately 0.4 mL of plasma from each 1 mL whole blood sample.
- Transfer all separated plasma immediately with a clean, disposable glass or polyethylene pipette (use 1 new pipette per sample) to a pre-labeled storage tube (3.6-mL NUNC™ Cryotube™, Cat. No. 366524 or 379189).
- Store plasma samples in an upright position in a freezer, at a set temperature of –20°C until transfer to the central laboratory.
- The time between blood collection and freezing the plasma should not exceed 2 hours.

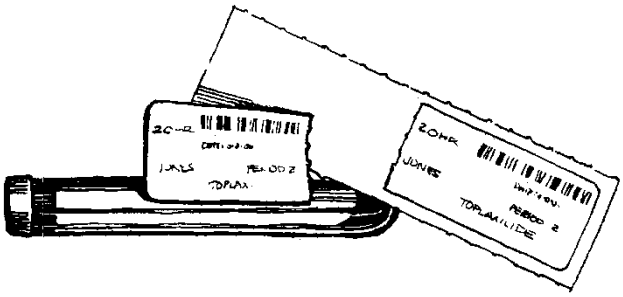
- Ship specimens to the central laboratory according to the instructions provided.
- Questions regarding handling the plasma PK specimens should be addressed to the contact person for the sponsor.
- Alternative procedures will not result in a protocol amendment if approved by the Bioanalysis Scientist.

Attachment 4: Labeling Instructions for Pharmacokinetic Samples

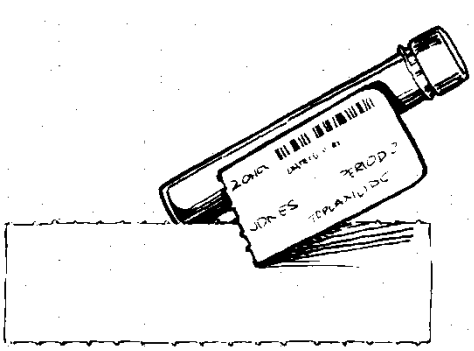
STRUCTURE OF THE LABEL:
1. Each label has 2 identical parts.
2. The backing of the label and the label itself are perforated.

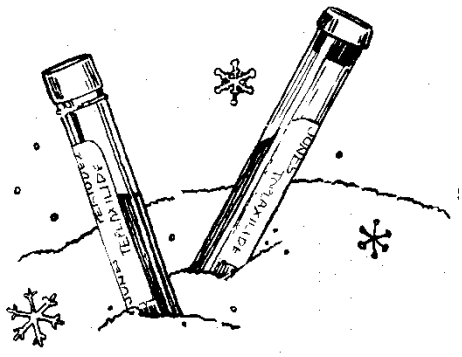


STEP 1: Remove part 1 of the label and completely attach it to the Vacutainer®, lengthwise. Centrifuge the Vacutainer.



STEP 2: Remove part 2 of the label and attach it to the empty plasma storage tube. The label must be attached to the tube lengthwise. Labels should be attached to the storage tubes at least 12 hours before being frozen to ensure proper adherence. You are now able to match the alphanumeric code, subject identification, and time point on the plasma collecting tube with the corresponding information on the Vacutainer. After the tubes are matched, the plasma may be transferred from the Vacutainer to the plasma storage tube.





STEP 3: Freeze the sample in an upright position.
Pack and ship the samples as instructed in the protocol.

Attachment 5: Shipment of Pharmacokinetic Samples

All PK samples will be sent to the central laboratory at the intervals agreed upon. The laboratory manual from the central laboratory provides details regarding packaging and shipment of the samples. The following general guidelines should be considered:

- For all international shipments, World Courier will be used. For domestic shipments, a domestic courier, as recommended by the central laboratory, will be used.
- Notify central laboratory and courier at least 24 hours in advance of the planned shipment. Provide the courier with the appropriate account number to be used, if applicable.
- Place the frozen samples for each subject in the appropriate containers, as specified in the central laboratory manual.
- Pack the frozen samples in sufficient quantity of dry ice, to maintain a frozen state for at least 3 days.
- Avoid direct contact between sample bags and dry ice, by separating them with a dry ice resistant material (eg, newspaper).
- For all biological samples, follow the International Air Transport Association (IATA) regulations for shipment.
- Ensure that the total package weight does not exceed 27.2 kg (60 lb).
- Label the package with the study number and all other information required by the central laboratory.
- Include a return address (which includes the investigator's name) on the outside of each shipping container.
- Comply with all courier regulations for the shipment of biological specimens (include all paperwork).
- Retain all documents indicating date, time, and signature(s) of person(s) making the shipment, in the study files.

Samples should be shipped via overnight delivery only on Monday through Wednesday, excluding holidays. As soon as shipment day and air bill number(s) are available, the site will call, fax, or e-mail the central laboratory. The call, fax, or e-mail must specify the study number, the number of PK samples, and the time of shipment pick-up.

Samples must be sent to the name and address indicated in the central laboratory manual.

NOTE: If there are changes regarding the courier or location to which samples are shipped during the course of the clinical study, written notification will be provided to the investigator and will not require (a) protocol amendment(s).

Attachment 6: CBCL-Preschool

Please print. Be sure to answer all items.

CHILD BEHAVIOR CHECKLIST FOR AGES 1½-5

For office use only ID #

CHILD'S INITIALS First	Middle	Last
CHILD'S GENDER ☐ Boy ☐ Girl	CHILD'S AGE	TODAY'S DATE Mo. ____ Day ____ Year _____

Please fill out this form to reflect *your* view of the child's behavior even if other people might not agree. ***Be sure to answer all items.***

Below is a list of items that describe children. For each item that describes your child ***now or within the past 2 months***, please circle the ***2*** if the item is ***very true or often true*** of the child. Circle the ***1*** if the item is ***somewhat or sometimes true*** of the child. If the item is ***not true*** of the child, circle the ***0***. Please answer all items as well as you can, even if some do not seem to apply to the child.

0 = Not True (as far as you know) **1 = Somewhat or Sometimes True** **2 = Very True or Often True**

0 1 2	1. Aches or pains (without medical cause; ***do not*** include stomach or headaches)	0 1 2	30. Easily jealous
0 1 2	2. Acts too young for age	0 1 2	31. Eats or drinks things that are not food – ***don't*** include sweets
0 1 2	3. Afraid to try new things	0 1 2	32. Fears certain animals, situations, or places
0 1 2	4. Avoids looking others in the eye	0 1 2	33. Feelings are easily hurt
0 1 2	5. Can't concentrate, can't pay attention for long	0 1 2	34. Gets hurt a lot, accident-prone
0 1 2	6. Can't sit still, restless, or hyperactive	0 1 2	35. Gets in many fights
0 1 2	7. Can't stand having things out of place	0 1 2	36. Gets into everything
0 1 2	8. Can't stand waiting; wants everything now	0 1 2	37. Gets too upset when separated from parents
0 1 2	9. Chews on things that aren't edible	0 1 2	38. Has trouble getting to sleep
0 1 2	10. Clings to adults or too dependent	0 1 2	39. Headaches (without medical cause)
0 1 2	11. Constantly seeks help	0 1 2	40. Hits others
0 1 2	12. Constipated, doesn't move bowels (when not sick)	0 1 2	41. Holds his/her breath
0 1 2	13. Cries a lot	0 1 2	42. Hurts animals or people without meaning to
0 1 2	14. Cruel to animals	0 1 2	43. Looks unhappy without good reason
0 1 2	15. Defiant	0 1 2	44. Angry moods
0 1 2	16. Demands must be met immediately	0 1 2	45. Nausea, feels sick (without medical cause)
0 1 2	17. Destroys his/her own things	0 1 2	46. Nervous movements or twitching
0 1 2	18. Destroys things belonging to his/her family or other children	0 1 2	47. Nervous, highstrung, or tense
0 1 2	19. Diarrhea or loose bowels (when not sick)	0 1 2	48. Nightmares
0 1 2	20. Disobedient	0 1 2	49. Overeating
0 1 2	21. Disturbed by any change in routine	0 1 2	50. Overtired
0 1 2	22. Doesn't want to sleep alone	0 1 2	51. Shows panic for no good reason
0 1 2	23. Doesn't answer when people talk to him/her	0 1 2	52. Painful bowel movements (without medical cause)
0 1 2	24. Doesn't eat well	0 1 2	53. Physically attacks people
0 1 2	25. Doesn't get along with other children	0 1 2	54. Picks nose, skin, or other parts of body
0 1 2	26. Doesn't know how to have fun; acts like a little adult		
0 1 2	27. Doesn't seem to feel guilty after misbehaving		
0 1 2	28. Doesn't want to go out of home		
0 1 2	29. Easily frustrated		

Be sure you answered all items. Then see other side.

Please print your answers. Be sure to answer all items.

0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True

0 1 2 55. Plays with own sex parts too much	0 1 2 79. Rapid shifts between sadness and excitement
0 1 2 56. Poorly coordinated or clumsy	0 1 2 80. Strange behavior
0 1 2 57. Problems with eyes (without medical cause)	0 1 2 81. Stubborn, sullen, or irritable
0 1 2 58. Punishment doesn't change his/her behavior	0 1 2 82. Sudden changes in mood or feelings
0 1 2 59. Quickly shifts from one activity to another	0 1 2 83. Sulks a lot
0 1 2 60. Rashes or other skin problems (without medical cause)	0 1 2 84. Talks or cries out in sleep
0 1 2 61. Refuses to eat	0 1 2 85. Temper tantrums or hot temper
0 1 2 62. Refuses to play active games	0 1 2 86. Too concerned with neatness or cleanliness
0 1 2 63. Repeatedly rocks head or body	0 1 2 87. Too fearful or anxious
0 1 2 64. Resists going to bed at night	0 1 2 88. Uncooperative
0 1 2 65. Resists toilet training	0 1 2 89. Underactive, slow moving, or lacks energy
0 1 2 66. Screams a lot	0 1 2 90. Unhappy, sad, or depressed.
0 1 2 67. Seems unresponsive to affection	0 1 2 91. Unusually loud
0 1 2 68. Self-conscious or easily embarrassed	0 1 2 92. Upset by new people or situations
0 1 2 69. Selfish or won't share	0 1 2 93. Vomiting, throwing up (without medical cause)
0 1 2 70. Shows little affection toward people	0 1 2 94. Wakes up often at night
0 1 2 71. Shows little interest in things around him/her	0 1 2 95. Wanders away
0 1 2 72. Shows too little fear of getting hurt	0 1 2 96. Wants a lot of attention
0 1 2 73. Too shy or timid	0 1 2 97. Whining
0 1 2 74. Sleeps less than most kids during day and/or night	0 1 2 98. Withdrawn, doesn't get involved with others
0 1 2 75. Smears or plays with bowel movements	0 1 2 99. Worries
0 1 2 76. Speech problems	
0 1 2 77. Stares into space or seems preoccupied	
0 1 2 78. Stomachaches or cramps (without medical cause)	*Please be sure you have answered all items. Underline any you are concerned about.*

PAGE 2

Attachment 7: CBCL School Age

Please print

CHILD BEHAVIOR CHECKLIST FOR AGES 6-18

For office use only
ID #

CHILD'S INITIALS First Middle Last

CHILD'S GENDER ☐ Boy ☐ Girl

CHILD'S AGE

TODAY'S DATE Mo. ____ Day ____ Year _____

Please fill out this form to reflect *your* view of the child's behavior even if other people might not agree. ***Be sure to answer all items.***

Please print. Be sure to answer all items.

Below is a list of items that describe children and youths. For each item that describes your child now or within the past 6 months, please circle the 2 if the item is very true or often true of your child. Circle the 1 if the item is somewhat or sometimes true of your child. If the item is not true of your child, circle the 0. Please answer all items as well as you can, even if some do not seem to apply to your child.

0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True

0 1 2 1. Acts too young for his/her age
0 1 2 2. Drinks alcohol without parents' approval
0 1 2 3. Argues a lot
0 1 2 4. Fails to finish things he/she starts
0 1 2 5. There is very little he/she enjoys
0 1 2 6. Bowel movements outside toilet
0 1 2 7. Bragging, boasting
0 1 2 8. Can't concentrate, can't pay attention for long
0 1 2 9. Can't get his/her mind off certain thoughts; obsessions
0 1 2 10. Can't sit still, restless, or hyperactive
0 1 2 11. Clings to adults or too dependent
0 1 2 12. Complains of loneliness
0 1 2 13. Confused or seems to be in a fog
0 1 2 14. Cries a lot
0 1 2 15. Cruel to animals
0 1 2 16. Cruelty, bullying, or meanness to others
0 1 2 17. Daydreams or gets lost in his/her thoughts
0 1 2 18. Deliberately harms self or attempts suicide
0 1 2 19. Demands a lot of attention
0 1 2 20. Destroys his/her own things
0 1 2 21. Destroys things belonging to his/her family or others
0 1 2 22. Disobedient at home
0 1 2 23. Disobedient at school
0 1 2 24. Doesn't eat well
0 1 2 25. Doesn't get along with other kids
0 1 2 26. Doesn't seem to feel guilty after misbehaving
0 1 2 27. Easily jealous
0 1 2 28. Breaks rules at home, school, or elsewhere
0 1 2 29. Fears certain animals, situations, or places, other than school
0 1 2 30. Fears going to school
0 1 2 31. Fears he/she might think or do something bad
0 1 2 32. Feels he/she has to be perfect
0 1 2 33. Feels or complains that no one loves him/her
0 1 2 34. Feels others are out to get him/her
0 1 2 35. Feels worthless or inferior
0 1 2 36. Gets hurt a lot, accident-prone
0 1 2 37. Gets in many fights
0 1 2 38. Gets teased a lot
0 1 2 39. Hangs around with others who get in trouble
0 1 2 40. Hears sound or voices that aren't there
0 1 2 41. Impulsive or acts without thinking
0 1 2 42. Would rather be alone than with others
0 1 2 43. Lying or cheating
0 1 2 44. Bites fingernails
0 1 2 45. Nervous, highstrung, or tense
0 1 2 46. Nervous movements or twitching
0 1 2 47. Nightmares
0 1 2 48. Not liked by other kids
0 1 2 49. Constipated, doesn't move bowels
0 1 2 50. Too fearful or anxious
0 1 2 51. Feels dizzy or lightheaded
0 1 2 52. Feels too guilty
0 1 2 53. Overeating
0 1 2 54. Overtired without good reason
0 1 2 55. Overweight
0 1 2 56. Physical problems ***without known medical cause***:
0 1 2 a. Aches or pains (***not*** stomach or headaches)
0 1 2 b. Headaches
0 1 2 c. Nausea, feels sick
0 1 2 d. Problems with eyes (***not*** if corrected by glasses)
0 1 2 e. Rashes or other skin problems
0 1 2 f. Stomachaches
0 1 2 g. Vomiting, throwing up

Be sure you answered all items. Then see other side.

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Please print. Be sure to answer all items.

0 = Not True (as far as you know) 1 = Somewhat or Sometimes True 2 = Very True or Often True

0 1 2 57. Physically attacks people	0 1 2 84. Strange behavior
0 1 2 58. Picks nose, skin, or other parts of body	0 1 2 85. Strange ideas
0 1 2 59. Plays with own sex parts in public	0 1 2 86. Stubborn, sullen, or irritable
0 1 2 60. Plays with own sex parts too much	0 1 2 87. Sudden changes in mood or feelings
0 1 2 61. Poor school work	0 1 2 88. Sulks a lot
0 1 2 62. Poorly coordinated or clumsy	0 1 2 89. Suspicious
0 1 2 63. Prefers being with older kids	0 1 2 90. Swearing or obscene language
0 1 2 64. Prefers being with younger kids	0 1 2 91. Talks about killing self
0 1 2 65. Refuses to talk	0 1 2 92. Talks or walks in sleep
0 1 2 66. Repeats certain acts over and over; compulsions	0 1 2 93. Talks too much
	0 1 2 94. Teases a lot
0 1 2 67. Runs away from home	0 1 2 95. Temper tantrums or hot temper
0 1 2 68. Screams a lot	0 1 2 96. Thinks about sex too much
0 1 2 69. Secretive, keeps things to self	0 1 2 97. Threatens people
0 1 2 70. Sees things that aren't there	0 1 2 98. Thumb-sucking
0 1 2 71. Self-conscious or easily embarrassed	0 1 2 99. Smokes, chews, or sniffs tobacco
0 1 2 72. Sets fires	0 1 2 100. Trouble sleeping
0 1 2 73. Sexual problems	0 1 2 101. Truancy, skips school
0 1 2 74. Showing off or clowning	0 1 2 102. Underactive, slow moving, or lacks energy
0 1 2 75. Too shy or timid	0 1 2 103. Unhappy, sad, or depressed
0 1 2 76. Sleeps less than most kids	0 1 2 104. Unusually loud
0 1 2 77. Sleeps more than most kids during day and/or night	0 1 2 105. Uses drugs for nonmedical purposes (***don't*** include alcohol or tobacco)
0 1 2 78. Inattentive or easily distracted	0 1 2 106. Vandalism
0 1 2 79. Speech problem	0 1 2 107. Wets self during the day
0 1 2 80. Stares blankly	0 1 2 108. Wets the bed
0 1 2 81. Steals at home	0 1 2 109. Whining
0 1 2 82. Steals outside the home	0 1 2 110. Wishes to be of opposite sex
0 1 2 83. Stores up too many things he/she doesn't need	0 1 2 111. Withdrawn, doesn't get involved with others
	0 1 2 112. Worries

PAGE 2 ***Please be sure you answered all items.***

Attachment 8: Columbia Suicide Severity Scale: Baseline Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Attachment 9: Columbia Suicide Severity Scale: Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Henry M. Richards, MD

Institution: Janssen Research & Development

Signature: PPD Date: 03 November 2017

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE