Sub-study Protocol

Study Title:	An Exploratory, Pilot Study to Assess the Usability of the Embrace Seizure Detection Watch in Children and Young Adults with Dravet Syndrome: A Sub-study to the ZX008-1503 Open-Label Extension Trial
Study Number:	ZX008-1503-SS01
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797
Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5858 Horton Street, Suite 455 Emeryville, CA 94608 USA
Sponsor's Medical Contact	[redacted] Zogenix, Inc.
Date/Version of Study Protocol:	28 August 2017 (Protocol Amendment 2.0) 14 June 2017 (Protocol Amendment 1.0) 13 January 2017 version 1.0 (Original Protocol)

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator Study File. This list will be updated by the sponsor or the sponsor's agent and provided to study sites as needed.

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SIGNATURE OF SPONSOR

Study Number: ZX008-1503-SS01

Study Title: An Exploratory, Pilot Study to Assess the Usability of the Embrace Seizure Detection Watch in Children and Young Adults with Dravet Syndrome: A Sub-study to the ZX008-1503 Open-Label Extension Trial

Sponsor's Responsible Officer: [redacted]

Zogenix International Limited
A wholly owned subsidiary of Zogenix, Inc.
5858 Horton Street, Suite 455
Emeryville, CA 94608 USA

[redacted]

(Signature)

24 Aug 2017

(Date [DD/MMM/YYYY])

SIGNATURE OF COORDINATING INVESTIGATOR

Study Number: ZX008-1503-SS01

Study Title: An Exploratory, Pilot Study to Assess the Usability of the Embrace Seizure Detection Watch in Children and Young Adults with Dravet Syndrome: A Sub-study to the ZX008-1503 Open-Label Extension Trial

Coordinating Investigator: [redacted]

Institute of Neurology and Neurosurgery at St. Barnabas
Research Department
Livingston, NJ USA

[redacted]

(Signature)

08/30/2017.

(Date [DD/MMM/YYYY])

SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)

Study Number: ZX008-1503-SS01

Study Title: An Exploratory, Pilot Study to Assess the Usability of the Embrace Seizure Detection Watch in Children and Young Adults with Dravet Syndrome: A Sub-study to the ZX008-1503 Open-Label Extension Trial

I have read this study protocol, including all appendices. By signing this study protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Name and affiliation to be filled out by the investigator

Principal Investigator

Name and affiliation: _____

_____

_____ _____

(Signature) (Date [DD/MMM/YYYY])

LIST OF ABBREVIATIONS

ABBREVATION	DEFINITION
AE	adverse event
BID	bis in die; two times per day
BRIEF	Behavior Rating Inventory of Executive Function
CBD	whole blood cannabidiol
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
DS	Dravet syndrome
ECG	electrocardiogram
EDA	electrodermal activity
EmB	Embrace treatment population
EMBRACE	Empatica Embrace watch system
EOS	end of study
EQ-5D-5L	standardized measure of health status
ERT	Seizure Diary custom built by ERT
ET	Early Termination
EU-REACH	European Union Registration, Evaluation, Authorisation and Restriction of Chemicals
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonization
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
IPCAB	International Pediatric Cardiology Advisory Board
IRB	Institutional Review Board
LED	light-emitting diode
MMRE	mixed model repeated measures
OLE	open-label extension
PSS	Perceived Stress Scale
QoL	Quality of Life
SAF	safety analysis population
SMEI	Severe Myoclonic Epilepsy Of Infancy
SUDEP	Sudden Unexpected Death in Epilepsy
THC	tetrahydrocannabinol
ULN	upper limit of normal
USA	United States of America
ZX008	Fenfluramine Hydrochloride Oral Solution

STUDY SYNOPSIS

Study Title: An Exploratory, Pilot Study to Assess the Usability of the Embrace Seizure Detection Watch in Children and Young Adults with Dravet Syndrome: A Sub-study to the ZX008-1503 Open-Label Extension Trial	
Study Number: ZX008-1503-SS01	
Study Product: Fenfluramine Hydrochloride, ZX008	
Type of Study: Exploratory	**Indication Studied:** Dravet syndrome
Phase of Development: III	**Countries:** North America
Sponsor: Zogenix International Limited	
Coordinating Investigator: [redacted] Institute of Neurology and Neurosurgery at St. Barnabas Research Department Livingston, New Jersey USA	
Estimated Duration of Individual Subject Participation: The duration of the study for an individual subject is expected to be approximately 12 weeks with the option to extend to 24 weeks.	

Objectives:

The primary objective of the study is:

- To assess the overall usability and performance (correct use and ease of use) of the Empatica Embrace Seizure Detection watch system (Embrace) in outpatients with Dravet syndrome.

The secondary exploratory objectives of the study are:

- To compare objective convulsive seizure count, as captured by the Embrace, to convulsive seizure count captured manually in the seizure diary.
- To compare objective convulsive seizure count during periods of sleep, as captured by the Embrace, to convulsive seizure count during periods of sleep captured manually in the electronic seizure diary.
- To examine if the size of the electrodermal activity (EDA) response during and after a convulsive seizure is reduced over time with the ZX008 treatment.
- To examine if skin-surface temperature changes with ZX008 treatment.
- To examine if skin-surface temperature levels are different during periods of time preceding convulsive seizures than during times that are seizure-free.
- To examine correlation of study drug dose and fever-induced convulsive seizure frequency, severity, and duration.
- To examine the timing of diary-reported events vs. automatically detected events.
- To assess quality of life while using the Embrace system with the following measures:
  - Quality of Life (QoL) of the parent/caregiver using the EQ-5D-5L scale.
  - Affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS).
- To assess caregiver stress using the Perceived Stress Scale (PSS).

Methodology: This is a sub-study to the ZX008-1503 OLE study. All participants in this sub-study will have participated in Study ZX008-1501 or ZX008-1504 Cohort 2 and then continued in Study ZX008-1503, which is a multicenter, open-label, long-term safety study of ZX008 (fenfluramine hydrochloride) in pediatric and young adult subjects with Dravet syndrome. The main Study ZX008-1503 consists of a 12-month OLE Treatment Period and a 2-week Post-Dosing Period. Details of dose and dose-adjustments are described in the main Study ZX008-1503.

This sub-study will include up to 20 participants who meet the entry criteria for the main Study ZX008-1503 and who are willing to wear the Embrace watch and use the Embrace system per the user instructions for 12 consecutive weeks. Those invited to participate will undergo all procedures included in the main Study ZX008-1503 during their participation in this sub-study, plus any additional procedures specific for the sub-study. At the conclusion of the sub-study, participants will revert to only using the ERT seizure diary for the remainder of their participation in the main Study ZX008-1503. Efficacy analyses for sub-study participants that rely on the ERT seizure diary or that are specific to the Embrace watch will not be included in the main ZX008-1503 analyses.

At the time of consent for the main Study ZX008-1503, subjects will also be presented with the consent for this sub-study. Subjects who consent for the sub-study will be fitted with an Embrace watch at Study Visit 1. Subjects (and/or parents/caregivers) will also be given instructions on how to use the Embrace system. The Alert app must be running on the provided iPod touch and remain in close proximity of the patient. However, parents/caregivers will continue to use the ERT seizure diary to record the number/type of seizures, rescue medications, and study drug administration.

At pre-determined assessment times, parents/caregivers will complete questionnaires specific for the sub-study, including the Ease of Use Questionnaire and the Perceived Stress Scale (PSS), to measure user experience.

External Committees: The ZX008 clinical program will employ an Independent Data and Safety Monitoring Committee (IDSMC) that will be responsible for safety oversight. A separate International Pediatric Cardiology Advisory Board (IPCAB) will monitor the cardiac safety of the ZX008 clinical trials.

Number of Subjects: Up to 20 subjects will be enrolled from the main Study ZX008-1503.

Inclusion Criteria: Subject must meet all of the entry criteria for the main Study ZX008-1503 to be eligible for the sub-study. In addition to meeting the above listed criteria, subjects in the sub-study must also be willing to wear and use the Embrace watch and parents/caregivers must be willing to use the Alert app per the user instructions. This includes:

1. Subject is willing to wear the Embrace watch on the wrist (alternatively ankle, if needed for younger children). Subjects are asked to wear the watch for as many hours of the day as possible, and for the entire night, if possible, for the 12-week duration of the sub-study.
2. Subject's parent/caregiver is willing to use the Alert App and receive voice and SMS notifications on their personal smart-phone, and ensure the smart-phone has internet connectivity; iOS 8.2 or higher is required for iPhone users.
3. Subject/subject's caregiver is willing to ensure that the Embrace watch remains within close proximity of the paired iPod Touch running the Empatica Alert app.

4. Subject/subject's caregiver is willing to ensure that the Embrace system is properly stored when not in use, and is not left exposed to direct sunlight, moisture, humidity or rain while in storage. The Embrace watch is water resistant but should never be submerged in water. Bathing and/or showering with the watch is acceptable, however.
5. Subject/subject's caregiver is willing to regularly clean the Embrace watch, routinely inspect the watch for sharp edges and damage, and ensure the watch is never worn over damaged or broken skin.
6. Subject/subject's caregiver is willing to ensure that the Embrace system is properly charged daily during a time when the subject is being observed so any seizures that occur during times that the device is not being worn are able to be added to the record manually.

Exclusion Criteria: Subjects meeting any of the exclusion criteria for main Study ZX008-1503 are not eligible for the sub-study. In addition, subject must not be enrolled into the sub-study if:

1. Subject has a known hypersensitivity to any of the Embrace device materials.
2. Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to Visit 1, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

Study Product, Dose, and Mode of Administration:
ZX008: supplied as an oral solution in a concentration of 2.5 mg/mL. Subjects will be titrated to an effective dose beginning with 0.2 mg/kg/day (maximum: 30 mg/day). Study medication will be administered twice a day (BID) in equally divided doses with food.

Empatica Embrace watch system (Embrace)/Embrace Alert app: The noninvasive Embrace wrist-worn monitoring device, reads physiological data (EDA, skin temperature, and motion) from the surface of the skin and can transmit it wirelessly to a receiver. The watch is used in conjunction with the Embrace Alert app. The Alert app detects events from user physiology, such as convulsive seizures, and sends an alert to a caregiver via a phone call or text message. The Alert app runs on an iPod Touch and must remain in close proximity of the patient.

Duration of Treatment: Subjects will be permitted to participate in the sub-study for the initial 12 weeks of participation in the main OLE study (ZX008-1503). Subjects may have the opportunity to extend participation in the sub-study for up to 24 weeks.

Criteria for Evaluation:

Safety:

Safety criteria are identical to those in the main Study ZX008-1503 and include AEs, laboratory safety parameters (hematology, chemistry, urinalysis), vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, 12-lead ECGs, Doppler ECHOs, and body weight.

Efficacy:

The primary criteria for evaluation in the sub-study is the change over time in the 5-point Likert Ease of Use Questionnaire to measure user experience.

Secondary exploratory efficacy criteria for evaluation include change over time in the following:

- Perceived Stress Scale (PSS) to measure caregiver burden.
- Correlation of monthly (28-day) convulsive seizure count between the Embrace watch and seizure diary.
- Size of EDA response during and in the post-ictal hour of convulsive seizures.
- Skin-surface temperature (measured on wrist).
- Frequency of fever-related convulsive seizures.
- Comparison of convulsive seizure count during periods of sleep, and during the combined titration and maintenance periods, between the Embrace watch and seizure diary.
- Correlation of convulsive seizure time and classification as determined by Embrace watch and seizure diary.
- EQ-5D-5L to measure quality of life of the parent/caregiver while using the Embrace.
- HADS to measure affective symptoms of the parent/caregiver while using the Embrace.

All other efficacy criteria are identical to those in the main Study ZX008-1503.

Sample Size Determination: This sub-study is designed as a pilot exploratory study to provide preliminary information on the ease of use of the Embrace watch to detect seizures in outpatients with Dravet syndrome, therefore, the sample size is based more on feasibility than on power to detect differences.

Statistical Methods:

All safety data will be summarized as described in the ZX008-1503 protocol and associated Statistical Analysis Plan. Efficacy analyses for sub-study participants that rely on the ERT seizure diary or that are specific to the Embrace watch will not be included in the main ZX008-1503 analyses. Exploratory data for the Embrace watch system data will be processed as follows:

- Embrace's automated convulsive seizure detection results will be manually compared to the diary counts of convulsive seizures. Cohen's Kappa values will be computed for agreement.

- The above will be repeated separately for events during periods of sleep vs. events while awake, based on Embrace's determination of sleep/wake (periods of sleep will be based on actigraphy and EDA as measured by the Embrace watch).

- For each seizure detected by the Embrace watch, the peri-ictal EDA recording will be segmented from 60 minutes before detected seizure onset to 120 minutes afterward. A"significant EDA response" is declared when an increase in skin conductance level of more than 2 times the standard deviation of the pre-ictal baseline occurs. Significant EDA responses will be analyzed in terms of the amplitude of their EDA_peak, the response duration, defined as the difference between "EDA_end" and "EDA_start," and the natural logarithm of the area under the curve (AUC) of the rising phase (from "EDA_start" to "EDA_peak") and of the total response (from "EDA_start"to "EDA_end"), ie, LogAUCrise and LogAUCtot. These measures will be examined to see if they vary over time with the treatment.

- Skin-surface temperature changes will be averaged daily and compared over time, with separate comparisons made for "seizure-free" periods and for "pre-seizure periods." The duration of these periods will be based on average 60-minute intervals, but may also be examined with shorter intervals.

- Each episode of fever, defined as any body temperature above 98.6°F (37°C), and number, severity, and duration of each seizure detected by Embrace will be correlated to dose of study drug.

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND

ZX008 (fenfluramine hydrochloride) is under clinical development for the adjunctive treatment of patients with Dravet syndrome (DS).

Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The condition most commonly appears during the first year of life as frequent febrile seizures. As the condition progresses, other types of seizures typically occur, including myoclonic seizures and status epilepticus (Dravet 1978). Following the appearance of these seizures, affected children develop several co-morbid conditions including psychomotor regression, ataxia, sleep disturbance, and cognitive impairment. Intellectual impairment begins to become apparent around age 2 years due to lack of intellectual/behavioral progression. Dravet children often have a lack of coordination, poor development of language, hyperactivity, and difficulty relating to others (Dravet 1978; Hurst 1990). The degree of cognitive impairment appears to correlate, at least in part, with the frequency of seizures, and might be a result of repeated cerebral hypoxia. Children with DS also encounter a higher incidence of Sudden Unexpected Death in Epilepsy (SUDEP; Nashef 2012) than other populations with epilepsy. Indirect evidence has linked SUDEP to several possible etiologies, including seizure-induced apnea, pulmonary edema, dysregulation of cerebral circulation, and cardiac arrhythmias (Shorvon 2011), although the actual etiology remains unknown and other mechanisms have not been ruled out. The vast majority of patients who survive to adulthood are wholly dependent on around-the-clock caregivers and eventually live in institutional care homes.

Zogenix is conducting an international, multicenter, open-label, long-term safety study of ZX008 in pediatric and young adult subjects with Dravet syndrome who have successfully completed 14 weeks of treatment in core study ZX008-1501, ZX008-1502, and ZX008-1504 Cohort 2, or successfully completed core study ZX008-1504 Cohort 1, and are candidates for continuous treatment for an extended period of time. The ZX008-1503 trial will consist of a 12-month open-label extension (OLE) Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who complete this trial will have been treated with ZX008 for a minimum of up to 1 year (including their participation in both the core study and this study).

1.2 RATIONALE FOR CURRENT SUB-STUDY, ZX008-1503-SS01

This is a sub-study to the ZX008-1503 OLE trial, which will include up to 20 participants who are enrolled in Study ZX008-1503. This is an exploratory sub-study to provide preliminary information on the overall usability and performance of the Empatica Embrace watch system (Embrace) in outpatients with Dravet syndrome.

Seizure frequency is the primary outcome measure for individual treatment and for clinical trials. The current gold standard for demonstrating efficacy of new anti-epileptic drugs is a 50% reduction in seizure frequency. This efficacy standard is based on patients or their caregivers maintaining seizure diaries.

Use of sensitive seizure detection technology may allow greater accuracy in seizure counting. Seizure detection technology may also provide means to address specific clinical questions, such as the occurrence of unwitnessed seizures during periods of sleep.

The Embrace has been designed for automated convulsive seizure detection and characterization. The Embrace watch monitors electrodermal activity (EDA) and accelerometer-sensed changes in motion to analyze the information and detect patterns that are typically observed in convulsive seizures in real-time. The data can then be used to compare seizure detections, false alarms, and seizures that are not detected, to e-diary seizure report information.

This sub-study for patients enrolled in the open-label extension study may provide insights into seizure triggers, such as temperature, or facilitate seizure counts during sleep and allow for comparison of various endpoints captured by the Embrace to the same endpoints captured in an electronic hand-held seizure diary.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To assess the overall usability and performance (correct use and ease of use) of the Empatica Embrace Seizure Detection watch system (Embrace) in outpatients with Dravet syndrome.

2.2 SECONDARY OBJECTIVES

The secondary exploratory objectives of the study are:

- To compare objective convulsive seizure count, as captured by the Embrace, to convulsive seizure count captured manually in the electronic seizure diary.
- To compare objective convulsive seizure count during periods of sleep, as captured by the Embrace, to convulsive seizure count during periods of sleep captured manually in the electronic seizure diary.
- To examine if the size of the electrodermal activity (EDA) response during and after a convulsive seizure is reduced over time with ZX008 treatment.
- To examine if skin-surface temperature changes with ZX008 treatment.
- To examine if skin-surface temperature levels are different during periods of time preceding convulsive seizures than during times that are seizure-free.
- To examine correlation of study drug dose and fever-induced convulsive seizure frequency, severity, and duration.
- To examine the timing of diary-reported events vs. automatically detected events.
- To assess quality of life while using the Embrace system with the following measures:
    - Quality of Life (QoL) of the parent/caregiver using the EQ-5D-5L scale.
    - Affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS).
- To assess caregiver stress using the Perceived Stress Scale (PSS).

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a sub-study to the ZX008-1503 OLE study. All participants in this sub-study will have participated in Study ZX008-1501 or ZX008-1504 Cohort 2 in the United States or Canada and then continued in Study ZX008-1503, which is a multicenter, open-label, long-term safety study of ZX008 (fenfluramine hydrochloride) in pediatric and young adult subjects with Dravet syndrome. The main Study ZX008-1503 consists of a 12-month OLE Treatment Period and a 2-week Post-Dosing Period in which all subjects will receive ZX008 starting at 0.2 mg/kg, titrating to an effective dose, up to 0.8 mg/kg/day (not to exceed 30 mg/day). Thus, subjects who complete the main study will have been treated with ZX008 for a minimum of up to 1 year. This sub-study will include up to 20 participants who meet the entry criteria for the main Study ZX008-1503 and who are willing to wear the Embrace watch and their parent/caregiver who is willing to use the Embrace Alert app per the user instructions for 12 consecutive weeks. Those invited to participate will undergo all procedures included in the main Study ZX008-1503, plus any additional procedures for the sub-study. At the conclusion of the sub-study, participants will only use the ERT seizure diary for the remainder of their participation in the main Study ZX008-1503. Efficacy analyses for sub-study participants that rely on the ERT seizure diary or that are specific to the Embrace watch will not be included in the main ZX008-1503 analyses.

At the time of consent for the main Study ZX008-1503 subjects will also be presented with the consent for this sub-study. Subjects who consent to participate in the sub-study will be fitted with an Embrace watch at Study Visit 1. Subjects (and/or parents/caregivers) will also be given instructions on how to use the Embrace system. The Alert app must be running on the provided iPod touch and remain in close proximity of the patient. However, parents/caregivers will continue to use the ERT seizure diary to record the number/type of seizures, use of rescue medication, and study drug administration.

At pre-determined assessment times, parents/caregivers will complete questionnaires specific for the sub-study, including:

1. Ease of Use Questionnaire, which comprises a 5-point Likert scale (1- Very easy, to 5- Very difficult).

2. Perceived Stress Scale (PSS), which consists of 10 items.

3. Parents/caregivers will also complete the EQ-5D-5L and HADS in order to assess quality of life while using the Embrace.

A schedule of sub-study assessments is provided in Table 1.

Table 1: Schedule of Additional Assessments for Subjects Enrolled in the Sub-study

Study Assessments		**OLE Treatment Period**			
Visit Number	**Visit 1[a]**	**Visit 2**		**Visits 3-4 (Months 1-2)[b]**	**Visit 5 (EOS/ET) Month 12[c]**
Study Day	**1[a]**	**15**		**30, 60**	**90**
		Clinic	**Phone**		
Informed Consent	X				
Entry Criteria	X				
Issue/fit Embrace watch system and provide instructions on its use	X				
Perceived Stress Scale (PSS)	X			X	X
Ease of Use Questionnaire		X		X	X
EQ-5D-5L (QoL of parent/caregiver)	X			X	X
HADS (Affect of parent/caregiver)	X			X	X

Abbreviations: EOS/ET=End of Study/Early Termination; HADS=Hospital Anxiety and Depression Scale; OLE=open-label extension; PSS=Perceived Stress Scale; QoL=Quality of Life
Note: All other Study ZX008-1503 procedures must be completed as described in the main study protocol.
[a] Visit 1/Day 1 for sub-study ZX008-1503-SS01 corresponds to Visit 1/Day 1 for the main Study ZX008-1503.
[b] Subjects who continue for an additional 3 months will repeat Study Day 30 and 60 procedures on Study Days 90 and 120, and the end of study visit will be Study Day 150.
[c] At EOS/ET, subjects will be required to return the Embrace watch and study iPod.

3.2 NUMBER OF SUBJECTS

Up to 20 subjects from the main Study ZX008-1503 will have the option to participate in sub-study ZX008-1503-SS01 upon separate consent and fulfillment of entry criteria as detailed in Sections 4.1 and 4.2. Subjects will be approached sequentially until the target number of participants is reached.

3.3 STUDY DURATION

The duration of the main Study ZX008-1503 for an individual who enters from Study ZX008-1501 or ZX008-1504 Cohort 2 is up to approximately 54 weeks. All subjects will receive ZX008 for up to approximately 52 weeks in Study ZX008-1503 and all subjects, including those who prematurely discontinue from the study, will undergo an up to 2-week taper of study medication, at the conclusion of the study. Subjects will be permitted to participate in the sub-study for the initial 12 weeks of participation in the main OLE study (ZX008-1503). Subjects may have the opportunity to extend participation in the sub-study for up to 24 weeks.

3.4 NUMBER OF STUDY CENTERS

It is anticipated that sub-study subjects will be enrolled from approximately 5 to 10 study sites participating in both Study ZX008-1501 or ZX008-1504 and Study ZX008-1503.

3.5 STUDY MONITORING PROCEDURES

As in the main Study ZX008-1503, an Independent Data and Safety Monitoring Committee (IDSMC) will be responsible for safety oversight, and a separate International Pediatric Cardiology Advisory Board (IPCAB) will monitor the cardiac safety of the ZX008 clinical trials and provide advice to the IDMSC.

4. SELECTION OF STUDY POPULATION

Patients must fulfill all the entry criteria for Study ZX008-1503 and none of the exclusion criteria, as shown in Sections 4.1 and 4.2, respectively, to qualify for randomization into this sub-study.

4.1 INCLUSION CRITERIA

In addition to meeting all of the main Study ZX008-1503 inclusion criteria subjects in the sub-study must also be willing to wear and use the Embrace watch and parents/caregivers must be willing to use the Alert app. This includes:

1. Subject is willing to wear the Embrace watch on the wrist (alternatively ankle, if needed for younger children). Subjects are asked to wear the watch for as many hours of the day as possible and for the entire night, if possible, for the duration of the sub-study.
2. Subject's parent/caregiver is willing to use the Alert App and receive voice and SMS notifications on their personal smart-phone, and ensure the smart-phone has internet connectivity; iOS 8.2 or higher is required for iPhone users.
3. Subject/subject's caregiver is willing to ensure that the Embrace watch remains within close proximity of the paired iPod Touch running the Empatica Alert app.
4. Subject/subject's caregiver is willing to ensure that the Embrace system is properly stored when not in use, and is not left exposed to direct sunlight, moisture, humidity or rain while in storage. The Embrace watch is water resistant but should never be submerged in water. Bathing and/or showering with the watch is acceptable, however.
5. Subject/subject's caregiver is willing to regularly clean the Embrace watch, routinely inspect the watch for sharp edges and damage, and ensure the watch is never worn over damaged or broken skin.
6. Subject/subject's caregiver is willing to ensure that the Embrace system is properly charged daily during a time when the subject is being observed so any seizures that occur during times that the device is not being worn are able to be added to the record manually.

4.2 EXCLUSION CRITERIA

Subjects meeting any of main Study ZX008-1503 exclusion criteria must not be enrolled into the sub-study. In addition, subject must not be enrolled into the sub-study if:

1. Subject has a known hypersensitivity to any of the Embrace device materials.
2. Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to Visit 1, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

4.3 SUBJECTS OF REPRODUCTIVE POTENTIAL

Female subjects who are sexually active and are of child-bearing potential and male subjects who are sexually active with a partner of child-bearing potential must adhere to the contraception requirements as outlined in the main protocol ZX008-1503.

4.4 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

While subjects are encouraged to complete all study evaluations, subjects may voluntarily withdraw from the sub-study for any reason at any time. Subjects who withdraw from the sub-study may still remain in the main study ZX008-1503. These subjects will then use only the ERT seizure diary. Subjects who are withdrawn from the main Study ZX008-1503 (either voluntarily or by the sponsor or investigator) must also be withdrawn from the sub-study. Subjects may be considered withdrawn or withdrawn by the investigator if they fail to return for visits, refuse to follow instructions regarding use of the Embrace watch or associated apps, lose or damage the Embrace in circumstances that do not support replacement, or become lost to follow-up for any other reason. All subjects who withdraw from the study early are required to return the Embrace watch and study iPod.

If premature withdrawal occurs for any reason, the investigator must make a genuine effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the case report form (CRF). All subjects who withdraw from the study with an ongoing adverse event (AE) must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge.

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they failed to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the subject (eg, dates of telephone calls, registered letters).

Subjects may withdraw their consent to participate in the study at any time without having to justify the reason for doing so. The decision to withdraw consent and discontinue participation in the study will not prejudice the subject's future medical treatment in any way.

In the event that the study is terminated prematurely then the procedure for termination should be followed as described in the main Study ZX008-1503 protocol. Concern for the interests of the subject will always prevail over the interests of the study.

The reason for, and date of discontinuation from participation in the study must be recorded in detail in the CRF and in the subject's medical records (eg, AEs, lack of compliance, lost to follow-up, etc.). If possible, the subject/subject's legal representative should confirm his decision in writing.

The investigator will attempt to complete all procedures usually required at the end of the study at the time when the subject's participation in the study is discontinued or as close as possible to that time, as described in the ZX008-1503 protocol. As far as possible, a complete final examination must be performed on all subjects who do not complete the study according to the study protocol.

Data collected until the time a subject discontinues participation in the study will be handled in the same manner as data for subjects completing the study. Where possible, further information will be collected if any AEs are experienced by a subject after discontinuing participation in the study.

4.5 TERMINATION OF THE SUB-STUDY

If the investigator, the sponsor, the Medical Monitor, or the IDSMC becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study or sub-study continues, then the sub-study may be terminated. The sub-study may be terminated at the sponsor's discretion at any time also in the absence of such a finding.

Conditions that may warrant termination of the sub-study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study.
- Failure to enroll subjects at the required rate.
- A decision of the sponsor to suspend or discontinue development of ZX008.
- Lack of availability of the Embrace detection device.

4.6 REPLACEMENT OF SUBJECTS

Enrolled subjects will not be replaced.

5. STUDY VISITS AND PROCEDURES

Subjects participating in the sub-study will undergo all clinic visits and procedures included in the main Study ZX008-1503, plus additional procedures for the sub-study, as described in Table 1. The following questionnaires/scales will be completed at the specified time points:

- To assess user experience with the Embrace watch system, a 5-point Likert Ease of Use Questionnaire (Appendix 1) will be completed at Clinic Visit 2 (Day 15), monthly at Clinic Visits 3-7, and at the end of study participation (Clinic Visit 8).

- The Perceived Stress Scale (PSS) (Appendix 2) is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. It is a 10-item scale that asks about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way. The PSS will be used to evaluate whether objective seizure detection and automated seizure alerts have any impact on perceived stress of the parent/caregiver. This scale will be completed at Clinic Visit 1 (Day 1), monthly at Clinic Visits 3-7, and at the end of study participation (Clinic Visit 8).

- The EQ-5D-5L (see main StudyZX008-1503) is a standardized measure of health status used to provide a simple, generic assessment for clinical and economic appraisal. It consists of 6 questions and can be completed in less than 10 minutes. The EQ-5D-5L is included in the main study ZX008-1503, but for the sub-study the assessment should be as it relates to use of the Embrace watch. This questionnaire will be completed at Clinic Visit 1 (Day 1), monthly at Clinic Visits 3-7, and at the end of study participation (Clinic Visit 8).

- The Hospital Anxiety and Depression Scale (HADS) (see main StudyZX008-1503) is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing. It is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression. The HADS is included in the main study ZX008-1503, but for the sub-study the assessment should be as it relates to use of the Embrace watch. This scale will be completed at Clinic Visit 1 (Day 1) monthly at Clinic Visits 3-7, and at the end of study participation (Clinic Visit 8).

6. INVESTIGATIONAL PRODUCT INFORMATION

6.1 ZX008 (FENFLURAMINE HYDROCHLORIDE ORAL SOLUTION)

Sub-study subjects will receive ZX008 as part of their treatment in main Study ZX008-1503. A brief description of the ZX008 product is provided in Table 2.

Table 2: Investigational Medicinal Product – ZX008

	Study Product
Substance Code	ZX008
Active Substance (INN)	Fenfluramine Hydrochloride
Trade Name	Not applicable
Formulation (including dosage form and strength)	Solution 2.5 mg/mL
Route/Mode of Administration	Oral
Manufacturer	PCI Pharma Services on behalf of Zogenix International Limited

ZX008 is supplied as an oral solution in a concentration of 2.5 mg/mL. Subjects will be titrated to an effective dose beginning with 0.2 mg/kg/day (maximum: 30 mg/day). Study medication will be administered twice a day (BID) in equally divided doses with food. Please refer to the ZX008-1503 protocol for a detailed description of the ZX008 drug product and its administration.

6.2 EMPATICA EMBRACE SYSTEM

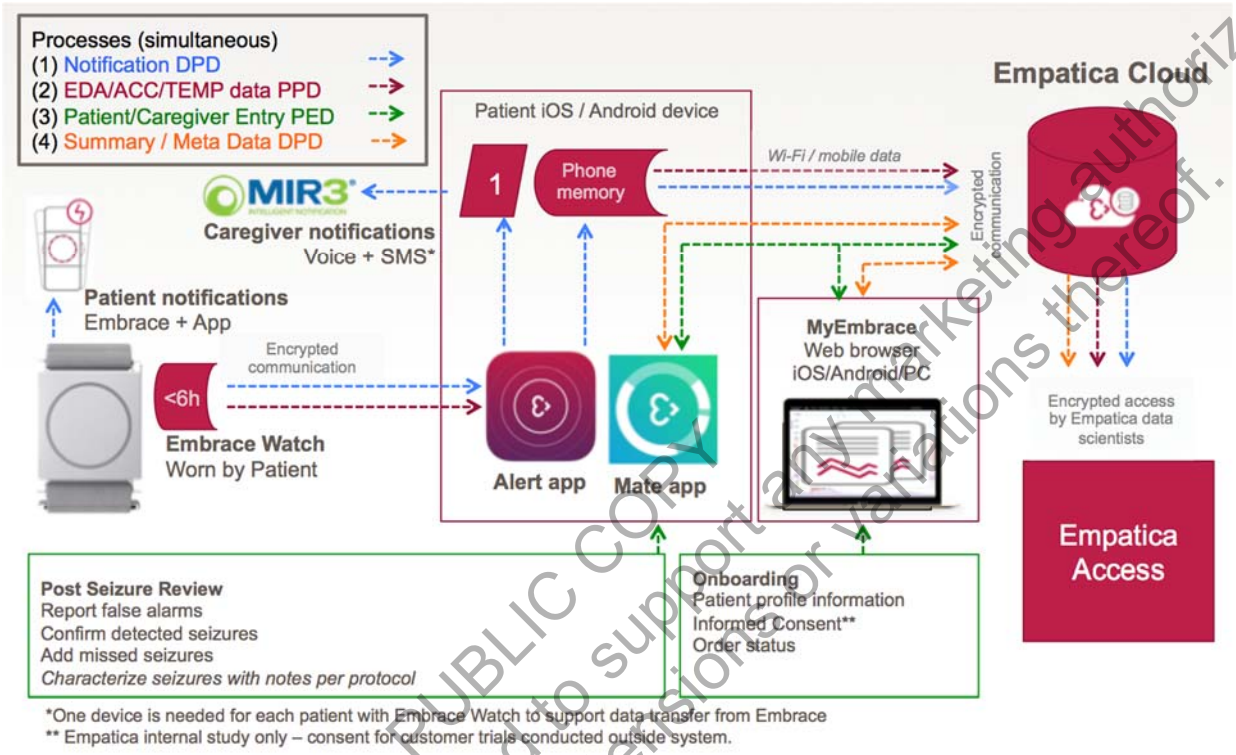
6.2.1 Hardware

The Embrace wrist-worn monitoring device (Embrace watch; Figure 1) reads physiological data from the surface of the skin and can transmit it wirelessly to a receiver. More specifically the electronic device measures: EDA, skin temperature, and motion (3-axis acceleration and 3D orientation with a gyroscope). Designed to be non-stigmatising for patients, the device also displays time in an analog-like display. User interactions are via a 12- full-color light-emitting diode (LED) circular display, vibration motor for haptic feedback and capacitive touch button.

Figure 1: Embrace Wrist-worn Monitoring Device (Embrace Watch)

6.2.2 Software

Figure 2: Embrace System Architecture



6.2.2.1 Embrace Alert App

The Embrace Alert app detects events from user physiology, such as a convulsive seizure, and sends an alert to a caregiver through a phone call or text message. Real-time seizure detection and alerting is still experimental and is for investigational use only. It also collects raw data from Embrace hardware and sends is to a receiver (smart phone memory) and consequently to a cloud storage system for later retrieval. The Alert app runs on an iPod Touch and must remain in close proximity of the patient. The Alert app is also used for device configuration (eg, setting the clock and activating/deactivating night-mode which suppresses interactions) and firmware management.

6.2.2.2 MyEmbrace

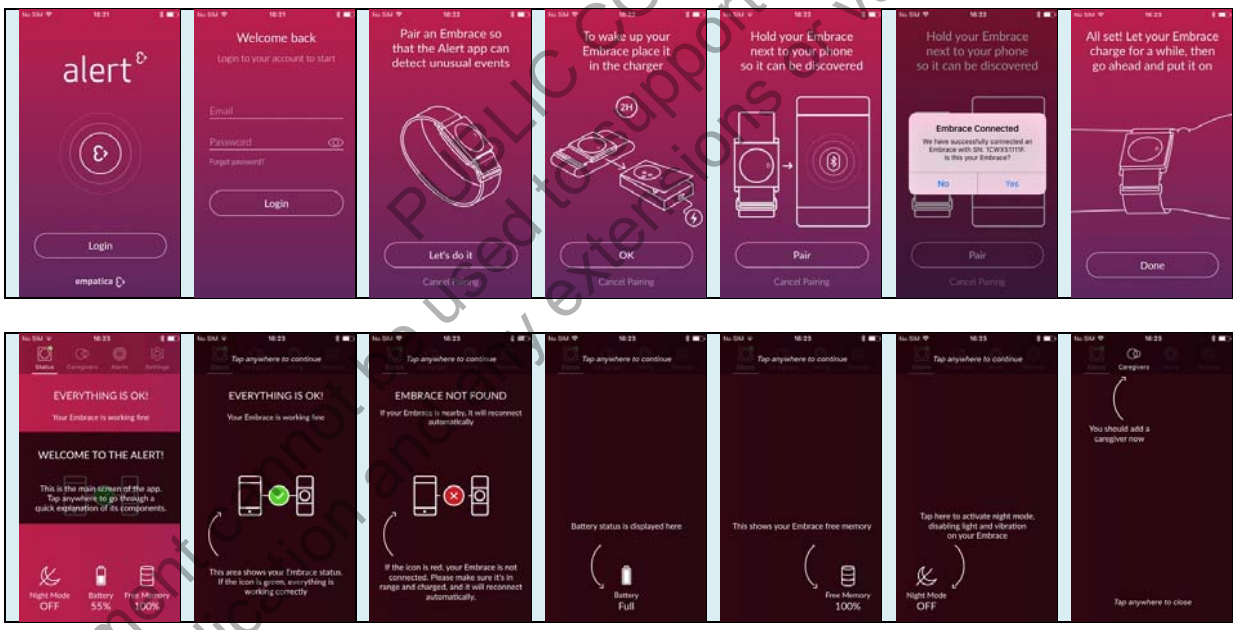
MyEmbrace is a secure web portal used to configure an Empatica account for patients. The MyEmbrace includes profile configuration and user guides. There is no user-data visualization in the MyEmbrace portal.

The study coordinator will configure the Embrace watch and paired phone on behalf of the patient and/or parent/caregiver. Custom documentation is to be prepared so patients and their parents/caregiver need not be exposed to the MyEmbrace interface at any time.

6.2.3 Usability of the Empatica Embrace Watch System (Embrace)

In the context of investigational use, the experimental seizure detection and alert components can be activated for patients and caregivers with their informed consent about the experimental nature of the functionality. Usability testing to support patient home-use has been underway since March 2016 with eight iterations introduced prior to August 2016 (revision history on hand as per the Embrace Change-log). In-app getting started guides, quick-start documentation and troubleshooting guides are sufficient to support the vast majority of patient caregiver groups in current trials. Due to the fact that patients/caregivers will be enrolled by study staff, those who might otherwise be unable to get set-up independently should be able to be enrolled and on-boarded without issue. The Empatica Alert app Onboarding screens are shown in Figure 3, and also provided in Appendix 3.

Figure 3: Empatica Alert App Onboarding Screens



6.2.4 Device Risks

The Embrace watch system is currently marketed in the United States for consumer use in sleep and activity tracking without the seizure detection and alerting components. It does not currently have FDA 510(k) clearance but was designed in compliance with IEC

60601-1-2:2014 standards. Empatica, the maker of the Embrace system, is a medical device company in compliance with EN ISO 13485 standards (cert No. 9124.EPTC).

6.3 BLINDING

This is an open-label sub-study to OLE Study ZX008-5103.

7. SAFETY INSTRUCTIONS AND GUIDANCE

The Embrace is similar to other smartwatches that have been worn by patients over multiple days, and is believed to present minimal risk. The device passes a small current across the skin surface (similar to capacitive sensors in nature). It is non-invasive composed of well-established materials used in wearable devices and designed with ISO 10993-5 standards. The only notable risk so far has been that some wearers of similar devices occasionally develop contact dermatitis. Risk of contact dermatitis has been mitigated by restricting the use of common allergens – including nickel and cobalt, which affect 11.8% and 2.3% of the population, respectively (Mortz, et al 2013) – in the device materials and selecting grades of stainless steel that have nickel levels well below those required by EU REACH regulations. Occasionally skin reactions in similar devices may be caused by bacterial build-up on a watch or watch band as opposed to the material of the device itself so users will be reminded to clean the devices regularly.

To date, there have been two reports of allergic reaction related to wearing the Embrace watch.

Subjects will be instructed to use the sensor only on the surface of healthy skin, to clean the sensor regularly, and to stop wearing it if the skin becomes red, itchy, or broken in any way.

The Embrace system does not transmit radio signals that may interfere with hospital equipment or life-sustaining medical equipment. While the device has the capability of wireless transmission, it uses the Bluetooth standard, which is a reserved 2.4 GHz frequency band used in consumer electronics and within transmission power requirements. The device is compliant with IEC 60601-1-2:2014, EN 300 301 328 489 standards on electromagnetic emissions and interference. The rechargeable LiPol battery has an integrated protection circuit and the power system meets IEC 62133 standards.

Any unanticipated adverse device events (regardless of seriousness or severity) and unanticipated problems related to study participation should be reported as in the main Study ZX008-1503.

The physiological signals recorded using this device will not be used to make diagnostic or treatment decisions.

Safety monitoring will be done as per the main Study ZX008-1503 protocol.

8. STATISTICS

8.1 SAMPLE SIZE

This sub-study is designed as a pilot exploratory study to provide preliminary information on the ease of use of the Embrace watch to detect seizures in outpatients with Dravet syndrome, therefore, the sample size is based on feasibility.

8.2 ANALYSIS POPULATIONS

8.2.1 Safety (SAF) Population

Participants in the sub-study will be included in the main Study 1503 safety analyses, which will be performed on the SAF Population defined as all subjects who receive at least one dose of ZX008 during the open label extension.

8.2.2 Embrace Treatment (EmB) Population

The EmB Population for the sub-study is defined as all subjects who receive at least one dose of ZX008 and have valid Embrace seizure data for at least one week during the open label extension. Effectiveness analyses for the sub-study will be performed on the EmB Population.

8.3 DATA ANALYSIS

8.3.1 Safety Analysis

Safety criteria will be identical to that in the main study ZX008-1503, and include AEs, laboratory safety parameters (hematology, chemistry, and urinalysis), vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, 12-lead electrocardiograms (ECGs), Doppler ECHOs, and body weight. The BRIEF will be administered to track cognitive function. Adverse events considered to be related to the Embrace watch will be analyzed separately for participants in the sub-study.

8.3.2 Efficacy Analysis

The primary criteria for evaluation in the sub-study is the change over time in the 5-point Likert Ease of Use Questionnaire to measure user experience.

Secondary exploratory efficacy criteria for evaluation include change over time in the following:

- Perceived Stress Scale (PSS) to measure caregiver burden.
- Correlation of monthly (28-day) convulsive seizure count between the Embrace watch and seizure diary.
- Size of EDA response during and in the post-ictal hour of convulsive seizures.
- Skin-surface temperature (measured on wrist).
- Frequency of fever-related convulsive seizures.
- Comparison of convulsive seizure count during periods of sleep, and during the combined titration and maintenance periods between the Embrace watch and seizure diary.
- Correlation of convulsive seizure time and classification as determined by Embrace watch and seizure diary.
- EQ-5D-5L to measure quality of life of the parent/caregiver quality of life while using the Embrace.
- HADS to measure affective symptoms of the parent/caregiver while using the Embrace.

All other efficacy criteria are identical to those in the main Study ZX008-1503.

8.4 STATISTICAL METHODS

All safety data will be summarized as described in the main Study ZX008-1503 protocol and associated Statistical Analysis Plan. Efficacy analyses for sub-study participants that rely on the ERT seizure diary or are specific to the Embrace will not be included in the main Study ZX008-1503 analyses. Exploratory data for the Embrace watch system data will be processed as follows:

Continuous data will be summarized using descriptive statistics including means, standard deviations, medians, lower and upper quartiles, and ranges. Categorical variables will be summarized with frequencies and percentages. Confidence intervals will be calculated for key parameters or estimates as warranted.

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before the database is locked.

The primary analysis will rely on descriptive statistics to summarize responses to the Ease of Use Questionnaire from each time point where the questionnaire is administered. In particular, the modal, ie, most frequent, response to each item on the questionnaire will be reported at each time point. Responses across all items on the questionnaire will be summed to create an overall index that will also be reported at each time point.

Exploratory data for the Embrace watch system data will be processed as follows:

- Embrace's automated convulsive seizure detection results will be manually compared to the diary counts of convulsive seizures. Spearman rank correlation will be used to quantify agreement.

- The Spearman rank correlation described above will be repeated separately for events during periods of sleep and for events while awake, based on Embrace's determination of sleep/wake (periods of sleep will be based on actigraphy and EDA as measured by the Embrace watch).

- For each seizure, the peri-ictal EDA recording will be segmented from 60 minutes before detected seizure onset to 120 minutes afterward. A"significant EDA response" is declared when an increase in skin conductance level of more than 2 times the standard deviation of the pre-ictal baseline occurs. The time of the beginning of such an EDA response is defined as "EDA_start," the time of the maximum peak of the EDA response is defined as "EDA_peak," and the point in time following this peak, when the EDA falls below 10% of the peak amplitude is defined as "EDA_end." Significant EDA responses will be analyzed in terms of the amplitude of their EDA_peak, the response duration, defined as the difference between "EDA_end" and "EDA_start," and the natural logarithm of the area under the curve (AUC) of the rising phase (from "EDA_start" to "EDA_peak") and of the total response (from "EDA_start"to "EDA_end"), ie, LogAUCrise and LogAUCtot. These measures will be examined to see if they vary over time with the treatment. Each of the measures will be evaluated for changes over time using a mixed model repeated measures (MMRE) that allows for a different intercepts for each subject (ie, a random effect) but a common slope over time (ie, a fixed effect).

- Skin-surface temperature changes will be averaged daily and compared over time, with separate comparisons made for "seizure-free" periods and for "pre-seizure periods." The duration of these periods will be based on average 60-minute intervals, but may also be examined more with shorter intervals. Changes in skin-surface temperature over time will be evaluated using similar MMREs as described above for EDA endpoints.

9. DATA HANDLING PROCEDURES

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, study-required information and data, and other notes as appropriate. These records constitute source data.

A CRF will be provided by the sponsor (or delegate) for each subject enrolled into the sub-study. Study site staff will enter data directly into the validated electronic data capture (EDC) system by completing the CRF via a secure internet connection. The investigator is

responsible for ensuring accurate and proper completion of the CRF for recording data according to the instructions given in the CRF.

All entries in the CRF must be backed up by the relevant source data at the study site. All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the sub-study and signed by the investigator (or delegate).

Data entry in the CRF must be completed in a timely manner so that they always reflect the latest observations on the subjects enrolled in the sub-study.

All Embrace data will be automatically captured and stored in a de-identified manner on a secure MySQL database and/or secured Amazon S3 buckets as part of the Empatica production server and analytics backend. Individual subjects will be tracked by the de-identified subject id assigned to each subject at the consent. No personally identifiable information will be directly linked to BPT data.

10. ETHICAL & REGULATORY CONSIDERATIONS

The procedures set out in this study protocol are designed to ensure that the sponsor and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 Guideline. ICH GCP 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, and that the clinical study data are credible.

The sub-study will also be carried out according to all applicable international and national regulatory requirements.

The sponsor and the investigator must inform each other (eg, during a study initiation visit, via e-mail, etc.) that all ethical and legal requirements have been met before the first subject is enrolled into the sub-study.

10.1 INFORMED CONSENT

The investigator is responsible for obtaining a subject's written informed consent to participate in the sub-study.

A Subject Information Sheet and a master ICF will be prepared by the sponsor according to the provisions of ICH GCP and local legal requirements.

Before undergoing screening for possible enrollment into the sub-study, subjects must be informed, in an understandable form, about the nature, scope, and possible consequences of the study. This information must be given orally to subjects by a physician or medically qualified person (according to applicable regulatory requirements) who is well informed about the nature, scope, and possible consequences of the study. Written information about the study will also be provided in a Subject Information Sheet. The date on which this oral and written information on the study was provided to the subject, and by whom it was provided, must be documented in the ICF.

As specified in ICH GCP Section 4.8 and the US 21CFR Section 50.25, the informed consent discussion must emphasize that participation in the sub-study is voluntary and that subjects have the right to withdraw their consent at any time without giving a reason and without any disadvantage for their subsequent care.

Subjects must be given ample time and opportunity to inquire about details of the sub-study and to consider their participation in the sub-study. If, after reading the Subject Information Sheet and the ICF, consent is given to participate in the sub-study, then the ICF must be signed and personally dated by the subject and the person conducting the informed consent discussion (and an impartial witness, if required). The subject will be provided with a copy of the signed ICF.

Verification of the signed ICF will be recorded in the subject's CRF. The original signed ICF will be filed with the subject's records and/or in the Investigator Study File.

The Subject Information Sheet and ICF have to be approved by the IEC/IRB before they can be used in the study.

The Subject Information Sheet and ICF must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revision of these documents must be approved by the IEC/IRB before they can be used in the study. Subjects must be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented by having all parties concerned sign and personally date the revised ICF.

Subject or Subject's Legally Acceptable Representative Unable to Read

If a subject is unable to read, or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information provided to the subject, parent or guardian has been read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's

participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Assent for Subjects Under the Age of Consent (Pediatric Subjects)

All subjects are under the age of consent (ie, pediatric subjects under 18 years of age); the written informed consent of a legally acceptable representative is required. Pediatric subjects who can understand the nature, scope, and possible consequences of the study must also give their assent, orally and/or in writing via the assent document, as appropriate. After the ICF and any other written information to be provided to subjects has been read and explained to the subject and the subject's legally acceptable representative, and after the subject and the legally acceptable representative have orally consented to the subject's participation in the study and, if capable of doing so, the subject has signed and personally dated the assent document, the legally acceptable representative should sign and personally date the ICF. By signing the ICF, the legally acceptable representative attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject, and that assent was freely given by the subject.

10.2 REGULATORY CONSIDERATIONS AND INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

The sponsor (or delegate) will submit the appropriate documents to all applicable competent regulatory authorities and IEC/IRBs, and will await all relevant approval before enrolling any subjects into the study. Written approval should mention the study protocol by study title, study number, and version date.

This study will be conducted under Investigational New Drug (IND) Application and documented in accordance with the applicable regulatory guidelines and requirements.

The sponsor (delegate) will ensure that the investigators conduct the study as stipulated in this study protocol and in accordance with all applicable regulatory requirements. The sponsor (delegate) is obliged to obtain evidence of the investigator's qualification to perform the clinical study. Therefore, the investigator has to provide a signed and dated copy of his or her professional curriculum vitae (prepared no more than 2 years beforehand and preferably written in English) before the start of the study, including information on his or her experience in conducting clinical studies according to ICH GCP and other applicable regulatory requirements.

Written notification of the identity and occupation of the members of the IEC/IRB is also required by the sponsor (delegate). Should the IEC/IRB be unwilling to provide this information, a letter stating that the committee was constituted in accordance with applicable regulatory requirements should be provided.

10.3 PROTOCOL COMPLIANCE

The investigator must conduct the study in compliance with this sub-study protocol as agreed to by the sponsor and, if required, by any competent regulatory authority, and which has been approved by, or given a favorable opinion by, the IEC/IRB.

The investigator should not implement any deviation from, or changes to, the sub-study protocol without agreement by the sponsor (delegate) and prior review and documented approval or favorable opinion from the IEC/IRB of an amendment to the sub-study protocol. Exceptions include only cases of medical emergency to address immediate hazards to sub-study subjects, or when the changes involve only logistic or administrative aspects of the sub-study.

In the event of a medical emergency, the investigator at each site may institute any medical procedures deemed appropriate to address an immediate hazard to a subject without prior IEC/IRB approval or favorable opinion. As soon as possible, the implemented deviation or change, the reason(s) for it, and, if appropriate, the proposed study protocol amendment(s) should be submitted to:

- The sponsor (delegate) for agreement.
- The IEC/IRB for review and approval or favorable opinion (if required).
- The applicable competent regulatory authority (if required).

At the earliest opportunity, the investigator (or delegate) must inform the sponsor (delegate) about any notable protocol deviations and explain any deviation from the approved sub-study protocol in the CRF and/or in the Protocol Deviation Log, if applicable.

11. ADMINISTRATIVE ASPECTS

The administrative aspects of this sub-study are described in the main Study ZX008-1503 protocol.

12. REFERENCE LIST

Dravet C. Les epilepsies graves de l'enfant. Vie Med. 1978;8:543–548.

Hurst, DL. Epidemiology of severe myoclonic epilepsy of infancy. Epilepsia 1990;31:397-400.

Mortz, C. G., Bindslev-Jensen, C., & Andersen, K. E. (2013). Prevalence, incidence rates and persistence of contact allergy and allergic contact dermatitis in the Odense Adolescence Cohort Study: a 15-year follow-up.*British Journal of Dermatology*, *168*(2), 318-325.

Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia 2012;53, 227–233.

Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet 2011;378: 2028–38.

13. APPENDICES

APPENDIX 1 – LIKERT EASE OF USE QUESTIONNAIRE

Over the last week, using the Embrace watch was:

- ○ 1 – Very difficult
- ○ 2 – Difficult
- ○ 3 – Neutral
- ○ 4 – Easy
- ○ 5 – Very easy

Over the last week, using the Mate App was:

- ○ 1 – Very difficult
- ○ 2 – Difficult
- ○ 3 – Neutral
- ○ 4 – Easy
- ○ 5 – Very easy

Over the last week, using the Alert App was:

- ○ 1 – Very difficult
- ○ 2 – Difficult
- ○ 3 – Neutral
- ○ 4 – Easy
- ○ 5 – Very easy

APPENDIX 2 – PERCEIVED STRESS SCALE (PSS)

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

	0 = Never	1 = Almost Never	2 = Sometimes	3 = Fairly Often	4 = Very Often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and "stressed"?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside of your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

APPENDIX 3 – SUMMARY OF CHANGES

Clarifications and changes were made to the protocol amendment 2.0, including removal of the Empatica Mate app (Empatica Mate Onboarding for iOS Devices) to collect and summarize seizure activity data, and inclusion of subjects who have successfully completed 14 weeks of treatment with ZX008 in Cohort 2 of study ZX008-1504. Parents/caregivers will use the ERT seizure diary to record the number/type of seizures.

List of Specific Changes

Additions are marked in **bold** and deletions are marked in ~~strikethrough~~. Minor editorial and non-substantive changes, such as the correction of typing or formatting errors, updated use of abbreviations, updating headers and footers, tables of contents, list of abbreviations, signature pages, etc, are not listed. Note that the list of specific changes below is presented in the order in which they appear in the protocol.

Rationale: Remove the Empatica Mate app for collecting and summarizing seizure activity data and clarify use of Embrace system for assessing quality of life.	
Original Text	**Amendment Text**
Synopsis Objectives and Section 2.2 Secondary Objectives: The secondary exploratory objectives of the study are: • To compare objective convulsive seizure count, as captured by the Embrace, to convulsive seizure count captured manually in the Embrace electronic seizure diary (Empatica's Mate app, hand-held diary software running on an Apple iPod Touch ™ or Apple/Android smartphone). • To compare objective convulsive seizure count during periods of sleep, as captured by the Embrace, to convulsive seizure count during periods of sleep captured manually in the Embrace electronic seizure diary. • To assess quality of life while using the Embrace and Alert app with the following measures:	Synopsis Objectives and Section 2.2 Secondary Objectives: The secondary exploratory objectives of the study are: • To compare objective convulsive seizure count, as captured by the Embrace, to convulsive seizure count captured manually in the ~~Embrace electronic~~ seizure diary ~~(Empatica's Mate app, hand-held diary software running on an Apple iPod Touch ™ or Apple/Android smartphone)~~. • To compare objective convulsive seizure count during periods of sleep, as captured by the Embrace, to convulsive seizure count during periods of sleep captured manually in the ~~Embrace~~ electronic seizure diary. • To assess quality of life while using the Embrace ~~and Alert app~~ **system** with the following measures:
Rationale: Update study plan to include subjects who have successfully completed 14 weeks of treatment with ZX008 in Cohort 2 of study ZX008-1504	
Original Text	**Amendment Text**
Synopsis Methodology: This is a sub-study to the ZX008-1503 OLE study. All participants in this sub-study will have	Synopsis Methodology: This is a sub-study to the ZX008-1503 OLE study. All participants in this sub-study will have

participated in Study ZX008-1501 and then continued in Study ZX008-1503, which is a multicenter, open-label, long-term safety study of ZX008 (fenfluramine hydrochloride) in pediatric and young adult subjects with Dravet syndrome. The main Study ZX008-1503 consists of a 12-month OLE Treatment Period and a 2-week Post-Dosing Period. Details of dose and dose-adjustments are described in the main Study ZX008-1503.	participated in Study ZX008-1501 **or ZX008-1504 Cohort 2** and then continued in Study ZX008-1503, which is a multicenter, open-label, long-term safety study of ZX008 (fenfluramine hydrochloride) in pediatric and young adult subjects with Dravet syndrome. The main Study ZX008-1503 consists of a 12-month OLE Treatment Period and a 2-week Post-Dosing Period. Details of dose and dose-adjustments are described in the main Study ZX008-1503.
Rationale: Remove the Empatica Mate app for collecting and summarizing seizure activity data and clarify use of ERT seizure diary at conclusion of sub-study.	
Original Text	**Amendment Text**
Synopsis Methodology: This sub-study will include up to 20 participants who meet the entry criteria for the main Study ZX008-1503 and who are willing to wear the Embrace watch and use the Embrace Alert app and Mate app per the user instructions for 12 consecutive weeks. Those invited to participate will undergo all procedures included in the main Study ZX008-1503 during their participation in this sub-study, except recording seizures in the ERT seizure diary, plus any additional procedures specific for the sub-study. At the conclusion of the sub-study, participants will revert to using the ERT seizure diary for the remainder of their participation in the main Study ZX008-1503. The sub-study participants will be included in the safety analyses for the main Study ZX008-1503, but will not be included in any efficacy analyses that require the ERT seizure diary, or are specific to the Embrace. At the time of consent for the main Study ZX008-1503 subjects will also be presented with the consent for this sub-study. Subjects who consent for the sub-study will be fitted with an Embrace watch at Study Visit 1. Subjects (and/or parents/caregivers) will also be given instructions on how to use the Embrace, the Embrace Alert app, and the Embrace Mate app. Parents/caregivers will use the Embrace Mate app instead of the ERT seizure diary to record the	Synopsis Methodology: This sub-study will include up to 20 participants who meet the entry criteria for the main Study ZX008-1503 and who are willing to wear the Embrace watch and use the Embrace ~~Alert app and Mate app~~**system** per the user instructions for 12 consecutive weeks. Those invited to participate will undergo all procedures included in the main Study ZX008-1503 during their participation in this sub-study, ~~except recording seizures in the ERT seizure diary,~~ plus any additional procedures specific for the sub-study. At the conclusion of the sub-study, participants will revert to **only** using the ERT seizure diary for the remainder of their participation in the main Study ZX008-1503. **Efficacy analyses for sub-study participants that rely on the ERT seizure diary or that are specific to the Embrace watch will not be included in the main ZX008-1503 analyses.** ~~The sub-study participants will be included in the safety analyses for the main Study ZX008-1503, but will not be included in any efficacy analyses that require the ERT seizure diary, or are specific to the Embrace.~~ At the time of consent for the main Study ZX008-1503 subjects will also be presented with the consent for this sub-study. Subjects who consent for the sub-study will be fitted with an Embrace watch at Study Visit 1. Subjects (and/or

number/type of seizures. The Mate app has the option to be installed on a parent's smartphone (iOS or Android). When installed on a smartphone the Mate app can be accessed from more than one device simultaneously (eg, two parents can both have it installed). The Alert app must be running on the provided iPod touch and remain in close proximity of the patient.	parents/caregivers) will also be given instructions on how to use the Embrace~~, the Embrace Alert app, and the Embrace Mate app~~ **system**. **The Alert app must be running on the provided iPod touch and remain in close proximity of the patient. However, ~~P~~p**arents/caregivers will **continue to** use the ~~Embrace Mate app instead of the~~ ERT seizure diary to record the number/type of seizures**, rescue medications, and study drug administration**. ~~The Mate app has the option to be installed on a parent's smartphone (iOS or Android). When installed on a smartphone the Mate app can be accessed from more than one device simultaneously (eg, two parents can both have it installed). The Alert app must be running on the provided iPod touch and remain in close proximity of the patient.~~
Rationale: Remove inclusion criteria for using the Empatica Mate app for collecting and summarizing seizure activity data.	
Original Text	**Amendment Text**
Synopsis Inclusion Criteria and Section 4.1: Subject must meet all of the entry criteria for the main Study ZX008-1503 to be eligible for the sub-study. In addition to meeting the above listed criteria, subjects in the sub-study must also be willing to wear and use the Embrace watch and parents/caregivers must be willing to use the Alert app and Mate app per the user instructions. Inclusion Criteria 4: Subject/subject's caregiver is willing to ensure that the Embrace system is properly stored when not in use, and is not left exposed to direct sunlight, moisture, humidity or rain while in storage. The Embrace watch is water resistant but should never be submerged in water.	Synopsis Inclusion Criteria and Section 4.1: Subject must meet all of the entry criteria for the main Study ZX008-1503 to be eligible for the sub-study. In addition to meeting the above listed criteria, subjects in the sub-study must also be willing to wear and use the Embrace watch and parents/caregivers must be willing to use the Alert app ~~and Mate app~~ per the user instructions. Inclusion Criteria 4: Subject/subject's caregiver is willing to ensure that the Embrace system is properly stored when not in use, and is not left exposed to direct sunlight, moisture, humidity or rain while in storage. The Embrace watch is water resistant but should never be submerged in water. **Bathing and/or showering with the watch is acceptable, however.**

Rationale: Remove description of the Empatica Mate app for collecting and summarizing seizure activity data.	
Original Text	**Amendment Text**
Synopsis: Study Product, Dose, and Mode of Administration: Empatica Embrace watch system (Embrace)/Embrace Alert app/ Embrace Mate app: The noninvasive Embrace wrist-worn monitoring device, reads physiological data (EDA, skin temperature, and motion) from the surface of the skin and can transmit it wirelessly to a receiver. The watch is used in conjunction with the Embrace Alert app and Embrace Mate app. The Alert app detects events from user physiology, such as convulsive seizure, and sends an alert to a caregiver via a phone call or text message. The Alert app runs on an iPod Touch and must remain in close proximity of the patient. The Mate app is a diary-based interface running on an iPod Touch (or optionally on the parent/caregiver personal smartphone) for displaying summarized data pertaining to the user's behavior. The Mate app can be used to log and characterize seizures that are detected by the Alert app in a semi-automated fashion; all seizure data reported by the Alert app will be visualized in the Mate app unless it is characterized as a False-Alarm. Seizures that are not detected can be manually entered into the record by patient/caregiver.	Synopsis: Study Product, Dose, and Mode of Administration: Empatica Embrace watch system (Embrace)/Embrace Alert app~~/ Embrace Mate app~~: The noninvasive Embrace wrist-worn monitoring device, reads physiological data (EDA, skin temperature, and motion) from the surface of the skin and can transmit it wirelessly to a receiver. The watch is used in conjunction with the Embrace Alert app~~and Embrace Mate app~~. The Alert app detects events from user physiology, such as convulsive seizure**s**, and sends an alert to a caregiver via a phone call or text message. The Alert app runs on an iPod Touch and must remain in close proximity of the patient. ~~The Mate app is a diary-based interface running on an iPod Touch (or optionally on the parent/caregiver personal smartphone) for displaying summarized data pertaining to the user's behavior. The Mate app can be used to log and characterize seizures that are detected by the Alert app in a semi-automated fashion; all seizure data reported by the Alert app will be visualized in the Mate app unless it is characterized as a False-Alarm. Seizures that are not detected can be manually entered into the record by patient/caregiver.~~
Rationale: Clarify study objectives	
Original Text	**Amendment Text**
Synopsis Sample Size Determination and Section 8.1 This sub-study is designed as a pilot exploratory study to provide preliminary information on the Embrace watch in outpatients with Dravet syndrome, therefore, the sample size is based more on feasibility than on power to detect differences.	Synopsis Sample Size Determination and Section 8.1 This sub-study is designed as a pilot exploratory study to provide preliminary information on **the ease of use of the** Embrace watch **to detect seizures** in outpatients with Dravet syndrome, therefore, the sample size is based more on feasibility than on power to detect differences.

Rationale: Clarify evaluation criteria	
Original Text	**Amendment Text**
Synopsis Criteria for Evaluation and Section 8.3.2 Secondary exploratory efficacy criteria for evaluation include change over time in the following: • Perceived Stress Scale (PSS) to measure caregiver burden. • Correlation of monthly (28-day) convulsive seizure count between the Embrace watch and seizure diary. • Size of EDA response during and in the post-ictal hour following convulsive seizures. • Skin-surface temperature (measured on wrist). • Frequency of fever-related convulsive seizures. • Comparison of convulsive seizure count during periods of sleep, during titration and maintenance, between the Embrace watch and seizure diary. • Correlation of convulsive seizure time and classification as determined by Embrace watch and seizure diary. • EQ-5D-5L to measure quality of life of the parent/caregiver while using the Embrace. • HADS to measure affective symptoms of the parent/caregiver while using the Embrace. All other efficacy criteria are identical to those in the main Study ZX008-1503.	Synopsis Criteria for Evaluation and Section 8.3.2 Secondary exploratory efficacy criteria for evaluation include change over time in the following: • Perceived Stress Scale (PSS) to measure caregiver burden. • Correlation of monthly (28-day) convulsive seizure count between the Embrace watch and seizure diary. • Size of EDA response during and in the post-ictal hour ~~following~~ **of** convulsive seizures. • Skin-surface temperature (measured on wrist). • Frequency of fever-related convulsive seizures. • Comparison of convulsive seizure count during periods of sleep, **and** during **the combined** titration and maintenance **periods**, between the Embrace watch and seizure diary. • Correlation of convulsive seizure time and classification as determined by Embrace watch and seizure diary. • EQ-5D-5L to measure quality of life of the parent/caregiver while using the Embrace. • HADS to measure affective symptoms of the parent/caregiver while using the Embrace. All other efficacy criteria are identical to those in the main Study ZX008-1503.
Rationale: Update study plan to include subjects who have successfully completed 14 weeks of treatment with ZX008 in Cohort 2 of study ZX008-1504	
Original Text	**Amendment Text**
Section 3.1 Overall Study Design and Plan This is a sub-study to the ZX008-1503 OLE study. All participants in this sub-study will have participated in Study ZX008-1501 in the United	Section 3.1 Overall Study Design and Plan This is a sub-study to the ZX008-1503 OLE study. All participants in this sub-study will have participated in Study ZX008-1501 **or**

States or Canada and then continued in Study ZX008-1503, which is a multicenter, open-label, long-term safety study of ZX008 (fenfluramine hydrochloride) in pediatric and young adult subjects with Dravet syndrome.	**ZX008-1504 Cohort 2** in the United States or Canada and then continued in Study ZX008-1503, which is a multicenter, open-label, long-term safety study of ZX008 (fenfluramine hydrochloride) in pediatric and young adult subjects with Dravet syndrome.
Rationale: Remove the Empatica Mate app for collecting and summarizing seizure activity data, and clarify use of ERT seizure diary at conclusion of sub-study and at time of consent for main study.	
Original Text	**Amendment Text**
Section 3.1 Overall Study Design and Plan This sub-study will include up to 20 participants who meet the entry criteria for the main Study ZX008-1503 and who are willing to wear the Embrace watch and their parent/caregiver who is willing to use the Embrace Alert app and Embrace Mate app per the user instructions for 12 consecutive weeks. Those invited to participate will undergo all procedures included in the main Study ZX008-1503, plus any additional procedures for the sub-study. At the conclusion of the sub-study, participants will revert to using the ERT seizure diary for the remainder of their participation in the main Study ZX008-1503. The sub-study participants will be included in the safety analyses for the main Study ZX008-1503, but will not be included in any efficacy analyses that require the ERT seizure diary, or are specific to the Embrace. At the time of consent for the main Study ZX008-1503 subjects will also be presented with the consent for this sub-study. Subjects who consent to participate in the sub-study will be fitted with an Embrace watch at Study Visit 1. Subjects (and/or parents/caregivers) will also be given instructions on how to use the Embrace, the Embrace Alert app, and the Embrace Mate app. Parents/caregivers will use the Embrace Mate app instead of the ERT seizure diary to record the number/type of seizures. The Mate app has the option to be installed on a parent's smartphone (iOS or Android). When installed on a smartphone the Mate app can be accessed from more than one device simultaneously (eg, two parents can both have it installed). The Alert app	Section 3.1 Overall Study Design and Plan This sub-study will include up to 20 participants who meet the entry criteria for the main Study ZX008-1503 and who are willing to wear the Embrace watch and their parent/caregiver who is willing to use the Embrace Alert app ~~and Embrace Mate app~~ per the user instructions for 12 consecutive weeks. Those invited to participate will undergo all procedures included in the main Study ZX008-1503, plus any additional procedures for the sub-study. At the conclusion of the sub-study, participants will ~~revert to using~~ **only use** the ERT seizure diary for the remainder of their participation in the main Study ZX008-1503. **Efficacy analyses for sub-study participants that rely on the ERT seizure diary or that are specific to the Embrace watch will not be included in the main ZX008-1503 analyses.** ~~The sub-study participants will be included in the safety analyses for the main Study ZX008-1503, but will not be included in any efficacy analyses that require the ERT seizure diary, or are specific to the Embrace.~~ At the time of consent for the main Study ZX008-1503 subjects will also be presented with the consent for this sub-study. Subjects who consent to participate in the sub-study will be fitted with an Embrace watch at Study Visit 1. Subjects (and/or parents/caregivers) will also be given instructions on how to use the Embrace **system**~~,the Embrace Alert app, and the Embrace Mate app~~. **The Alert app must be running on provided iPod touch and remain in close proximity of the patient. However,**

must be running on provided iPod touch and remain in close proximity of the patient.	~~P~~**p**arents/caregivers will **continue to** use the ~~Embrace Mate app instead of the~~ ERT seizure diary to record the number/type of seizures**, use of rescue medication, and study drug administration**. ~~The Mate app has the option to be installed on a parent's smartphone (iOS or Android). When installed on a smartphone the Mate app can be accessed from more than one device simultaneously (eg, two parents can both have it installed). The Alert app must be running on provided iPod touch and remain in close proximity of the patient.~~
Rationale: Update study duration to include subjects who enter the study from ZX008-1504, Cohort 2	
Original Text	**Amendment Text**
Section 3.3 Study Duration The duration of the main Study ZX008-1503 for an individual who enters from Study ZX008-1501 is up to approximately 54 weeks. All subjects will receive ZX008 for up to approximately 52 weeks in Study ZX008-1503 and all subjects, including those who prematurely discontinue from the study, will undergo an up to 2-week taper of study medication, at the conclusion of the study.	Section 3.3 Study Duration The duration of the main Study ZX008-1503 for an individual who enters from Study ZX008-1501 **or ZX008-1504 Cohort 2** is up to approximately 54 weeks. All subjects will receive ZX008 for up to approximately 52 weeks in Study ZX008-1503 and all subjects, including those who prematurely discontinue from the study, will undergo an up to 2-week taper of study medication, at the conclusion of the study.
Rationale: Increase the number of study centers and clarify that subjects from ZX008-1504, Cohort 2 can participate in the study.	
Original Text	**Amendment Text**
Section 3.4 Number of Study Centers It is anticipated that sub-study subjects will be enrolled from approximately 3 to 5 study sites participating in both Study ZX008-1501 and Study ZX008-1503.	Section 3.4 Number of Study Centers It is anticipated that sub-study subjects will be enrolled from approximately ~~3 to 5~~ **5 to 10** study sites participating in both Study ZX008-1501 **or ZX008-1504** and Study ZX008-1503.
Rationale: Remove the Empatica Mate app for collecting and summarizing seizure activity data.	
Original Text	**Amendment Text**
Section 4.1 Inclusion Criteria In addition to meeting all of the main Study ZX008-1503 inclusion criteria subjects in the sub-study must also be willing to wear and use the Embrace watch and parents/caregivers must be willing to use the Alert app and Mate app.	Section 4.1 Inclusion Criteria In addition to meeting all of the main Study ZX008-1503 inclusion criteria subjects in the sub-study must also be willing to wear and use the Embrace watch and parents/caregivers must be willing to use the Alert app ~~and Mate app~~.
Rationale: Clarify use of ERT seizure diary for subjects who withdraw early from sub-study.	
Original Text	**Amendment Text**
Section 4.4 Removal of Subjects from Therapy or Assessment	Section 4.4 Removal of Subjects from Therapy or Assessment

While subjects are encouraged to complete all study evaluations, subjects may voluntarily withdraw from the sub-study for any reason at any time. Subjects who withdraw from the sub-study may still remain in the main study ZX008-1503. These subjects will then use the ERT seizure diary. Subjects who are withdrawn from the main Study ZX008-1503 (either voluntarily or by the sponsor or investigator) must also be withdrawn from the sub-study.	While subjects are encouraged to complete all study evaluations, subjects may voluntarily withdraw from the sub-study for any reason at any time. Subjects who withdraw from the sub-study may still remain in the main study ZX008-1503. These subjects will then use **only** the ERT seizure diary. Subjects who are withdrawn from the main Study ZX008-1503 (either voluntarily or by the sponsor or investigator) must also be withdrawn from the sub-study.
Rationale: Remove description of the Empatica Mate app for collecting and summarizing seizure activity data.	
Original Text	**Amendment Text**
Section 6.2.2.1 Embrace Alert App The Embrace Alert app detects events from user physiology, such as a convulsive seizure, and sends an alert to a caregiver through a phone call or text message. Real-time seizure detection and alerting is still experimental and is for investigational use only. It also collects raw data from Embrace hardware and sends is to a receiver (smart phone memory) and consequently to a cloud storage system for later retrieval. The Alert app runs on an iPod Touch and must remain in close proximity of the patient. The Mate app is a diary-based interface for displaying summarized data pertaining to the user's behavior. The Alert app is also used for device configuration (eg, setting the clock and activating/deactivating night-mode which suppresses interactions) and firmware management.	Section 6.2.2.1 Embrace Alert App The Embrace Alert app detects events from user physiology, such as a convulsive seizure, and sends an alert to a caregiver through a phone call or text message. Real-time seizure detection and alerting is still experimental and is for investigational use only. It also collects raw data from Embrace hardware and sends is to a receiver (smart phone memory) and consequently to a cloud storage system for later retrieval. The Alert app runs on an iPod Touch and must remain in close proximity of the patient. ~~The Mate app is a diary-based interface for displaying summarized data pertaining to the user's behavior.~~ The Alert app is also used for device configuration (eg, setting the clock and activating/deactivating night-mode which suppresses interactions) and firmware management.
Rationale: Remove description of the Empatica Mate app for collecting and summarizing seizure activity data.	
Original Text	**Amendment Text**
Section 6.2.2.2 Embrace Mate App The Embrace Mate app is a diary-based interface running on an iPod Touch (or optionally on the parent/caregiver personal smartphone) for displaying summarized data pertaining to user's behaviour. Among these, there is detailed information about sleep behaviour, physical activity summarization, and the display of seizures detected by Embrace. The Mate app can	~~Section 6.2.2.2~~ ~~The Embrace Mate app is a diary-based interface running on an iPod Touch (or optionally on the parent/caregiver personal smartphone) for displaying summarized data pertaining to user's behaviour. Among these, there is detailed information about sleep behaviour, physical activity summarization, and the display of seizures detected by Embrace. The Mate app can~~

be used to log and characterize seizures that are detected by the Alert app in a semi-automated fashion; all seizure data reported by the Alert app will be visualized in the Mate app unless it is characterized as a False-Alarm. Seizures that are not detected can be manually entered into the record by the patient/caregiver. The Mate app retrieves information from Empatica's cloud, not the Embrace directly, so it can be optimally installed on a parent's/caregiver's smartphone that is not in continuous proximity to the Embrace watch. Mate can be used to characterize seizures detected with the Alert app, report missed seizures, and report false alarms. The Empatica Mate App Seizure Logging screens are shown in Figure 3. Figure 3: Empatica Mate App Seizure Logging Screens [figure not shown]	~~be used to log and characterize seizures that are detected by the Alert app in a semi-automated fashion; all seizure data reported by the Alert app will be visualized in the Mate app unless it is characterized as a False-Alarm. Seizures that are not detected can be manually entered into the record by the patient/caregiver. The Mate app retrieves information from Empatica's cloud, not the Embrace directly, so it can be optimally installed on a parent's/caregiver's smartphone that is not in continuous proximity to the Embrace watch. Mate can be used to characterize seizures detected with the Alert app, report missed seizures, and report false alarms. The Empatica Mate App Seizure Logging screens are shown in Figure 3.~~ ~~Figure 3: Empatica Mate App Seizure Logging Screens [figure not shown]~~
Rationale: Remove the appendix describing the Empatica Mate app for collecting and summarizing seizure activity data.	
Original Text	**Amendment Text**
Appendix 3 Empatica Mate Onboarding [Appendix 3 text and graphics not shown]	~~Appendix 3 Empatica Mate Onboarding~~ ~~[Appendix 3 text and graphics not shown]~~