Scheffer IE, Hulihan J, Messenheimer J, et al. Safety and tolerability of transdermal cannabidiol gel in children with developmental and epileptic encephalopathies: a nonrandomized controlled trial. *JAMA Netw Open.* 2021;4(9):e2123930. doi:10.1001/jamanetworkopen.2021.23930

CONFIDENTIAL

Statistical Analysis Plan

ZYN002 Cannabidiol (CBD)

ZYN2-CL-025

Open Label Study to Assess the Safety and Efficacy of ZYN002 Administered as a Transdermal Gel to Children and Adolescents (3 to <18 years) with Developmental and Epileptic Encephalopathy (BELIEVE 1)

Final Version 1.0

PIND Number:	[redacted]
Date of Plan:	30 August 2019
Based on:	[redacted]
	CRF Version Date: 19 Nov 2018

[redacted]

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1 Abbreviations

AE	Adverse Event
AED	Anti-epileptic drug
BMI	Body Mass Index
CBD	Cannabidiol
CRA	Clinical Research Associate
C-SSRS	Columbia Suicide Severity Rating Scale
ECG	Electrocardiogram
ELDQOL	Epilepsy and Learning Disabilities Quality of Life
eCRF	Electronic Case Report Form
g	Grams
H	Hour
mg	Milligram
MedDRA	Medical Dictionary for Regulatory Affairs
MWC	Marijuana Withdrawal Checklist
N	Number
NSAID	Nonsteroidal Anti-inflammatory Drugs
OTC	Over the counter
PK	Pharmacokinetic
POS	Partial onset Seizures
SAP	Statistical Analyses Plan
SDSC	Sleep Disturbance Scale for Children
SF28	Seizure frequency per 28 day period
TEAE	Treatment Emergent Adverse Events
THC	Δ^9-Tetrahydrocannabinol
UWCSS	University of Washington Caregiver Stress Scale
VABS-3	The Vineland Adaptive Behavior Scale™ -3
WHO Drug	World Health Organization dictionary of medical codes

2 Study Overview

2.1 Brief Review of Study Design

This is a sequential, multi-stage, open-label, multi-national, multiple-center, multiple-dose study to assess the long-term safety and tolerability of ZYN002 (transdermal CBD gel) in child and adolescent epilepsy patients 3 to <18 years of age having seizures associated with developmental and epileptic encephalopathies (DEE) according to the International League Against Epilepsy (ILEA) classification (Scheffer et al. 2017). In Period A, patients will undergo a baseline period of 4-weeks, followed by a 4-week titration period, and a 22-week flexible dosing maintenance period. Patients will be treated for a total of 26 weeks in Period A.

In Period B, patients will continue to receive ZYN002 for up to an additional 24 weeks at the same maintenance dose they were receiving at Week 26 (e.g. end of Period A). At any time, upon treatment termination, the patient will be required to complete the taper and follow-up period. After the final tapered dose, patients will be followed weekly for 4 weeks by telephone to complete the Marijuana Withdrawal Checklist short form (Behavior Checklist). After the 4 weeks of follow-up, the patient will be discharged from the study.

2.1.1 Methodology

2.1.1.1 Period A

Baseline Period

During the 4-week Baseline period, parents and/or caregivers will record the number of seizures of the following types in a seizure diary:

- Generalized tonic-clonic (“primary generalized tonic-clonic’) seizures
- Focal impaired awareness seizures
- Focal to bilateral tonic-clonic seizures
- Focal aware seizures with motor signs
- Tonic seizures
- Clonic seizures
- Atonic seizures
- Epileptic spasms (A cluster of epileptic spasms should be counted as a single seizure.)

Seizures of the following types will be captured in the daily diary at the same time and for the same duration every day, as determined by the investigator (e.g. 6:00 PM for 30 minutes):

- Myoclonic seizures
- Absence seizures
- Focal aware seizures without motor signs (e.g. focal sensory seizures)

In addition, caregivers will rate their impression of absence, myoclonic and focal sensory seizures daily using a 3-point Likert-type scale of 0= no seizures, 1=some seizures and 2 = lots of seizures as directed by the Investigator.

The Investigator will identify the most disabling seizure type the patient experiences during the baseline period. This is based on the clinical view of the Investigator.

Video electroencephalograms (video-EEGs) of 2, 4, or 24 hours duration will be performed at the beginning and end of the study. Information to be captured via video-EEG will include characteristics of the waking and sleep EEG background, interictal epileptiform and non-epileptiform abnormalities, and EEG and clinical features of seizures that occur during the video-EEG. Interpretation will be completed by an independent reviewer. Where additional consent is required to transfer EEG data to the central reviewer, the investigator must obtain the consent before the EEG leaves the site. If the subject/caregiver does not provide consent, the EEGs will not be provided for central review.

Patients must continue to meet inclusion/exclusion criteria to proceed to the treatment period.

4-Week Titration Period

Prior to the initial dosing on Study Day 1, patients will report to the clinic to have a pre-dose blood sample drawn for plasma levels of CBD and anti-epileptic drugs (AEDs). All concomitant medications (prescription and over-the-counter [OTC]) will be recorded including dose and reason for use. Parents/caregivers will be provided instructions on how to apply the gel and the first dose of study drug will be applied by the patient/caregiver while at this study visit.

The initial dose for patients < 25 kg is 125 mg CBD Q12H (±2 hours), for a total daily dose of 250 mg CBD for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose can remain at 250 mg CBD daily or be increased to 250 mg CBD Q12H (±2 hours), for a total daily dose of 500 mg CBD (4 sachets) for the remaining 22 weeks of the treatment period.

Patients weighing > 25 kg will receive 250 mg CBD Q12H (±2 hours), for a total daily dose of 500 mg CBD for the four-week titration period. At the week four visit (Visit 4), based on Investigator discretion, the dose can remain at 500 mg CBD daily or be increased to 375 mg CBD Q12H (±2 hours), for a total daily dose 750 mg CBD (6 sachets) for the remaining 22 weeks of the treatment period.

22-Week Maintenance Period

The first dose of study drug will be applied by the patient/caregiver at the clinic visit under the direction of the site. Where feasible, the dose will be administered after the blood sample collection for plasma CBD and AEDs.

No sooner than Week 10, based on the investigator's assessment of seizure frequency, tolerability of study medication and CBD level determinations from Weeks 4 and/or 6, the CBD dose may be increased. [redacted] At Week 10, patients taking 500 mg CBD daily may be increased to 750 mg CBD daily (6 sachets) and patients taking 750 mg CBD daily may be increased to 1000 mg CBD (8 sachets). [redacted]

The Investigator may decrease the dose as needed based on safety and tolerability after the patient starts the maintenance period. Patients taking CBD 250 mg Q12H (±2 hours); total daily dose 500 mg CBD may have their dose decreased to 125 mg CBD Q12H (±2 hours); total daily dose 250 mg CBD. Patients taking CBD 375 mg Q12H (±2 hours); total daily dose 750 mg CBD dose may have their dose decreased to 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. Patients taking CBD 500 mg Q12H (±2 hours); total daily dose 1000 mg CBD dose may have their dose decreased to CBD 375 mg Q12H (±2 hours); total daily dose 750 mg or 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. Patients whose weight changes during the course of the study may have their dose increased or decreased following discussions with the Sponsor Medical Monitor.

[redacted]

The safety evaluations include: physical and neurological exams, vital signs, skin check diary, skin check examination, Columbia Suicidality Severity Rating Scale (C-SSRS) for Children, Marijuana Withdrawal Checklist short form (Behavior Checklist) and AE review. Concomitant medication check (including AEDs) and review of all daily diaries will occur at each visit. In Period A, the Misuse Abuse and Diversion Drug Event Reporting System (MADDERS®) will be used in this study to systematically capture and adjudicate potential abuse-related events (Treister et al. 2016).

Parents/caregivers will be instructed to capture seizure frequency and type, and skin irritation scores, within daily diaries. The Investigator will review the daily diaries during each subsequent visit at Weeks 2, 4, 6, 14, and 26. Parents/caregivers/investigators will also complete:

(1) The University of Washington Caregiver Stress Scale at Day 1, Week 14, and Week 26

(2) Epilepsy and Learning Disabilities Quality of Life scale (ELDQOL - modified) at Day 1, Week 14 and Week 26 of the study

(3) Sleep Disturbance Scale for Children (SDSC) at Day 1, Week 14 and Week 26 of the study

(4) Vineland Adaptive Behavior Scale™ – 3 (VABS-3) at Day 1 and Week 26 of the study

(5) Parents/caregivers will also complete a daily Likert-type "good day/bad day" questionnaire

(6) Investigators will complete a qualitative assessment about patient quality of life and general well-being and any drawbacks associated with use of ZYN002 at Week 26.

These assessments will also be completed at the Early Termination visit for patients who discontinue from the study before Week 26.

Parents/caregivers will be instructed on proper application of the gel. Patients will be permitted to bathe/shower 30 minutes prior to each study dose. Parents/caregivers will apply all study drug to clean, dry, intact skin, thoroughly massaging it into the application site(s) until the area is no longer shiny and is dry to the touch.

Table 1: Study Drug Application

Daily Dose (mg)	# of Sachets in Morning	# of Sachets in Evening	Primary Application Site(s) Q12H (± 2 hrs)	Alternative Application Site
250	1	1	1 sachet to right or left upper arm/shoulder. Gel should be applied to alternating arms (i.e. right at night, left in the morning). Where possible, parents/caregivers should apply the gel to the upper arms/shoulder area that the child does not lean on while sitting to avoid prematurely removing the gel.	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right or left upper thighs.
500	2	2	1 sachet to **each** right **and** left upper arm/shoulder.	
750	3	3	2 sachets to **either** the right **or** left upper arm/shoulder **and** 1 sachet to the opposite arm/shoulder. For the arm receiving 2 sachets parent/caregiver should ensure it is dry before applying the second sachet. It is acceptable for the parent/caregiver to apply the third sachet to the opposite arm and then come back to the first arm to apply the 2nd sachet. For the evening dose alternate the application site receiving 2 sachets from the morning dose (i.e. if 2 sachets were applied to the left arm and 1 sachet was applied to the right arm for the morning dose, apply 2 sachets to the right arm and 1 sachet to the left arm at the evening dose).	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right and left upper thighs. Patients with low BMIs and/or small arms are allowed to have ZYN002 applied to the upper right **or** left thighs after consultation with Zynerba Medical Monitor. Sequence of application would be 1 sachet to **each** upper left **and** right arms **and** 1 sachet to the right **or** left upper thigh.
1000	4	4	2 sachets to **each** right **and** left upper arm/shoulder.	If redness occurs at the application sites, after consultation with Investigator, ZYN002 may temporarily be applied to the right and left upper thighs. Patients with low BMIs and/or small arms are allowed to have ZYN002 applied to the upper right **or** left thighs after consultation with Zynerba Medical Monitor. Sequence of application would be 1 sachet to **each** upper left **and** right arm/shoulder **and** 1 sachet to **each** right **and** left upper thigh.

2.1.1.2 Period B

<u>24-Week Extension Period</u>

To be eligible to continue to Period B, patients must have completed Period A (i.e. must have completed 26 weeks of open-label treatment) and have had at least a 35% reduction from Baseline to Weeks 23 through 26 in any one (or more) qualifying seizures listed below. If seizure reduction is less than 35%, the evaluation may be extended from Baseline to Weeks 19 through 26.

- Generalized tonic-clonic ("primary generalized tonic-clonic') seizures (GTCS)
- Focal impaired awareness seizures (FIAS)
- Focal to bilateral tonic-clonic seizures (BTCS)
- Focal aware seizures with motor signs (FM)
- Tonic seizures (T)
- Clonic seizures (C)
- Atonic seizures (AT)
- Epileptic spasms (ES)*
  *A cluster of epileptic spasms should be counted as a single seizure.

These patients can immediately progress to Period B where they will receive up to an additional 24 weeks of open-label treatment (for a total treatment period of up to 50 weeks). Period B study visits will occur at Week 38 and Week 50 / Early Termination (ET).

A reduction in seizure frequency of less than 35% in the above seizure types or changes in other seizure types felt to represent a clinically meaningful improvement will be discussed with the Zynerba Medical Monitor for approval to continue to Period B. Patients must continue to remain compliant (at least 90% compliant) with study medication use, daily seizure diary and skin check diary throughout the study. If at any time, medication compliance falls below 90% or seizure diary completion falls below 80% of days in a 28-day period patients will not be eligible for study continuation and will be discontinued from the study.

The first dose of study drug will be applied by the parent/caregiver at Week 26 before leaving the study site. Patients will then be required to attend study visits at Week 38, Week 50/ET and End of Study to have the following study procedures completed: [redacted] blood sample for AED plasma level, clinical laboratory tests, [redacted] urine pregnancy test (females of childbearing potential only), vital signs, Marijuana Withdrawal Checklist (MWC), skin check examination, and the C-SSRS. ECGs, targeted physical and targeted neurological examinations will be completed at the End of Study Visit. At each study visit, sites will also review concomitant medications, study drug compliance and adverse events (AEs).

On a daily basis throughout Period B up to Week 50, parents/caregivers are required to complete diaries capturing seizure frequency and type, skin irritation scores, and the 'good-day-bad-day' questionnaire. The Investigator will review the diaries during each Period B visit. At the Week 50 / ET and End of Study visits during Period B parents /caregivers will also be required to complete the following measures:

(1) The University of Washington Caregiver Stress Scale

(2) ELDQOL – Modified

(3) SDSC

(4) The Vineland Adaptive Behavior Scale™ -3 (VABS-3)

(5) Investigators will complete a qualitative assessment about patient quality of life and general well being and any drawbacks associated with use of ZYN002 at Week 50

During Period B, patients will continue to receive the same dose of ZYN002 as received at Week 26 (e.g. end of Period A). However, the Investigator may decrease the dose of ZYN002 as needed during treatment based on safety and tolerability. Patients taking CBD 250 mg Q12H (±2 hours); total daily dose 500 mg CBD may have their dose decreased to 125 mg CBD Q12H (±2 hours); total daily dose 250 mg CBD. Patients taking CBD 375 mg Q12H (±2 hours); total daily dose 750 mg CBD dose may have their dose decreased to 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD. Patients taking CBD 500 mg Q12H (±2 hours); total daily dose 1000 mg CBD dose may have their dose decreased to CBD 375 mg Q12H (±2 hours); total daily dose 750 mg or 250 mg CBD Q12H (±2 hours); total daily dose 500 mg CBD.

[redacted]

Patients will complete an End of Study Visit (EOS) after completing their taper period. Patients who discontinue before Week 50 will be asked to attend the ET visit and then taper off the study medication. If the skin irritation score at the EOS or an ET visit is > 0, the patient will continue to be followed through Unscheduled Visits until the skin irritation score is recorded as '0'. [redacted]

2.2 Investigational Product, Dosage and Mode of Administration

ZYN002 (Cannabidiol: CBD) comes in [redacted] and is topical. Study drug will be supplied as sachets containing [redacted] gel to deliver 125 mg of CBD per sachet.

Study drug will be applied by using one (1) to four (4) sachets in the morning and evening to achieve the appropriate total daily dose for each patient based upon the treatment group.

The Treatments are as follows:

Treatment A - 125 mg CBD Q12H (±2 hours); for a total daily dose 250 mg CBD (1 sachet in morning and 1 sachet in evening).

Treatment B – 250 mg CBD Q12H (±2 hours); for a total daily dose of 500 mg CBD (2 sachets in morning and 2 sachets in evening).

Treatment C – 375 mg CBD Q12H (±2 hours); for a total daily dose of 750 mg CBD (3 sachets in morning and 3 sachets in evening).

Treatment D - 500 mg CBD Q12H (±2 hours); for a total daily dose of 1000 mg CBD (4 sachets in morning and 4 sachets in evening).

2.3 Objectives

2.3.1 Primary

To evaluate, over the entire treatment period, the safety and tolerability of ZYN002 in child and adolescent epilepsy patients with developmental and epileptic encephalopathies (DEE).

2.3.2 Secondary

To evaluate the efficacy of ZYN002 in terms of seizure frequency, caregiver stress, quality of life, sleep disturbances, adaptive behavior among epilepsy patients and an overall daily assessment of the patient's day ("good day / bad day").

To evaluate the pharmacokinetics of CBD and CBD metabolite(s) following administration of ZYN002 in child and adolescent epilepsy patients with DEE.

2.3.3 Exploratory

The identification of CBD metabolite(s) from collected plasma or urine may be conducted and analyzed outside the scope of this report.

2.4 Study Procedures

Study procedures are outlined in Table 2 below.

Table 2: Schedule of Assessments

Assessment	Screening (Period A)	Baseline (Period A)	Treatment (Titration) Period (Period A)			Maintenance Treatment (Period A)			Extension Treatment (Period B)		Taper Period[n]	End of Study Visit	Telephone Follow-up Period[o]	Unscheduled Visits[j]
	Visit 1 Days -60 to -29	Days -28 to -1	Visit 2 Day 1 (±3 days)	Visit 3 Week 2 (±3 days)	Visit 4 Week 4 (±3 days)	Visit 5 Week 6 (±3 days)	Visit 6 Week 14 (±3 days)	Visit 7 Week 26 (±3 days)	Visit 8 Week 38 (±3 days)	Visit 9 / ET[i] Week 50 (±3 days)	1 to 4 weeks following withdrawal of treatment	±3 days after last taper dose	4 weeks following End of Study Visit	
Informed consent	X							X[m]						
Review eligibility criteria	X		X											
Medical History & Demographics	X													
Concomitant medications	X		X	X	X	X	X	X	X	X		X		X
Physical and neurological examination	X							X		X				
Targeted Physical and neurological examination			X		X		X					X[k]		X
Vital signs[a.]	X		X	X	X	X	X	X	X	X		X		X
12-lead ECG	X				X		X	X	X	X		X		
Laboratory tests and urinalysis[b]	X				X		X	X	X	X		X		
Urine Drug Screen	X													
Pregnancy Test[c]	X		X		X	X	X	X	X	X		X		
C-SSRS (Children) [d]	X		X	X	X	X	X	X	X	X		X		X
Tanner Staging Scale	X							X		X				
Marijuana Withdrawal Checklist (short form) [e]			X					X		X	X		X	
Seizure Diary (Daily)		X	X	X	X	X	X	X	X	X				X
Video EEG		X						X		X				
Skin Check Diary (Daily)[f]			X	X	X	X	X	X	X	X	X	X		X
[redacted]			[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				
AED blood	X		X		X	X	X	X	X	X				
Seizure Diary		X	X	X	X	X	X	X	X	X				X

Assessment	Screening (Period A)	Baseline (Period A)	Treatment (Titration) Period (Period A)			Maintenance Treatment (Period A)			Extension Treatment (Period B)		Taper Period[n]	End of Study Visit	Telephone Follow-up Period[o]	Unscheduled Visits[j]
	Visit 1 Days -60 to -29	Days -28 to -1	Visit 2 Day 1 (±3 days)	Visit 3 Week 2 (±3 days)	Visit 4 Week 4 (±3 days)	Visit 5 Week 6 (±3 days)	Visit 6 Week 14 (±3 days)	Visit 7 Week 26 (±3 days)	Visit 8 Week 38 (±3 days)	Visit 9 / ET[i] Week 50 (±3 days)	1 to 4 weeks following withdrawal of treatment	±3 days after last taper dose	4 weeks following End of Study Visit	
Skin Check Diary Review			X	X	X	X	X	X	X	X		X		X
Skin check examination			X	X	X	X	X	X	X	X		X		X
Univ Washington Caregiver Stress Scale			X				X	X		X				
Daily Questionnaire ("Good Day, Bad Day")		X	X	X	X	X	X	X		X				
ELDQOL Quality of Life (Modified)			X				X	X		X				
SDSC Sleep Questionnaire			X				X	X		X				
Vineland Adaptive Behavior Scale™-3 (VABS-3)			X					X		X				
Genetic Seizure Panel	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose			X	X	X	X	X	X	X	X	X			

a. Vital signs (including blood pressure, heart rate, respiratory rate, and oral, tympanic or forehead temperature) will be recorded after the patient has been sitting for at least 5 minutes. Vital signs will be taken prior to blood draws.
b. Fasting laboratory tests will be completed at approximately the same time of day. Male patients will have serum testosterone measured.
c. Women of child-bearing potential. Can be serum or urine pregnancy test.
d. Patients six years of age and older and capable of understanding and answering the questions, in the investigator's opinion.
e. [redacted]
f. Parents/caregivers will assess their dosing site and record all skin redness in their daily skin check diary once per day in the evening. When skin redness exists, efforts will be made to apply the gel to a non-red area of the shoulders and/or upper arms. If the skin check score is higher than a "2", the patient/caregiver will contact the Investigator to determine if an Unscheduled Visit is required.
g. Patients will have a blood sample drawn for plasma level of AED(s). Where possible, effort should be made to get a trough sample for the AED. If not, the AED morning dose may be administered prior to the clinic visit. The time of the prior doses of study drug and AEDs in addition to the time of each blood sample collection will be recorded
h. A complete skin check examination will be conducted at each study visit, including unscheduled visits and End of Study visit for skin redness follow-up. Skin erythema scores >0 at the EOS or an ET visit will be followed until score = 0.
i. ET applies to a patient who discontinues from the study before Week 50.
j. An unscheduled visit must be conducted at Week 10 for all patients with any AE ongoing from the previous visit assessed as moderate in severity or higher.
k. A complete physical exam may be conducted at the EOS visit if considered clinically relevant by the Principal Investigator (PI).
l. A de-identified photograph of the skin finding of interest may be taken after consultation with and approval of the sponsor.
m. Consent for Period B to be obtained prior to first extension dose

n. [redacted]

2.5 Study Endpoints

2.5.1 Seizure Endpoints

The primary efficacy assessment will be the median percent change from baseline in the monthly (28 day) frequency of seizures (SF28) during Period A for the following types of seizures, in total (“ select countable seizures”):

- Generalized tonic-clonic (“primary generalized tonic-clonic’) seizures (GTCS)
- Focal impaired awareness seizures (FIAS)
- Focal to bilateral tonic-clonic seizures (BTCS)

Secondary seizure endpoints include the median percent change from baseline in the SF28 for the following (as defined in Table 3):

- All countable seizures
- Tonic seizures (T)
- Clonic seizures (C)
- Atonic seizures (AT)
- Epileptic spasms (ES)
- Each seizure type individually
- Focal aware seizures with motor signs (FM)
- All motor seizures
- Focal motor seizures
- All focal-onset seizures
- Seizure type identified (at baseline) as the most disabling overall

The frequency of the following types of seizures during the daily period of observation that consistently occur with a countable frequency:

- Myoclonic seizures (M)
- Absence seizures (A)
- Focal aware seizures without motor signs (focal sensory seizures) (FAS)

Table 3: Seizure Types by Category

Seizure Type	Select Countable Seizures	All Countable Seizures	Motor Seizures		Focal Motor	All Focal Onset	Set Period Daily Count	None/Some/Lots	Seizure Free Days (Select Countable)
Easy to count:									
Generalized Tonic-Clonic (GTCS)	X	X	X						X
Focal Impaired Awareness Seizures (FIAS) - With Motor Features	X	X	X		X	X			X
Focal Impaired Awareness Seizures (FIAS) - Without Motor Features	X	X				X			X
Focal Impaired Awareness Seizures (FIAS) – Indeterminate	X	X				X			X
Focal To Bilateral Tonic-Clonic Seizures (BTCS)	X	X	X		X	X			X
Focal Aware Seizures With Motor Signs (FM)		X	X		X	X			
Tonic Seizures (T)		X	X						
Clonic Seizures (C)		X	X						
Atonic Seizures (AT)		X	X						
Epileptic Spasms (ES)		X	X						
Difficult to count:									
Absence Seizures (AS)							X	X	
Myoclonic Seizures (M)							X	X	
Focal Aware Seizures (FAS)							X	X	

Seizure count endpoints will be summarized monthly, for Periods A and B individually and overall for the entire treatment period. Seizure count endpoints will also be summarized for the last four and eight weeks of treatment in Periods A and B.

2.5.2 Other Seizure Endpoints

Other seizure endpoints include:

- A three point Likert-type scale (none, some seizures and lots of seizures) captured on a daily diary will be used to assess myoclonic, absence and focal sensory seizures
- The number of seizure free days (select countable seizures)
- The percentage of patients defined as a 35%, 50% and 90% responder for a specified period if for that patient the RedSF is $\geq$ 35%, 50% and 90% respectively

2.5.3 Other Efficacy Endpoints

The following are the other secondary endpoints:

- Change from Baseline to Weeks 14, 26 and 50/ET in The University of Washington Caregiver Stress Scale – total score
- Change from Baseline to Weeks 14, 26 and 50/ET in the subscale scores of the ELDQOL-modified
- Change from Baseline to Weeks 14, 26 and 50/ET in the total and subscale scores of the SDSC
- Change from Baseline in the "good day/bad day" assessment will be assessed for each period utilized to assess seizure frequency.
- Change from Baseline to Week 26 and Week 50/ET in the VABS-3 composite and subscale scores

2.5.4 Safety Endpoints

Safety Endpoints include:

- Physical exams
- Neurological exams
- Prior and concomitant medications
- Clinical Labs (hematology, chemistry, urinalysis, urine drug screen, and [redacted])
- Skin at application site
- Vital signs
- ECGs
- C-SSRS (children)
- Adverse Events
- Tanner Staging Scale
- MADDERS
- MWC

2.5.5 Pharmacokinetic and Other Exploratory Endpoints

2.5.5.1 [redacted]

[redacted].

2.5.5.2 AED Medications

Plasma concentration will also be determined for select AEDs at various time points.

2.5.5.3 Video EEG

Video EEG findings will be explored and summarized separately.

3 General Considerations for statistical analysis

3.1 Determination of Sample Size

This study is exploratory in nature and as such, a formal sample size was not determined. Approximately 55 patients are planned to enter the 4-week Baseline period with 50 patients progressing to receive open-label treatment [redacted]

3.2 Analysis Populations

3.2.1 Modified Intent-to-treat (mITT) Analysis Set

The modified Intent-to-Treat (ITT) population is defined as all patients who have received at least 80 days of study medication and have completed at least 80% of seizure diaries.

3.2.2 Period B Modified Intent-to-treat (mITT) Analysis Set

The Period B modified Intent-to-Treat (ITT) population is defined as all patients who have received at least 80 days of study medication, entered Period B and have completed at least 80% of seizure diaries in Period B.

3.2.3 Safety Analysis Set

The safety analysis set is defined as all patients who receive at least one dose of study drug.

3.2.4 Period B Safety Analysis Set

The period B safety analysis set is defined as all patients who receive at least one dose of study drug during period B.

3.2.5 Pharmacokinetic (PK) Analysis Set

[redacted]

4 DATA HANDLING RULES AND DEFINITIONS

Descriptive statistics for continuous variables include n, mean, standard deviation, standard error, median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts, percentages and 95% confidence intervals where appropriate.

4.1 Diary Data Windowing

Seizure frequency will be summarized based on monthly treatment periods with windows found in Table 4. Unless otherwise noted, all other summaries will use the nominal visit assessments.

Table 4: 28 Day Monthly Windows for Efficacy Collected in the Daily Diary

Month	Interval (Days)
Baseline	[-56, -1]
1	[1,28]
2	[29,56]
3	[57,84]
4	[85, 112]
5	[113,140]
6	[141, 168]
7	[169, 196]
8	[197,224]
9	[225,252]
10	[253,280]
11	[281,308]
12	[309,336]
13	[337,364]
Period A	[1, Day before Visit 7/ET]
Period B	[Day of Visit 7, Day before Visit 9/ET]
Overall	[1, Day before Visit 9 ET]]

If a patient discontinues before visit 7, the monthly efficacy diary data for that period will include the start of the windowed month through the day they discontinued.

Table 5: 28 Day Monthly Windows for Patient Daily Skin Irritation Scores

Month	Interval (Days)
Baseline	[-56, -1]
1	[1,28]
2	[29,56]
3	[57,84]
4	[85, 112]
5	[113,140]
6	[141, 168]

Month	Interval (Days)
7	[169, 196]
8	[197,224]
9	[225,252]
10	[253,280]
11	[281,308]
12	[309,336]
13	[337,364]
Period A	[1, Day before Visit 7/ET]
Period B	[Day of Visit 7, Day before Visit 9/ET]
Overall	[1, Day prior to V9/ET]

If a patient discontinues before visit 7, the monthly safety diary data for that period will include the start of the windowed month through the day they discontinued.

4.2 Scheduled Study Evaluations and Study Periods

4.2.1 Day 1

Day 1 is the date of first dose of treatment with study drug.

4.2.2 Study Day

Study days will be numbered relative to the first day of study drug administration.

- Study days will be numbered relative to study start (i.e., ..., –2, –1, 1, 2, ...; with Day 1 being the start of study drug and Day –1 being the day before the start of study drug).
- The elapsed time since Day 1 for an event (e.g. onset of an adverse event) will be calculated as [date of event – date of Day 1 + 1].
- For the purpose of converting days to years or months, one year = 365.25 days, and one month = 30.44 days.

4.2.3 Baseline Value

Baseline is the last observed non-missing data prior to the first dose of study drug. Per the protocol, this should be the assessment on Day 1 before the first study drug dose with the exception of medical history, demographics, physical and neurological examinations, ECGs, and labs, which are assessed at the screening, visit. Seizure information is collected daily during the entire 28-day baseline period.

4.2.4 Enrollment Date

The date the patient was enrolled into the study (the baseline visit date).

4.2.5 End of Treatment Value

End of treatment value is the last non-missing post-baseline value for each patient.

4.3 Variable Definitions

4.3.1 Age

Patient age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1)/365.25.

4.3.2 Body Mass Index (BMI)

Body mass index (BMI) will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m^2)]

4.3.3 Dose Calculations

[redacted]

4.3.4 [redacted]

[redacted]

4.3.5 Prior and Concomitant Medication

A prior medication is defined as any non-study medication that started before the date of first dose of study drug.

Concomitant medication is defined as any non-study medication that:

- Started before the date of first dose of study drug and is ongoing throughout the study or ends on/after the date of first study medication administration.
- Started on/after the date of first dose of study drug and is ongoing or ends during the course of study medication.

The start/stop dates recorded in the CRF will be used to determine when a medication prior to or during the study. A medication can be considered both prior and concomitant if it was started prior to the first dose of study drug and continues to be taken after the first dose of study medication. Unresolved missing start dates will be handled as follows for determination of concomitance:

- If the date is completely missing, the medication will be considered concomitant.
- If only the day is missing, and the last day of the month is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as the last day of the month.
- If only the day is missing, and the first day of the month is after the first dose date on Day 1, then the concomitant medication will be considered as starting after Day 1, and the incomplete date will be imputed as the first day of the month.
- If only the day is missing, and the month is equal to the month of the first dose date on

Day 1, then the incomplete date will be imputed as the first day of the month.
- If both the month and day are missing, and the last day of the year is before the first dose date on Day 1, then the concomitant medication will be considered as starting before Day 1, and the incomplete date will be imputed as if it is the last day of the year. Otherwise, the incomplete date will be imputed as if it is the first day of the year.

4.3.6 Treatment Emergent Adverse Events (TEAEs)

Treatment emergent adverse events (denoted as TEAE hereafter) are defined as adverse events with onset dates on or after the first start of study drug.

All reports of adverse events should include the severity and relationship to study drug that are determined by the investigators. In the event of missing information, the following rules will be applied for the adverse event summaries:

- AEs with missing onset dates will be included as treatment- emergent (unless end date is prior to the first dose date)
- AEs with missing severity will be counted as severe in severity
- AEs with missing relationship to study drug will be counted as related
- AEs with missing seriousness will not be counted as serious

4.3.7 Taper Period/EOS/Telephone Follow-Up

The safety data collected during the taper period, EOS and Telephone F/U data will be summarized in the Overall Study tables.

4.3.8 Missing Data

4.3.8.1 Diary Data

There are 5 sections included in the daily diary: Overall, Countable seizures, difficult to count seizures, skin rating and good day/bad day rating.

Overall: If 'Diary not completed' is selected this means the entire diary was not completed (at all) on that day, and all diary items will be set to missing.

Countable seizures: 'No countable seizures' means the subject didn't experience any countable seizures on that day (all countable seizure counts =0).

Difficult to count: 'Not recorded' means the subject failed to complete the difficult count (missing data).

Skin Rating: 'Not recorded' means the subject failed to complete this section of the diary (missing data). If no questions are answered, the data will be considered missing.

Good day/Bad Day: 'Not recorded' means the subject failed to complete this section of the diary (None or 0 means no seizures or erythema). If no questions are answered, the data will be considered missing.

4.3.8.2 Diary Data

Missing data for all other assessments will not be imputed.

5 STUDY POPULATION SUMMARY

All population summaries will be summarized on the safety analysis set unless otherwise noted.

5.1 Patient Disposition

The number of patients enrolled, patients in the safety analysis set, patients in the mITT analysis set, patients who completed the treatment/study, and patients who discontinued the treatment/study, will be summarized using descriptive statistics (Summary Table 14.1.1). Reasons for treatment and study discontinuation will also be summarized for patients who discontinued the treatment/study. Additionally, the number of patients who completed Period A, who qualified for period B (and reason for qualification) and number of patients who completed Period B will also be summarized. This summary will include the set of enrolled patients.

Reasons for qualifications for Period B include 35% reduction from baseline in total countable seizures to the last 4 weeks of the study (Week 23 [day 158] through Week 26 [day185]), the last 8 weeks (Week 19 [Day 133] through Week 26 [day 185]) of the study, protocol waiver, or protocol deviation.

5.2 Demographics

The continuous variables of patient age, weight (kg), height (cm), and body mass index (BMI) (kg/m^2) will be summarized using descriptive statistics. The categorical variables of patient sex, ethnicity, and race will be summarized using descriptive statistics for each category (Summary Table 14.1.2). Missing categories will be presented if necessary.

5.3 Baseline Characteristics

Diagnosis, time since diagnosis (informed consent date-date of diagnosis+1/365.25), female reproductive status, urine pregnancy test results for female patients of childbearing potential, and number of patient seizures by type will be summarized (Summary Table 14.1.3) using descriptive statistics.

5.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or greater. Patients with a medical history assessment, patients with at least 1 finding, and findings for each category will be summarized using descriptive statistics by system organ class, preferred term, and overall (Summary Table 14.1.4).

5.5 Prior Medications

All prior medications will be coded using the World Health Organization dictionary of medical codes (WHO Drug). The incidence of prior medications will be summarized using descriptive statistics by therapeutic class and preferred term (Summary Table 14.1.5). Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior medications will include all medications taken on or before the first dose of study drug treatment.

5.6 Electrocardiogram

Electrocardiogram findings (normal, abnormal not clinically significant, abnormal clinically significant, and missing) at baseline will be summarized (Summary Table 14.1.6) using descriptive statistics.

5.7 Physical Examination/Neurological Examination

Physical/Neurological examination findings for each body system will be summarized at baseline (Summary Tables 14.1.7, 14.1.8) using descriptive statistics including the number of patients with at least one clinically significant abnormal finding.

6 Efficacy Analyses

All efficacy analyses will be on the mITT Analysis Set or Period B mITT Analysis Set and presented by diagnosis and total.

6.1 Primary Seizure Endpoint Analysis

The primary efficacy endpoint is the median percent change from baseline to Period A in the monthly (28-day) frequency (%RedSF) of seizures by seizure type as defined in Section 2.5.1. Seizures will be captured via the daily diary and will be analyzed per monthly period. SF28 is calculated as the number of seizures in the period divided by the number of non-missing days in the period multiplied by 28. In addition to monthly, SF28 will be calculated overall for treatment period A, treatment period B and over the entire study treatment period.

Patients must complete 80% of their seizure diaries in period A to be included in the seizure summaries for Period A. Patients must complete 80% of their seizure diaries in period B to be included in the seizure summaries for Period B. To be included in the Overall summaries patients must complete 80% of their diaries in period A and 80% of diaries overall. In addition, if a patient meets the overall study seizure diary compliance criteria but does not complete 80% of their seizure diaries during any one SF28 period, that monthly period for that patient will be excluded from the summary.

Table 6: Diary Compliance Criteria for Seizures

Period	Summary Table Inclusion Criteria
Monthly Period	80% Compliant within the monthly period (≥22 days of diary)
Period A	80% compliant with diaries in period A
Period B	80% compliant with diaries in period B
Overall	80% compliant with diaries in period A and Overall

The reduction from baseline in seizure frequency (RedSF) is defined for each period as:

RedSF=SF28(Baseline)-SF28(Period X)

The percent reduction from baseline in seizure frequency is defined as:

%RedSF=100*[SF28(Baseline)-SF28 (Period X)/SF28(Baseline)

In addition, a patient will be defined as a 35%, 50% or 90% responder for a specified period if for that patient the %RedSF is ≥ 35%, ≥ 50% or ≥ 90%.

Baseline period, monthly period, change and percent change from baseline to each monthly period will be summarized by seizure type and for all seizure types as described in Table 3 using descriptive statistics [redacted] Change and percent change from

baseline will also be summarized over the last four and eight weeks of treatment in Periods A and B (Summary Tables to).

All seizure summaries will be by diagnosis using the following diagnoses as columns: Dravet Syndrome, Lennox-Gastaut Syndrome, Combined, and Other.

6.2 Other Seizure Endpoint Analysis

Additionally, difficult to count seizures will be counted by the caregiver every day during a pre-specified time period defined by the investigator. These difficult to count seizures will be transformed into an hourly number of seizures per monthly period. SF24 will be calculated based off the calculated hourly rate. Baseline period, monthly period, change and percent change from baseline to each monthly period will be summarized using descriptive statistics (Summary Tables 14.2.2.1.1 through 14.2.2.1.3).

Responder rates (35%, 50%, and >90% responder rate) by seizure type as defined in Table 3 will also be summarized using descriptive statistics and binomial confidence intervals around response rates will be presented (Summary Tables 14.2.3.1.1 through 14.2.3.7.3). [redacted]:

[redacted]

Difficult to count seizures (A, M, FAS) are classified as “None”, “Some seizures” and “Lots of Seizures”. These categories will be re-coded as: None=0, Some seizures=1, Lots of Seizures=2. The total number of days with “some” or “lots” of seizures will be considered a seizure day. SF28 will be calculated based off the number of difficult to count seizure days. The change and percent change from baseline to each monthly period in total seizure days will be summarized for each category [redacted] Additionally, the total number of days for each category (None, Some, Lots) will be summed up for each month and SF28 will be calculated based off the number of days in each category. SF28 for each category will be presented using descriptive statistics [redacted]

The number of countable seizure free days (no select countable seizures) will be summed for each patient for each monthly period and overall. Seizure free days will be summarized for each period and overall [redacted]

Video EEG results will be summarized in a separate report.

6.3 Other Efficacy Endpoint Analysis

6.3.1 Good Day/Bad Day

The Good day/Bad day information will be captured via the daily diary and will be analyzed per monthly period. A specific period includes the day after the previous period to the end of the current period (refer to Table 4). In addition to monthly, SF28 will be calculated overall for treatment period A, treatment period B and over the entire study treatment period. The daily diary has the caregiver

assess their child's overall functioning each day. The scoring is: 1=terrible day, 2=bad day, 3=so-so day, 4=good day, 5=fantastic day. The good day/bad day assessment will be averaged over the same monthly periods as seizure frequency and descriptive statistics will be provided for the average monthly scores and change from baseline in the scores ([redacted]). If no good day/bad day assessments are captured during the baseline period, the patient will not be included for analysis of good day/bad day summaries. Change from baseline will also be summarized over the last four and eight weeks of treatment in Periods A and B ([redacted]). Additionally, overall daily counts for each category (terrible day, bad day, etc.) will be summarized monthly using descriptive statistics ([redacted]

Patients must be on study drug for at least 80 days to be included in any good day/bad day summaries. In addition, they must complete 80% of their good day/bad day diaries in period A to be included in the summaries for Period A. Patients must complete 80% of their good day/bad day diaries in period B to be included in the seizure summaries for Period B. To be included in the Overall summaries patients must complete 80% of their diaries in period A and 80% of good day/bad day diaries overall. In addition, if a patient meets the overall study good day/bad day diary compliance criteria but does not complete 80% of their good day/bad day diaries during any one SF28 period, that monthly period for that patient will be excluded from the summary.

Table 7: Good Day/Bad Day Diary Compliance Criteria

Period	Summary Table Inclusion Criteria
Period A	80% compliant with good day/bad day diaries in period A
Period B	80% compliant with good day/bad day diaries in period B
Overall	80% compliant with good day/bad day diaries in period A and Overall

6.3.2 The University of Washington (UW) Caregiver Stress Scale

The UW Caregiver Stress Scale consists of 19 questions total, 14 have possible responses 1="Not at All", 2="A little bit", 3="Somewhat", 4="Quite a bit" and 5="Very Much". The other 5 have possible responses of 1="Never", 2="Rarely", 3="Sometimes", 4="Often" and 5="Always". If there are no missing responses, the 19 individual items are summed and the total sum (ranging from 19-95) is then transformed to a T-score score using the scoring tables in Section 12.1. If any item from question 11 through 19 is missing, only the first 10 questions (the 10-item short form) will be used for scoring. If more than 2 of the 8 items are missing, the score will be missing. For missing responses on any of the first 8 (out of 10) items follow these steps:

Step 1: For respondents with missing data, first check how many items were answered and confirm that at least 6 items of the 8 items were answered before proceeding.

Step 2: Next, sum the response scores from the items that were answered. Multiply this sum by 8 (i.e. the number of items used in scoring the short form).

Step 3: Next divide by the number of items that were answered (this will be either 6 or 7). If the result is a fraction, round up to the nearest whole number. This will give a pro-rated summary score that ranges from 8 to 40. This is **not** a score that can be used for clinical or analytical purposes.

Step 4: Finally, using the Summary Score to T-score conversion table (Section 12.1), translate the pro-rated summary score into a T-score. The total score based on adding corresponding results for each item should not be used for any purposes. All reliability and validation information relates to the T-scores. A higher T-score represents a higher level of caregiver burden (0).

The change from baseline to weeks 14, 26 and 50/ET in The University of Washington Caregiver Stress Scale T-Score will be summarized descriptively ([redacted]). Additionally, changes from baseline will be compared using a paired t-test and nominal p-values will be presented.

6.3.3 Epilepsy and Learning Disabilities Quality of Life Questionnaire (ELDQOL-modified Version)

The ELDQOL consists of 44 questions relating to the quality of life from the caregivers perspective during the last 4 weeks. Once the answers are re-scaled according to Table 8, the mean score for each subscale is computed as the sum of the re-scaled items divided by the number of items answered. To take account of any missing data in a subscale, the mean of the completed items can be imputed, providing at least 50% of the items are completed. If more than 50% of the items in the subscale are missing, then the total subscale score should be classed as a missing value. For each subscale, higher score = poorer QOL/functioning.

The change from baseline to weeks 14, 26 and 50/ET in ELDQOL scales will be summarized descriptively ([redacted]) Additionally, changes from baseline will be compared using a paired t-test and nominal p-values will be presented. [redacted] paired t-test is as follows:

[redacted]

Table 8: ELDQOL Subscale Transformations and Scoring

Scale	Questions	Scoring	Range
Seizure Severity Scale (Questions 1 to 14)	1, 5, 7, 8, 9, 10, 11, 13	Reverse the individual item scoring so that: 1 = 4 2 = 3 3 = 2 4 =1 5 = define as a missing value	10-56
	4, 12	Reverse the individual item scoring so that: 1 = 4 2 = 3 3 = 2 4 =1 5 = 0 6 = define as a missing value	
	2, 14	5 = define as a missing value Other scores unchanged.	
	3, 6	5 = 0 6 = define as a missing value. Other scores unchanged	
Side Effect Profile (Questions 17 and 18)	Only items in Q.18 used to compute sub-scale	Reverse the individual scoring of each of the 19 items in Q.18 so that: 1 = 4 2 = 3 3 = 2 4 =1 5 = define as a missing value	19-76
Behavior Scale (Questions 19-27)	19, 24, 25, 26	5 = define as a missing value Other scores unchanged	9-36
	20, 21, 27	Reverse scoring so that: 1 = 4 2 = 3 3 = 2 4 =1 5 = define as a missing value	
	22, 23	Recode so that: 5 = 4 6 = define as a missing value Other scores unchanged	
Mood Scale (Question 28 – 16 items)	Aggressive, irritable, tearful, hyperactive, sad, agitated, restless, tantrum-prone, frustrated, withdrawn	Reverse scoring of negative items, so that: 1 = 4 2 = 3 3 = 2 4 =1 5 = define as a missing value	16-64
	Happy, calm, friendly, relaxed, cheerful, cooperative/helpful	Scores remain unchanged for positive items.	

6.3.4 Sleep Disturbance Scale for Children (SDSC)

The SDSC is a 26 item Likert-type rating scale with scores ranging from 1 to 5, with the wording arranged so that higher numerical values reflect a greater clinical severity of symptoms (Bruni et. Al., 1996.). There are 6 factor subscales and a total score described in Table 9. The factor scores and total score are then transformed to a T-score score using the scoring tables in Appendix 2.

Table 9: Factors for Sleep Disturbance Scale for Children

Factor #	Subscale	Sum of Items	Range
Factor 1	Disorders of initiating and maintaining sleep (DIMS)	1, 2 ,3, 4, 5, 10, 11	7 to 35
Factor 2	Sleep breathing disorders (SBD)	13, 14, 15	3 to 15
Factor 3	Disorders of arousal/nightmares (DA)	17, 20, 21	3 to 15
Factor 4	Sleep wake transition disorders (SWTD)	6, 7, 8, 12, 18, 19	6 to 30
Factor 5	Disorders of excessive somnolence (DOES)	22, 23, 24, 25, 26	5 to 25
Factor 6	Sleep hyperhidrosis (SHY)	9, 16	2 to 10
	Total Score	All 26 items	26 to 130

Changes from Baseline to Weeks 14, 26 and 50/ET in the total and subscale and total scores of the SDSC will be summarized descriptively ([redacted] Additionally, changes from baseline will be compared using a paired t-test and nominal p-values will be presented. . [redacted]:

[redacted]

6.3.5 Vineland Adaptive Behavior Scale™ – 3 (VABS-3)

The VABS-3 scale is administered to patients and scored through proprietary scoring software online. There are domains and subdomains, and an overall adaptive behavior composite score (ABC).

Change from Baseline to Week 26 and Week 50/ET in the VABS-3 domain, subdomain and Adaptive Behavior Composites scores will be summarized descriptively [redacted]. Additionally, changes from baseline will be compared using a paired t-test and nominal p-values will be presented. Sample SAS code for the paired t-test is as follows:

[redacted]

6.4 Interim Analysis

[redacted]. There is a plan to summarize the interim results of the study once all patients have completed Week 26 or early terminated from the study.

[redacted]

Therefore TGG will do the following record selection to include only records associated with Period A before conducting the interim analyses for Period A only.

A) Subjects who completed Period A and went into Period B
- Diary Parameters: include all records ≤ the day before Visit 7
- Safety Parameters: include all records ≤ Visit 7 Date
- Non-Diary/Safety (i.e., study status, demo, etc.): include all records ≤ Visit 7 Date or occurring at nominal Visit 7

B) Subjects who completed A and did not go into Period B or Subjects who Discontinued in Period A
- Include all records

For [redacted] Period A summary tables with the exception of Tanners Staging Scale, Physical Exam, Neurological Exam, MADDERs and MWC will be reported out. All Period B related parameters on the disposition table will be excluded. Taper Period A efficacy records will be excluded from this analysis. Taper period A safety data will be included.

Listings will not be produced for the [redacted]

7 SAFETY ANALYSIS

The safety analysis set will be used for all safety analyses and the summaries will be presented by most frequent dose including a total column, unless otherwise specified. All AE/concomitant medications data will be summarized for each treatment period (Period A, B, Overall, Taper Period A, and Taper Period B - unless otherwise specified) by the actual treatment dose of drug received at the time of initiation of the AE or concomitant medication.

7.1 Study Drug Administration

Total dose is the total dose (mg/kg) of study medication taken at each visit during each treatment period. Duration of treatment will also be calculated by summing together (last dose date- first dose date +1) across all dosing intervals for a specific dose. Average daily dose (mg/kg) is the total dose divided by the number of days in the treatment period. Patient compliance is measured by taking the number of sachets used since last visit and dividing by the number of days since last visit times the number of sachets intended to be used at the dose level per day and multiplying by 100.

Table 10: Daily Sachets per Dose Level

Dose Level	Sachets per Day (125 mg per sachet)
250 mg	2
500 mg	4
750 mg	6
1000 mg	8

The number of patients treated at Day 1, and each visit and during the taper period will be summarized using descriptive statistics by assigned dose. Duration of treatment, total dose, and average daily dose will be summarized by dose level. In addition, study drug compliance (%) will be summarized for using descriptive statistics. Study drug administration will be summarized separately for each treatment period (A, B) and Overall (the whole study) ([redacted]). Additionally, all possible combinations of study drug dose changes (in mg) throughout treatment period A, period B and overall will be summarized with counts and percentages ([redacted]

7.2 Adverse Events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or greater and summarized by the actual treatment dose of drug received at the time of initiation of the adverse event. Treatment emergent adverse events (TEAEs) are defined as adverse events with onset dates on or after the first dose of study drug. All AE summaries will include total number of TEAEs and total number of patients with AEs. The incidence of adverse events will be summarized using descriptive statistics by system organ class and preferred term. Patients are counted only once in each system organ class category, and only once in each preferred term category. Treatment-related adverse event summaries will include adverse events with missing relationship to study drug. For the summaries by severity, patients are counted at the greatest severity.

AEs will be summarized separately for each treatment period (A, B) taper period (A, B) and Overall (the whole study).

An overall summary of adverse events will include number (%) of patients with TEAEs (and number of AEs), treatment-related TEAEs, SAEs, severe TEAEs, TEAEs that resulted in treatment discontinuation, TEAEs that resulted in study discontinuation, and fatal AEs [redacted]

Additionally, summaries will be presented for all TEAEs by system organ class and preferred term (overall and by severity) ([redacted]). TEAEs determined by the investigator to be treatment-related (overall and by severity) will be summarized ([redacted]). Serious AEs will also be summarized ([redacted] 1[redacted]). Adverse events causing permanent discontinuation from treatment will be summarized ([redacted]). Fatal Adverse events will also be summarized ([redacted] Summary of TEAEs by preffered term in descending order of frequency (based on the total column) will also be summarized ([redacted]

Listings for pre-treatment AEs, fatal AEs, SAEs, TEAEs leading to treatment discontinuation will also be presented.

7.2.1 Misuse Abuse and Diversion Drug Event Reporting System (MADDERS)

Adverse Events or drug accountability events considered to be potentially MADDERS related will be sent for adjudication. The adjudication will result in events categorized into the following categories as adverse events or abuse, misuse, suicide-related, therapeutic error and unknown. Summaries will be presented for all MADDERS categories (AE or Drug Accountability related) by type and treatment group (Treister et al. 2016) ([redacted] Additionally, MADDERS medication use survey responses (Never, Seldom, Sometimes, Often) will be summarized descriptively for each question by treatment group [redacted]

7.3 Vital Signs

Vitals signs at each visit and changes from baseline to each visit will be summarized using descriptive statistics ([redacted]).

7.4 Electrocardiogram

ECG results including HR, RR, PR, QRS, QT, QTC_B, QTC_F will be summarized by nominal visit using descriptive statistics ([redacted]). Shifts in ECGs (normal, abnormal not clinically significant, abnormal clinically significant) from baseline to each visit will be summarized descriptively ([redacted]).

7.5 Physical Examination

Shifts (normal [not clinically significant] and abnormal [clinically significant]) from baseline to each visit will be summarized using patient counts for each category [redacted].

7.6 Neurological Examination/Targeted Neurological Examination

Shifts (normal and abnormal) from baseline to each visit collected will be summarized using patient counts for each category ([redacted] in the full neurological examination. Targeted neurological results will also be summarized at each visit collected ([redacted].

7.7 Clinical Laboratory Tests

Clinical labs - Chemistry [redacted], Hematology [redacted] Urinalysis ([redacted] and Testosterone [redacted] results at each visit and change from baseline to each visit will be summarized using descriptive statistics. A summary of clinically significant lab values will be summarized for Chemistry and Hematology [redacted]. Additionally, shifts from baseline to each visit will be presented for chemistry and hematology ([redacted]).

7.8 Concomitant Medications

All concomitant medications will be coded using WHO Drug. The incidence of concomitant medications will be summarized by the actual treatment dose of drug received at the time of initiation of the concomitant medication using descriptive statistics by therapeutic class and preferred term [redacted]). Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Concomitant medications will include all medications taken on or after Day 1.

Concomitant medications will be summarized separately for each treatment period (A, B) and Overall (the whole study).

7.8.1 Patient Skin Irritation Score

The patient skin irritation score will be summarized during the same treatment periods for SF28. The total number of scores (“0”: No redness or “1”: Redness) will be displayed within each treatment period and dose administered([redacted]). In addition, the number of unique patients who reported a score of ≥2 will be included ([redacted]

7.8.2 Investigator Skin Irritation Score

The investigators skin irritation score (0=No Erythema to 4=Intense Erythema with Edema and Blistering/Erosion) will be summarized at each visit using descriptive statistics by dose administered ([redacted]).

7.9 Columbia Suicide Severity Rating Scale - Childrens (Baseline and Since Last Visit)

Descriptive statistics (count, percentage of yes/no responses) will be provided for children 6 and over for each item of the C-SSRS that is completed at each time point. Note that if a patient answers "No" to question "1" or question "2", then the patient will not be asked to answer question "4" or question "5" ([redacted]).

7.10 Pharmacokinetic Analyses

7.10.1 AED Medications

The following data will be summarized separately for each AED medication:

- Plasma concentration
- Elapse time between last AED dose and the time of plasma sample collection.

Descriptive statistics (arithmetic mean, median, SD, minimum, maximum, coefficient of variation, geometric mean [plasma concentration]) for the AED plasma trough concentrations and elapse time will be presented for all patients at each nominal PK sampling time ([redacted]).

7.10.2 [redacted]

[redacted]

8 STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® Version 9 or higher. All data collected on the electronic case report form (eCRF) will be listed.

9 Changes from the protocol

The ITT population is defined in the protocol as all patients who have taken at least one dose of study medication and have at least one post-baseline efficacy assessment. This definition is a modified intent-to-treat definition, so the population was changed to mITT throughout the SAP.

The protocol states:

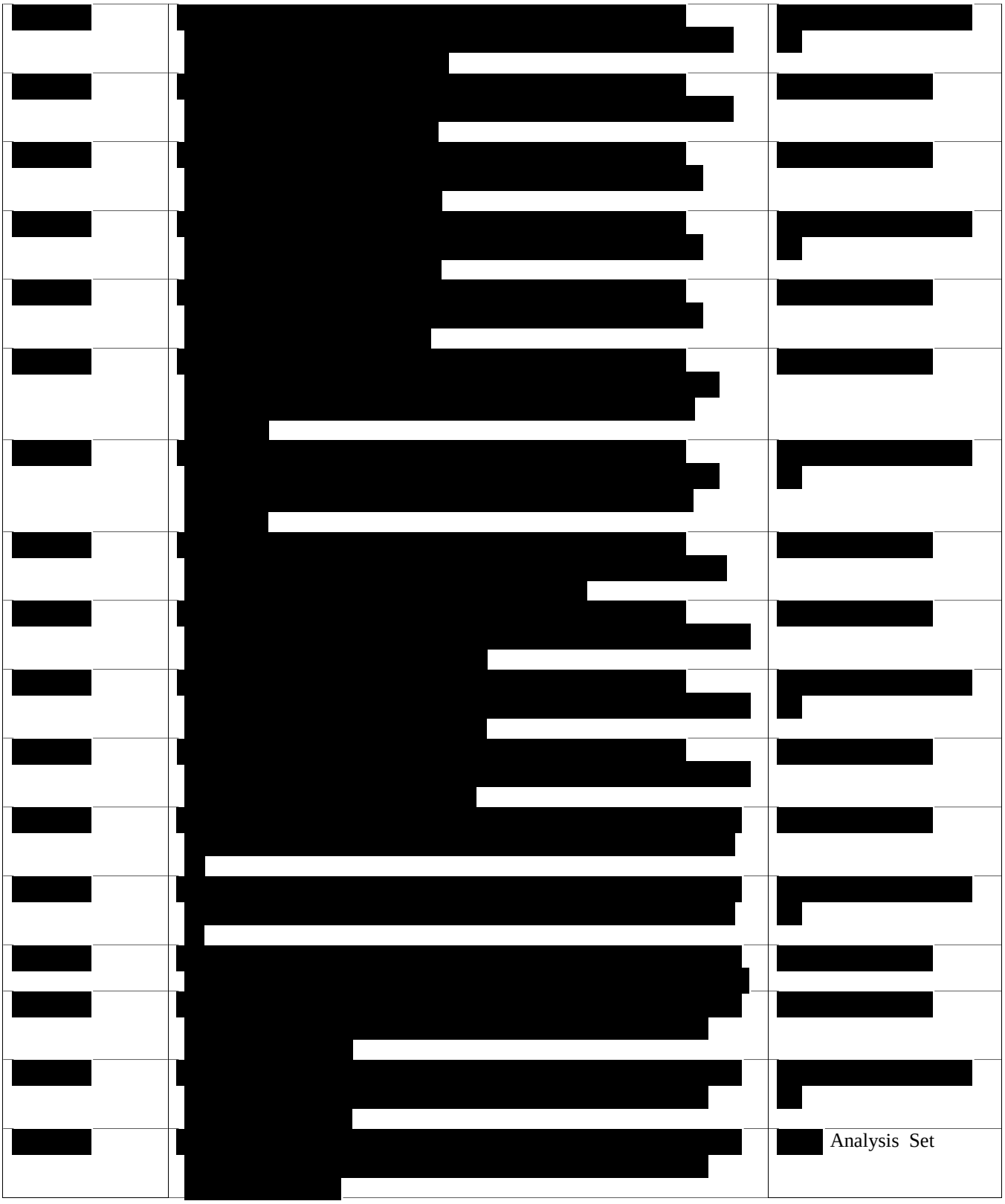
"The primary efficacy assessment will be the median percent change from baseline in the mean monthly (28 day) frequency of seizures (SF28) over 26 weeks (Period A) for the following types, in total ("countable seizures"):

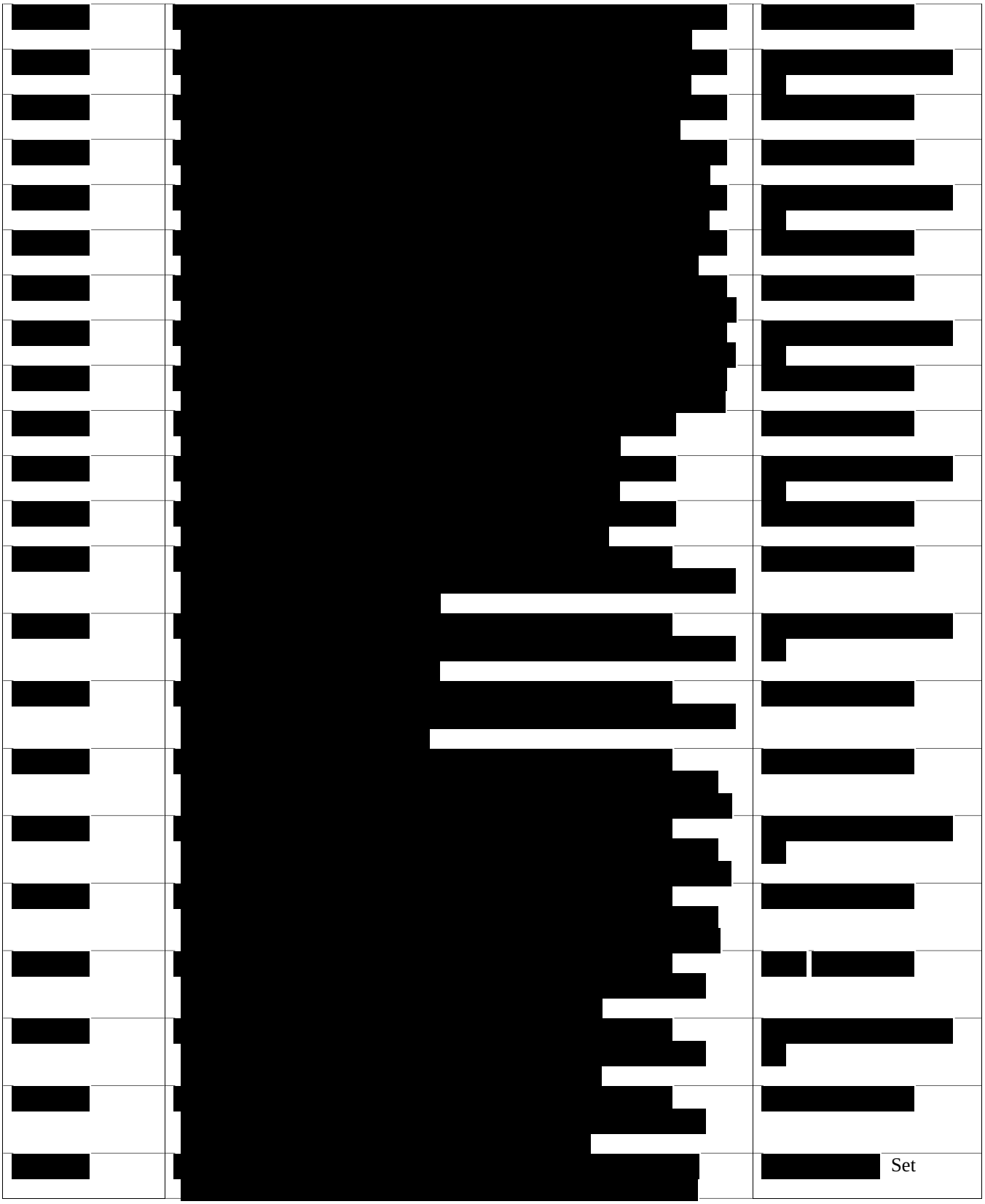
- Generalized tonic-clonic ("primary generalized tonic-clonic') seizures
- Focal impaired awareness seizures
- Focal to bilateral tonic-clonic seizures
- Focal aware seizures with motor signs
- Tonic seizures
- Clonic seizures
- Atonic seizures
- Epileptic spasms"

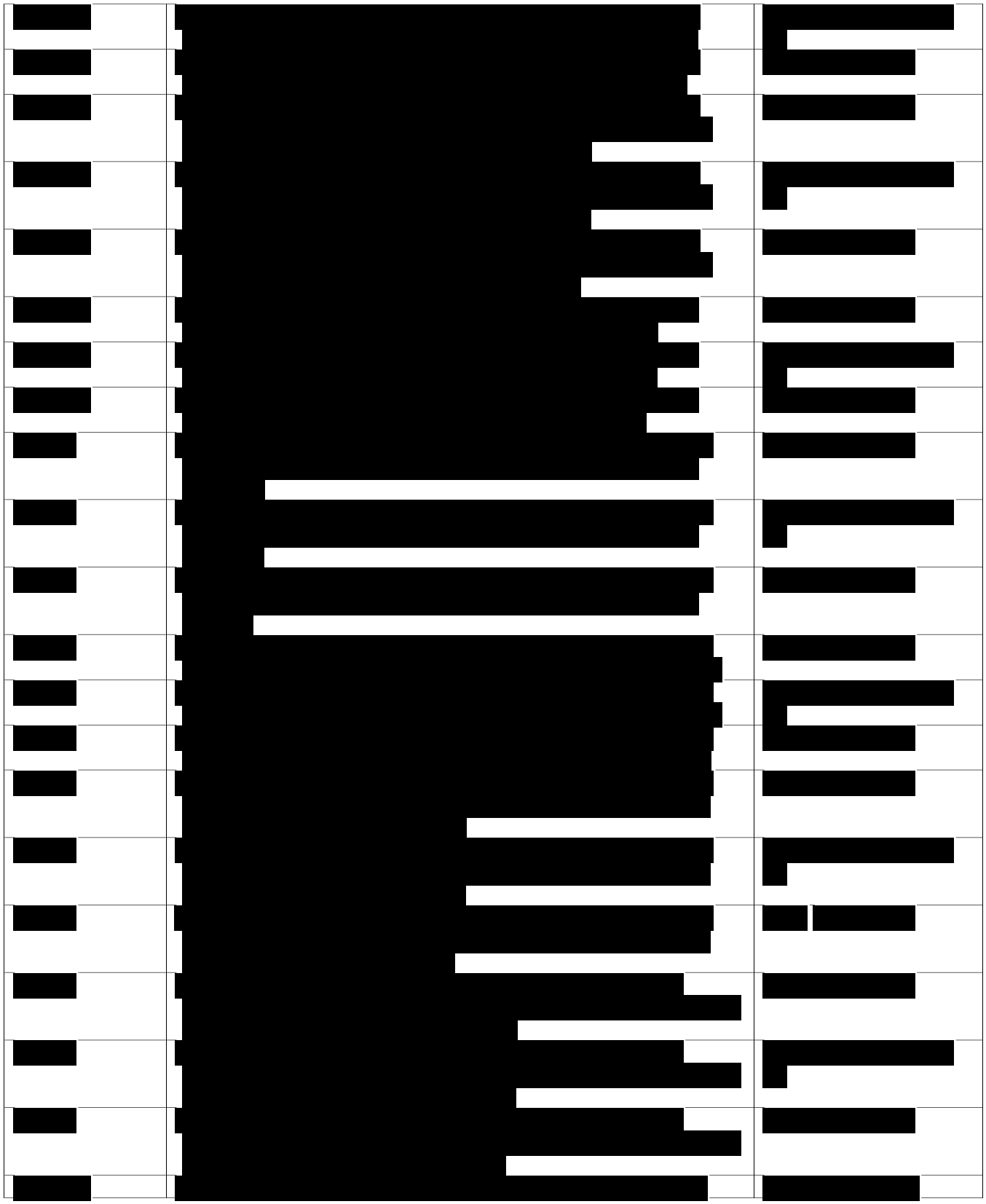
The SAP was changed to reflect a subset of countable seizures (called "select countable seizures") and including : Generalized tonic-clonic ("primary generalized tonic-clonic') seizures (GTCS), Focal impaired awareness seizures (FIAS), and Focal to bilateral tonic-clonic seizures (BTCS).

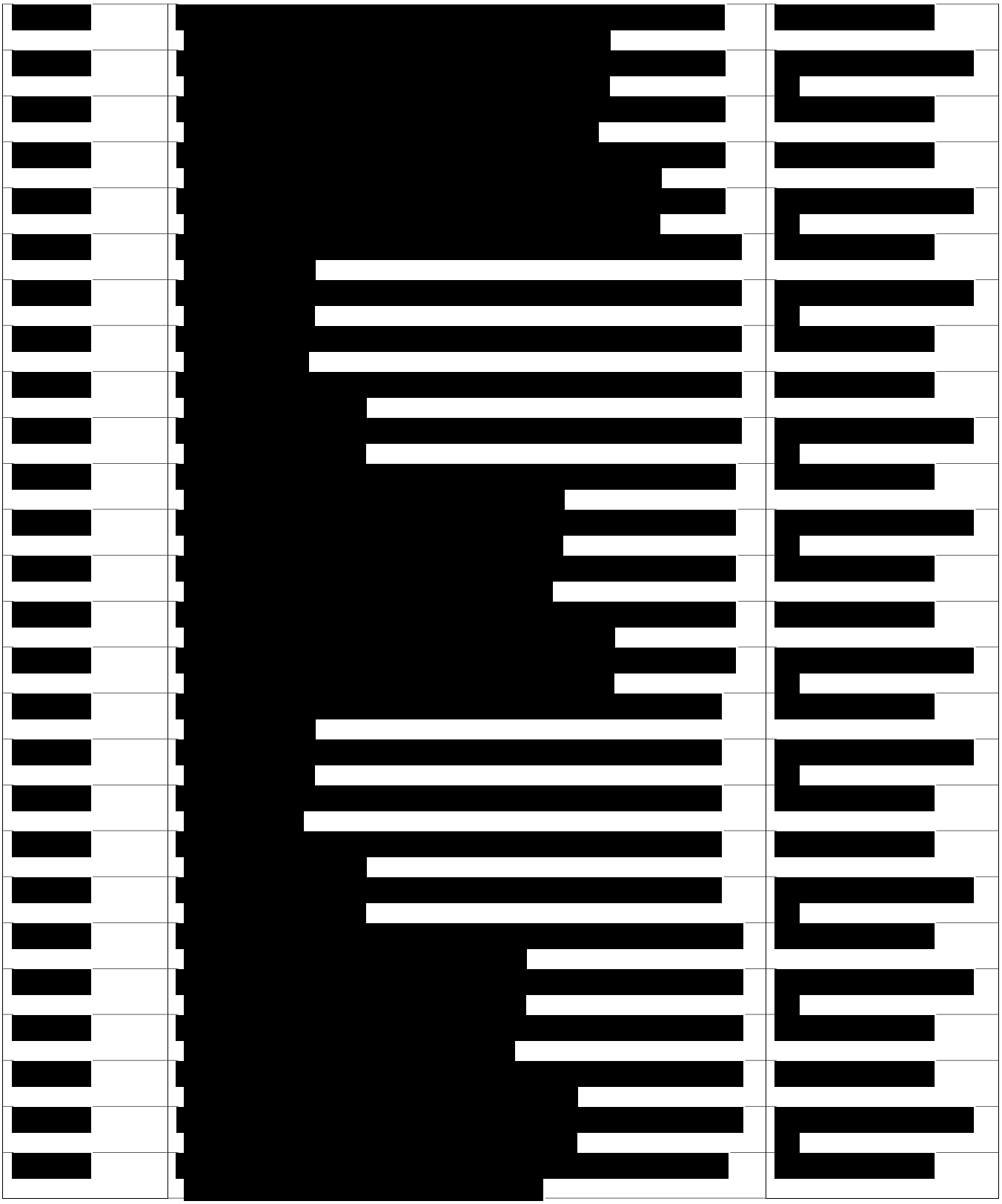
10 LIST OF SUMMARIES AND LISTINGS

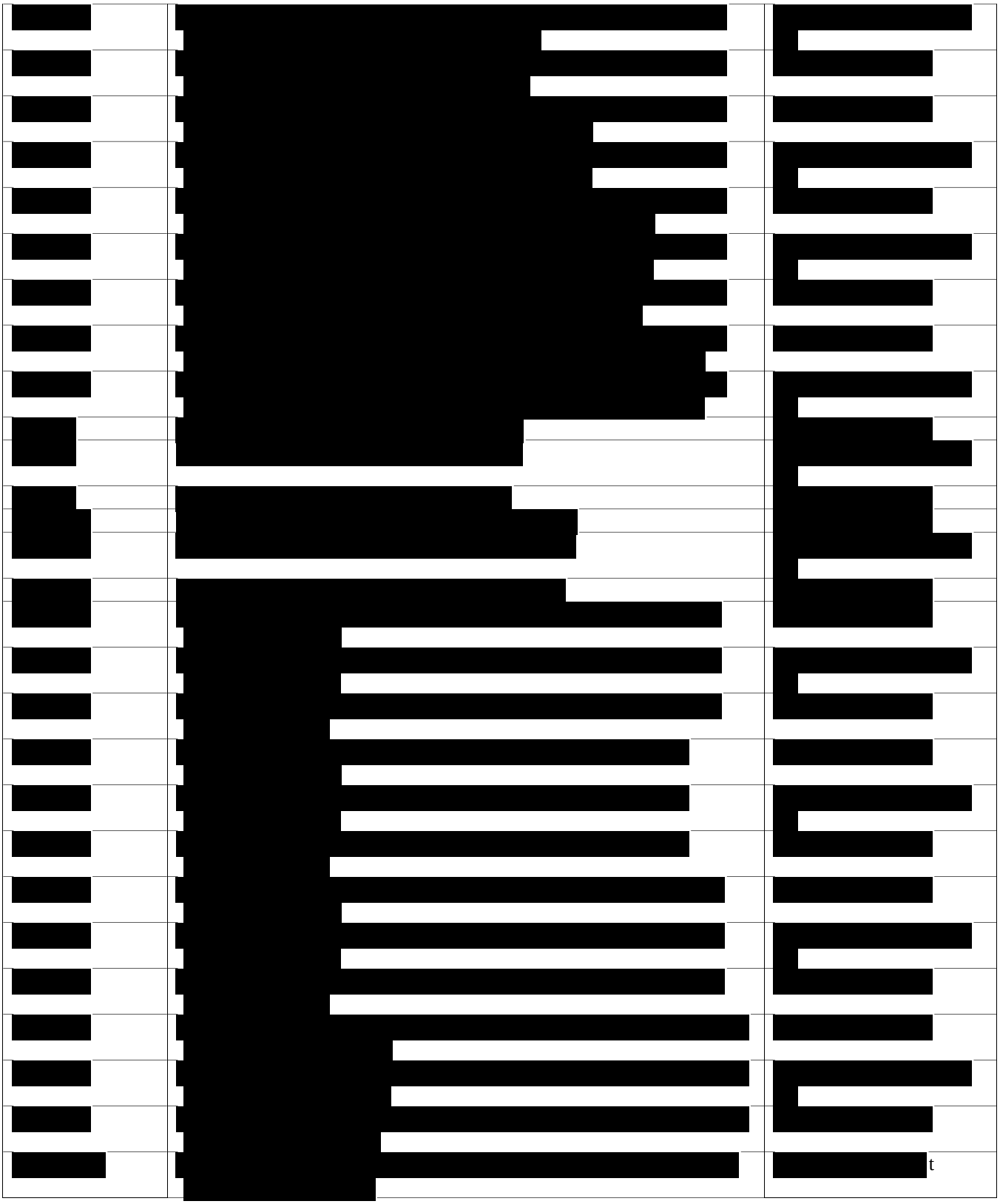
10.1 Overall Summary Tables

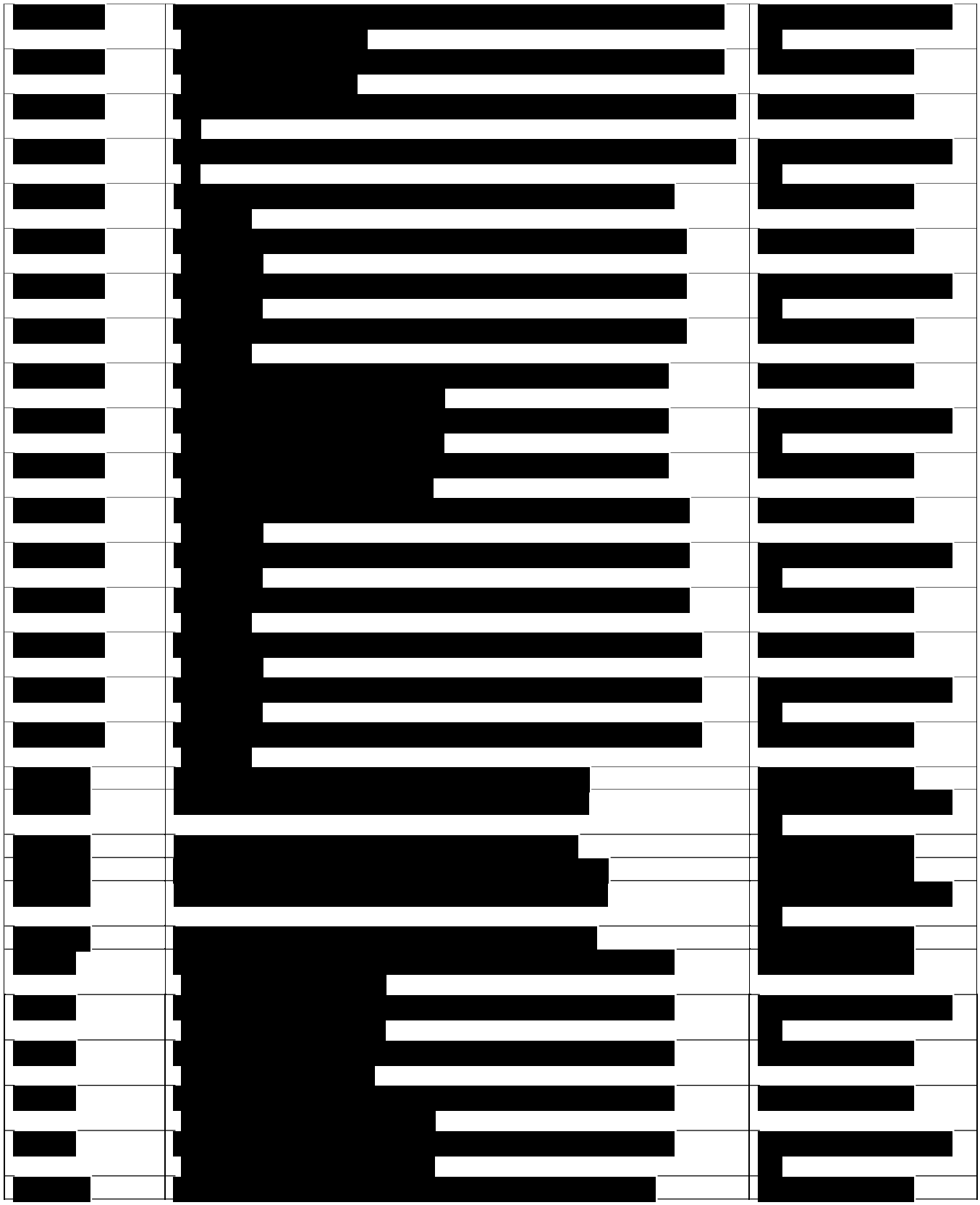

Analysis Set


Set









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12 APPENDICES

12.1 Appendix 1: The University of Washington Caregiver Stress Scale Summary Score to T-Score Conversion Table[0]

Summary Score	T-score	SD of T-score
19	23.1	4.4
20	25.9	3.8
21	27.9	3.4
22	29.5	3.2
23	30.9	3.0
24	32.1	2.8
25	33.2	2.7
26	34.2	2.6
27	35.1	2.5
28	35.9	2.4
29	36.7	2.3
30	37.5	2.3
31	38.2	2.2
32	39.0	2.2
33	39.7	2.2
34	40.3	2.1
35	41.0	2.1
36	41.6	2.1
37	42.2	2.1
38	42.9	2.1
39	43.5	2.1
40	44.1	2.1
41	44.7	2.1
42	45.3	2.1
43	45.8	2.1
44	46.4	2.1
45	47.0	2.1
46	47.6	2.1
47	48.1	2.1
48	48.7	2.1
49	49.2	2.0
50	49.8	2.0
51	50.4	2.0
52	50.9	2.0
53	51.4	2.0
54	52.0	2.0
55	52.5	2.0
56	53.1	2.0
57	53.6	2.0
58	54.1	2.0
59	54.7	2.0
60	55.2	2.0
61	55.7	2.0
62	56.3	2.0
63	56.8	2.0
64	57.3	2.0
65	57.9	2.0
66	58.4	2.0
67	59.0	2.0
68	59.5	2.0
69	60.0	2.0
70	60.6	2.0
71	61.1	2.0
72	61.7	2.0
73	62.3	2.0
74	62.8	2.0
75	63.4	2.0
76	64.0	2.0
77	64.6	2.1
78	65.2	2.1
79	65.8	2.1
80	66.4	2.1
81	67.1	2.1
82	67.8	2.2
83	68.5	2.2
84	69.2	2.3
85	70.0	2.3
86	70.8	2.4
87	71.6	2.5
88	72.6	2.6
89	73.6	2.7
90	74.7	2.9
91	76.0	3.1
92	77.4	3.3
93	79.1	3.6
94	81.2	4.0
95	84.0	4.6

12.2 Appendix 2: The Sleep disturbance Scale for Children Summary Scores to T-Score Conversion Table[0]

T-Score	Total	DIMS	SBD	DA	SWTD	DOES	SHY
100	74+	26+	11+	8+	21+	20+	
99	73	25			20		
98	72						
97	71						
96						19	
95	70	24			19		
94	69			7			
93	68		10				
92		23				18	10
91	67				18		
90	66						
89	65	22					
88	64					17	
87					17		
86	63	21	9				9
85	62					16	
84	61						
83					16		
82	60	20		6			

T-Score	Total	DIMS	SBD	DA	SWTD	DOES	SHY
66	47	15			12		
65			6			11	
64	46						
63	45	14					5
62	44				11		
61						10	
60	43	13					
59	42						
58	41		5	4	10		
57		12				9	4
56	40						
55	39						
54	38	11			9		
53	37					8	
52			4				
51	36						3
50	35	10			8	7	
49	34						
48							

81	59					15	
80	58						8
79	57	19	8		15		
78							
77	56					14	
76	55	18					
75	54						
74					14		7
73	53	17				13	
72	52		7				
71	51						
70		16		5	13		
69	50					12	6
68	49						
67	48						

47	33	9		3			
46	32					6	
45	31		3		7		2
44		8					
43	30						
42	29					5	
41	28	7			6		
40	27						
39							1
38	26		2			4	
37					5		
36							
35				2			
34							