Janssen Research & Development Statistical Analysis Plan

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

Protocol TOPMATEPY4067; Phase 3

Amendment 3

RWJ-17021-000 (topiramate)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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LIST OF IN-TEXT TABLES

AMENDMENT HISTORY

SAP version	issue date
Original	December 03, 2019
1st Amendment	February 24, 2020
2nd Amendment	May 13, 2020
3rd Amendment	June 4, 2020

The overall reason for the amendment 1:

Major: 1. re-insertion of MMRM analysis in a pre-specified way of analysis & 2. additional sensitivity analysis for subjects who took concomitant AED after the first study medication intake.

MMRM analysis:

An MMRM analysis is included as sensitivity analysis to explore longitudinal safety data and will be analyzed in the following order.

1. The model includes treatment group, study center, age group (4 age groups), visit, treatment-by- visit interaction, baseline measure, and baseline-by-visit interaction with the unstructured covariance matrix.
2. If this model experiences convergence issues, then the same model with compound symmetric matrix followed by AR1 will be explored instead of unstructured.
3. If the above doesn't work, then a reduced model with treatment group, age group, visit, treatment-by-visit interaction, and baseline measure will be explored. Age will be collapsed to two categories: 2-9 years of age (pre-pubertal) and 10-15 years of age (pubertal). The unstructured covariance matrix will be explored first and if it doesn't work, then compound symmetric followed by AR1 will be applied.
4. If above doesn't work, then no additional MMRM analysis will be performed.

Sensitivity analyses:

Sensitivity analyses for height z-scores, weight-z-scores and BMD z-scores will be conducted for subset of safety analysis set: for subjects who started taking at least one concomitant AED, data collected after the start of taking AED medication will be excluded from the analysis.

Minor: 1. Insertion of correct schedule of events, 2. Addition of AED medication list in the Appendix, 3. Widening of screening window. 4. Age calculation at each visit for markedly abnormal labs and vital signs. 5. Update to SAS code for Vineland score calculation.

The overall reason for the amendment 2:

1. Widen the interval for DEXA scan to include 4 subject whose scans were done after baseline but within 1 month post-baseline
2. Calculate the exact age at each dosing visit
3. Total daily dose calculation for overlapping intervals: capped at their maximum allowed dose

The overall reason for the amendment 3:

1. Baseline is defined as the last non-missing observation (including an unscheduled visit) prior to or equal to Day 1 (except for DEXA and Bone age, where baseline includes up to 30 days and 180 days post-baseline, respectively).

ABBREVIATIONS

AE	Adverse event
AED	anti-epileptic drug
ATC	Anatomical Therapeutic Chemical
BMC	bone mineral content
BMD	bone mineral density
BMDCS	Bone Mineral Density in Childhood Study
BMI	Body Mass Index
CBCL	Child Behavior Checklist
CDC	Centers for Disease Control
CI	confidence interval
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DEXA	dual energy x-ray absorptiometry
DMC	data monitoring committee
IWRS	interactive web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
PGTCS	primary generalized tonic-clonic seizures
POS	partial-onset seizures
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SOC	system organ class
SSG	statistical support group
TEAE	treatment-emergent adverse event
TLF	table, listing, figure
WHO	World Health Organization

1. CHANGES IN CONDUCT OF THE STUDY

On 12 December 2018, the independent Data Monitoring Committee (DMC) recommended to stop the TOPMATEPY4067 study because of futility of study enrollment. On 12 August 2019, Janssen has received the US FDA decision as follows:

- Stop enrolling new subjects at all sites and discontinue the study at all the sites that do not have either subject under study treatment or subjects who require a repeat bone mineral density (BMD) measurement 6 months after discontinuing study treatment.
- All sites with any subject on treatment in the study should continue following the subject according to the protocol until treatment has been completed, the subject has discontinued prematurely, or a repeat DEXA scan (which is indicated 6 months after treatment discontinuation) has been completed.

The US FDA decision is based on the slow rate of study enrollment of subjects despite continuous efforts to improve recruitment in the study. The decision is not related to any safety issues.

Interim analyses on the key endpoints (change in BMD z-score at Month 12, change in height z- score at Month 12 and change in weight z-score at Month 12) were conducted on 13 December 2018. This SAP has been modified based on the early termination of the study.

2. INTRODUCTION

Protocol TOPMATEPY4067 is a randomized (1:1), active-controlled, open-label, flexible-dose, multicenter, Phase 3 study of approximately 282 eligible subjects to evaluate the effects of topiramate monotherapy compared with levetiracetam, another standard antiepileptic drug (AED), as monotherapy for new-onset or recent-onset epilepsy on pediatric growth and maturation, bone mineralization, and kidney stone formation in children 2 to 15 years of age.

The purpose of the Statistical Analysis Plan is to lay out key elements including definition, statistical methods, and tables, listings, and graphs (TLFs).

2.1. Trial Objectives

Primary Objective:

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

Secondary Objective:

To evaluate the effects of topiramate monotherapy compared with levetiracetam, another standard AED, as monotherapy for new-onset or recent-onset epilepsy on kidney stone formation in children 2 to 15 years of age.

Overall safety will be assessed.

2.2. Trial Design

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

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

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

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

2.3. Statistical Hypotheses for Trial Objectives

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

2.4. Sample Size Justification

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

- Annual change in BMD (L1-L4) Z-score: In the Bone Mineral Density in Childhood Study (BMDCS), mean annual change in BMD (L1-L4) Z-score in 6- to 15-year-old healthy subjects was, as expected, minimal (0.01-0.07). The standard deviation (SD) varied from 0.3 to 0.48 across sex and age groups. Assuming an SD of 0.4, with 100 completed subjects per group, the 95% CI for the treatment difference will have a precision of 0.12.

- Annual change in height Z-score in the 2- to 9-year-old age group: In the monotherapy epilepsy study TOPMAT-EPMN-106, the observed change from baseline in mean height Z-score at 1 year among the 2- to 9-year-old subjects treated with topiramate 400 mg/day was -0.18, with an SD of 0.28. Assuming that 53% of the subjects will be recruited in the 2 to 9-year-old age group, i.e., 53 completed subjects per treatment group, the 95% CI for the treatment difference will have a precision of 0.11.
- Change in weight Z-score in the 2- to 15-year-old age group: In the monotherapy epilepsy study TOPMAT-EPMN-106, a -0.59 decrease from baseline in weight Z-score, with an SD of 0.43, was observed after 1 year of treatment with topiramate 400 mg/day. Assuming an SD of 0.43, a sample size of 100 completed subjects per treatment group will provide a 95% CI with a precision of 0.12.

2.5. Randomization and Blinding

Procedures for Randomization and Stratification

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

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

Blinding

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

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

Renal ultrasound will be read/interpreted centrally (local reading at the screening visit is acceptable to determine eligibility for study enrollment). Both the technicians administering the renal ultrasound scans and the local and central readers will be blinded to the study treatment group.

All DEXA scans will be centrally analyzed (the baseline scans will be read locally to determine eligibility for the study). Both the technicians administering the DEXA scans and the central reader will be blinded to the treatment group.

Height will be measured by a trained individual who is blinded (unaware of the treatment).

Nominal blinding or "non-disclosure" of study treatment (i.e., study assessor is not aware of the subject's study treatment assignment) will also be made for assessments related to bone age and cognitive studies (excluding CBCL and Vineland). Nominal blinding will also be applicable to Tanner Staging, in the event site has available a pediatric endocrinologist/trained physician obtaining assessments. The assessors' non-disclosure status at each visit of these assessments will be captured in the eCRF. A sensitivity analysis of these endpoints (bone age, cogstate batteries and Tanner staging) based on nominal blinding may be considered if deemed necessary.

2.6. Time and Events Schedule

The flow chart showing trial phases and timing of treatment and assessments is given in Table 1.

Table 1: Time and Events Schedule

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

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Study Day	≤-28	1[c]	30	60	90	180	270	360	390[d]
Study Day Window	-7days	±7days	±7days	±7days	±7days	±7days	±7days	±7days	±7days
Visit[e]	1	2	3	4	5	6	7	8	NA
Renal ultrasound[o]	X					X		X	
Biochemical bone markers[p]	X					X		X	
DEXA scan[b,q]		X				X		X	
Bone age x-ray[r]		X						X	
Dispense seizure diary and take-		X	X	X	X	X	X		
Review seizure diary and take-			X	X	X	X	X	X	
Cogstate Battery[t]	X	X				X		X	
Animal Fluency Test NEPSY-II[u]	X	X				X		X	
Vineland Adaptive Behavior Scales[v]		X			X	X		X	
CBCL–Parent Version[w]		X			X	X		X	
C-SSRS[x]		X	X	X	X	X	X	X	
Ongoing Review									
Concomitant therapy	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X	X	X	X

Footnotes appear on the following page.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3. GENERAL ANALYSIS DEFINITIONS

Unless otherwise specified, all continuous endpoints (e.g., height, weight, BMD [observed and change from baseline values], etc.) will be summarized using descriptive statistics, which will include the number of subjects with a valid measurement (n), mean, SD, median, minimum, and maximum. Pharmacokinetics will be summarized using descriptive statistics including geometric mean and coefficient of variation (CV in percent will be defined as CV(%) = 100* SD / mean). All categorical endpoints (e.g., sex, adverse events, BMD Z-score decrease [>0.5, >1.0, >2.0], etc.) will be summarized using frequencies and percentages. In general, percentages will be calculated by dividing the number of subjects with the characteristic of interest by the number of subjects in the analysis population.

3.1. Visit Windows

The statistical analysis for safety will be based on time intervals that are constructed according to the number of days in trial from day 1. (See table 2-8)

The analysis windows for height, weight, exposure, vital signs, laboratory tests, physical examination and neurological examinations is given in Table 2.

Table 2: Definition of windows for height, weight, exposure, vital signs, laboratory tests, physical examination and neurological examinations:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1,2	Baseline	-35 to1	1
3	Month 1	2 to 60	30
5	Month 3	61 to 135	90
6	Month 6	136 to 225	180
7	Month 9	226 to 315	270
8	Month 12	>=316	360

[a] The randomization day is Day 1.

The analysis windows for Renal Ultrasound, Cogstate, Tanner Staging and 24 hour urine collection is given in Table 3.

Table 3: Definition of windows for Renal Ultrasound, Cogstate, Tanner Staging and 24 hour urine collection:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1, 2	Baseline	-35 to1	1
6	Month 6	2 to 270	180
8	Month 12	>=271	360

[a] The randomization day is Day 1.

The analysis windows for C-SSRS is given in Table 4.

Table 4: Definition of windows for C-SSRS:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1, 2	Baseline	-35 to1	1
3	Month 1	2 to 45	30
4	Month 2	46 to 75	60
5	Month 3	76 to 135	90
6	Month 6	136 to 225	180
7	Month 9	226 to 315	270
8	Month 12	>=316	360

[a] The randomization day is Day 1.

The analysis windows for Vineland Scale and CBCL is given in Table 5.

Table 5: Definition of windows for Vineland Scale and CBCL:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1, 2	Baseline	-35 to1	1
5	Month 3	2 to 135	90
6	Month 6	136 to 270	180
8	Month 12	>=271	360

[a] The randomization day is Day 1.

The analysis windows for Bone Age is given in Table 6.

Table 6: Definition of windows for Bone age:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1	Baseline	-35 to180	1
8	Month 12	>=181	360

[a] The randomization day is Day 1.

The analysis windows for seizure count is given in Table 7.

Table 7: Definition of windows for seizure count:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
3	Month 1	2 to 45	30
4	Month 2	46 to 75	60
5	Month 3	76 to 135	90
6	Month 6	136 to 225	180
7	Month 9	226 to 315	270
8	Month 12	>=316	360

[a] The randomization day is Day 1.

The analysis windows for DEXA is given in Table 8.

Table 8: Definition of windows for DEXA:

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1, 2	Baseline	-35 to30	1
6	Month 6	31 to 270	180
8	Month 12	>=271	360

[a] The randomization day is Day 1.

The analysis windows for Pharmacokinetics is given in Table 9.

Table 9: Definition of windows for Pharmacokinetics

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
3	Month 1	2 to 45	30
5	Month 3	46 to 135	90
6	Month 6	136 to 270	180
8	Month 12	>=271	360

[a:] The randomization day is Day 1

Baseline is defined as the last non-missing observation (including an unscheduled visit) prior to or equal to Day 1 (except for DEXA and Bone age, where baseline includes up to 30 days and 180 days post-baseline, respectively).

For post baseline observations, if more than one visit (including an unscheduled visit) occurs in the same time window, the visit nearest to the target day will be used in the analysis. In the case of an equal distance in time, the latest visit will be used.

Data that are not used in the analysis due to multiple observations or being excluded from the above defined time intervals will be displayed in the data listing.

3.2. Pooling Algorithm for Analysis Centers

NA

3.3. Analysis Sets

All analyses, except for subject disposition, will use data for the safety analysis set. Demographics will also be summarized based on all randomized set and subject disposition will be based on all subjects.

3.3.1. Efficacy Analysis Set(s)

There will be no efficacy analysis set.

3.3.1.1. Primary Efficacy Analysis Set

NA

3.3.1.2. Secondary Efficacy Analysis Set

NA

3.3.2. All Randomized Set

This will include all randomized subjects.

3.3.3. Safety Analysis Set

This will include all randomized subjects who received at least 1 dose of study medication. This population will be used for all analyses, including any DMC analyses. All subjects will be analyzed according to treatment they received by first study drug dispensation.

3.3.4. Pharmacokinetics Analysis Set

The PK analysis set will consist of all subjects in the safety analysis set with available plasma concentrations.

3.3.5. Pharmacodynamics Analysis Set

NA

3.4. Definition of Subgroups

Data will be summarized in addition by age group of 2 to 5 years of age, 6 to 9 years of age, 10 to 12 years of age, and 13 to 15 years of age, separately. For height, Z-scores for height, height velocity and height velocity Z-scores, data will also be summarized by 2 to 9 years of age.

4. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

There will be no interim analyses, but an external, independent DMC will be established to review safety data on a quarterly basis or less frequent basis (but not more than six months) when deemed necessary and ensure the continuing safety of the subjects enrolled in this study. Additional adhoc meetings can be requested by the DMC or the Sponsor. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

The DMC is comprised of four clinicians and one statistician. The Chairperson and one member are pediatric endocrinologists with expertise in bone, growth and maturation; the other two clinicians are a pediatric nephrologist and a pediatric neurologist. Mention one member is statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

The safety analyses will be performed by Statistical Support Group (SSG) independent of the Sponsor. The output tables in the data package will be displayed by each age group (2-5, 6-9, 10- 12, and 13-15) and overall. All data and output should be held in strict confidentiality with access to DMC and SSG only before they can be transferred to the Sponsor.

Separate outputs will be generated for the open- and closed-sessions of the DMC meetings. The outputs in the data package for the open-session will be unblinded, except for Ultra Sound, DEXA and height analyses. These will present summaries for all subjects combined (e.g., tables will only present a Total column). All outputs in the data package for the closed-session will be unblinded and will present the data by the subjects' true treatment group assignment.

Before each scheduled DMC meeting, data cut-off dates (6 to 8 weeks prior to the meeting) will be identified and the clinical database will be made as clean as possible, with particular focus on safety data. For the purpose of the DMC review of the results, all available data needed for the TLFs up to the time of data cut-off dates, unless otherwise specified will be included in the TLFs.

The Contract Research Organization, PAREXEL, will provide the SDTM datasets containing the electronic case report form (eCRF) data, the cognitive battery data (computerized cognitive battery as well as NEPSY testing), and the central laboratory data to the SSG statistician using the Janssen MBOX. The DEXA and US data will be provided directly to the SSG statistician by Bioclinica. Given that this is an open-label study, the treatment assignment will be included in the CRF data.

5. SUBJECT INFORMATION

5.1. Demographics and Baseline Characteristics

Subject demographics and baseline disease characteristics will be listed and summarized for the randomized analysis set by treatment group. Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be presented for age, height, weight, body mass index (BMI), and years since diagnosis of epilepsy. Frequency counts and percentages will be presented for categorical variables sex, age group (2-5 years, 6-9 years, 10-12 years, 13-15 years), ethnicity, race, geographic region, , seizure types present within the last 2 years, seizure occurred within the last 2 years beyond 3 or 5 month , seizure occurred in last 3 or 5 months and any AED drug/therapy at study entry and bicarbonate categories. Bicarbonate values are categorized as low (<20 mEq/L at screening) and non-low bicarbonate values (>=20 mEq/L at screening).

Age in years will be used from eCRF. In case of missing eCRF for age, 15th of the month will be used as day. Missing day and moth at date of birth will be imputed by June 30. Years since diagnosis of epilepsy will be calculated based on year of Day 1 minus year of diagnosis (if both in the same year it will be 0).

- Age calculation:
  - For Height and Weight Z-Scores, it is given in CDC guidance document, age is in month with one decimal.
  - For demographics, it is floor (ICF date minus birth date)/365.25), age is in full years.
  - For Vineland it is floor ((intck ('month', birth date, visit date)-(day (visit date)<day(birth date)))), age is in full month.
  - For CBCL it is floor (visit date minus birth date)/365.25), age is in full years.
  - For Cogstate it is floor (visit date minus birth date)/365.25), age is in full years.
  - For vital signs it is floor (visit date minus birth date)/365.25), age is in full years.
  - For labs it is floor (visit date minus birth date)/365.25), age is in full years.
  - Age for determination of max daily dose for Topiramate or Levetiracetam it is floor (date of dosing minus birth date)/365.25), age is in full years.
- BMI is calculated as weight (kg) / height $(m)^2$.

Geographic region will be summarized as North America, South America, Europe and Asia Pacific.

- North America: US, Canada
- South America: Argentina, Mexico
- Europe: Belgium, France, Germany, Hungary, Italy, Poland, Russian Federation, Austria, South Africa, UK
- Asia Pacific: Australia, Taiwan, Philippines

5.2. Disposition Information

Distribution of subjects will be provided for the all randomized analysis set. The number of subjects screened, screen failures, randomized, dosed, completed, and discontinued will be listed and summarized. Treatment discontinuation will be summarized according to reasons of discontinuation as documented in the CRF. The screen failures and the reasons will be listed.

5.3. Treatment Compliance

Treatment compliance will not be summarized.

5.4. Extent of Exposure

Treatment duration is defined as time between the first dose date and last dose date of topiramate or levetiracetam and will be presented as a continuous summary and classified into the following categories by the amount of time on study medication: 0 to <3 months, 3 to <6 months, 6 to <9 months, 9 to <12 months, and ≥ 12 months. The number and percentage of subjects in each category will be reported.

A summary of the average total daily dose and the weight-adjusted average daily dose (mg/kg) will also be presented. The weight will be used at start of the respective period (titration and maintenance). For exposure with overlapping records, if a 'total daily dose' exceeds the maximum dose allowed for the subject, a total daily dose of 350 mg or 400 mg for Topiramate will be used for the subject with age <10 years or >=10 years, respectively. For Levetiracetam, the total daily dose of 3,000 mg will be used if the exposure with overlapping records exceeds the maximum allowed dose of 3,000 mg. It will also be summarized by the treatment period (titration and maintenance). The start of maintenance period is defined as "date maintenance achieved" from titration CRF, and the end of titration period is defined as "start of maintenance period minus 1".

A listing of dispensed medication will also be provided.

5.5. Protocol Deviations

The major protocol deviations will be listed and summarized by treatment group. A subject can be counted under multiple deviation categories.

The major Protocol Deviation categories

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or dose deviation
- Selection criteria not met
- Informed consent not correctly signed
- Visit schedule is not followed according to protocol
- Safety assessments not performed according to protocol

- Safety assessments not documented properly

The minor protocol deviations will not be summarized.

5.6. Prior and Concomitant Medications

Medications administered prior to the first dose of study medication will be considered prior medications. Concomitant medications include those taken on or after first dose date. Incidence of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) code levels 2 and 4, and preferred term. Only prior anti-epileptic drugs (AEDs) will be summarized. Concomitant medications will be listed and summarized separately for AED and non-AED medications. Tables will be sorted by decreasing frequency in incidence (the highest to lowest incidence) first within ATC code level 2, followed by ATC code level 4, and then preferred term. Medications with partial onset date will be handled as follows: a missing day should be set to first of month. If month is missing the missing month should be set to January.

Please see Appendix 7 for the list of AED medications.

5.7. Medical History

Medical history will be listed only.

6. EFFICACY

There are no efficacy data collected for the study.

6.1. Analysis Specifications

6.1.1. Level of Significance

NA

6.1.2. Data Handling Rules

NA

6.2. Primary Efficacy Endpoint(s)

NA

7. SAFETY

The safety variables to be summarized include kidney stones, height, weight, BMD and bone mineral content (BMC), biochemical markers of bone mineralization, bone age XR, seizure counts, cognitive, developmental, and behavioral assessments, treatment-emergent AEs, Columbia-Suicide Severity Rating Scale (C-SSRS), cognitive, developmental and behavioral assessments (COGSTATE computerized battery and NEPSY Language scale; Vineland Adaptive Behavioral Scale, Child Behavior Checklist (CBCL)), clinical laboratory tests (hematology, chemistry, urinalysis, and 24-hour urine collection), vital signs and physical exam. Safety variables are to be tabulated by descriptive statistics (n, mean, median, SD, minimum, and maximum; or n and percent). No formal statistical testing is planned.

For markedly abnormal labs and vital signs, age will be calculated at each visit to determine the criteria. Similarly, Vineland, CBCL and Cogstate will be calculated by age at each visit.

Z-scores for weight and height will be calculated using the SAS programs provided by the Centers for Disease Control (CDC) for the calculation of the 2000 CDC growth charts. Z-scores for the BMD and BMC will be provided by the central DEXA reading center (Bioclinica).

Z-scores for the DEXA scans will be calculated locally at baseline only to determine eligibility for the study, and centrally for all statistical analyses. The Z-score calculation will take the DEXA machine and the subject's age, sex, height, and ethnicity into consideration. The reference databases for calculating the Z-scores are provided in the DEXA Manual for this study (please see the imaging charter of attachment 1 for more details).

Longitudinal endpoints will be analyzed using a mixed-model repeated measures (MMRM) analysis. An MMRM analysis is included as sensitivity analysis to explore longitudinal safety data and will be analyzed in the following order.

1. The model includes treatment group, study center, age group (4 age groups), visit, treatment-by-visit interaction, baseline measure, and baseline-by-visit interaction with the unstructured covariance matrix.
2. If this model experiences convergence issues, then the same model with compound symmetric matrix followed by AR1 will be explored instead of unstructured.
3. If the above doesn't work, then a reduced model with treatment group, age group, visit, treatment-by-visit interaction, and baseline measure will be explored. Age will be collapsed to two categories: 2-9 years of age (pre-pubertal) and 10-15 years of age (pubertal). The unstructured covariance matrix will be explored first and if it doesn't work, then compound symmetric followed dby AR1 will be applied.
4. If above doesn't work, then no additional MMRM analysis will be performed. 95% CI for the estimated treatment differences will be provided.

Example of MMRM is as follows:

```
ods output estimates=est;
PROC MIXED data=dat method=REML noclprint=10;
CLASS trt center usubjid age_group visit;
MODEL change=trt base visit center age_group trt*visit base*visit /
solution; repeated visit / type=un subject=usubjid;
lsmeans trt/diff cl;
```

Sensitivity analyses for height z-scores, weight-z-scores and BMD z-scores will be conducted for subset of safety analysis set: for subjects who started taking at least one concomitant AED, data collected after the start of taking AED medication will be excluded from the analysis.

7.1. Kidney Stones

Percentage of subjects with kidney stones and other US findings suggestive of stones will be summarized by treatment group.

The renal ultrasound findings will also be presented in a listing.

7.2. Weight

Observed weight values, change from baseline, Z-scores for weight, and change from baseline in Z-scores for weight will be listed and summarized by visit using descriptive statistics. The change in weight z-scores will also be summarized by subject's serum bicarbonate categories.

MMRM analysis will also be performed for changes from baseline and changes in Z-Scores from baseline.

7.3. Height

Observed height values, change from baseline, Z-scores for height, change from baseline in Z-scores for height, height velocity at 1 year, and height velocity Z-score will be summarized by visit using descriptive statistics. Height, Z-scores for height, height velocity and height velocity Z-scores will be calculated as the mean of the three measurements. The number and percentage of subjects with a height Z-score decrease of >0.5, >1.0, and >2.0 will be listed and summarized by visit using descriptive statistics. MMRM analysis will also be performed for changes from baseline and changes in Z-Scores from baseline.

The change in height z-scores will also be summarized by subject's serum bicarbonate categories.

Height velocity values and associated Z-scores will be computed for each post-baseline year in the study, based on the methods described in Appendix 6.

7.4. Bone Mineral Density (BMD) and Bone Mineral Content (BMC)

DEXA measurements will include posterior-anterior spine and total body less head areal (TBLH) BMD and BMC. Observed BMD (spine and TBLH) and BMC (spine and TBLH) values change from baseline, Z-scores as well as height adjusted Z-scores for BMD and BMC, change from baseline in Z-scores and height adjusted Z-scores for BMD and BMC, and percent change from baseline in BMD and BMC will be summarized by visit using descriptive statistics. The number and percentage of subjects with a BMD Z-score and adjusted Z-score decrease of >0.5, >1.0, and >2.0 will be listed and summarized by visit using descriptive statistics. MMRM analysis will also be performed for changes from baseline, changes in Z-Scores from baseline, and changes in height adjusted Z-Scores from baseline.

Subjects with a clinically important reduction in BMD defined as change in Z-score and height adjusted Z-score of -0.5 or greater) at 6 months or 12 months, will have a repeat DEXA scan 6 months after discontinuation of study drug. These subjects will be summarized and listed in the DEXA table and listing.

The change in BMD z-scores will also be summarized by subject's serum bicarbonate categories.

7.5. Biochemical Markers of Bone Mineralization

Observed and change from baseline in biochemical markers of bone mineralization (serum levels of alkaline phosphatase, calcium, phosphorus, parathyroid hormone (intact), 25-hydroxy vitamin D, 1,25-dihyroxy vitamin D, and IGF-1) will be listed and summarized by visit using descriptive statistics.

7.6. Bone Age

Observed and change from baseline in bone age will be listed and summarized by visit using descriptive statistics. Bone age will be summarized as "chronological age" and "bone age" as reported as XR report.

7.7. Seizure Count

Observed seizure counts will be listed and summarized by visit using descriptive statistics, for both the overall seizure count and by seizure type (Partial, Partial Evolving into Secondary Generalized, Primary Generalized Tonic-Clonic, and Other).

7.8. Cognitive, Developmental, and Behavioral Assessments

Cognitive Assessments

For the cognitive assessments (Detection Test, Identification Test, One Card Learning Test, One Back Test, and Groton Maze Learning Test) the standardized observed scores and change from baseline in standardized scores will be listed and summarized by visit using descriptive statistics. The standardized scores will be calculated by setting the observed raw score in relation to the expected within-subject standard deviations for each Cogstate task (see table 1-5 of Appendix 1 for normative data). For the tasks which lower scores indicate improvement (e.g., Detection Test and Identification Test), the score will be multiplied by (-1), so that a negative change in standardized scores represent a decline in cognitive performance consistently across all tasks.

A meaningful decline in cognition has been defined as a change in standardized score of less than -1.65 from the baseline standardized score. These calculations will indicate meaningful decline at the subject level. Each individual change in standardized scores that meet the definition of a meaningful decline will be identified using a binary flag, where 1 represents a meaningful decline from baseline and 0 otherwise. The number and percentage of subjects with a meaningful decline in cognition will be listed and summarized by visit.

Cognitive assessments will be provided to subjects of 4 years and older. Cognitive data collected after a subject turn 16 will not be included in the analysis.

For example, if a 10-year-old female subject has an observed raw score at baseline of 1.2 for the detection test, then the standardized score will be 1.2/0.0882*(-1)=-13.605. For a post baseline visit the subject had an observed raw score of 1.0, which is a standardized score of -11.338. The

change from baseline would be 2.267. The lower score at post baseline indicates an improvement in Detection Test which is reflected by the positive change (see table 1 of Appendix 1).

Developmental Assessments

The Vineland Scales of Adaptive Behavior provide age-specific assessment of function in the domains of communication, daily living, socialization, and motor skills, as well as a composite scale. The subject's sub-domain raw scores are entered on the CRF. The derived domain scores (standardized scores) based on the national standardization sample must be obtained from these raw scores. The derived scores are used in the analyses. The Vineland standardized scores for domain scores have a mean of 100 and a standard deviation of 15.

The composite score will be the sum of 4 standardized domain scores. If a subject has only 3 domains, then the standardized score for the missing domain will be prorated and the composite score will be calculated as sum of 4 domains. If a subject has less than 3 domains, then the composite score will not be calculated.

The standardized scores and the changes in standardized scores from baseline will by listed and summarized by visit using descriptive statistics.

For manuals and SAS program calculating the standardized domain scores, please see Appendix 4.

The Vineland Adaptive Behavior Scale will be administered for subjects 2 to 5 years of age only.

Behavioral Assessments

For CBCL preschool (up to 5 years of age), a raw total score will be sum of 99 non-missing answers (range of 0-198).

For CBCL school age (6 to 18 years of age), a raw total score will be the sum of 112 non-missing answers (range of 0-224).

The domains will be:

CBCL preschool	CBCL school age
1. Emotionally Reactive 2. Anxious/Depressed 3. Somatic Complaints 4. Withdrawn 5. Sleep Problems 6. Attention Problems 7. Aggressive Behavior 8. Internalizing Problems 9. Externalizing Problems 10. Total Problems	11. Anxious/depressed 12. Withdrawn/depressed 13. Somatic complaints 14. Social problems 15. Thought problems 16. Attention problems 17. Rule breaking behavior 18. Aggressive behavior 19. Internalizing Problems 20. Externalizing Problems 21. Total Problems

The standardized total scores (T score) for all domains will be derived using the charts based on the raw scores (Appendix 5).

The standardized scores and the changes in standardized scores from baseline will by listed and summarized by visit using descriptive statistics.

7.9. Adverse Events

Adverse events are coded to System Organ Class (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) coding system, version 21.1 or higher. Treatment-emergent adverse events (TEAEs) are those AEs which start or worsen after receipt of the first study drug and before the end of the REACH. REACH is defined as follows: AEs with onset date within therapeutic reach (i.e. 3 days) or SAEs/deaths with onset date within 30 days, inclusive, after end of treatment. AE's with partial onset date will be handled as follows: a missing day should be set to first of month. If month is missing the missing month should be set to January.

Summaries of TEAEs will be provided as incidence tables (number of subjects experiencing an event) by treatment group within each age group and overall (age 2-15). For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by decreasing frequency in incidence (the highest to lowest incidence) first within the SOC and then the PT. Treatment-emergent serious AEs (SAEs), TEAEs leading to discontinuation, TEAEs by severity, TEAEs by relationship and TEAEs of special interest will be summarized. Adverse events of special interest for topiramate include: effects on liver function; metabolic acidosis; effects on growth and maturation; vision abnormalities; oligohidrosis, hyperthermia and secondary rash; hyperammonemia and/or encephalopathy; kidney stones; neuropsychiatric and cognitive disorders; and suicidality. Adverse events of clinical interest for levetiracetam are as listed previously, notably somnolence, asthenia, and behavior disturbances

(especially hostility and nervousness). Please see Appendix 3 for the MedDRA codes for these AE of clinical interest.

A listing of AEs will also be provided.

7.10. Clinical Laboratory Tests

Figures of the mean change from screening (+/- Standard Error) values in continuous hematology, urinalysis and serum chemistry laboratory parameters will be presented by visit. The observed and change from baseline values of lab parameters will also be summarized by visit. For calculation, the signs "<" or ">" will be removed and resulting numerical value will be used. The reference ranges for labs from the SAP will be used, not the reference ranges provided from the Covance.

The shift table of pre- vs. post-treatment with classes for below, within, and above normal ranges will be presented.

The number and percentage of subjects with markedly abnormal (low, high) laboratory hematology, urinalysis/24-hour urine and serum chemistry parameters during the study (from treatment start to 30 days after last dose or the end of treatment visit date, whichever is later) that were not present at baseline will be provided. Appendix 2 presents the markedly abnormal criteria. The conversion factors for 25 Vitamin D, 1, 25 Vitamin D and PTH are also listed.

The laboratory data will be listed. The subjects with any laboratory results outside the reference ranges and the subjects with any markedly abnormal laboratory results will be listed.

7.11. Vital Signs and Physical Examination Findings

At baseline, 3 orthostatic vital signs will be measured 10 min apart and the baseline score will be calculated as the average of 3 scores.

Observed and change from baseline in vital sign parameters (temperature, pulse/heart rate, respiratory rate, and blood pressure [standing and supine]]) will be summarized by visit using descriptive statistics.

The number and percentage of subjects with any clinically important vital sign values during the study will also be summarized by visit. Table 10 presents the criteria for the clinically important values.

Table 10: Clinically Important Vital Sign Values

Parameter	Age group (Years)	Low	High
Systolic Blood Pressure	2-5 yrs	<75	>110
	6-9 yrs	<80	>120
	≥10 yrs	<90	>130
Diastolic Blood Pressure	2-5 yrs	<35	>65
	6-9 yrs	<45	>75
	≥10 yrs	<50	>80
Heart Rate	1-2 yrs	<89	>151
	3-4 yrs	<73	>137
	5-7 yrs	<65	>133
	8-11 yrs	<62	>130
	≥12 yrs	<60	>119
Respiratory Rate	1-3 yrs	<22	>30
	4- 6 yrs	<20	>24
	7-9 yrs	<18	>24
	10-14 yrs	<16	>22
	15-18 yrs	<14	>20
Temperature	All ages	< 35° C (95° F)	≥ 37.5° C (99.5° F)

The vital signs data will be listed. The subjects with any clinically important vital signs data will be listed in addition.

The number and percentage of subjects with abnormal physical examination will be listed and summarized by body system and visit.

7.12. Electrocardiogram

ECG at screening will not be listed.

7.13. Other Safety Parameters

Columbia-Suicide Severity Rating Scale (C-SSRS):

From the C-SSRS, the number and percentage of subjects reporting (1) at least one occurrence of suicidal ideation or behavior, (2) any type of suicidal behavior, and (3) any type of suicidal ideation during the study (from treatment start to 30 days after last dose or the end of treatment visit date, whichever is later) will be summarized.

Tanner Staging:

Observed and change from baseline in Tanner Staging will be listed and summarized by visit using descriptive statistics. Frequency distribution of tanner staging (1 thru 5) will also be summarized by visit.

8. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

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

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

Topiramate and Levetiracetam plasma concentrations will be provided as listings.

8.2. Immune Response

NA

8.3. Pharmacodynamics

NA

8.4. Pharmacokinetic/Pharmacodynamic Relationships

NA

9. HEALTH ECONOMICS

NA

10. APPENDICES

Appendix 1: Cogstate Pediatric Normative Data

Table 1: CogState Pediatric Normative Data for the Detection Task.

	Males			Females		
Age (years)	***N***	***M***	***SD***	***N***	***M***	***SD***
2	–	–	–	–	–	–
3	–	–	–	1	2.9041	–
4	2	2.8775	0.0534	3	2.8581	0.1732
5	4	2.7714	0.1001	10	2.7341	0.0871
6	5	2.6002	0.0717	11	2.8240	0.1660
7	6	2.6733	0.1357	9	2.7294	0.0622
8	4	2.6115	0.1769	6	2.8202	0.1598
9	4	2.5632	0.1146	3	2.5398	0.0714
10	1224	2.5631	0.0870	210	2.5882	0.0882
11	1499	2.5388	0.0826	506	2.5641	0.0899
12	1882	2.5290	0.0842	816	2.5447	0.0831
13	2322	2.5177	0.0851	1076	2.5255	0.0767
14	6551	2.5121	0.0853	3315	2.5252	0.0826
15	6399	2.5086	0.0810	3347	2.5213	0.0821

Note: The primary outcome variable for the Detection task is Reaction Time (Log10 transformation).

Table 2: CogState Pediatric Normative Data for the Identification Task.

	Males			Females		
Age (years)	***N***	***M***	***SD***	***N***	***M***	***SD***
2	–	–	–	–	–	–
3	–	–	–	1	3.1028	–
4	2	3.0312	0.0142	3	3.1244	0.0795
5	4	2.9061	0.0266	10	2.9546	0.1075
6	5	2.9199	0.0931	11	2.9938	0.1276
7	6	2.9238	0.1067	9	2.9310	0.0849
8	4	2.8885	0.1575	6	2.9726	0.1053
9	4	2.7421	0.0453	3	2.7632	0.0634
10	1198	2.7637	0.0759	203	2.7796	0.0735
11	1456	2.7323	0.0739	499	2.7453	0.0727
12	1823	2.7163	0.0712	811	2.7186	0.0726
13	2279	2.7007	0.0725	1073	2.6973	0.0711
14	6470	2.6889	0.0731	3300	2.6903	0.0719
15	6324	2.6809	0.0700	3335	2.6800	0.0717

Note: The primary outcome variable for the Identification task is Reaction Time (Log10 transformation).

Table 3: CogState Pediatric Normative Data for the One Card Learning Task.

	Males			Females		
Age (years)	***N***	***M***	***SD***	***N***	***M***	***SD***
6	5	1.0120	0.1845	11	1.0029	0.1441
7	6	0.9715	0.1175	9	0.9300	0.1616
8	4	1.1346	0.0765	6	0.9942	0.1889
9	4	1.0406	0.0376	3	0.9863	0.1306
10	1147	0.9639	0.0880	201	0.9636	0.0910
11	1449	0.9646	0.0889	485	0.9650	0.0892
12	1837	0.9719	0.0889	807	0.9692	0.0875
13	2249	0.9722	0.0858	1053	0.9767	0.0874
14	6435	0.9715	0.0870	3347	0.9679	0.0858
15	6559	0.9739	0.0868	3434	0.9718	0.0854

Note: The primary outcome variable for the One Card Learning task is Accuracy (arcsine square-root transformation).

Table 4: CogState Pediatric Normative Data for the One Back Task.

	Males			Females		
Age (years)	***N***	***M***	***SD***	***N***	***M***	***SD***
6	5	3.0924	0.0965	11	3.1386	0.1728
7	6	3.0799	0.0686	9	3.0789	0.0926
8	4	2.9574	0.0691	6	3.1290	0.1488
9	4	2.9524	0.0589	3	2.9646	0.1824
10	1278	2.9597	0.0984	218	2.9840	0.0990
11	1576	2.9225	0.0958	548	2.9405	0.0962
12	1973	2.8977	0.0962	879	2.9139	0.0972
13	2437	2.8824	0.0945	1130	2.8931	0.0938
14	7000	2.8673	0.0935	3604	2.8851	0.0930
15	7061	2.8547	0.0926	3663	2.8716	0.0952

Note: The primary outcome variable for the One Back task is Reaction Time (Log10 transformation).

Table 5: CogState Pediatric Normative Data for the Groton Maze Learning Test.

	Males			Females		
Age (years)	***N***	***M***	***SD***	***N***	***M***	***SD***
6	–	–	–	2	63.5000	16.2635
7	1	102.0000	–	–	–	–
8	–	–	–	1	68.0000	–
9	3	64.6667	24.0069	1	27.0000	–
10	20	73.8500	31.0251	6	67.3333	25.5943
11	14	67.6429	22.4828	12	64.1667	14.9595
12	20	62.9500	18.9667	6	61.0000	14.0855
13	10	53.2000	19.0660	11	65.0000	15.7861
14	5	61.6000	16.7422	2	46.0000	19.7990
15	–	–	–	1	39.0000	–

Note: The primary outcome variable for the Groton Maze Learning Test is Total Errors.

Appendix 2: Markedly Abnormal Laboratory Parameter Values

Chemistry

Laboratory Value (SI Unit)	Lower Limit of Normal (LLN) Range	Upper Limit of Normal (ULN) Range	DNP Recommended Markedly Abnormal: Low	DNP Recommended Markedly Abnormal: High
Alanine Amino Transferase – ALT (SGPT) (U/L)	1	30	NA	≥ 3 X ULN, OR ≥ 5 X ULN, OR ≥ 10 X ULN
Aspartate Amino Transferase - AST (SGOT) (U/L)	0	35	NA	≥ 3 X ULN, OR ≥ 5 X ULN, OR ≥ 10 X ULN
Albumin (g/L)	<5 years: 29 ≥5 years: 31	<5 years: 58 ≥5 years: 54	<5 years: ≤ 20 ≥5 years: ≤ 25	<5 years: ≥ 65 ≥5 years: ≥ 60
Alkaline Phosphatase (U/L)	*Females:* 2-10 years: 100 11-17 years: 100 ≥18 years: 30 *Males:* 2-10 years: 100 11-17 years: 100 ≥18 years: 30	*Females:* 2-10 years: 320 11-17 years: 320 ≥18 years: 120 *Males:* 2-10 years: 320 11-17 years: 390 ≥18 years: 120	NA	> 3 X ULN
Ammonia (umol/L)	≤18 years: 21 >18 years: 0	≤18 years: 50 >18 years: 35.7	NA	≥ 1.5 X ULN
Bicarbonate/			Value < 17, OR	

Laboratory Value (SI Unit)	Lower Limit of Normal (LLN) Range	Upper Limit of Normal (ULN) Range	DNP Recommended Markedly Abnormal: Low	DNP Recommended Markedly Abnormal: High
Carbon Dioxide (CO_2) (mmol/L)	20	26	(Value <17 and decrease from pre-treatment baseline >5 when pre-treatment baseline ≥ 20)	≥ 31
Bilirubin – Total (umol/L)	1.7	20.5	NA	≥ 41
Blood Urea Nitrogen (BUN) (mmol/L)	2.5	7.9	NA	≥ 16
Calcium (mmol/L)	2	2.6	≤ 1.7	≥ 3
Chloride (mmol/L)	96	109	NA	≥ 112 OR ≥ 115
Total Cholesterol (mmol/L)	<18 years: 0 ≥18 years: 0	<18 years: 5.18 ≥18 years: 6.2	NA	≥ 1.2 X ULN
Creatinine (umol/L)	2-12 years: 27 13-17 years: 44 ≥18 years: *Males* 53 *Females*	2-12 years: 62 13-17 years: 88 ≥18 years: *Males* 115 *Females*	NA	≥ 1.6 X ULN

	44	106		
Creatine Kinase (CK) (U/L) – *collected only in TOPMAT-MIG-3006*	*Females:* 0-3 years: 18 4-6 years: 18 7-9 years: 18 10-12 years: 18 13-15 years: 18 16-17 years: 18 ≥18 years: 18 *Males:* 0-3 years: 18 4-6 years: 18 7-9 years: 18 10-12 years: 18 13-15 years: 18 16-17 years: 18 ≥18 years: 18	*Females:* 0-3 years: 134 4-6 years: 147 8-9 years: 295 10-12 years: 184 13-15 years: 187 16-17 years: 169 ≥18 years: 169 *Males:* 0-3 years: 163 4-6 years: 158 7-9 years: 354 10-12 years: 363 13-15 years: 363 16-17 years: 408 ≥18 years: 198	NA	≥1.6 X ULN
G-Glutamyl Transferase(GGT)	<18 years: 0	<18 years: 23	NA	≥3 X ULN
Glucose (mmol/L)	<16 years: 3.3 ≥16 years: 3.9	<16 years: 5.8 ≥16 years: 6.4	≤0.8 X LLN (e.g., ≤2.6 for ≤ 16 years and ≤ 3.1 for > 16 years	≥1.2 X ULN (e.g., ≥7.0 for ≤16 years and ≥7.7 for ≥ 16 years

Phosphorus Inorg. (mmol/L)	<18 years: 1.03 ≥18 years: 0.87	<18 years: 2.10 ≥18 years: 1.45	< 0.8 X LLN	> 1.4 X ULN
Lactate Dehydrogenase (U/L)	<18 years: 150 ≥18 years: 0	<18 years: 300 ≥18 years: 220	NA	> 2 X ULN
Potassium (mmol/L)	3.5	5	≤ 3.0	≥ 5.7
Sodium(mmol/L)	135	148	≤ 127	≥ 158
Total Protein (g/L)	<6 years: 49 ≥6 years: 60	<6 years: 81 ≥6 years: 80	≤ 0.7 X LLN	≥ 1.25 X ULN
Triglycerides (mmol/L)	*Females:* 0-5 years: 0.3616 6-11 years: 0.3955 12-15 years: 0.4633 16-19 years: 0.452 *Males:* 0-5 years: 0.339 6-11 years: 0.3503 12-15 years: 0.4068 16-19 years: 0.452	*Females:* 0-5 years: 1.1187 6-11 years: 1.2882 12-15 years: 1.5594 16-19 years: 1.4464 *Males:* 0-5 years: 0.9718 6-11 years: 1.2204 12-15 years: 1.5594 16-19 years: 1.8419	NA	> 1.6 X ULN
Uric Acid (umol/L)	140	380	≤ 80	≥ 570

Magnesium	*Females:* 1-3 years: 0.7 4-6 years: 0.7 7-12 years: 0.7 13-15 years: 0.66 16-18 years: 0.62 *Males:* 1-3 years: 0.7 4-6 years: 0.7 7-12 years: 0.7 13-15 years: 0.66 16-18 years: 0.62	*Females:* 1-3 years: 0.98 4-6 years: 0.90 7-12 years: 0.90 13-15 years: 0.94 16-18 years: 0.90 *Males:* 1-3 years: 0.98 4-6 years: 0.98 7-12 years: 0.90 13-15 years: 0.94 16-18 years: 0.90	<0.5	>2

In addition, the MAL low and high for additional parameters will be as follows:

Parameter	MAL low	MAL high
25 Vitamin D (ng/ml)	<20	>55
1, 25 D (pg/ml)	<15	>90
IGF-1 (nmol/L)	2-8: <6	>50
	9-10: <8	>65
	11-12: <15	>100
	13-16: <20	>140
PTH (pg/mL)	2-7: <40	>350
	8-10: <50	>490
	11-12: <70	>750
	13-16: <100	>1100

The conversion factors for 25 Vitamin D, 1, 25 Vitamin D and PTH are listed below.

Parameter	Units	Conversion factor
25 Vitamin D	nmol/L to ng/mL	0.4
1, 25 Vitamin D	Pmol/L to pg/ml	1.355
PTH	Pmol/L to pg/mL	9.434

Hematology

Laboratory Value (SI Unit)	Lower Limit of Normal (LLN) Range	Upper Limit of Normal (ULN) Range	DNP Recommended Markedly Abnormal: Low	DNP Recommended Markedly Abnormal: High
Hemoglobin (g/L)	*Females:* 1-4 years: 109 5-10 years: 119 11-17 years: 119 ≥18 years: 119 *Males:* 1-4 years: 109 5-10 years: 119 11-17 years: 127 ≥18 years: 132	*Females:* 1-4 years: 150 5-10 years: 150 11-17 years: 150 ≥18 years: 155 *Males:* 1-4 years: 150 5-10 years: 150 11-17 years: 170 ≥18 years: 177	≤ 90	≥ 180

Hematocrit (proportion of 1.0)	*Females:* 1-4 years: 0.31 5-10 years: 0.35 11-17 years: 0.34 ≥18 years: 0.35 *Males:* 1-4 years: 0.31 5-10 years: 0.35 11-17 years: 0.37 ≥18 years: 0.40	*Females:* 1-4 years: 0.44 5-10 years: 0.44 11-17 years: 0.44 ≥18 years: 0.47 *Males:* 1-4 years: 0.44 5-10 years: 0.44 11-17 years: 0.48 ≥18 years: 0.52	≤ 0.85 X LLN	≥ 1.15 X ULN
RBC – Total (10E12/L)	*Females:* 1-4 years: 3.8 5-10 years: 4.1 11-17 years: 3.9 ≥18 years: 4.2 *Males:* 1-4 years: 3.8 5-10 years: 4.3 11-17 years: 4.3 ≥18 years: 4.5	*Females:* 1-4 years: 5.2 5-10 years: 5.2 11-17 years: 5.1 ≥18 years: 5.4 *Males:* 1-4 years: 5.5 5-10 years: 5.2 11-17 years: 5.6 ≥18 years: 6.2	≤ 0.85 X LLN	≥ 1.15 X ULN

WBC – Total (10E9/L)	2-5 years: 5 6-17 years: 4.5 ≥18 years: 4.5	2-5 years: 15.5 6-17 years: 13.5 ≥18 years: 11	< 0.85 X LLN	> 1.15 X ULN
Neutrophils – WBC Differential Count (Proportion of 1)	0.38	0.80	≤ 0.15	≥ 0.90
Lymphocytes – WBC Differential Count (Proportion of 1)	0.15	0.40	≤ 0.10	≥ 0.60
Monocytes – WBC Differential Count (Proportion of 1)	0	0.13	NA	≥ 0.20
Eosinophils – WBC Differential Count (Proportion of 1)	0	0.08	NA	≥ 0.10
Basophils – WBC Differential Count (Proportion of 1)	0	0.02	NA	≥ 0.06
Platelet Count (x10E9/L)	150	350	≤ 0.75 X LLN	≥ 1.3 X ULN

11. URINALYSIS

Laboratory Value (SI Unit)	Lower Limit of Normal (LLN) Range	Upper Limit of Normal (ULN) Range	Markedly Abnormal: Low	Markedly Abnormal: High
PH	4.5	8	≤4	≥8
Specific Gravity	1.007	1.03	≤1.001	≥1.035

Appendix 3: AE of clinical interest

AETERM	AEBODSYS in MedDRA 22.0	AEDECOD (PT) In MedDRA 22.1
5'nucleotidase increased	Investigations	5'nucleotidase increased
Abulia	Psychiatric disorders	Abulia
Accommodation disorder	Eye disorders	Accommodation disorder
Acidosis	Metabolism and nutrition disorders	Acidosis
Acidosis hyperchloraemic	Metabolism and nutrition disorders	Acidosis hyperchloraemic
Acquired epidermolysis bullosa	Skin and subcutaneous tissue disorders	Acquired epidermolysis bullosa
Acquired pigmented retinopathy	Injury, poisoning and procedural complications	Acquired pigmented retinopathy
Activation syndrome	Psychiatric disorders	Activation syndrome
Acute generalised exanthematous pustulosis	Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
Acute hepatic failure	Hepatobiliary disorders	Acute hepatic failure
Renal failure acute	Renal and urinary disorders	Acute kidney injury
Adjustment disorder with anxiety	Psychiatric disorders	Adjustment disorder with anxiety
Adjustment disorder with depressed mood	Psychiatric disorders	Adjustment disorder with depressed mood
Adjustment disorder with mixed anxiety and depressed mood	Psychiatric disorders	Adjustment disorder with mixed anxiety and depressed mood
Adjustment disorder with mixed anxiety and depressed mood	Psychiatric disorders	Adjustment disorder with mixed anxiety and depressed mood
Affect lability	Psychiatric disorders	Affect lability
Agitated depression	Psychiatric disorders	Agitated depression
Agitation	Psychiatric disorders	Agitation
Alanine aminotransferase abnormal	Investigations	Alanine aminotransferase abnormal
Alanine aminotransferase increased	Investigations	Alanine aminotransferase increased
Albumin urine present	Investigations	Albumin urine present
Alpha 1 foetoprotein abnormal	Investigations	Alpha 1 foetoprotein abnormal
Alpha 1 foetoprotein increased	Investigations	Alpha 1 foetoprotein increased

Alpha 1 globulin increased	**Investigations**	**Alpha 1 globulin increased**
Alpha 2 globulin increased	**Investigations**	**Alpha 2 globulin increased**
Alpha globulin increased	**Investigations**	**Alpha globulin increased**
Alpha-2 macroglobulin increased	**Investigations**	**Alpha-2 macroglobulin increased**
Altered state of consciousness	**Nervous system disorders**	**Altered state of consciousness**
Altered visual depth perception	**Eye disorders**	**Altered visual depth perception**
Amaurosis	**Eye disorders**	**Amaurosis**
Amaurosis fugax	**Eye disorders**	**Amaurosis fugax**
Ammonia abnormal	**Investigations**	**Ammonia abnormal**
Ammonia abnormal	**Investigations**	**Ammonia abnormal**
Ammonia increased	**Investigations**	**Ammonia increased**
Ammonia increased	**Investigations**	**Ammonia increased**
Amnesia	**Nervous system disorders**	**Amnesia**
Global amnesia	**Nervous system disorders**	**Amnesia**
Angle closure glaucoma	**Eye disorders**	**Angle closure glaucoma**
Anhedonia	**Psychiatric disorders**	**Anhedonia**
Anhidrosis	**Skin and subcutaneous tissue disorders**	**Anhidrosis**
Anorexia and bulimia syndrome	**Psychiatric disorders**	**Anorexia and bulimia syndrome**
Anorexia and bulimia syndrome	**Psychiatric disorders**	**Anorexia and bulimia syndrome**
Anorexia nervosa	**Psychiatric disorders**	**Anorexia nervosa**
Anorexia nervosa	**Psychiatric disorders**	**Anorexia nervosa**
Anterograde amnesia	**Nervous system disorders**	**Anterograde amnesia**
Anticipatory anxiety	**Psychiatric disorders**	**Anticipatory anxiety**
Antidepressant therapy	**Surgical and medical procedures**	**Antidepressant therapy**
Antimetropia	**Eye disorders**	**Antimetropia**
Anxiety	**Psychiatric disorders**	**Anxiety**
Anxiety disorder	**Psychiatric disorders**	**Anxiety disorder**
Apathy	**Psychiatric disorders**	**Apathy**
Dysphasia	**Nervous system disorders**	**Aphasia**
Aphonia psychogenic	**Nervous system disorders**	**Aphonia psychogenic**
Apocrine miliaria	**Skin and subcutaneous tissue disorders**	**Apocrine miliaria**

Apraxia	**Nervous system disorders**	**Apraxia**
Ascites	**Gastrointestinal disorders**	**Ascites**
Aspartate aminotransferase abnormal	**Investigations**	**Aspartate aminotransferase abnormal**
Aspartate aminotransferase increased	**Investigations**	**Aspartate aminotransferase increased**
Asterixis	**Nervous system disorders**	**Asterixis**
Asterixis	**Nervous system disorders**	**Asterixis**
Asthenia	**General disorders and administration site conditions**	**Asthenia**
Astigmatism	**Eye disorders**	**Astigmatism**
Attention deficit/hyperactivity disorder	**Psychiatric disorders**	**Attention deficit/hyperactivity disorder**
Atypical attention deficit syndrome	**Psychiatric disorders**	**Atypical attention deficit syndrome**
Autoimmune hepatitis	**Hepatobiliary disorders**	**Autoimmune hepatitis**
Beta 2 microglobulin increased	**Investigations**	**Beta 2 microglobulin increased**
Beta globulin increased	**Investigations**	**Beta globulin increased**
Bile duct obstruction	**Hepatobiliary disorders**	**Bile duct obstruction**
Bile duct pressure increased	**Investigations**	**Bile duct pressure increased**
Bile duct stenosis	**Hepatobiliary disorders**	**Bile duct stenosis**
Bile duct stent insertion	**Surgical and medical procedures**	**Bile duct stent insertion**
Bile output abnormal	**Investigations**	**Bile output abnormal**
Bile output decreased	**Investigations**	**Bile output decreased**
Biliary cirrhosis	**Hepatobiliary disorders**	**Biliary cirrhosis**
Biliary dyskinesia	**Hepatobiliary disorders**	**Biliary dyskinesia**
Biliary fibrosis	**Hepatobiliary disorders**	**Biliary fibrosis**
Bilirubin conjugated abnormal	**Investigations**	**Bilirubin conjugated abnormal**
Bilirubin conjugated increased	**Investigations**	**Bilirubin conjugated increased**
Bilirubin excretion disorder	**Hepatobiliary disorders**	**Bilirubin excretion disorder**
Bilirubinuria	**Renal and urinary disorders**	**Bilirubinuria**
Biopsy liver abnormal	**Investigations**	**Biopsy liver abnormal**

Blepharospasm	**Eye disorders**	**Blepharospasm**
Blindness	**Eye disorders**	**Blindness**
Blindness cortical	**Eye disorders**	**Blindness cortical**
Blindness day	**Eye disorders**	**Blindness day**
Blindness transient	**Eye disorders**	**Blindness transient**
Blindness traumatic	**Injury, poisoning and procedural complications**	**Blindness traumatic**
Blindness unilateral	**Eye disorders**	**Blindness unilateral**
Blister	**Skin and subcutaneous tissue disorders**	**Blister**
Blood alkaline phosphatase abnormal	**Investigations**	**Blood alkaline phosphatase abnormal**
Blood alkaline phosphatase increased	**Investigations**	**Blood alkaline phosphatase increased**
Blood bicarbonate abnormal	**Investigations**	**Blood bicarbonate abnormal**
Blood bicarbonate decreased	**Investigations**	**Blood bicarbonate decreased**
Blood bilirubin abnormal	**Investigations**	**Blood bilirubin abnormal**
Blood bilirubin increased	**Investigations**	**Blood bilirubin increased**
Blood bilirubin unconjugated increased	**Investigations**	**Blood bilirubin unconjugated increased**
Blood cholinesterase abnormal	**Investigations**	**Blood cholinesterase abnormal**
Blood cholinesterase decreased	**Investigations**	**Blood cholinesterase decreased**
Blood urine	**Investigations**	**Blood urine**
Blood urine present	**Investigations**	**Blood urine present**
Blunted affect	**Psychiatric disorders**	**Blunted affect**
Body height abnormal	**Investigations**	**Body height abnormal**
Body height below normal	**Investigations**	**Body height below normal**
Body height decreased	**Investigations**	**Body height decreased**
Body mass index decreased	**Investigations**	**Body mass index decreased**
Body temperature decreased	**Investigations**	**Body temperature decreased**
Body temperature increased	**Investigations**	**Body temperature increased**
Bone development abnormal	**Musculoskeletal and connective tissue disorders**	**Bone development abnormal**
Bone development abnormal	**Musculoskeletal and connective tissue disorders**	**Bone development abnormal**
Bone disorder	**Musculoskeletal and connective tissue disorders**	**Bone disorder**
Bone disorder	**Musculoskeletal and connective tissue disorders**	**Bone disorder**

Bone formation decreased	**Musculoskeletal and connective tissue disorders**	**Bone formation decreased**
Bone metabolism disorder	**Musculoskeletal and connective tissue disorders**	**Bone metabolism disorder**
Bone pain	**Musculoskeletal and connective tissue disorders**	**Bone pain**
Borderline glaucoma	**Eye disorders**	**Borderline glaucoma**
Borderline mental impairment	**Nervous system disorders**	**Borderline mental impairment**
Bradyphrenia	**Psychiatric disorders**	**Bradyphrenia**
Bromosulphthalein test abnormal	**Investigations**	**Bromosulphthalein test abnormal**
Budd-Chiari syndrome	**Hepatobiliary disorders**	**Budd-Chiari syndrome**
Cachexia	**Metabolism and nutrition disorders**	**Cachexia**
Calculus bladder	**Renal and urinary disorders**	**Calculus bladder**
Calculus bladder	**Renal and urinary disorders**	**Calculus bladder**
Calculus prostatic	**Reproductive system and breast disorders**	**Calculus prostatic**
Calculus prostatic	**Reproductive system and breast disorders**	**Calculus prostatic**
Calculus ureteric	**Renal and urinary disorders**	**Ureterolithiasis**
Calculus urethral	**Renal and urinary disorders**	**Calculus urethral**
Calculus urinary	**Renal and urinary disorders**	**Calculus urinary**
Carbon dioxide decreased	**Investigations**	**Carbon dioxide decreased**
Cardiac arrest	**Cardiac disorders**	**Cardiac arrest**
Cardiac death	**General disorders and administration site conditions**	**Cardiac death**
Cardiac failure	**Cardiac disorders**	**Cardiac failure**
Cardiac failure acute	**Cardiac disorders**	**Cardiac failure acute**
Cardiac failure chronic	**Cardiac disorders**	**Cardiac failure chronic**
Cardiac failure congestive	**Cardiac disorders**	**Cardiac failure congestive**
Cardiac output decreased	**Investigations**	**Cardiac output decreased**
Cardiac ventriculogram abnormal	**Investigations**	**Cardiac ventriculogram abnormal**

Cardiac ventriculogram left abnormal	**Investigations**	**Cardiac ventriculogram left abnormal**
Cells in urine	**Investigations**	**Cells in urine**
Change in sustained attention	**Psychiatric disorders**	**Change in sustained attention**
Charles Bonnet syndrome	**Eye disorders**	**Charles Bonnet syndrome**
Childhood disintegrative disorder	**Psychiatric disorders**	**Child-Pugh-Turcotte score increased**
Child-Pugh-Turcotte score increased	**Investigations**	
Chills	**General disorders and administration site conditions**	**Chills**
Chloropsia	**Eye disorders**	**Chloropsia**
Cholaemia	**Hepatobiliary disorders**	**Cholaemia**
Cholelithiasis	**Hepatobiliary disorders**	**Cholelithiasis**
Cholelithiasis obstructive	**Hepatobiliary disorders**	**Cholelithiasis obstructive**
Cholelithotomy	**Surgical and medical procedures**	**Cholelithotomy**
Cholestasis	**Hepatobiliary disorders**	**Cholestasis**
Cholestatic liver injury	**Hepatobiliary disorders**	**Cholestatic liver injury**
Cholestatic liver injury	**Hepatobiliary disorders**	**Cholestatic liver injury**
Cholestatic pruritus	**Skin and subcutaneous tissue disorders**	**Cholestatic pruritus**
Chorioretinitis	**Infections and infestations**	**Chorioretinitis**
Choroid tubercles	**Infections and infestations**	**Choroid tubercles**
Choroiditis	**Eye disorders**	**Choroiditis**
Urine colour abnormal	**Renal and urinary disorders**	**Chromaturia**
Chronic fatigue syndrome	**General disorders and administration site conditions**	**Chronic fatigue syndrome**
Chronic hepatic failure	**Hepatobiliary disorders**	**Chronic hepatic failure**
Chronic hepatitis	**Hepatobiliary disorders**	**Chronic hepatitis**
Ciliary muscle spasm	**Eye disorders**	**Ciliary muscle spasm**
Circumstantiality	**Psychiatric disorders**	**Circumstantiality**

Clang associations	Psychiatric disorders	Clang associations
Cognitive disorder	Nervous system disorders	Cognitive disorder
Cold sweat	Skin and subcutaneous tissue disorders	Cold sweat
Coma	Nervous system disorders	Coma
Coma hepatic	Nervous system disorders	Coma hepatic
Communication disorder	Psychiatric disorders	Communication disorder
Completed suicide	Psychiatric disorders	Completed suicide
Confabulation	Psychiatric disorders	Confabulation
Confusional arousal	Psychiatric disorders	Confusional arousal
Confusional state	Psychiatric disorders	Confusional state
Confusional state	Psychiatric disorders	Confusional state
Conjunctival ulcer	Eye disorders	Conjunctival ulcer
Conjunctivitis	Infections and infestations	Conjunctivitis
Consciousness fluctuating	Nervous system disorders	Consciousness fluctuating
Constricted affect	Psychiatric disorders	Constricted affect
Coprolalia	Psychiatric disorders	Coprolalia
Corneal deposits	Eye disorders	Corneal deposits
Corneal exfoliation	Eye disorders	Corneal exfoliation
Corneal oedema	Eye disorders	Corneal oedema
Corneal opacity	Eye disorders	Corneal opacity
Corneal perforation	Eye disorders	Corneal perforation
Creatine urine abnormal	Investigations	Creatine urine abnormal
Creatine urine decreased	Investigations	Creatine urine decreased
Creatine urine increased	Investigations	Creatine urine increased
Creatinine urine decreased	Investigations	Creatinine urine decreased
Creatinine urine increased	Investigations	Creatinine urine increased
Crocodile tears syndrome	Nervous system disorders	Crocodile tears syndrome
Crying	General disorders and administration site conditions	Crying
Cryptogenic cirrhosis	Hepatobiliary disorders	Cryptogenic cirrhosis
Crystal urine	Investigations	Crystal urine
Crystal urine present	Investigations	Crystal urine present
Cyanopsia	Eye disorders	Cyanopsia
Cycloplegia	Eye disorders	Cycloplegia
Cysteine urine present	Investigations	Cysteine urine present
Cystine urine present	Investigations	Cystine urine present

Daydreaming	**Psychiatric disorders**	**Daydreaming**
Deaf mutism	**Congenital, familial and genetic disorders**	**Deaf mutism**
Decreased activity	**General disorders and administration site conditions**	**Decreased activity**
Anorexia	**Metabolism and nutrition disorders**	**Decreased appetite**
Anorexia	**Metabolism and nutrition disorders**	**Decreased appetite**
Decreased interest	**Psychiatric disorders**	**Decreased interest**
Dehydration	**Metabolism and nutrition disorders**	**Dehydration**
Delirium	**Psychiatric disorders**	**Delirium**
Depressed level of consciousness	**Nervous system disorders**	**Depressed level of consciousness**
Depressed mood	**Psychiatric disorders**	**Depressed mood**
Depression	**Psychiatric disorders**	**Depression**
Depression postoperative	**Injury, poisoning and procedural complications**	**Depression postoperative**
Depression suicidal	**Psychiatric disorders**	**Depression suicidal**
Depressive symptom	**Psychiatric disorders**	**Depressive symptom**
Derailment	**Psychiatric disorders**	**Derailment**
Dermatitis bullous	**Skin and subcutaneous tissue disorders**	**Dermatitis bullous**
Dermatitis exfoliative	**Skin and subcutaneous tissue disorders**	**Dermatitis exfoliative**
Dermatitis exfoliative generalised	**Skin and subcutaneous tissue disorders**	**Dermatitis exfoliative generalised**
Detachment of retinal pigment epithelium	**Eye disorders**	**Detachment of retinal pigment epithelium**
Developmental coordination disorder	**Nervous system disorders**	**Developmental coordination disorder**
Developmental delay	**General disorders and administration site conditions**	**Developmental delay**
Diplopia	**Eye disorders**	**Diplopia**
Disorientation	**Psychiatric disorders**	**Disorientation**
Disorientation	**Psychiatric disorders**	**Disorientation**
Dissociative amnesia	**Psychiatric disorders**	**Dissociative amnesia**
Distractibility	**Psychiatric disorders**	**Distractibility**

Disturbance in attention	**Nervous system disorders**	**Disturbance in attention**
Disturbance in attention	**Nervous system disorders**	**Disturbance in attention**
Drug eruption	**Skin and subcutaneous tissue disorders**	**Drug eruption**
Drug rash with eosinophilia and systemic symptoms	**Skin and subcutaneous tissue disorders**	**Drug reaction with eosinophilia and systemic symptoms**
Dry eye	**Eye disorders**	**Dry eye**
Keratoconjunctivitis sicca	**Eye disorders**	**Dry eye**
Keratoconjunctivitis sicca	**Eye disorders**	**Dry eye**
Dry skin	**Skin and subcutaneous tissue disorders**	**Dry skin**
Duodenal varices	**Gastrointestinal disorders**	**Duodenal varices**
Dwarfism	**Musculoskeletal and connective tissue disorders**	**Dwarfism**
Dysarthria	**Nervous system disorders**	**Dysarthria**
Dysgraphia	**Nervous system disorders**	**Dysgraphia**
Dyshidrosis	**Skin and subcutaneous tissue disorders**	**Dyshidrotic eczema**
Dyshidrosis	**Skin and subcutaneous tissue disorders**	**Dyshidrotic eczema**
Dyslalia	**Nervous system disorders**	**Dyslalia**
Dysmetropsia	**Eye disorders**	**Dysmetropsia**
Dysphemia	**Psychiatric disorders**	**Dysphemia**
Dysphonia	**Respiratory, thoracic and mediastinal disorders**	**Dysphonia**
Dysphonia psychogenic	**Nervous system disorders**	**Dysphonia psychogenic**
Dysphoria	**Psychiatric disorders**	**Dysphoria**
Dysprosody	**Nervous system disorders**	**Dysprosody**
Dyssomnia	**Psychiatric disorders**	**Dyssomnia**
Dysthymic disorder	**Psychiatric disorders**	**Persistent depressive disorder**
Echolalia	**Psychiatric disorders**	**Echolalia**

Electric shock	**Injury, poisoning and procedural complications**	**Electric shock**
Electroconvulsive therapy	**Surgical and medical procedures**	**Electroconvulsive therapy**
Electroencephalogram abnormal	**Investigations**	**Electroencephalogram abnormal**
Emotional distress	**Psychiatric disorders**	**Emotional distress**
Encephalopathy	**Nervous system disorders**	**Encephalopathy**
Epidermal necrosis	**Skin and subcutaneous tissue disorders**	**Epidermal necrosis**
Epidermolysis	**Congenital, familial and genetic disorders**	**Epidermolysis**
Epidermolysis bullosa	**Congenital, familial and genetic disorders**	**Epidermolysis bullosa**
Epiphyses delayed fusion	**Musculoskeletal and connective tissue disorders**	**Epiphyses delayed fusion**
Erythema multiforme	**Skin and subcutaneous tissue disorders**	**Erythema multiforme**
Erythropsia	**Eye disorders**	**Erythropsia**
Excessive eye blinking	**Eye disorders**	**Excessive eye blinking**
Exfoliative rash	**Skin and subcutaneous tissue disorders**	**Exfoliative rash**
Eye disorder	**Eye disorders**	**Eye disorder**
Eye pain	**Eye disorders**	**Eye pain**
Eyelid function disorder	**Eye disorders**	**Eyelid function disorder**
Eyelid ptosis	**Eye disorders**	**Eyelid ptosis**
Eyelid retraction	**Eye disorders**	**Eyelid retraction**
Failure to thrive	**Metabolism and nutrition disorders**	**Failure to thrive**
Fanconi syndrome	**Congenital, familial and genetic disorders**	**Fanconi syndrome**
Fanconi syndrome acquired	**Renal and urinary disorders**	**Fanconi syndrome acquired**
Fanconi syndrome acquired	**Renal and urinary disorders**	**Fanconi syndrome acquired**
Fatigue	**General disorders and administration site conditions**	**Fatigue**

Feeling cold	**General disorders and administration site conditions**	**Feeling cold**
Feeling drunk	**General disorders and administration site conditions**	**Feeling drunk**
Feeling guilty	**Psychiatric disorders**	**Feeling guilty**
Feeling hot	**General disorders and administration site conditions**	**Feeling hot**
Feeling of body temperature change	**General disorders and administration site conditions**	**Feeling of body temperature change**
Feeling of despair	**Psychiatric disorders**	**Feeling of despair**
Feelings of worthlessness	**Psychiatric disorders**	**Feelings of worthlessness**
Flight of ideas	**Psychiatric disorders**	**Flight of ideas**
Floppy iris syndrome	**Injury, poisoning and procedural complications**	**Floppy iris syndrome**
Flushing	**Vascular disorders**	**Flushing**
Folliculitis	**Infections and infestations**	**Folliculitis**
Fracture delayed union	**Musculoskeletal and connective tissue disorders**	**Fracture delayed union**
Fracture malunion	**Musculoskeletal and connective tissue disorders**	**Fracture malunion**
Fracture nonunion	**Musculoskeletal and connective tissue disorders**	**Fracture nonunion**
Fundoscopy	**Investigations**	**Fundoscopy**
Fundoscopy abnormal	**Investigations**	**Fundoscopy abnormal**
Galactose elimination capacity test abnormal	**Investigations**	**Galactose elimination capacity test abnormal**
Galactose elimination capacity test decreased	**Investigations**	**Galactose elimination capacity test decreased**
Gallbladder cholesterolosis	**Hepatobiliary disorders**	**Gallbladder cholesterolosis**
Gallbladder disorder	**Hepatobiliary disorders**	**Gallbladder disorder**
Gallbladder enlargement	**Hepatobiliary disorders**	**Gallbladder enlargement**
Gallbladder fistula	**Hepatobiliary disorders**	**Gallbladder fistula**

Gallbladder mucocoele	**Hepatobiliary disorders**	**Gallbladder mucocoele**
Gallbladder necrosis	**Hepatobiliary disorders**	**Gallbladder necrosis**
Gallbladder non-functioning	**Hepatobiliary disorders**	**Gallbladder hypofunction**
Gallbladder obstruction	**Hepatobiliary disorders**	**Gallbladder obstruction**
Gallbladder oedema	**Hepatobiliary disorders**	**Gallbladder oedema**
Gallbladder pain	**Hepatobiliary disorders**	**Biliary colic**
Gamma-glutamyltransferase abnormal	**Investigations**	**Gamma-glutamyltransferase abnormal**
Gamma-glutamyltransferase increased	**Investigations**	**Gamma-glutamyltransferase increased**
Gastric varices	**Gastrointestinal disorders**	**Gastric varices**
Generalised anxiety disorder	**Psychiatric disorders**	**Generalised anxiety disorder**
Genital ulceration	**Reproductive system and breast disorders**	**Genital ulceration**
Gianotti-Crosti syndrome	**Infections and infestations**	**Gianotti-Crosti syndrome**
Glare	**Eye disorders**	**Glare**
Glaucoma	**Eye disorders**	**Glaucoma**
Glaucomatous optic disc atrophy	**Eye disorders**	**Glaucomatous optic disc atrophy**
Globulin urine present	**Investigations**	**Globulin urine present**
Globulins increased	**Investigations**	**Globulins increased**
Glucose urine	**Investigations**	**Glucose urine**
Glucose urine present	**Investigations**	**Glucose urine present**
Glyceric acid urine increased	**Investigations**	**Glyceric acid urine increased**
Gonioscopy	**Investigations**	**Gonioscopy**
Gonioscopy abnormal	**Investigations**	**Gonioscopy abnormal**
Granulomatous liver disease	**Hepatobiliary disorders**	**Granulomatous liver disease**
Growth retardation	**Musculoskeletal and connective tissue disorders**	**Growth retardation**
Guanase increased	**Investigations**	**Guanase increased**
Haematuria	**Renal and urinary disorders**	**Haematuria**
Haemoglobin urine	**Investigations**	**Haemoglobin urine**
Haemoglobin urine present	**Investigations**	**Haemoglobin urine present**
Haemorrhagic ascites	**Gastrointestinal disorders**	**Haemorrhagic ascites**

Haemorrhagic hepatic cyst	**Hepatobiliary disorders**	**Haemorrhagic hepatic cyst**
Halo vision	**Eye disorders**	**Halo vision**
Heat exhaustion	**Injury, poisoning and procedural complications**	**Heat exhaustion**
Heat illness	**Injury, poisoning and procedural complications**	**Heat illness**
Heat oedema	**Injury, poisoning and procedural complications**	**Heat oedema**
Heat stroke	**Injury, poisoning and procedural complications**	**Heat stroke**
Hemianopia	**Nervous system disorders**	**Hemianopia**
Hemianopia heteronymous	**Nervous system disorders**	**Hemianopia heteronymous**
Hemianopia homonymous	**Nervous system disorders**	**Hemianopia homonymous**
Hemiapraxia	**Nervous system disorders**	**Hemiapraxia**
Hepaplastin abnormal	**Investigations**	**Hepaplastin abnormal**
Hepaplastin decreased	**Investigations**	**Hepaplastin decreased**
Hepatic atrophy	**Hepatobiliary disorders**	**Hepatic atrophy**
Hepatic calcification	**Hepatobiliary disorders**	**Hepatic calcification**
Hepatic cirrhosis	**Hepatobiliary disorders**	**Hepatic cirrhosis**
Hepatic congestion	**Hepatobiliary disorders**	**Hepatic congestion**
Hepatic encephalopathy	**Nervous system disorders**	**Hepatic encephalopathy**
Hepatic encephalopathy prophylaxis	**Surgical and medical procedures**	**Hepatic encephalopathy prophylaxis**
Hepatic enzyme abnormal	**Investigations**	**Hepatic enzyme abnormal**
Hepatic enzyme decreased	**Investigations**	**Hepatic enzyme decreased**
Hepatic enzyme increased	**Investigations**	**Hepatic enzyme increased**
Hepatic failure	**Hepatobiliary disorders**	**Hepatic failure**
Hepatic fibrosis	**Hepatobiliary disorders**	**Hepatic fibrosis**
Hepatic function abnormal	**Hepatobiliary disorders**	**Hepatic function abnormal**

Hepatic haemorrhage	**Hepatobiliary disorders**	**Hepatic haemorrhage**
Hepatic hydrothorax	**Respiratory, thoracic and mediastinal disorders**	**Hepatic hydrothorax**
Hepatic infarction	**Hepatobiliary disorders**	**Hepatic infarction**
Hepatic infiltration eosinophilic	**Hepatobiliary disorders**	**Hepatic infiltration eosinophilic**
Hepatic lesion	**Hepatobiliary disorders**	**Hepatic lesion**
Hepatic mass	**Hepatobiliary disorders**	**Hepatic mass**
Hepatic necrosis	**Hepatobiliary disorders**	**Hepatic necrosis**
Hepatic pain	**Hepatobiliary disorders**	**Hepatic pain**
Hepatic steatosis	**Hepatobiliary disorders**	**Hepatic steatosis**
Cytolytic hepatitis	**Hepatobiliary disorders**	**Hepatitis**
Hepatitis	**Hepatobiliary disorders**	**Hepatitis**
Hepatitis acute	**Hepatobiliary disorders**	**Hepatitis B**
Hepatitis fulminant	**Hepatobiliary disorders**	**Hepatitis chronic active**
Hepatitis toxic	**Hepatobiliary disorders**	**Hepatitis toxic**
Hepatobiliary disease	**Hepatobiliary disorders**	**Hepatobiliary disease**
Hepatobiliary scan abnormal	**Investigations**	**Hepatobiliary scan abnormal**
Hepatocellular foamy cell syndrome	**Hepatobiliary disorders**	**Hepatocellular foamy cell syndrome**
Hepatocellular injury	**Hepatobiliary disorders**	**Hepatocellular injury**
Hepatomegaly	**Hepatobiliary disorders**	**Hepatomegaly**
Hepatopulmonary syndrome	**Respiratory, thoracic and mediastinal disorders**	**Hepatopulmonary syndrome**
Hepatorenal failure	**Hepatobiliary disorders**	**Hepatorenal failure**
Hepatorenal syndrome	**Hepatobiliary disorders**	**Hepatorenal syndrome**

Hepatosplenomegaly	**Hepatobiliary disorders**	**Hepatosplenomegaly**
Hepatotoxicity	**Hepatobiliary disorders**	**Hepatotoxicity**
Hidradenitis	**Skin and subcutaneous tissue disorders**	**Hidradenitis**
Hippus	**Eye disorders**	**Hippus**
Holmes-Adie pupil	**Eye disorders**	**Holmes-Adie pupil**
Homocysteine urine	**Investigations**	**Homocysteine urine**
Homocysteine urine present	**Investigations**	**Homocysteine urine present**
Hot flush	**Vascular disorders**	**Hot flush**
Hydrocholecystis	**Hepatobiliary disorders**	**Hydrocholecystis**
Hydronephrosis	**Renal and urinary disorders**	**Hydronephrosis**
Hydronephrosis repair	**Surgical and medical procedures**	**Hydronephrosis repair**
Hyperammonaemia	**Metabolism and nutrition disorders**	**Hyperammonaemia**
Hyperammonaemic encephalopathy	**Nervous system disorders**	**Hyperammonaemic encephalopathy**
Hyperbilirubinaemia	**Hepatobiliary disorders**	**Hyperbilirubinaemia**
Hypercalcaemia	**Metabolism and nutrition disorders**	**Hypercalcaemia**
Hypercalcaemic nephropathy	**Renal and urinary disorders**	**Hypercalcaemic nephropathy**
Hypercalciuria	**Renal and urinary disorders**	**Hypercalciuria**
Hypercholia	**Hepatobiliary disorders**	**Hypercholia**
Hypergammaglobulinaemia	**Blood and lymphatic system disorders**	**Hypergammaglobulinaemia**
Hyperglobulinaemia	**Blood and lymphatic system disorders**	**Hyperglobulinaemia**
Hyperhidrosis	**Skin and subcutaneous tissue disorders**	**Hyperhidrosis**
Hypermetropia	**Eye disorders**	**Hypermetropia**
Hyperplastic cholecystopathy	**Hepatobiliary disorders**	**Hyperplastic cholecystopathy**
Hyperpyrexia	**General disorders and administration site conditions**	**Hyperpyrexia**

Hypersomnia	**Nervous system disorders**	**Hypersomnia**
Hyperthermia	**General disorders and administration site conditions**	**Hyperthermia**
Hyperthermia malignant	**General disorders and administration site conditions**	**Hyperthermia malignant**
Hypertransaminasaemia	**Hepatobiliary disorders**	**Hypertransaminasaemia**
Hyperventilation	**Respiratory, thoracic and mediastinal disorders**	**Hyperventilation**
Hyphaema	**Eye disorders**	**Hyphaema**
Hypoalbuminaemia	**Metabolism and nutrition disorders**	**Hypoalbuminaemia**
Hypohidrosis	**Skin and subcutaneous tissue disorders**	**Hypohidrosis**
Hypophosphataemia	**Metabolism and nutrition disorders**	**Hypophosphataemia**
Hypophosphataemic rickets	**Musculoskeletal and connective tissue disorders**	**Hypophosphataemic osteomalacia**
Hypophosphatasia	**Congenital, familial and genetic disorders**	**Hypophosphatasia**
Hyposomnia	**Psychiatric disorders**	**Hyposomnia**
Hypothermia	**General disorders and administration site conditions**	**Hypothermia**
Icterus index increased	**Investigations**	**Icterus index increased**
Illogical thinking	**Psychiatric disorders**	**Illogical thinking**
Impaired self-care	**General disorders and administration site conditions**	**Impaired self-care**
Incoherent	**Nervous system disorders**	**Incoherent**
Initial insomnia	**Psychiatric disorders**	**Initial insomnia**
Intentional self-injury	**Psychiatric disorders**	**Intentional self-injury**
Intentional self-injury	**Psychiatric disorders**	**Intentional self-injury**
Iridoplegia	**Eye disorders**	**Iridoplegia**
Iritis	**Eye disorders**	**Iritis**
Ischaemic hepatitis	**Hepatobiliary disorders**	**Ischaemic hepatitis**
Jaundice	**Hepatobiliary disorders**	**Jaundice**

Jaundice cholestatic	**Hepatobiliary disorders**	**Jaundice cholestatic**
Jaundice hepatocellular	**Hepatobiliary disorders**	**Jaundice hepatocellular**
Judgement impaired	**Nervous system disorders**	**Judgement impaired**
Kayser-Fleischer ring	**Eye disorders**	**Kayser-Fleischer ring**
Keratitis	**Eye disorders**	**Keratitis**
Kussmaul respiration	**Respiratory, thoracic and mediastinal disorders**	**Kussmaul respiration**
Lack of spontaneous speech	**Psychiatric disorders**	**Lack of spontaneous speech**
Lacrimal disorder	**Eye disorders**	**Lacrimal disorder**
Lacrimation decreased	**Eye disorders**	**Lacrimation decreased**
Lacrimation increased	**Eye disorders**	**Lacrimation increased**
Lactic acidosis	**Metabolism and nutrition disorders**	**Lactic acidosis**
Expressive language disorder	**Nervous system disorders**	**Language disorder**
Mixed receptive-expressive language disorder	**Nervous system disorders**	**Language disorder**
Laurence-Moon-Bardet-Biedl syndrome	**Congenital, familial and genetic disorders**	**Laurence-Moon-Bardet-Biedl syndrome**
Learning disability	**Social circumstances**	**Learning disability**
Learning disorder	**Psychiatric disorders**	**Learning disorder**
Lenticular opacities	**Eye disorders**	**Lenticular opacities**
Lethargy	**Nervous system disorders**	**Lethargy**
Leucine aminopeptidase increased	**Investigations**	**Leucine aminopeptidase increased**
Libido decreased	**Psychiatric disorders**	**Libido decreased**
Libido disorder	**Psychiatric disorders**	**Libido disorder**
Libido increased	**Psychiatric disorders**	**Libido increased**
Lip exfoliation	**Gastrointestinal disorders**	**Lip exfoliation**
Listless	**Psychiatric disorders**	**Listless**
Liver disorder	**Hepatobiliary disorders**	**Liver disorder**
Liver function test abnormal	**Investigations**	**Liver function test abnormal**
Liver induration	**Hepatobiliary disorders**	**Liver induration**
Liver injury	**Hepatobiliary disorders**	**Liver injury**
Liver palpable subcostal	**Investigations**	**Liver palpable**
Liver tenderness	**Hepatobiliary disorders**	**Liver tenderness**

Cluttering	**Psychiatric disorders**	**Logorrhoea**
Loose associations	**Psychiatric disorders**	**Loose associations**
Loss of consciousness	**Nervous system disorders**	**Loss of consciousness**
Loss of libido	**Psychiatric disorders**	**Loss of libido**
Loss of visual contrast sensitivity	**Eye disorders**	**Loss of visual contrast sensitivity**
Low cardiac output syndrome	**Cardiac disorders**	**Low cardiac output syndrome**
Lupoid hepatic cirrhosis	**Hepatobiliary disorders**	**Lupoid hepatic cirrhosis**
Macular cyst	**Eye disorders**	**Macular cyst**
Macular degeneration	**Eye disorders**	**Macular degeneration**
Macular hole	**Eye disorders**	**Macular hole**
Macular ischaemia	**Eye disorders**	**Macular ischaemia**
Macular oedema	**Eye disorders**	**Macular oedema**
Macular opacity	**Eye disorders**	**Macular opacity**
Macular pseudohole	**Eye disorders**	**Macular pseudohole**
Macular scar	**Eye disorders**	**Macular scar**
Macular vasospasm	**Eye disorders**	**Macular vasospasm**
Maculopathy	**Eye disorders**	**Maculopathy**
Major depression	**Psychiatric disorders**	**Major depression**
Memory impairment	**Nervous system disorders**	**Memory impairment**
Menopausal depression	**Psychiatric disorders**	**Menopausal depression**
Mental impairment	**Nervous system disorders**	**Mental impairment**
Mental retardation	**Nervous system disorders**	**Intellectual disability**
Metabolic acidosis	**Metabolism and nutrition disorders**	**Metabolic acidosis**
Metamorphopsia	**Eye disorders**	**Metamorphopsia**
Microlithiasis	**General disorders and administration site conditions**	**Lithiasis**
Middle insomnia	**Psychiatric disorders**	**Middle insomnia**
Mikulicz's disease	**Gastrointestinal disorders**	**Mikulicz's disease**
Mikulicz's syndrome	**Gastrointestinal disorders**	**Mikulicz's syndrome**
Mild mental retardation	**Nervous system disorders**	**Intellectual disability**
Milia	**Skin and subcutaneous tissue disorders**	**Milia**

Heat rash	**Skin and subcutaneous tissue disorders**	**Miliaria**
Miosis	**Eye disorders**	**Miosis**
Mitochondrial aspartate aminotransferase increased	**Investigations**	**Mitochondrial aspartate aminotransferase increased**
Mixed hepatocellular cholangiocarcinoma	**Neoplasms benign, malignant and unspecified (incl cysts and polyps)**	**Mixed hepatocellular cholangiocarcinoma**
Mixed liver injury	**Hepatobiliary disorders**	**Mixed liver injury**
Moderate mental retardation	**Nervous system disorders**	**Intellectual disability**
Molar ratio of total branched-chain amino acid to tyrosine	**Investigations**	**Molar ratio of total branched-chain amino acid to tyrosine**
Mood altered	**Psychiatric disorders**	**Mood altered**
Mood swings	**Psychiatric disorders**	**Mood swings**
Morose	**Psychiatric disorders**	**Morose**
Mouth ulceration	**Gastrointestinal disorders**	**Mouth ulceration**
Mucocutaneous ulceration	**Skin and subcutaneous tissue disorders**	**Mucocutaneous ulceration**
Mucosa vesicle	**General disorders and administration site conditions**	**Mucosa vesicle**
Mucosal erosion	**General disorders and administration site conditions**	**Mucosal erosion**
Mucosal exfoliation	**General disorders and administration site conditions**	**Mucosal exfoliation**
Mucosal necrosis	**General disorders and administration site conditions**	**Mucosal necrosis**
Mucosal ulceration	**General disorders and administration site conditions**	**Mucosal ulceration**
Musculoskeletal chest pain	**Musculoskeletal and connective tissue disorders**	**Musculoskeletal chest pain**
Musculoskeletal pain	**Musculoskeletal and connective tissue disorders**	**Musculoskeletal pain**
Mutism	**Psychiatric disorders**	**Mutism**

Mydriasis	**Eye disorders**	**Mydriasis**
Myopia	**Eye disorders**	**Myopia**
Necrotising retinitis	**Eye disorders**	**Necrotising retinitis**
Negative cardiac inotropic effect	**Cardiac disorders**	**Negative cardiac inotropic effect**
Negative thoughts	**Psychiatric disorders**	**Negative thoughts**
Neglect of personal appearance	**Psychiatric disorders**	**Neglect of personal appearance**
Neologism	**Psychiatric disorders**	**Neologism**
Nephrocalcinosis	**Renal and urinary disorders**	**Nephrocalcinosis**
Nephrocalcinosis	**Renal and urinary disorders**	**Nephrocalcinosis**
Nephrolithiasis	**Renal and urinary disorders**	**Nephrolithiasis**
Nephrolithiasis	**Renal and urinary disorders**	**Nephrolithiasis**
Nervousness	**Psychiatric disorders**	**Nervousness**
Neurodevelopmental disorder	**Psychiatric disorders**	**Neurodevelopmental disorder**
Neuroleptic malignant syndrome	**Nervous system disorders**	**Neuroleptic malignant syndrome**
Night blindness	**Eye disorders**	**Night blindness**
Night sweats	**Skin and subcutaneous tissue disorders**	**Night sweats**
Nikolsky's sign	**Skin and subcutaneous tissue disorders**	**Nikolsky's sign**
Nitrite urine	**Investigations**	**Nitrite urine**
Nitrite urine present	**Investigations**	**Nitrite urine present**
Nodular regenerative hyperplasia	**Hepatobiliary disorders**	**Nodular regenerative hyperplasia**
Normal tension glaucoma	**Eye disorders**	**Normal tension glaucoma**
Obsessive rumination	**Psychiatric disorders**	**Obsessive rumination**
Ocular hypertension	**Eye disorders**	**Ocular hypertension**
Ocular icterus	**Eye disorders**	**Ocular icterus**
Oculomucocutaneous syndrome	**Skin and subcutaneous tissue disorders**	**Oculomucocutaneous syndrome**
Oedema due to cardiac disease	**General disorders and administration site conditions**	**Oedema due to cardiac disease**
Oedema due to hepatic disease	**General disorders and administration site conditions**	**Oedema due to hepatic disease**
Oesophageal varices haemorrhage	**Gastrointestinal disorders**	**Oesophageal varices haemorrhage**

Open angle glaucoma	**Eye disorders**	**Open angle glaucoma**
Ophthalmoplegia	**Eye disorders**	**Ophthalmoplegia**
Optic atrophy	**Eye disorders**	**Optic atrophy**
Optic disc disorder	**Eye disorders**	**Optic disc disorder**
Optic disc drusen	**Eye disorders**	**Optic disc drusen**
Optic discs blurred	**Eye disorders**	**Optic discs blurred**
Optic ischaemic neuropathy	**Eye disorders**	**Optic ischaemic neuropathy**
Optic nerve cupping	**Eye disorders**	**Optic nerve cupping**
Optic nerve disorder	**Eye disorders**	**Optic nerve disorder**
Optic nerve infarction	**Eye disorders**	**Optic nerve infarction**
Optic neuritis	**Nervous system disorders**	**Optic neuritis**
Optic neuropathy	**Eye disorders**	**Optic neuropathy**
Oral mucosal exfoliation	**Gastrointestinal disorders**	**Oral mucosal exfoliation**
Oropharyngeal blistering	**Respiratory, thoracic and mediastinal disorders**	**Oropharyngeal blistering**
Oscillopsia	**Eye disorders**	**Oscillopsia**
Osteomalacia	**Musculoskeletal and connective tissue disorders**	**Osteomalacia**
Osteoporosis	**Musculoskeletal and connective tissue disorders**	**Osteoporosis**
Osteoporosis-pseudoglioma syndrome	**Congenital, familial and genetic disorders**	**Osteoporosis-pseudoglioma syndrome**
Osteoporotic fracture	**Musculoskeletal and connective tissue disorders**	**Osteoporotic fracture**
Papilloedema	**Eye disorders**	**Papilloedema**
Paracentesis eye	**Investigations**	**Paracentesis eye**
Paracentesis eye abnormal	**Investigations**	**Paracentesis eye abnormal**
Paralytic lagophthalmos	**Eye disorders**	**Paralytic lagophthalmos**
Paramnesia	**Psychiatric disorders**	**Paramnesia**
Pars plana cyst	**Eye disorders**	**Pars plana cyst**
Malignant myopia	**Eye disorders**	**Pathologic myopia**
Pathological fracture	**Musculoskeletal and connective tissue disorders**	**Pathological fracture**
Pemphigoid	**Skin and subcutaneous tissue disorders**	**Pemphigoid**
Pemphigus	**Skin and subcutaneous tissue disorders**	**Pemphigus**

Penile exfoliation	**Reproductive system and breast disorders**	**Penile exfoliation**
Perihepatic discomfort	**Hepatobiliary disorders**	**Perihepatic discomfort**
Perihepatitis gonococcal	**Infections and infestations**	**Perihepatitis gonococcal**
Perseveration	**Psychiatric disorders**	**Perseveration**
pH urine abnormal	**Investigations**	**pH urine abnormal**
pH urine decreased	**Investigations**	**pH urine decreased**
pH urine increased	**Investigations**	**pH urine increased**
Phonological disorder	**Psychiatric disorders**	**Speech sound disorder**
Photophobia	**Eye disorders**	**Photophobia**
Phosphenes	**Eye disorders**	**Photopsia**
Photopsia	**Eye disorders**	**Photopsia**
Poor quality sleep	**Nervous system disorders**	**Poor quality sleep**
Poor weight gain neonatal	**Pregnancy, puerperium and perinatal conditions**	**Poor weight gain neonatal**
Porcelain gallbladder	**Hepatobiliary disorders**	**Porcelain gallbladder**
Portal hypertension	**Hepatobiliary disorders**	**Portal hypertension**
Portal triaditis	**Hepatobiliary disorders**	**Portal tract inflammation**
Portal vein flow decreased	**Investigations**	**Portal vein flow decreased**
Portal vein pressure increased	**Investigations**	**Portal vein pressure increased**
Portopulmonary hypertension	**Respiratory, thoracic and mediastinal disorders**	**Portopulmonary hypertension**
Postpartum depression	**Psychiatric disorders**	**Perinatal depression**
Poverty of speech	**Psychiatric disorders**	**Poverty of speech**
Poverty of thought content	**Psychiatric disorders**	**Poverty of thought content**
Presbyopia	**Eye disorders**	**Presbyopia**
Pressure of speech	**Psychiatric disorders**	**Pressure of speech**
Profound mental retardation	**Nervous system disorders**	**Intellectual disability**
Protein urine	**Investigations**	**Protein urine**
Protein urine present	**Investigations**	**Protein urine present**
Pseudarthrosis	**Musculoskeletal and connective tissue disorders**	**Pseudarthrosis**
Pseudo-blepharoptosis	**Eye disorders**	**Pseudo-blepharoptosis**
Pseudopapilloedema	**Eye disorders**	**Pseudopapilloedema**
Psychomotor hyperactivity	**Nervous system disorders**	**Psychomotor hyperactivity**

Psychomotor retardation	**Psychiatric disorders**	**Psychomotor retardation**
Psychomotor skills impaired	**Nervous system disorders**	**Psychomotor skills impaired**
Psychosocial support	**Surgical and medical procedures**	**Psychosocial support**
Psychotherapy	**Surgical and medical procedures**	**Psychotherapy**
Pupil fixed	**Eye disorders**	**Pupil fixed**
Pupillary deformity	**Eye disorders**	**Pupillary deformity**
Pupillary disorder	**Eye disorders**	**Pupillary disorder**
Pupillary reflex impaired	**Eye disorders**	**Pupillary reflex impaired**
Pupillotonia	**Eye disorders**	**Pupillotonia**
Pupils unequal	**Eye disorders**	**Pupils unequal**
Pyrexia	**General disorders and administration site conditions**	**Pyrexia**
Rash maculo-papular	**Skin and subcutaneous tissue disorders**	**Rash maculo-papular**
Rash pustular	**Infections and infestations**	**Rash pustular**
Reading disorder	**Psychiatric disorders**	**Reading disorder**
Red blood cells urine	**Investigations**	**Red blood cells urine**
Red blood cells urine positive	**Investigations**	**Red blood cells urine positive**
Refraction disorder	**Eye disorders**	**Refraction disorder**
Renal colic	**Renal and urinary disorders**	**Renal colic**
Renal failure	**Renal and urinary disorders**	**Renal failure**
Renal function test abnormal	**Investigations**	**Renal function test abnormal**
Renal pain	**Renal and urinary disorders**	**Renal pain**
Renal tubular acidosis	**Renal and urinary disorders**	**Renal tubular acidosis**
Repetitive speech	**Nervous system disorders**	**Repetitive speech**
Residual urine volume decreased	**Investigations**	**Residual urine volume decreased**
Residual urine volume increased	**Investigations**	**Residual urine volume increased**
Respiration abnormal	**Respiratory, thoracic and mediastinal disorders**	**Respiration abnormal**
Retinal artery spasm	**Eye disorders**	**Retinal artery spasm**
Retinal artery stenosis	**Eye disorders**	**Retinal artery stenosis**
Retinal cyst	**Eye disorders**	**Retinal cyst**

Retinal degeneration	**Eye disorders**	**Retinal degeneration**
Retinal depigmentation	**Eye disorders**	**Retinal depigmentation**
Retinal deposits	**Eye disorders**	**Retinal deposits**
Retinal detachment	**Eye disorders**	**Retinal detachment**
Retinal disorder	**Eye disorders**	**Retinal disorder**
Retinal dystrophy	**Eye disorders**	**Retinal dystrophy**
Retinal haemorrhage	**Eye disorders**	**Retinal haemorrhage**
Retinal infarction	**Eye disorders**	**Retinal infarction**
Retinal infiltrates	**Eye disorders**	**Retinal infiltrates**
Retinal ischaemia	**Eye disorders**	**Retinal ischaemia**
Retinal oedema	**Eye disorders**	**Retinal oedema**
Retinal pallor	**Eye disorders**	**Retinal pallor**
Retinal pigment epitheliopathy	**Eye disorders**	**Retinal pigment epitheliopathy**
Retinal pigmentation	**Eye disorders**	**Retinal pigmentation**
Retinal scar	**Eye disorders**	**Retinal scar**
Retinal tear	**Eye disorders**	**Retinal tear**
Retinal toxicity	**Eye disorders**	**Retinal toxicity**
Retinal vascular occlusion	**Eye disorders**	**Retinal vascular occlusion**
Retinal vascular thrombosis	**Eye disorders**	**Retinal vascular thrombosis**
Retinal vasculitis	**Eye disorders**	**Retinal vasculitis**
Retinal vein occlusion	**Eye disorders**	**Retinal vein occlusion**
Retinal vein thrombosis	**Eye disorders**	**Retinal vein thrombosis**
Retinitis	**Infections and infestations**	**Retinitis**
Retinogram	**Investigations**	**Retinogram**
Retinogram abnormal	**Investigations**	**Retinogram abnormal**
Retinol binding protein decreased	**Investigations**	**Retinol binding protein decreased**
Retinoschisis	**Eye disorders**	**Retinoschisis**
Retinoschisis congenital	**Congenital, familial and genetic disorders**	**Retinoschisis congenital**
Retrograde amnesia	**Nervous system disorders**	**Retrograde amnesia**
Retrograde portal vein flow	**Hepatobiliary disorders**	**Retrograde portal vein flow**
Reye's syndrome	**Hepatobiliary disorders**	**Reye's syndrome**
Scintillating scotoma	**Eye disorders**	**Scintillating scotoma**
Screaming	**Psychiatric disorders**	**Screaming**
Sedation	**Nervous system disorders**	**Sedation**
Selective mutism	**Psychiatric disorders**	**Selective mutism**
Self esteem decreased	**Psychiatric disorders**	**Self esteem decreased**
Self injurious behaviour	**Psychiatric disorders**	**Intentional self-injury**
Self-injurious ideation	**Psychiatric disorders**	**Self-injurious ideation**

Severe mental retardation	**Nervous system disorders**	**Intellectual disability**
Sicca syndrome	**Musculoskeletal and connective tissue disorders**	**Sjogren's syndrome**
Sjogren's syndrome	**Musculoskeletal and connective tissue disorders**	**Sjogren's syndrome**
Skin erosion	**Skin and subcutaneous tissue disorders**	**Skin erosion**
Skin exfoliation	**Skin and subcutaneous tissue disorders**	**Skin exfoliation**
Skin necrosis	**Skin and subcutaneous tissue disorders**	**Skin necrosis**
Somnolence	**Nervous system disorders**	**Somnolence**
Speech disorder	**Nervous system disorders**	**Speech disorder**
Speech disorder developmental	**Nervous system disorders**	**Speech disorder developmental**
Spider naevus	**Skin and subcutaneous tissue disorders**	**Spider naevus**
Stag horn calculus	**Renal and urinary disorders**	**Stag horn calculus**
Stag horn calculus	**Renal and urinary disorders**	**Stag horn calculus**
Stevens-Johnson syndrome	**Skin and subcutaneous tissue disorders**	**Stevens-Johnson syndrome**
Stomatitis	**Gastrointestinal disorders**	**Stomatitis**
Strabismus	**Eye disorders**	**Strabismus**
Stupor	**Nervous system disorders**	**Stupor**
Subacute hepatic failure	**Hepatobiliary disorders**	**Subacute hepatic failure**
Subacute myelo-opticoneuropathy	**Nervous system disorders**	**Subacute myelo-opticoneuropathy**
Subretinal fibrosis	**Eye disorders**	**Subretinal fibrosis**
Sudden cardiac death	**General disorders and administration site conditions**	**Sudden cardiac death**

Sudden visual loss	**Eye disorders**	**Sudden visual loss**
Suicidal behaviour	**Psychiatric disorders**	**Suicidal behaviour**
Suicidal ideation	**Psychiatric disorders**	**Suicidal ideation**
Suicide attempt	**Psychiatric disorders**	**Suicide attempt**
Sweat discolouration	**Skin and subcutaneous tissue disorders**	**Sweat discolouration**
Sweat gland disorder	**Skin and subcutaneous tissue disorders**	**Sweat gland disorder**
Synostosis	**Musculoskeletal and connective tissue disorders**	**Synostosis**
Taciturnity	**Psychiatric disorders**	**Taciturnity**
Tangentiality	**Psychiatric disorders**	**Tangentiality**
Tear discolouration	**Eye disorders**	**Tear discolouration**
Tearfulness	**Psychiatric disorders**	**Tearfulness**
Temperature intolerance	**General disorders and administration site conditions**	**Temperature intolerance**
Temperature regulation disorder	**General disorders and administration site conditions**	**Temperature regulation disorder**
Temperature regulation disorder	**General disorders and administration site conditions**	**Temperature regulation disorder**
Terminal insomnia	**Psychiatric disorders**	**Terminal insomnia**
Thinking abnormal	**Psychiatric disorders**	**Thinking abnormal**
Thought blocking	**Psychiatric disorders**	**Thought blocking**
Thought withdrawal	**Psychiatric disorders**	**Thought withdrawal**
Tongue exfoliation	**Gastrointestinal disorders**	**Tongue exfoliation**
Total bile acids increased	**Investigations**	**Total bile acids increased**
Toxic epidermal necrolysis	**Skin and subcutaneous tissue disorders**	**Toxic epidermal necrolysis**
Toxic skin eruption	**Skin and subcutaneous tissue disorders**	**Toxic skin eruption**
Transaminases abnormal	**Investigations**	**Transaminases abnormal**
Transaminases increased	**Investigations**	**Transaminases increased**
Tunnel vision	**Nervous system disorders**	**Tunnel vision**
Uhthoff's phenomenon	**Nervous system disorders**	**Uhthoff's phenomenon**

Ultrasound biliary tract abnormal	**Investigations**	**Ultrasound biliary tract abnormal**
Ultrasound bladder abnormal	**Investigations**	**Ultrasound bladder abnormal**
Ultrasound eye abnormal	**Investigations**	**Ultrasound eye abnormal**
Ultrasound kidney abnormal	**Investigations**	**Ultrasound kidney abnormal**
Ultrasound liver abnormal	**Investigations**	**Ultrasound liver abnormal**
Underweight	**Metabolism and nutrition disorders**	**Underweight**
Urea urine abnormal	**Investigations**	**Urea urine abnormal**
Urea urine decreased	**Investigations**	**Urea urine decreased**
Urea urine increased	**Investigations**	**Urea urine increased**
Urine abnormality	**Renal and urinary disorders**	**Urine abnormality**
Urine albumin/creatinine ratio abnormal	**Investigations**	**Urine albumin/creatinine ratio abnormal**
Urine albumin/creatinine ratio decreased	**Investigations**	**Urine albumin/creatinine ratio decreased**
Urine albumin/creatinine ratio increased	**Investigations**	**Urine albumin/creatinine ratio increased**
Urine bilirubin increased	**Investigations**	**Urine bilirubin increased**
Urine calcium decreased	**Investigations**	**Urine calcium decreased**
Urine calcium increased	**Investigations**	**Urine calcium increased**
Urine calcium/creatinine ratio decreased	**Investigations**	**Urine calcium/creatinine ratio decreased**
Urine calcium/creatinine ratio increased	**Investigations**	**Urine calcium/creatinine ratio increased**
Urine flow decreased	**Renal and urinary disorders**	**Urine flow decreased**
Urine homocystine present	**Investigations**	**Urine homocystine present**
Urine ketone body	**Investigations**	**Urine ketone body**
Urine ketone body present	**Investigations**	**Urine ketone body present**
Urine lactic acid decreased	**Investigations**	**Urine lactic acid decreased**
Urine lactic acid increased	**Investigations**	**Urine lactic acid increased**
Urine nitrogen	**Investigations**	**Urine nitrogen**
Urine odour abnormal	**Renal and urinary disorders**	**Urine odour abnormal**
Urine osmolarity decreased	**Investigations**	**Urine osmolarity decreased**
Urine osmolarity increased	**Investigations**	**Urine osmolarity increased**
Urine output decreased	**Investigations**	**Urine output decreased**
Urine output increased	**Investigations**	**Urine output increased**
Urine oxalate decreased	**Investigations**	**Urine oxalate decreased**
Urine oxalate increased	**Investigations**	**Urine oxalate increased**
Urine phosphate abnormal	**Investigations**	**Urine phosphorus abnormal**
Urine phosphate decreased	**Investigations**	**Urine phosphorus decreased**
Urine phosphate increased	**Investigations**	**Urine phosphorus increased**

Urine protein/creatinine ratio abnormal	**Investigations**	**Urine protein/creatinine ratio abnormal**
Urine protein/creatinine ratio decreased	**Investigations**	**Urine protein/creatinine ratio decreased**
Urine protein/creatinine ratio increased	**Investigations**	**Urine protein/creatinine ratio increased**
Urine sodium abnormal	**Investigations**	**Urine sodium abnormal**
Urine sodium decreased	**Investigations**	**Urine sodium decreased**
Urine sodium increased	**Investigations**	**Urine sodium increased**
Urine transitional cells present	**Investigations**	**Urine transitional cells present**
Urine uric acid abnormal	**Investigations**	**Urine uric acid abnormal**
Urine uric acid decreased	**Investigations**	**Urine uric acid decreased**
Urine uric acid increased	**Investigations**	**Urine uric acid increased**
Urine viscosity abnormal	**Investigations**	**Urine viscosity abnormal**
Urine viscosity decreased	**Investigations**	**Urine viscosity decreased**
Urine viscosity increased	**Investigations**	**Urine viscosity increased**
Urobilin urine present	**Investigations**	**Urobilinogen urine increased**
Uveitis	**Eye disorders**	**Uveitis**
Vaginal exfoliation	**Reproductive system and breast disorders**	**Vaginal exfoliation**
Vaginal ulceration	**Reproductive system and breast disorders**	**Vaginal ulceration**
Varices oesophageal	**Gastrointestinal disorders**	**Varices oesophageal**
Caput medusae	**Gastrointestinal disorders**	**Varicose veins of abdominal wall**
Vasodilatation	**Vascular disorders**	**Vasodilatation**
Venoocclusive liver disease	**Hepatobiliary disorders**	**Venoocclusive liver disease**
Venous stasis retinopathy	**Eye disorders**	**Venous stasis retinopathy**
Verbigeration	**Psychiatric disorders**	**Verbigeration**
Vision abnormal neonatal	**Eye disorders**	**Vision abnormal neonatal**
Vision blurred	**Eye disorders**	**Vision blurred**
Visual acuity reduced	**Eye disorders**	**Visual acuity reduced**
Visual brightness	**Eye disorders**	**Visual brightness**
Visual evoked potentials	**Investigations**	**Visual evoked potentials**
Visual evoked potentials abnormal	**Investigations**	**Visual evoked potentials abnormal**
Scotoma	**Nervous system disorders**	**Visual field defect**
Visual field defect	**Nervous system disorders**	**Visual field defect**
Visual field tests	**Investigations**	**Visual field tests**
Visual field tests abnormal	**Investigations**	**Visual field tests abnormal**
Visual impairment	**Eye disorders**	**Visual impairment**

Visual pathway disorder	**Nervous system disorders**	**Visual pathway disorder**
Vitreous abscess	**Infections and infestations**	**Vitreous abscess**
Vitreous detachment	**Eye disorders**	**Vitreous detachment**
Vitritis	**Eye disorders**	**Vitritis**
Vulval ulceration	**Reproductive system and breast disorders**	**Vulval ulceration**
Vulvovaginal ulceration	**Reproductive system and breast disorders**	**Vulvovaginal ulceration**
Weight abnormal	**Investigations**	**Weight abnormal**
Weight decrease neonatal	**Pregnancy, puerperium and perinatal conditions**	**Weight decrease neonatal**
Weight decreased	**Investigations**	**Weight decreased**
Weight fluctuation	**Metabolism and nutrition disorders**	**Weight fluctuation**
Weight gain poor	**Metabolism and nutrition disorders**	**Weight gain poor**
White blood cells urine	**Investigations**	**White blood cells urine**
White blood cells urine positive	**Investigations**	**White blood cells urine positive**
X-ray hepatobiliary abnormal	**Investigations**	**X-ray hepatobiliary abnormal**
X-ray hepatobiliary abnormal	**Investigations**	**X-ray hepatobiliary abnormal**
Yellow skin	**Skin and subcutaneous tissue disorders**	**Yellow skin**

Appendix 4: Vineland scores

OVERVIEW

The Vineland Adaptive Behavior Scale is a composite of four Vineland domains:

- Communications (Receptive, Expressive, Written)
- Daily Living Skills (Personal, Domestic, Community)
- Socialization (Interpersonal Relationships, Play and Leisure Time, Coping Skills)
- Motor Skills (Gross, Fine)

Reference: Vineland Adaptive Behavior Scales, Interview Edition, Survey Form Manual,

S. Sparrow et al, 1984.

The KVINLAND.XPT dataset includes standard scores, age-equivalences, the adaptive levels for subdomains, domains, and adaptive Behavior Composite, and percentile ranks for domains and adaptive behavior composite. These variables are based on the 1984 Vineland scale analyses from the Vineland Interview Edition.

Standard scores (mean 100, SD=15) were analyzed for each of the four adaptive behavior domains and the Adaptive Behavior composite. The standard score is *"based on the performance of a representative national standardization sample of 3000 individuals between birth and age 18-11-30"* (p. 116).

STANDARD SCORES

As stated in the Vineland manual (p. 116), *"standard scores express in standard deviation units the extent to which the individual's score exceeds or falls below the mean score of persons the same age with whom the instrument was standardized. Adaptive Behavior Composite and adaptive behavior domain standard scores range from 20 to 160, or 5.5 SD below the mean to 4 SD above the mean … Standard scores have the advantage of being equal units across the full range of scores The difference in performance between standard scores of 100 and 115 is the same as that between 130 and 145. Because they are of equal units, standard scores can easily be manipulated statistically."*

PERCENTILE RANKS

As stated in Vineland manual (p. 117), *"although standard scores are superior to percentile ranks in a psychometric sense, they are not easily understood by many people. Percentile ranks aid in giving meaning to standard scores. Percentile ranks range from 0.1 to 99.9. A percentile rank of 50 indicates median performance … The chief advantage of percentile ranks is that they are easily understood. A major limitation is that unlike standard score units, percentile rank units are unequal … The difference between percentile ranks of 50 and 55 is much smaller than the difference of percentile ranks of 90 and 95. This occurs because percentile ranks are compressed near the center of the distribution and less heavily concentrated at the extremes."*

ADAPTIVE LEVELS

Adaptive levels are a categorical representation of the standard scores (p. 118):

Adaptive Level Standard Score Percentile Rank
High ≥ 131 ≥ 98

Moderately High	116-130	85-97
Adequate	85-115	16-84
Moderately Low	70-84	3-15
Low	≤ 69	≤ 2

AGE EQUIVALENTS

As described on page 119, the age equivalent represents the raw score that was the average of individuals of a given chronological age in the national standardization sample. They are not used for statistical analysis because the scale units are unequal. In the communication domain, for example, performance increases more between the ages of 2 and 3 than between 10 and 11, for example.

VARIABLES IN KVINLAND.XPT

12. VARIABLE DESCRIPTION

VNSS Standard score. Standard scores of '<20' are set to 19. Standard scores of 'Above 160' are set to 161.

VNSS_PRORATED Standard score - prorated. For adaptive behavior composite scores, VNSS_PRORATED not equal to VNSS means that the

standard score was prorated. VNSS_PRORATED equal to VNSS means the score was not prorated. VNSS_PRORATED is missing (not applicable) for the adaptive behavior composite. The Vineland manual describes the rules for prorating on pages 89 and 107.

VNP Percentile rank
VN_AL Adaptive level

VN_AE Age equivalent. VN_AE is computed using methods given on p. 101 of the Vineland manual (median used only if one or more

subdomain age equivalents are below 0-1 and above 18-11).

VNSCORE Raw score. For domain totals (VNEXAMC=100) VNSCORE is the raw score total for that domain. The raw score total is

undefined for adaptive behavior composite

Records for domain and ADAPTIVE BEHAVIOR COMPOSITE results are derived. These records are identified as follows:

- VNEXAMC=100: domain scores
- VNEXAMC=101: adaptive behavior composite scores

Composite score

The composite score will be the sum of 4 standardized domain scores. If a subject has only 3 domains, then the standardized score for the missing domain will be prorated and the composite score will be calculated as sum of 4 domains. If a subject has less than 3 domains, then the composite score will not be calculated.

SAS code:

```
/* Program: vineland.sas
   Author:    Dr. PPD , University of Texas PPD
   Date:      18-S

   Purpose: The program implements the 1984 Vineland scale analyses from the
Vineland Interview Edition) to calculate standard score,
            age-equivalence, the Adaptive Levels for Subdomains and Domains and
Adaptive Behavior Composite, and percentile ranks
            for Domains and Adaptive Behavior Composite to Johnson & Johnson
Pharmaceutical Research & Development, L.L.C. (J&J PRD)
            for use in analyzing Vineland data in any J&JPRD study.

   Vineland variables:
```

```
   The output dataset contains all variables in the input dataset.    In
addition, the following variables are created:
   - VNSS:             standard score
   - VN_AL:            adaptive level
   - VN_AE:            age equivalent.
   - VNSS_PRORATED:    standard score - prorated.   For adaptive behavior
composite scores, VNSS_PRORATED ^= VNSS means the score was
                       prorated, and VNSS_PRORATED = VNSS means the score was
not prorated.   VNSS_PRORATED is missing (not applicable) for

                       the adaptive behavior composite.
   - VNP:              percentile rank
   - VNSCORE:          raw score.   For domain totals (VNEXAMC=100) VNSCORE is
the raw score total for that domain. The raw score total is
                       undefined for adaptive behavior composite

   Records Created:
   The program adds records for domain and ADAPTIVE BEHAVIOR COMPOSITE
results.    The records are identified as follows:
   - VNEXAMC=100:    domain scores
   - VNEXAMC=101:    adaptive behavior composite scores

   Supporting Data Files:
   The program expects the seven lookup data sets to be associated with a SAS
libname of "NORMDATA".   These datasets are:
   - vineland_table1.sas7bdat
   - vineland_table2.sas7bdat
   - vineland_table5_2.sas7bdat
   - vineland_table6.sas7bdat
   - vineland_table8.sas7bdat
   - vineland_table10.sas7bdat
   - vineland_table11.sas7bdat

   Notes:
   - Standard scores of '<20' are set to 19.
   - Standard scores of 'Above 160' are set to 161.
   - The program assumes that the combination of SUBJECT and VNDT uniquely
identify each record.
   - VN_AE is computed using methods given on p. 101 of the Vineland manual
(median used only if one or more subdomain age
       equivalents are below 0-1 and above 18-11).

   Modified: M. Todd 21-Sep-2007 - added header block and macro parameters
(INDATA and OUTDATA).
*/

%macro vineland(indata=,
                outdata=);

%let sortby=SUBJECT VNDT VNMAINC VNSEQ;

data vineland_1(index=(complex=(&sortby))); length
  vnmain $40; set
  &indata(rename=(vnscore=_vnscore));
  length vnscore 3; vnscore=left(_vnscore);
  drop _vnscore; run;

proc means data=vineland_1 noprint nway;
```

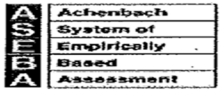
```
  class SUBJECT VNDT VNMAIN VNMAINC agevisit; var
  vnscore;
  output out=vineland_2 n=n_within_domain sum=vnscore;
  where vnexam ne "DON'T KNOW" and VNSCORE NE . and agevisit ne .; run;

proc sort data=vineland_1 out=vineland_dk_too_high(keep=subject vndt vnmain);
  by subject vndt vnmain;
  where vnexam="DON'T KNOW" and VNSCORE>=5;
run;

data vineland_3; merge
  vineland_2
        vineland_dk_too_high(in=indk);
  by subject vndt vnmain;
  if indk then delete;
  if (vnmain in ('COMMUNICATION' 'DAILY LIVING SKILLS' 'SOCIALIZATION') and
n_within_domain=3) or
     (vnmain='MOTOR SKILLS' and n_within_domain=2);
  drop _:;
run;

proc sql noprint;
  create table vineland_4 as
    select a.*,b.standscore as vnss
    from vineland_3 a left join
    normdata.vineland_table1 b
    on b.agemin<=agevisit<=b.agemax and a.vnscore=b.raw and a.vnmain=b.domain
    order by subject,vndt,vnmainc;
quit;
proc means data=vineland_4 noprint nway;
  class subject vndt agevisit;
  var vnss;
  output out=vineland_5(drop=_:) n=n_domains sum=sum_ss_across_domains;
run;
data vineland_5a; set
  vineland_5;
  if (n_domains=3 and 0<=agevisit<=71) or (n_domains=2 and agevisit>71) and
sum_ss_across_domains ne . then
    prorated_flag='X';
run;
proc sql noprint;
  create table vineland_5b as
  select a.*,case when prorated_flag='X' and n_domains=3 then
prorated_sum_for_4_domains
                  when prorated_flag='X' and n_domains=2 then
prorated_sum_for_3_domains
                  else . end as prorated_sum from
    vineland_5a a left join
    normdata.vineland_table5_2 b
    on  a.sum_ss_across_domains=b.actual;
quit;
data vineland_5c; set
  vineland_5b;
  if prorated_sum ne . then do;
    sum_ss_across_domains=prorated_sum;
    n_domains=n_domains+1;
  end;
  drop prorated_sum; run;
```

```
proc sql noprint;
  create table vineland_6 as
    select a.*,b.domain as vnmain,b.ss as vnss
    from vineland_5c a left join
    normdata.vineland_table2 b
    on b.ndomain=a.n_domains and b.minsum<=a.sum_ss_across_domains<=b.maxSUM
    where (n_domains=4 and 0<=agevisit<=71) or (n_domains=3 and agevisit>71)


order by subject,vndt; quit;
proc sort data=vineland_1 out=vnunique nodupkey; by
  subject vndt;
run;
data combined1;
  merge vineland_4(in=ins keep=subject vndt vnmain vnmainc vnss vnscore)
        vnunique(drop=vnmain vnmainc vnscore);
  by subject vndt; if
  ins; vnexamc=100;
  vnseq=vnmainc+1-.001;
  vnexam=vnmain;
run;
data combined2;
  merge vineland_6(in=ins keep=subject vndt vnmain vnss prorated_flag)
        vnunique(drop=vnmain);
  by subject vndt; if
  ins; vnexam=vnmain;
  vnmainc=5;
  vnexamc=101;
  vnseq=5.1;
  vnscore=.;
run;

data combined3;
  set vineland_1
      combined1
      combined2;
run;

proc sql noprint;
  create table vineland_7 as
    select a.*,b.adaptive_level as vn_al,c.adaptive_level as vn_al2,d.ae as
vn_ae,e.ae as vn_ae2
    from combined3 a left
    join
    normdata.vineland_table6 b
    on b.domain=a.vnmain and b.subdomain=a.vnexam and
b.agemin<=a.agevisit<=b.agemax  and  b.minraw<=a.vnss<=b.maxraw
    left join normdata.vineland_table8
    c
    on c.domain=a.vnmain and c.subdomain=a.vnexam and
c.agemin<=a.agevisit<=c.agemax  and  c.minraw<=a.vnscore<=c.maxraw
    left join normdata.vineland_table10
    d
    on a.vnmain=d.domain and a.vnexam=d.domain and a.vnscore=d.raw left
    join
    normdata.vineland_table11 e
    on a.vnmain=e.domain and a.vnexam=e.subdomain and a.vnscore=e.raw
    order by subject,vndt,vnmainc,vnseq;
```

```
quit;

data &outdata;
  set vineland_7; by
  subject vndt;
  length _avg_method $6;
  retain _ae1 _ae2 _ae3 _ae4 _avg_method;
    if first.vndt then do;
      _ae1=.; _ae2=.; _ae3=.; _ae4=.; _avg_method='MEAN'; _count=1;
    end;
    array ae(4) _ae1 _ae2 _ae3 _ae4;
    length vnss_prorated 3 ;
    if vn_ae2 ne '' then vn_ae=vn_ae2;
    if vn_al2 ne '' then vn_al=vn_al2;
    if vnmain=vnexam and vnmain ne 'ADAPTIVE BEHAVIOR COMPOSITE' then do;
      if vn_ae ne '' then do;
        if index(vn_ae,'>') or index(vn_ae,'<') then do;
          _avg_method='MEDIAN';
          if index(vn_ae,'>') then ae(_count)=228;
          else ae(_count)=.1;
        end;
        else do;
          ae(_count)=12*scan(vn_ae,1,'-')+scan(vn_ae,2,'-');
        end;
        _count+1;
      end;
    end;

    if vnmain='ADAPTIVE BEHAVIOR COMPOSITE' then do;
      vnss_prorated=vnss;
      if prorated_flag='X' then vnss=.;
      if _avg_method='MEAN' then _ae_avg=round(mean(of _ae1-_ae4));
      else _ae_avg=median(of _ae1-_ae4);
      if _ae_avg=.1 then vn_ae='<0-1';
      else   vn_ae=cats(int(_ae_avg/12),'-',int(mod(_ae_avg,12)));
    end;

    _ss=vnss;
    if vnss=. then _ss=vnss_prorated;
    if _ss ne . then vnp=probnorm((_ss-100)/15);

    if      52<=_ss<=61 or 139<=_ss<=148 then vnp=round(vnp,.001);
    else if 62<=_ss<=138 then vnp=round(vnp,.01);
    format vnp percent7.1;

    label vnss='VINELAND Standard Score'
          vnss_prorated='VINELAND Standard Score - Prorated'
          vn_ae='VINELAND Age Equivalent'
          vnp   ='VINELAND Percentile'
          vn_al='VINELAND Adaptive Level';

    drop vn_ae2 vn_al2 prorated_flag _:;
  run;

  proc sql noprint;
  drop table   COMBINED1, COMBINED2, COMBINED3, VINELAND_1, VINELAND_2,
  VINELAND_3, VINELAND_4, VINELAND_5,
```

```
            VINELAND_5A, VINELAND_5B, VINELAND_5C, VINELAND_6, VINELAND_7,
VINELAND_DK_TOO_HIGH,  VNUNIQUE;
quit;
%mend vineland;
```

Appendix 5: CBCL scoring instruction



INSTRUCTIONS FOR HAND SCORING THE 2001 CBCL/6-18, YSR, AND TRF ON THE 2001 PROFILES

Note. There are some small differences between the hand-scored and computer-scored data entry formats, but they produce the same results. ***Be sure to use the CBCL and TRF profile forms appropriate for the child's gender.*** For information on computer-scoring programs, check our web site: www.ASEBA.org

Scoring the CBCL and YSR Competence Scales

ACTIVITIES SCALE

Do ***not*** score if data are missing for more than 1 of the 6 scores indicated beside the Roman numerals below. The Roman numerals correspond to those on pages 1 and 2 of the CBCL and YSR and on the profile scoring form. If a respondent checked more than 1 box where only 1 should be checked, score the box closest to "average."

I-A. # of sports.

If respondent checked box for *None*—enter 0 below profile
If respondent reported: 1 sport—enter 1 below profile
2 sports—enter 2 below profile
3 or more sports—enter 3 below profile

I-B. Mean of participation & skill in sports.

If respondent checked box for *None*—enter 0 below profile
For each response of *less than average* or *below average*—score 0
***average*—score 1**
***more than average* or *above average*—score 2**

Excluding blanks and "don't know" responses, compute the *mean* of these scores by summing them and dividing by the number of scores you have summed. Enter this mean on the profile.

II-A. # of other activities.

If respondent checked box for *None*—enter 0 below profile
If respondent reported: 1 activity—enter 1 below profile
2 activities—enter 2 below profile
3 or more activities—enter 3 below profile

Do not count listening to radio or TV, goofing off, or the like as activities.

II-B. Mean of participation & skill in activities. Compute in the same way as specified in I-B for sports.

IV-A. # of jobs.

If respondent checked box for *None*—enter 0 below profile
If respondent reported: 1 job—enter 1 below profile
2 jobs—enter 2 below profile
3 or more jobs—enter 3 below profile

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www.aseba.org; E-mail: Mail@ASEBA.org; Fax: (802) 264-6433

IV-B..Mean job quality. Compute as specified in I-B.

Total score for Activities Scale. Sum the 6 scores just entered for the items of the Activities scale. If missing data prevent computation of 1 score, substitute the *mean* of the other 5 scores for the missing score in computing the total. If item I-B, II-B, or IV-B is missing and the mean of the other 5 scores exceeds 2.0, round it down to 2.0. Round off total to nearest .5.

SOCIAL SCALE

Do *not* score if data are missing for more than 1 of the 6 scores.

III-A. # of organizations. If respondent checked box for *None-enter* 0 below profile
If respondent reported: 1-enter 1 below profile
2-enter 2 below profile
3 or more--enter 3 below profile

III-B. Mean of participation in organizations. Compute as specified in I-B.

V-1. # of friends. If respondent checked box for *None- enter* 0 below profile
I-enter 1 below profile
2 or 3-enter 2 below profile
4 or more-enter 3 below profile

V-2. Contacts with friends. (Item V-2 can be scored 1 or 2 even if no close friends were reported in item V-1.)

If respondent checked *less than* I-enter 0 below profile
1 or 2-enter 1 below profile
3 or more-enter 2 below profile

VI-A. Behavior with others (items a,.b, & c). If the respondent checked *worse-score* 0
average-score 1
better-score 2

Excluding any items for which the respondent did not check a box, compute the *mean* of these scores and enter- it below the profile.

VI-B. Does things alone (item d). If the respondent checked *worse-enter* 0 below profile
<1verage---enter 1 below profile
better-enter 2 below profile

Total score for Social Scale. Sum the 6 scores just entered for the items of the Social scale. If missing data prevent computation of 1 score, substitute the *mean* of the other 5 scores for the missing score in computing the total. If item 111-B, V-2, VI-A, or VI-B is missing and the mean of the other 5 scores exceeds 2.0, round it down to 2.0. Round off total to nearest .5.

CBCL SCHOOL SCALE

Do *not* score if the child does not attend school or if data are missing for any of the 4 scores indicated below for items VII-1 through VII-4, which appear on Page 2 of the CBCL and on the *School* scale of the profile scoring form.

VII-1. Academic performance. For each academic subject checked by respondent:

failing- score 0
below average-score 1
average-score 2
above average-score 3

Enter the *mean* of these scores on the profile. (Academic subjects include reading, writing, arithmetic, spelling, science, English, foreign language, history, social stlldies, and similar subjects. Do *not* count physical education, a1i,music, home economics, driver education, industrial arts, typing, or the like.)

VII-2. Special services, special class, or special school.

For any type of remedial special services, class, or school (for retarded, emotionally disturbed, learning diability, perceptual-motor handicapped, reading readiness, resource room, behavior problems, etc): -enter 0 below profile
not in re1nedial class-enter 1below profile

VII-3. Repeated grade. If any grades were repeated- enter 0 below profile
no grades repeated- enter 1below profile

VII-4. School problems.

If the respondent entered any school problem that was present in the last 6 mouths but was not already scored above: -enter 0 below profile
no problem beside those scored above---enter 1below profile

Total score for School Scale. Sum the 4 scores just entered on the *School* scale of the profile, unless any score is missing. After computing the total, round off to the nearest .5.

CBCL TOTAL COMPETENCE SCORE

Compute the Total Competence score by summing the total scores for the Activities, Social, and School scales. Do *not* compute a Total Competence score if any of these 3 scale scores is inissing. *T scores* for Total Competence scores are listed in the box to the right of the profile. Circle the child's Total Competence score in the column for the child's age. After you circle the child's raw score, look to the right to find the *T* score.

YSR ACADEMIC PERFORMANCE

Compute in the same way as specified in VII- I for CBCL Academic Performance.

YSR TOTAL COMPETENCE SCORE

Sum the total scores for Activities, Social, and Academic Performance. Do 11oi- ompute a Total Competence score if any of these 3 scores is missing. *T* scores for Total Competence scores are in the box to the right of the profile. Circle the youth's Total Competence raw score in the column for the youth's gender. After you circle the youth's raw score, look to the right to find the *T score.*

Scoring the TRF Academic Performance mid Adaptive Functioning

Item VII. For each academic subject, score the teacher's ratings as follows:

Far below grade = 1
Somewhat below grade = 2
At grade level = 3
Somewhat above grade = 4
Far above grade = 5

If a teacher checked two boxes for one subject, use the mean of the two scores assigned to these boxes.

Enter the *mean* of the teacher's ratings for all academic subjects beneath the heading *Academic Performance* on the profile. (Academic subjects include reading, writing, aritlnnetic, spelling, science, English, foreign language, history, social studies, computer programming, etc. Do *not* count physical education, art, music, home economics, driver education, industrial arts, typing, or the like.)

Iten1 VIII. For each of the questions 1-4, score the teacher's ratings as follows:

Much less = 1
.S Somewhat less =
2 Slightly less = 3
About ave1·age= 4
Slightly more = 5
Somevhat more = 6
Much more = 7

Enter the score for each rating beneath the appropriate heading on the profile.

Sum of Items VIII. 1-4. Sum the scores for Items VIII. 1, 2, 3, and 4. Enter this sum beneath the appropriate heading on the profile. Do *not* compute this sum if any of the 4 items is missing.

Scoring the CBCL/6-18, YSR, and TRF Problem Scales

Do *not* score the problem scales if data are missing for more than 8 items, not counting open-ended items *56h* and *113,* or YSR socially desirable items 6, 15, 49, 59, 60, 73, 80, 88, 92, 98, 106, 107, 108, 109. If TRF items 56a-56g were left blank, score them 0.

TRANSFERRING PROBLEM ITEM SCORES TO THE PROFILES

Templates. Templates are available to aid in transferring data from the school-age fonns to the profiles. Different templates are needed for the CBCL/6-18, YSR, and TRF. To transfer problem item scores onto the profile, place the Page 3 template on Page 3 of the form. For each problem item, the template indicates whether the item's score is to be entered on a syndrome scale or on the *OTHER PROBLEMS* list of the profile of empirically based syndromes. The template also indicates the DSMcoriented scale on which to score each item. Repeat using the Page 4 template pn Page 4 of the form.

Item Seo.res. For each problem item, print the respondent's 0, 1, or 2 response in the appropriate space beside the item on the profile form. If the respondent circled two numbers for an item, print 1 beside the item on the profile form. Comments written by the respondent should be used in judging whether items deserve to be scored, with the following guidelines:

1. For each problem reported by the respondent, only the item that most specifically describes the problem should be scored. If the respondent's comments show that more than

one item has been scored for a particular problem, or if the respondent wrote in a problem for item 56h or 113 that is specifically covered elsewhere, score only the most specific item.

2. For items on which the respondent noted "used to do this,"score as the respondent scored it, unless it clearly occurred earlier than the 6 months specified in the instructions for the CBCL and YSR, or 2 months for the TRF.
3. When in doubt, score the item the way the respondent scored it, except on the following items:

CBCL & TRF 9.-0bsessions--exclude anything that is clearly *11ot* obsessional; e.g., do *not* score "won't **take no for an answer."**

YSR 9. Can't get mind off certain thoughts-On the YSR, this item is *11ot* restricted to obsessions. Itcan include almost anything the youth lists here except problems that are specifically listed elsewhere. Ifthe youth wrote "sex" for this item, for example, it would be more appropriately scored on Item 96, *I think about sex too much.* Ifnot covered by another item, responses that might be considered normal for the youth's age should be scored the way the youth scored them; e.g., "cars,""girls,""boys."

YSR 40. Hears sounds and 70. Sees things core experiences such as "ringing in ears" and "spots befo1eeyes" the way the youth scored them; do *not* score experiences while under the influence of drugs or alcohol.

46. Nervous movements-if "can't sit still" or anything entirely covered by item 10 is entered here, score *only* item 10.

56d. Problems with eyes-do *not* score "wears glasses," "near-sighted," and other visual problems having an organic basis.

CBCL & TRF 66. Compulsions--Oo *not* score noncompulsive behavior; e.g., "keeps hitting brother."

YSR 66. Repeats actions-On the YSR, this item is *not* restricted to compulsions . It can include almost anything the youth lists here except problems that are specifically listed elsewhere. Speech repetitions or stammers, for example, would be more appropriately scored on Item 79. *Speechproblem.*

CBCL 72. Sets fires-score playing with matches or lighter if parent reported it.

77. Sleeps more than most--Oo *not s.core* "wants to stay in bed,"but score difficulties in waking child.

83. Stores up too many things-do *not* Score hobby collections, such as stamps, dolls.

84. Strangebehavior and 85. Strange ideas-if what the respondent describes is specifically covered by another item, score then lore specific item instead.

CBCL & YSR 105. Drugs-if alcohol or tobacco are entered here, score item 2 or 99, if they are not already scored.

TRF 105. Drugs-if tobacco is entered here, score item 99, if it is not already scored.

113. Additional problems-score only if *not* specifically covered by another item; if respondent listed inore than 1 "other" item, count only highest toward total problem score. For example, if a respondent

scored one additional problem "2" and another additional problem "1," add 2 to the total problem score.

Syndrome and DSM-Oriented Scale Scores. To obtain the total raw score for each scale, sum the 1s and 2s you have entered for the scale. The *OTHER PROBLEMS* do not form a scale, but should be summed to help in computing the Total Problems score, as described later.

GRAPHIC DISPLAY AND T SCORES

To complete the graphic displays for the syndrome and DSM-oriented scales, circle the number above each scale that equals the total score obtained for that scale. *Be sure to circle the 11umber i11 the co/um11 approp1;iatefor the child's age a11d gende1:* Then draw a line to connect the circled numbers. Percentiles based on the normative sample can be read from the left side of the graphic display. Tscores can be read from the right side.

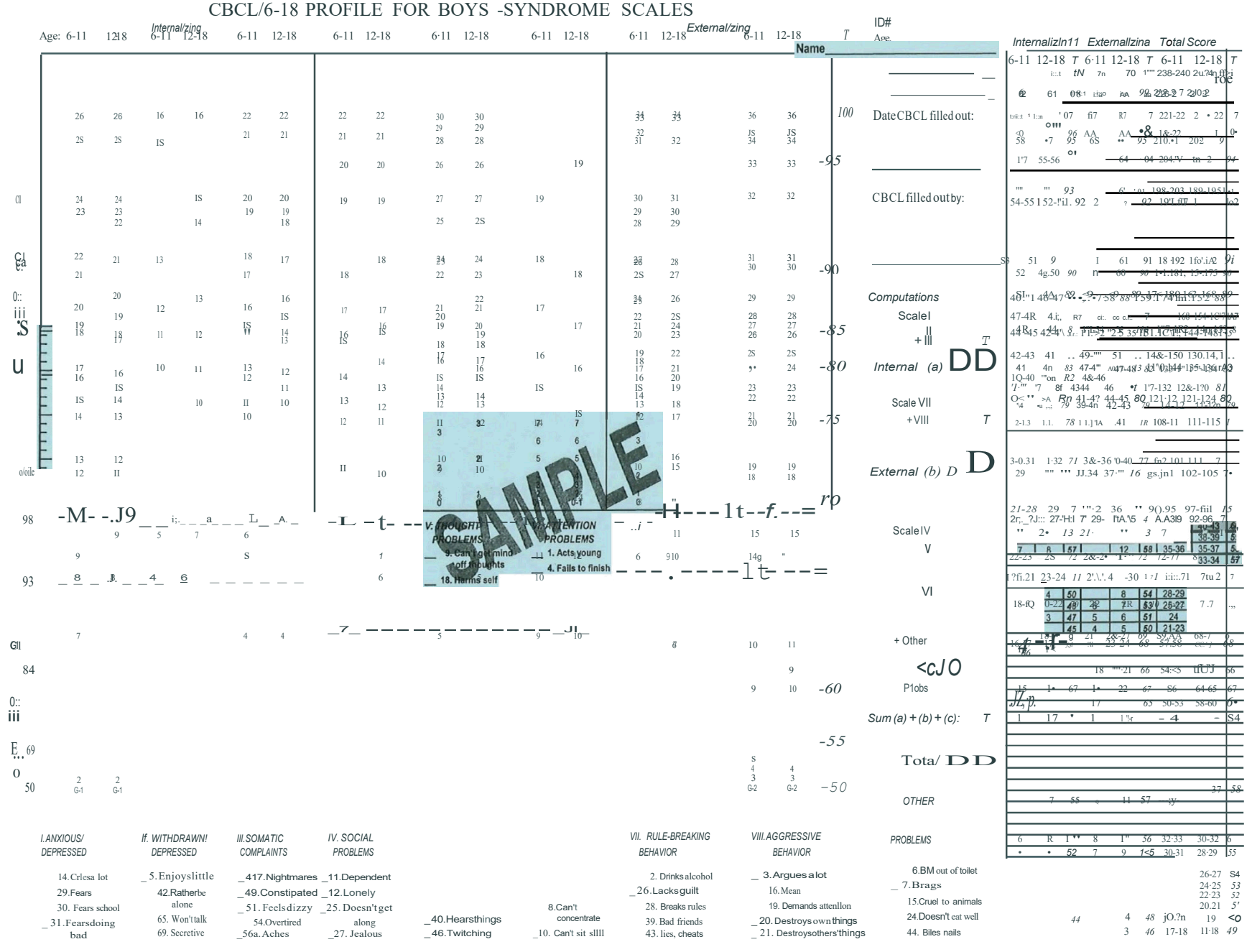
INTERNALIZING, EXTERNALIZING, TOTAL PROBLEMS

Computatio11 of Scores. On the profile of syndrome scales, look to the right of the graphic display. You will see a column headed *Computatio11s.* Under *Computatio11s,* enter the raw scores that you have obtained for each of the syndrome scales and for the *OTHER PROBLEMS* as follows:

1. Enter the scores for the 3 leftmost syndrome scales in the spaces provided.
2. Enter their sum in the *box marked I11ter11al (a).*
3. Enter the scores for the 2 rightmost syndrome scales in the spaces provided.
4. Enter their sum in the box marked *External (b).*
5. Enter the total score for the 3 middle syndrome scales and *OTHER PROBLEMS* in the spacesprovided.
6. Ente1· the sum of scores from # 5 in the box marked *(c).*
7. Enter the sum of scores from boxes *(tt), (b),* and *(c)* in the box marked *Totttl.*

TScores. Obtain Tscores for Internalizing, Externalizing, and Total Problems as follows:

1. Look in the appropriate columns of the large box on the right side of the profile forn1.
2. In the appropriate column under the heading *Internalizing,* circle the raw score that corresponds to the score you have entered in the box beside *Internal.*
3. Look to the right in the *I11ternalizi11g* column headed Tand circle the Tscore that corresponds to the Internalizing raw score that you have obtained.
4. Enter this Tscore in the box marked *Internal* Tunder the *Computtttio11s* heading.
5. Look under the *Exter11alizi11g* and *Total Problems* headings to obtain *T* scores-in the same way as was done for Internalizing; enter the *Externalizing* and *Totttl Problems T* scores in the appropriate boxes.


CBCL/6-18 PROFILE FOR BOYS -SYNDROME SCALES
Internal/zing
External/zing
Age: 6-11 12-18
ID#
Name
Date CBCL filled out:
CBCL filled out by:
Computations
Scale I
Internal (a) DD
Scale VII
External (b) D D
Scale IV
Scale VI
+ Other
P1obs
Sum (a) + (b) + (c):
Tota/ DD
OTHER
PROBLEMS
SAMPLE
I. ANXIOUS/ DEPRESSED
14. Crlesa lot
29. Fears
30. Fears school
31. Fearsdoing bad
II. WITHDRAWN! DEPRESSED
5. Enjoyslittle
42. Ratherbe alone
65. Won't talk
69. Secretive
III. SOMATIC COMPLAINTS
417. Nightmares
49. Constipated
51. Feelsdizzy
54. Overtired
56a. Aches
IV. SOCIAL PROBLEMS
11. Dependent
12. Lonely
25. Doesn't get along
27. Jealous
40. Hearsthings
46. Twitching
8. Can't concentrate
10. Can't sit slll
VII. RULE-BREAKING BEHAVIOR
2. Drinks alcohol
26. Lacks guilt
28. Breaks rules
39. Bad friends
43. lies, cheats
VIII. AGGRESSIVE BEHAVIOR
3. Argues a lot
16. Mean
19. Demands attenllon
20. Destroys own things
21. Destroysothers'things
6. BM out of toilet
7. Brags
15. Cruel to animals
24. Doesn't eat well
44. Biles nails
Internalizln11 Externallzina Total Score

32. Must be perfect
_7S. Shy, timid
_102. Lacks
_56b. Headaches,
_56e. Nausea
:W. Others out to — get him
58. Picks skin
_ 59. Sex part spublic
_13. Confused
_17. Daydreams
63. Prefers older kids
_67. Run away
22. Disobedient at home
23. Disobedient at school
_ 53. Overeating
_55. Overweight
n
I 40
n 34
44 16
43 1"
14-15 '7
13 46

_33. Feels unloved
35. Feels worthless
_45. Nervous
50. Fearful
_52. Feels too guilty
71. Self-conscious
energy
_103. Sad
_111. Withdrawn
Tolaf
_56d. Eyeprobs.
_56e. Skin probs.
_56f. Stomach
_56g. Vomiting
Totaf
_36. Accident1>rone
_38. Gels teased
_48. Not liked
_62. Clumsy
_64. Prefers younger kids
_79. Speech prob.
Total
_60. Sex parts too much
_ 66. Repeats acts
_70. Sees things
_76. Sleeps lass
_ 83. Stores things
_84. Strange behavior
_ 85. Strange Ideas
_41. Impulsive
_61. Poor schoolwork
_78. Ina Henlive
_80. Stares
Total
72. Sets fires
Sax problems
_73.
81. Steals at home
82. Steals outside horn•
_ 90. Swearing
96. Thinks of sax loomuch
99. Uses tobacco
_37. Gets Infights
_57. Attacks people
68. Screams a lot
_ 86. Stubborn, sullen
_87. Mood changes
88. Sulks
_ 89. Suspicious
94. Teases a lot
_56h. Other physical problems
74. Shows off
_ 77. Sleeps more
93. Talks too much
_ 98. Thumbsucklng
_107. Wets salf (day)
_108. Wets the bad
34 12-13 11·12 45
33 II 9 '·'
10 8 42
19
S -,.
4 37
36
34

_91. Tatks of suicide
_112. Worries
Total

_ 92. Sleep talks/walks
_100. Trouble sleeping
Total
Broken lines = borderline clinical range
_101. Truant
_105. Uses drugs
_106. Vandalism
Total
_ 95. Temper
97. Threatens others
104. oud
Total
_109. Whining
110. Wishes to be — os) posite sex
_113. Other problems
Total
6·1-01 Edition-202
2 JI
I 27
26
n 24

Appendix 6: Method for computing height velocity values and z-scores for individual subjects

For each subject, a height velocity value will be assigned to each calendar year according to the following algorithm:

Notations:

AB = age at baseline height measurement (Months)

A1 = age at measurements assigned to years 1 (months)
HB = height at baseline (cm)

H1 = height at measurements assigned to years 1 (cm)

HV1 = height velocity at measurements assigned to years 1 (cm/year); computed only if the corresponding year was assigned a non-missing height.

Note: HB and AB are required to be non-missing for all subjects included in the height velocity analysis

Year	Time Interval (months)	Assigned height value (cm)	Assigned height velocity value (cm/year)
1	[AB, AB+12)	H1 = height value closest to the upper limit of the time interval	If H1 is non-missing, HV1=12*(H1-HB)/(A1-AB) If H1 is missing then HV1 is missing

For each non-missing height velocity value assigned to a year, the z-score will be computed as

Year	Z-score
1	If HV1 is non-missing, Z1 = (HV1 – Mean at mid-point age in years MA1)/Standard deviation at age MA1) , where the mid-point age in years MA1 = ((A1+AB)/2)/12 = (A1+AB)/24 (rounded to closest first decimal) and the mean (same as 50th percentile) and standard deviation (SD) will be read from the following tables with height velocity normative data for the corresponding gender and mid-point age in years MA1 If HV1 is missing then Z1 is missing

Height Velocity Normative Data Based on Tanner et al[6]

Notes:

The 3rd, 50th and 97th percentiles are interpolated from the height velocity charts from Tanner et

al[6] for the average maturing children. These percentiles were provided by Dr. Paul Boepple, who used them in his previous research.

Mean and standard deviation (SD) derived based on the normal (and therefore symmetrical) distribution assumption:

Mean = 50^{th} percentile

SD = [(50^{th} percentile – 3^{rd} percentile) + (97^{th} percentile – 50^{th} percentile)]/2*1.88

The 2.5 years mean and SD is applied for all subjects with age 2 - 2.5 years. For girls, the 15.5 years mean is applied for subjects with age >15.5 years, the 14.5 years SD is applied for subjects age >14.5 years; For boys, the 17.5 years mean and SD is applied for all subjects with age > 17.5 years. The values carried forward have been filled up to age 18.5 years for both boys and girls.

Girls:

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
2.5	8.6	5.9	11.3	1.4
2.6	8.5	5.8	11.2	1.4
2.7	8.4	5.7	11.0	1.4
2.8	8.3	5.7	10.9	1.4
2.9	8.2	5.6	10.7	1.4
3.0	8.1	5.5	10.6	1.4
3.1	8.0	5.4	10.5	1.3
3.2	7.9	5.4	10.3	1.3
3.3	7.8	5.3	10.2	1.3
3.4	7.7	5.3	10.0	1.3
3.5	7.6	5.2	9.9	1.3
3.6	7.5	5.1	9.8	1.2
3.7	7.4	5.1	9.7	1.2
3.8	7.4	5.0	9.5	1.2
3.9	7.3	5.0	9.4	1.2
4.0	7.2	4.9	9.3	1.2
4.1	7.1	4.9	9.2	1.2
4.2	7.0	4.8	9.2	1.2
4.3	7.0	4.8	9.1	1.2
4.4	6.9	4.7	9.1	1.1
4.5	6.8	4.7	9.0	1.1
4.6	6.8	4.7	8.9	1.1
4.7	6.7	4.7	8.8	1.1
4.8	6.7	4.6	8.8	1.1
4.9	6.6	4.6	8.7	1.1
5.0	6.6	4.6	8.6	1.1
5.1	6.6	4.6	8.5	1.1
5.2	6.5	4.6	8.5	1.0
5.3	6.5	4.5	8.4	1.0
5.4	6.4	4.5	8.4	1.0
5.5	6.4	4.5	8.3	1.0
5.6	6.4	4.5	8.2	1.0
5.7	6.3	4.5	8.2	1.0
5.8	6.3	4.4	8.1	1.0
5.9	6.2	4.4	8.1	1.0
6.0	6.2	4.4	8.0	1.0
6.1	6.2	4.4	8.0	1.0
6.2	6.2	4.4	7.9	0.9
6.3	6.1	4.3	7.9	0.9
6.4	6.1	4.3	7.8	0.9
6.5	6.1	4.3	7.8	0.9

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
6.6	6.1	4.3	7.8	0.9
6.7	6.1	4.3	7.7	0.9
6.8	6.0	4.3	7.7	0.9
6.9	6.0	4.3	7.6	0.9
7.0	6.0	4.3	7.6	0.9
7.1	6.0	4.3	7.6	0.9
7.2	6.0	4.3	7.6	0.9
7.3	5.9	4.3	7.5	0.9
7.4	5.9	4.3	7.5	0.9
7.5	5.9	4.3	7.5	0.9
7.6	5.9	4.3	7.5	0.9
7.7	5.9	4.3	7.5	0.9
7.8	5.8	4.2	7.4	0.9
7.9	5.8	4.2	7.4	0.9
8.0	5.8	4.2	7.4	0.9
8.1	5.8	4.2	7.4	0.8
8.2	5.8	4.2	7.4	0.8
8.3	5.7	4.2	7.3	0.8
8.4	5.7	4.2	7.3	0.8
8.5	5.7	4.2	7.3	0.8
8.6	5.7	4.2	7.3	0.8
8.7	5.7	4.2	7.3	0.8
8.8	5.7	4.2	7.3	0.8
8.9	5.7	4.2	7.3	0.8
9.0	5.7	4.2	7.3	0.8
9.1	5.7	4.2	7.3	0.8
9.2	5.7	4.2	7.3	0.8
9.3	5.8	4.3	7.4	0.8
9.4	5.8	4.3	7.4	0.8
9.5	5.8	4.3	7.4	0.8
9.6	5.9	4.3	7.5	0.9
9.7	6.0	4.3	7.6	0.9
9.8	6.0	4.4	7.8	0.9
9.9	6.1	4.4	7.9	0.9
10.0	6.2	4.4	8.0	1.0
10.1	6.3	4.5	8.1	1.0
10.2	6.4	4.5	8.3	1.0
10.3	6.5	4.6	8.4	1.0
10.4	6.6	4.6	8.6	1.0
10.5	6.7	4.7	8.7	1.1
10.6	6.9	4.9	8.9	1.1
10.7	7.1	5.1	9.1	1.1
10.8	7.4	5.3	9.3	1.1
10.9	7.6	5.5	9.5	1.1
11.0	7.8	5.7	9.7	1.1

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
11.1	7.9	5.8	9.8	1.1
11.2	8.0	5.9	10.0	1.1
11.3	8.1	5.9	10.1	1.1
11.4	8.2	6.0	10.3	1.1
11.5	8.3	6.1	10.4	1.1
11.6	8.1	5.9	10.2	1.2
11.7	7.9	5.7	10.1	1.2
11.8	7.7	5.5	9.9	1.2
11.9	7.5	5.3	9.8	1.2
12.0	7.3	5.1	9.6	1.2
12.1	7.0	4.8	9.3	1.2
12.2	6.7	4.5	9.0	1.2
12.3	6.5	4.2	8.6	1.2
12.4	6.2	3.9	8.3	1.2
12.5	5.9	3.6	8.0	1.2
12.6	5.6	3.3	7.7	1.1
12.7	5.3	3.1	7.3	1.1
12.8	4.9	2.8	7.0	1.1
12.9	4.6	2.6	6.6	1.1
13.0	4.3	2.3	6.3	1.1
13.1	4.0	2.1	6.0	1.0
13.2	3.8	1.9	5.7	1.0
13.3	3.5	1.6	5.4	1.0
13.4	3.3	1.4	5.1	1.0
13.5	3.0	1.2	4.8	1.0
13.6	2.8	1.0	4.5	0.9
13.7	2.5	0.9	4.2	0.9
13.8	2.3	0.7	3.8	0.8
13.9	2.0	0.6	3.5	0.8
14.0	1.8	0.4	3.2	0.7
14.1	1.6		2.9	0.7
14.2	1.4		2.6	0.6
14.3	1.3		2.4	0.6
14.4	1.1		2.1	0.5
14.5	0.9		1.8	0.5
14.6	0.8			0.5
14.7	0.7			0.5
14.8	0.6			0.5
14.9	0.5			0.5
15.0	0.4			0.5
15.1	0.3			0.5
15.2	0.3			0.5
15.3	0.2			0.5
15.4	0.2			0.5
15.5	0.1			0.5

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
15.6	0.1			0.5
15.7	0.1			0.5
15.8	0.1			0.5
15.9	0.1			0.5
16.0	0.1			0.5
16.1	0.1			0.5
16.2	0.1			0.5
16.3	0.1			0.5
16.4	0.1			0.5
16.5	0.1			0.5
16.6	0.1			0.5
16.7	0.1			0.5
16.8	0.1			0.5
16.9	0.1			0.5
17.0	0.1			0.5
17.1	0.1			0.5
17.2	0.1			0.5
17.3	0.1			0.5
17.4	0.1			0.5
17.5	0.1			0.5
17.6	0.1			0.5
17.7	0.1			0.5
17.8	0.1			0.5
17.9	0.1			0.5
18.0	0.1			0.5
18.1	0.1			0.5
18.2	0.1			0.5
18.3	0.1			0.5
18.4	0.1			0.5
18.5	0.1			0.5

Boys:

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
2.5	8.3	5.7	10.9	1.4
2.6	8.2	5.6	10.8	1.4
2.7	8.1	5.6	10.6	1.3

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
2.8	8.0	5.5	10.5	1.3
2.9	7.9	5.5	10.3	1.3
3.0	7.8	5.4	10.2	1.3
3.1	7.7	5.3	10.1	1.3
3.2	7.6	5.3	10.0	1.2
3.3	7.6	5.2	9.8	1.2
3.4	7.5	5.2	9.7	1.2
3.5	7.4	5.1	9.6	1.2
3.6	7.3	5.1	9.5	1.2
3.7	7.3	5.0	9.4	1.2
3.8	7.2	5.0	9.4	1.2
3.9	7.2	4.9	9.3	1.2
4.0	7.1	4.9	9.2	1.1
4.1	7.0	4.9	9.1	1.1
4.2	7.0	4.8	9.0	1.1
4.3	6.9	4.8	9.0	1.1
4.4	6.9	4.7	8.9	1.1
4.5	6.8	4.7	8.8	1.1
4.6	6.8	4.7	8.8	1.1
4.7	6.7	4.7	8.7	1.1
4.8	6.7	4.6	8.7	1.1
4.9	6.6	4.6	8.6	1.1
5.0	6.6	4.6	8.6	1.1
5.1	6.6	4.6	8.5	1.1
5.2	6.5	4.6	8.5	1.0
5.3	6.5	4.5	8.4	1.0
5.4	6.4	4.5	8.4	1.0
5.5	6.4	4.5	8.3	1.0
5.6	6.4	4.5	8.3	1.0
5.7	6.3	4.4	8.2	1.0
5.8	6.3	4.4	8.2	1.0
5.9	6.2	4.3	8.1	1.0
6.0	6.2	4.3	8.1	1.0
6.1	6.2	4.3	8.0	1.0
6.2	6.1	4.3	8.0	1.0
6.3	6.1	4.2	7.9	1.0
6.4	6.0	4.2	7.9	1.0
6.5	6.0	4.2	7.8	1.0
6.6	6.0	4.2	7.8	1.0
6.7	6.0	4.2	7.8	0.9
6.8	5.9	4.2	7.7	0.9
6.9	5.9	4.2	7.7	0.9
7.0	5.9	4.2	7.7	0.9
7.1	5.9	4.2	7.7	0.9
7.2	5.9	4.2	7.6	0.9

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
7.3	5.8	4.1	7.6	0.9
7.4	5.8	4.1	7.5	0.9
7.5	5.8	4.1	7.5	0.9
7.6	5.8	4.1	7.4	0.9
7.7	5.7	4.0	7.4	0.9
7.8	5.7	4.0	7.3	0.9
7.9	5.6	3.9	7.3	0.9
8.0	5.6	3.9	7.2	0.9
8.1	5.6	3.9	7.2	0.9
8.2	5.5	3.9	7.1	0.9
8.3	5.5	3.8	7.1	0.9
8.4	5.4	3.8	7.0	0.9
8.5	5.4	3.8	7.0	0.9
8.6	5.4	3.8	7.0	0.8
8.7	5.4	3.8	6.9	0.8
8.8	5.3	3.8	6.9	0.8
8.9	5.3	3.8	6.8	0.8
9.0	5.3	3.8	6.8	0.8
9.1	5.3	3.8	6.8	0.8
9.2	5.3	3.8	6.8	0.8
9.3	5.2	3.7	6.7	0.8
9.4	5.2	3.7	6.7	0.8
9.5	5.2	3.7	6.7	0.8
9.6	5.2	3.7	6.7	0.8
9.7	5.2	3.7	6.6	0.8
9.8	5.1	3.7	6.6	0.8
9.9	5.1	3.7	6.5	0.8
10.0	5.1	3.7	6.5	0.7
10.1	5.1	3.7	6.5	0.7
10.2	5.1	3.7	6.5	0.7
10.3	5.1	3.7	6.5	0.7
10.4	5.1	3.7	6.5	0.7
10.5	5.1	3.7	6.5	0.7
10.6	5.1	3.7	6.5	0.8
10.7	5.1	3.7	6.5	0.8
10.8	5.2	3.7	6.6	0.8
10.9	5.2	3.7	6.6	0.8
11.0	5.2	3.7	6.6	0.8
11.1	5.2	3.7	6.6	0.8
11.2	5.2	3.7	6.6	0.8
11.3	5.3	3.8	6.7	0.8
11.4	5.3	3.8	6.7	0.8
11.5	5.3	3.8	6.7	0.8
11.6	5.4	3.8	6.8	0.8
11.7	5.5	3.9	6.9	0.8

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
11.8	5.5	3.9	7.1	0.8
11.9	5.6	4.0	7.2	0.9
12.0	5.7	4.0	7.3	0.9
12.1	5.9	4.2	7.6	0.9
12.2	6.1	4.3	8.0	1.0
12.3	6.4	4.5	8.3	1.0
12.4	6.6	4.6	8.7	1.1
12.5	6.8	4.8	9.0	1.1
12.6	7.2	5.1	9.4	1.2
12.7	7.6	5.3	9.9	1.2
12.8	7.9	5.6	10.3	1.3
12.9	8.3	5.8	10.8	1.3
13.0	8.7	6.1	11.2	1.4
13.1	8.9	6.3	11.3	1.3
13.2	9.0	6.5	11.5	1.3
13.3	9.2	6.7	11.6	1.3
13.4	9.3	6.9	11.8	1.3
13.5	9.5	7.1	11.9	1.3
13.6	9.3	6.9	11.7	1.3
13.7	9.0	6.7	11.5	1.3
13.8	8.8	6.4	11.2	1.3
13.9	8.5	6.2	11.0	1.3
14.0	8.3	6.0	10.8	1.3
14.1	7.9	5.6	10.4	1.3
14.2	7.6	5.2	10.0	1.3
14.3	7.2	4.9	9.6	1.3
14.4	6.9	4.5	9.2	1.3
14.5	6.5	4.1	8.8	1.3
14.6	6.1	3.7	8.4	1.3
14.7	5.8	3.4	8.1	1.3
14.8	5.4	3.0	7.7	1.3
14.9	5.1	2.7	7.4	1.3
15.0	4.7	2.3	7.0	1.3
15.1	4.4	2.1	6.7	1.2
15.2	4.1	1.9	6.4	1.2
15.3	3.9	1.6	6.1	1.2
15.4	3.6	1.4	5.8	1.2
15.5	3.3	1.2	5.5	1.1
15.6	3.1	1.0	5.2	1.1
15.7	2.9	0.9	4.9	1.1
15.8	2.6	0.7	4.7	1.0
15.9	2.4	0.6	4.4	1.0
16.0	2.2	0.4	4.1	1.0
16.1	2.1		3.9	1.0
16.2	1.9		3.7	0.9

AGE (YEARS)	50th percentile / Mean	3rd percentile	97th percentile	Derived SD
16.3	1.8		3.4	0.9
16.4	1.6		3.2	0.8
16.5	1.5		3.0	0.8
16.6	1.4		2.8	0.8
16.7	1.3		2.7	0.8
16.8	1.1		2.5	0.7
16.9	1.0		2.4	0.7
17.0	0.9		2.2	0.7
17.1	0.8		2.1	0.7
17.2	0.7		2.0	0.6
17.3	0.7		1.8	0.6
17.4	0.6		1.7	0.6
17.5	0.5		1.6	0.6
17.6	0.5			0.6
17.7	0.5			0.6
17.8	0.5			0.6
17.9	0.5			0.6
18.0	0.5			0.6
18.1	0.5			0.6
18.2	0.5			0.6
18.3	0.5			0.6
18.4	0.5			0.6
18.5	0.5			0.6

Appendix 7: List of generic and brand names of AED medications

Generic names

Acetazolamide
Cannabidiol
Carbamazepine
Clobazam
Clonazepam
Diazepam
Eslicarbazepine
acetate Ethosuximide
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Nitrazepam
Oxcarbazepine
Perampanel
Piracetam
Phenobarbital
Phenytoin
Pregabalin
Primidone
Retigabine
Rufinamide
Sodium
valproate
Stiripentol
Tiagabine
Topiramate
Valproic acid
Vigabatrin
Zonisamide

Brand names (available as):

Carbogen modified release
Convulex
Desitrend
Diacomit

Diamox SR
Emeside
Epanutin
Epidiolex
Epilim
Epilim Chrono
Epilim Chronosphere
Episenta (prolonged release) Epival
Frisium
Fycompa
Gabitril
Inovelon
Keppra
Lamictal
Lyrica
Neurontin
Nootropil
Phenytoin Sodium Flynn
Rivotril
Sabril
Tapclob
Tegretol
Tegretol Prolonged Release
Topamax
Trileptal
Trobalt
Valium
Vimpat
Zarontin
Zebinix
Zonegran