
Research Report On: *An Open Label, Multicentre Study of Topiramate (Topamax®) as Adjunctive Therapy in Patients with Partial Onset Seizures with or without Secondary Generalisation, that are Inadequately Controlled*

Candidate's Name: *Dr. Paul Sussman*

Candidate's Current Qualifications: *MBChB*

Student Number: *8901824/M*

Year Started Degree: *February 2001*

Degree Submitting For: *MSc (Med) Pharmacotherapy*

Departmental Registration: *Department of Pharmacy and Pharmacology*

Supervisor's Name: *Dr. Gareth Lowndes*

Supervisor's Qualification: *PhD (Bath, UK)*

Supervisor's Department: *Department of Pharmacy and Pharmacology*

Declaration:

I, Paul Sussman declare that I supervised and implemented all aspects of developing and conducting this trial and subsequently authored this Research Report. I further declare that it has not been submitted previously towards gaining any other qualification.

Signed _____ on the

_____ day of _____.

Abstract

Background: Topiramate is an effective adjunctive anticonvulsant with a favourable safety profile. Topiramate is a sulphamate-substituted monosaccharide derived from D-fructose and is structurally unrelated to other anti-epileptic drugs. It is available in variable strength, tablet and sprinkle capsule formulations. It acts by multiple mechanisms that suggest it may be effective in several types of epilepsy. Registered recommended maximum daily doses of topiramate have decreased twice since it was first registered in South Africa. A similar trend has been seen globally. Selected trial data suggest that topiramate may be effective at lower doses than previously used. One such trial reports on a dose of less than 200 mg being used in patients who demonstrated a significant seizure rate reduction. In the majority of clinical trials 200 mg was the lowest effective dose studied. It is for this reason that this is considered the minimal effective dose. This study sets out to primarily build on the body of evidence supporting topiramate efficacy at lower doses than used previously but also examines tolerability to the drug at these doses.

Methods: A total of eighteen patients (mean age, 33.9 years) with partial onset seizures, with or without secondary generalisation, previously resistant to anti-epileptic drug therapy (mean baseline seizure rate of twelve seizures per month) were treated with open label topiramate of 150 mg per day. Combinations of 25 mg and 50 mg tablets were administered during the trial. A minimum four-week Baseline Phase was instituted at the outset during which baseline seizure rates were recorded. A six-week Titration Phase followed the Baseline Phase, after which patients received 150 mg topiramate per day during a Maintenance Phase lasting twelve weeks. Seizure reduction was calculated from seizure counts during the last four weeks and last six weeks of the Maintenance Phase compared to the baseline.

Results: Sixty-seven percent and sixty-one percent of patients demonstrated a reduction, relative to the baseline, of fifty percent or greater in their seizure counts over the last six and four weeks respectively of the Maintenance Phase. Two (eleven percent) patients reported having no seizures during the last four weeks of the Maintenance Phase. The most commonly reported adverse events were related to the central nervous system. No patients discontinued topiramate therapy due to adverse events.

Conclusion: Findings from this study suggest that topiramate, even at lower than usual doses, is a useful agent for longstanding seizure control, with some patients becoming free of seizures.

Acknowledgements

I would like to thank the investigators for their participation in this study and Janssen-Cilag, South Africa for funding it.

List of Abbreviations

AED	Anti-Epileptic Drug
AZM	Acetazolamide
BZD	Benzodiazepine
CBZ	Carbamazepine
CI	Confidence Interval
CRF	Case Record Form
ESM	Ethosuximide
FBM	Felbamate
GABA	Gama-Aminobutyric Acid
GBP	Gabapentin
LTG	Lamotrigine
MSM	Methsuximide
NMDA	N-Methyl-D-Aspartate
PB	Phenobarbital
PHT	Phenytoin
TGB	Tiagabine
TPM	Topiramate
VGB	Vigabatrin
VPA	Valproic Acid
ZNA	Zonisamide

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1. Introduction

Topiramate (TPM) is an effective adjunctive anticonvulsant with a favourable safety profile. Clinical trials have provided data supporting the safety and efficacy profile of TPM in patients with uncontrolled partial onset seizures with or without secondary generalisation^{1, 2, 3, 4, 5}.

In the majority of clinical trials 200 mg was the lowest effective dose studied^{1, 2, 3, 4, 5}. It is for this reason that this is considered the minimal effective dose.

Subsequent trials are providing data supporting efficacy in these patients at lower doses than used previously^{2, 6, 7}. One such trial reports on a dose of less than 200 mg being used in patients who demonstrated a significant seizure rate reduction⁶.

This study assesses the efficacy of TPM (150 mg per day) in patients with partial onset seizures with or without secondary generalisation, that are inadequately controlled.

1.1 Background

1.1.1 Epilepsy Perspectives

Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process⁹. Using the definition of epilepsy as two or more unprovoked seizures its prevalence has been estimated at five to ten persons per thousand⁹.

Approximately twenty-five percent to thirty percent of patients with epilepsy have seizures that are only partially controlled despite combination anti-epileptic drug (AED) therapy being used³. Seizure frequency is the most important predictor of epilepsy's impact on quality of life³. For some patients, the new AEDs like TPM may provide more effective treatment than was possible with conventional AEDs³.

Seizures are broadly classified into partial seizures, primarily generalised seizures and unclassified seizures. Simple partial seizures cause motor, sensory, autonomic, or psychic symptoms without an obvious alteration in consciousness ⁹. Generalised seizures arise from both cerebral hemispheres simultaneously, and include tonic-clonic seizures occurring in approximately ten percent of all persons with epilepsy ⁹.

1.1.2 Topiramate: Classification and Indications

Topiramate is classified as follows: A.2.5 Anticonvulsants, including anti-epileptics ⁸.

When first available, new AEDs, like TPM, are typically used as adjunctive therapy i.e., added to an existing anti-epileptic regimen when traditional first-line therapies have failed.

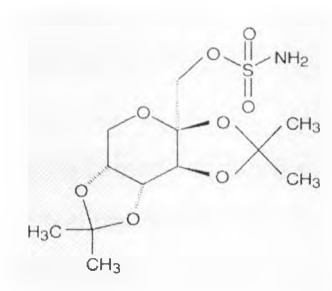
Topiramate is an effective adjunctive anticonvulsant with a favourable safety profile. Clinical trials have provided data supporting the safety and efficacy profile of TPM in patients with uncontrolled partial onset seizures with or without secondary generalisation ^{1, 2, 3, 4, 5}. It is furthermore indicated as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome and for primary generalized tonic-clonic seizures.

Lennox-Gastaut Syndrome is a rare disorder of infancy or early childhood characterized by frequent episodes of uncontrolled electrical disturbances in the brain (seizures) and, in many cases, abnormal delays in the acquisition of skills that require the coordination of mental and muscular activity (psychomotor retardation). Individuals with the disorder may experience several different types of seizures.

1.1.3 Topiramate: Structure

Topiramate is an anti-epileptic agent classified as a sulfamate-substituted monosaccharide ⁸. The structural formula is depicted in figure 1 ³.

Fig. 1. Structural Formula of Topiramate



1.1.4 Topiramate: Pharmacological Action

Table 1 contains the main molecular actions of clinically important anti-epileptic drugs and more specifically represents the extended pharmacological activity of TPM¹⁰.

Table 1. Principal Molecular Actions of Clinically Important Anti-Epileptic Drugs

	PHY CBZ	BZD	PR	ESM MSM	VPA	AZM	FBM	GBP	LTG	TPM	TGB	VGB	ZNA
Inhibits voltage-gated sodium channels	+						+			+			
Inhibits sodium currents through non-NMDA receptors													
Inhibits calcium currents through NMDA receptors													
Inhibits low-threshold T-type voltage-gated calcium channels													
Enhances GABA _A -receptor mediated chloride currents													
Inhibits pre-synaptic GABA reuptake													
Increases brain GABA by inhibiting GABA transaminase													
Increases brain GABA through unknown mechanisms													
Inhibits brain carbonic anhydrase activity													
Novel actions not yet clearly defined													

PHY, phenytoin; CBZ, carbamazepine; BZD, benzodiazepine; PR, phenobarbital; ESM, ethosuximide; MSM, methsuximide; VPA, valproic acid; AZM, acetazolamide; FBM, felbamate; GBP, gabapentin; LTG, lamotrigine; TPM, topiramate; TGB, tiagabine; VGB, vigabatrin; ZNA, zonisamide.

In summary the pharmacological properties of TPM that have been identified as possibly contributing to its anticonvulsant activity include ^{2, 8, 10}:

- Topiramate reduces the frequency at which action potentials are generated when neurones are subjected to a sustained depolarisation indicative of a state-dependent blockade of voltage-sensitive sodium channels;
- Topiramate markedly enhances the activity of gamma-aminobutyric acid (GABA) at some types of GABA receptors;
- Topiramate weakly antagonises the excitatory activity of a kainate subtype of glutamate receptor but has no apparent effect on the activity of N-methyl-D-aspartate (NMDA) at the NMDA receptor subtype;
- Topiramate inhibits some isoenzymes of carbonic anhydrase but this is not thought to be a major component of its anti-epileptic activity.

1.1.5 Topiramate: Pharmacokinetics

Topiramate exhibits low intersubject variability in plasma concentrations and, therefore, has predictable pharmacokinetics ^{2, 3, 8}. In healthy subjects, pharmacokinetics of TPM are linear over a single oral dose range of 100 mg to 400 mg ^{2, 3, 8}.

Topiramate is not extensively metabolised and is primarily eliminated renally ^{2, 3, 8}. Patients with normal renal function may take four to eight days to reach steady-state plasma concentrations ⁸. Following administration of multiple doses of 50 mg and 100 mg of TPM twice a day, the mean plasma elimination half-life was approximately twenty-one hours ^{3, 8}.

Topiramate is rapidly and well absorbed ^{3, 8}. Following oral administration of 100 mg TPM to healthy subjects, a mean peak plasma concentration of 1.5 microgram per millilitre was achieved within two to three hours ⁸. Based on the recovery of radioactivity from the urine the mean extent of absorption of a 100 mg oral dose of ¹⁴C-topiramate was at least eighty-one percent. There was no clinically significant effect of food on the bioavailability of TPM ⁸.

Generally, thirteen percent to seventeen percent of TPM is bound to plasma protein^{3, 8}.

The mean apparent volume of distribution was 0.55 to 0.80 litres per kilogram for a single dose range of 100 mg to 1200 mg^{3, 8}.

The addition of TPM to other anti-epileptic drugs (phenytoin, carbamazepine, valproic acid) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TPM to phenytoin may result in an increase of plasma concentrations of phenytoin^{3, 8}.

Phenytoin and carbamazepine decrease the plasma concentration of TPM^{3, 8}.

1.1.6 Topiramate: Contra-Indications

Hypersensitivity to any component of this product⁸.

1.1.7 Topiramate: Adverse Events

The most commonly reported treatment-emergent adverse events in adults in double-blind, placebo-controlled trials were related to the central nervous system, including somnolence, fatigue, ataxia, dizziness and confusion².

1.1.8 Topiramate: Dosing Perspectives

When TPM was first registered, the recommended maximum dosage was 800 mg per day. Follow-up trials conducted globally led to the recommended maximum dosage to come down to 600 mg per day and again to 400 mg per day. Presently the registered usual maximum dose in most countries, including South Africa, is 400 mg per day. The registered minimum dose remained 200 mg per day during the above period since it was the lowest effective dose studied in the majority of clinical trials^{1, 2, 3, 4, 5, 8}. A dose of less than 200 mg has demonstrated a significant seizure rate reduction in one trial⁶. Other

trials also provide data supporting efficacy in patients at lower doses than used previously^{2, 7}. A dose of 150 mg per day was chosen in this trial to further evaluate lower doses than used previously. Daily doses were divided into two during this study. The largest dose was taken at night in an attempt to minimise adverse events, especially fatigue, during daytime hours.

1.2 Aims and Objectives

The primary objective of the study was to determine the percentage of patients that demonstrated a significant reduction in their seizure rate. This is deemed to be a reduction by fifty percent or more in the seizure rate of a particular patient.

This reduction is the variation from the baseline seizure rate achieved on the concomitant AED therapy alone.

The secondary objective is to identify the number of adverse events related to the TPM therapy and interventions that occurred.

1.3 Subjects and Methods

1.3.1 Study Design

This clinical trial was a multicentre, open-label, single-group study of twenty-three patients with partial onset seizures, with or without secondary generalisation that were inadequately controlled. All patients received TPM after a baseline seizure record was established. The daily dosing was escalated to 150 mg per day on which patients were maintained for twelve weeks. Topiramate was taken orally twice daily i.e. 75 mg in the morning and 75 mg at night independent of meals. Patients who wished to continue with TPM therapy after their twelve weeks of trial maintenance therapy were able to do so. Participation in the trial ended for these patients after the Maintenance Phase. Alternatively patients could have chosen to stop TPM therapy. At the end of the

Maintenance Phase their TPM doses were down-titrated and finally discontinued, at which point trial participation ended for this group of patients.

Ten investigators at nine South African centres participated in this study, following approval of independent ethics committees. Appendix 1 to this report contains ethics approval notifications. The trial was performed in accordance with relevant articles of the Declaration of Helsinki (fifth revision) and national and international Good Clinical Practice guidelines. The nature of the trial was explained in detail to patients prior to participation, and voluntary written informed consent was obtained prior to trial entry. Appendix 2 to this report contains the patient information and informed consent form.

1.3.2 Patients

The specific inclusion and exclusion criteria for enrolling subjects in this study are noted in Table 2 and Table 3.

Table 2. Inclusion Criteria

- | |
|---|
| <ol style="list-style-type: none">1. Male and female patients twelve years of age or older may participate.2. Patients must have partial epilepsy treated with one or more AEDs.3. Patient records of the frequency and type of seizure and adverse events during at least the past four weeks (i.e. a reliable retrospective baseline phase seizure history and adverse event profile) or diary records of a prospective four-week to eight-week baseline phase frequency and type of seizure before TPM is commenced.4. Patients, their parents, or legally authorised guardian must sign the informed consent after the nature of the study has been fully explained. |
|---|

Table 3. Exclusion Criteria

1. Patients that have received topiramate previously.
2. Patients who do not have epilepsy, e.g. pseudoseizures and those with a treatable cause of seizures (e.g. a metabolic disturbance, toxic exposure, or an active infection).
3. Patients with progressive neurological disorders.
4. Patients with a documented history (in the past three months) of status epilepticus (tonic/clonic) whilst complying with appropriate anticonvulsant therapy.
5. Patients with any medical or social condition which may impair their reliable participation or safety in the study.
6. Patients whose current therapy include any experimental agent or have received an experimental agent within thirty days of study entry.
7. Patients with a history of nephrolithiasis.
8. Patients who are unable to take their medication as requested and/or maintain a seizure calendar either independently or with assistance. If assistance is required for reliable compliance, then it is expected that this assistance will be consistently available throughout the study.
9. Women of childbearing potential should be instructed not to become pregnant during the course of the study. Patients using an oral contraceptive should receive a preparation containing not less than 50 µg of oestrogen. If pregnancy should nevertheless occur, treatment with TPM should be discontinued, an adverse event form completed and the sponsor informed immediately. The outcome of the pregnancy should be documented.
10. Subjects who have a history of poor compliance with past drug therapies, as judged by the investigator.

Healthy patients older than seventy years, were eligible for enrolment while they met the inclusion criteria. Like any other patient being considered for enrolment they required no exclusion criteria to be present i.e. medical condition which may impair their safety in the study.

1.3.3 Evaluation and Treatment

This trial comprised four phases: Baseline Phase, Titration Phase, Maintenance Phase and Termination/Exit Phase.

1.3.3.1 Baseline Phase

The Baseline Phase lasted for up to fifty-six days. Patients requiring a longer Baseline Phase were not eligible for the trial. During the Baseline Phase the patient did not receive any trial medication but continued their epileptic drug treatment received before they entered the study. The doctor explained the trial to the patient and/or guardian at the outset and voluntary written informed consent was obtained prior to performing any trial related procedures. An accurate record of the patient's seizure history (type and number) was required for at least four weeks prior to commencing the Titration Phase and acquired in one of two ways.

The patient was instructed to keep a record of their seizure frequency and seizure type for the ensuing twenty-eight to fifty-six days. This was documented in a specifically designed patient diary issued by the investigator. Appendix 3 to this report contains the specifically designed patient diary issued by the investigator. The patient also recorded any adverse events possibly attributed to medication taken during this period.

Alternatively, a reliable seizure history of the four-week period, as a minimum, just prior to trial participation, was taken from the patient and/or their family by the doctor and documented in the source notes. The patient was also required to report any possible adverse events attributed to medication taken during this period. This was also documented in the source (doctor's) notes.

Recordings in a diary were preferred but the alternative approach described above shortened the Baseline Phase i.e. the Titration Phase could commence as soon as the

laboratory results were known. This option excluded the patient from a prospective Baseline Phase.

An inclusion/exclusion criteria checklist was completed. A medical history was taken and a physical examination done. The appropriate clinical laboratory investigations were ordered and are listed in Table 4. As appropriate, a pregnancy test was performed. Urine dipstick analysis was performed. The patient's case record form (CRF) was completed. Appendix 4 to this report contains the CRF used during this study.

Clinical laboratory investigations ordered are summarised in Table 4. Investigations were performed by Ampath and Van Drimmelen laboratories.

Table 4. Clinical Laboratory Investigations Done Prior to Receiving Topiramate

Haematology: white cell count, haemoglobin, platelets
Chemistry: urea, electrolytes
Liver enzyme tests: alanine transaminase, aspartate transaminase, gamma-glutamyltransferase

1.3.3.2 Titration Phase

This phase immediately followed the Baseline Phase and extended for six weeks. The doctor dispensed the study medication during this phase. Dosing was titrated by 25 mg per week to reach the assigned target dose of 150 mg per day. Topiramate was taken twice daily with the largest dose taken at night. The largest dose was taken at night in an attempt to minimise adverse events, especially fatigue, during daytime hours. Compliance throughout the trial was monitored by recording unused trial medication and histories from patients and those in attendance with them. Dose adjustments were allowed only if the subject was experiencing tolerability problems. The most commonly reported treatment-emergent adverse events include somnolence, fatigue, ataxia, dizziness and confusion. The investigator together with the patient decided on back

titration to alleviate adverse events. This period was accounted for. Re-challenge then took place attempting to reach the target dose. Seizure rates were recorded in specific patient diaries. Appendix 3 to this report contains the specifically designed patient diary issued by the investigator. The patient's vital signs were monitored at each visit throughout this phase.

1.3.3.3 Maintenance Phase

This period immediately followed the Titration Phase. The patients were directed to appropriate pharmacies to acquire the medication. During this period the dose of study medication remained constant unless the subject was having tolerability problems in which case the dose may have been reduced. Any period during which back titration occurred to alleviate adverse events was accounted for. Dose adjustments permitted during the trial are discussed under 1.3.3.5 Dose Adjustments with Tolerability Problems.

Subjects were considered as having completed the Maintenance Phase if they had completed a full twelve-week period at a dose of 150 mg per day. This period was continuous or interrupted by adverse-event management.

Seizure rates were recorded in specific patient diaries. Appendix 3 to this report contains the specifically designed patient diary. The patient's vital signs were monitored at each visit throughout this phase i.e. at six and twelve weeks. The investigating doctor did a complete physical examination at the end of this phase. At this point the investigating doctor, together with the patient, decided whether TPM therapy would continue after the trial has ended. If it was decided to continue TPM therapy after the trial ended, the trial ended at this point. This would then be the final trial visit. If discontinuation was decided upon the patient entered the Termination or Exit Phase. Efficacy, tolerability and affordability determined whether patients continued or discontinued TPM.

1.3.3.4 Termination or Exit Phase

The daily TPM dose was tapered by 100 mg weekly i.e. the patient received 50 mg TPM as a total daily dose for one week and no TPM for a further week. Seizure rates were recorded in specific patient diaries. Appendix 3 to this report contains the specifically designed patient diary. The investigating doctor did a complete physical examination at the end of this phase.

1.3.3.5 Dose Adjustments with Tolerability Problems

The following dose adjustments were permitted in the event of tolerability problems throughout the trial.

If adverse events attributed to the use of TPM occurred, the investigator could reduce the dose of TPM by up to 50 mg per day. This dose reduction was done in increments of 25 mg per day each week, over a two to four week period. The daily dose was then escalated again by twenty-five-milligram increments each week until the maintenance daily dose was reached i.e. 150 mg per day. Attribution to the use of TPM was supported if adverse events resolved.

The fixed dose maintenance period had to encompass a total of twelve weeks during which the patient received a dose of 150 mg per day. If intervention for possible adverse events attributed to TPM took place; the period of intervention was accounted for and was not included in this twelve-week period. Thus the fixed-dose maintenance period was extended and the visit dates adjusted accordingly.

If adverse events were not adequately alleviated patients exited the trial after their doses were tapered by 100 mg each week.

A maximum of three attempts to reach the target dose was allowed throughout the trial. If this failed the patient ended their participation in the study. They were either tapered off

the study drug or continued to take their maximum tolerated dose of TPM independent of the trial per se.

2. Data Analysis

Efficacy of the topiramate (TPM) therapy was assessed by evaluating the reduction in seizures from the Baseline Phase to the end of the Maintenance Phase. Seizure rates were evaluated from specific diary cards that the patients were asked to keep. Appendix 3 to this report contains the specifically designed diary card. Adverse events were also noted and their management documented.

A consultant group of neurologists noted that a fifty percent reduction in seizure rate is a commonly accepted reduction rate aimed for in epilepsy trials. Janssen-Cilag, the manufacturer of TPM reports through personal communication, that treatment maintenance with 150 mg per day should yield a fifty percent reduction in seizure rate in approximately two thirds of patients.

The Baseline Phase seizure rate was compared to the seizure rate during the last four weeks and six weeks of the Maintenance Phase.

Continuous variables were summarized by mean, median, standard deviation, minimum and maximum values. Categorical variables were summarized by frequency counts in the different response categories. Narrative variables were summarized by listings and frequency counts.

Temporal changes in mean and median values were tested for significance by the paired t test and the Wilcoxon signed ranks test respectively.

Statistical analysis was performed by ClinStat CC, Pretoria, South Africa. All analyses were carried out using SAS[®] run under Microsoft[®] Windows NT[®].

P-values ≤ 0.05 were considered significant.

3. Results

A total of twenty-two patients were recruited into the study. Four patients were withdrawn from the study. Two of these patients demonstrated poor compliance i.e. poor diary keeping and missing follow-up appointments. One patient had used TPM prior to commencing the trial and another enrolled at a research site that was closed subsequent to being recruited.

The eighteen patients that completed the trial comprised eleven male patients and seven female patients. The average age of these patients was 33.9 years ranging from fifteen years to fifty-four years.

Seizure counts were reported for varying time intervals throughout the study. For purposes of the analysis all seizure counts were converted to counts over a thirty-day interval.

The efficacy of TPM treatment was measured by the reduction in seizures from baseline to the end of the Maintenance Phase, and was determined in two ways in each patient, namely:

1. The absolute reduction in seizure count, obtained by subtracting the seizure count at the end of the Maintenance Phase from the baseline seizure count;
2. The percentage reduction in seizure count, obtained by expressing the absolute reduction in seizure count as a percentage of the baseline seizure count.

For purposes of the statistical analysis the end of the Maintenance Phase was interpreted in two ways, namely as the last six weeks (forty-two days) and the last four weeks (twenty-eight days) of the Maintenance Phase. Seizure counts taken over these two intervals, converted to counts over a thirty-day interval, were taken as the seizure counts at the end of the Maintenance Phase.

The primary efficacy variable was the percentage of patients that demonstrated at least a fifty percent reduction in their seizure counts from baseline to the end of the Maintenance Phase.

3.1 Absolute Reduction in Seizure Count

Appendix 5 to this report contains a summary of the following information on a per patient basis:

- The baseline time interval (days) over which baseline seizure counts were taken;
- Actual seizure counts over the baseline time interval, the last six weeks (forty-two days) and the last four weeks (twenty-eight days) of the Maintenance Phase;
- Converted actual seizure counts to seizure counts in thirty days over the baseline time interval, the last six weeks (forty-two days) and the last four weeks (twenty-eight days) of the Maintenance Phase.

Table 5 contains the basic statistics for the numbers of seizures in thirty days at baseline, over the last six weeks (forty-two days), and over the last four weeks (twenty-eight days) of the Maintenance Phase, together with the reductions in seizure counts during the last six weeks and the last four weeks relative to the seizure count at baseline. Also included are ninety-five percent confidence intervals (CIs) for the mean reductions in seizure counts. The p-values in columns six and eight indicate the significance of the reduction in the mean and median seizure counts.

Table 5. Absolute Reduction in Seizure Count

	Number of seizures in 30 days						
	Base-line	Last 6 weeks	Last 4 weeks	Reduction from baseline during last			
				6 weeks	p	4 weeks	p
Number of patients	18	18	18	18		18	
Mean number of seizures	11.52	5.71	5.77	5.81	0.003*	5.75	0.004*
Median number of seizures	5.31	2.86	3.21	4.19	<0.001 *	3.70	<0.001 *
Standard deviation	16.46	13.48	12.60	7.21		7.38	
Minimum	0.88	0	0				
Maximum	70.38	59.29	55.71				
95% CI for mean reduction				2.22 – 9.40		2.08 – 9.42	

* Statistically highly significant

The mean absolute reductions of seizure counts in thirty days, relative to baseline, were statistically highly significant over the last six weeks as well as over the last four weeks of the Maintenance Phase. The power of the (paired) t test was eighty-nine percent for the last six weeks and eighty-seven percent for the last four weeks.

The median absolute reductions of seizure counts in thirty days, relative to baseline, were also statistically highly significant over the last six weeks as well as over the last four weeks of the maintenance phase.

3.2 Percentage Reduction in Seizure Count

Appendix 6 to this report contains a summary of the percentage reductions in seizure counts, relative to baseline, for all patients over the last six weeks (forty-two days) of the Maintenance Phase, and the last four weeks (twenty-eight days) of the Maintenance Phase:

- Twelve out the eighteen patients, i.e. approximately sixty-seven percent, with a ninety-five percent confidence interval of approximately forty-five percent to eighty-nine percent, demonstrated a reduction, relative to baseline, of greater than fifty percent in their seizure counts over the last six weeks (forty-two days) of the Maintenance Phase;
- Eleven out of the eighteen patients, i.e. approximately sixty-one percent, with a ninety-five percent confidence interval of approximately thirty-nine percent to eighty-four percent, demonstrated a reduction, relative to baseline, of fifty percent or greater in their seizure counts over the last four weeks (twenty-eight days) of the Maintenance Phase.

3.3 Concomitant Anti-Epileptic Drugs

Appendix 7 to this report contains a per patient listing of all the concomitant Anti-Epileptic Drugs (AEDs) that patients were using upon entry into the study, together with the total daily dose. All these drugs were continued during the study.

A summary of all the different drugs, and the number and percentage of patients that used each drug, is given in Table 6 below. Note that the numbers of patients don't add up to eighteen since a patient could have been on more than one drug (see Appendix 7).

Table 6. Concomitant Anti-Epileptic Drugs at Start of the Study

	Number (%) of patients
Lamotrigine (Lamictin®)	6 (33.3)
Carbamazepine (Tegretol®)	6 (33.3)
Sodium valproate (Epilim®)	5 (27.8)
Phenytoin	4 (22.2)
Clonazepam (Rivotril®)	2 (11.1)
Valproic acid (Convulex®)	1 (5.6)
Oxcarbazepine (Trileptal®)	1 (5.6)
Clobazam (Urbanol®)	1 (5.6)
Carbamazepine (Degranol®)	1 (5.6)
Phenytoin (Epanutin®)	1 (5.6)

3.4 Adverse events

Adverse events were reported for five out of the eighteen patients. A detailed description of the events is given in Appendix 8 to this report.

One patient presented with a decrease in concentration on two occasions (probably and very likely related to the test drug), headaches (probably related to the test drug) and weight loss (very likely related to the test drug). One patient presented with paresthesia (probably related to the test drug). One patient experienced weight loss (very likely related to the test drug). One patient presented with a tender abdomen and one patient presented with an episode of pre-syncope, both of which were reported as not related to the test drug.

No serious adverse events were reported and no deaths occurred.

4. Discussion

Adjunctive topiramate (TPM) therapy resulted in a significant decrease in seizure rates in patients with partial onset seizures with or without secondary generalisation, that were inadequately controlled. This result was achieved using lower doses than previously used.

TPM's pharmacological actions are unique when comparing them with other anti-epileptic drugs (AEDs) ¹⁰. It could be postulated that TPM's unique range of activity lends itself to being an appropriate adjunctive therapy in previously uncontrolled epilepsy.

It is becoming increasingly more difficult to categorize a specific AED on the basis of its effects on a particular molecular substrate ¹⁰. Several AEDs likely possess important mechanisms that are not yet clearly defined, and we have much more to learn about the impact of these drugs on epileptogenesis per se ¹⁰.

Future research may furthermore assist in delineating the exact pathophysiological mechanisms responsible for each type of epilepsy allowing for the application of specifically targeted therapy.

Even though similar pharmacological actions of AEDs used in combination may suggest a synergistic outcome, the pharmacokinetics related to drug interactions between these drugs also need to be noted. These kinetics relate to differing metabolism involving the cytochrome-P450 system. The kinetics of other AEDs are generally not affected by concomitant TPM therapy ^{3, 5, 8}. However, in some patients phenytoin plasma concentrations increase significantly ^{3, 5, 8}.

In this study two patients demonstrated an increase in seizure rates. One of these patients was receiving lamotrigine, 300 mg per day and the other phenytoin, 600 mg per day prior to receiving TPM. These doses were not altered during the trial.

Phenytoin plasma concentration measurements were not performed after commencing TPM therapy in the patient noted above. In view of the phenytoin levels potentially being increased rather than decreased, an interaction of this nature does not support an increase in seizure rate. At upper therapeutic and toxic levels of phenytoin, nausea, vomiting, tremor, mental confusion and several other symptoms may be reported⁸. This patient did not report any adverse events during the trial. It is thus also reasonable to assume that if the phenytoin plasma concentration did increase, it did not reach upper therapeutic or toxic levels. Phenytoin's potent induction of the hepatic cytochrome-P450 system could however account for an increase in seizure rate in this patient.

Topiramate pharmacokinetic drug interactions with lamotrigine have not generally been described according to their manufacturers. As such it remains difficult to relate the increase in seizure rate, in the other patient noted above, to a topiramate-lamotrigine kinetic drug-interaction.

Other possible explanations for seizure rate increases in the two patients noted above also include factors outside of drug-interactions like an increase in daily stress, environmental exposure etc. These factors were not explored during the study.

It should furthermore be noted that the increased seizure counts reflected in the two patients mentioned above seem very large but are exaggerated since percentage-changes were calculated that incorporated small numbers.

A statistically significant number of patients demonstrated a reduction in their seizure rate by fifty percent or more. It is reasonable to assume that this outcome relates to the unique pharmacological action of TPM described in this chapter. The ultimate goal albeit a difficult one to achieve, in historically refractory patients, remains being seizure-free. Two of the eighteen (eleven percent) patients were seizure-free at the end of the trial. Results from this study highlight TPM's potential, at lower doses than previously used, to reduce seizure-rates significantly and even to zero in some patients and should urge those prescribing TPM to actively identify the lowest effective doses for patients.

5. Conclusions

The findings from this study are supportive of other trials providing data supporting efficacy in patients at lower doses than used previously ^{2, 6, 7}. It provides evidence that some patients can achieve significant seizure rate reduction and even achieve the goal of becoming seizure free at these doses. Further research, with emphasis on long-term outcomes, is necessary to build on this body of support for using lower doses than used previously.

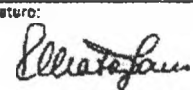
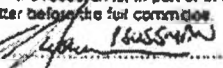
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Appendices

Ethics Approval Notifications

Appendix 1.

INDEPENDENT ETHICS COMMITTEE FORM		
Reference No.: 010903	Date of Meeting: 7 th September 2001	
Principal Investigator: Dr Paul Gossman		
Protocol title: "An open label, multi centre study of topiramate (topamax) as adjunctive therapy in patients with partial onset seizures with or without secondary generalisation, that are inadequately controlled. The aim is to assess efficacy at 150 milligrams per day"		
DOCUMENTS REVIEWED		TICK AS APPROPRIATE
Protocol Name: TOP-RSA-01; PHASE IV	Date: 11 September 2000	☒
Protocol Amendment No.: 1	Date: 9 May 2001	☒
Investigator's Brochure:		☒
Subject Information/Consent form: Final Version date: 11/09/2000, Amendment 01 date: 09/03/2001		☒
Adverse events (if applicable):		☒
Insurance/Compensation for subjects:		☒
Synopsis of Study:		☒
Other:		☐
DETAILS OF COMMITTEE		
Name: University of the Witwatersrand Committee for Research on Human Subjects (Medical)		
Address: Division of the Deputy Registrar (Research) Department of Research Senate House University of the Witwatersrand 1 Jan Smuts Avenue BRAAMFONTEIN Johannesburg		
DETAILS OF MEETING		
Is the Investigator a member of the committee?	YES	NO
If "Yes" did he/she vote?	☒	☐
Is the Committee organised and operated according to applicable laws and regulations together with:		
Local GCP requirements	☒	☐
ICH GCP requirements	☒	☐
FDA GCP requirements	☒	☐
Progress reports required on a 6 monthly basis	☒	☐
DECISION ON APPROVAL: Is approval given to conduct the trial?		Tick as appropriate
Yes - with no conditions		☐
Yes - with conditions		☐
Specify conditions:		
No		☐
Specify reasons:		
SIGNATURES		
I confirm that the details on this form are correct:		
Name:	Signature:	Date:
Chairperson of Committee		19 11 01
DECLARATION OF INVESTIGATOR(S)		
To be completed in duplicate and ONE COPY returned to the Secretary at Wits Health Consortium, Healthcare Park, 27 Eton Road, Parktown, 2193		
I/We fully understand the conditions under which I am/we are authorised to carry out and complete the above-mentioned research and I/we agree to ensure full compliance with these conditions. Should any amendment, alteration or departure be contemplated from the research procedure methodology or manner of execution I/we will communicate with the Chairman of the Committee for Research on Human Subjects (Medical) for approval prior to acting on any of the above mentioned proposed amendments, alterations or departures. I am/we are fully aware that any unauthorised amendment, alteration or departure as above will amount to misconduct and may lead to the institution of disciplinary procedures.		
Any approval given by the CRHS is conditional upon consent being obtained by the Investigator/s from the Superintendent (or equivalent official) of the hospital, clinic or institution in which the research is, in part or in full, to take place. The Chairman may of course at his discretion place the matter before the full committee.		
DATE: 29 NOVEMBER 2001	SIGNATURE: 	
PROTOCOL NUMBER: TOP-RSA-01		

Attachments: Members of the Ethics Committee involved in approval

RCO Box 786
Pretoria 0082
Republic of South Africa



PHARMA-ETHICS

Pharma-Ethics (Pty) Ltd
Registration No. 99/13446/07
123 Amcar Road,
Lyttelton Manor 0157
Tel: (012) 664-7976/7
Fax: (012) 664-6355
E-mail: barbara@shibboleth.co.za

ETH/J-C06789/BR

16 MAY 2001

Tania Wales
JANSSEN-CILAG
P.O. Box 785939
SANDTON
2146

Dear Tania,

RE: AMENDMENT 01

PROTOCOL NO: TOP-RSA-01, PHASE IV

PROTOCOL TITLE: An open label, multicentre study of topiramate (topamax®) as adjunctive therapy in patients with partial onset seizures with or without secondary generalization, that are inadequately controlled. The aim is to assess efficacy at 150 milligrams per day

Your letter dated 14 May 2001 refers.

Quorum approval is hereby given for the following documents for the above-mentioned study:

- 1) Protocol: TOP-RSA-01; PHASE 4, Amendment 01 issue date 09 May 2001
- 2) Informed Consent Form and Patient Information Sheet in English RSA Version 2, dated 09/05/01, Pharma-Ethics Version, dated 14/05/01

Thank you for the MCC letter of notification of the proposed Amendment 01, for the above-mentioned study.

The contents have been noted.

Regards,


MR V.E. JANSE VAN RENSBURG
ACTING CHAIRMAN: PHARMA-ETHICS


DR E. HAMMANN
MBChB DOH MPharmMed

PATIENT INFORMATION AND INFORMED CONSENT FORM**PROJECT NUMBER:** TOP-RSA-01**STUDY DRUG:** TOPIRAMATE**SPONSOR:** JANSSEN-CILAG**TITLE:** AN OPEN LABEL, MULTICENTRE STUDY OF TOPIRAMATE (TOPAMAX®) AS ADJUNCTIVE THERAPY IN PATIENTS WITH PARTIAL ONSET SEIZURES WITH OR WITHOUT SECONDARY GENERALISATION, THAT ARE INADEQUATELY CONTROLLED. THE AIM IS TO ASSESS EFFICACY AT 150 MILLIGRAMS PER DAY**PROTOCOL DATE:** Final 11 September 2000**AMENMENT DATE** 09 May 2001

INTRODUCTION

Dear patient

You are invited to volunteer for a Phase IV research study regarding a drug named Topiramate. This information leaflet is to help you decide if you would consider participating. Before you agree to take part in this study, you should fully understand the reasons for your involvement. If you have any questions that are not fully explained in this leaflet, you should not hesitate to ask the investigator.

_____ for an explanation.

WHAT IS THE OBJECTIVE OF THE STUDY

You have been diagnosed with partial onset seizures.

The investigator would like you to take part in the research of a drug called Topiramate. Topiramate is an approved drug for the treatment of one type of epilepsy (partial onset seizures) in adults and children when it is given with other epilepsy drugs in South Africa and other countries.

The objective of the study is to assess the efficacy of Topiramate and to see if it can reduce the number of seizures (fits) you are having in combination with other anti-epileptic medication

Approximately 60 patients in South Africa will take part in the trial.

During the study you will receive Topiramate 150 mg.

ALTERNATIVE TREATMENT

You are aware that there are other treatments available for the treatment of epilepsy. Your doctor has explained the other treatments and you understand their advantages and risks.

QUALIFICATIONS TO PARTICIPATE

To volunteer for this research product you must satisfy the following inclusion criteria

- Subjects who are Male or female patients ≥ 12 years of age may participate.
- Subjects must have partial epilepsy treated on one or more anti-epileptic drug/s (AED/s).
- Subjects must record the frequency and type of seizure they experience during the 4 to 8 weeks prior to entering the study.

OR

- Subjects and/or family must be able to provide the investigator with a reliable seizure history in the past month prior to entering the study. A diarised history is desirable but not essential if this retrospective Baseline Phase is to be used.
- Subjects, their parents, or legally authorized guardian must sign the informed consent after the nature of the study has been fully explained.

STUDY PROCEDURES

The study will last up to 9 months depending on when you enter the study or less if the sponsor discontinues the study. During this time approximately 60 patients must be included in South Africa.

The following study procedures will be followed during the course of the study if you decide to participate in the trial:

The doctor will do screening tests to see if you are eligible for this study. These tests will include a review of your medical history, a physical examination including blood pressure, pulse, weight, and height, smoking history (if applicable) and laboratory tests of your blood and urine. If you are female and of childbearing potential, a test will be done to see if you are pregnant. Urine pregnancy tests may also be done at anytime during the study to ensure that females of childbearing potential are not pregnant.

During the study you will continue to take the anti-epileptic drugs previously prescribed by your doctor. You will continue to be responsible for the cost of these medications. The dosages of these drugs will be adjusted throughout the trial at your doctor's discretion. In addition to these anti-epileptic drugs you will receive the study drug (topiramate) 150 mg per day. You will begin taking a low dose of study medication, which will be gradually increased over approximately 42 days to the maximum study drug (topiramate) 150 mg per day.

You will then continue on the study drug (topiramate) 150 mg per day for another 12 weeks, the maintenance period. If you are having problems tolerating the study medication, your doctor may instruct you to reduce the dose. He/she may also instruct you to increase the dose again if he/she feels it is necessary.

To ensure that you receive the correct dose of study medication it is very important that you follow instructions carefully. Your doctor will provide study medication at the second and third visit, while the dosages are being increased to the maintenance dose of 150 mg per day. After this period you will collect your study medication (topiramate) from an allocated pharmacy after presenting a prescription from your doctor. Your doctor will tell you which pharmacy you must use and how to obtain your study medication. The sponsor of the trial (Janssen-Cilag) will bare the costs of the study medication for the duration of the trial.

You will stay on the medication until one of the following criteria is met:

- Your doctor determines that your therapy needs to be changed.
- You experience a side effect that causes you to stop the medication.
- You decide to withdraw from the study.
- You complete the study.
- The sponsor discontinues the study.

Should intervention by your doctor be needed for side effects due to the use of topiramate, this will take the form of a dose reduction of up to 50 mg per day in increments of 25 mg per day over a 2 to 4 week period. This will be followed by an increase in the dose again, according to the schedule used to reach the maintenance dose of 150 mg per day. If intolerable side-effects do not respond to this intervention you will exit the trial.

If you decide to stop taking the medication for any reason before the study is over you will return for a final visit. At the final visit, you will have a physical examination including blood pressure, pulse, and weight, a neurological examination. If necessary, you will be given instructions on how to decrease and discontinue your study medication dose. After your medication is completely discontinued, you will return for a follow up visit.

You will have your first visit scheduled approximately 28 to 56 days before taking the trial medication. Alternatively you may take trial medication shortly after your first visit if and only if you can provide your doctor with a reliable record of seizure history and adverse events over the past month. Your doctor will decide on the best approach permitted to assess your seizure history at the start of the trial. The approach chosen will be in your best interests. Subsequent visits will occur on approximately Study Days 28 to 56, 49 to 77, 70 to 98, 112 to 140 and 154 to 182 (ie 5 visits). At the end of the trial you will together with my doctor decide on whether you should continue with topiramate beyond the trial or not. You will be responsible for drug costs beyond the trial. Should the decision be to discontinue topiramate a further visit would take place on Study Day 168.

At each visit you will have your blood pressure and pulse measured.

You will be given a diary card to record your seizures. At each visit, you will return the diary to your doctor and be issued with a new one. You will also return any study medication bottles whether they are empty or still have unused drug in them at each visit.

During the study you will have blood drawn for laboratory tests. Approximately two teaspoons of blood will be drawn when these tests are done which include chemical testing of your blood and studies of your blood cells. If any of your laboratory test results need re-testing additional blood samples may have to be drawn. A pregnancy test may be done at any time during the study if you are female and can have children.

POSSIBLE RISKS OF PARTICIPATION

All medicines carry risks. The most commonly observed side effects associated with the use of topiramate in previous studies, in doses of 200 to 400 mg/day were: sleepiness, fatigue, dizziness, loss of balance with a possibility of falling (ataxia), speech problems, slowed thinking and movement, involuntary eye movements (nystagmus), and tingling of the skin. Other reported side effects may include confusion, difficulty with concentration or attention, tremor, nervousness, anxiety, depression, mood problems, and loss of weight or appetite.

Kidney stones occurred in 1.5% of patients taking topiramate; you are advised to drink plenty of fluids while taking topiramate.

Other risks are the possibility of bruising, swelling and/or infection at the site of the blood collection. It is possible that the study medication may not help your seizures.

Not all effects of topiramate are known at this time. There may be risks, which are not known now. You will be notified if significant new findings become known that may affect my willingness to continue.

You must be aware of the potential hazards of operating machinery, automobiles, or doing other dangerous tasks because of my epilepsy. You should understand that these risks might increase with changes in anti-seizure medication.

Kidney stones have occurred in 1.5% of the patients taking Topiramate; you are advised to drink plenty of fluids while taking Topiramate.

You have the right to ask any questions concerning the potential and/or known hazards of this trial at any time. Should you, as a result of participation in this trial, be harmed in any way, you will receive appropriate emergency or other medical treatment. If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately inform the investigator Dr _____ at phone number _____. You may call any time, day or night, to tell them about your health experiences.

BIRTH CONTROL AND PREGNANCY

There may be unknown risks to an embryo, foetus or unborn child: therefore if you are female, you must agree to use an acceptable method of birth control so that you do not become pregnant while participating in this trial. You will use one of the following methods of birth control for at least one month before entering and then during the study: hormonal contraceptives, intrauterine device, spermicide and barrier or abstinence. Topiramate may cause serious birth defects. If you become pregnant, you will be discontinued from the study. The study medication will be decreased and stopped. The doctor will explain the possible dangers to the foetus, and options that may include ending the pregnancy.

BENEFITS OF PARTICIPATION

You may benefit from this study by experiencing relief from your seizures, although no absolute benefits from your participation in the study can be guaranteed.

You will receive the benefits of a general physical examination, evaluation of symptoms, general health discussions with the investigator, help in finding additional treatment if needed, health information, laboratory tests and finally the chance to contribute to a scientific investigation which may benefit patients in the future. Knowledge gained from this study may help you and others with partial onset seizures (epilepsy).

You may benefit by the study medication helping your epilepsy. The study medication will be provided free of charge. You must however collect the medication at the designated pharmacy. The sponsor will meet additional costs incurred by oral contraception adjustments due to the addition of topiramate. Oral contraception related to these adjustments will be issued by allocated pharmacies. There are no additional costs as a result of participation in the study.

TREATMENT DISCONTINUATION

Special care needs to be taken for the discontinuation of trial medication. Uncontrolled discontinuation is not advisable. The investigator will supervise any discontinuation of treatment, with your health as first priority.

YOUR RIGHTS AS A PATIENT

You have the right to privacy, and all information that is collected during this study is confidential. However, Case Report Forms and other medical records about you will be sent to the sponsor (JANSSEN-CILAG), although none of these documents will identify you personally in any way. For purposes of reporting the information collected during this study, you will be identified by initials and numbers only. Auditors and clinical monitors from JANSSEN-CILAG or regulatory authorities will be granted direct access to your records to ensure accuracy, however, no information which identifies you personally will ever be passed outside the hospital/consulting rooms.

You do not have to take part in this study. If you do change your mind at any time you have the right to withdraw. Your decision to withdraw will not affect future medical care. In addition, your doctor may also withdraw you from the study if he/she believes that this is best for you. You must notify your doctor if you wish to stop and you must return to the clinic for one visit while the study medication is reduced. Once you the medication has been completely reduced and discontinued you will return to the clinic for a follow-up visit.

Your doctor can stop this study at any time if it is in your best interest medically. Your participation may be discontinued if you do not follow the procedures required. This includes not taking your study medication as prescribed, taking too much rescue medication, not recording the use of rescue medication on your diary, and not returning the study drug at every visit. If your doctor stops the study, you agree to return for visits until you are no longer taking the study medication.

You understand that the Sponsor Company, JANSSEN-CILAG, can stop this study at any time.

In addition you may be withdrawn from the study due to changes made by the Drug Safety Monitoring Board or the regulatory authority.

COSTS

The sponsor (JANSSEN-CILAG) will provide payment for all trial-related procedures. Neither you nor your medical aid will be expected to pay for these.

The sponsor agrees to pay for all reasonable and customary costs incurred for treatment of the trial-related injury caused by the drug under investigation, but not for injury caused by other licensed medicinal products administered. Compensation will not be paid to the extent that the injury has arisen through a significant departure from the agreed protocol, through the wrongful act or default of a third party, including a doctor's failure to deal with an adverse reaction or through contributory negligence by the patient. The guidelines of the association of British Pharmaceutical Industry are thus followed.

*In the event of a research-related injury, necessary medical treatment will be provided to assist your recovery from the injury. The sponsor will pay for any immediate care and/or treatment beyond what is covered by your health insurance. This agreement to provide free medical treatment does not include treatment for any injury/illness, which is not the result of research. No financial compensation other than free immediate medical treatment of the injury will be provided.

You will not be paid to participate in this trial.

GETTING MORE INFORMATION

The investigator has been provided with all relevant information on the study drug and will continue to receive updates during the study. If at any time you have any questions or concerns about the study or the study product, you should ask the investigator.

The contact numbers are:

Work:

Home:

Cellular:

(If applicable)

INFORMED CONSENT

PROTOCOL: PRI/TOP-INT-29 (TOPMAT-NP-002) PATIENT NUMBER: _____

PATIENT STATEMENT AND SIGNATURE:

You the undersigned declare that you have read the above information and that you had adequate time to ask questions and you understand the purpose of the study. You understand that this is a research study and that taking part in this study is voluntary. You may withdraw from the study at any time without justifying your decision and without affecting your normal care and medical management.

You have received a copy of the Patient Information Leaflet. You understand the nature of the study, the implication of your involvement and you are aware of all known possible side effects of participation.

You have had the opportunity to ask questions regarding the nature, conduct, benefits and risks of the study and received satisfactory answers. You undertake to follow the reasonable instructions of the investigator and will not do anything that you know or suspect will affect the integrity of the study.

You will inform the investigator of any symptoms or deterioration in your health during or immediately following the study.

You understand that appropriate company personnel from the Sponsor and the Regulatory authorities will need to review the relevant sections of your medical records, but that all information will be treated as confidential.

You are at present practising an effective form of birth control. You are not pregnant or breast-feeding and understand that if you do become pregnant, this treatment may involve risks to the foetus.

In case of trial related injury you can contact:

Name of the investigator: _____

Phone number: _____ **at any time during the trial.**

You are not giving up any of my legal rights by signing this consent form.

You willingly consent to participate in the study.

Signed at _____ on this _____ day of _____ 20 ____.

PATIENT SIGNATURE:

DATE (D/M/Y)

NAME: (Block capitals)

REPRESENTATIVE SIGNATURE:
(If applicable)

DATE (D/M/Y)

NAME: (Block capitals)

You the under signed, have fully explained the relevant details of this study to the patient named above
(And/or the patient's legally acceptable representative).

INVESTIGATOR SIGNATURE:

DATE (D/M/Y)

INVESTIGATOR NAME: (Block capitals)

WITNESS SIGNATURE:

DATE (D/M/Y)

WITNESS NAME: (Block capitals)

*This is the RWJPRI standard liability statement required by the legal counsel for inclusion in the patient consent form.

Card Number. _____

Janssen-Cilag

Protocol No. TOP-RSA-01

Seizure Diary Card

From: ___/___/___ To: ___/___/___

Subject Initials: _ _ _

Subject Number: _____

[illegible]

Patient Diary

Appendix 3.

A copy of the CRF is available from the postgraduate office at the University of the Witwatersrand.

Seizure Counts

Appendix 5.

Patient number	Baseline time interval, days	Actual seizures count over			Number of seizures in 30 days		
		Baseline time interval	Last 6 weeks	Last 4 weeks	Baseline time interval	Last 6 weeks	Last 4 weeks
01	32	34	2	2	31.875	1.429	2.143
02	30	4	5	3	4.000	3.571	3.214
03	27	14	10	7	15.556	7.143	7.500
04	29	15	5	4	15.517	3.571	4.286
05	28	5	1	0	5.357	0.714	0
06	36	6	0	0	5.000	0	0
07	103	40	7	3	11.651	5.000	3.214
08	35	3	1	1	2.571	0.714	1.071
09	97	17	4	2	5.258	2.857	2.143
10	30	12	5	4	12.000	3.571	4.286
11	104	244	83	52	70.385	59.286	55.714
12	41	9	4	4	6.585	2.857	4.286
13	34	1	2	1	0.882	1.429	1.071
14	31	3	2	2	2.903	1.429	2.143
15	28	8	4	4	8.571	2.857	4.286
16	26	3	2	1	3.462	1.429	1.071
17	28	4	4	4	4.286	2.857	4.286
18	61	3	3	3	1.475	2.143	3.214

Patient number	Percentage reduction in seizure count relative to baseline over	
	Last 6 weeks	Last 4 weeks
01	95.52	93.28
02	10.71	19.64
03	54.08	51.79
04	76.98	72.38
05	86.67	100.00
06	100.00	100.00
07	57.08	72.41
08	72.22	58.33
09	45.66	59.24
10	70.24	64.29
11	15.77	20.84
12	56.61	34.92
13	- 61.91*	- 21.43*
14	50.79	26.19
15	66.67	50.00
16	58.73	69.05
17	33.33	0
18	- 45.24*	- 117.86*

* This figure indicates an increase in the seizure count. The increased seizure counts reflected above seem very large but are exaggerated since the percentages were calculated on such small numbers. From Appendix 5 it follows that patient thirteen experienced only two seizures over the last six weeks, and one seizure over the last four weeks of the Maintenance Phase. Similarly patient eighteen experienced three seizures over the last six weeks as well as over the last four weeks of the Maintenance Phase (i.e. no seizures between four and six weeks).

Patient number	AED	Total daily dose, mg per day
1	Sodium valproate (Epilim®)	800
	Lamotrigine (Lamictin®)	200
	Clonazepam (Rivotril®)	0.5
2	Phenytoin (Epanutin®)	350
	Lamotrigine (Lamictin®)	300
3	Lamotrigine (Lamictin®)	200
4	Sodium valproate (Epilim®)	1700
5	Carbamazepine (Tegretol®)	800
6	Lamotrigine (Lamictin®)	100
7	Oxcarbazepine (Trileptal®)	2700
	Clonazepam (Rivotril®)	1.5
8	Phenytoin	400
9	Sodium valproate (Epilim®)	1200
	Carbamazepine (Tegretol®)	800
10	Phenytoin	400
	Clobazam (Urbanol®)	10
11	Carbamazepine (Tegretol®)	700/800
12	Sodium valproate (Epilim®)	2000
	Carbamazepine (Degranol®)	800
13	Phenytoin	600
14	Phenytoin	400
15	Carbamazepine (Tegretol®)	1200
16	Sodium valproate (Epilim®)	1400
17	Lamotrigine (Lamictin®)	400
	Carbamazepine (Tegretol®)	800
18	Lamotrigine (Lamictin®)	300

Adverse Events

Appendix 8.

Patient number	Adverse event	Trial Phase	Severity	Relationship to drug	Action taken	Outcome
1	Concentration down	Maintenance	Moderate	Probable	Dose reduced to 50 mg twice daily	Resolved
	Concentration down	Maintenance	Moderate	Very likely	None	Unknown
	Headaches	Maintenance	Mild	Probable	None	Resolved
	Weight loss	Maintenance	Moderate	Very likely	None	Persisted
2	Weight loss	End-titration*	Marked	Very likely	Dose reduced to 50 mg twice daily	Persisted
	Bleeding gums	End-titration*	Mild	Doubtful	None	Resolved
5	Tender abdomen	Maintenance	Mild	None	None	Unknown
6	Paresthesia	Maintenance	Mild	Probable	None	Persisted
	Slowing of thoughts	Maintenance	Mild	Probable	None	Persisted
8	Pre-syncope	Start-titration*	Mild	None	None	Resolved

* Titration following on baseline period