Title Page

Protocol Title: A Phase II Clinical Trial of PRX-00023 Therapy in localization-related Epilepsy
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Total requested accrual
30 Patients with localization-related epilepsy

Project Uses Ionizing Radiation: □ No X Yes
□□Medically-indicated only
X Research-related only
□□Both

IND/IDE □ No xYes
Drug/Device/#
1) 18FCWAY IND # 59163 Sponsor: NIH Nuclear Medicine Department
2) PRX-00023 IND # 110522 Sponsor William H Theodore MD

Durable Power of Attorney x No □ Yes
Multi-institutional Project x No □ Yes
Institution_____ FWA #_____
Date of IRB approval_____ *(attach IRB documentation)*

Data and Safety Monitoring Board xNo □Yes

Technology Transfer Agreement □ No x Yes
Agreement type and number _CRADA 2010-0071_Expiration Date: June 2020

The protocol is being carried out under a cooperative research and development agreement with the pharmaceutical company, Proximagen Limited. Proximagen will provide the study drug to NIH without cost. Proximagen will receive data from the study but will not receive any personally-identifying information on participants.

None of the NIH investigators has any financial arrangements with Proximagen or receives any payment related to the study.

Confidential Disclosure Agreement □ No □ Yes

Samples are being stored □ No x Yes

Flesch-Kincaid reading level of consent form: ____10.3_____

2. Table of Contents

3. Precis:

Introduction: PRX-00023 is a selective 5HT1A agonist being developed as an oral therapeutic treatment for epilepsy.

Objective: To initiate a pilot clinical trial assessing the safety, tolerability and efficacy of the 5HT1A receptor agonist PRX-00023 in patients with localization-related epilepsy. PRX-00023 is a 5HT1A receptor agonist that has shown promise in clinical trials of depression (Rickels et al 2008). Patients with localization-related epilepsy have reduced 5HT1A receptor binding on 18FCWAY positron emission tomography (PET). (Toczek et al 2003) Increasing neurotransmitter activity at 5HT1A receptor sites might ameliorate seizures. Moreover, depression is a common co-morbidity in people with epilepsy (Theodore et al 2006). Altered 5HT1A receptor binding has been found in depression.

Study Population: Thirty adults with localization-related epilepsy.

Design: A randomised, double blind, placebo-controlled cross-over, phase II clinical trial. Subjects will be screened under protocol 01-N-0139 and will undergo medical and epilepsy history and physical examination, vital signs, ECG,clinical laboratory studies including standard clinical chemistry and hematology studies, urinalysis, pregnancy test for females of childbearing potential, and MRI scan and video EEG monitoring will be performed if not previously completed successfully, and measurement of plasma AED levels (for those AEDs in which an assay is available at NIH).

The trial will have a baseline phase, which will last up to 6 weeks. Baseline may occur concurrent with screening procedures. The baseline phase will include measurement of seizure frequency (patient will record via seizure calendar). In addition the following will be administered, unless previously completed: Columbia Suicide Severity Rating Scale, neuropsychological and mood evaluations, FCWAY PET (if not already performed), EEG, measurement of plasma AED levels (if assay available), and pregnancy test (for women of child bearing potential), saliva samples will be obtained for genetic testing (if not previously obtained) and blood samples will be obtained during the PET procedure for cortisol and ACTH levels.

Following baseline, patients will begin the treatment phase (consisting of Period 1 and Period 2). Patients will be randomized to PRX-00023 (120mg BID) or matching placebo. After completion of the first treatment period, patients will undergo a washout period after which patients will be crossed over to the alternate treatment period.

Outcome measures:

1. Seizure frequency counts during the 3 month placebo and active treatment phases
2. Neuropsychological and mood indices
3. Safety assessment will include adverse events, vitals signs, laboratory signs and physical examination.

4. Introduction/ Scientific Rationale

Despite the introduction of a range of new antiepileptic drugs, about 30% of patients, particularly with localization-related epilepsy, have uncontrolled seizures. Uncontrolled epilepsy is a serious disorder associated with increased morbidity and mortality, neuropsychological and mood disorders, particularly depression and anxiety as well as social and economic disadvantages.

Unfortunately many current anti-epileptic drugs (AEDs) share common mechanisms, possibly accounting for the failure to reduce the proportion of patients with intractable epilepsy (French and Faught 2009). Enhancing activity at 5HT1A receptors would offer a novel mechanism of action that could potentially treat depression and anxiety as well as seizures.

4.1 The role of 5HT in epilepsy

4.11 Preclinical studies

5-HT1A receptor activation shows antiseizure effects in partial seizure models, including picrotoxin in rat hippocampal slices (Lu and Gean 1998), hippocampal kindled seizures in cats (Wada et al 1992, 1993), bicuculline-induced (Salgado and Alkadhi 1995), kainic acid-induced seizures in rat hippocampal slice preparations (Salgado-Comissariat 1997), and intrahippocampal kainic acid induced seizures in freely-moving rats (Gariboldi et al 1996). 5HT1A agonists decreased the incidence of tonic seizures and the mortality rate induced by PTZ in male Wistar rats (Lopez-Meraz et al 2005). The highly selective 5-HT1A antagonist WAY100635 blocked the protective effect of 5HT infusion on pilocarpine-induced seizures in conscious rats (Clinckers et al 2004).

5HT inhibited stellate and pyramidal neuron excitability in entorhinal cortex, and led to hippocampal inhibition. The effects of 5HT were mediated via 5HT1A receptors (Deng et al 2007). Application of 5HT inhibited low-Mg(2+)-induced seizure activity in slices via 5HT1A and 5HT2A receptors, suggesting that 5HT-mediated depression of neuronal excitability and increase in GABA release contribute to its anti-epileptic effects in the EC (Deng and Lei 2008).

Genetic epilepsy prone rats showed reduced hippocampal 5HT1A receptor density (Dailey et al 1992). Moreover, these rats showed depressive-like behaviors (as measured on the forced swimming test) that responded to antidepressant drugs and abnormal stress responses (Sarkisova et al 2003). Dietary fluoxetine supplementation abolished handling-induced seizure susceptibility in El mice.

4.12 Clinical Studies - AED mechanisms

Carbamazepine (Yan et al 1992, Dailey et al 1997) and valproate (Biggs et al 1992) release 5-HT as part of their mechanism of action, while lamotrigine inhibits 5-HT re-uptake (Southam et al 1998). In the genetically epilepsy-prone rat (GEPR) carbamazepine, produced dose-related anticonvulsant effects and increases in extracellular serotonin (Dailey et al 1996). Accentuation of serotonin release by treating GEPRs with fluoxetine and 5-hydroxytryptophan increased the anticonvulsant effect produced by fluoxetine. Pretreating animals with PCPA to block 5HT synthesis significantly reduced the antiseizure effect of carbamazepine in GEPRs (Yan et al 1992).

Antidepressant SSRIs may decrease seizures. A meta-analysis of Food and Drug Administration (FDA) Phase II and III clinical trials including 75,873 patients between 1985 and 2004 showed that incidence of seizures was significantly lower among patients on antidepressants (except buproprion) compared to placebo (standardized incidence ratio 0.48; 95% CI, 0.36-0.61). In patients assigned to placebo, seizure incidence was greater than the published incidence of unprovoked seizures in community nonpatient samples (Alper et al 2007).

Fluoxetine, a selective serotonin reuptake inhibitor (SSRI) reduced complex partial seizures by 30% in 17 patients (Favale et al 1995). An open-label trial of citalopram 20 mg/day was given to 11 non-depressed patients with poorly controlled epilepsy as add-on treatment for 8–10 months (Favale et al 2003). Median seizure frequency dropped by 55.6% in the whole group, with nine patients improving by at least 50%.

Very large intentional overdoses of fluoxetine (up to 1400 mg) have been reported to cause seizures (Suchard 2008). In animals, proconvulsant effects are observed at doses of 10-20 mg/kg, although antiseizure effects have been observed in other studies in the same dose range (Hernandez et al 2002; Pericic et al 2005, Freitas et al 2006).

4.13 Sudden death in epilepsy

Serotonergic mechanisms may also be involved in sudden unexplained death in epilepsy (SUDEP). Transgenic mice lacking serotonin neurons have severe apnea and high mortality during development (Hodges et al 2009). Raphé 5-HT neurons excite key circuit components required for generation of respiratory motor output (Ptak et al 2009). Fluoxetine reduced respiratory arrest after audiogenic seizures in DBA/2 mice, a proposed model for human SUDEP (Tupal and Faingold 2006).

4.2 Depression and Epilepsy

Depression is one of the most common and severe co-morbidities of patients with epilepsy, affecting up to 55% of patients in some studies (Hasler et al 2007), higher than those for other chronic health conditions including asthma and diabetes, with a severe impact on quality of life (Ettinger et al 2004). Patients with depression in addition to epilepsy report greater seizure severity than those with epilepsy alone (Cramer et al 2003). Patients with temporal lobe epilepsy (TLE) appear to be more likely to suffer from depression than those with other seizure types; the majority has unipolar depression (Jones et al 2005). Several factors might lead to depression in people with TLE, including social and psychological stresses, as well as biological factors such as the side of the focus, and the presence of mesial temporal sclerosis (MTS) (Quiske et al., 2000). Epidemiological data suggest a potential biological link: Longitudinal studies in epilepsy and depression reported a bidirectional temporal association between the two conditions: epilepsy was frequently followed by depression, and a history of depression was a considerable risk factor for subsequent epilepsy onset (Hesdorfer et al, 2000). Both epilepsy and depression are associated with reduced hippocampal volume (Geuze et al 2005). Decreased serotonergic function may be a major pathogenic mechanism underlying development of depression (Hasler et al 2004). In patients with major depressive disorders (MDD), bilateral limbic 5HT1A receptor binding reductions have been reported in regions including raphe and mesiotemporal cortex (Drevets et al., 2007).

4.3 Human Imaging data

Reduced 5HT1A receptor binding may be related to increased limbic excitability in patients with TLE as well as in animal models. Since our first PET study using ^{18}FCWAY, a WAY100,635 analog (Toczek et al 2003), additional studies using 5HT1A receptor ligands showed reduced binding in mesial temporal structures ipsilateral to the epileptic focus, as well as in additional regions including insula and anterior cingulate (Merlet et al 2004, Savic et al 2004, Giovacchini et al 2005). Moreover, PET results suggest that altered 5HT1A receptor binding may be a mediator of depression in people with epilepsy (Hasler et al 2007, Theodore et al 2007, Lothe et al 2008).

4.31 Genetic markers

Several allelic variations may affect serotonergic neurotransmission, epileptogenesis, and depression in patients with epilepsy. Serotonin transporter polymorphisms affecting serotonin transporter mRNA synthesis lead to changes in SERT expression and 5HT cellular uptake (Lesch et al 1996). The short SERT variant is associated with a 50% reduction in transcriptional activity and serotonin uptake (Heils et al 1996). The frequency of SERT alleles in patients with epilepsy with or without depression is not known.

Differences in COMT genotype may affect frontal lobe function (Egan et al 2001). This is potentially relevant for our study, as our preliminary data links frontal lobe 5HYT1A receptor binding strongly to depression in epilepsy (Hasler). The TPH1 allele in the gene regulating activity of the serotonin synthesis enzyme tryptophan hydroxylaze (TPNH) may play a significant role in the etiology of psychiatric disorders in at least one population studied (Liu et al 2006).

BDNF alleles may be genetic markers that indicate an enhanced susceptibility to seizures (Kanemoto et al 2003). BDNF is associated with 5HT neuronal sprouting in animal epilepsy models (Scharfman 2005). GABAA and GABAB polymorphisms have been associated with the development of both partial and generalized epilepsies (Urak et al 2006, Kinirons et al 2006).

4.4 PRX-00023

4.41 Pre-Clinical Experience

PRX-00023 has a high affinity for serotonin (5-HT1A) receptors (Ki = 5-11nM) and displays agonist activity on that receptor with an EC_{50} of 20nM. PRX-00023 has no significant affinity for benzodiazepine receptors and does not affect GABA binding in vitro or in vivo when tested in preclinical models. PRX-00023 has no significant binding to other serotonin receptors, α_1 (K_i=1600nM) or α_2 adrenergic receptors. In vitro testing of PRX-00023 demonstrated no significant inhibition of the following P450 enzymes: 1A2, 2C9, 2C19, 2D6, and 3A4). Non-sedating doses of PRX-00023 reduce ultrasonic vocalizations in infant rats bred for high anxiety (Brunelli et al 2009).

The repeated administration of PRX-00023 for 90 days in rat (Study 801097) defined a No-Observed-Adverse-Effect-Levels (NOAEL) of 6 mg/kg/day compared to a NOAEL of 10 mg/kg/day in Beagle dog (5.6 mg/kg; study 801098).

At the dose level of 30 mg/kg/day in rat the major observations were slight anemia and other hematological changes, slight decrease in serum albumin and total protein levels in females, increased liver and spleen weights and decreased uterus weight; all changes were absent in the recovery group. Increased and persistent diestrus, mucification of the vagina and mammary hyperplasia were observed in females with decreased incidence in the recovery group. None of these changes found in rat were observed at the next dose level (50 mg/kg/day) above the NOAEL in dog.

Common findings between rat and dog were ptosis, with inactivity and poor coordination in dog only. These effects were observed post dosing and were transient in nature. Additionally pigment deposition in macrophages was observed in rat (minimal) and dog (minimal to slight). In rat deposition was predominately in the mesenteric lymph node and occasionally in spleen. In dog deposition was observed in liver, mesenteric lymph node, gastrointestinal tract, gall bladder, bone marrow and thymus, but not spleen. The incidence was higher in dog than rat, and in dog more noticeable in females. These findings were partially resolved in recovery animals. The pigment deposition was not correlated with any pathological findings in either species.

4.42 Clinical Experience

A total of 442 human subjects have received at least one dose (up to 320 mg/day) of PRX-00023 in the seven single or repeat-dose clinical studies (Table 1) conducted to date. Adverse events have generally been reported as mild to moderate with no treatment-related serious adverse event (SAE) having occurred throughout the development program to date. Pharmacokinetic analyses from these studies provide evidence that the drug is absorbed, with peak concentrations within four hours and an elimination half-life estimated to be 9.8 to 13.5 hours. Of the several metabolites identified to date (include deacylated and hydroxylated species) none have been determined to be active.

Table 1: Completed Clinical Studies with PRX-00023

Study Number	Study Design	Number (population)	Age (gender)	Dosage (regimen)	Primary Endpoints
CP-001	single-dose escalation	52 (healthy)	18-45 (male)	10-60 mg (single dose)	safety, PK
CP-002	multiple-dose escalation	32 (healthy)	18-55 (male & female)	10-60 mg (28 days)	safety, PK, PD
CP-003	multiple-dose escalation	20 (healthy)	18-45 (male & female)	30-120 mg qd (12 days) then 150 mg qd (4 days)	safety, PK, food effect
CP-006	open-label, Phase II	21 (GAD)	18-65 (male & female)	40 mg qd (4 days) then 80 mg qd (10 days) then 120 mg (14 days)	HAM-A
CP-007	randomized, double-blind, placebo-controlled, phase II	311 (GAD)	18-65 (male & female)	80 mg qd (8 weeks)	HAM-A (primary) MADRS (secondary)
CP-019	multiple-dose escalation	18 (healthy)	18-55 (male & female)	80 mg qd/bid (4 day) then 160 mg qd/bid (10 day) then 320 mg qd/bid (7 days)	safety, PK
CP-020	randomized, double-blind, placebo-controlled, phase II	360 (MDD)	18-65 (male & female)	120 mg bid (8 weeks)	MADRS

Table 2 summarizes the most common (cumulative) AEs across the first four clinical studies of PRX-00023 (CP-001, CP-002, CP-003, CP-006), Table tabulates the severities of the drug

related (defined as those which the Investigator considered possibly, probably, or definitely related to study drug) AEs of the same trials (Iyer et at, 2007, Mathew et al, 2008)

Table 2: Most Common Adverse Events Observed with PRX-00023 in Clinical Trials CP-001, CP-002, CP-003 and CP-006.

Adverse Event	Placebo (n=39)	≤ 90mg (n=101)	120-150mg (n=38)
Headache	1 (2.6%)	4 (4%)	7 (18.4%)
Nausea	1 (2.6%)	6 (5.9%)	6 (15.7%)
Dizziness	1 (2.6%)	7 (6.9%)	6 (15.7%)
Diarrhoea	0	4 (4%)	3 (7.8%)
Abdominal Pain	3 (7.7%)	7 (6.9%)	1 (2.6%)
Flatulence	0	9 (8.9%)	2 (5.2%)
Infection	4 (10.3%)	8 (7.9%)	1 (2.6%)

Table 3: Severity of Adverse Events, Attributed to PRX-00023, in Clinical Trials CP-001, CP-002, CP-003 and CP-006.

Severity	Placebo	≤ 90mg	120-150mg
Mild	4%	26.3%	75.0%
Moderate	0	11.1	15.0
Severe	0	1.0	5.0

A Phase II study (CP-007) of PRX-00023 in 311 subjects with general anxiety disorder (GAD) was conducted to evaluate the efficacy, safety, and tolerability of PRX-00023 in patients with GAD.

Adult (18-65 years old) subjects with ≤ 20% reduction in HAM-A scores from screening to the end of the placebo run-in were randomized to double-blind study medication (PRX-00023 40 mg or placebo), once daily by mouth. On study Day 4, the subjects' dose of study drug was increased to 80 mg for the remainder of the 8-week double-blind treatment period.

A total of 448 subjects were screened, of which 311 entered the placebo run-in phase and 277 were randomized to receive either placebo (N=137) or PRX-00023 (N=140) (Rickels et al, 2008). The primary efficacy measure was the mean change in total HAM-A score from baseline (Week 0) to study end (Week 8). By Week-8, the PRX00023 group decreased to 14.7 ± 7.73 and the placebo group decreased to 16.3 ± 8.21. The difference in change from baseline values was not statistically significant (p =0.116). A significant reduction in MADRS depression score was observed, following 8 weeks of treatment. One-hundred and two (72.9%) of subjects receiving PRX-00023 and 88 (64.2%) of those receiving placebo reported at least one AE. All AEs were rated as mild to moderate. One subject experienced an SAE (diverticulitis) that was not attributed to the study medication. Early terminations due to AEs consisted of 2 subjects receiving PRX-00023 (rash; palpitations) and 4 subjects receiving placebo (rash; infection; injury; dizziness). Headache was the most common AE, having been reported in 22 (15.7%) and 15 (10.9%) of the subjects receiving PRX-00023 and placebo, respectively (Table 4).

Table 4: Adverse Events Occurring in at Least 5% of Subjects Who Received PRX-00023 in Clinical Trial CP-007.

Preferred Term	PRX-00023 (n=140)	Placebo (n=137)
Headache	22 (15.7%)	15 (10.9%)

Nasopharyngitis	11 (7.9%)	10 (7.3%)
Diarrhoea	10 (7.1%)	8 (5.8%)
Nausea	12 (8.6%)	2 (1.5%)

A dose escalating study (CP-019) entitled: "A phase I randomized, placebo-controlled, double-blind, multiple dose titration study to evaluate the safety, tolerability, and pharmacokinetics of PRX-00023 in healthy subjects" has been completed.

Eighteen healthy adult (18-55 years old) volunteers were enrolled to either of two PRX-00023 dosing regimens (or matching placebo). Subjects were randomized to double-blind, dose escalating regimens of 80-160-320 mg qd PRX-00023 (N=8) (or matching placebo; N=2) or 40-80-160 mg bid PRX-00023 (N=6) (or matching placebo; N=2). In each cohort, dose escalation occurred on Days 5 and 15.

Six (60%) of the subjects in the qd cohort and 4 (50%) of those in the bid cohort reported at least one AE though the cumulative total was 38. The most prevalent AEs reported during the study period are summarized in a blinded manner by cohort (qd vs. bid) in table 5. There were no clinically significant alterations in blood pressure, heart rate, or ECG values in any subject in this study.

Table 5: Adverse Events (Blinded) Reported in ≥2 Subjects During Clinical Trial CP-019.

Adverse Event	Total (N=18)	PRX-00023 qd or Placebo (N=10)	PRX-00023 bid or Placebo (N=8)
headache	5 (28%)	4 (40%)	1 (13%)
rash/inflammation	3 (17%)	2 (20%)	1 (13%)
pruritis/itch	2 (11%)	0	2 (25%)
dizziness/lightheadedness	2 (11%)	2 (20%)	0
pectoral pain/muscular pain to chest & back on inspiration	2 (11%)	1 (10%)	1 (13%)
tired	2 (11%)	1 (10%)	1 (13%)

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Table 6 summarizes the results of the PK analysis conducted on the PRX-00023 concentration data.

Table 6: Preliminary Pharmacokinetic Profile of PRX-00023 in Clinical Trial CP-019.

Parameters	PRX-00023 QD Dosing Regimen Geometric mean (%CV)			PRX-00023 BID Dosing Regimen Geometric mean (%CV)		
	80 mg (N=8)	160 mg (N=7)	320 mg (N=7)	40 mg (N=6)	80 mg (N=4)	160 mg (N=4)
T_{max} (h) (Median)	3	2	2	2	1.5	2
C_{max} (ng/mL)	81.8 (44)	353 (59)	762 (22)	42.1 (84)	140(100)	332 (92)
$AUC_{0\text{-last}}$ (ng*h/mL)	472 (54)	1640 (48)	3674 (29)	N/C	N/C	N/C
$AUC_{0\text{-}8}$ (ng*h/mL)	361 (56)	1333 (48)	2878 (26)	159 (90)	522 (117)	1373 (100)

A Phase II study (CP-020) of PRX-00023 in 360 subjects with major depressive disorder (MDD) was conducted to evaluate the efficacy, safety, and tolerability of PRX-00023 in patients with MDD.

Adult (18-65 years old) subjects who met the DSM-IV diagnostic criteria for MDD (single or recurrent episode) and with > 20% reduction in HAM-D17 scores with the psychic anxiety > 2 were randomized to double-blind study medication (PRX-00023 40 mg or placebo), twice daily by mouth. On study Day 4, the subjects' dose of study drug was increased to 80 mg twice daily and on Day 8 the subjects' dose of study drug was increased to 120 mg twice daily for the remainder of the 8-week double-blind treatment period.

A total of 419 subjects were screened, of whom 359 entered the placebo run-in phase and 360 were randomized to receive either placebo (N=180) or PRX-00023 (N=180)

The primary efficacy measure was the mean MADRS score change from baseline (Week 0) to study end (Week 8). The active treatment group showed a decline in the MADRS score that was 0.7 greater than the placebo group but the difference was not statistically significant. However, in study CP007, a significant reduction in MADRS depression score was observed following 8 weeks of treatment.

Treatment emergent adverse events (TEAEs) were reported by 202 subjects (56.3%), overall. The frequency of TEAEs was similar between the 2 treatment groups: 58.3% of PRX-00023 vs, 54.2% of placebo subjects.

The 2 most frequently reported TEAEs were in the category of Nervous System Disorders. Headache was the most frequent TEAE, occurring most frequently in PRX-00023 subjects, 25 (13.9%) compared to placebo subjects, 14 (7.8%). Dizziness was the next most frequently reported TEAE and was also more frequent in PRX-00023 subjects, 16 (8.9%), compared to 4 (2.2%) of placebo subjects.

The next most frequently reported TEAE was in Gastrointestinal Disorders: nausea, occurring in 15 (8.3%) of PRX-00023 subjects and 9 (5.0%) of placebo. In Infections and Infestations, upper respiratory tract infection was reported with similar frequency in both PRX-00023 and placebo subjects; 8 (4.4%) and 6 (3.4%), respectively. In Psychiatric Disorders, insomnia was the fifth most frequently reported TEAE and occurred more frequently in PRX-00023 subjects, 10 (5.6%) compared to placebo, 3 (1.7%).

Most AEs were rated mild to moderate. Only a few were considered to be severe in the PRX-00023 group: cholecystitis, increase in alanine aminotransferase, fibromyalgia, pain in extremity, headache, depression in one subject each, and insomnia in two subjects: in the placebo group, fungal infection, depression, restlessness and urine retention were rated severe in one subject each and headache in two subjects.

The overall frequency of SAEs was low, occurring in only 5 (1.4%) of subjects. The frequency of SAEs was somewhat higher in the placebo group 4 (2.2%) than in the PRX-00023 group, 1 (0.6%). There were no SAEs that occurred in more than 1 subject and none of the SAE was considered treatment related.

4.43 Dose Justification

The repeated administration of PRX-00023 for 90 days in rat (Study 801097) defined a No Observed Adverse Effect Levels (NOAEL) of 6 mg/kg/day (HED =0.97 mg/kg) compared to a NOAEL of 10 mg/kg/day in Beagle dog (Study 801098; HED =5.6 mg/kg). Therefore the rat is

considered the more sensitive species, compared to dog, for evaluating the toxicological profile of PRX-00023.

Exposure and C_{max} levels of PR-00023 in dog and rat at the respective NOAELs were comparable (65 - 71%) to the estimated exposure and C_{max} levels for a total daily dose of 240 mg (given as a 120 mg dose twice daily) administered to humans (Table 7).

Table 7: Summary of Select Pre-Clinical Pharmacokinetics and Estimated Human Equivalencies.

Species	Total Daily Dose	C_{max} (ng/mL)	AUC_{last} (ng*h/mL)[a]
Human[b]	360 mg	332	NC
Human[c]	360mg	762	3674
Human[d]	240 mg	191	1311
90-Day Rat	6[e] mg/kg	534	1416
	30 mg/kg	2029	17256
90-Day Dog	10[e] mg/kg	556	1564
	50 mg/kg	4088	15405

[a] Last serum concentration measurement was 24 hours postdose (human) and 8 hours postdose (rat and dog)
[b] 160mg BID at Day 21 (CP-019)
[c] 360mg QD at Day 21 (CP-019)
[d] Administered as two 120 mg doses in a 24 hour period, values estimated from results of the maximum tolerated dose PK study (CP-019) using bid dosing regimen
[e] NOAEL

At the next dose level of PRX-00023 above the NOAEL in rat (30 mg/kg) and dog (50 mg/kg) C_{max} levels are 10 fold and 20 fold, respectively, above the estimated human C_{max} for a single 120 mg dose, given twice daily. Additionally, the exposures (AUC_{last}) observed in rats and dogs are 13-fold and 11-fold higher, respectively, than that estimated for a 240 mg daily dose (120 mg bid dosing).

In the Phase II clinical study where 180 patients with major depressive disorder were randomized to receive PRX-00023 120mg BID, and 180 patients were randomized to the placebo, PRX-00023 was generally well tolerated. The overall frequency of TEAEs and those leading to discontinuation were similar between treatment groups. Some TEAEs occurred more frequently in PRX-00023-treated subjects compared to placebo, particularly those in the CNS system organ class and that were study drug related (i.e. dizziness headache). There were no obvious trends in mean laboratory values over time in either treatment group. There were some differences between treatment groups for certain AEs, laboratory shift frequencies, and QTcB and QTcF ranges; however, these were either transitory and/or not of significant clinical importance, and did not result in a difference between the 2 groups in withdrawals due to AEs.

This data is supported by the maximum tolerated dose study CP-019. Oral doses of 80, 160 and 320mg PRX-00023 administered QD or 40, 80, and 160mg administered BID for up to 21 days appeared to be safe and well-tolerated in healthy adult men and women. Following ascending multiple oral PRX-00023 dose titration, absorption of PRX-00023 was fairly rapid (Tmax one to four hours) and mean serum concentrations appear to increase with increasing doses of 80 to 320mg QD or 40 mg BID to 160 mg BID, respectively.

Overall, 41% of patients on active drug and 30% on placebo reported an adverse event. 1.4% of patients on active drug and 2.9% of patients on placebo stopped the study due to an adverse event.

Based on these preclinical and clinical data, oral administration of PRX-00023 120 mg twice daily to patients with localization related epilepsy for up to 12 weeks is expected to be safe and well tolerated.

5. Study Objectives or Hypotheses

The aim of this study is to evaluate the efficacy, safety, and tolerability of PRX-00023 following 12 weeks of treatment in patients with localization-related epilepsy.

5.1 Primary Hypothesis:

PRX-00023 treatment will lead to reduced seizure frequency compared with placebo.

5.2 Secondary Hypotheses

1. PRX-00023 will lead to improved anxiety and depression rating scores compared with placebo.
2. The degree of baseline 5HT1A receptor binding reduction in the epileptic focus will predict drug response.
3. Polymorphisms in SERT, TPNH, COMT, BDNF and GABA genes that have been associated with psychiatric disorders and epileptogenesis may be related to drug response.

5.3 Safety Hypothesis

PRX-00023 is safe and well tolerated in adult patients with localization-related epilepsy.

6. Subjects

6.1 Description of Study Population

The study will accrue up to thirty patients aged 18 to 65 inclusive with localization-related epilepsy with the goal of obtaining 20 completers, unless a carry-over effect is detected, in which case 24 completers would be required (see statistical analysis section 11. 4 and 11.41).

6.2 Inclusion criteria

1. Enrolled in protocol 01-N-0139

2. Age 18 – 65 years

3. Localization-related epilepsy diagnosed by standard clinical criteria that has not responded to treatment with up to two standard antiepileptic drugs either sequentially or in combination.

4. Patients must be able to provide informed consent.

5. Patients must be able to remain on their baseline AED drugs and doses for the duration of the study.

6. Patients must be able to use seizure calendars to record seizures throughout the trial.

7. Experience 4 seizures within a 6-week period.

6.3 Exclusion Criteria

1. Pregnancy or lactation
2. Women of child-bearing potential and men who are unable or unwilling to take adequate contraceptive precautions, including one of the following:

hormonal contraception (birth control pills, injected hormones or vaginal ring); intrauterine device; barrier methods (condom or diaphragm) combined with spermicide; surgical sterilization (hysterectomy, tubal ligation, or vasectomy in a partner).

2. Current treatment for another significant medical disorder, such as diabetes, or heart disease, or an untreated disorder, that is discovered during the screening examination and might interfere with the study and is determined by the PI to warrant exclusion of the participant.

3. An abnormality on clinical laboratory tests, physical examination, EEG or ECG that might increase the risk associated with trial participation or investigational product administration, such as hepatic enzyme elevation greater than twice normal, or hematocrit lower than 30.

4. A level 4 or 5 on the Columbia Suicide Severity Rating Scale rating for symptoms during the last month

5. Concomitant treatment with more than 2 AEDs.

6. Evidence for a potentially progressive neurologic disorder, such as an astrocytoma

7. Use of sublingual lorazepam for seizure clusters more than once per week.

8. Use of any of the following with less than required interval

Prohibited Medications/Classes	Required interval Period (Weeks Prior to baseline)
Any other Investigational drugs	4
benzodiazepines	Chronic or daily use: 4 Occasional or PRN use: 1
MAO Inhibitors anti depressant	4
Citalopram	4
Buspirone	2
other psychotropic medicines	2
potent CYP3A4 inducers/inhibitors: • itraconazole • ketoconazole • HIV antivirals • clarithromycin • phenytoin • barbiturates • rifampin • St. John's Wort	2
propranolol	2

7 Study Design and Methods

7.1 Study Overview

The study is a single center, Phase II randomised, double-blind crossover placebo-controlled trial in patients with localization-related epilepsy. Patients and examining physicians will be blinded to the treatment arm in which the patient is enrolled. Patients will use seizure calendars to record seizure frequency during baseline, active, and placebo phases. The study will last approximately 42-46 weeks (+/- 4 weeks). There will be up to 8 clinic visits. Patients may be inpatients for some study visits.

7.2 Recruitment

Subjects will be recruited from referrals to the NINDS Clinical Epilepsy Section (CES). Self-referral is permitted. We may make presentations at meetings of the Epilepsy Foundation and other non-profit venues to inform the public of the study. Patients and families who express interest will be given the approved NIH protocol description and appropriate contact information. We will advertise on IRB approved patient focused and research focused websites.

7.3 Screening

Patients will be screened in the Clinical Epilepsy Section (CES) outpatient clinic for inclusion in the protocol by CES physicians or licensed and credentialed practitioners under protocol 01-N-0139. MRI will be done under the screening protocol 01-N-0139. If inpatient video-EEG monitoring is needed to confirm seizure type, it will be performed under 01-N-0139 as well. That screening will include the following procedures which are standard care for intractable epilepsy:

Physical examination, vital signs, ECG
Clinical laboratory studies including standard clinical chemistry and hematology studies, urinalysis
Pregnancy test for females of child-bearing potential
Review of epilepsy and general medical history
MRI scan if an adequate scan has not been performed before
Video-EEG monitoring if not performed previously
Measurement of plasma AED levels, if assay available

7.4 Study design

Following screening and a baseline phase (up to 6 weeks), patients will enter a treatment phase of 2 periods (Period 1 and Period 2) with a washout phase between periods 1 and 2. If patients have 4 seizures in less than six weeks during the baseline phase, they do not need to wait the entire 6-weeks to begin the treatment phase (Period I) of the study. Each treatment period will last approximately 12-16 weeks.. Following Period 1, there will be a wash-out of 4 – 6 weeks where no study medication will be taken. During each treatment period, there will be two Clinical Center visits. The first visit will entail clinical assessments and will occur 6-week +/- 2 weeks after starting the study drug and the second visit will entail clinical assessments and neuropsychological and mood assessment and will occur at the end of each maximum tolerated dose (MTD) treatment period. In addition, a follow-up visit will occur approximately one month following the end of the second treatment period that will include a physical examination and review of any adverse events.. The total duration of the study is 42-46 weeks (+/- 4 weeks). Each clinic visit will last approximately one hour. The neuropsychological and mood evaluation at the end of each treatment period will last up to three hours.

7.5 Study procedures:

All specific study procedures are research-related. The PET scans and study drug administration are performed under INDs.

7.51 Baseline:

Baseline phase may occur concurrent with screening procedures and may last up to 6 weeks. During baseline, patients will record seizures on a seizure calendar, while on their baseline treatment with one or two AEDs. They will be eligible for this study if they have at least four seizures during a 6-week baseline phase. If patients have 4 seizures in less than six weeks, they do not need to wait the entire 6-weeks to begin Period 1 of the treatment phase. No changes in

patients' baseline AEDs will be allowed during this period, or subsequent study phases. Patients who use sublingual lorazepam for seizure clusters may continue to do so.

During the Baseline phase the following tests (described in section 7.57 and 7.58) will be performed (unless previously completed, as noted):

Columbia Suicide Severity Rating Scale
Neuropsychological testing
Mood testing
Measurement of plasma AED levels, if assay available
Pregnancy test
EEG
18F-FCWAY PET to measure 5HT1A receptor binding (if not already performed)
Saliva samples to test for polymorphisms in SERT, TPNH, COMT, BDNF and GABA genes that have been associated with psychiatric disorders and epileptogenesis (if not previously performed)
Blood samples for cortisol and ACTH level will be obtained at the time of PET (if performed).

7.52 Randomization to Active drug or Placebo

Subjects will be randomized at the end of baseline to either active drug or placebo using a 1:1 ratio per the randomization schedule. The randomization schedule will be generated, secured, distributed, and stored by the NIH Pharmacy. Patients may be outpatients or inpatients during titration depending on their geographical location, need for additional education on the titration process or if they are participating in concurrent studies with the Clinical Epilepsy Section. All patients will be given an exact written titration schedule to follow.

7.53 Period 1:

During Period 1 there will be regular communication with patients/families by phone, secure email, and/or the clinical trial database. Communication with patients/families will occur approximately 6 times during each treatment period, about once every two weeks.

PRX-00023 or matching placebo will be titrated up starting at an oral dose of 40 milligrams (Mg) twice daily for five days; the dose will then be increased to 80 milligrams twice daily for five days, and then to 120 milligrams twice daily for approximately 70 days. After which the dose will be tapered off as follows: 80 milligrams twice daily for five days, 40 milligrams twice daily for five days, followed by discontinuation of study drug. If patients experience side effects during the titration up, the next scheduled dose increase will be delayed until they abate. If this does not occur, the dose will be reduced in 40mg per day increments. Period 1 will last approximately 12-16 weeks. The above description and table below provides a targeted dosing schedule, however, adjustments may be made if, for example, the patient experiences side effects during titration.

	Titration		MTD	Taper	
Day	Day 0-4	Day 5-9	Day 10-79	Day 80-84	Day 85-90
No. of days	5 days	5 days	70 days	5 days	5 days
Dose	40mg bid	80mg bid	120mg bid	80mg bid	40 mg bid

Patients will keep seizure calendars. Patients will return to NIH 6 weeks +/- 2 weeks after the start of Period 1 and the tests listed in section 7.571 will be performed. At the end of the Maximum Tolerated Dose (MTD) period, patients will again return to NIH for repeat of baseline testing (see section 7.572). Following testing, patients will be tapered off of Period 1 study drug and begin washout period.

7.54 Washout Period

Following the completion of Period 1, there will be a washout period for approximately 4 to 6 weeks.

7.55 Period 2

Following a washout period, patients will be crossed over to the alternative treatment arm, using the same titration schedule as for Period 1. Patients may be outpatients or inpatients during titration. Outpatients will be given an exact written titration schedule to follow. During Period 2, there will be regular communication with patients/families by phone, secure email and/or the clinical trial database. Communication with patients/families will occur approximately 6 times during treatment Period 2; about once every two weeks. Patients will keep seizure calendars. Patients will return to NIH 6 weeks +/- 2 weeks after the start of Period 2 and the tests listed in section 7.571 will be performed. At the end of the Maximum Tolerated Dose period, patients will again return to NIH for repeat of baseline testing (see section 7.572). Following testing, patients will be tapered off of Period 2 study drug..

The same titration, MTD treatment, and taper schedule as described in Period 1 will be used for Period 2. Period 2 will last approximately 12-16 weeks..

7.56 End of study

Patients will have a final follow-up visit approximately one month after the last dose of study drug. During this visit patients will have a physical examination and review any adverse events, ECG, blood and urine testing, and.mood tests.

7.57 Tests during the study

7.571 During the 6 week +/- 2 week visit the following evaluations will be completed:

Physical Exam
Blood drawing for: CBC, acute care panel, hepatic panel
Measurement of plasma AED levels, if assay available
Urine Pregnancy test (for women of child bearing potential)
Seizure calendar review
Adverse event and toxicity record review
Hamilton depression rating scale

7.572 At the end of each MTD treatment Period the following evaluations will be completed:

Physical Exam
ECG
EEG
Blood drawing for: CBC, acute care panel, hepatic panel
Measurement of plasma AED levels, if assay available
Urine Pregnancy test (for women of child bearing potential)
Neuropsychological tests and mood rating scales (see section 7.581)
Columbia Suicide Severity Rating Scale

7.573 Patient Monitoring

Patients will be monitored carefully by CES for any change in their clinical status, using reports of seizure frequency, adverse events and toxicity at regular patient contact about once every 2 weeks, and clinical exam, laboratory studies, and Hamilton Depression rating scale at clinic visits. Criteria to be used to decide whether a report or test result requires intervention include Grade 3 NCI CTC toxicity, a laboratory test twice the upper limit of normal, an abnormal finding on EEG or ECG not present at baseline, or an increase of 7 on the Hamilton Depression Scale. Intervention will be determined by the safety monitor and may include consultation, additional studies, or withdrawing the patient from the protocol.

7.58 Description of procedures

7.581 Neuropsychological and Mood Assessments

Attention:
Brief Test of Attention (Schretlen 1997)
Cancellation test from the WAIS-IV (Wechsler 2008).

Memory:
Hopkins Verbal Learning Test, versions 1,3 &4 (Brandt and Benedict 2001).
Brief Visuospatial Memory Test-Revised (Benedict 1997)

Executive Functions:
Controlled Oral Word Association Test: 3 different forms (FAS, CFL, PRT) (Spreen and Strauss 1998)
Trail Making Test (Spreen and Strauss 1998)
Design Fluency (Delis et al 2001).

Mood rating scales:
Hamilton Depression Rating Scale-24 item
Hamilton Anxiety Rating Scale
Beck-2 Depression Self Inventory
Columbia Suicide Severity Rating Scale

7.582 PET Scan:

A PET scan with 18F-FCWAY and a transmission scan will be performed once (if patients have not had them already) in a single session before initiation of study drug.

For the PET scans, patients will be in a fasting state for three hours prior to the procedure. Patients may not use any alcohol or recreational drugs for the two weeks preceding the PET scan. EEG leads may be attached to the scalp to record EEG during the PET scan if warranted by the patient's seizure pattern. The thermoplastic facemask will be used in the standard manner for NIH PET scans. An IV infusion of 0.9% saline solution will be started to provide IV access for radiotracer administration.

Following transmission scans, 10 mCi of [F-18]FCWAY will be administered. Scanning will proceed for 120 minutes. If necessary, scanning can be interrupted to allow the patient to sit up and rest, and resumed for the remainder of the predetermined time.

During the [F-18]FCWAY study, up to 40 arterial blood samples (approximately 250 cc) will be collected and radioactivity concentration in whole blood and plasma will be determined. A catheter will be placed in the patient's radial artery by the NIH Anesthesia Department. The skin at the site of the puncture will be anesthetized with 1% lidocaine. The catheter will be perfused (3ml/hr) with heparin solution (600 units/l) during the procedure. The amount of heparin infused will be much smaller than the amount necessary to produce any systemic anticoagulant effect. The arterial input function is necessary for quantitation of $5HT_{1A}$ receptor volume of distribution. In addition, at selected sample times, samples will be used to measure the fraction of the radioactivity in plasma that has not been metabolized. The fraction of plasma radioactivity unbound to protein will also be determined.

Scans will be performed with the PET/CT or the High Resolution Research Tomograph (HRRT). The slice separation is 2.0 mm. The transverse resolution is 4.4 mm in HIREZ and the axial resolution is 4.5 mm in HIRES. All scans will be acquired in 3D mode and start with an 8-min transmission scan with 2 rotating rod sources for the purpose of attenuation correction.

Blood samples for cortisol and ACTH level will be obtained at the time of PET, through the A line or IV line.

IV and arterial catheters will be removed after scanning is completed. The patient will be asked to urinate after the scan and again two hours later.

7.583 Genetic Testing:

Testing for polymorphisms in genes related to serotonin transport, depression, and epileptogenesis

If patients have not provided DNA samples previously, we will obtain saliva samples to test for polymorphisms in SERT, TPNH, COMT, BDNF and GABA genes that have been associated with psychiatric disorders and epileptogenesis. DNA testing is optional.
Samples and data may be used for comparison with samples from epilepsy patients and normal controls obtained in future studies.

DNA and cell lines will be processed, tested for polymorphisms, and maintained in the Laboratory of Dr David Goldman, NIAAA, using the established procedures of his laboratory.

7.584 Total blood to be drawn

Screen	Baseline	Treatment Phase Period 1 6 Weeks (+/- 2 weeks) and 12 -16 Weeks	Wash out 4-6 weeks	Treatment Phase Period 2 6-weeks (+/- 2 weeks) and 12-16 Weeks	Approx.1 month post study follow up
Acute care panel and Hepatic panel 10 mL	AED level 8 – 16 mL	Acute care panel and Hepatic panel 30 mL		Acute care panel and Hepatic panel 30 mL	Acute care panel and Hepatic panel 8 mL
CBC 3 mL	ACTH 2 mL Done with PET	CBC 9 mL		CBC 9 mL	CBC 3 mL
AED level 8 – 16 mL	Cortisol 10 mL Done with PET	AED level 24 - 48 mL		AED level 24 – 48 mL	AED level 8 – 16 mL

	PET study 250 mL				
Max 29 mL	Max 278 mL	Max 87 mL		Max 87 mL	Max 29 mL

7.6 Follow-up and termination procedures

7.61 Transfer / Continuity of care

During the study, AEDs will be managed by NINDS neurology staff. At the end of the study, patients may be considered for inclusion in additional NINDS protocols. If they do not qualify or wish to participate, they will be referred to the care of their referring physicians. Patients who do not have a referring physician or wish to find an alternative will be assisted in locating a neurologist skilled in the care of people with epilepsy.

7.62 Information to be shared with subjects or health care providers

All clinical data obtained during screening, as well as any other data relevant to standard epilepsy care obtained during the protocol, will be shared with patients and with the participant's written permission, their health care providers.

7.7 Research and clinical care procedures

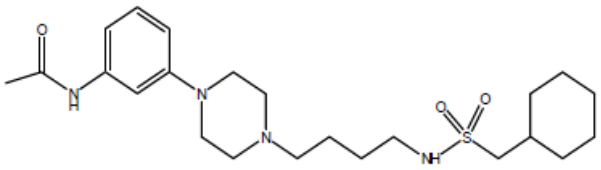
All procedures performed under this protocol are research-related.

7.71 Medications requiring IND

18F-FCWAY: Sponsor NIH PET Department. Approved
PRX-00023: Sponsor William H Theodore MD. Approved

7.72 Study Drug (see Investigator's Brochure).

INN:	Naluzotan
CAS number:	[740873-07-08]
Molecular weight	537.57 g/mol
Empirical formula:	C23H38N4O3S.2HCl
Chemical name:	N-{3-[4-(4-cyclohexylmethanesulfonylamino-butyl)-piperazin-1-yl]-phenyl}-acetamide dihydrochloride
Chemical structure:	



PRX-00023

Following ascending multiple oral PRX-00023 dose titration, absorption of PRX-00023 was fairly rapid (Tmax one to four hours) and mean serum concentrations appear to increase with

increasing doses of 80 to 320mg QD or 40 mg BID to 160 mg BID, respectively. Elimination half-life is estimated to be 9.8 to 13.5 hours. Plasma protein binding is approximately 90%.

PRX-00023 is metabolized mainly by CYP 3A4 and to a lesser extent by CYP 2D6. It may interact with inducers such as phenobarbital or phenytoin. Felbamate, oxcarbazepine, and topiramate are weak inductors of the CYP isoenzyme 3A4, and would be less likely to alter the metabolism of PRX-00023. For carbamazepine, potential induction of metabolism may be balanced by inhibition of PgP brain efflux transport, for which PRX-00023 is a substrate. PRX-00023 does not to inhibit or induce any CYP enzymes.

7.73 Source of materials/storage/handling

Trial Product	
Compound	PRX00023
Product Name	PRX-00023 (Naluzotan)
Dosage Route	Oral Capsule
Strength	37.2mg (equivalent to 40mg bis salt)
Manufacturer	Clinical Center Pharmacy Department Building #10 Room 1N-257 MSC-1196 10 Center Drive Bethesda, MD 20892-1196
Comparator	
Product	PRX-00023 Placebo capsule
Manufacturer	Clinical Center Pharmacy Department Building #10 Room 1N-257 MSC-1196 10 Center Drive Bethesda, MD 20892-1196
	Drug Substance (API) has been manufactured by Johnson Matthey Pharma Services, 70 Flagship Drive, North Andover, MA 01845in accordance with the Clinical Trials Directive 2001/20/EC, GMP Directive 2003/94 and 21 CFR Parts 210 and 211 for Investigational Medicinal Products.

The NIH Pharmacy will dispense three month's supply of study drug (PRX-002 or placebo) to subjects. Patients will be encouraged to bring pill bottles to each visit. If patients bring pill bottles, pill counts will be performed. Patients will be advised to take a missed dose they remember within 4 hours; otherwise, to take the next scheduled dose and record the missed dose on their seizure calendar. Patients will be advised to take their study drug with food.

All unused investigational product will be returned to the NIH Pharmacy for disposal.

7.73 Radiation

All radiation administered under the protocol is for research only.

7.74 Relationship of this study to other protocols

Patients will be screened under protocol 01-N-0139.

7.75 Storage of data and samples

Study data will be stored in password-protected NINDS and NIH Clinical Center computer systems.

DNA and cell lines will be maintained in the Laboratory of Dr David Goldman, NIAAA, using the established data protection procedures of his laboratory.

8. Risks and discomforts

8.1 PRX-00023

PRX-00023 has been studied in approximately 100 healthy human volunteers and in 340 patients with generalized anxiety disorder (GAD) and major depression disorder (MDD). Safety data for doses up to 320 mg per day have been reported. The most common side effects include headache, dizziness, nausea, diarrhea, dyspepsia and insomnia. In clinical trials, 5-10% more patients on active drug than on placebo reported at least one side effect (see section 4.42). Drug side effects are expected to be transient, and respond to dose reduction if necessary.

Considering PRX-00023 pharmacokinetics, patients not on the AEDs listed in exclusion criteria are considered unlikely to show significant drug interactions, although unexpected risks are possible.

A possible small increase in 'suicidality' has been associated with SSRIs and AEDs but not direct 5HT1A agonists.

The potential risk for birth defects in children of parents taking PRX-00023 is unknown. Men and Women must use an effective method of contraception during the study and for three months afterwards. If a woman becomes pregnant, she will be dropped from the study and the blind will be broken. Appropriate counseling will be provided.

PRX-00023 has not been given to patients with epilepsy. Risk will be minimized by screening for exclusion criteria, and careful clinical monitoring, weekly contact, and at each clinic visit.

8.2 PET

PET scans require exposure to radiation. All tests requiring patient exposure to ionizing radiation should be considered to be potentially hazardous. Detailed breakdown of the radiation exposures to be expected in subjects enrolled in this protocol are included in the attached radiation safety form (NIH 88-23(a) revised). Although each organ will receive a different dose, the amount of radiation exposure is equal to a uniform whole-body exposure of 0.77 rem. This calculated value is known as the “effective dose” and is used to relate the dose received by each organ to a single value. The doses to be administered have been approved by the NIH radiation safety committee. The total anticipated 'effective dose,' equivalent to whole-body exposure, is less than the RSC exposure limit for research subjects of 5.0 REM per year. Some patients may become uncomfortable while lying in the scanner.

8.4 Venous and arterial blood sampling

Venous blood sampling is associated with possible bruising, discomfort, and superficial infection.

Some discomfort is associated with the placement of the arterial needle. Bruising or swelling at the site of the arterial catheter occurs in 5 to 20 percent of patients, but is only temporary. Fainting is remotely possible. Permanent damage from these complications is extremely rare. Blockage of the artery by the catheter can occur, but is unlikely because the catheter is left in for only a short period of time. There have been two delayed complications from wrist arterial catheters at NIH. One person developed a small radial artery aneurysm 2 years after arterial catheterization. A second developed a blocked artery a few days after arterial catheterization. Both required surgical repair.

8.5 EEG and ECG

EEG and ECG may cause skin irritation. This risk will be minimized by following the standard procedures of the NIH EEG lab.

8.6 Neuropsychological and mood testing

Neuropsychological and mood testing have minor risks, including boredom and frustration. Some patients may be disturbed by test results, or by questions about issues such as depression and suicide risk. Counseling will be provided under the supervision of the psychiatrist co-investigator should this occur.

8.7 Genetic Testing:

Risks of genetic testing include emotional distress due to learning about increased risk of disease, and problems, such as with insurance or employment discrimination. All data from this protocol will be kept confidential. In addition, the polymorphisms to be tested for are still undergoing study and have not definitely been associated with any specific illnesses or shown to have any clear medical implications.

9. Subject Monitoring

9.1 Parameters to be monitored

Patient reports of seizure frequency, adverse events and toxicity at regular phone/secure email/computer contact. Clinical exam, laboratory studies, seizure calendars, adverse events and toxicity reports and Hamilton Depression rating scale at clinic visits.

9.2 Toxicity tables/ criteria to be used

Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (appendix). Dose limiting toxicities will be considered any NCI grade 3 toxicity felt to be probably or definitely related to study medication; grade 4 or 5 toxicity judged to be possibly, probably or definitely related to study medication by the safety monitor.

In the event of a Grade 3 toxicity felt to be probably or definitely related to study medication by the study investigator or safety monitor a one-step dose reduction will be initiated (i.e., from 240 to160 milligrams per day) until the toxicity resolves to Grade 0 or decreases to Grade 1. If NCI Common Terminology Grade 4 toxicity is felt to be possibly, probably or definitely related to study medication by the study investigator, the patient will be withdrawn from treatment. All dose

changes and/or dose interruptions will be recorded on case report forms.

9.3 Criteria for Breaking the Blind and Premature Termination or withdrawal

Criteria to be used to decide whether a report or test result requires intervention include Grade 3 NCI CTC toxicity, a laboratory test twice the upper limit of normal, an abnormal finding on EEG or ECG not present at baseline, an increase of 7 on the Hamilton Depression Scale. Intervention will be determined by the safety monitor and may include consultation, additional studies, or withdrawing the patient from the protocol.

The blind for an individual may need to be broken even for non-serious, expected, or unrelated AEs or as requested by local regulatory authorities or where, in the view of the safety monitor, knowledge of the identity of the study drug is essential to appropriately manage an adverse event.

Patients will be removed from the study if they become pregnant, are unable to continue to cooperate, or have an alteration in clinical status, other than that related to their epilepsy, needing medical intervention. Patients may withdraw from the trial at any time at their own request. The Investigators may withdraw a subject for safety or behavioral reasons.

10. Outcome Measures

The primary outcome measures for drug efficacy will be:
Mean difference in seizure frequency comparing the active and placebo periods.

Secondary outcome measures for efficacy will be:
Proportion of patients with ≥ 50% lower seizure rate on PRX-00023 than placebo
Hamilton Depression and Anxiety Rating scales
Performance on neuropsychological testing scales

Outcome measures for safety will include:
Columbia Suicide Severity Rating Scale
Hamilton Depression Rating Scale
Clinical examination
CBC and clinical chemistry studies
ECG
Adverse event reports
Seizure Calendars

11. Statistical Analysis

11.1 Analysis of Primary Endpoint

Analysis of variance will be used to test for a treatment order effect. A carry-over effect is unlikely due to the long washout period. A paired samples Student's T-test will then be used to compare seizure frequencies during placebo and active treatment periods (see sample size calculation below). If the carry-over effect is significant, a two group T-test will be applied separately for each period.

11.2 Analysis of Secondary Endpoints

11.21 Neuropsychological testing and mood scores

Analysis of variance with repeated measures will be used to compare neuropsychological and mood rating scores for the baseline, placebo, and active drug periods.

11.22 5HT1A Receptor Binding

FCWAY functional images will be corrected for partial volume effects as previously described, and gray-white matter ratios on a pixel by pixel basis. Regions of interest drawn on MRI scans will be co-registered with the PVC-corrected V images. For each patient, side-side asymmetry values will be obtained, in order to detect alterations of binding ipsilateral to the epileptic focus.

A binding potential measurement will be derived using the cerebellum as a region devoid of 5-HT_{1A} receptors, and calculated as:

$$BP = [(V_{ROI}-V_{CEREB})/f_1)] \quad \text{(Eq. 1)}$$

where V_{ROI} and V_{CEREB} are the distribution volumes in the target ROI and in the cerebellum respectively, and f_1 is [^{18}F]FCWAY plasma free fraction.

Values in regions of interest will be compared between baseline and peak dose scans using a paired Student's T-test with correction for repeated measures. It is anticipated that 12 subjects will have a scan at baseline and on active drug, while 12 will have a scan at baseline and on placebo, providing a measure of test-rest reliability.

11.23 Polymorphism analysis

The presence or absence of the polymorphisms detected will be compared to 5HT1A receptor PET binding and seizure frequency outcome in an exploratory manner.

11.3 Safety Analysis

Adverse events will be recorded at each clinic visit or more frequently as reported by patients. Safety data (adverse events, vital signs, laboratory tests and physical examination) will be subject to clinical review and summarized by appropriate descriptive statistics.

11.4 Sample size and power calculation

We assume that the mean difference between drug and placebo will be a 15% lower seizure rate, (representing a 30% improvement on drug versus 15% improvement on placebo versus baseline), and that the standard deviation of difference is 22%.

Based on a paired t-test, the estimated sample size is 19 to obtain 80% power at a significance level of 0.05. In order to balance the two arms we will accrue patients until 20 completers have been obtained. We request a total of 30 subjects to take into account a possible 20% dropouts.

Paired t-test of mean difference equal to zero

	1	2	3	4
Test significance level, □	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2
First condition mean, □1	30.000	30.000	30.000	30.000

Second condition mean, μ_2	15.000	15.000	15.000	15.000
Mean difference, $\mu_d = \mu_1 - \mu_2$	15.000	15.000	15.000	15.000
Standard deviation of differences, σ_d	22.000	23.000	20.000	25.000
Effect size, $\delta = \lvert\mu_d\rvert / \sigma_d$	0.682	0.652	0.750	0.600
Power (%)	80	80	80	80
n	19	21	16	24

11.41 Independent period analysis

Based on calculations by the NINDS statistician, 24 completers would be needed in the event of detection of a carryover effect. If we detect a carryover effect, the additional sample size of 24 patients will have 80% power to detect a 45% decrease in seizure frequency in the PRX 00023 group, versus 15% in the placebo group, assuming the 25% common standard deviation.

Alpha = 0.050
Power = 0.800
Model = Two Sample t-test
Effect Size = 1.200
Pooled S.D. = 0.250

Mean(01) = 0.450
Mean(02) = 0.150

GROUP 1	GROUP 2	POWER
2	2	0.114
3	3	0.207
4	4	0.299
5	5	0.386
6	6	0.468
7	7	0.541
8	8	0.608
9	9	0.667
10	10	0.718
11	11	0.763
12	12	0.802

Total Sample Size = 24

11.42 Analysis populations

Intent To Treat (ITT)

The Intent-to-Treat (ITT) population includes all randomised subjects with at least one efficacy evaluation for at least one double-blind treatment period. The Safety Population consists of all subjects who administered at least one application of trial medication. The primary statistical analyses of efficacy will be performed on the ITT population and will compare the treatment groups on the basis of randomized treatment sequence regardless of the treatment actually received. All secondary efficacy analyses will be performed on the ITT population. Safety analyses will be performed on the safety population on the basis of treatment actually received where possible.

11.5 Accrual number request

In order to accrue 24 subjects, we are requesting a total potential sample size of 30. This should account for patients who do not have enough seizures to qualify during baseline, as well as dropouts.

12. Human Subjects Protection

12.1 Rationale for Subject Selection

Subjects will be selected based upon their meeting the study's eligibility criteria. Subjects will be admitted to the protocol without regard to 'race,' 'ethnicity,' gender, 'sexual orientation,' or other regardless of any non-medical personal characteristics.

12.2 Justification for exclusion of children

PRX-00023 has not yet been given to children. Children are excluded from this study because safety has not been established in children and the efficacy for epilepsy is undetermined.

12.3 Justification for exclusion of those over age 65

Patients over age 65 years old are excluded form this study because they are more likely than younger persons to have co-morbid conditions. Furthermore, previous clinical experience with PRX-00023 has been limited to those ages 18 – 65.

12.4 Vulnerable subjects

Adults unable to give consent will not be included. If capacity is uncertain, NIH/CC/Bioethics/HSPU will be consulted. Pregnant women will be excluded, as PRX-00023 teratogenicity potential is unknown. Woman who are able to become pregnant, and men will be required to use contraception throughout the protocol participation.

12.5 Justification for use of placebo

Placebo-controlled studies are the only way to obtain reliable data on AED efficacy in a clinical trial in any epilepsy syndrome, including localization-related epilepsy. Seizures are largely self-reported, and placebo effects occur in all AED trials. Since this is an add-on study, patients will still be on their baseline AEDs during all treatment phases, and will not be exposed to any risk greater than their standard therapy while on placebo.

12.6 Qualifications of investigators

The Principal Investigator, William H. Theodore MD is board-certified in Internal Medicine, Neurology, and Clinical Neurophysiology, and has extensive experience in epilepsy research, including serving as principal investigator on several AED trials. He may obtain consent.

Rosemarie Cuento CRNP has many years of experience in the evaluation and treatment of patients in the clinical research setting. Ms Cuento will participate in patient care. She may obtain consent.

Peter Herscovitch MD will participate in FCWAY PET studies. He is Chief of the NIH PET Department.

Sara Inati MD will participate in patient evaluation and care. She is Chief of the NIH EEG laboratory and has extensive experience in Epilepsy, EEG, and AED Clinical trials. She may obtain consent.

Edythe Wiggs PhD, the NINDS clinical psychologist will perform neuropsychological evaluations.

Carlos Zarate MD is a board-certified psychiatrist and NIMH Senior Investigator with extensive experience in the evaluation, treatment, and investigation of depression. He will provide psychiatric consultation and oversee evaluation.

Dr Goldenholz is a fellow who has completed a neurology residency and two years of epilepsy fellowship. He will participate in patient evaluation and care. He may obtain consent.

Dr. Agrawal and Dr. Joshua are clinical fellows who have completed a neurology residency. They are starting their epilepsy fellowship. They will participate in patient evaluation and care. They may obtain consent.

David Goldman MD is a geneticist who is Chief of the NIAAA/DICBR/LN/SHN. He will be responsible for polymorphism analysis.

13. Potential Benefits

Patients may experience direct benefit while on the active medication due to:
Reduction of seizure frequency
Amelioration of depression and anxiety
Increased information on localization of their epileptic focus due to 18F-FCWAY PET

14. Summary/ classification of risk: for the study as a whole

This protocol is more than minimal risk.

The risks are reasonable in relation to anticipated benefit. Uncontrolled epilepsy is a serious illness with increased morbidity and mortality compared with the general population. Previous experience suggests that PRX-00023 has low toxicity. The radiation exposure from the PET scans to be performed is within the limits set by the NIH Radiation Safety Committee.

15. Consent documents and process

The study investigators authorized to obtain consent are indicated in section 12.6.

15.1 Non-English Speaking Participants

If a non-English speaking participant is unexpectedly eligible for enrollment, the CC standard short written consent form in the appropriate language and a written summary of what the

Investigator will say to the participant will be used as part of an oral consent process. The IRB approved English written consent form will serve as the written summary if the short form process is used. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (i.e., not a family member). Interpreters will be found through the Department of Social Work. The interpreters will translate the current IRB-approved English version of the consent verbatim and facilitate discussion between the participant and investigator.

The written summary will be signed by the investigator obtaining consent and a witness to the oral presentation. The short written consent form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of the signed form will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record, including the name of the interpreter. Further, all instances of use of the short form process will be reported to the IRB at the time of annual review.

16. Data and Safety monitoring

This protocol will utilize a Safety Monitoring Committee (SMC) and an Independent Medical Monitor (IMM) to review AEs and safety reports. The Safety Monitoring Committee will be composed of:

Dr. Mohamad Koubeissi MD. Board Certified in Neurology, Clinical Neurophysiology and Epilepsy, GW Medical Faculty Associates
Dr Gerald Overman NIH CC Pharmacy Pharm.D., BCPP, Clinical Pharmacy Specialist for NIMH
Ms Jean Radcliffe RN NIMH

The Safety Monitoring Committee (SMC) will meet in advance of enrolling the first subject to confirm the monitoring plan. The SMC will meet at intervals specified by the needs of the trial, via conference call, email, or web-meeting by a password protected phone line/secured email/web meeting. The SMC will meet at least annually while the study is open to enrollment or has participants in active follow-up, and more frequently if needed. Additional meetings may be scheduled when necessary for adequate monitoring. Safety data reports will be provided annually, including seizure frequency, toxicity reports, neuropsychological and mood testing, laboratory tests, EEG, ECG and clinical examination until the end of the trial. Results will be reported to the Principal Investigator, IRB, and NINDS Clinical Director. Data review will be blinded, and no interim analysis is planned.

Dr Eric Wassermann, a Board-Certified neurologist with extensive clinical trial experience, will serve as Independent Medical Monitor (IMM). Patients will be monitored carefully by CES clinicians for any change in their clinical status, using reports of seizure frequency, adverse events and toxicity during patient/family communications, clinical exam, laboratory studies, and Hamilton Depression rating scale at clinic visits. The IMM will be notified regarding clinical issues that may arise during this trial. Intervention may be determined by the IMM and may include consultation, additional studies, or withdrawing the patient from the protocol.

16.1 Criteria for stopping the study

The study will be suspended if a serious adverse event, as determined by the SMC, occurs in a patient found to be on active treatment after breaking the blind occurs. The study will not be restarted until reviewed by the IRB. The study may be stopped if in the judgment of the SMC

there is evidence that Grade 3 toxicity on the NCI CTC, or an increase in seizures of more than three times baseline, has occurred in more than 50% of the patients.

17. Quality Assurance (QA)

a. Quality assurance monitor

The EMMES Corporation will perform protocol monitoring.

b. Quality assurance plan

QA review will performed in accordance with the QA Monitoring/Auditing algorithm included in the NINDS Quality Assurance Protocol Audit Plan. The EMMES Corporation will perform protocol monitoring annually.

18. Reporting of Unanticipated problems, adverse events and protocol deviations

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the CD.

Serious unanticipated problems, serious adverse events (including deaths) that are not unanticipated problems, and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing not more than 7 days after the PI first learns of the event, unless immediate reporting is waived for specific serious adverse events as noted below. Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing not more than 14 days after the PI first learns of the event. Written reports will be submitted in PTMS.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

The PI will immediately report SAEs to the Sponsor according to the requirements of 21 CFR 312.64(b) and as agreed upon with the sponsor. The PI will record nonserious AEs and report them to the Sponsor at the time of Continuing Review.

The following expected Serious Adverse Events will not be reported to the IRB immediately and within 7 days unless they occur at a rate or severity greater than expected:
Emergency Room visits and hospitalization related to seizure activity including seizure clusters, falls and injuries related to falls.

19. Alternative therapies

There is no other way to receive PRX-00023 for epilepsy. Alternative possible approaches include additional current marketed AEDs, participation in other experimental drug trials, brain stimulation therapy, and surgical evaluation.

20. Privacy

All research activities will be conducted in as private a setting as possible.

21. Confidentiality

To ensure confidentiality, research records will be kept in locked files in the principal investigator's office, and clinical files will be kept in the NIH Medical Records department. Image files that include experimental details will be maintained in file systems accessible only to the physicians and other scientific and technical staff working with the principal investigator. Subjects will be identified by code on all case report forms.

22. Conflict of Interest

NIH guidelines on conflict of interest have been distributed to all investigators. No NIH investigators have reported a conflict-of-interest.

23. Technology Transfer

The study will be carried out under CRADA 2010-0071_with Proximagen Limited, Hodgkin Building, Guy's Campus, King's College London, London UK, SE1 1UL.

Proximagen is providing drug to NIH, and allowing NIH to cross-reference it's previous IND filings in filing the IND for the study. NIH will provide Proximagen the results of the study, with all data deindentified, as well as copies of annual and other reports to the FDA.

24. Research and Travel Compensation

No financial compensation will be provided to patients in the study.
Reimbursement for travel expenses will be provided, based on NINDS and NIH guidelines.

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26. Attachments/ Appendices

Study Calendar
Eligibility checklist
Case report / monitoring form
NCI CTC
Investigator's Brochure
NIH 88-23a
Jump Text Page

27. Consent forms

Adult subject