Protocol Title: Phase 2 Clinical Trial of SGS-742 Therapy in Succinic Semialdehyde Dehydrogenase Deficiency

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Explanation of dates:

The protocol uploaded to the Documents Section of clinicaltrials.gov represents the final IRB approved version of the protocol.

The study team submitted the final amended version of the protocol on March 26, 2019, which was approved by the IRB on April 3, 2019.

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Protocol Title: Clinical Trial of SGS-742 Therapy in Succinic Semialdehyde Dehydrogenase Deficiency
Abbreviated Title: SGS-742 in SSADH Deficiency
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Principal Investigator

Sara Inati M.D.	OCD NINDS	10/7-5680	301-435-6269	inatisk@mail.nih.gov	

Adjunct Principal Investigator

Phillip L. Pearl, M.D	Boston Children's Hospital, Boston, MA	300 Longwood Avenue 9th floor Boston, MA 02115	202- 884-5439	PPEARL@cnmc.org

Lead Associate Investigator

William H Theodore MD	CES/NINDS	10/7D-43	301-496-1505	theodorw@ninds.nih.gov

Associate Investigators

Rosemarie Cuento CRNP	NINDS CTU	10-CRC 7-5644	rosemarie.cuento@nih.gov 301-451-9284
John Schreiber MD	CNMC NEUROLOGY Washington DC		John.schreiber@cnmc.org 202-884-5439
Eric Wassermann MD	BNU DIR NINDS	10/7D-41	WassermannE@ninds.nih.gov
K Michael Gibson PhD	Professor and Chair) WSU College of Pharmacy	PBS Building room 347 412 E. Spokane Falls Blvd Spokane, WA 99202	Mike.gibson@wsu.edu
Edythe Wiggs, PhD	NINDS/DIR/CNP/OCD	10-CRC 7-5685	wiggsse@ninds.nih.gov 301-451-9285
Gina Norato, ScM	NINDS CTU	10/2A23	gina.norato@nih.gov 301-496-4358

Research Contact

Rosemarie Cuento CRNP	NINDS CTU	10-CRC 7-5644	rosemarie.cuento@nih.gov 301-451-9284

Total requested accrual:
22 adults and children, 4 and older, with documented SSADH Deficiency

Project Uses Ionizing Radiation: x No oYes

IND/IDE o No x Yes (attach FDA documentation)
Drug/Device/#: SGS-742
Sponsor: National Institute of Neurological Disorders and Stroke (NINDS)

Durable Power of Attorney o No X Yes

Multi-institutional Project o No x Yes
Institution#1: Washington State University 119535-001 FWA # 00000326
Approval Date: 5/29/14
Data and Safety Monitoring Board o No x Yes

Technology Transfer Agreement o No x Yes
Agreement type and number: MTA 119535 Expiration Date: None

Samples are being stored o No x Yes

Flesch-Kincaid reading level of consent form & single patient consent form: 9.0
Minor Assent 12-17 & Adult Assent: 5.3
Minor Assent 8-11: 4.2

Précis:

Objective: To perform a clinical trial assessing the safety, tolerability and efficacy of the GABA(B) receptor antagonist SGS-742 in patients with SSADH deficiency.

Study Population: Twenty-two children and adults with SSADH deficiency.

Design: Double-blind, cross-over, phase II clinical trial. SGS-742 is a GABA (B) receptor antagonist that has shown to be safe and well-tolerated in clinical trials in adults with cognitive impairment. In addition, preliminary data in the SSADH knockout mouse model suggest efficacy in this specific syndrome. The primary outcome measure will be a change in the Auditory Comprehension subtest of the Neuropsychological Assessment Battery Language Module score; the secondary outcome measure will be a change in cortical excitation and inhibition measured by transcranial magnetic stimulation (TMS). Additional evaluations will include neurological and neuropsychological examinations, magnetic resonance spectroscopy and CSF collection to measure GABA levels. The trial will have a baseline phase in which each patient will undergo a neurological examination and a neuropsychological evaluation. During the subsequent treatment phase, patients will be randomized to SGS-742, supplied by IRIX Pharmaceuticals, and based on weight given a maximum tolerated dose not to exceed 600 mg t.i.d. orally, or placebo, each for 6 months. Patients will then have repeat TMS, neurological and neuropsychological evaluations, followed by cross-over to the alternate treatment arm, and re-evaluation after 6 months.

Outcome Measures: The primary outcome measures for drug efficacy will be performance on neuropsychological testing and responses to parent questionnaire. The secondary outcome measure will be TMS parameters of cortical excitation and inhibition. The outcome measures for safety will include clinical examination and neuropsychological tests.

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1. INTRODUCTION

SSADH deficiency, also called 4-hydroxybutyric aciduria (McKusick 279180), is a rare autosomal recessive disorder caused by an enzyme deficiency in the GABA degradation pathway (Gibson and Jakobs 2001). In the absence of SSADH, transamination of GABA to succinic semialdehyde is followed by its conversion to 4-hydroxybutryic acid (gamma-hydroxybutyric acid, or GHB). About 400 patients with SSADH deficiency have been identified and more than 80 clinical cases have been reported in the primary literature, which makes this the most prevalent PND (Pediatric Neurotransmitter Disorder) (Gibson et al 1998; Gibson 1997; Pearl et al 2003a; Pearl and Gibson 2004). SSADH deficiency is linked to GABA and γ-hydroxy butyrate (GHB) accumulation in the CNS. GHB possesses a number of neuropharmacological properties (Maitre 1997, Wong et al. 2003), most notably the ability to inhibit presynaptic dopamine release and potentate dopamine turnover.

The index case of SSADH was identified in 1981 (Jakobs et al 1981). The investigators' studies utilizing a detailed clinical questionnaire and standardized interview in 60 patients have documented the clinical features of the syndrome, including early history of developmental delay (100%), intellectual disability with disproportionate deficit in expressive language (100%), hypotonia (82%), ataxia (77%), seizures (45%), and multiple neuropsychiatric symptoms including sleep disturbances (45%), attention deficit (45%), anxiety (27%), obsessive-compulsive disorder (25%), and autistic traits (25%) (Pearl et al 2009). Some patients have occasional, relatively mild seizures; others, recurrent bouts of generalized convulsive status epilepticus (Pearl et al 2003b). An initial diagnosis of autism spectrum disorder has occurred in a disproportionate amount in patients subsequently identified as having SSADH deficiency (Gibson et al 2003).

CSF metabolite profiles from 13 unrelated patients demonstrated significantly elevated GHB (65- to 230-fold), high free and total GABA (up to threefold), and low glutamine (Gibson et al 2003). These findings, including a drop in glutamine over time, have been documented in the affected animal model (Gupta et al 2003). In addition, there was a linear correlation in both HVA and 5-HIAA levels with increasing GHB concentration, suggesting enhanced dopamine and serotonin turnover (Gibson et al 2003).

Preliminary studies in animal and human subjects have identified three systems with significant changes: 1) the GABA neurotransmitter system with marked elevations of GABA; 2) glutamine alterations which may affect both GABAergic and glutamatergic systems; and 3) GHB elevations which likely disrupt dopamine and serotonin homeostasis. The investigators hypothesize that the elevated GABA combined with low glutamine suggest disruption of the glial-neuronal glutamine/GABA/glutamate shuttle necessary for replenishment of neuronal neurotransmitters. In addition, the altered dopamine and serotonin metabolism

may be causally linked to the behavior disturbances seen in SSADH deficient patients (Gibson et al 2003).

1.1 Background and Significance

SSADH deficiency is a human condition that presents itself through dysfunction of the developing nervous system, which is associated with chronic elevation of GABA and GHB. The biochemical hallmark, GHB, is increased in the physiological fluids (CSF, plasma and urine) for all patients of SSADH that have been studied clinically. GABA is increased in the CSF of those patients for whom a diagnostic lumbar puncture was performed.

GABA is the earliest neurotransmitter expressed during development with several critical roles during CNS development. Elevated GABA levels in early development may result in altered neuronal migration, neurogenesis, myelination and synaptogenesis. While detailed neurometabolic and genetic studies of the murine model of this disorder are in progress, there have been no prospective studies of the human condition.

GHB is employed to induce a model of absence in rodents, to treat cataplexy and alcohol/opiate-withdrawal syndromes, as a recreational drug of abuse, and to subdue victims for the purpose of sexual assault (Okun et al 2001). Indeed, GHB has emerged as an increasingly common drug of abuse, associated with psychosis. GHB consumption may be associated with addiction and withdrawal (Mason and Kerns 2002).

The role of GHB and GABA (both elevated in this disorder) in the pathophysiology of SSADH deficiency remains unclear. Developed as an anesthetic/sedative (Roth and Giarman 1966), GHB is an endogenous metabolite (< 1% of GABA levels) and may be a neurotransmitter (Snead 2000). The primary literature suggests that physiologic levels of GHB (~2 uM in mammalian brain) act on the high-affinity GHB receptor (GHBR, a G protein coupled receptor that may be a $GABA_B$ receptor ($GABA_BR$) subtype). However, at non-physiologic concentrations (~ 200-1000 uM, as in SSADH deficiency), GHB acts as a weak $GABA_BR$ agonist (Lingenhoehl et al 1999). As a $GABA_BR$ agonist, it is possible that increased GHB activity results in increased inhibition of interneurons having $GABA_B$ receptors, leading subsequently to disinhibition of glutamatergic neurons. MR spectroscopy studies have revealed decreased cellular GABA levels in some adult and pediatric patients with epilepsy (Petroff et al, 1996, 2001; Novotny et al, 1999), unipolar depression, alcohol withdrawal, and hepatic encephalopathy (Behar et al, 1999; Sanacora et al, 1999; Goddard et al, 2001); the latter diseases show impaired GABAergic function.

To our knowledge, SSADH deficiency represents the first pediatric/adult epilepsy disorder with increased GABA levels. However, the pathogenesis of seizures in

SSADH deficiency remains unknown. The accumulation of GABA and GHB may underlie the pathology of seizures and hyperactive behavior in SSADH deficiency. There may be down-regulation of pre- and post-synaptic GABA receptor (GABAR) expression by accumulated GHB/GABA. This may be associated with increased glutamatergic excitatory transmission, linked to disinhibition and glutamate release, with the subsequent appearance of seizures. In addition, a primary pharmacologic action of high-dose GHB is inhibition of presynaptic dopamine release (Maitre 1997). Subsequent increased dopamine turnover, as demonstrated by elevated CSF HVA levels in SSADH-deficient mice, may help to explain hyperactive behavior in humans. Evidence from the murine SSADH-deficient model (discussed below), and preliminary metabolite findings in human patients have supported these hypotheses (Gibson et al 2003; Gupta et al 2003).

1.2 Murine SSADH Deficiency

The murine knockout of SSADH was developed using standard gene-targeting methodology in the 129Sv/C57Bl background (Hogema et al 2001b). Deletion of exon 7 (encompassing an active-site cysteine) led to the complete absence of SSADH enzyme activity in neural and peripheral tissue extracts. $SSADH^{-/-}$ mice are born in the expected autosomal-recessive inheritance pattern with a phenotype paralleling the human disease including neurological impairment, ataxia, and seizures. At postnatal day 16-22, $SSADH^{-/-}$ mice demonstrate a transition from absence to myoclonic to repetitive tonic-clonic seizures resulting in 100% mortality (Cortez et al 2004). The reason for seizure onset remains unknown, although it may relate to the switching of GABA from excitatory to inhibitory synaptic transmission during development (Ganguly et al 2001). Other factors, including the appearance of new receptors and the relative resistance of the central nervous system (CNS) of immature animals to convulsant assault, may also be involved. Continuous inbreeding of the SSADH-/- strain has led to an attenuated phenotype, with average life expectancy for mutant mice extending just beyond 2 months (KM Gibson personal communication).

Absence of SSADH enzyme activity is associated with a significant elevation of GHB (35-40 fold) and total GABA (2.5-3.0 fold) in urine, brain and peripheral tissue extracts (Hogema et al 2001b; Gibson et al 2002a), similar to metabolite findings in human patients. $SSADH^{-/-}$ mice manifested regional brain abnormalities for both GABA and glutamine, with normal glutamate levels.

Glutamine is interconverted to glutamate, which may in turn be metabolized to GABA, glutathione (tripeptide of glutamate/cysteine/glycine) or 2-oxoglutarate. Glutamine is incorporated into glutamate and GABA in neurons and synaptosomes (Sonnewald and McKenna 2002). The “glutamine-glutamate” shuttle provides astrocytic glutamine as precursor for neuronal glutamate and GABA. Thus, trafficking of glutamine between glia and neurons is essential for

neuronal neurotransmitter pool maintenance. Decreased glutamine suggests dysregulation of extracellular fluid glutamate, possibly leading to lethal seizure activity in the mouse. Glutamine synthetase is exclusively localized within glia, while L-glutaminase (producing glutamate) is neuron specific. High-dose GHB application results in absence seizures (Hu et al 2000). It is thus proposed that GABA and glutamate play a prominent role in generalized seizures in murine and human SSADH deficiency. Alterations in these amino acids may underlie the pathology in mice with homozygous deficiency for SSADH. Further animal studies of these transmitter pools, with repeated measurements of concentration changes over the lifetime of the SSADH deficient mouse, are in progress (Gupta et al 2003).

1.2.1 Receptor binding studies in SSADH$^{-/-}$ Mouse brain

Based upon high GABA and GHB levels in SSADH$^{-/-}$ brain, the Gibson lab investigated [^{3}H]NCS-382 (a specific GHB receptor antagonist) binding in brain membrane preparations (Mehta 2001). Homozygous deficient mice displayed decreased NCS-382 binding in cerebral cortex (binding decreased by 12% as compared with controls) and hippocampus (21% decrease), consistent with downregulation of GHB receptors. Even heterozygous animals exhibited lower binding of NCS-382 in hippocampus in comparison to wild type animals. Mehta et al (2002) demonstrated [3H]GABA binding was decreased in the SSADH -/- mice by 43% in cerebral cortex.

Further receptor binding and electrophysiologic studies have demonstrated use-dependent downregulation of $GABA_A$ and $GABA_B$ activity. A progressive decrease in binding of the selective $GABA_A$ receptor antagonist (35)STBPS (tert-butylbicyclophosphorothionate) was observed in the mutant strain cerebral cortex, hippocampus, and thalamus from postnatal day seven until its nadir at three weeks, coincident with the emergence of generalized convulsive seizures (Wu et al., 2006). There were also reduced $GABA_A$ mediated inhibitory postsynaptic potentials and enhanced postsynaptic population spikes recorded from hippocampal slices. There was a significant decrease in binding of a specific $GABA_B$ receptor antagonist in SSADH null mice compared to wild type control animals, and decreased $GABA_B$ mediated synaptic potentials (Buzzi et al., 2006). Taken together, these results suggest that SSADH deficiency results in down-regulation of GHB, $GABA_A$ and $GABA_B$ receptors, and suggest a heterozygote effect on GHB binding as well.

1.2.2 SGS 742 Application in Mouse Model

Preliminary animal work in the SSADH mutant model has suggested benefit from treatment with SGS 742, a $GABA_B$ receptor antagonist. Early reports showed cognitive enhancement such as improved attention, reaction time, visual information processing and working memory in mice, rats and monkeys (Helm et al 2005). Electrocorticography (ECoG) has been used to study the effects of

SGS 742 vs topiramate vs saline in SSADH deficient (Aldh5a1-/-) mice (Pearl et al 2009). Topiramate is a polymechanistic antiepileptic, with properties including enhancement of GABAergic effects, attenuation of voltage-gated Na+ currents, and inhibitory actions on kainate and AMPA receptors (Landmark 2007). ECoG recordings (n=4) were taken from frontal and parietal cortex bilaterally following electrode implantation at day-of-life 18 (P18). The drugs were administered intraperitoneally under continuous ECoG monitoring at P19 with topiramate (3, 4.5, and 6 mg/kg) and SGS-742 (30, 100 mg/kg). SGS-742 showed a dramatic dose-dependent improvement in the ECoG tracings, while topiramate was ineffective. As the ECoG is state dependent, the doses of SGS-742 and topiramate utilized were chosen by experimentally determining the dose below the threshold for sleep.

The minimum level of SGS-742 found to be effective in the ECoG studies was used for assessment of spike-wave discharges and survival. At baseline (no drug administered), Aldh5a1-/- mice displayed significantly higher spike-wave discharge duration as compared to their wild-type (Aldh5a1+/+) littermates ($p<0.05$) (Pearl et al 2009). SGS742 significantly improved the spike-wave duration in dose-dependent fashion and controlled absence seizures. These data support earlier data using CGP 35348 (Cortez et al 2004) and verify a prominent $GABA_B$ component associated with the absence seizures in Aldh5a1-/- mice. SGS742 significantly reduced spike-wave duration in animals of both mutant SSADH-deficient mice and wildtype mice who received gamma-butyrolactone, a precursor of GHB.

1.3 Human SSADH Deficiency

1.3.1 Neuroimaging Findings

Neuroimaging modalities utilized in the evaluation of patients with SSADH deficiency have included cranial MRI, CT, FDG PET, and MRS. Human neuroimaging data, identified in 29 published cases studied with cranial MRI (23 patients) or CT (6 patients), combined with data from our new cohort, show specific results. These methods revealed T2 hyperintensities in multiple regions, most commonly of the globus pallidus. A pattern of dentate-pallidal hyperintensity has been described (Yalcinkaya et al 2000; Ziyeh et al, 2002). There are also areas of abnormal T2-weighted signal in cerebral white matter and brainstem. Other findings on structural imaging have included atrophy of the cerebrum and cerebellum, the latter preferentially affecting the midline vermis. PET scanning using the FDG radioisotope revealed cerebellar hypometabolism in two patients previously identified with cerebellar atrophy on MRI, and otherwise was normal in one patient (Al-Essa et al 2000; Pearl et al 2003b). Both of these patients had known cerebellar atrophy on standard MRI.

Neuroimaging has shown abnormalities in two thirds of patients in our database, most characteristically increased T2-weighted signal in the globus pallidus, subcortical white matter, cerebellar dentate nucleus, and brainstem (Pearl et al.,

2007a). Other findings include cerebral atrophy, cerebellar atrophy, delayed myelination, and a pattern of dentate-pallidal hyperintensity (Yalcinkaya et al., 2000; Ziyeh et al., 2002). While the pallidal hyperintensity is usually homogeneous and equally affects the internal and external portions, we have had occasional patients with heterogeneous involvement and persistent asymmetry of the signal abnormality of the globus pallidus. Of seven patients studied in our recent clinical protocol at NIH, five had bilaterally symmetric homogeneous signal abnormalities in the globus pallidus and dentate nuclei, as well as subthalamic nuclei (Pearl et al 2009). One patient had asymmetric involvement of the globus pallidus which has proven to be stable over seven years, with minimal abnormality on the right but marked increased T2-weighted and decreased T1-weighted signal on the left accompanied by expansion of the left globus pallidus and bilateral ventriculomegaly. In the oldest patient studied (age 27 years), the pallidal signal abnormality was subtle, but associated with clear volume loss and commensurate ex vacuo dilatation of the third ventricle, without abnormalities of the subthalamic or dentate nuclei. Magnetic resonance spectroscopy that is edited for small molecules has shown elevated levels of GABA and related compounds (including GHB and homocarnosine) in patients but not obligate heterozygotes (Ethofer et al 2004; Pearl et al 2004a)

PET has been used to image a number of receptor systems successfully in man, including benzodiazepines (Henry et al 1993; Richardson et al 1996; Richardson et al 1997; Savic et al 1993; Savic et al 1995; Savic et al 1996) as well as opiates (Frost et al, 1988; Madar et al 1997; Mayberg et al, 1991; Theodore et al, 1992) and monoamine oxidase (Kumlien et al, 1995). Mu-opiate receptor binding is increased in temporal neocortex ipsilateral to the epileptogenic area (Frost et al 1988). Not all studies on receptors have adequately corrected the data for possible alterations in brain volume, or underlying pathology.

The most widely used $GABA_A$ ligand currently used for PET is [(11)C] Flumazenil, a highly selective benzodiazepine antagonist. A number of studies have shown reduced FMZ binding in patients with partial seizures, closely correlated with EEG distribution of epileptiform discharges (Koepp et al 1997, 1998). In some cases, reduced FMZ binding has been found in patients with normal MRI, as well as after partial volume correction in patients with MTS (Koepp et al 2000, Lamusuo et al 2000).

A flumazenil PET study of 15 children (ages 1-8 years) showed that prolonged vigabatrin (VGB) treatment is associated with decreased binding in children with epilepsy (Juhasz et al 2001). Regional flumazenil volume of distribution values of the VGB-treated patients were significantly lower in all cortical regions and the cerebellum, whereas the difference was not significant in the thalamus and basal ganglia. The authors concluded that VGB induces a decrease in $GABA_A$ receptor binding in the cortex and cerebellum of the developing epileptic brain. These results suggested down regulation of GABA receptors related to increased GABA levels.

We compared 11C-FMZ PET $GABA_A$ receptor binding in patients, their parents (obligate heterozygotes) and healthy volunteers. Flumazenil attaches to the benzodiazepine binding site on the $GABA_A$ receptor and has been used as a ligand to image the distribution of $GABA_A$ receptors in patients with epilepsy (Koepp et al 2000). Patients had decreased binding compared to controls and obligate heterozygotes for SSADH deficiency (Pearl et al 2009b). This is consistent with downregulation of receptors due to increased agonist availability, as demonstrated in the transgenic animal model.

Altered $GABA_A$ receptor function may be related to increased GHB levels as well as increased GABA levels. GHB is a $GABA_B$ receptor agonist, and several studies have shown that $GABA_B$ receptor activation may modulate neurotransmission at $GABA_A$ synapses (Patenaude et al 2003, Balasubramanian et al 2004).

1.3.2 Neurophysiologic findings

Electroencephalography: A majority (64%) of patients in our database have abnormal electroencephalograms, characterized by background slowing, epileptiform abnormalities (usually generalized and sometimes multifocal), and rarely photoparoxysmal responses and electrographic status epilepticus of slow wave sleep (Pearl et al 2007a).

Polysomnography: A study of a single patient having two nights of polysomnography demonstrated prolonged stage REM onset and, on the second consecutive night, excessive EEG background slowing after a generalized seizure during stage 4 sleep (Arnulf et al., 2005). We have studied ten patients with overnight polysomnography and daytime multiple sleep latency testing and have reported prolonged REM latency and reduced stage REM percentage with over 90% sleep efficiency and absence of decreased daytime sleep latency or sleep-onset REM (Pearl et al., 2005a). Thus, there appears to be a reduction in REM sleep in SSADH deficiency. Animal models have demonstrated that hyperGABAergic states, e.g. via inhibition of GABA transaminase using L-cycloserine, are associated with reduction of REM sleep and prolongation of the transition phase between sleep stages NREM and REM (Scherschlicht, 1985).

We quantified the magnitude of excitation and inhibition in primary motor cortex (M1) in SSADH deficiency patients, their parents (obligate heterozygotes), age-matched healthy young controls and healthy adults using single and paired pulse transcranial magnetic stimulation (TMS) (Reis et al, in Press). Long interval intracortical inhibition was significantly reduced and the cortical silent period significantly shortened in SSADH deficiency patients compared to heterozygous parents and control groups. Since long interval intracortical inhibition and cortical silent period are thought to reflect $GABA_B$ receptor mediated inhibitory circuits, our results point to $GABA_B$ –related motor cortex dysfunction in SSADH deficiency

patients. This human phenotype is consistent with the proposed mechanism of use-dependent downregulation of postsynaptic $GABA_B$ receptors in SSADH deficiency animal models. Additionally, the results suggest autoinhibition of GABA-ergic neurons. This first demonstration of altered $GABA_B$ function in patients with SSADH deficiency may help to explain clinical features of the disease, and suggest pathophysiological mechanisms in other neurotransmitter-related disorders. Moreover, the TMS findings provide a reliable measure of altered cortical excitability that can be used in a clinical trial.

1.4 Treatment

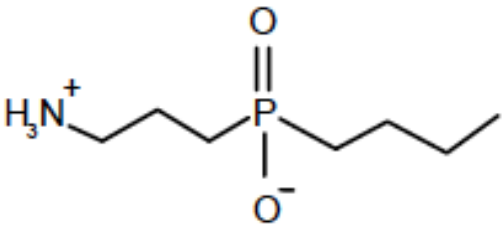
The treatment for SSADH deficiency remains problematic and no consistently successful therapy has emerged (Gropman, 2003). Treatment is generally symptomatic and targeted. Options include anxiolytic agents or SSRI and related medications for obsessive-compulsive disorder. Appropriate antiepileptics are chosen for generalized epilepsy other than avoidance of valproate due to its ability to inhibit any residual SSADH enzymatic activity (Shinka et al., 2003). Vigabatrin, an irreversible inhibitor of GABA-transaminase, is a logical choice because it will inhibit the conversion of GABA to gamma-hydroxybutyrate, a putative pathogen in this condition. Vigabatrin, however, has not been consistently helpful, with many reports of inefficacy or, worse, worsening of symptoms ranging from seizure control to alertness. While vigabatrin will lead to at least transient decreases in CSF GHB levels (Ergezinger et al., 2003), there may be a deleterious effect related to attendant increases in CSF (and brain) GABA levels (Pearl & Gropman, 2004). Further, there have been concerns regarding vigabatrin, resulting thus far in absence of United States Food and Drug Administration approval, initially because of intramyelinic edema and white matter vacuolation in rats and dogs (Butler et al., 1987; Qiao et al., 2000; Peyster et al., 1995). In clinical trials, 30% of patients treated with vigabatrin for epilepsy report visual field defects following one year of treatment (Krauss et al., 1998; Spence & Sankar, 2001; Vanhatalo et al., 2002). As this deficit begins with peripheral visual field constriction, it would be particularly difficult for patients with a neurodevelopmental disorder such as SSADH deficiency to be alert to the early signs of visual toxicity. We have recently identified MRI signal changes, particularly prominent in the thalamus and basal ganglia, in infants treated with relatively high doses of vigabatrin (Pearl et al, 2008).

The $GABA_B$ receptor antagonist SGS-742, an investigational drug that has shown positive effects in the SSADH deficiency mouse model, and has demonstrated good safety and tolerability in clinical trials for dementia, is the best candidate for a human experimental trial (Froestl et al 2004; Investigator's Brochure).

SGS-742, 3-aminopropyl-n-butyl phosphinic acid, is an achiral molecule with a

molecular weight of 179.2 and occurs as a white crystalline solid.

Chemical formula: $C_7H_{18}NO_2P$



In man, drug absorption is rapid, with peak plasma concentration within 4 hours of single oral doses, with maximum AUC at a dose of 900 mg. Absorption was reduced by food intake. > 99% of drug is excreted unchanged in urine. Elimination t ½ was about 4 hours. There was no difference in pharmacokinetic profile between young and older healthy volunteers. Interaction potential appears to be low, although specific data are not available.

In rhesus monkeys and rats, the drug improved performance on several cognitive assessments. In rats there was no evidence of overt toxicity at single i.v. doses up to 300 mg/kg, or 100 mg/kg i.p. Similar results were found in dogs. In two-week daily intravenous dosing, there was no observable effect in rats up to 30 mg/kg; daily oral doses of 100 mg/kg for 12 months produced no toxicity in dogs. There was no evidence of mutagenic potential in vitro; adverse maternal and fetal effects in rats were noted at 2000 but not 600 mg/kg.

At 50 to 400 mg/kg administered intraperitoneally to genetically epilepsy prone rats, SGS742 induced a dose dependent and progressive suppression of spike-wave discharges (Investigator's Brochure).

SGS–742 was compared to topiramate in immature SSADH-deficient (Aldh5a1j/j) mice who had continuous electrocorticography recordings (Pearl et al 2009a). SGS–742 showed a dramatic dose-dependent improvement in reduction of spike-wave discharges and absence seizures while topiramate was ineffective.

In fasting adult healthy volunteers given single oral doses of 250-1200 mg, peak plasma levels were reached in 4 hours. More than 99% was excreted unchanged in urine, with a half-life of 4-5 hours. In phase 1 studies, using single oral doses from 10 to 2100 mg, multiple oral doses from 300 to 1200 mg t.i.d. (900 to 3600 mg/day), and single intravenous doses from 315 to 1800 mg, there were no serious adverse events. One of two subjects who received 1800 mg i.v. had moderate to severe headache, drowsiness, nausea and vomiting. Other subjects had mild to moderate headache, tiredness, sleepiness, and dizziness. All AEs resolved fully and spontaneously.

In a Phase II double-blind, placebo-controlled study in 110 adults with mild cognitive impairment, oral administration of 600 mg t.i.d. for 8 weeks significantly improved attention, reaction time, visual information processing, and working memory (Froestl et al., 2004, Tomlinson et al 2004). No clear drug-related serious adverse events or drug related effects on cardiovascular or laboratory variables were reported (Froestl et al 2004). One patient had a syncopal episode; the patient had experienced a similar episode two years before starting SGS-742 treatment. One patient had AST elevation present at screening that did not worsen during the study, and persisted afterwards. One patient had an eye hemorrhage attributed to concomitant warfarin use. Mild to moderate nonspecific and non-dose-related adverse events included headache, tiredness, diarrhea, nausea and vomiting, sleepiness and dizziness. There was no difference in incidence between patients on active drug and placebo, except possibly for nausea and dizziness, which occurred in 7-10% of patients on active drug (Investigator's Brochure). All adverse events resolved fully and spontaneously. The drug has not yet been used in children.

2 STUDY OBJECTIVES

The aims of this proposal are to conduct a clinical study of a small group of patients with SSADH deficiency before and during a therapeutic trial of SGS-742, assessing the effect on cortical excitability and neuropsychological function. We hope to establish validated markers in SSADH-deficient patients that can be measured during therapeutic intervention. Data acquired in this study should have relevance to conditions beyond SSADH deficiency, as they will enhance our ability to understand inborn metabolic errors that present with prevalent phenotypes such as intellectual disability or autism spectrum disorder, and to make optimal therapeutic decisions in SSADH deficiency patients.

2.1 Hypotheses:

H1: Patients will show improvement in the Auditory Comprehension subtest of the Neuropsychological Assessment Battery Language Module during treatment with SGS-742 and improvements in activities of daily living based on parent questionnaire.

H2: Patients with SSADH deficiency will have lengthening toward normal values of the cortical silent period, and return of long interval intracortical inhibition, during a therapeutic trial of SGS-742

H3: Patients will show improvement on global assessment ratings

3. SUBJECT POPULATION

3.1 Description of Study Population

The proposed research protocol will investigate patients with documented succinic semialdehyde dehydrogenase deficiency, a rare autosomal-recessively inherited defect of 4-aminobutyric acid (GABA) metabolism. We propose to enroll 22 patients with SSADH deficiency with the goal of obtaining 16 completers for the cross-over study. Those who withdraw before completion of at least 3 months of their second treatment phase will be replaced.

3.2 Inclusion Criteria (See checklist Appendix 1)

- 4-hydroxybutyric aciduria (gamma-hydroxybutyric aciduria) on two separate tests.
- Documented succinic semialdehyde dehydrogenase enzyme deficiency.
- Patients must have clinical features consistent with SSADH deficiency including developmental delay especially deficit in expressive language, hypotonia, ataxia, seizures, and other neuropsychiatric symptoms including sleep disturbances (45%), attention deficit (45%), anxiety (27%), obsessive-compulsive disorder (25%), and autistic traits (25%).
- During the study, women of child-bearing potential must use a reliable method of birth control until one month after the final drug taper is complete.
- Patients will be 4 years or older.
- Based on HSPU/ACAT evaluation must meet one of the following criteria:
    - subject has capacity to consent
    - subject has a documented legal guardian to provide consent
    - subject lacks capacity and no legal guardian but HSPU determines 1) the subject has a DPA, or 2) the subject has capacity to designate an NIH DPA, or 3) a Next of Kin surrogate may be appointed as outlined in MAS 87-4.

3.3 Exclusion Criteria (See checklist Appendix 1)

- Current alcohol use (>14 drinks/wk in men and >7 drinks/wk in women) or recreational drug use for the 16 month period of this study.
- Patients with a history of other major medical disorders with clinical fluctuations, or requiring therapy that might affect study participation or drug response such as severe depression or psychoses, renal or hepatic disease.

- Patients requiring treatment with drugs known to affect the GABAergic system, including vigabatrin and benzodiazepines.
- Pregnant and lactating women

4. STUDY DESIGN AND METHODS:

4.1 Study overview

This is a 16-21 month randomized, double-blind cross-over phase two clinical trial of SGS-742 versus placebo in 22 patients age 4 years and older with SSADH deficiency.

4.1.1 Study Phases (see Study Schedule Appendix 2):

- Screening (1-3 days)—outpatient. May be combined with baseline visit.
- Baseline visit (1 - 3 days)—inpatient or outpatient. The first dose of study pills will be administered at the NIH. The patient will stay for 30 – 90 minutes following the first dose. The patient will be permitted to return to local accommodations overnight and return 12 - 24 hours after the first dose to be assessed for any skin reactions, and then discharged home.
- Titration one: 9 - 15 days (titration is 9 days and if they only get one or two doses on day one they will have an additional day of drug titration).

Phase 1 (six months +/- 2 weeks of SGS-742 or placebo)—during phase one there will be regular communication, at least once every two weeks, with patients/families by phone and/or the clinical trial database. If indicated, based on reports during these regular communications, an outpatient visit will be arranged at NIH or with a local provider for safety monitoring or pregnancy testing. If this is to be done by local providers, we will have patients designate the local provider in advance. We will contact the local provider and arrange for payment of any visits or testing by the NIH and also document a plan in the progress notes for how individual providers will communicate findings and test results. We will request local providers provide written documentation of outpatient visits and pregnancy testing results by facsimile to include in the NIH patient medical record.

- End of phase 1 testing: (At 6 mo +/-2 weeks of phase 1) inpatient or outpatient 3 day evaluation including: EEG, TMS, neuropsychological tests, blood and urine tests, and optional LP, MRI/MRS.
- Washout 9 weeks (+/- 2 weeks), including 9 days to taper and discontinue phase I medication, at least 7 weeks medication free and titration to phase 2 medication 9 - 15 days **(taper is 9 - 15 days and if they only get one or two doses on day one they will have an additional day of drug taper).**

Phase 2 (six months +/- 2 weeks of phase 2 treatment)— during phase two there will be regular communication, at least once every two weeks, with patients/families by phone and/or the clinical trial database. If indicated, based on reports during these regular communications, an outpatient visit will be arranged at NIH or with a local provider for safety monitoring or pregnancy testing. If this is to be done by local providers, we will have patients designate the local provider in advance. We will contact the local provider and arrange for payment of any visits or testing by the NIH and also document a plan in the progress notes for how individual providers will communicate findings and test results. We will request local providers provide written documentation of outpatient visits and pregnancy testing results by facsimile to include in the NIH patient medical record.

- End of phase 2 testing: (At 6 mo +/-2 weeks of phase 2) inpatient or outpatient evaluation including: EEG, TMS, neuropsychological tests, blood and urine tests, and optional LP, MRI/MRS.
- Taper off drug: 9 – 15 days.
- Final visit: 4-7 weeks after completion of the final drug taper.

Some variability in scheduling will be based on whether a participant has a seizure.

4.2 Recruitment

Most subjects will be patients with SSADH deficiency followed by Dr. Pearl in the Boston Children's Hospital Neurology Department. Dr. Pearl may be the treating clinician for these patients or patients may be referred to him by their treating physicians specifically for consultation regarding management and treatment of SSADH deficiency. During the course of routine clinical care, patients will be informed about the study and, upon their request, will be provided the information to contact the NIH personnel on their own initiative. The referral will not be made directly by Dr.Pearl and the NIH is not contacted by Dr. Pearl on behalf of the patient.

Letters will also be mailed to families with a history of SSADH and the letter will be posted to the SSADH Association website (See Appendix VII).

4.3 Screening

Consent will be obtained before any study procedures, including screening procedures, are done.

Patients will be screened in the CES outpatient clinic for inclusion in the protocol by CES physicians or licensed practitioners. Dr Pearl, who is a special volunteer at NIH with clinical privileges, will supervise confirmation of the diagnosis. Screening will include review of the information collected by the referring doctors to determine suitability for the protocol, physical and neurological examination, urine tests to confirm the diagnosis if not performed previously, electrocardiogram, CBC, blood chemistries, and antiepileptic drug levels if clinically indicated and the testing is available in our lab.

4.4 Study Procedures

All procedures performed at NIH will be for research. Each procedure will be performed at baseline and at the end of each 6-month treatment arm (3 total). Procedures include electroencephalogram, neuropsychological testing, transcranial magnetic stimulation, and optional lumbar puncture and optional MRI/MRS. All participants will be asked to undergo LP, however, refusal to have an LP or inability to tolerate an LP will not be exclusionary for the study.

TMS and optional MRS will not be done within 24 hours of a reported seizure. The studies will be rescheduled.

At each visit during drug treatment, patients will have a medical history and physical examination and will review seizure calendars and be asked about adverse effects. Laboratory tests, including urine pregnancy for females of child bearing potential, will be obtained if indicated based on a change in clinical status.

4.4.1 Structural MRI Scans (OPTIONAL)

3.0 Tesla anatomical T1 and T2-weighted MRI images will be obtained both for clinical evaluation and partial volume correction / co-registration for MRS. Approximately 45 minutes will be needed to obtain the images.

4.4.2 Magnetic Resonance Spectroscopy (MRS) (OPTIONAL)

MRS will be performed using a 3-T whole-body scanner and a transmit-receive head coil. MRS spectra will be acquired from 2 voxels globus pallidus and cerebral cortex (frontal or parietal). GABA will be measured using an interleaved PRESS-based J editing method (Hasler et al 2005). The study will last a maximum of 90 minutes.

4.4.3 Transcranial Magnetic Stimulation (TMS) Procedure

Before and after TMS, patients will be screened for hearing by the NIH Audiology Service. Each test will take up to 30 minutes. TMS will be applied using a coil placed on the scalp. Surface EMG will be recorded from the first dorsal interosseus (FDI) muscle. The coil will be manually positioned, and the electrode position will be marked with a pen for eliciting motor evoked potentials (MEPs)

from the FDI muscle. After the subject is seated in a comfortable position, an adjustable head restraint will be applied to prevent head movements. Indices for cortical excitability will be obtained including motor threshold (MT), recruitment curve, intracortical inhibition (ICI), intracortical facilitation (ICF), and cortical silent period (CSP) from motor cortex.

The MT is defined as the minimum percentage of the stimulator output that evoked a motor evoked potential of more than 50 μV in at least 5 out of 10 trials. For recruitment curve determination, TMS will be applied over the same hemisphere from which MT is measured, while 5 responses are recorded at each of a range of different stimulus intensities. Stimulus intensity will be increased in steps of 10% of the individual MT from 90 to 160% MT. MEP size will be measured peak-to-peak in single trials and averages will be calculated for each intensity. ICI and ICF will be studied using a paired stimulus paradigm. The conditioning stimulus (70% MT) followed by the test stimulus (120% MT) will be delivered at 3 different interstimulus intervals (ISI); 2 ms for short ICI, 10 ms for ICF, and 100 ms for long ICI. Each run will consist of 10 trials, and the amplitude ratio of the mean conditioned MEP to control MEP will be determined for each ISI. Measurement of the CSP will be carried out from the tonically active FDI, performing 10 trials each of the intensities at 10, 20, 30, and 40% above MT. CSP onset and termination will be measured in the rectified single trials as the times of the end of the preceding MEP and the return of sustained activity in the EMG, respectively. The conditional averages will be calculated from the single-trial data. TMS will take up to 90 minutes.

4.4.4 Neuropsychological Assessments
Patients will undergo comprehensive language and cognitive evaluations using a selection of assessments based on age and ability such as the following:

1. WNV (Wechsler Nonverbal Scale of Ability) for patients up to age 22, an individually-administered, standardized test that provides an IQ score and insights into cognitive functioning. The test requires approximately 30 minutes to administer.

2. WAIS-IV (Wechsler Adult Intelligence Scale) for patients age 22 and older, also an individually-administered test of ability will be administered using the subtests that overlap the WNV. These are nonverbal because of the language limitations of this population.

3. The Neuropsychological Assessment Battery: Language Module. Subtests to be administered include confrontation Naming and following directions (Auditory Comprehension) to assess language competence.

4. Rule Shift from the Behavioral Assessment of Dysexecutive Syndrome is a short (5 minute) test of working memory.

5. Computerized tests of reaction time and go-no-go to assess the constructs of reaction time and attention.

6. Texas Functional Living Scale is an assessment of practical reading, math, language comprehension and memory developed for individuals with cognitive limitations.

7. ABAS: Adaptive Behavior Assessment Scale to be completed by parent. Queries on functional skills.

8. Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV), for patients between the ages of 2.5 and 7, is an individually-administered, standardized test that provides scores for verbal and nonverbal domains of intellectual ability. The test requires between 45 minutes and 75 minutes to administer, depending on the age.

9. Wechsler Intelligence Scale for Children-V (WISC-V), for patients 6 years of age through age 17, is an individually administered, standardized test of cognitive ability. This test provides scores for verbal and nonverbal domains of intellectual ability. The test requires between 60 minutes and 90 minutes to administer, depending on age

4.4.5 Lumbar Puncture Procedure (OPTIONAL):

Lumbar puncture will be performed according to standard procedure utilizing sterile technique in the lateral recumbent position. Lumbar puncture will be carried out in the awake state utilizing local 1% lidocaine anesthesia. Approximately ten ml of CSF will be collected for routine studies and special metabolites including GABA-related compounds and biogenic amines. The fluid designated for special metabolites will be placed immediately in dry ice and then stored in a -70 degree freezer.

4.4.6 EEG

EEG will be performed according to standard procedures using the international 10-20 standard method of electrode placement.

4.4.7 Blood draw

Approximately ten cubic centimeters of blood will be drawn at screening, and at the end of each treatment phase, for CBC, clinical chemistry, and hepatic panels.

4.4.8 Seizure and side effect calendar

Patients and families will be asked to keep a record of seizures and any possible medication side effects.

4.4.9: Pregnancy tests
Patients of child-bearing potential will have a urine pregnancy test at screening and each out-patient visit. Pregnancy testing may also be done based on safety monitoring and clinical assessment. Pregnancy testing may be done by local providers. In this case, we will have patients designate the local provider in advance. We will contact the local provider and arrange for payment of testing by the NIH and also document a plan in the progress notes for how individual providers will communicate test results. We will request local providers provide written documentation of pregnancy testing results by facsimile to include in the NIH patient medical record.

As outlined in the minor assents, if the pregnancy testing for a minor patient, performed at the NIH or through a local provider, is positive, we will inform the parent or guardian.

4.5 Drug Treatment

4.5.1 Randomization

A crossover design will be employed where patients are randomized into a six-month trial of treatment versus placebo.

Subjects will be randomized at the end of baseline testing 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.

4.5.2 Study Drug Administration

Patients may be outpatients or inpatients during titration. The first dose of study pills will be administered at the NIH. The patient will stay for 30 – 90 minutes following the first dose. The patient will be permitted to return to local accommodations overnight and return 12 - 24 hours after the first dose to be assessed for any skin reactions, and then discharged home.

All patients will be given an exact written titration schedule to follow, and will be contacted by phone and/or clinical trials database at least every two weeks during the study.

Following a 9 week +/- 2 weeks total washout period, including drug taper, described below, patients will enter the other treatment arm. For the second phase of the study patients may also be inpatients or outpatients. The first dose of study pills will be administered at the NIH. The patient will stay for 30 – 90 minutes following the first dose. The patient will be permitted to return to local accommodations overnight and return 12 – 24 hours after the first dose to be assessed for any skin reactions, and then discharged home.

The active treatment will be SGS-742, synthesized by IRIX pharmaceuticals in a GCP facility. The target dose will be 10 mg/kg with a maximum of 600 mg given orally three times daily for six months, with an increasing titration over nine to fifteen days. The placebo arm will be inert placebo given orally three times daily. It is recommended to take the medication three times each day prior to meals because administration of food decreases oral systemic availability of SGS-742. The drug and matching placebo will be encapsulated by the NIH pharmacy. The pharmacy will draw up a randomization schedule and ensure blinding.

Patients and examining physicians will be blinded as to the treatment arm in which the patient is enrolled.

The NIH Pharmacy will dispense three month's supply of study drug SGS-742 or placebo) to subjects for each study treatment phase. The second three-month supply can be picked up by the patient or sent by mail. Patients will be asked to bring study pill bottles to each clinic visit. Pill counts will be performed at each visit if patients bring study pill bottles. Patients will be advised to take a missed dose if they remember within 4 hours; otherwise, to take the next scheduled dose and record the missed dose on their seizure/medication calendar. Patients will be advised to take their study drug about one hour before food.

All unused investigational product will be returned to the NIH Pharmacy for disposal if patients bring study pill bottles.

At the end of phase 2, the study drug will be tapered off as described below. If patients only get one or two doses the first day, an additional day may be added to the titration and taper schedule. Patients will have a final follow-up visit four to seven weeks after completion of the final drug taper.

4.5.3 Drug titration

The following drug /placebo titration schedule will be used for patients weighing 30 kg or greater:

2.5 mg/kg/dose (up to 150 mg) tid X 3 days;
5 mg/kg/dose (up to 300 mg) tid X 3 days;
7.5 mg/kg/dose (up to 450 mg) tid X 3 days;
10 mg/kg/dose (up to 600 mg) tid (target dose).

The drug is only available in 75- and 150-mg capsules. Thus, for patients weighing less than 30 kg, the dosing regimen may be modified to reflect the use of specific size capsules and dose limits for small participants.

Dosing may be modified as close as possible to the weight-specified dose without exceeding it. Modified dosing schedules for children weighing less than 30 kg will allow us to come as close as possible to the final weight-based protocol-specified dose without exceeding it. The dosing schedule in these

children may be modified from TID dosing to QD and BID to extend the titration period to avoid large dose jumps between titration levels.

If patients experience side effects, the next scheduled dose increase will be delayed until they abate. If this does not occur, the dose will be reduced in 2.5 mg/kg per day increments until side effects abate.

The final maximum dose will be determined by the patient's weight but will not exceed 600 milligrams three times per day.

4.5.4 Drug taper schedule

The following drug /placebo taper will follow the reverse schedule of the drug titration:

For patients weighing 30 kg or greater:
7.5 mg/kg/dose (up to 450 mg) tid X 3 days;
5 mg/kg/dose (up to 300 mg) tid X 3 days;
2.5 mg/kg/dose (up to 150 mg) tid X 3 days;
then stop.

For patients weighing less than 30 kg:

The drug /placebo taper will follow the reverse schedule of the drug titration for each patient.

Placebo will be titrated and tapered in capsules matching the SGS-742 dosing stages.

4.6 Sedation

For adults needing sedation for optional MRI/MRS, the NIH Anesthesia Department will use Dexmedetomidine, a highly selective alpha-adrenoreceptor agonist that exerts its hypnotic effects at the locus coeruleus, and has minimal cardiovascular and virtually no respiratory depressant effects (Correa-Sales 1992; Maze et al 2001; Nelson LE 2003). In addition, the drug has no effect on release or extracellular levels of glutamate, aspartate and GABA (Valtonen et al 1995). It has been shown to be a safe and well-tolerated agent, and is approved by the FDA for use in the intensive care unit setting. The drug is routinely used clinically in intensive care units and operating rooms, and for imaging studies (Mason 2008, Yuen 2008). According to the package insert, adverse effects in clinical trials included hypotension (28% versus 13% in patients receiving placebo), hypertension (16% versus 18%), nausea (11% versus 9%) and bradycardia (7% versus 3%). This medication was used without incident in our previous SSADH deficiency study. If sedation is required for MRI/MRS, the LP

may be done while under sedation. No sedation will be used for research purposes in minors.

4.7 End of Participation

Participants will remain under the care of their own physicians while in this study. The study physicians may, in cooperation with the treating physicians, manage neurologic treatment.

Clinically relevant results of study procedures such as MRI findings will be given to the patients and their parents or guardians.

Study phase	Length	Clinic visit, physical exam	SGS-742 or placebo	EEG	Blood tests	Urine tests	EKG	Lumbar puncture *	MRI MRS*	TMS	NP tests
Screening	1-3 days	X			X	X	X				
Baseline	1-3 days	X		X				X	X	X	X
Titration	9 -15 days		X								
Phase 1	Month 1										
	Month 2										
	Month 3										
	Month 4										
	Month 5										
	Month 6 (+/- 2 additional weeks)	X	X	X	X	X		X	X	X	X
Washout	Month 1										
	Month 2 (+/- 2 additional weeks)										
Titration	9 – 15 days		X								
Phase 2	Month 1										
	Month 2										
	Month 3										
	Month 4										
	Month 5										
	Month 6 (+/- 2 additional weeks)	X	X	X	X	X		X	X	X	X
Taper off	9 – 15 days										
FINAL VISIT	4-7 weeks later	X									

4.8 Study Schedule

* OPTIONAL

5. STORAGE OF DATA AND SAMPLES

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

Deidentified coded CSF samples will be stored in the Laboratory of Dr K Michael Gibson, WSU, using the established data protection procedures of his laboratory.

6. ADDITIONAL CONSIDERATIONS

Research with investigational drugs or devices:
SGS-742 requires an IND.
SGS-742 will be obtained from IRIX pharmaceuticals, and encapsulated and stored by the NIH Pharmacy.
Investigator's brochure Attached

7. RISKS AND DISCOMFORTS

7.1 SGS-742

Patients are at risk for developing an allergic reaction to the study pills.
Animal toxicology studies showed development of ataxia at doses of 100-300 mg/kg in mice and rats, and seizures at > 300 mg/kg. In 6/12-month oral toxicity studies, the clear "no observable effect" level in dogs was 100 mg/kg; in rats, the only observation was a slight reduction in body weight gain in males at 200 and 600 mg/kg. Gastrointestinal and hepatic toxicity was found after administration of 300 mg/kg for three months in rats.

In the phase 2 blinded placebo-controlled study, the following side effects occurred in more than 5% of subjects:

	Active drug (n=75)	Placebo (n=35)
Diarrhea	8%	8%
Nausea	8%	6%
Dizziness	7%	3%

Side effects reported less frequently included headache, arthralgia, peripheral edema, unspecified infections, infestations, respiratory, and skin disorders. These did not differ between subjects taking active drug and placebo.

Three serious adverse events were reported. One syncopal episode occurred in a patient with a previous history of transient ischemic attacks lasted 30 minutes, resolving spontaneously without medical intervention or sequelae. One

intraocular hemorrhage occurred in a patient on warfarin. One subject had a preexisting liver function test elevation that did not change on SGS-742.

There were no clinically significant changes in laboratory tests, vital signs, weight, or ECG results.

SGS-742 is not metabolized, and >99% of the drug is excreted unchanged in urine. Thus, no clinically important drug interactions are anticipated.

Pregnancy testing and contraception:
Since the teratogenic potential of SGS-742 is unknown, women of child-bearing potential must use an effective form of birth control during the study and for a month after final drug taper is complete. Patients should not breast-feed during the study or for one month after the study is completed.

Effective methods of contraception for this study include

1. hormonal contraception (birth control pills, injected hormones or vaginal ring);

2. intrauterine device;

3. barrier methods (condom or diaphragm) combined with spermicide;

4. surgical sterilization (hysterectomy, tubal ligation, or vasectomy in a partner).

Should a subject have a positive pregnancy test, the principal investigator or lead associate investigator will meet with the family to discuss the results and will be referred to the NIH OB-gyn service for counseling. The study drug will be stopped and patients followed until pregnancy outcome.

7.2 MRI and MRS (OPTIONAL)

People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. Subjects will be screened for these conditions before having any scan, and if they have any, they will not receive an MRI scan.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in

people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. Subjects will be asked to complete an MRI screening form for each MRI scan you have. There are no known long-term risks of MRI scans.

A pregnancy test will be performed before MRI/MRS for any subject of child bearing potential. The scan will not be done if the pregnancy test is positive.

7.3 TMS

Both single and paired-pulse TMS will be performed. Single pulse TMS is a minimal risk procedure. Side effects include headaches and scalp tingling. The noise of the TMS magnet can potentially damage hearing; patients will be fitted with earplugs by technicians trained to do so. Additionally, hearing in participants will be tested before and after exposure to TMS in order to check whether the TMS caused a change in hearing. If there is an auditory threshold shift of 15dB at any frequency, auditory testing will be repeated after 24 hours. If three people have a change in auditory threshold after TMS, the TMS portion of the study will no longer be carried out. Children may be more susceptible to hearing adverse events from TMS due to immaturity of the young brain and ear canal. TMS can interfere with implanted medical devices and will not be done in people who have pacemakers, implanted pumps, or stimulators, such as cochlear implants or in people who have metal objects inside the eye or skull.

Garvey et al employed a self-report questionnaire to collect children's subjective response to single-pulse TMS. They found that TMS was well tolerated by the majority of subjects, and was favorably compared to seven common childhood experiences. Notably, of the 40 children in the study, 34 subjects (85%) said they would voluntarily undergo TMS again. Because it presents no greater risk of discomfort than other potentially distressing childhood experiences of daily life, the study concluded that TMS falls within the category of no greater than minimal risk. (Garvey et al, 2001). Paired-pulse TMS carries no more than a minor increment over minimal risk.

7.4 Lumbar Puncture (OPTIONAL)

Lumbar puncture is a routine clinical procedure that has a minimal level of risk of local infection and discomfort. All efforts will be made to minimize these risks, including performance of the procedure during the provision of generalized anesthesia when applicable, use of local anesthesia when generalized anesthesia is not applicable, and use of sterile technique. Post-lumbar puncture headache may occur in one-third of people, which is usually not severe and improves without treatment other than a mild pain reliever. Headaches lasting longer than 7 days develop with one in 50 to 200 lumbar punctures and usually

improve gradually over 2 weeks. In rare cases, headaches have persisted longer. Prolonged headaches may be due to persistent leakage of CSF from the area of the lumbar puncture, and will be treated with an epidural blood patch.

7.5 Neuropsychological testing

Neuropsychological testing has only minor risk, including boredom and frustration.

7.6 Sedation

Sedating medicines may cause decreased blood pressure, irregular heartbeats, depressed breathing, and muscle spasms. Uncommon side effects are very low blood pressure, nausea and vomiting, respiratory insufficiency, and a severe allergic reaction. On extremely rare occasions breathing may stop. Dexmedetomidine has been shown to be a safe and well-tolerated agent, and was used without incident in our previous SSADH deficiency study. The drug is routinely used clinically in intensive care units and operating rooms, and as a sedative for individuals undergoing imaging studies (Mason 2008, Yuen 2008). According to the package insert, adverse effects in clinical trials included hypotension (28% versus 13% in patients receiving placebo, hypertension (16% versus 18%), nausea (11% versus 9%) and bradycardia (7% versus 3%).

7.7 EEG

There is no risk associated with having an EEG. The patient may feel uncomfortable while the electrodes are attached to their scalp. The conductive gel sometimes causes some mild irritation. They may not like the smell of the paste or the glue remover, but they are not harmful.

7.8 Blood Draw

There may be some discomfort and bruising at the site of needle entry. There is a very small risk of fainting. Infection in the area of the needle insertion is rare. 10 CC will be drawn three times during the protocol for CBC, liver function tests and electrolytes.

8. SUBJECT SAFETY MONITORING

Patients will be monitored by CES Staff, including PI, nurse practitioner and fellows, and by Dr Phillip Pearl, a board-certified pediatric neurologist, who is a

special volunteer with clinical privileges at NIH, and has the world's largest experience with SSADH deficiency.

Dr Debra Ehrlich will serve as Independent Study Safety Monitor (ISSM). Dr Ehrlich is a Board-Certified Neurologist with Fellowship training in Movement Disorders who is conducting clinical research with Dr Mark Hallett.

The ISSM will serve as the IND sponsor's medical monitor and will make the final determinations of relatedness of safety events to the investigational product on behalf of the sponsor (NINDS). The ISSM will review serious adverse events, and serious unanticipated problems. SAEs that are at least temporally associated with the use of the study drug (whether assumed to be related or not) will be given to the ISSM immediately, but no later than 48hrs from the time the PI learns of an event. The PI will record nonserious AEs and report them to the ISSM at the time of 1) IRB continuing review and 2) the annual Safety Monitoring Committee's annual meeting. The ISSM will review these reports and provide feedback to the PI and NINDS in a timely manner.

Patients will be monitored carefully by CES clinicians for any change in their clinical status during clinic visits and self-report during phone and computer contact. Intervention will be determined by the independent subject safety monitor and may include consultation, additional studies, or withdrawing the patient from the protocol.

Parameters to be monitored include seizure frequency, neurological examination, fluctuations in cognitive and behavioral features. Specific drug-related side effects to be monitored include headache, tiredness, nausea and vomiting, sleepiness and dizziness.

Patients who cannot tolerate the study drug will be taken off of it. Following review and approval by the Independent Subject Safety Monitor, patients who stopped taking the study drug can remain in the study and complete follow-up visits and assessments.

Females who become pregnant will stop the study drug however will remain in the study and can be followed under the protocol. They will not complete any assessments that pose risk to the pregnancy or fetus but can do other non-invasive procedures such as neuropsychological testing. They will be followed until the end of the study or pregnancy outcome, whichever is later.

Patients will be removed from the study if they are unable to cooperate, or have an alteration in clinical status 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.

Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (appendix 2). 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, one-step dose reductions will be initiated until the toxicity resolves. 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 the study medication. All dose changes and/or dose interruptions will be recorded on case report forms.

8.1 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 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.

9. OUTCOME MEASURES

9.1 Primary outcome measure

The primary outcome measures for drug efficacy will be:
Performance on neuropsychological testing and responses to parent questionnaire.

9.2 Secondary outcome measures for efficacy will be:

TMS parameters of cortical excitation and inhibition

9.3 Outcome measures for safety will include:

Clinical examination
Neuropsychological tests

10. DATA ANALYSIS

10.1 Power calculation:

We performed a power analysis, in Systat 11. Using a paired Student's t design, comparing measurements on placebo and SGS-742, 16 patients would be needed to detect a change in the Auditory Comprehension subtest of the Neuropsychological Assessment Battery Language Module score of 0.75 SD.

Thus, we are requesting 22 subjects to allow for dropouts. Dropouts will be replaced with new subjects until we attain 16 completers.

We will record the reasons for any dropouts, allowing performance of sensitivity analyses to account for a number of scenarios, including assuming dropouts all had a negative outcome in our analysis of efficacy, and using imputation to model the effects of dropouts based on the profile of each dropout.

10.2 TMS

Indices for cortical excitability will be obtained including motor threshold (MT), recruitment curve, intracortical inhibition (ICI), intracortical facilitation (ICF), and cortical silent period (CSP) from motor cortex. Motor evoked potential (MEP) size will be measured peak-to-peak in single trials and averages will be calculated for each intensity. ICI and ICF will be studied using a paired stimulus paradigm. CSP onset and termination will be measured in the rectified single trials as the times of the end of the preceding MEP and the return of sustained activity in the EMG, respectively. The conditional averages will be calculated from the single-trial data. These parameters will be compared for intra-individual and inter-individual differences pre- and post-therapy with SGS 742.

10.3 MRS

MRS will be analyzed with the GABA editing sequence provided by the NIH/NIMH MRS Core.

10.4 Neuropsychological tests

The neuropsychological tests were selected by the investigators as representing those assessments which could be completed by this group of patients with adjustments made for the cohort's age group, including WNV (Wechsler Nonverbal Scale of Ability) for patients up to age 22; WAIS-IV (Wechsler Adult Intelligence Scale) for patients age 22 and older; the Neuropsychological

Assessment Battery: Language Module; Rule Shift from the Behavioral Assessment of Dysexecutive Syndrome; Computerized tests of reaction time and go-no-go to assess the constructs of reaction time and attention; Texas Functional Living Scale; ABAS: Adaptive Behavior Assessment Scale to be completed by parent and Queries on functional skills.

The combination of clinical interview, observations, intellectual testing, and executive function tests was devised for a logistically achievable assessment of cognitive and executive function. The testing will be administered at baseline and then at the end of the two six-month treatment arms, which includes a two-month washout period between arms.

10.5 CSF analysis

Quantitation of GABA, GHB, succinic semialdehyde, homocarnosine, 4,5-dihydroxyhexanoic acid (DHHA) and D-2-hydroxyglutaric acid in CSF samples will be achieved using isotope dilution liquid chromatography-tandem mass spectrometry. These metabolites (all of which are interrelated to GABA metabolism) are increased to varying degrees in both CSF derived from SSADH deficient patients and brain tissue derived from SSADH-deficient mice.

In addition, for all CSF samples comprehensive amino acid analysis will be performed. The rationale of this analysis is based upon the clear depletion of glutamine observed in the brain of SSADH-deficient mice. Amino acid analysis is performed by HPLC with ninhydrin post column detection. As well, we have documented in earlier studies that glutamine is low, to borderline-low, in CSF samples derived from SSADH-deficient individuals.

11. HUMAN SUBJECTS PROTECTION

11.1 Subject Selection

Subjects will be selected equitability, based upon their meeting the study's eligibility criteria. Although there is no known human subpopulation incidence variation, the majority of the patients identified have been of ‘Caucasian’ background.

11.2. Justification for inclusion of children

SSADH is a severe pediatric neurotransmitter disease without any effective therapy. The majority of the patients identified are under 18. Patients over the age of four are included because the parent questionnaires measuring activities of daily living as primary outcome data are valid at any age. Early intervention is desirable in a genetic disease.

11.3 Justification for inclusion of vulnerable subjects

Patients with SSADH deficiency frequently have cognitive impairment and may lack consent capacity. The effect of SGS-742 on neuropsychological function is one of the main outcome measures of the protocol.

11.4 Justification of sensitive procedures (using placebo)

Placebo-controlled studies are the best way to obtain reliable data on drug efficacy in a clinical trial in any neurological disorder. Patients will still be on their baseline drug therapy during all treatment phases, and will not be exposed to any risk greater than their standard therapy while on placebo.

11.5 Safeguards for vulnerable populations

Protections for vulnerable populations will include evaluation by the HSPU/ACAT, obtaining consent from DPA for adults without capacity, assent from participants, pregnancy testing for women of childbearing potential, and use of pediatric-trained staff and facilities. Dissent will be respected.

11.6 Qualifications of investigators

Sara Inati, MD will serve as the principal investigator. She is a board-certified in Neurology, Epilepsy and Clinical Neurophysiology, and has extensive experience in clinical research, including serving as principal investigator on several trials. She will oversee all aspects of the protocol, including study procedures and data analysis. Dr. Inati will be obtaining informed patient consent.

William H. Theodore, MD is board-certified in Internal Medicine, Neurology, and Clinical Neurophysiology, and has extensive experience in clinical research. He will serve as the lead associate investigator, and will be obtaining informed patient consent and will participate in study procedures and data analysis.

Dr Philip Pearl, MD is a board-certified pediatric neurologist with extensive experience in the treatment of pediatric seizure disorders and SSADH deficiency

and is credentialed at NIH. He will be participating in study procedures.

Drs John Schreiber, MD is a board-certified neurologist and pediatrician. He will participate in patient evaluation and data analysis and will be obtaining informed consent.

Dr Eric Wassermann, MD is a neurologist with extensive experience in neurophysiological and behavioral research. He will not be obtaining informed patient consent. He will supervise TMS.

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

Dr. Edythe Wiggs, PhD is the NINDS clinical neuropsychologist who will perform neuropsychological evaluations. She will not be obtaining informed patient consent.

Dr. K. Michael Gibson, PhD has extensive experience in heritable disorders of human metabolism. Patients with heritable SSADH deficiency have been a focus of the Gibson laboratory for more than 25 years. He will not be obtaining informed patient consent. He will perform CSF analyses.

Gina Norato is a statistician with extensive experience in clinical trials. She will perform data analysis. She will not obtain consent.

12. ANTICIPATED BENEFIT

The clinical trial has the prospect of direct benefit to the patients with SSADH deficiency since the patients may show improvement on neuropsychological testing in the areas of attention, reaction time, visual information, and working memory during treatment with SGS-742.

The clinical trial is likely to result in generalized knowledge about the effect of $GABA_B$ antagonists on cerebral function, thereby possibly leading to new diagnostic and/or treatment options for individuals with other disorders as well as SSADH deficiency, especially neurometabolic disorders featuring epilepsy.

13. CLASSIFICATION OF RISK (FOR THE STUDY AS A WHOLE)

<u>For adults</u> the study is more than minimal risk due to the paired pulse TMS.

For Adults without consent capacity the study is research involving a minor increment over minimal risk due to the paired pulse TMS presenting the prospect of direct benefit to the individual

For Children the study is 45CFR46.405 Research involving greater than minimal risk but not more than a minor increment over minimal risk, due to the paired pulse TMS but presenting the prospect of direct benefit to the individual child

Overall risk and benefit consideration
The risks are reasonable in relation to anticipated benefit

14. CONSENT DOCUMENTS AND PROCESS

Study investigators designated as able to obtain consent in section 11.6 above, will obtain informed consent. Each subject will receive an oral and written explanation of the purposes, procedures, and risks of this study in a language appropriate for the individual's level of understanding. A copy of the signed consent form will be placed in the medical record, and a copy will be given to each study participant. A member of the protocol team will be available to answer questions about the study to be performed. Assent will be obtained from minor subjects age 8 and older, when possible, and adults found not capable of giving informed consent.

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.

The consent form contains all required elements

The consent documents submitted with this protocol include adult patient or parent consent, as well as adult and minor assent forms.

2-Parent Consent Procedures:

If the parents are married, written consent may be obtained from one parent only. If the parents are not married, written consent will be obtained from: 1) the custodial parent if only one parent has legal custody, or 2) from both parents if they share legal custody for medical decision-making. For unmarried parents, signature of one parent will suffice if the other parent is deceased, unknown, incompetent, or not reasonably available. When signature of both parents is required, written consent will be obtained in-person from at least one parent. When the second parent is unable to attend the consent process conference in person, the following telephone process to obtain written consent will be used.

Telephone Consent Procedures: The unavailable parent will be provided with a copy of the consent form, usually by fax, email, or hard copy mail. Once the consent form is received, an Investigator authorized to obtain consent will arrange for a telephone call with the parent in the presence of a witness to review study and the consent form and to answer any questions. If the parent cannot arrange for a witness in his/her location, the consenting investigator will have a witness present for the teleconference at NIH. Once the parent agrees to his/her child's participation, the parent and witness (if present with the parent) will sign and date their copy of the consent form. The Investigator will enter a note documenting the consent process in the Medical Record. The 2nd parent will return their signed copy to the Investigator. Once the copy with the parent signature is received, the Investigator and witness (if present at NIH) will sign and date the 2nd parent consent form, place the original copy with all signatures in the Medical Record, retain a copy for research records, and mail a copy to the parent.

Capacity Assessment:

ADULT SUBJECTS

Adult subjects in this protocol will be evaluated by HSPU/ACAT to determine, based on a protocol specific capacity assessment, if the subject has capacity to give informed consent. In all cases involving a guardian or an outside DPA (Durable Power of Attorney), the investigator will have the NIH legal department review the guardianship or DPA papers for authorization of research prior to consenting process.

1) If HSPU/ACAT determines that the subject has capacity, informed consent will be obtained by a designated investigator with consent monitoring by HSPU.

2) If HSPU/ACAT determines that the subject lacks capacity to give informed consent, and has a legal guardian, the HSPU will conduct an assessment of surrogate understanding. Once understanding by the subject's legal guardian has been established, an investigator will obtain informed consent from the subject's legal guardian and HSPU will monitor the consent/assent process.

3) If HSPU determines that the subject lacks consent capacity and there is no legal guardian, the PI has 3 options:

    A. If HSPU determines that the subject lacks capacity to provide informed consent, and if the subject has a Durable Power of Attorney (DPA) for health care, this DPA may be invoked by the medically responsible investigator or an investigator with credentials to obtain informed consent under this protocol. HSPU will conduct an assessment of surrogate understanding. Once understanding by the DPA has been established, the designated investigator will obtain informed consent from this DPA with HSPU monitoring the consent/assent process.

    B. If HSPU determines that the subject lacks capacity to give informed consent and has no guardian or DPA, HSPU will determine if the subject understands the meaning and intent to assign an NIH DPA. The NIH DPA will be invoked by the medically responsible investigator or by an investigator with credentials to obtain informed consent under this protocol. HSPU will perform an Assessment of Surrogate Understanding. An investigator will then obtain informed consent from the NIH DPA, and assent from the subject, with HSPU monitoring the process.

    C. If HSPU determines that the subject lacks capacity to give consent, the subject does not have a guardian or DPA and is unable to appoint an NIH DPA, then a Next of Kin surrogate may be appointed as outlined in MAS 87-4. ACAT will perform an Assessment of Surrogate Understanding. An investigator will obtain consent from the surrogate and assent from the subject with HSPU monitoring the process.

15. DATA AND SAFETY MONITORING

15.1 Study Monitor

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

Dr. Codrin Lungu is the Program Director of the Division of Clinical Research, NINDS. He is a board-Certified neurologist with extensive clinical trial experience. Dr. Lauren Bowen is a board-certified neurologist and a member of Dr. Avindra Nath's research section at NIH. She has extensive neurology experience.

The monitoring plan will include SMC review once six subjects have completed the treatment phase (Period 1 and Period 2) of the study. Thereafter, the SMC will review safety data, including seizure frequency, toxicity reports, neuropsychological and mood testing, laboratory tests, EEG, ECG and clinical examination once per year 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.

15.2 Criteria for stopping the study

New enrollment will be halted 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 of Grade 3 toxicity on the NCI CTC.

16. QUALITY ASSURANCE

The purpose of QA monitoring is to assess compliance with applicable regulatory requirements and good clinical practice guidelines, as well as to provide recommendations for improving the management of clinical research data over the life-cycle of the protocol. The protocol will be monitored according to the NINDS Monitoring SOP.

A Contract Research Organization (CRO) will provide on-site monitoring of this protocol. The study team and the monitor will determine the frequency of monitoring visits which will be described in the QA Monitoring Plan. The frequency of visits will include, at a minimum, annual interim monitoring visits until the protocol has undergone a close-out visit, unless otherwise indicated by the Sponsor. The sponsor via the CRO, will be responsible for providing adequate oversight of the investigation to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data.

17. 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 iRIS.

It is anticipated that participants in this study will occasionally miss or fail to complete an assessment or procedure, such as a completion of a rating scale or a blood draw, or fail to complete a procedure or visit within protocol-specified time frames. Omissions such as these will be considered expected events and not protocol deviations provided they are infrequent and do not include data needed to assess safety or the primary study outcome. Cumulative proportions of these missed events in the study population will be presented to the IRB annually. In addition, the rate of omissions will be monitored by the Investigators. If an individual misses more than 15% of the required assessments/procedures or if more than 15% of the participants miss completion of the same assessment or procedure, it will be considered a deviation and a deviation report will be sent to the IRB within two weeks.

If the total number of expected items (study visits, study assessments/procedures) is less than 16, then two or more missed items are reportable. If the total number of expected items is greater than 16, then, if more than 15% are missed, it is reportable.

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

Seizures are a clinical feature of SSADH and an expected event for this population. This patient population may experience seizures and resulting emergency room visits and/or hospitalization. We will record these events including the resulting emergency room visits and/or hospitalization as part of the adverse events reported at the time of continuing review. Reporting of seizures

and emergency-related treatment at the time of the CR is limited to emergency related seizure treatment only and all other SAEs will be reported immediately.

The ISSM will serve as the IND sponsor's medical monitor and will make final determination of relatedness of safety events to the investigational product on behalf of the sponsor (NINDS). The PI will immediately (no later than 48hrs) report SAEs that are at least temporally associated with the use of the study drug to the ISSM 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 ISSM at the time of 1) IRB continuing review and 2) the annual Safety Monitoring Committee's annual meeting. The PI will send the AE log to the IRB with the next continuing review.

18. ALTERNATIVES TO PARTICIPATION

There is no current proven or approved therapy for SSADH deficiency. There is no other way to obtain SGS-742.

19. PRIVACY

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

20. CONFIDENTIALITY

a. For Medical Records
All medical records are property of the Clinical Center and maintained in secured files by the Clinical Center. The Section staff does not release any information to the patient or others involved in the patients care without the patient signing a release form. Only the medical records staff of the Clinical Center has authority to release documents.

b. For Research Data
Samples and data will be stored using codes that we assign. Data will be kept in password-protected computers. Coded samples will be in locked storage at WSU. The key to the code will be kept at NIH.

Hard copy data/records with identifiers with be maintained under double lock, in a locked cabinet in a room that is locked when unoccupied. Electronic data with identifiers will be maintained in password protected files on secured servers.

Only study investigators, study sponsors, and study monitors will have access to the samples and data.

De-identified results from clinical trials will be posted on cctrials.gov

c. Special precautions
None

21. CONFLICT OF INTEREST

21.1 Distribution of NIH Guidelines

NIH guidelines on conflict of interest have been distributed to all investigators.

21.2 Conflict of interest

There are no conflicts-of-interest to report for NIH investigators. Non-NIH investigators will abide by the conflict-of-interest policies of their own institutions.

21.3 Role of a commercial company

NIH will purchase SGS-742 from IRIX Pharmaceuticals, using funds provided by the Pediatric Neurotransmitter Disease Association and a bench-to-Bedside grant. IRIX has no further interest in the study and will have no further participation. All rights to use SGS-742 for the study have been transferred to NIH by the original IND holder.

22. TECHNOLOGY TRANSFER

A material transfer agreement has been established with Dr K Michael Gibson of Washington State University for CSF analysis.

23. 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.

Travel for an escort will be provided.

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25. ATTACHMENTS/ APPENDICES

1. Eligibility checklist
2. Study Calendar
3. NCI common terminology/toxicity table
4. Case report forms (CRFs)

5. Symptom/side effect questionnaire
6. Investigator's Brochure
7. WSU recruitment letter (no longer in use)

26. CONSENT FORMS

a. Adult or parent consent
b. Single patient consent
c. Child assent 8 – 11
d. Child assent 12 – 17
e. Adult Assent