# A Randomized Controlled Trial of SGS-742, a γ-aminobutyric acid B (GABA-B) Receptor Antagonist, for Succinic Semialdehyde Dehydrogenase Deficiency

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## Abstract

We examined safety, tolerability, and efficacy of SGS-742, a γ-aminobutyric acid B (GABA-B) receptor antagonist, in patients with succinic semialdehyde dehydrogenase deficiency. This was a single-center randomized, double-blind crossover phase II clinical trial of SGS-742 versus placebo in patients with succinic semialdehyde dehydrogenase deficiency. Procedures included transcranial magnetic stimulation and the Adaptive Behavior Assessment Scale. Nineteen subjects were consented and enrolled; the mean age was 14.0 ± 7.5 years and 11 (58%) were female. We did not find a significant effect of SGS-742 on the Adaptive Behavior Assessment Scale score, motor threshold, and paired-pulse stimulation. The difference in recruitment curve slopes between treatment groups was 0.003 ($P = .09$). There was no significant difference in incidence of adverse effects between drug and placebo arms. SGS-742 failed to produce improved cognition and normalization of cortical excitability as measured by the Adaptive Behavior Assessment Scale and transcranial magnetic stimulation. Our data do not support the current use of SGS-742 in succinic semialdehyde dehydrogenase deficiency.

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Succinic semialdehyde dehydrogenase deficiency (also termed 4-hydroxybutyric aciduria) is a rare autosomal recessive disorder because of pathogenic variants in *ALDH5A1*. Loss of function in succinic semialdehyde dehydrogenase results in reduced γ-aminobutyric acid (GABA) catabolism, leading to elevated levels of GABA and γ-hydroxybutyric acid (GHB) and additional metabolites in body fluids and brain parenchyma.[1,2] More than 450 cases have been identified worldwide,[3] making this the most prevalent pediatric neurotransmitter disorder. Diagnosis is primarily based on detection of elevated GHB in the urine organic acid profile[4] but can also be made by detecting low succinic semialdehyde dehydrogenase levels or the pathogenic ALDH5A1 gene variant. Most patients present with developmental delay noted in the first 2 years of life, in addition to hypotonia, ataxia, speech disturbance, and intellectual disability. At least half develop epilepsy. As patients age,

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they exhibit more compulsive behavior, sleep disturbances, and seizures.[5]

The signs and symptoms of succinic semialdehyde dehydrogenase deficiency result from various metabolic derangements, primarily the elevations in GHB and GABA that affect GABAergic neurotransmission, disrupt the glial-neuronal glutamate/GABA-glutamine shuttle, and alter dopamine and serotonin homeostasis. At physiologic levels, GHB acts primarily at high affinity GHB and $\alpha_4\beta_1\delta$-GABA-A receptors, and other yet-identified sites.[6] In succinic semialdehyde dehydrogenase deficiency, where GHB concentrations typically reach 100 to 500 times normal levels, GHB acts as a weak GABA-B receptor agonist.[7] This GABA-B receptor activation modulates neurotransmission at GABA-A synapses,[8,9] disproportionately impacting inhibitory interneurons, and leads to disinhibition of excitatory neurons. These changes result in downregulation of GABA-A receptors evident on flumazenil-PET[10] and decreased GABA-B function as measured by transcranial magnetic stimulation in patients with succinic semialdehyde dehydrogenase deficiency.[11]

Despite an expanding literature on the pathophysiology and diverse metabolic disruptions in succinic semialdehyde dehydrogenase deficiency, there are no successful targeted therapies. Pharmacologic treatment is generally aimed at ameliorating symptoms of the disease, primarily seizures and psychiatric sequelae. No one antiseizure medication has emerged as the treatment of choice for succinic semialdehyde dehydrogenase deficiency. Vigabatrin, an irreversible inhibitor of GABA-transaminase, has been proposed as a logical intervention because it inhibits the conversion of GABA to GHB. However, multiple reports detail lack of efficacy,[12] or worsening of specific symptoms such as seizures or level of alertness.[13] Although vigabatrin will lead to at least transient decreases in cerebrospinal fluid GHB levels,[14] there may be a deleterious effect related to increases in cerebrospinal fluid (and brain) GABA levels.[15] Similarly, clinicians may wish to avoid valproic acid, which inhibits residual succinic semialdehyde dehydrogenase activity, though there are reports of efficacy.[16] Enzyme replacement therapy is challenging, in part because succinic semialdehyde dehydrogenase is a mitochondrial enzyme whose delivery into the mitochondria is coupled with its ribosomal biosynthesis.[17]

One hurdle in developing effective therapies is the nature of the disorder. As mentioned above, succinic semialdehyde dehydrogenase deficiency is extremely rare. The variability in phenotypic severity makes selection of standardized assessments able to capture the range of neurocognitive symptoms rather difficult. And because only about half develop seizures (which may be infrequent), measuring changes in seizure frequency is unlikely to prove useful. Only transcranial magnetic stimulation has detected a significant change in a therapeutic trial of taurine for succinic semialdehyde dehydrogenase deficiency.[18]

Preliminary animal work in the succinic semialdehyde dehydrogenase mutant model has suggested benefit from treatment with SGS-742 (3-aminopropyl-*n*-butyl phosphinic acid),

a GABA-B receptor antagonist. SGS-742 is orally absorbed, with peak plasma concentration achieved after 4 hours and elimination half-life of approximately 4 hours, >99% being excreted unchanged in the urine. Early reports showed improved attention, reaction time, visual information processing, and working memory in mice, rats and monkeys.[19] It may yield a preferential effect at pre-synaptic GABA-B receptors which generally act to reduce neurotransmitter release.[20] In succinic semialdehyde dehydrogenase deficient (Aldh5a1$^{-/-}$) mice, SGS-742 showed a dramatic dose-dependent improvement in spike-wave discharges and absence seizures identified by electrocorticography, whereas topiramate was ineffective.[21] In a phase II double-blind, placebo-controlled study in 110 adults with mild cognitive impairment, oral administration of SGS742 600 mg 3 times daily for 8 weeks significantly improved attention, reaction time, visual information processing, and working memory.[22,23] No clear drug-related serious adverse events or drug-related effects on cardiovascular or laboratory variables were reported.[22] The drug has not yet been used in children.

We aimed to examine safety, tolerability, and efficacy of SGS-742 on the neuropsychological function and cortical excitability in a small group of patients with succinic semialdehyde dehydrogenase deficiency. We hypothesized that (1) patients would show improvements in activities of daily living based on parent questionnaire, (2) patients would have lengthening toward normal values of the cortical silent period, and return of long interval intracortical inhibition, and (3) patients would show improvement on global assessment ratings.

## Methods

### Patients

Eligible patients were age 4 years and older with succinic semialdehyde dehydrogenase deficiency as determined by documented 4-hydroxybutyric aciduria on two separate tests, documented succinic semialdehyde dehydrogenase quantitative enzyme deficiency or presence of two pathogenic ALDH5A1 gene variants, and clinical features consistent with succinic semialdehyde dehydrogenase deficiency. We excluded patients with 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, and patients requiring treatment with drugs known to affect the GABAergic system, including vigabatrin and benzodiazepines (except for acute seizure treatment). Pregnant and lactating women were also excluded, and women of child-bearing potential were required to use a reliable form of contraception (abstinence included).

Letters were mailed to families of patients with a history of succinic semialdehyde dehydrogenase deficiency. This letter was posted to the SSADH Association website. We also recruited patients from a cohort followed by, or referred to, PLP in the Boston Children's Hospital Neurology Department. During the course of routine clinical care, patients were informed about the study and, on their request, were provided the information to contact the National Institutes of
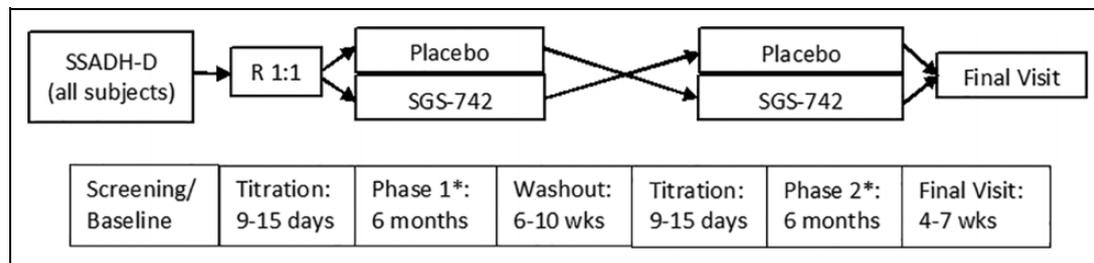
**Figure 1.** Randomized, double-blinded crossover study design.

Health (NIH) personnel on their own initiative. Several patients had participated in previous NIH succinic semialdehyde dehydrogenase deficiency studies.[10,11]

Patients were screened in the National Institute of Neurological Disorders and Stroke (NINDS) Clinical Epilepsy Section (CES) outpatient clinic for inclusion in the protocol by CES physicians or licensed practitioners. PLP supervised confirmation of the diagnosis.

## Study Design

This was a single-center randomized, double-blind crossover phase II clinical trial of SGS-742 versus placebo. Figure 1 depicts the overall study design. Patients underwent baseline testing as detailed in the assessments section below and were then randomized to first receive either active drug or placebo at a 1:1 ratio. Patients received their first dose of study pills at the NIH, returned 12-24 hours later to be assessed for adverse reactions, then returned home. All patients were given an exact written titration schedule to follow. Patients and families were contacted at least once every 2 weeks by phone and/or completion of patients surveys on the Clinical Trial Survey System. These surveys included questions regarding the severity and chronicity of symptoms. Patients and families were also asked the following data and safety monitoring questions: Has the patient seen a health care provider since last visit? Has the patient had any seizures since last visit? Has the patient had a change in medications over the past week? Any missed doses of study drug? and Any unexpected/unusual symptoms over the past week? Treatment during this first phase continued for 6 months before tapering and washout. Following a 9-week total washout period ($\pm 2$ weeks), including drug taper, patients entered the other treatment arm (phase 2). Repeat assessments were conducted at the conclusion of each treatment arm. The final visit occurred 4-7 weeks after completion of the final drug taper.

SGS-742 was synthesized by IRIX pharmaceuticals in a GCP facility. We recommended that patients take the study drug 3 times each day prior to meals because administration of food decreases oral systemic availability of SGS-742. The drug and matching placebo were encapsulated by the NIH pharmacy. The pharmacy created the randomization schedule and ensured blinding of patients, family, and investigators. The study was approved by the NIH Combined Neurosciences Institutional Review Board. We obtained written informed consent for all participants, their legal guardian, or legally authorized representative, as appropriate.

During titration of SGS-742, patients received an initial dose of 2.5 mg/kg/dose (up to 150 mg) 3 times a day for 3 days, which was then increased in increments of 2.5 mg/kg/dose every 3 days up to the target dose of 10 mg/kg/dose (up to 600 mg) 3 times a day. If patients experienced side effects, the next scheduled dose increase was delayed until side effects abated or the dose was reduced in 2.5 mg/kg/d

increments until side effects abated. The drug taper schedule exactly mirrored this increase: 7.5 mg/kg/dose (up to 450 mg) 3 times a day for 3 days, 5 mg/kg/dose (up to 300 mg) 3 times a day for 3 days, 2.5 mg/kg/dose (up to 150 mg) 3 times a day for 3 days, then stop. Placebo was titrated and tapered in capsules matching the SGS-742 dosing stages.

## Assessments

Assessments were conducted at baseline, end of first treatment arm (phase 1), and end of second treatment arm (phase 2). Procedures included neurologic and systemic physical examination, electroencephalogram (EEG), transcranial magnetic stimulation, neuropsychological testing, and blood and urine tests. Transcranial magnetic stimulation was not done within 24 hours of a reported seizure. At each visit during drug treatment, patients had a medical history and physical examination and review of seizure calendars and any adverse effects. Laboratory tests were obtained when indicated for change in clinical status. Patients and families kept a record of seizures and any possible medication side effects.

## Neuropsychological Assessments

We planned a comprehensive language and cognitive evaluation using a selection of assessments based on age and ability. Planned language assessments included the Wechsler Nonverbal Scale of Ability[24] for patients up to age 22 years, the Wechsler Adult Intelligence Scale[25] for patients age 22 years and older, and the Neuropsychological Assessment Battery Language Module Confrontation Naming and Auditory Comprehension Subtests.[26] Other tools used for cognitive assessment were the Rule Shift from the Behavioral Assessment of Dysexecutive Syndrome[27] (a short test of working memory), a computerized test of reaction time and go / no-go to assess reaction time and attention, the Texas Functional Living Scale[28] (an assessment of practical reading, math, language comprehension and memory developed for individuals with cognitive limitations), the Adaptive Behavior Assessment Scale (ABAS)[29] to be completed by parent or guardian that assesses functional skills, the Wechsler Preschool and Primary Scale of Intelligence-IV[30] for patients between the ages of 2.5 and 7 years, and the Wechsler Intelligence Scale for Children-V[31] for patients aged 6 through 17 years. The Vineland Adaptive Ability (VABS) Composite–Parent Form[32] was given to all parents and guardians. This questionnaire provides an estimate of the patient's communication, daily living, socialization, and motor functioning.

However, the functional level for both child and adult patients was too low to derive statistically analyzable data for any but the Adaptive Behavior Assessment Scale. The Adaptive Behavior Assessment Scale is a widely used parent/guardian questionnaire that assesses adaptive

abilities including communication, social adaptability, and practical skills regarding their child. Each of the 232 items is rated on a scale of 0 (unable to perform) to 2 (performs independently). Raw scores are converted to age-adjusted normative data (mean = $100 \pm 15$).

## Other Procedures

Routine video EEG was performed according to standard procedures using the international 10-20 standard method of electrode placement. Blood was collected for complete blood count, clinical chemistry, and hepatic panels. We performed urine pregnancy testing on women of child-bearing age.

## Transcranial Magnetic Stimulation

Transcranial magnetic stimulation was delivered through a round coil (90 mm diameter) connected to 2 Magstim $200^2$ magnetic stimulators via a BiStim-module (Magstim, Dyfed, UK). The coil was placed over the contralateral motor cortex at the site, and in the orientation, that consistently produced the maximum motor evoked potential amplitude from the right first dorsal interosseus muscle.

Subjects were seated in a comfortable chair with their hands resting on a pillow. Electrodes were applied to the skin over the right first dorsal interosseus in a belly-tendon montage with the reference electrode placed at least 4 cm distal to the active electrode and a ground electrode positioned over the dorsum of the hand. The electromyogram signal was amplified (Coulburn Isolated Bioamplifier, model V75-04), bandpass filtered (90 Hz to 1 kHz), digitized (analog/digital rate 40 kHz), and recorded (Signal version 4.05, Cambridge Electronics, UK) for offline analysis. The electromyogram was monitored continuously for relaxation by visual inspection. The resting motor threshold was determined by increasing stimulus intensity in increments of 5% of maximum output until a motor evoked potential was recorded and then adjusting by 1% increments to the lowest stimulator output required to produce MEPs of at least 50 µV on 5 of 10 consecutive trials.

Motor evoked potential recruitment curve, cortical silent period, short- and long-interval intracortical inhibition, and intracortical facilitation were measured. Subjects were instructed to rest during the recruitment curve and paired pulse paradigms, and to sustain a contraction of the first dorsal interosseus by pinching the thumb and first finger during cortical silent period determination. Individual trials were repeated or later excluded if muscle activity was apparent in the 100 ms before stimulation in the recruitment curve and paired pulse paradigms, or if electromyogram amplitude dropped below baseline, determined visually, in the 100 ms prior to stimulation for cortical silent period. For recruitment curve determination, 5 MEPs were recorded at each of 8 percentages (when possible, some percentages of the motor threshold exceeded maximum stimulator output for certain patients) of the motor threshold in the following order: 90%, 130%, 100%, 140%, 110%, 150%, 120%, and 160%. The cortical silent period was measured visually from the end of stimulus artifact to the first return of sustained electromyogram activity for 10 trials at 110%, 120%, 130%, and 140% motor threshold. For short-interval intracortical inhibition and intracortical facilitation measurements, we set the conditioning stimulus at 70%, and the test stimulus at 120%, of motor threshold. Interstimulus intervals were 2 and 10 ms. For long-interval intracortical inhibition, we used 120% of motor threshold for both stimuli with an interstimulus interval of 100 ms. We used the mean motor evoked potential to the conditioning stimulus in the long-interval intracortical inhibition experiment as the control motor evoked potential. Intracortical inhibition and intracortical facilitation were determined by the ratio of the mean conditioned motor evoked potential to this control. We delivered and averaged 10 trials for each measurement.

## Statistical Analysis

The sample size was calculated based on detecting a change in the auditory comprehension subtest of the Neuropsychological Assessment Battery Language Module. Using a 2-tailed, paired $t$ test, an effect size of 0.75 would require 16 patients at 80% power and an alpha-level of 0.05.

Descriptive statistics were provided for demographic variables using mean and standard deviation, as well as number and percentage. Linear mixed effects models were used with Adaptive Behavior Assessment Scale, motor threshold, and short-interval intracortical inhibition, intracortical facilitation, and long-interval intracortical inhibition as outcome variables, and treatment group and baseline effect as predictor variables. Subject was specified as a random effect to account for repeated observations within an individual (one on each treatment). Recruitment curves were analyzed with the outcome as average motor evoked potential and percentage of motor threshold (90%-160%), treatment group, and the interaction of motor threshold and treatment as the main predictors of interest. Order of administration was added into the primary model (Adaptive Behavior Assessment Scale) as a sensitivity analysis to check for order effect, as well as an interaction between treatment and baseline age. Raw changes for each outcome measure were also described using the mean (SD) change between follow-up and baseline for each treatment group, to descriptively supplement the model results. Adverse events were investigated and described by system and treatment group. Graphical displays were also used to show the relationship between treatment and various outcome measures.

## Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the NIH NINDS Institutional Review Board. Written informed consent was obtained from all participants (or guardians of participants) in the study. The clinical trial identifier number is NCT02019667.

## Data Availability Statement

The study protocol, statistical analysis plan, and deidentified data are available for qualified individuals on reasonable request. Data will be stored for at least 3 years as per federal guidelines.

## Results

Nineteen subjects were consented and enrolled at the NIH between March 2014 and October 2017. Details on recruitment and handling of subjects is found in the CONSORT flow diagram (Figure 2). The final follow-up visit was in January 2019. Mean age was $14.0 \pm 7.5$ years at enrollment (range 5-34.5) and 11 (58%) were female. Mean age at diagnosis was $4.7 \pm 4.6$ years (range 0-20 years). Table 1 provides details on diagnosis, neuroimaging, and clinical findings for each subject.
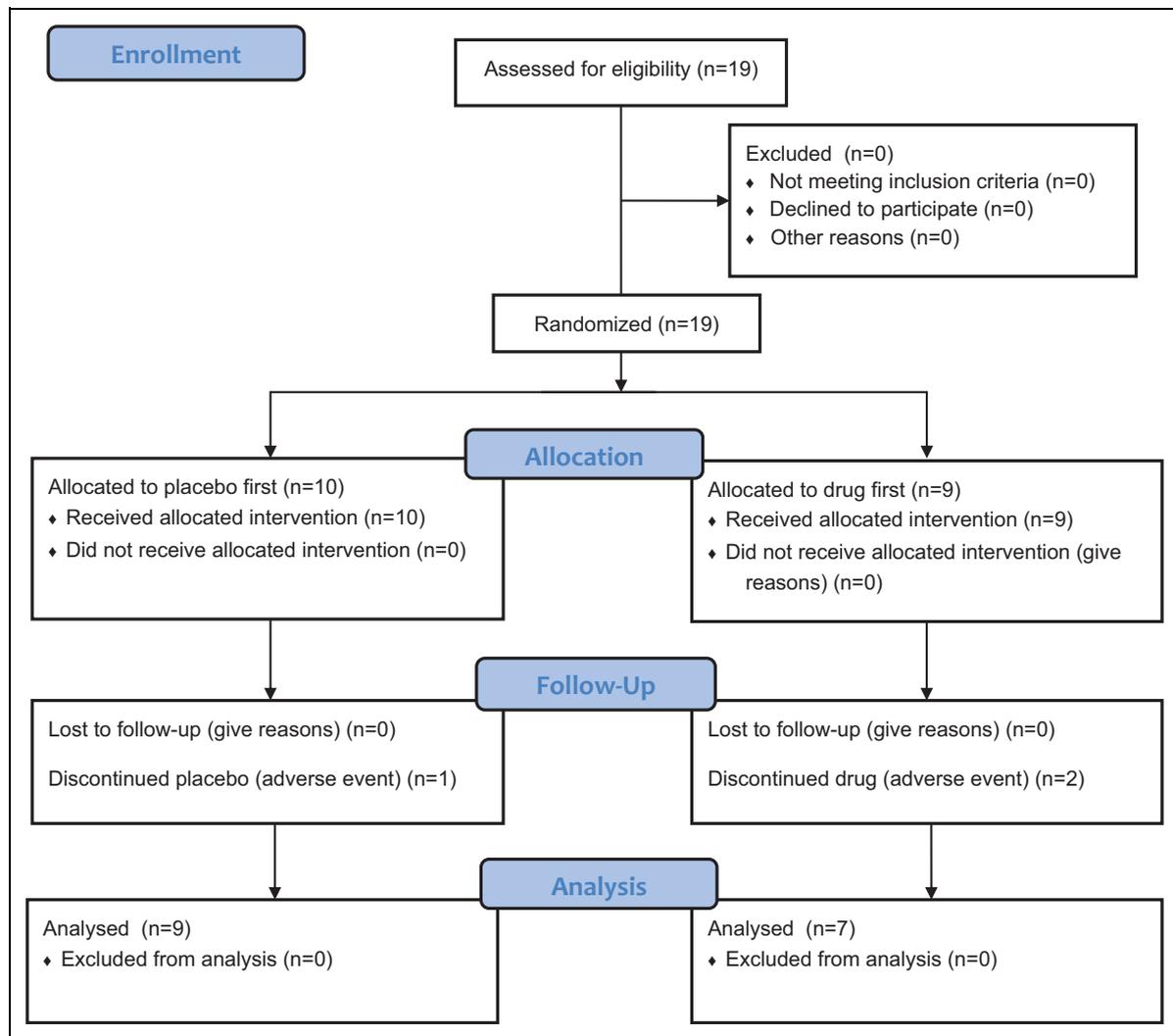
**Figure 2.** CONSORT flow diagram detailing recruitment and handling of subjects.

Summary findings are presented in Table 2. In the mixed model with Adaptive Behavior Assessment Scale score as an outcome variable, we did not find a significant effect of SGS-742 on the Adaptive Behavior Assessment Scale score (baseline-adjusted treatment effect = –0.69, $P$ = .80; Figure 3). Not surprisingly, baseline score had a significant relation to scores on both drug and placebo, meaning higher follow-up scores in either treatment group came from individuals with higher baseline scores ($\beta$ = 1.20, $P$ < .001). Order of treatment administration did not significantly alter the findings, and was not significantly related to the outcome.

The data from other neuropsychological tests were too limited by patient performance to allow statistical analysis. Fourteen participants between the ages 10 and 24 were assessed using standardized tests of intellectual ability, word retrieval, and attention. The Wechsler Nonverbal Scale of Intelligence was attempted at baseline. Five were unable to attend and focus. These individuals (4 children and 1 young adult) were observed by the neuropsychologist while parent/guardian responded to the interview edition of the Vineland Adaptive Behavior Scale. These participants were either too young for individually administered standardized tests of ability or were unable to attend, focus, or respond meaningfully.

Cognitive ability was determined by achieved Full Scale standard score (mean 100 $\pm$ 15) on the Wechsler Nonverbal Scale of Intelligence (mean: 52.7 $\pm$ 18.8). Of the 14 patients, one obtained a Full Scale IQ score in the average range (T1 = 93, T2 = 93, T3 = 97); for the remainder of the subjects (n = 9), the mean Full Scale IQ scores ranged from 31 to 61. The results of the Vineland were used for 4 individuals unable to respond meaningfully either verbally or in writing. The mean of the scores on Vineland Adaptive Composite for those unable to complete the Wechsler Nonverbal Scale of Intelligence was 66.6 $\pm$ 7.05 (mean = 100 $\pm$ 15). The VABS General Adaptive Composite mean of 66.6 $\pm$ 7 (mean = 100 $\pm$ 15) is in the deficient range. Examination of the results suggests that individuals generally had more well-developed social skills in the context of less well developed conceptual or practical skills.

**Table 1.** Clinical Findings, MRI Brain Findings, and ALDH5A1 Variant or Other Method of Succinic Semialdehyde Dehydrogenase Deficiency Diagnosis for each Subject.

| Patient | Clinical | Brain MRI | ALDH5A1 Variants (NM_001080.3) or other diagnosis |
|---|---|---|---|
| 1 | Developmental delay, seizures, depression | Bilateral GP increased T2 | c.612G>A (p.Trp204Ter); c.1015-2A>C |
| 2 | Global delay, juvenile rheumatoid arthritis | Bilateral GP, thalami, subthalamic nuclei increased T2 | c.803G>A (p.Gly268Glu); c.1558G>C (p.Gly520Arg) |
| 3 | Global delay, mild ataxia | Bilateral GP increased T2 | c.803G>A (p.Gly268Glu); c.1558G>C (p.Gly520Arg) |
| 4 | Global delay, seizures, strabismus, poor fine motor | Bilateral GP increased T2 | c.612G>A (p.Trp204Ter); c. 1402+2T>C |
| 5 | Global delay, strabismus, OCD, ADHD, prediabetes | Bilateral GP, dentate nuclei increased T2, deep/subcortical WM gliosis, L>R; left frontal PVWM cavitation (small) | Homozygous c.612G>A (p.Trp204Ter) |
| 6 | Global delay, ataxia, seizures | Bilateral GP, dentate increased T2 | c.104_127del (p.Ser35Ter); c.1015-2A>C |
| 7 | Global delay, seizures, ataxia, hypotonia, behavior disorder | Bilateral GP increased T2 | c.608C>T (p.Pro203Leu); c.819delT (p.Asp274Ilefs*27) |
| 8 | Global delay, ataxia, seizures, OCD, poor fine motor | Bilateral GP, subthalamic nn., superior substantia nigra, caudate, putamen, and dentate increased T2; vermian and paravermian cerebellar atrophy | Homozygous c.923G>A (p.Gly308Asp) |
| 9 | Global delay, OCD, possible seizures | Bilateral GP increase T2, watershed zone ischemia | c.278G>T (p.Cys93Phe); c.566_567insTTGCCCT (p.Val190 fs) |
| 10 | Global delay, OCD, ataxia | Normal | Enzymatic quantification |
| 11 | Global delay, behavior disorder | Not done | Enzymatic quantification |
| 12 | Mild developmental delay | Normal | Elevated urine $\gamma$-hydroxybutyrate in multiple samples |
| 13 | Global delay | Bilateral GP increased T2 | c.612G>A (p.Trp204Ter); c.1234C>T (p.Arg412Ter) |
| 14 | Global delay, hypotonia | Bilateral GP, cerebellar dentate increased T2 | c.612G>A (p.Trp204Ter); c.1234C>T (p.Arg412Ter) |
| 15 | Global delay, movement disorder | Bilateral GP, subthalamic nuclei increased T2 | c.517C>T (p.Arg173Cys); c.1015-2A>C |
| 16 | Global delay; asthma, seizures | Bilateral GP increased T2 | Homozygous c.608 C>T (p.Pro203Leu) |
| 17 | Global delay, behavior disorder | Not done | c.664delG (p.Gly222Alafs*5); c.803G>A (p.Gly268Glu) |
| 18 | Global delay | Bilateral GP, cerebellar dentate nuclei increased T2 | c.967_968dupCA (p.Gln323Hisfs*4); c.1597G>A (p.Gly533Arg) |
| 19 | Global delay, OCD, ataxia, possible Seizures | Bilateral GP increased T2 | c.803G>A (p.Gly268Glu); c.851G>A (p.Gly284Asp) |

Abbreviations: ADHD, attention deficit-hyperactivity disorder; GP, globus pallidus; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder.

**Table 2.** Baseline, Placebo, and SGS-742 Descriptives of Primary (ABAS) and Secondary (TMS) Outcome Measures With Mean, Standard Deviation, and Number Who Completed Testing.[a]

| Variable | Baseline | Placebo | SGS |
|---|---|---|---|
| ABAS | 50.5 (14.0); 17 | 58.1 (18.6); 15 | 58.7 (17.2); 15 |
| MT | 68.3 (14.9); 18 | 66.6 (14.8); 16 | 68.1 (13.2); 17 |
| PPS | | | |
|   ICF | 1.0 (46.9); 18 | 53.0 (65.6); 16 | 44.0 (61.5); 17 |
|   LICI | −10.9 (79.5); 18 | 37.7 (240); 16 | −8.34 (115); 17 |
|   SICI | −25.2 (52.0); 18 | 15.4 (120); 16 | −34.1 (46.0); 17 |

Abbreviations: ABAS, Adaptive Behavior Assessment Scale; ICF, intracortical facilitation; LICI, long-interval intracortical inhibition; MT, motor threshold; PPS, paired-pulse stimulation; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation.
[a] ABAS data are presented are the standardized scores. MT is presented as the percentage of maximum stimulator output. PPS are presented as a percentage of the baseline mean motor evoked potential elicited by stimulation at 120% of the MT.
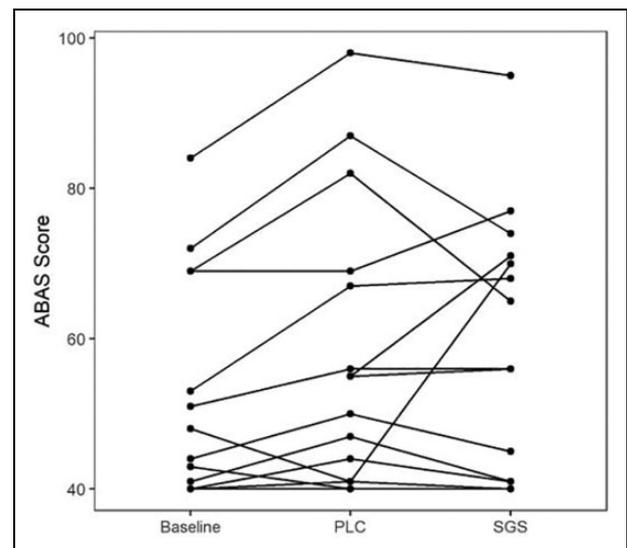


**Figure 3.** General adaptive composite standardized scores on the adaptive behavior assessment system, third edition (Adaptive Behavior Assessment Scale-3) for each subject in each condition.
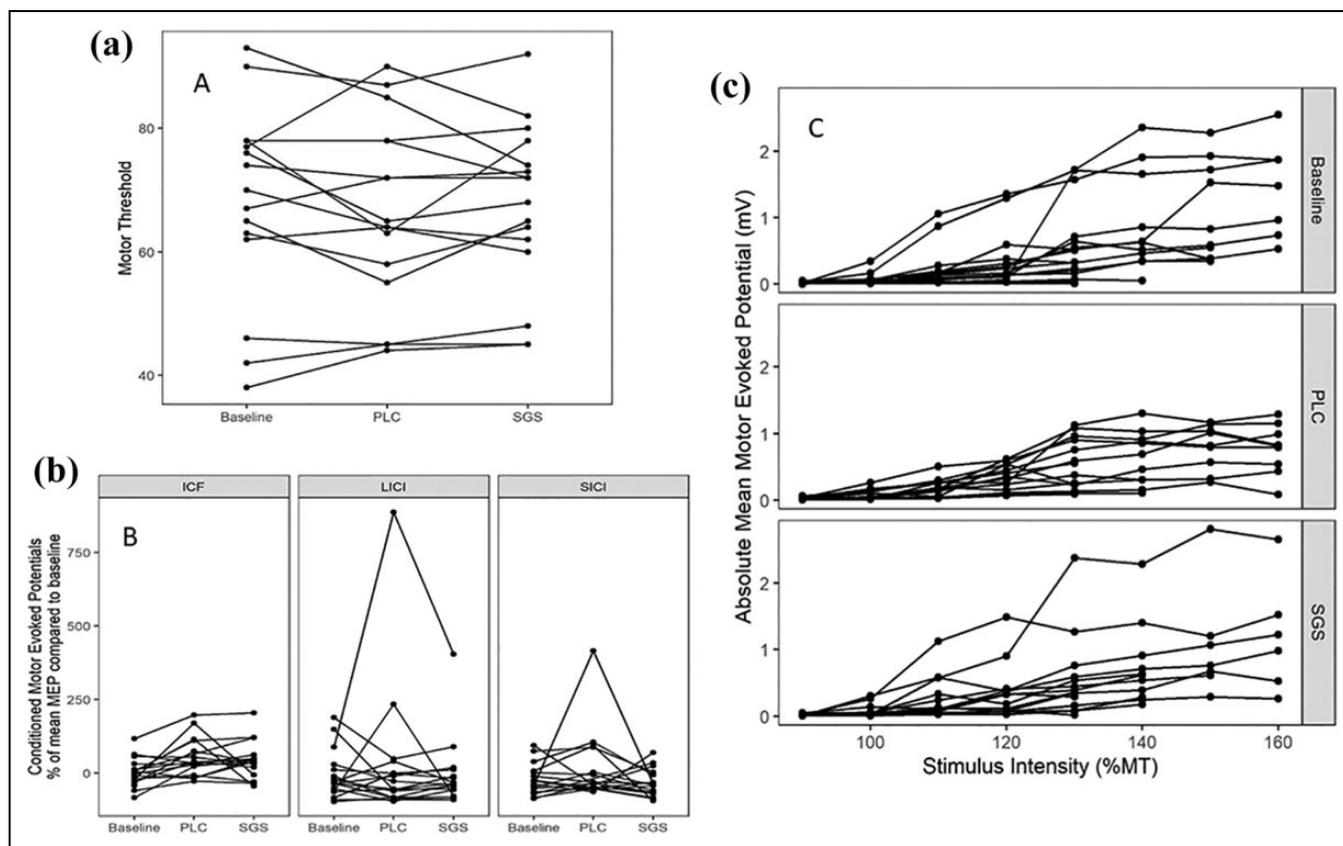
**Figure 4.** Results of transcranial magnetic stimulation. (A) Motor threshold, expressed as a percentage of maximal stimulator output for each patient in each condition. (B) Conditioned motor evoked potentials (MEP) for paired-pulse stimuli including intracortical facilitation (ICF), long-interval intracortical inhibition (LICI), and short-interval intracortical inhibition (SICI). Values are expressed as a percentage of the mean MEP compared to the baseline (conditioning) MEP in each patient for each study condition. (C) Recruitment curves for each subject across each condition, expressed as absolute mean MEP amplitude in millivolts at increasing stimulus intensities (expressed as a percentage of the motor threshold).

For those patients able to respond to the individually administered scales of intellectual ability, VABS scores were consistent with ability on the Wechsler tests. Thus, the majority (13 of 14 participants) of these subjects meet established criteria for Intellectual Disability (*Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*).

Results were similar for transcranial magnetic stimulation measures. There was no significant effect of treatment on motor threshold (Figure 3) (baseline-adjusted treatment effect = 1.22%, $P = .47$). Paired-pulse stimulation and recruitment curve results also showed no significant drug effects (Figure 4). Baseline-adjusted treatment effect was –49.4% ($P = .13$) for short-interval intracortical inhibition, –10.5% ($P = .53$) for intracortical facilitation, and –41.2% ($P = .27$) for long-interval intracortical inhibition. Results were robust to removal of a single patient outlier. The difference in recruitment curve slopes between treatment groups was 0.003 ($P = .09$).

We attempted to obtain a cortical silent period for all patients but were often unsuccessful because of lack of patient cooperation. Furthermore, there was no observational difference when we examined the results graphically. Therefore, we did not analyze the cortical silent period formally.

Five patients had a well-documented history of seizures and were taking antiseizure medications. Three of the five had seizures during the study; there was no difference in frequency or severity between active drug and placebo periods. One, not currently on treatment, had a history of past seizures, and two patients reported episodes of staring and unresponsiveness, or "spacing out," but had had previous nondiagnostic studies including 24-hour continuous EEG. Neither of these two had any observed or reported episodes during the drug study.

There was no interaction between patient age and treatment; younger patients were not more likely to show improvement in Adaptive Behavior Assessment Scale on active drug.

## Adverse Effects

Adverse effects were generally mild, usually requiring either no intervention or over-the-counter or transient medical outpatient treatment. The number of events reported per patient varied from 0 to 19. There was no difference in incidence between drug and placebo arms for any body system (Table 3). One subject had a large number of reported side effects on placebo. Two developed molluscum contagiosum. Upper

**Table 3.** Adverse Events, by System, Reported on SGS-742 and Placebo.

| System | AEs on SGS-742 | AEs on placebo | Total |
|---|---|---|---|
| CNS | 14 | 21 | 35 |
| GI | 20 | 18 | 38 |
| GU | 0 | 1 | 0 |
| HEENT | 2 | 9 | 11 |
| Infection | 7 | 16 | 23 |
| Musculoskeletal | 1 | 0 | 1 |
| Skin | 3 | 9 | 12 |
| General | 5 | 9 | 14 |
| Total | 52 | 83 | 135 |

Abbreviations: AE, adverse events; CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; HEENT, head, eyes, ears, nose and throat.

respiratory infections were common, perhaps because of the preponderance of children in the study.

Central nervous system and gastrointestinal systems were most frequently affected. Common central nervous system complaints included lethargy, fatigue, increased irritability or emotional lability, anxiety, and insomnia. The most common GI adverse events were abdominal pain, and decreased appetite; diarrhea and vomiting were reported less frequently. Two patients required transient dose reductions for gastrointestinal complaints, both while taking placebo.

Three patients were withdrawn from the study for an adverse event, two during drug treatment and one during placebo treatment. One patient developed a rash after the fourth dose of study drug. Another patient developed priapism on placebo. He was also taking risperidone. A third patient had exacerbation of a previously existing behavior disorder while on study drug. The first two adverse events resolved spontaneously, and the third after symptomatic treatment. All 16 study completers achieved and were maintained on the full goal dose of 10 mg/kg (up to 600 mg) three times daily.

### Laboratory Tests

No consistent changes in blood counts or chemistry parameters were noted in either active drug or placebo periods. Two patients had mildly elevated liver function tests (alanine amino transferase and alkaline phosphatase) on active drug, and one (alkaline phosphatase) on placebo. Eight patients had positive urine urobilinogen (6 at baseline) intermittently during the study. One had had a positive test on previous evaluation.

### EEG

One patient had only a single EEG, and two had two EEGs rather than three. There were no changes on serial records for 13 patients. Three patients had a better organized background/decreased slowing on placebo, and one on active drug, compared to baseline. Spike-wave discharges seen on the baseline EEG in the latter patient were not present on the record at the end of the active drug phase, but reappeared at the end of the placebo phase. One patient's record at the end of the placebo phase showed increased slowing and occasional interictal epileptiform discharges not present at baseline, but these features were seen as well on the EEG at the end of the active drug phase.

## Discussion

Our study failed to find an effect of SGS-742 on our primary outcome measure of the Adaptive Behavior Assessment Scale score, or on the secondary outcome measures of transcranial magnetic stimulation parameters. We enrolled only 19 subjects, with 16 completers. Nevertheless, our data do not support a current role for the drug in succinic semialdehyde dehydrogenase treatment.

The side effects we observed were expected based on previous clinical trial data. Only two patients needed dose adjustment because of gastrointestinal distress. We do not know if the patient who developed a rash on the fourth dose of SGS-742 was reacting to the active drug or to other components of the capsule. Risperidone may have been responsible for the priapism experienced by one patient. Considering reports of increased anxiety and insomnia, SGS-742 may have led to the exacerbation of the behavior disorder leading to withdrawal. The increased urine urobilinogen, present before drug initiation, was not associated with any hematologic abnormalities, and may have been due to a laboratory cross-reaction.

It is possible that the dose we used was too low to show an effect. The lack of increased reported adverse reactions with SGS-742 may lend support to this notion. However, the maximum dose achieved by patients in this study was equivalent to prior studies demonstrating clinical improvement in adults with mild cognitive impairment.[22,23]

Our underlying hypothesis and strategy of blocking GABA-B receptors may have been inadequate, or wrong. The biochemical perturbations underlying the clinical symptoms of the disorder may be too complex to respond to a single targeted approach. Oxidative damage, mitochondrial dysfunction, and aberrant lipid biosynthesis are a component of various organic acidemias, including succinic semialdehyde dehydrogenase deficiency.[33-37] Altered autophagy, mitophagy, and pexophagy, through increased GABA-mediated activation of the mTOR complex,[38] may further contribute to oxidative stress and impaired mitochondrial function, and are implicated in a variety of neurodegenerative diseases. Perhaps a multifaceted therapeutic approach addressing these mechanisms would yield positive results.

Blockade of additional receptors may be required to achieve therapeutic effects. There are multiple types of GABA-A and GABA-B receptors, in addition to GHB receptors, with different distribution and function. Succinic semialdehyde dehydrogenase deficiency results in markedly elevated cerebrospinal fluid GHB and GABA levels.[1,2,18] GABA levels are well above elevations that may be seen in other neuropediatric disorders.[39] At physiologic levels, GHB acts at high-affinity sites including GHB receptor(s), $\alpha_4\beta_1\delta$-GABA-A receptors (largely located at

extrasynaptic sites), and other unidentified GHB receptors—only about 40% of GHB high-affinity sites have been identified.[6] However, at the extreme levels of GHB seen in succinic semialdehyde dehydrogenase deficiency, GHB also activates low-affinity targets, namely, GABA-B receptors[7,40] and $\alpha_4\beta_{2/3}\delta$-GABA-A receptors. Counterintuitively, activation of these δ-preferring GABA-A receptors induces spike-wave discharges and absence seizures in naïve rats,[41] speaking to the complexity inherent in the balance of excitation and inhibition exacted through GABA.

In addition to altered GABA receptor activation, succinic semialdehyde dehydrogenase deficiency has broad effects on various neurotransmitter systems. GHB inhibits presynaptic dopamine release and potentiates dopamine turnover.[42,43] Cerebrospinal fluid metabolite profiles from 13 unrelated patients with succinic semialdehyde dehydrogenase deficiency demonstrated significantly elevated GHB (65- to 230-fold), high free and total GABA (up to 3-fold), and low glutamine.[44] These findings, including a drop in glutamine over time, have been documented in the affected animal model.[45] In addition, there was a linear correlation in both HVA and 5-HIAA levels with increasing GHB concentration, suggesting enhanced dopamine and serotonin turnover.[44] Elevated GABA combined with low glutamine suggests disruption of the glial-neuronal glutamine/GABA/glutamate shuttle necessary for replenishment of neuronal neurotransmitters.

It is also possible that the patients were already too old to benefit from the therapy, despite our inclusion of patients down to 4 years old. We did not see any age-related trends toward improvement. Multiple lines of evidence from animal models and human subjects demonstrate an early shift in GABAergic receptor activation from depolarizing to hyperpolarizing shortly after birth.[46] Use-dependent downregulation of GABA-A and GABA-B receptors occurs in the first few weeks of life in the succinic semialdehyde dehydrogenase–deficient mouse.[47,48] An age-dependent decrease in GABA and GHB levels toward more normal values follows.[49,50] This decrease in GABA and GHB levels, paired with downregulation of GABA-A and GABA-B receptors,[10,48] may explain the evolving phenotype seen in human subjects, who show more tendency toward compulsive behavior, sleep disturbance, and seizures with age.[5]

The outcome measures we used, the Adaptive Behavior Assessment Scale and transcranial magnetic stimulation parameters, may not have been sensitive enough to show therapeutic effects. Individuals with succinic semialdehyde dehydrogenase deficiency have a fairly broad range of phenotypes and cognitive abilities,[4] generally performing in the moderately impaired range,[18] making it quite challenging to select appropriate neuropsychological tests that can be compared across subjects. Unfortunately, despite incorporating multiple measures into our neuropsychological evaluation, none except the Adaptive Behavior Assessment Scale allowed for analysis because of poor patient performance. The Adaptive Behavior Assessment Scale is a widely used parent/guardian questionnaire that assesses adaptive abilities including communication,

social adaptability, and practical skills regarding their child. Items focus on practical, everyday activities required to function, care for oneself, and interact with others effectively and independently. On a 4-point response scale, raters indicate whether, and how frequently, the individual performs each activity. It is particularly useful for people with intellectual disability and can provide a measure of change in adaptive skills over time.

Transcranial magnetic stimulation provides surrogate measures of neurotransmitter system function, and has previously indicated abnormal GABA-B receptor–mediated inhibition in this population, as evidenced by shortening of the cortical silent period and loss of long-interval intracortical inhibition.[11] Other measures, including motor threshold, short-interval intracortical inhibition, intracortical facilitation, and recruitment curve, principally reflecting voltage-gated sodium channel activity, GABA-A receptor activity, and excitatory neurotransmitter function,[51] are no different among patients and controls. Because only disruption in GABA-B function in these patients has been demonstrated by transcranial magnetic stimulation, and because SGS-742 blocks both pre- and postsynaptic GABA-B receptors, the lack of normalization in the cortical silent period and long-interval intracortical inhibition may be due to these competing effects. If one could selectively block presynaptic GABA-B receptors without affecting postsynaptic GABA-B receptors, one might see the desired effect on long-interval intracortical inhibition and cortical silent period.

In conclusion, we found no change in cognition or normalization of cortical excitability as measured by the Adaptive Behavior Assessment Scale and transcranial magnetic stimulation in this randomized, placebo-controlled trial of SGS-742 in patients with succinic semialdehyde dehydrogenase deficiency. Our data do not support the current use of SGS-742 in succinic semialdehyde dehydrogenase deficiency.

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## Ethical Approval

The study was approved by the National Institutes of Health (NIH) Combined Neurosciences Institutional Review Board.

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