



SPG601-01

A Phase 2a, Randomized, Double-Blinded, Study Evaluating the Neurophysiologic vs Clinical Effects of Single-Dose SPG601 and Placebo in Adult Men with Fragile X Syndrome

| | |
|-------------------------------------|---|
| Sponsor: | Spinogenix, Inc. 1901 Avenue of the Stars Suite 200 Los Angeles, CA 90067 646-401-3122 |
| Protocol Short Title: | Phase 2a Study of Single-Dose SPG601 and Placebo in Adult Men with Fragile X Syndrome |
| Protocol Identification number: | SPG601-01 |
| IND | 169282 |
| Study Drug/Investigational Product: | SPG601 |
| Indication(s): | Fragile X Syndrome |
| Study Type: | Interventional |
| Clinical Phase: | Phase 2a |
| Date of Protocol: | 17 June 2024 |
| Protocol Version: | 1.4 |
| Amendment(s): | 1.0 |
| Principal Investigator: | <div></div> Associate Professor, UC Department of Psychiatry and Behavioural Science Director, Fragile X Syndrome Research and Treatment Center |
| Trial Site | Cincinnati Children’s Hospital Medical Center 3333 Burnet Avenue Cincinnati, OH 45229 <div></div> |

COMPLIANCE STATEMENT

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as “Guidance for Good Clinical Practice,” International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

SIGNATURE PAGE

Sponsor’s Approval

The protocol has been reviewed and approved by Spinogenix.

Responsible Medical Officer: [Redacted]

Sponsor’s Authorized Officer: [Redacted]

Ron Newbold

Signer Name: Ron Newbold
Signing Reason: I approve this document
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73E5D4FC08D84FE39EA25949B2D22BCD

19-Jun-2024 | 06:25:53 ACST

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INVESTIGATOR’S AGREEMENT

I have received and read the Investigator’s Brochure for SPG601. I have read the protocol SPG601-01 and agree to conduct the study as described.

[Redacted Signature]

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Printed Name of Investigator
Craig Erickson
Signer Name: Craig Erickson
Signing Reason: I approve this document
Signing Time: 18-Jun-2024 | 14:01:42 PDT
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Signature of Investigator

18-Jun-2024 | 14:02:03 PDT

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PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

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1. GENERAL STUDY INFORMATION

| | |
|--|---|
| Protocol Title: | A Phase 2a, Randomized, Double-Blinded, Study Evaluating the Neurophysiologic and Clinical Effects of Single-Dose SPG601 and Placebo in Adult Men with Fragile X Syndrome |
| Protocol Short Title: | Phase 2a Study of Single-Dose SPG601 and Placebo in Adult Men with Fragile X Syndrome |
| IND | 169282 |
| Name of Sponsor/Company: | Spinogenix, Inc. |
| Sponsor Study Identification Number | SPG601-01 |
| Version Number: | 1.4 |
| Version Date: | 17 Jun 2024 |
| Responsible Party Type | Industry |
| Keywords | SPG601, Fragile X Syndrome, Spinogenix, FMR1 |

2. SPONSOR CONTACT INFORMATION

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3. RESEARCH SITE LOCATION(S)

Recruitment for the study will be conducted by the Cincinnati Fragile X Research and Treatment Center.

| | |
|------------------------|---|
| Site | Cincinnati Children’s Hospital Medical Center 3333 Burnet Avenue Cincinnati OH 45229 United States |
| Principal Investigator | <div></div> <div>Associate Professor, UC Department of Psychiatry and Behavioural Science Director, Fragile X Syndrome Research and Treatment Center Cincinnati Children’s Hospital Medical Center 3333 Burnet Avenue Cincinnati OH 45229 United States</div> <div><div></div><div></div></div> |

4. ABBREVIATIONS

| | |
|------------------|--|
| ADOS | Autism Diagnostic Observation Schedule |
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| AP | Action Potential |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Concentration-Time Curve |
| BID | Dosing Performed Twice Per Day |
| CBC | Complete Blood Count |
| CCHMC | Cincinnati Children's Hospital Medical Center |
| CGI-I | Clinical Global Impressions Improvement |
| CFR | Code of Federal Regulations |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CL | Clearance |
| CLIA | Clinical Laboratory Improvement Act |
| C _{max} | Maximum Serum Concentration |
| CMP | Comprehensive Metabolic Panel |
| CNS | Central Nervous System |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DSMB | Data Safety Monitoring Board |
| EEG | Electroencephalogram |
| ECG | Electrocardiogram |
| EOG | Electroculography |
| FDA | Food and Drug Administration (US) |
| FFT | Fast Fourier Transform |
| FMRP | Fragile X Mental Retardation Protein |
| FXS | Fragile X Syndrome |
| GCP | Good Clinical Practice |
| H&P | History & Physical Exam |
| Hz | Hertz |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICF | Informed Consent Form |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| KO | Knockout |
| KPS | Karnofsky Performance Status |
| mcL | Microliter |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |

| | |
|--------------|--|
| mL | Milliliter |
| mm | Millimeter |
| ms | Millisecond |
| MS | Multiple Sclerosis |
| NIH | National Institutes of Health |
| PCR | Polymerase Chain Reaction |
| PE | Physical Exam |
| PI | Principal Investigator |
| PIV | Peripheral IV |
| PK | Pharmacokinetics |
| PO (or p.o.) | Per os/by mouth/orally |
| POC | Proof of Concept |
| PPI | Pre-Pulse Inhibition |
| PTFE | Polytetrafluoroethylene |
| QOL | Quality of Life |
| RBC | Red Blood Cells |
| RBANS | Repeatable Battery for the Assessment of Neuropsychological Status |
| SAE | Serious Adverse Event |
| SOC | System Organ Class |
| t_{\max} | Time to Reach Maximum Serum Concentration |
| TEAE | Treatment Emergent Adverse Events |
| USV | Unscheduled Visit |
| VAS | Visual Analog Scale |
| WBC | White Blood Cells, or Leukocytes |
| WHO | World Health Organization |
| WHO-DD | WHO Drug Dictionary |

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6. PROTOCOL SYNOPSIS

| | |
|------------------------------|---|
| Protocol Title: | A Phase 2a, Randomized, Double-Blinded, Study Evaluating the Neurophysiologic vs Clinical Effects of Single-Dose SPG601 and Placebo in Adult Men with Fragile X Syndrome |
| Protocol Short Title: | Phase 2a Study of Single-Dose SPG601 and Placebo in Adult Men with Fragile X Syndrome |
| Sponsor | Spinogenix, Inc. |
| Phase | Phase 2a |
| Methodology | Randomized, double-blinded, 2-period balanced crossover |
| Study Duration | 12 months |
| Investigational Product Name | SPG601 (formerly VSN16R), Placebo |
| Investigational Product Type | FDA Regulated Drug |
| Indication | Fragile X Syndrome |
| Proposed Mechanism of Action | SPG601 demonstrates high oral bioavailability, a mechanism of action (on β 4 subunits) that offsets molecular deficits present in FXS |
| Objectives | <p>Primary:</p> <ul style="list-style-type: none"> Assess the clinical efficacy of a single dose of SPG601 and Placebo in patients with Fragile X Syndrome. <p>Secondary:</p> <ul style="list-style-type: none"> Assess cognitive outcomes of a single dose of SPG601 and Placebo in patients with Fragile X Syndrome. Evaluate the safety and tolerability of SPG601 administered in patients with with Fragile X Syndrome. |
| Endpoints | <p>Primary:</p> <ul style="list-style-type: none"> Improvement in symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Clinical Global Impressions Improvement (CGI-I) scale, as determined by the treating clinician. Improvement in symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Clinical Global Impressions Improvement (CGI-I Caregiver) scale, as determined by the patient's caregiver. Improvement in anxiety symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Visual Analog Scale Caregiver (VAS Caregiver, as determined by the patient's caregiver. |

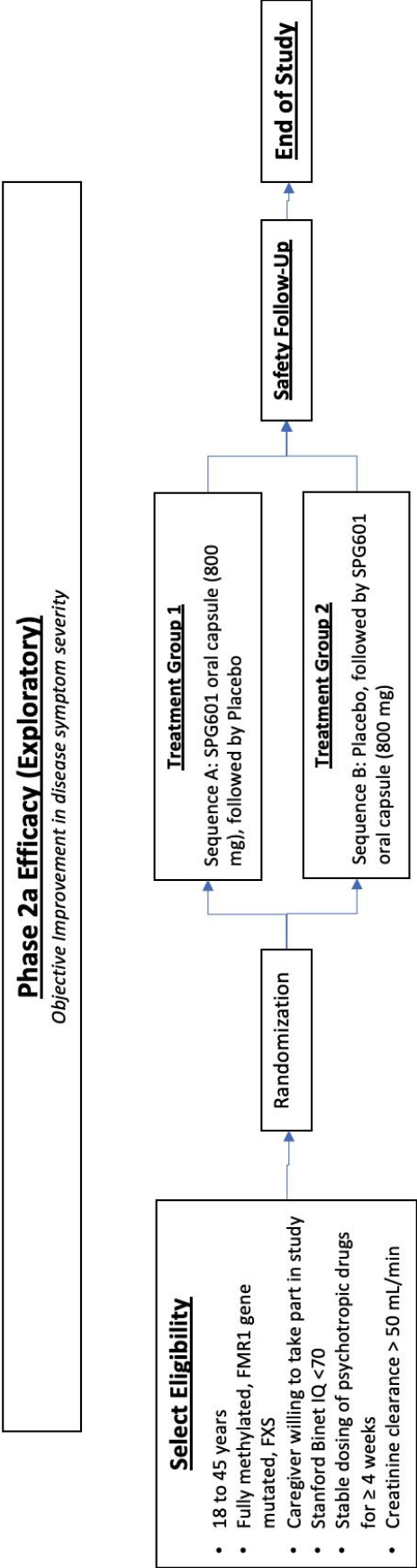
| | |
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| | <ul style="list-style-type: none"> Improvement in auditory intertrial phase coherence following treatment of a single dose of SPG601 and Placebo compared to pre-dose, in the gamma range in response to the chirp stimulus. <p>Secondary:</p> <ul style="list-style-type: none"> Improvement in attention and inhibition following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the KiTAP Test of Attentional Performance for Children. Improvement in oral reading, vocabulary, and speed matching following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the NIH Cognitive Toolbox. Improvement in social gaze aversion following treatment of a single dose of SPG601 and Placebo compared to pre-dose, assessed using eye-tracking. Improvement in immediate memory following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using RBANS: List Learning. Improvement in auditory intertrial phase coherence to the steady state stimuli and relative power in the alpha, theta, and gamma bands during rest following treatment of a single dose of SPG601 and Placebo compared to pre-dose. Improvement in electroretinography following treatment of a single dose of SPG601 and Placebo compared to pre-dose. Incidence of treatment emergent AEs, serious AEs, and AEs leading to drug interruption or discontinuation. |
| Planned Number of Sites | 1 |
| Target Study Setting | Academic medical center in the United States |
| Study Arms | |
| Number of Study Arms | 2 |
| Interventions | SPG601 100mg oral capsule (total dose 800 mg), and Placebo |
| Description of Investigational Treatment | <p>Active: SPG601 oral capsule (100 mg): SPG601 oral capsules are standard gelatin capsules containing SPG601 powder.</p> <p>SPG601 is a benzamide derivative that was designed to mimic the activity of anandamide, an agonist of the CB1 cannabinoid receptor, but which was found to lack cannabinoid activity.</p> <p>Placebo: SPG601 oral capsule (100 mg): placebo oral capsules are standard gelatin capsules containing starch with no active ingredient.</p> |
| Study Design | This Phase 2a pharmacologic study employs a randomized, double-blinded, 2-period balanced-crossover design. Ten male patients aged 18 to 45 years, with full mutation Fragile X Syndrome characterized by greater than 200 CGG repeats in the FMR1 gene |

| | |
|---------------------------|---|
| | <p>by Southern Blot and PCR genetic testing and full FMR1 gene methylation, will be recruited.</p> <p>Subjects will be randomly assigned to one of two different sequences for receiving SPG601 800mg and placebo, with a 1-week washout (± 2 days) between administrations. The study is expected to enroll 10 subjects. Once they are randomized, subjects will not be replaced. Subjects and legally authorized representatives will be informed during consent that they will be blinded to treatment status throughout the study. The timing of evaluations in relation to the single dose of each agent/placebo is guided primarily by the time to maximum plasma concentration (T_{max}) of the drug (1 hour fasted; 2 hours fed state) but is also supported by considerable preclinical and clinical literature. All subjects in this trial will be dosed in the fed state per usual clinical research standards allowing patients breakfast and snacks prior to dosing day activities. The primary outcome electroencephalogram (EEG) will be conducted 2 hours post-dosing, with post-dose clinical and cognitive evaluations being done immediately thereafter. Pharmacokinetic data regarding $\frac{1}{2}$-life of SPG601 (~3-4 hours) support a 1-week washout period between drug or placebo exposure. Exploratory outcome will be changes in electroretinography data measured at screening visit, and dosing visits.</p> |
| Number of Subjects | 10 |
| Target Patient Population | Adult men aged between 18 and 45 years |
| Eligibility Criteria | <p>Inclusion Criteria</p> <ul style="list-style-type: none"> • Patient must have a full methylated, full mutation (>200 CGG repeats) in the FMR1 gene confirmed by Southern Blot and PCR testing. • Adult males aged 18 to 45 years. • Patient must have caregiver (parent, guardian, or other legally authorized representative) who is willing to participate in the study. • Patient must be in general good health as determined by physical exam, medical history and laboratory work up. • Stanford Binet IQ <70 • Stable dosing of psychotropic drugs for at least 4 weeks. • Patient or patient's parent/legal guardian must be able to understand, and willing to sign, a written informed consent and the assent document, as appropriate. <p>Exclusion Criteria</p> <ul style="list-style-type: none"> • Subjects with a history of intolerance to SPG601 or large conductance potassium channel agonists. |

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| | <ul style="list-style-type: none"> • Subjects who have taken any investigational drug within one month of planned receipt of SPG601 and Placebo, have a history of substance abuse or dependence within six months, or significant psychiatric or CNS neurological disease unrelated to FXS. • Uncontrolled seizures or history of epilepsy with a seizure in the past 6 months. • A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds (ms). • Patients with myocardial infarction and poorly controlled arrhythmia (including QTc intervals ≥ 470 ms) (QTc intervals are calculated by Fridericia's formula) within 6 months prior to the first dose of the investigational products. • Auditory or visual impairments that cannot be corrected based on visual and auditory screener benchmarks. • Potential subjects with a creatinine clearance < 50 mL/min (calculated by Cockcroft-Gault) will be excluded. • Potential patients with eGFR <90mL/min will be excluded. • Potential patients with mild, moderate, and severe hepatic impairment, corresponding to 5-6, 7-9 and 10-15 Child-Pugh scores, will be excluded. • Columbia Suicide Severity Risk Scale (or equivalent) score of Category 2- "suicidal ideation." • Identified medical issues, inability to tolerate study procedures or study drug, or risk of suicidality per the discretion of the Principal Investigator. |
| Length of Study | 12 months |
| Investigational Medical Product(s) Dose/Route/Regimen | SPG601 100 mg oral capsule (800 mg dose), and placebo |
| Comparator Product (or Standard of Care) Dose/Route/Regimen | Alternate sequence for receiving SPG601 100 mg oral capsule (800 mg dose), and placebo |
| Randomization | Subjects will be randomly assigned 1:1 to one of two different sequences for receiving SPG601 100 mg oral capsule (800 mg dose), and placebo |
| <u>Statistical Method</u> | A 2-drug/placebo, 2-period, 2-sequence balanced-crossover design (Williams, 1989) will be used for the proposed pharmacologic study. |

7. STUDY SCHEMA

Figure 1: SPG601-01 Study Schema



8. INTRODUCTION

8.1 Background Information

Spinogenix, Inc. (Spinogenix) is developing SPG601 for treatment of Fragile X Syndrome (FXS), using an oral capsule route of administration. SPG601 is a benzamide derivative that was designed to mimic the activity of anandamide, an agonist of the CB1 cannabinoid receptor, but which was found to lack cannabinoid activity. It has a molecular weight of 318.41 Da. It is a white to off-white powder that is freely soluble in water (>100 uM). SPG601 is formulated as the drug substance in gelatin capsules and administered orally.

The Fragile X Syndrome is characterised by intellectual disability, behavioural features, and physical features, such as a long face with large protruding ears and macro-orchidism. In 1991 it was discovered that a large CGG triplet repeat expansion in the promoter region of the FMR1 gene in FXS results in reduced or extinct FMR1 RNA transcription and subsequent deficit in FMRP production.

Prior research has documented that pharmacological strategies targeting different neural mechanisms can reduce neocortical hyper-excitability in *Fmr1* knockout (KO) mouse models. Unlike nearly all areas of clinical psychopharmacology, marked to full recovery of function has been shown within hours of drug administration in animal models. We propose to leverage that observation to investigate single-dose drug effects on EEG biomarkers and behavior in humans with FXS.

FMR1 gene full mutation leads to a cascade of brain changes, which offer multiple potential pharmacologic targets to treat functional deficits associated with FXS (Wijetunge, Chattarji, Wyllie, & Kind, 2013). This study is designed to investigate clinical homologues in sensory processing abnormalities that can provide more sensitive and mechanism-related assessments of pharmacologic effects. The study will evaluate single-dose drug effects on a core symptom of FXS, auditory hypersensitivity, using robust EEG measures of auditory response that translate from mouse models to humans and back. Specifically, the study will evaluate the effects of a single-dose approach to test drug effects on putative EEG biomarkers and behavior of patients with FXS.

In 2009, Berry-Kravis et al. (Berry-Kravis et al., 2009) reported that a single oral dose of fenobam, an mGluR5 antagonist (Porter et al., 2005), was well tolerated and resulted in response (defined as 20% improvement) in auditory pre-pulse inhibition (PPI). These PPI effects were demonstrated just 60 minutes after oral dosing (Berry-Kravis et al., 2009). This study lays a foundation for using acute pharmacologic studies to probe putative etiologic pathways of FXS. Spinogenix intend to extend this pharmacologic strategy to test the neurophysiologic effects of multiple drugs targeting different mechanisms in the same patients.

BK Channel Target Justification

BK channels (also referred to as Slo1 and Maxi-K channels) are large conductance, Ca^{++} -activated potassium channels comprised of a homotetrameric assembly of a subunit encoded by the *Kcnma1a* gene and associated regulatory b and g subunits encoded by multiple genes. Localized predominantly to presynaptic terminals, BK channels are activated by depolarization and Ca^{++} entry (Ancatén-González et al. 2023). The resulting large K^+ conductance contributes to fast afterhyperpolarization and the regulation of glutamate release and action potential broadening. These regulatory influences of BK channels at the presynaptic terminal are involved in a wide range of local and circuit level dynamics in information processing and plasticity, particularly in the context of high frequency trains of neural activity (Deng et al. 2013; Ferron 2016; Ancatén-González et al. 2023; Gonzalez-Perez and Lingle 2019). Functional diversity of BK channels is imparted by alternative splicing of *Kcnma1a* transcripts and by cell type and tissue specific differences in the expression of regulatory b and g subunits (Gonzalez-Perez and Lingle 2019). In brain, the dominant BK channel regulatory subunit is b4, which attenuates BK channel function (Adelman et al. 1992; Behrens et al. 2000; Gonzalez-Perez and Lingle 2019).

A broad set of complementary findings at the molecular, electrophysiological, genetic and behavioral levels have provided strong support for the hypothesis that positive modulation of BK channels may be an effective therapeutic approach in FXS. At a molecular level, there is evidence that FXS impairs BK channel activity in two ways. First, early studies of the synaptic proteome in FXS revealed that *Kcnma1a* protein expression is reduced by ~50% (Liao et al. 2008). In light of a prior report on haploinsufficiency of the *Kcnma1a* gene in individuals with autism and intellectual disability (Laumonnier et al. 2006), this suggested that impaired translation of *Kcnma1a* in FXS may mimic haploinsufficiency in contributing to autism and ID symptoms. Second, it has been established that translation-independent effects of FMRP loss impair BK channel function in FXS. FMRP is a positive modulator of BK channels, increasing the Ca^{++} sensitivity and altering the gating kinetics of BK channels through direct associations with b4 subunits (Deng et al. 2013; Deng and Klyachko 2016) and a1 subunits (Kshatri et al. 2020); the more prominent effect is seen for b4-containing channels (Kshatri et al. 2020; Deng and Klyachko 2016; Myrick et al. 2015). Accordingly, studies in *Fmr1* KO mice have demonstrated an increase in action potential (AP) broadening during high frequency transmission, along with increases in glutamate release (Deng et al. 2013; Deng and Klyachko 2016; Myrick et al. 2015; Griguoli, Sgritta, and Cherubini 2016) and seizure susceptibility (Deng and Klyachko 2016). Genetic upregulation of BK channel activity by deletion of the b4 subunit rescued these synaptic and circuit phenotypes (Deng and Klyachko 2016). Further highlighting the importance of the b4 subunit, a mutation in FMRP (R138Q) associated with intellectual disability that blocks its association with the b4 subunit, while sparing its translational regulatory activity, results in channel hypoactivity and attendant AP broadening (Myrick et al. 2015). At a circuit level, knockdown of the b4 subunit in *Fmr1* KO mice rescued synaptic integration defects in layer V pyramidal cells that may play a role in sensory symptoms of FXS (Mitchell et al. 2023). Pharmacological rescue of synaptic and behavioral phenotypes of the *Fmr1* KO mouse has been demonstrated using BMS-204352, a clinical stage BK channel opener that was originally developed for stroke, but failed to meet endpoints and was not suitable for clinical development in chronic

indications such as FXS due to oral bioavailability limitations (Hebert et al. 2014). In the *Fmr1* KO mouse, this compound was also reported to rescue cortical circuit abnormalities thought to be related to sensory hypersensitivity in FXS (Carreno-Munoz et al. 2018). Pharmacological augmentation of BK channel function in the *Fmr1* KO mouse has also been shown to improve cochlear sensory abnormalities implicated in hyperacusis (Ferraguto et al. 2023). Recently, the novel small molecule SPG601 (VSN16R), a BK channel opener acting on the b4 subunit (Tabatabaee et al. 2019; Baker et al. 2017; Pryce et al. 2023), was found to rescue a range of behavioral phenotypes in the *Fmr1* KO mouse, including: activities of daily living, hyperactivity and memory (Hurley et al. 2022). SPG601 demonstrates high oral bioavailability, a mechanism of action (on b4 subunits) that offsets molecular deficits present in FXS, and a very favorable safety profile as demonstrated in a Phase 1 trial (EudraCT 2013-002765-18) and a Phase 2 trial in spasticity related to multiple sclerosis (NCT02542787). These properties of SPG601 make it a viable candidate for clinical development in FXS.

This pharmacologic study is designed to leverage clinical and preclinical preliminary data showing robust acute drug effects on neurophysiological parameters. If our strategy of single-dose rapid testing of drug effects on EEG biomarkers is effective, the approach would inform preclinical work on the mechanisms most relevant to auditory hyper-excitability, speed the identification of effective pharmacologic treatments, develop an urgently needed biomarker strategy for predicting and evaluating drug effects, and ultimately, could allow for rapid personalization of treatment in FXS.

8.2 Description and Justification for Dosage and Route of Administration

SPG601 drug product is an oral capsule for oral administration. It will be provided to the clinical site pharmacy in a single formulation of 100 mg.

A single dose using SPG601 will be administered orally, and placebo. Subjects will be randomly assigned to one of two different sequences for receiving SPG601 800 mg and placebo, with a 1-week washout (± 2 days) between administrations.

8.3 Disease Background

FXS is a family of genetic conditions caused by mutations in the FMR1 gene. FXS is the most prevalent cause of inherited intellectual disability (Crawford, Acuna, & Sherman, 2001). Approximately 1:4,000 males and 1:8,000 females have FXS (Crawford et al., 2001). This impairment ranges from learning disabilities to severe intellectual disability. Between 15% and 60% of individuals with FXS have autism (Budimirovic & Kaufmann, 2011). Other symptoms also can include characteristic physical (e.g. elongated face, prominent ears, and enlarged testes) and behavioral (e.g. stereotypic movements and social anxiety) features. Sensory hypersensitivities are an especially common, clinically distressing feature of FXS.

Prior research has documented that pharmacological strategies targeting different neural mechanisms can reduce neocortical hyper-excitability in *Fmr1* KO mouse models. Unlike nearly all areas of clinical psychopharmacology, marked to full recovery of function has been

shown within hours of drug administration in animal models. We propose to leverage that observation to investigate single-dose drug effects on EEG biomarkers and behavior in humans with FXS.

8.4 Prior studies with Investigational Product

The pharmacokinetics and safety profile of SPG601 have been evaluated in healthy volunteers at doses up to 800 mg. One Phase 1 study in healthy subjects has been completed to date with SPG601. This study evaluated the safety and pharmacokinetics of single and multiple ascending doses of SPG601 as well as the effect of food intake on the pharmacokinetics of SPG601. All enrolled subjects were healthy male subjects.

8.5 Summary of Clinical and Non-Clinical Findings

Non-Clinical Findings

Some initial non-clinical studies conducted in relation to the SPG601 product used a racemic mixture (VSN16), whilst later studies use either the (R) or (S)-enantiomer. The (R) -enantiomer was found to have a slightly higher potency than the (S) in two of the key early non-clinical studies; mesenteric artery vasorelaxation in vitro, and the anti-spasticity in vivo model.

The duration of the animal studies was based on the intended exposure in the initial clinical studies and toxicology studies have been performed in rat (1 month) and dog (1 month). In clinical trials, SPG601 is administered as a capsule, and hence non-clinical studies have been conducted accordingly, using the oral route of administration.

Investigations into the bioavailability of SPG601 in animal studies have demonstrated high levels of systemic exposure from the oral route in all species tested. These investigations also demonstrated that there may be a reduction in exposure during chronic dosing (with the exception of female dogs) and a trend towards supra-proportional increase in AUC levels with increasing dose.



The Investigational Brochure provides details of the non-clinical pharmacology, metabolism, pharmacokinetic and toxicology data that support the use of SPG601 for the treatment of

FXS.

Clinical Findings

SPG601 has been studied in a Phase 1 study, with a total of 60 healthy male subjects (aged between 18 to 50) having received SPG601 either as a single oral dose of between 25 and 800 mg, or as a twice daily oral dose of between 25 and 400 mg (b.i.d.) for 7 consecutive days. Taken together, the available safety data showed that single doses of SPG601 up to and including 800 mg (Part A) and multiple doses up to and including 400 mg b.i.d. (12-hourly for 13 doses; Part B) were well tolerated with no obvious effect of food on the safety and tolerability of SPG601 at a dose of 200 mg. All of the TEAEs reported by the SPG601-treated subjects were of mild intensity and there were no clinically relevant laboratory safety test results, vital signs, ECG findings or physical examination results following treatment with SPG601 in either Part A or Part B of the study.



SPG601 has also been studied in a Phase 2 clinical trial for the treatment of Multiple Sclerosis. This Proof of Concept (POC) study intended to show the effect of SPG601 on spasticity in subjects with MS. The study consisted of a screening period, two washout periods and two treatment periods, giving 21 days of comparative safety and efficacy data on SPG601 versus placebo.

The treatment phases were an ascending single dose-escalation phase (Study Period II) (first 50 patients recruited), followed by a stable dosing placebo-controlled phase (Study Period III). This enabled assessment of within-subject dose effect and ongoing safety and efficacy of treatment. Overall, the study periods were:

Study Period I: At V1 subjects were screened; inclusion and exclusion criteria checked, and excluded medications washed out. Key spasticity measurement NRS, spasm count, and pain assessed by a VAS were recorded during 7 days prior to randomization. An experienced neurologist or neuro-physiotherapist assessed spasticity using a mASH and mTS at V2.

Study Period II: The first 50 patients completed this period, consisting of a 5-day dose escalation period during which subjects received 4 ascending doses of the study drug and a placebo dose, which was randomly assigned within the dose escalation period. Efficacy and safety data were recorded at each dose level (100mg, 200mg, 400mg, and 800mg and placebo). Serial blood samples at 0 [pre-dose], 1, 3 and 6 hours post-dosing; and 9 and 24 hours post-dose were taken for PK analysis in the first 10 randomised subjects.

The 400mg BID dose of SPG601 did not show activity in reducing spasticity in MS patients. Efficacy could not be demonstrated in the planned analyses during repeated dosing at 400mg BID.

The 800 mg dose of SPG601, investigated in the dose escalation phase, showed sustained activity through 6 hours in comparison to placebo and all lower doses, although this did not reach statistical significance. However, in the 8 evaluable patients with PK and NRS data following the 800 mg dose, there appeared to be a relationship between peak plasma concentrations of SPG601 and maximal reduction in NRS post-dose (Pearson correlation coefficient: -0.743, $p < 0.035$). Maximal responses $> 20\%$ were seen in 4/4 patients with plasma concentrations above 6000 ng/mL but only 1/4 patients with plasma concentrations below 6000 ng/mL. It was determined this potential for efficacy at doses of 800 mg and higher warrants further investigation.

SPG601 was generally well tolerated. Most TEAEs were mild or moderate and not related to study drug, with no unexpected clinically significant changes in vital signs or clinical laboratory parameters. There were no severe events during treatment with SPG601 and no SAE were considered related to SPG601.

Previously Observed Adverse Events

A single Phase 1, double blind, placebo controlled clinical study (QLON-2013-VSN16R-001) has been completed which included a total of 80 healthy adult male subjects ranged in age from 18 to 50 years. In Part A, single ascending doses of SPG601 were evaluated in healthy subjects fasted or fed ($n=6$ per active treatment, $n=2$ placebo). In Part B, multiple ascending doses of SPG601 were administered b.i.d. on Days 1 to 6 (12 hours apart) followed by a single dose on Day 7.

In the SAD study (Part A), 36 fasted subjects received single oral doses of 25, 50, 100, 200, 400 or 800 mg of SPG601, and 6 subjects received a single dose of 200 mg after a high fat meal, while the other 14 subjects received a single dose of placebo. All subjects completed the study as planned. Single doses of SPG601, up to and including 800 mg, were well tolerated by all subjects. In total, 8 treatment-emergent adverse events (TEAEs) were reported by 6/42 (14.3%) SPG601-treated subjects, with the greatest number of subjects having reported TEAEs at the highest (800 mg) dose (2/6 subjects (33.3%)). In total 5/8 of

TEAEs reported by 5/42 SPG601 subjects (11.9%) were considered to have a possible relationship to treatment (none was considered to be definitely related).

Treatment-related TEAEs were dizziness postural (1 subject at 25 mg), dizziness (1 subject at 50 mg), headache (1 subject at 200 mg, fasted), dyspepsia (1 subject at 800 mg) and nausea (1 subject at 800 mg). There were no clinically relevant laboratory safety test results, vital signs, ECG findings or physical examination results following treatment with SPG601 in Part A. Treatment-emergent AEs were reported by 1/6 subjects (16.7%) in each of the 200 mg (fasted) and 200 mg (fed) treatment groups. All of the TEAEs reported by the SPG601-treated subjects were of mild intensity.

In the MAD study (Part B), 18 subjects received 12-hourly multiple doses of SPG601 (25, 100 or 400 mg b.i.d., 12 hours apart) and 6 subjects received 12 hourly doses of placebo. All doses of SPG601 were well tolerated by the healthy male subjects. A total of 10 TEAEs were reported by 6/18 SPG601 subjects (33.3%) and 3 TEAEs were reported by 2/6 (33.3%) placebo subjects. There was no consistent relationship between the number and percent of subjects reporting TEAEs and the dose of SPG601 with the greatest number of subjects (3/6 (50.0%)) having reported TEAEs after receiving the lowest dose (25 mg b.i.d.). All of the TEAEs reported by the SPG601 subjects were of mild intensity. In total 5/10 TEAEs reported by 3/18 SPG601 subjects (16.7%) were considered to have a possible relationship to treatment (none was considered to be definitely related). Treatment-related TEAEs reported by SPG601 subjects were: oropharyngeal pain and rhinitis (1 subject at 25 mg b.i.d.), abdominal distension (1 subject at 25 mg b.i.d.), abdominal pain and nausea (1 subject at 400 mg b.i.d.). There were no clinically relevant laboratory safety test results, vital signs, ECG findings or physical examination results following treatment with SPG601 in Part B.

Taken together, the available safety data collected from subjects receiving either single or repeated doses of SPG601 in this Phase 1 study showed that single doses of SPG601 up to and including 800 mg (Part A) and multiple doses up to and including 400 mg b.i.d. (12-hourly for 13 doses; Part B) were well tolerated by the healthy male subjects. There was no obvious effect of food on the safety and tolerability of SPG601 at a dose of 200 mg.

Overall, analysis of the results following administration of single (25-800 mg) and repeated (25-400 mg b.i.d.) doses of SPG601 in 60 healthy male adult subjects indicated that SPG601 was well tolerated with a good preliminary safety profile. All of the TEAEs reported by the SPG601-treated subjects were of mild intensity and there were no clinically relevant laboratory safety test results, vital signs, ECG findings or physical examination results following treatment with SPG601 in either Part A or Part B of the study.

8.6 Study Rationale, Summary of Known and Potential Risks and Benefits

Study Rationale

Prior research has documented that pharmacological strategies targeting different neural mechanisms can reduce neocortical hyper-excitability in *Fmr1* knockout (KO) mouse models. Unlike nearly all areas of clinical psychopharmacology, marked to full recovery of function has been shown within hours of drug administration in animal models. Spinogenix proposes to leverage that observation to investigate single-dose drug effects on EEG biomarkers and behavior in humans with FXS.

Data from this proposed single dose study will be used to justify and aid the study design of future potential multi-dose study of SPG601 in FXS if this is justified by the data generated from this study. In short, Spinogenix are attempting to establish potential efficacy in a population of patients that can benefit from the investigational product in the smallest number of patients and with the fewest number of doses possible.

The patients who consent to participate in this study will receive a single dose of SPG601 whose tolerability was demonstrated in pre-clinical studies, in a Phase I multiple sclerosis study and in a Phase II multiple sclerosis trial (IND2014-004412-11) (104 patients received SPG601 up to 800mg per day).

Overall, in the Phase I trial SPG601 was well tolerated.

The Phase II trial consisted of an initial placebo-controlled single escalating dose study following by a placebo-controlled 400mg BID chronic daily dosing component (21-day fixed dose). The only potential clinically relevant finding from the Phase II program was a trend towards 800mg of single dose SPG601 reducing spasticity compared to placebo. Given the nature of our human subjects' research population, this study will dose patients in the fed state and the study is designed to begin post-dose EEG testing 2 hours after dosing at the time of T_{max} in the fed state.

Starting with a multi dose trial of SPG601 without first demonstrating activity adult patients with FXS has the potential of exposing the population to o risks of an investigational product not fully demonstrated to be efficacious. By conducting the proposed single-dose study, the study design reduces the potential risks to a vulnerable patient population as Spinogenix develop a needed therapeutic in the setting.

Given the severity of impairments associated with FXS, this has the potential to dramatically impact the lives of affected individuals and their families. Given the potential for gain, the relatively modest risks are reasonable for the study participants, most of whom would stand to receive personal gains if the product is safe to administer as a single dose, can improve clinical symptoms and can safely be studied in a repeat dosing study.

Study Drug

All participants will receive a single dose of SPG601 (formerly VSN16R) a potassium channel agonist whose tolerability was demonstrated in Phase I study and in a Phase II trial (IND2014-004412-11) focused on the treatment of spasticity in multiple sclerosis (104 patients received SPG601 up to 800mg per day). Overall, in the Phase I trial SPG601 was well tolerated.

The Phase II trial consisted of an initial (referred to below as "Study Period II") placebo-controlled single escalating dose study following by a placebo-controlled 400mg BID chronic

daily dosing component (21-day fixed dose; referred to below as “Study Period III”). The only potential clinically relevant finding from the entire Phase II program was a trend towards 800mg of single dose SPG601 reducing spasticity compared to placebo. Regarding pharmacokinetics, SPG601 has an established T_{max} of 1 hour in the fasted state and 2 hours in the fed state. Given the nature of our human subjects research population, we dose patients in the fed state and our project is designed to begin post-dose EEG testing 2 hours after dosing at the time of T_{max} in the fed state. Treatment emergent adverse effects (TEAEs) from the Phase II study of SPG601 in multiple sclerosis are summarized below.

Table 2: Overview of TEAE During Study Period II

| Overview of TEAE during Study Period II | VSN16R | | | | Placebo |
|--|------------|-------------|------------|-----------|-------------|
| Dose (mg , OD) | 100 mg | 200 mg | 400 mg | 800 mg | 0 mg |
| N | N = 52 | N = 53 | N = 52 | N = 52 | N = 53 |
| Number of Treatment - Emergent AE (TEAE) * | 9 | 13 | 8 | 5 | 15 |
| Subjects with | | | | | |
| TEAE | 7 (13.5) | 11 (20.8) | 7 (13.5) | 5 (9.6) | 12 (22.6) |
| TEAE Leading to Early Termination | 0 | 0 | 0 | 0 | 0 |
| Serious TEAE | 0 | 0 | 0 | 0 | 0 |
| Drug - related TEAE | 5 (9.6) | 8 (15.1) | 5 (9.6) | 2 (3.8) | 11 (20.8) |
| Severe TEAE | 0 | 0 | 0 | 0 | 0 |
| Death | 0 | 0 | 0 | 0 | 0 |

Table 3: Overview of TEAE During Study Period III

| Overview of TEAE during Study Period III | mg N = 77 BID | Placebo N = 79 |
|--|---------------------|-------------------|
| Number of Treatment - Emergent AE (TEAE) * | 121 | 118 . |
| Subjects with | | |
| TEAE | 51 (66.2) | 46 (58.2) |
| TEAE Leading to Early Termination | 0 | 0 |
| Serious TEAE | 0 | 0 |
| Drug - related TEAE | 34 (44.2) | 34 (43.0) |
| Severe TEAE | 0 | 1 (1.3) |
| Death | 0 | 0 |
| TEAE in > 5 % of patients in either group | | |
| Headache | 14 (18.2) | 14 (17.7) |
| Fall | 5 (6.5) | 7 (8.9) |
| Nasopharyngitis | 11 (14.3) | 0 |
| Fatigue | 3 (3.9) | 4 (5.1) |
| Pruritus | 1 (1.3) | 5 (6.3) |
| Pollakiuria | 4 (5.2) | 1 (1.3) |
| Urinary tract infection | 0 | 4 (5.1) |
| Hot flush | 0 | 4 (5.1) |

Cognitive Testing

There are minimal risks anticipated to individuals participating in observational or clinical behavioral assessments. In the rare case that an individual becomes overly fatigued or distressed during assessment sessions, the session will be discontinued and rescheduled. Evaluation procedures, when appropriate, are designed in a way that is compatible with the attention span of a person with an intellectual disability, greater activity level, and need for access to his or her parents. In addition, specialized procedures for caregivers of patients with

FXS (e.g., reducing language demands, providing praise for task attention and attempts, using work-reward routines) will be utilized consistent with previous clinical experience at this site in this field. Three clinical psychology investigators with extensive experience working clinically with developmentally disabled patients are investigators in the study and implement these supportive procedures.

Neurophysiology Procedures

There are minimal risks associated with participation in the neurophysiology part of the study. The auditory stimuli presented are relatively benign and have been well tolerated in our pilot studies. We are sensitive to monitoring participant distress associated with sensory paradigms, which we have found more commonly in participants younger than 12 years of age. The most common risk associated with these tasks is boredom. In rare circumstances, the saline solution used to place the recording electrodes to the scalp can cause minor irritation to the skin, which resolves rapidly with no permanent effects.

Pregnancy and Protection against Risk

This study will be conducted in male subjects between the ages of 18 and 45 years. These individuals could engage in sexual activity resulting in pregnancy. The study team will stress the importance of preventing pregnancy during the course of participation in this study and for thirty (30) days following participation to reduce risks to an unborn fetus. Barrier contraception will be discussed with the patients during the consent process and will be described in the consent form. Caregivers will also be informed of the importance of preventing pregnancy during participation in this study.

Risk of Discrimination

There is a theoretical risk for discrimination towards individuals who are at risk for a medical disorder or have a medical disorder in their family. Potential discrimination may include barriers to insurability, employability, or other unidentified adverse effects. Extensive efforts are made to protect all research subjects from prejudice, discrimination, or uses of this information that will adversely affect them. Patients' decision to participate in this study will have no impact on availability of care and will be informed of such by the study team and in the consent form.

Venipuncture and Peripheral IV Placement Safety

The risks of venipuncture/peripheral IV (PIV) placement are modest and include mild discomfort, infection, bleeding, and fainting. Standard methods and precautions will be used to protect the puncture site from bleeding and infection. The Research Coordinator or Research Assistant will be familiar with the subjects and will accompany the subject and their parents to the blood drawing setting. Parents are encouraged to remain with the subject at all times. To minimize the subject's anxiety and phobic reactions, we utilize Child Life personnel when needed and available. We also suggest that the parents reassure the subject concerning their safety. At the discretion of the nurse or the investigator, to help reduce pain at the site of the venipuncture, we will offer the use of a topical anesthetic.

Procedures for Protecting Against and Minimizing Potential Risks

Effective screening will be used to eliminate subjects who are at greatest risk because of concurrent medical conditions. The subjects will be evaluated and cared for in an advanced well-staffed pediatric neuropsychiatric research environment. Thus, the direct observation by nursing staff and research psychiatrists will allow for careful monitoring of potential adverse effects including drug side effects. During study visits, subjects will be allowed to leave the research clinic, but will be asked to remain on the hospital campus. If adverse reactions become excessive, the subject will be treated and removed from the study. There will be repeated monitoring of behavior and vital signs that will allow the treatment team to assess the status of the subject and alter or terminate the study if this is warranted. All of the research data is kept in locked files to ensure confidentiality. The other procedures to ensure confidentiality follow the regulations and policies of the Medical Center.

All SAEs will be reviewed in detail by the PIs and chair of the DSMB. If the stopping rule is met, the study will close to enrollment for interim analysis of safety and efficacy data and the DSMB would provide a recommendation to the PI regarding continuation of the trial.

Suicide Risk

Suicidality is an aspect of psychiatric care in FXS that requires monitoring. At least 5% of patients with FXTAS and comorbid psychiatric disorders have reported suicidal ideation (Seritan et al, 2013).

The FDA issued a draft guidance document in August 2012 encouraging prospective collection of suicide risk in certain populations and drug therapies (FDA 2012). They recommended the use of the Columbia Suicide Risk Rating Scale and accepted the distinction between ideation, behavior and self-injurious behavior, no suicide intent. The following 11 categories of suicidal ideation and behavior subtypes have been designated as their standard:

Suicidal ideation:

1. Passive
2. Active: Nonspecific (no method, intent, or plan)
3. Active: Method, but no intent or plan
4. Active: Method and intent, but no plan
5. Active: Method, intent, and plan

Suicidal behavior:

1. Completed suicide
2. Suicide attempt
3. Interrupted attempt
4. Aborted attempt

5. Preparatory actions toward imminent suicidal behaviors 6. Self-injurious behavior, no suicidal intent

The Sponsor has conducted a product and study risk analysis. Causation between suicidal ideation, behavior, and study interventions has been deemed unlikely, as the interventions being studied are validated through clinical research, have shown no previous history of increased suicide risk in studied populations, will be adjunctive to current usual care, and will be used under clinician supervision.

However, given 1) aforementioned literature observing the correlation between FXS and suicide, 2) FDA draft guidance on prospective data collection for certain populations, and 3) target study population cohort, the Sponsor has decided to prospectively collect suicidal ideation and behavior data post each treatment dose, for all participants using the Columbia Suicide Risk Rating Scale instrument.

Respondents/Participants who indicate Suicidal Ideation Category 2 *Active: Nonspecific (no method, intent, or plan)* or greater, OR *Suicidal behavior* OR *Self-injurious behavior, no suicidal intent*, will be screen failed or withdrawn from the study AND will be triaged to a clinician for further psychological assessment and medical care according to an established physical and mental distress protocol within your institution. Treatment decisions, plans, and processes should be implemented according to approved institutional policies/SOPs and professional guidelines for mental distress.

The C-SSRS assessment will be conducted only if the patient is capable of understanding and answering the questions, in the Investigator's opinion. For patients who are not capable of understanding and answering the questions, the investigator will document a clinical note evaluating whether increased concern for suicidality or self-harm has occurred based on the investigator's interview of the subject, collateral information from the caregiver, and by direct observation. If a participant demonstrates possible evidence of suicidality based on indicated C-SSRS responses or based on clinical evaluation for those unable to complete the C-SSRS, clinical safety for the participant should be ascertained and established with immediacy (i.e. a safe holding environment), followed by an immediate clinical assessment performed to assess the risk of suicide, including a pertinent detailed history (intent, means, likelihood, impulsivity). If clinically indicated, urgent referral to a licensed mental health professional may be advisable (depending on the investigator's training and background), and the participant's safe transfer to an emergency department or behavioral health facility should be considered as a possible immediate clinical option in the event that such action is deemed warranted by the investigator. Documentation of the results of the assessment and actions taken should be appropriately recorded.

Potential Benefits:

Subjects may or may not benefit directly from study participation. The possibility of contributing to the discovery of treatments for FXS may benefit all affected individuals and their families.

The following knowledge can be gained from this research: a more detailed understanding of auditory processing abnormalities in FXS, a better understanding of the pathophysiology of FXS, new perspectives on pharmacologic mechanisms in FXS, and insight into possible biomarkers that can be used to track drug effects in FXS.

The potential gain in knowledge can change our clinical understanding and treatment of FXS and related disorders. This knowledge has the potential to inform further controlled studies that could lead to more effective treatments and possibly earlier identification and personalized treatment for patients. Given the severity of impairments associated with FXS, this could dramatically impact the lives of affected individuals and their families. Given the potential for gain, the relatively modest risks are reasonable for the study participants, most of whom stand to receive modest personal gains by participating in the research.

Risk vs Benefit Ratio

The subjects will be exposed to the risks of blood sampling and the potential side effects of SPG601. For the patients, the benefits potentially offsetting this will be a more intensive and thorough psychiatric and medical evaluation, future availability of a documented objective treatment trial, and the possibility of more accurate prescription of treatment designed to meet the individual subject's needs. Since some of the subjects will have had previous drug trials with poor response or intolerable or dangerous side effects, the opportunity for a more thorough evaluation and clinical trial may be beneficial. Thus, with the risk of drug treatment minimized, the more intensive evaluation and treatment may compensate for the negative risks. The overall benefit to family members and society is considerable.

8.7 Compliance Statement

This study will be conducted in compliance with the protocol, International Conference on Harmonization Guidelines for Good Clinical Practice (GCP), and the applicable FDA regulatory requirement(s).

8.8 Study Population

Male patients greater than 18 years of age and less than or equal to 45 years of age and have a full methylated, full mutation (>200 CGG repeats) in the FMR1 gene confirmed by Southern Blot and PCR testing. All patients must be in general good health as determined by physical exam, have a Stanford Binet IQ <70, and be on a stable dosing of psychotropic drugs for at least 4 weeks.

The patient must also have a caregiver (parent, guardian, or other legally authorized representative) who is willing to participate in the study.

9. TRIAL OBJECTIVES AND PURPOSE

9.1 Trial Descriptors/Trial Purpose Summary

Spinogenix is developing SPG601 for treatment of Fragile X Syndrome (FXS), using an oral capsule route of administration. Fragile X Syndrome is characterised by mental retardation, behavioural features, and physical features, such as a long face with large protruding ears and macro-orchidism. In 1991, the fragile X mental retardation (FMR1) gene and the cytogenetic marker (a fragile site at Xq27) were identified.

This Phase 2a pharmacologic study employs a randomized, double-blinded, 2-period balanced-crossover design. Ten male patients aged 18 to 45 years, with full mutation Fragile X Syndrome characterized by greater than 200 CGG repeats in the FMR1 gene by Southern Blot and PCR genetic testing and full FMR1 gene methylation, will be recruited.

9.2 Objectives

9.2.1 Primary Objective

- Assess the clinical efficacy of a single dose of SPG601 and Placebo in patients with Fragile X Syndrome.

9.2.2 Secondary Objectives

- Assess cognitive outcomes of a single dose of SPG601 and Placebo in patients with Fragile X Syndrome.
- Evaluate the safety and tolerability of SPG601 administered in patients with Fragile X Syndrome.

10. INVESTIGATIONAL PLAN (TRIAL DESIGN)

10.1 Endpoints

10.1.1 Primary Endpoint

- Improvement in symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Clinical Global Impressions Improvement (CGI-I) scale, as determined by the treating clinician.
- Improvement in symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Clinical Global Impressions Improvement (CGI-I Caregiver) scale, as determined by the patient's caregiver.
- Improvement in anxiety symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Visual Analog Scale (VAS Caregiver), as determined by the patient's caregiver.

- Improvement in auditory intertrial phase coherence following treatment of a single dose of SPG601 and Placebo compared to pre-dose, in the gamma range in response to the chirp stimulus.

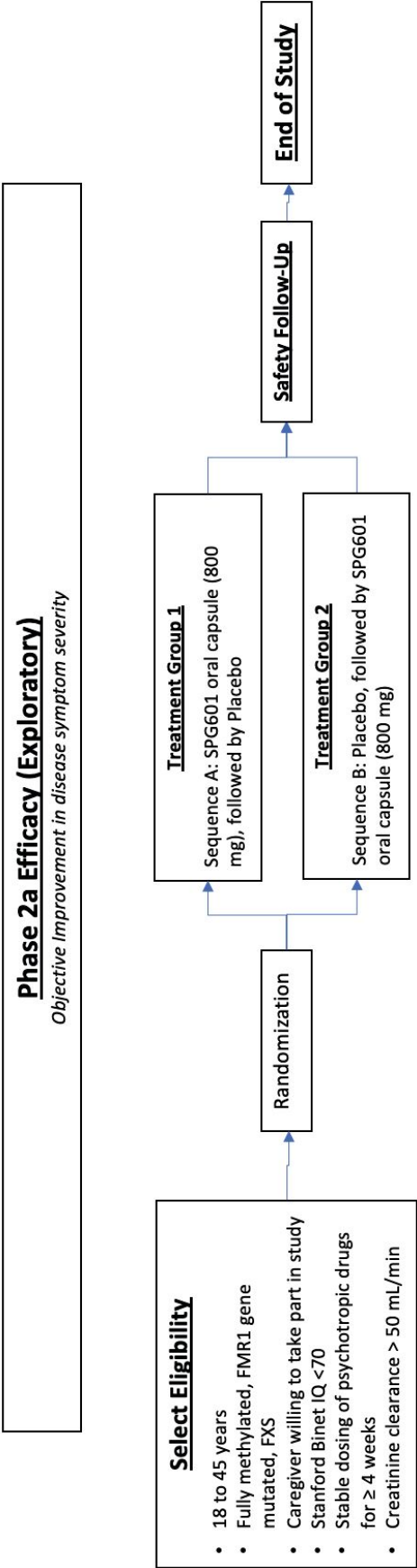
10.1.2 Secondary Endpoints

- Improvement in attention and inhibition following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the KiTAP Test of Attentional Performance for Children.
- Improvement in oral reading, vocabulary, and speed matching following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the NIH Cognitive Toolbox.
- Improvement in social gaze aversion following treatment of a single dose of SPG601 and Placebo compared to pre-dose, assessed using eye-tracking.
- Improvement in immediate memory following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using RBANS: List Learning.
- Improvement in auditory intertrial phase coherence to the steady state stimuli and relative power in the alpha, theta, and gamma bands during rest following treatment of a single dose of SPG601 and Placebo compared to pre-dose.
- Improvement in electroretinography following treatment of a single dose of SPG601 and Placebo compared to pre-dose.
- Incidence of treatment emergent AEs, serious AEs, and AEs leading to drug interruption or discontinuation.

10.2 Overall Study Design

10.2.1 Study Design and Schematic

This Phase 2a pharmacologic study employs a randomized, double-blinded, 2-period balanced-crossover design. Ten male patients aged 18 to 45 years, with full mutation Fragile X Syndrome characterized by greater than 200 CCG repeats in the FMR1 gene by Southern Blot and PCR genetic testing and full FMR1 gene methylation, will be recruited.



10.2.2 Minimization/Control of bias

Subjects will be randomly assigned to one of 2 different sequences for receiving SPG601 800mg and placebo, with a 1-week washout (± 2 days) between administrations. The study is expected to enroll and randomize 10 subjects. Once they are randomized, subjects will not be replaced. Subjects and legally authorized representatives (i.e., caregivers) will be informed during consent that they will be blinded to treatment status throughout the study.

10.2.3. Trial treatment(s) and dosage regimen of Investigational Product

SPG601 drug product is a capsule for oral administration. It will be provided to the clinical site pharmacy in a single formulation of 100 mg. A single dose using SPG601 will be administered orally, and placebo. Subjects will be randomly assigned to one of two different sequences for receiving SPG601 800mg and placebo, with a 1-week washout (± 2 days) between administrations.

The timing of evaluations in relation to the single-dose of each agent/placebo is guided primarily by the time to maximum plasma concentration (T_{max}) of the drug (1 hour fasted; 2 hours fed state) but is also supported by considerable preclinical and clinical literature. All subjects in this trial will be dosed in the fed state per our usual clinical research standards allowing patients breakfast and snacks prior to dosing day activities. The primary outcome EEG will be conducted 2 hours post-dosing, with post-dose clinical and cognitive evaluations being done immediately thereafter. Pharmacokinetic data regarding $\frac{1}{2}$ -life of SPG601 (~3-4 hours) support a 1-week washout period between drug or placebo exposure.

10.2.3 Packaging

SPG601 oral capsules (100 mg)

[REDACTED]

10.2.4 Comparator Description

Subjects will be randomly assigned to one of two different sequences for receiving SPG601 800mg and placebo, with a 1-week washout (± 2 days) between administrations.

The placebo is a hard gelatin capsule packaged into Size 0 White Opaque body and cap

([REDACTED])

Dosage form: Oral capsule

Route of administration: Oral

11. STUDY DESIGN / SCHEDULE OF ASSESSMENTS AND PROCEDURES

11.1 Baseline Visit Procedures

On the day of recruitment, safety labs including comprehensive metabolic panel (CMP), and complete blood count with differential (CBC with differential) will be collected at baseline. An ECG exam will also be performed, along with an EEG and Electroretinography and Eye Tracking. Triplicate 12-lead ECGs will be obtained at the timepoints indicated in the corresponding SoA with the following parameters: HR, PQ (PR), QRS, QT, RR and QTcF along with information on T- and U-waves. For inclusion, at least 2 out of 3 QTcF readings must be within acceptable range for study, and the abnormality in the single reading must be deemed to be not clinically significant by Investigator judgment. All ECGs will be obtained in supine position following a 5-minute rest. Any clinically significant ECG abnormalities will be captured and reported.

A Columbia Suicide Severity Risk Scale (C-SSRS) assessment will also be performed. Visual Analog Scale – Caregiver, RBANS, KiTAP, NIH Cognitive Toolbox, CGI-S assessments will be performed.

A comprehensive metabolic panel will minimally include the following tests:

- Albumin,
- Bilirubin (total)
- Calcium
- Carbon Dioxide or “Bicarbonate”
- Chloride
- Creatinine
- Glucose
- Alkaline Phosphatase
- Potassium
- Total Protein
- Sodium
- Alanine Amino Transferase (ALT)
- Aspartate Amino Transferase (AST)
- Urea Nitrogen or “BUN”

A CBC with differential will minimally include the following tests:

- Hemoglobin
- Hematocrit
- Red Blood Cells
- White Blood Cells
- Platelet Count

- Automated 5-Part Differential, to include:
 - Lymphocytes
 - Monocytes
 - Eosinophils
 - Basophils
 - Reticulocytes

Approximately 6 mL of blood will be collected to complete these safety tests. Baseline cognitive and clinical measures (described in further detail below) will be assessed. Each patient will have a medical examination performed by a study physician who will review medical history, and assess height, weight, vitals (blood pressure, heart rate, respiratory rate, and temperature), muscle tone, Tanner staging, head circumference, history of recurrent otitis media, dysmorphologies and other comorbid conditions at baseline. Baseline concomitant medications will be documented. Since the study drug pill is large, in some cases subjects may be given placebo pills to determine whether they are able to swallow the capsule or bring home to practice taking.

A urine drug screen will be performed at the baseline visit. A urine sample for urinalysis will be collected throughout the study. The following tests will be conducted by dipstick:

- Bilirubin
- Blood
- Glucose
- Ketones
- Leukocyte esterase
- Nitrites
- pH
- Protein
- Specific gravity
- Urobilinogen

As part of the disease medical history, each patient may complete a Stanford Binet-5th Edition IQ test (SBI) and Autism Diagnostic Observation Schedule (ADOS) if it has been more than a year since this was completed last. We will also collect the Columbia Suicide Rating Scale (C-SSRS) which will be reviewed by the clinical investigators on the team to assess suicidal risk of the patient. Study personnel will conduct the electroretinography.

When applicable, assessments and measures from other IRB approved studies conducted by the Neurobehavioral Research Team and associated PIs within 30 days prior to baseline can be transcribed and used for the baseline visit measures in order to minimize subject burden and the possibility of test-retest effects.

11.2 Drug Administration Visit Procedures

On each drug administration day, a medical evaluation/physical exam, vital signs (blood pressure, heart rate, respiratory rate, weight and temperature), urinalysis, EEG neurophysiology measures, Electroretinography, Eye Tracking, Visual Analog Scale – Caregiver, KiTap, CGI-S, concomitant medication and adverse event review will be

[REDACTED]

[REDACTED] being performed on drug administration days is provided below in Table 4: Study Schedule.

11.3 Follow Up Phone Call/Email Procedures

To further ensure the safety of study participants, weekly side effect/safety assessments will be attempted by phone or email the day following drug administration visits, and one (1) week after final study drug administration. Additional unscheduled visits may be conducted, at the discretion of the PI, at any time that signs of concern arise.

11.4 Schedule of Assessments

Table 4: Study Schedule

| Visit | Baseline Visit 1 | Treatment Period 1 | | Treatment Period 2 | | Safety Follow Up ² |
|---|---------------------|----------------------|-----------------|--------------------|-------------------|-------------------------------|
| | | Visit 2 ¹ | Visit 3 | Day 8 +/- 2 days | Day 15 +/- 2 days | |
| Day | -7 to 0 | Day 1 | Day 8 | Day 15 | Day 22 | |
| Week | | Week 1 | Week 2 | Week 3 | Week 4 | |
| Time | Baseline | Pre-dose | Post-dose | Pre-dose | Post-dose | Phone Call/E-mail |
| Informed Consent | X | | | | | |
| Physical Exam | X | X ⁹ | X ¹¹ | X ⁹ | X ¹¹ | |
| Urine Drug Screen ³ | X | | | | | |
| Medical History | X | | | | | |
| Vital Signs | X | X ⁹ | X ¹¹ | X ⁹ | X ¹¹ | |
| Safety Laboratory Tests ⁴ | X | X ⁸ | | X ⁸ | | |
| Laboratory Test – Urinalysis | | X ⁸ | | X ⁸ | | |
| ECG | X | | X ¹¹ | | X ¹¹ | |
| Biomarker Molecular Assays (optional includes FMRP) ⁵ | X | | X ⁶ | | X ⁶ | |
| Columbia Suicide Severity Rating Scale (C-SSRS) | X | | X ¹¹ | | X ¹¹ | |
| Randomization | X | | | | | |
| Study Drug Administration | | X | | X | | |
| PK Assays (optional) ⁶ | | | X | | X | |

¹ Visit 1/Baseline and Visit 2 may occur on the same day.

² The Safety Follow-up visit at week 3 will include phone call with study coordinator regarding participants overall health status and a general inquiry about AE's.

³ Urinalysis drug screening will be a 10-panel test that will test for marijuana, cocaine, opioids, benzodiazepines, amphetamines, barbiturates, phenylethylamine (PCP), methadone, methaqualone (qualudes), and propoxyphene

⁴ Safety Labs can include comprehensive metabolic panel, and CBC

⁵ Biomarker molecular assays will be used to isolate DNA, RNA or proteins related to FXS.

⁶ PK Samples and biomarker assays will be collected approximately 90 minutes post Study Drug Administration (+/- 5 minutes)

⁷ RETeval test completed after EEG

⁸ Performed within 72 hours prior to study drug administration

⁹ Performed 4 hours prior to study drug administration

¹⁰ Performed 4 hours post study drug administration + 30 minutes

¹¹ Performed 2 hours post study drug administration + 30 minutes

| | | | | | | | |
|---|---|----------------|-----------------|----------------|-----------------|-----------------|---|
| Eye Tracking | X | X ⁹ | X ¹⁰ | X ⁹ | X ¹⁰ | X ¹¹ | |
| CGI-I | | | X ¹¹ | | | X ¹¹ | |
| CGI-S | X | X ⁹ | | X ⁹ | | | |
| KiTap | X | X ⁹ | X ¹¹ | X ⁹ | | X ¹¹ | |
| EEG | X | X ⁹ | X ¹¹ | X ⁹ | | X ¹¹ | |
| Visual Analog Scale - Caregiver | X | X ⁹ | X ¹¹ | X ⁹ | | X ¹¹ | |
| Side Effects /Safety/Adverse Events | | X ⁹ | X ¹¹ | X ⁹ | | X ¹¹ | X |
| Safety Call ² | | | X | | | X | X |
| NIH Cognitive Toolbox | X | | X ¹¹ | | | X ¹¹ | |
| RBANS List Learning | X | | X ¹¹ | | | X ¹¹ | |
| Electroretinography Assessment ⁷ | X | X ⁹ | X ¹¹ | X ⁹ | | X ¹¹ | |

² Safety phone calls will occur 1 day post dose 1 and dose 2 and 7 days post dose 2to assess for AEs.

11.5 Neurophysiology Measures

For acquisition of electrophysiological data, up to 128 lead channels will be used, placed according to the standard 10-20 electroencephalography array (which allows for a brief 5–10-minute setup) referenced to the CMS-DRL ground. [REDACTED]

[REDACTED]

Resting state: Subjects will sit with for approximately 6 minutes to gather preliminary data.

Spectral Analysis: Spectral analysis will be completed on data acquired with eyes open for 5 minutes. [REDACTED]

[REDACTED]

Auditory Steady-State: Subjects will passively listen to auditory stimuli consisting of 3 sec click trains at 40 and 80 Hz. [REDACTED]

[REDACTED]

Chirp Modulated Sweep: Subjects will passively listen to auditory stimuli consisting of a 1000 Hz tone amplitude modulated (AM) by a chirp sinusoid [REDACTED]

[REDACTED]

[REDACTED]

11.6 Eye Tracking

Persons with full mutation FXS clinically show gaze avoidance. [REDACTED]

[REDACTED]

11.7 Electroretinography

Electroretinography measures the electrical responses of various cell types in the retina, including the photoreceptors (rods and cones), inner retinal cells (bipolar and amacrine cells), and the ganglion cells. Electrodes are placed on the surface of the cornea (DTL silver/nylon fiber string or ERG jet) or on the skin beneath the eye (sensor strips) to measure retinal responses. Retinal pigment epithelium (RPE) responses are measured with an EOG test with skin-contact electrodes placed near the canthi. During a recording, the patient's eyes are exposed to standardized stimuli and the resulting signal is displayed showing the time course of the signal's amplitude (voltage) (Peché 2021).

11.8 Blood Sampling

All subjects will have the option to provide a blood sample to complete both molecular pharmacodynamics and pharmacokinetic studies. Pharmacokinetic data will be collected approximately 90 minutes post-dose (+/- 5 minutes). We will record the times of drug dosing and food intake. Molecular assays will be drawn at the same time as pK draw and at Baseline. Blood samples may be used to isolate DNA, RNA or proteins related to Fragile X Syndrome using standard protocols. No more than 150 mL of blood will be collected for the total study volume.

11.9 Fragile X Messenger Ribonucleoprotein Assay

FMRP assay will be conducted to quantify of the level of the fragile X mental retardation protein in cells. Assays will be analyzed in Dr. Craig Erickson's Molecular Translational Biomarker Lab at CCHMC. All blood biomarker assays will be performed blinded to study assignment. Blood will be collected and spotted onto Whatman Bloodstain Cards. The samples will be allowed to dry between 4 and 24 hours before being stored in a gas-permeable bag with desiccant and frozen until analysis. Upon analysis, five 6-mm disk

punches will be collected from separate blood spots within the same card. The proteins from the disks will be eluted and analyzed in quintuplet using a custom bead-based Luminex assay to obtain quantitative measures of FMRP. All FMRP draws will be attempted, but are not required for study participation.

12. ELIGIBILITY CRITERIA AND WITHDRAWAL

12.1 Inclusion Criteria

1. Subjects must have a full methylated, full mutation (>200 CGG repeats) in the FMR1 gene confirmed by Southern Blot and PCR testing.
2. Adult males aged 18 to 45 years.
3. Subject must have caregiver (parent, guardian, or other legally authorized representative) who is willing to participate in the study.
4. Subject must be in general good health as determined by physical exam, medical history and laboratory work up.
5. Subject must have Stanford Binet IQ <70
6. Stable dosing of psychotropic drugs for at least 4 weeks.
7. Subject or subject's parent/legal guardian must be able to understand, and willing to sign, a written informed consent and the assent document, as appropriate.

12.2 Exclusion Criteria

1. Subjects with a history of intolerance to SPG601 or large conductance potassium channel agonists.
2. Subjects who have taken any investigational drug within one month of planned receipt of SPG601 and Placebo, have a history of substance abuse or dependence within six months, or significant psychiatric or CNS neurological disease unrelated to FXS.
3. Uncontrolled seizures or history of epilepsy with a seizure in the past 6 months.
4. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds (ms)).
5. Subjects with myocardial infarction and poorly controlled arrhythmia (including QTc intervals ≥ 470 ms) (QTc intervals are calculated by Fridericia's formula) within 6 months prior to the first dose of the investigational products.
6. Auditory or visual impairments that cannot be corrected based on visual and auditory screener benchmarks.
7. Subjects with a creatinine clearance < 50 mL/min (calculated by Cockcroft-Gault).
8. Subjects with eGFR <90mL/min.
9. Subjects with mild, moderate, and severe hepatic impairment, corresponding to 5-6, 7-9 and 10-15 Child-Pugh scores)
10. Subjects with Columbia Suicide Severity Risk Scale (or equivalent) score of Category 2 - "suicidal ideation." Subjects with identified medical issues, inability to tolerate study

procedures or study drug, or risk of suicidality per the discretion of the Principal Investigator.

12.3 Subject Withdrawal

12.3.1 Subject Withdrawal Criteria

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant non-compliance with study intervention by the subject.
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- If the patient responds affirmatively to the Columbia Suicide Severity Risk Scale, if patient responses show:
 - Suicidal ideation is Category 2 or greater, or
 - Suicidal behavior is indicated, or
 - Self-injurious behavior, but with no suicidal intent.

The reason for participant discontinuation or withdrawal from the study will be recorded.

12.3.2 Subject Withdrawal/Dropout Process/Procedure(s)

Participants are free to withdraw from participation in the study at any time upon request.

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension include but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

If the study is prematurely terminated or temporarily suspended, the PI will promptly inform the CCHMC IRB and provide the reason(s) for the termination or temporary suspension. Resumption of the study will not take place until the concerns related to the termination or suspension are addressed and satisfy the IRB.

Note: participants who receive a Columbia Suicide Severity Risk Scale Category 2 response or greater will be referred to a treating clinician according to the investigative site's

institutional policy for further clinical evaluation and intervention/treatment and will either be excluded from the study at the time of assessment.

If the study is prematurely terminated, a final visit will be scheduled for participants who are active in the study.

12.3.3 Follow-up Process for Withdrawn Subjects

Discontinued treatment due to AE(s): followed weekly until resolution to baseline or stabilization of the AE.

Discontinued treatment due to non-safety events (voluntary withdrawal, disease progression): return for a final safety evaluation 7 days (\pm 2 days) following last dose of drug.

Further collection of data will not occur from individuals who fail screening criteria. However, rescreening is permitted for those individuals who wish to participate. Rescreening will be performed by study personnel at the discretion of PI and medical monitor.

12.3.4 Type, Source and Timing of Follow-up Data on Withdrawn Subject

| | |
|--------------------------|--|
| Type of Data | <ul style="list-style-type: none"> • Adverse Events • Final Safety evaluation |
| Timing of Follow-up Data | <ul style="list-style-type: none"> • End of treatment • 7 day/s (+/- 2 days) following: last dose of drug • Weekly until: Resolution to baseline; stabilization of AE |

13. TREATMENT OF SUBJECTS

13.1 Description of Study Drug

SPG601 oral capsule (800 mg): SPG601 oral capsules are standard gelatin capsules containing SPG601 powder. SPG601 is a benzamide derivative that was designed to mimic the activity of anandamide, an agonist of the CB1 cannabinoid receptor, but which was found to lack cannabinoid activity.

13.2 Concomitant Medications

Prior Concomitant Medications

- The study team will collect information on all concomitant medications at screening and during participation in the study. Patients must be on stable dosing of psychotropic drugs for at least 4 weeks to participate in the study.

13.3 Treatment Compliance

Study drug(s) will be administered in the clinic, under study team observation, to ensure compliance.

13.4 Blinding

On Day 1 participants will be assigned a unique number (randomization number) at study site. The randomization number encodes the participant's assignment to one of the 2 arms of the study (active or placebo), according to the randomization schedule generated prior to the study by the CRO biostatistician. Each participant will be dispensed blinded study intervention, labeled with the participant's unique randomization number, throughout the study.

It is expected that in the majority of cases, AEs can be properly managed without the need for unblinding. However, in the event of a medical emergency in which knowledge of an individual participant's study drug assignment is considered critical to the participant's wellbeing and management, the PI (or documented delegated treating physician) may unblind the treatment assignment for the participant in question using the participant's code break envelope. A record, including date, time, name, and signature of the person opening the envelope and reason for unblinding must be made both on the opened envelope and in the participant's medical records. The unblinding and its cause will also be documented in the eCRF.

If the Investigator is not on site, the Investigator (or a Sponsor's written and preapproved designee documented as a note to file) can delegate the opening of the code break envelopes to an on-site staff member. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. Once the study is complete, all envelopes (sealed and opened) must be inventoried and returned to the Sponsor.

13.5 Treatment of Overdose

The criteria for overdose have not yet been defined. Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.

14. STUDY DRUG MATERIALS AND MANAGEMENT

14.1 Study Drug

There will be a single formulation of the product to be used in the Phase 2a clinical trial, described below in Table 5: Drug Product Formulations Used.

Table 5: Drug Product Formulations Used

| Component | Function | Concentration (mg) |
|-------------------------|----------------------------------|--------------------|
| SPG601 | Active pharmaceutical ingredient | 100 mg |
| Route of administration | | Oral |

14.2 Study Drug Packaging and Labeling

SPG601, 100mg [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

14.3 Study Drug Storage

The capsules are to be stored at ambient temperature (25°C +/- 10°C), protected from light and moisture. The capsules have been demonstrated to be stable for up to 12 months under these storage conditions; however, this shelf-life will be updated upon availability of continuing stability. Please refer to the investigational medicinal product label for shelf-life information.

14.4. Study Drug Handling and Disposal

Procedures relating to study drug preparation and dispensing are outlined in the Pharmacy Manual.

On completion of the study, the Investigational site will receive further direction on remaining study drug management. If the Investigational site is requested to destroy surplus study drug following written approval by Sponsor, evidence of the destruction of any surplus drug will be supplied to the study monitor. If no supplies remain, this will be documented in the dispensing record.

15. ASSESSMENT

15.1 Assessment of Efficacy

For clinical determination of efficacy, disease symptom response to treatment will be assessed by study site investigator. The following instruments will be used to assess primary efficacy endpoint:

- Improvement in symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Clinical Global Impressions Improvement (CGI-I) scale, as determined by the treating clinician.
- Improvement in symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Clinical Global Impressions Improvement (CGI-I Caregiver) scale, as determined by the patient's caregiver.
- Improvement in anxiety symptom severity following treatment of a single dose of SPG601 and Placebo compared to pre-dose, using the Visual Analog Scale (VAS Caregiver), as determined by the patient's caregiver.
- Improvement in auditory intertrial phase coherence following treatment of a single dose of SPG601 and Placebo compared to pre-dose, in the gamma range in response to the chirp stimulus.

15.2 Assessment of Safety

Assessment of safety will be performed for all patients having received at least one dose of study drug.

All AEs will be graded according to the NCI CTCAE, version 5.0, which can be found at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects the patient's clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

Safety assessment will be the primary concern for the DSMC which has been set up for this study. See Section 16 for the Committee's responsibilities.

16. DATA SAFETY MONITORING

The PI and Co-investigators at CCHMC will be primarily responsible for monitoring data quality and adverse events. A physician will monitor adverse effects at each visit during the physician clinical interview and exam using Common Terminology Criteria for Adverse Events (CTCAE). In addition, he or she will review vital signs and laboratory data, as they become available. All of these values are reviewed continuously by a physician. The monitor will review recruitment and adverse events every 6 months and report their assessment to the PI. The chair of the DSMB will also review any SAEs and significant unanticipated events as they occur.

Additional study safety oversight will be provided by a local Data and Safety Monitoring Board (DSMB) chaired by [REDACTED]

[REDACTED] The DSMB will meet prior to the onset of the study to approve the protocol, and follow-up meetings will take place throughout the study. At each follow-up meeting, the DSMB will evaluate the accumulated study data for participant safety and review study conduct and progress. The DSMB will provide written reports after each meeting that summarize the discussion and make recommendations to the study PIs and/or the IRB regarding the continuation, modification, or termination of the trial as they see fit.

All problems (i.e. adverse events, unanticipated events, etc.) will be characterized by the following:

- Severity = Mild, Moderate or Severe
- Relatedness = Definite, Probable, Possible, Unlikely or Unrelated
- Expectedness = Expected or Not Expected

A stopping rule for excessive toxicity is in place in the event of ≥ 2 SAEs considered possibly, probably or definitely related to treatment on study. All SAEs will be reviewed in detail by the DSMB. If a reason to stop the study presents, the study will close to enrollment for interim analysis of safety and efficacy data and the DSMB will provide a recommendation to the PI regarding continuation of the trial.

Events will be reported consistent with site IRB reporting policies. An aggregate listing of all safety events will be reported to the IRB in summary form at the time of continuing review. These reports will also be provided to any applicable regulatory agencies per applicable regulatory agency requirements. Data (such as lab values, vital signs, and outcome measure data) will be entered from source documents into electronic Case Report Forms by the study coordinator. The study coordinator will review case report form entries for accuracy by comparison with the source documents. Research records and source documents will be maintained in a research chart and securely stored by the research team. Information will be kept in a secure database that is password protected. Records will be kept secure, and individually identifiable information will not be included in any reports or data sets.

All subjects will be assured that data will be kept confidential. Data will be identified only by a unique identification number and not by the subject's name. Paper data will be stored in a locked office in a locked cabinet to which only staff affiliated with the project will have access. Any discrepancies in the maintenance of confidentiality or other irregularities involving the data will be reported to the PI. Any such events will be documented and reviewed by the PI and reported to the IRB within a timeframe set out by guidelines set forth by the CCHMC IRB.

17. ADVERSE AND SERIOUS ADVERSE EVENTS

17.1 Definitions

Adverse event:

“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.” (ICH E6:1.2)

Any adverse events--whether due to assessment, medication or other aspects of the study--will be reported to the PI. Adverse events will be documented and reviewed by the PI within 24 hours of receipt.

Serious adverse event (SAE):

Defined as: any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Serious adverse events (SAEs) will be reported to the IRB within 48 hours by phone, email, or fax. All adverse events will be compiled, and reported in summary form to the IRB, on an annual basis and at the conclusion of the study. A physician will monitor adverse effects at each visit during the physician clinical interview and exam using Common Terminology Criteria for Adverse Events (CTCAE).

Other Adverse Event (OAE) (e.g. Unexpected Adverse Event):

Unexpected adverse events will be reported to the IRB within 48 hours by phone, email, or fax. All adverse events will be compiled, and reported in summary form to the IRB, on an

annual basis and at the conclusion of the study. A physician will monitor adverse effects at each visit during the physician clinical interview and exam using Common Terminology Criteria for Adverse Events (CTCAE).

Experimental Therapy: Known safety issues

There are no known contraindications to receiving SPG601, however, SPG601 is contraindicated in patients who are hypersensitive to any component of the product (as described in section 3.2 of the IB).

Pediatric Use: There has been no pediatric experience with SPG601 to date.

17.2 Recording Adverse Events

Adverse events spontaneously reported by the patient/subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as AEs. However, abnormal values that constitute an SAE or lead to discontinuation of administration of study drug must be reported and recorded as an AE. Information about AEs will be collected from the first administration of study drug until the end of the study. Serious Adverse Event information will be collected from first administration of study drug until the end of study following the last dose of study drug. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section **Error! Reference source not found.** An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on Spinogenix's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

17.3 Reporting Adverse Events

All AEs that occur after the first dose of study product and through 30 days after the last dose of study drug will be recorded. Only AEs deemed “serious” and “related” will be recorded during treatment beyond the end of study time period.

17.4 Assessment of Severity/Grading of Adverse Events

All AEs will be graded according to the NCI CTCAE, version 5.0, which can be found at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

17.5 Relationship to Study Drug/Assessment of Causality

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered “related.”

If the relationship between the AE/SAE and the investigational product is determined to be “possible” or “probable” the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

17.6 Serious Adverse Event Reporting

All SAEs must be reported whether or not they are considered causally related to the investigational product or to the study procedure/s.

In the event of an SAE, the investigator must:

- Notify the Medical Monitor (MM) immediately by email amy.prawira@obatica.com or phone.
- Initially provide the MM with a completed AE CRF and with a complete SAE Report Form, which includes a statement as to whether the AE was or was not related to the use of the study medication.
- Provide follow-up copies of CRFs and worksheets to the MM until the SAE has resolved or has been deemed a permanent disability. Requests for additional information may continue as directed by the Sponsor.
- Obtain and maintain in his/her files all pertinent medical records and information.
- Notify the IRB, in accordance with the IRB's guidelines, of the SAE discovery, and file any SAE-related documents in the Site Regulatory Binder.

17.7 Contraception and Pregnancy

Patients must agree to use adequate contraception i.e. condoms (or abstinence) for 30 days prior to the first administration of study drug, for the duration of study participation, and for thirty (30) days following completion of therapy.

All confirmed pregnancies must be reported on a Pregnancy Report Form and submitted to the MM via email transmission within 24 hours of the Investigator's awareness of the pregnancy. The MM will distribute the completed form to the Sponsor.

All pregnancies will be followed until outcome even after study closure. The outcome of all pregnancies will be reported on a Pregnancy Outcome Report and submitted to the MM via email transmission once the outcome is learned. The MM will distribute the completed form to the Sponsor.

Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, certain pregnancy complications, such as stillbirth, neonatal death within 28 days of birth, spontaneous and therapeutic (elective) abortions (where allowed by law) for medical or non-medical reasons, as well as congenital anomaly or birth defect in a new-born or in an aborted fetus do constitute an SAE. In these cases, an individual Spinogenix SAE Report Form on a newborn must be reported within 24 hours. In other words, for all pregnancy complications (outcomes) listed in this paragraph, two separate reports should be submitted simultaneously to the Sponsor: The Pregnancy Outcome Report and the SAE Report on the newborn.

The contact for reporting pregnancies, pregnancy outcomes, SAEs on pregnancy complications in the newborn, as well as for reporting all other SAEs, is as follows:

Medical Monitor

Email: amy.prawira@obatica.com

Contraception and Pregnancy

The PI or his designee will discuss with the subject and legally authorized representative the acceptable contraception to be used by subjects participating in this study. The PI team will stress the importance of preventing pregnancy during the course of participation in this study and for thirty (30) days following participation to reduce risks to an unborn fetus. Barrier contraception will be discussed with the patients during the consent process and will be described in the consent form. Caregivers will also be informed of the importance of preventing pregnancy during participation in this study.

Abstinence will be considered an acceptable method for those who have never been sexually active.

18. STATISTICS

18.1 Statement of the Proposed Statistical Model

A 2-drug/placebo, 2-period, 2-sequence balanced-crossover design (Williams, 1989) will be used for the proposed pharmacologic study. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

18.2 Statistical Method Description

Sample Size

The study is a phase 2a, pilot, signal seeking and is not based on a statistically powered calculation.

Data Handling Conventions

Individual participant listings will be created for important variables from each eCRF module. Data will be presented by dose and timepoint, as appropriate.

Summary statistics will be calculated for each of the endpoints. For continuous variables, number (of participants), mean, SD, median, minimum, and maximum will be provided. For categorical variables, number and percent of participants will be provided for each category.

Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

Handling of Missing Data

All available data will be analyzed, with limited imputations for missing data.

Further details on handling of missing data, including partial or missing AE or concomitant medication dates, will be described in the Statistical Analysis Plan (SAP).

18.3 Analysis Populations

Safety Population

The safety population will include all participants who have received at least one dose of study drug per the SAP.

Efficacy Evaluable Population

All participants who receive any amount of SPG601 and have a post baseline PD response assessment may be included in the Efficacy Evaluable population. This may include protocol questionnaires and/or EEG assessment. This population will be used in the analysis of clinical efficacy as per the SAP.

18.4 Statistical Methods

Safety and Tolerability

Continuous safety data will be summarized with descriptive statistics (arithmetic mean, standard deviation [SD], median, minimum, and maximum) overall and within each dose level for all participants (i.e., including those who receive placebo).

Categorical safety data will be summarized with frequency counts and percentages overall and within dose level. Adverse events will be coded by system organ class and preferred term using the most current Medical Dictionary for Regulatory Activities (MedDRA) version available. The number of participants experiencing treatment-emergent adverse events as well as maximum severity and relationship to study drug will be summarized.

Laboratory evaluations, vital signs assessments, and ECG parameters will be summarized at protocol-specified collection time point. A summary of change-from-baseline at each protocol-specified timepoints will also be presented.

Concomitant Medications

Concomitant medications will be listed by participant and coded using the most current World Health Organization drug dictionary.

Medical History

Medical history will be listed by participant and coded using MedDRA. Further details will be provided in the Statistical Analysis Plan (SAP).

Efficacy Analyses

18.5 Efficacy Analyses

Clinical efficacy will be documented at each assessment by longitudinal changes in the following:

- Clinical Global Impressions Improvement Scale (CGI-I)
- Visual Analog Scale
- KiTAP assessment
- NIH Cognitive Toolbox
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The analysis of efficacy outcomes will be a linear mixed model analysis of repeated measures. A separate mixed model analysis will be conducted on each outcome. If deemed necessary, the outcomes will be appropriately transformed to obtain a more normal distribution. [REDACTED]

18.6 Interim Analysis

There is no planned interim analysis.

18.7 Data Management

Data will be collected on paper source documents, CRFs, and/or in the electronic medical record and will be entered by study staff in a password protected, encrypted EDC database. Data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by the research team. The EDC will provide a secure, web-based application that is flexible and provides 1) an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry; 2) HIPAA-compliant and 21 CFR Part 11-ready audit trails for tracking page views, data manipulation and export procedures; 3) record locking and electronic signature functions; 4) fine grained control of user rights to view and manipulate data; 5) a report

builder for reporting, monitoring and querying patient records; 6) automated export procedures for seamless data downloads.

18. ETHICS

19.1 Statement of Ethical Conduct

This protocol complies with the principles laid down by the 18th World Medical Association Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Association Assemblies.

This protocol also complies with the laws and regulations of the country(ies) and state(s) in which the study is performed (i.e., the United States Food and Drug Administration or FDA) as well as any applicable guidelines.

The collection and processing of personal data from patients enrolled in this study will be limited to that data which is necessary to investigate the efficacy, safety, quality, and utility of the investigational study product used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Sponsor and the Principal Investigator will ensure that the personal data are:

- Processed fairly and lawfully,
- Collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes,
- Adequate, relevant, and not excessive in relation to said purposes, accurate and, where necessary, kept up to date.

Explicit consent for the processing of personal data will be obtained from the participating patient before collection of data. Such consent/ should also address the transfer of the data to other entities and other countries.

19.2 Bioethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) as appropriate. The investigator must submit written IRB approval to Spinogenix before he or she can enroll any patient/subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the

investigational product. Spinogenix will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

19.3 Written Informed Consent

To take part in the consent and assent process, if the patient is his own legal guardian, the patient must be mature enough to understand the trial and what they will be required to do, and must give written informed consent to take part in the clinical trial. To take part in the study, the patient must be able to legally consent on his behalf (i.e., be legally autonomous) or have written consent from his legal guardian and provide assent to participate. Following this, the research team should explain the trial to the patient, including what their taking part means and what they can expect. This should be done in a language the patient can understand, and if required, this explanation may be aided via written forms, graphics, videos, or other visual aids. The patient should be encouraged to talk with their family and/or legally authorized guardian and ask questions of the research team. After the point at which it is felt the patient understands what the trial involves, they will be asked to show their assent or dissent.

The Principal Investigator(s) must maintain the original, signed Informed Consent/Assent Form. A copy of the signed Informed Consent/Assent Form must be given to the patient and parent/guardian.

During the consenting process, the caregiver will be given the opportunity to provide permission for storing the patient's specimens for future respiratory virus vaccine studies and for research purposes.

19.4 Data Handling and Record Keeping

In compliance with ICH/GCP guidelines, the investigator/institution will maintain copies of all source documents that support the data collected from each patient and all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least two years have lapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Spinogenix. It is the responsibility of Spinogenix to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Spinogenix must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from Spinogenix.

If it becomes necessary for Spinogenix or the appropriate regulatory authority to review any documentation relating to this study, the investigator must permit access to such reports.

Spinogenix will oversee all clinical monitoring and data management activities for sites participating in the study.

Procedures to Maintain Confidentiality:

Unique numeric identifiers that do not include any PHI will be assigned. All data will be maintained either in locked storage facilities with limited access or in secure, electronic facilities. Data transmitted electronically will be protected by encryption over a very secure network that limits access only to CCHMC faculty and staff who are reviewed and specifically cleared for access to the password protected, secure network. The data will be stored in protected hard drives in a server system that is protected by two firewalls, one at the hospital level and a second at the Departmental level. Data will be de-identified if shared.

19. PATIENT INFORMATION AND CONSENT

A full and adequate oral and written of the following information must be conveyed to the subject and their legally authorized representative:

- a. Statement that the study involves research, explanation of purposes of the research.
- b. Expected duration of subject's participation.
- c. Description of procedures to be followed.
- d. Description or any foreseeable risks or discomfort to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- e. Description of any benefits to the subject or to others which may be reasonably be expected from the research.
- f. Disclosure of appropriate alternative procedures or courses of treatment, if any, that may be advantageous to the subject.
- g. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the health authority e.g. FDA may inspect the records.
- h. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- i. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research-related injury to the subject.
- j. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- k. The anticipated expenses, if any, to the subject for participating in the trial.
- l. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

If subject is illiterate or visually impaired:

If a potential subject can understand and comprehend spoken English, but is unable to talk or write, they can be entered into the study if competent and able to indicate approval or disapproval (provide assent). An impartial witness must be assigned to observe the informed consent process with the legally authorized representative and allow for questions. The subject and legally authorized representative must sign the informed consent form to attest that informed consent an assent was freely given and understood. The method used for communication with the subject and the specific means by which the prospective subject communicated agreement to participate in the study should be documented.

Assent (if required by IRB) source:

To take part in the assent process, the patient must be cognitively able to understand the trial and what they will be required to do. A legally authorized representative must give informed permission for the patient to take part in the clinical trial. Following this, the research team should explain the trial to the patient, including what their taking part means and what they can expect. This should be done in a language the patient can understand, and if required, this explanation may be aided via written forms, graphics, videos, or other visual aids. The patient should be encouraged to talk with their family and ask questions of the research team. After the point at which it is felt the patient understands what the trial involves, they will be asked to show their assent or dissent.

20. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

21.1 Monitoring of Trial

Before an investigational site can enter a patient into the study, a representative of Spinogenix Technologies will qualify the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of Spinogenix or its representatives. This will be documented in a Clinical Study Agreement between Spinogenix and the investigator.

During the study, a monitor from Spinogenix or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Spinogenix.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to Spinogenix and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

21.2 Site Audits

Authorized representatives of Spinogenix, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Spinogenix audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Spinogenix immediately if contacted by a regulatory agency about an inspection.

21.3 IRB/IEC and Regulatory Inspection

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

21. DATA AND SAFETY MONITORING PLAN

22.1 Data Collection

Steps will be taken to assure the accuracy and reliability of the data collected. These steps will include the selection of qualified investigators and appropriate study centers, the thorough review of protocol procedures with the investigator and associated personnel before patients are enrolled, and periodic monitoring visits by the study monitor (CRA).

CRF completion training will be provided to and reviewed with study personnel. The CRA will review all CRFs for accuracy and completeness during the on-site monitoring visits.

22.2 Data Safety Monitoring Board

The PI and Co-investigators at CCHMC will be primarily responsible for monitoring data quality and adverse events. A physician will monitor adverse effects at each visit during the physician clinical interview and exam using Common Terminology Criteria for Adverse Events (CTCAE). In addition, he or she will review vital signs and laboratory data, as they become available. All of these values are reviewed continuously by a physician. The monitor will review recruitment and adverse events every 6 months and report their assessment to the PI. The chair of the DSMB will also review any SAEs and significant unanticipated events as they occur.

Additional study safety oversight will be provided by a local Data and Safety Monitoring Board (DSMB) chaired by [REDACTED] Assistant and Professor with the division of caregiver and adolescent psychiatry at Cincinnati Children's Hospital. The DSMB will meet prior to the onset of the study to approve the protocol then again, every six months beginning after six participants have been recruited. At each follow-up meeting, the DSMB will evaluate the accumulated study data for participant safety and review study conduct and progress. The DSMB will provide written reports after each meeting that summarize the discussion and make recommendations to the study PIs and/or the IRB regarding the continuation, modification, or termination of the trial as they see fit.

All problems (i.e. adverse events, unanticipated events, etc.) will be characterized by the following:

- Severity = Mild, Moderate or Severe
- Relatedness = Definite, Probable, Possible, Unlikely or Unrelated
- Expectedness = Expected or Not Expected

A stopping rule for excessive toxicity is in place in the event of ≥ 2 SAEs considered possibly, probably, or definitely related to treatment on study. All SAEs will be reviewed in detail by the PIs and chair of the DSMB. If a reason to stop the study presents, the study will close to enrollment for interim analysis of safety and efficacy data and the DSMB will provide a recommendation to the PI regarding continuation of the trial.

Events will be reported consistent with site IRB reporting policies. An aggregate listing of all safety events will be reported to the IRB in summary form at the time of continuing review. These reports will also be provided to any applicable regulatory agencies per applicable regulatory agency requirements. Data (such as lab values, vital signs, and outcome measure data) will be entered from source documents to Case Report Forms by the study coordinator. The study coordinator will review case report form entries for accuracy by comparison with the source documents. Research records and source documents will be maintained in a research chart and stored in the investigator's locked file cabinet. Information will be kept in a secure database that is password protected. Records will be kept secure, and individually identifiable information will not be included in any reports or data sets.

All subjects will be assured that data will be kept confidential. Data will be identified only by a unique identification number and not by the subject's name. Paper data will be stored in a locked office in a locked cabinet to which only staff affiliated with the project will have access. Any discrepancies in the maintenance of confidentiality or other irregularities involving the data will be reported to the PI. Any such events will be documented and reviewed by the PI and reported to the IRB within a timeframe set out by guidelines set forth by the CCHMC IRB.

22.3 Monitoring Rules for Safety

Safety and tolerability will be assessed by incidence, severity, and changes from baseline of all relevant parameters including AEs, laboratory values, and vital signs. AEs will be summarized by the number and percentage of patients who experienced the event according to System Organ Class (SOC). Additional summaries will also be provided by severity grade and relationship to study drug, and for SAEs and events resulting in the permanent discontinuation of therapy.

A patient reporting multiple cases of the same AE will be counted once within each SOC, and AEs will be graded by worst severity grade. The denominator for these calculations will be based on the number of patients in the respective drug cohort who receives at least one dose of study drug, irrespective of the total number of doses administered.

Vital sign results will be summarized descriptively for each scheduled protocol time point. Changes will be calculated relative to the assessments at baseline. The changes in hematology, chemistry, and other laboratory values will be summarized descriptively for each scheduled protocol assessment time point.

Data listings of all laboratory data collected during the study will be presented. Laboratory values outside normal limits will be identified; data listings will include flags for high and low values.

22. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Spinogenix may conduct a quality assurance audit. Please see Section 21.2 for more details regarding the audit process.

23.1 Investigator's Responsibility

The investigator is responsible for the following items:

- Reading and understanding the current protocol and the investigator's brochure with particular emphasis on the risks and side effects of the study product.
- Personally conducting or supervising the investigation.
- Ensuring that all study staff who are involved in training patients in the use of the drug delivery system have been adequately trained.
- .
- Ensuring that all PK are performed under close observation by trained study staff.
- Ensuring that the clinical study is performed in accordance with the relevant current protocol, FDA regulations, current ICH guidelines on GCP, and other applicable regulatory requirements.
- Informing patients that the study product is being used for investigational purposes, in a manner approved by the IRB, and in compliance with the requirements of the study and the regulatory requirements.
- Reporting of SAEs in accordance with the GCP standards and ICH guidelines.
- Informing patients of new information that becomes available that may adversely affect the safety of the patients or the conduct of the study.
- Notifying Spinogenix if a patient is no longer able to continue with the study.
- Complying with the IRB requirements that may include but are not necessarily limited to the following:
 - Reporting AEs.
 - Submitting protocol amendments, revised informed consent forms, and advertisements, if applicable, for IRB approval.
 - Maintaining IRB approval throughout the course of the study.
 - Submitting required IRB reports.
 - Notifying the IRB of the completion or termination of the study.

- Ensuring that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintaining adequate and accurate records and making those records available for inspection in accordance with federal regulations.

23. DATA HANDLING AND RECORD KEEPING

24.1 Inspection of Records

Spinogenix will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

24.2 Record Retention

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Spinogenix or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

24. FINANCING AND INSURANCE

Spinogenix will be the Sponsor for this clinical trial.

[REDACTED]

25. PUBLICATION POLICY

All information, including but not limited to information regarding SPG601 or the operations of Spinogenix (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, and formulation information) supplied by Spinogenix. to the investigator and not previously published, and any data generated as a result of this study, is considered confidential and remains the sole property of Spinogenix. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the prior written consent of Spinogenix.

The investigator understands that the information developed in the clinical study will be used by Spinogenix in connection with the continued development of SPG601, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide Spinogenix. with all data obtained in the study.

The result of the study will be reported in a Clinical Study Report generated by Spinogenix and will contain all data from all investigational sites. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of Spinogenix as author and owner of copyright in such work.

Spinogenix shall have the right to publish such data and information without approval from the investigator. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to Spinogenix for review at least six months prior to submission for publication or presentation. Investigator prepared manuscripts may be approved for publication or presentation by Spinogenix faster than six months and/or as described in a clinical trial agreement specific to this study. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by Spinogenix in writing, the investigator will withhold such publication for up to one year to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, Spinogenix will review these issues with the investigator. Spinogenix will not mandate modifications to scientific content and does not have the right to suppress information. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

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