# Guanfacine for Hyperactivity in Children with Down Syndrome (HYPEbeGONE_DS)

**NCT number** 06042257
**Document Date** 08/29/2023

# Pediatric Trials Network:

# Best Pharmaceuticals for Children Act

# Guanfacine for Hyperactivity in Children with Down Syndrome (HYPEbeGONE_DS)

**NICHD-2020-HYP01**

**Phase: 2**

**Funding Sponsor:**

## The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

**Funding Mechanism: Task Order**

| | |
|---|---|
| **Protocol Date:** | 29AUG2023 |
| **Protocol Version:** | 3.0 |
| **IND Number:** | 154035 |
| **NCT Number:** | 06042257 |

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# STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, International Council for Harmonisation (ICH) E6(R2) guideline for Good Clinical Practice (GCP), and the applicable regulatory requirements from the United States Code of Federal Regulations (CFR), including 45 CFR 46 (Human Subjects Protection); 21 CFR 312 (Investigational New Drug); 21 CFR 50 (Informed Consent), 21 CFR Part 54 (Financial Disclosure), and 21 CFR 56 (Institutional Review Board [IRB]); as well as international regulatory requirements, if applicable.

All individuals who are responsible for the conduct, management, or oversight of this study have completed Human Subjects Protection and ICH GCP Training.

# SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the investigator brochure or package insert/product label, and I agree that the protocol contains all necessary details for my staff and me to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to make all reasonable efforts to adhere to the attached protocol.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by the sponsor or the sponsor's representative. I will discuss this material with study personnel to ensure that they are fully informed about the efficacy and safety parameters and the conduct of the study in general. I am aware that, before beginning this study, the institutional review board (IRB), Research Ethics Board (REB) or Independent/ Institutional Ethic Committee (IEC) responsible for such matters must approve this protocol in the clinical facility where it will be conducted.

I agree to either obtain informed consent from participants, or obtain a waiver of informed consent (applicable to minimal risk studies only), as required by the IRB/REB/IEC of record and according to government regulations and International Council for Harmonisation guidelines. I further agree to report to the sponsor or its representative any adverse events in accordance with the terms of this protocol and the U.S. Code of Federal Regulations, Title 21, part 312.64, ICH GCP 4.11, as well as international regulatory requirements, if applicable. I further agree to ensure the study is conducted in accordance with the provisions as stated and will comply with the prevailing local laws and customs.

_____
Site Principal Investigator Name (Print)

_____ _____
Site Principal Investigator Signature Date

# STUDY PRINCIPAL INVESTIGATOR AND IND SPONSOR SIGNATURES

The signature below documents the review and approval of this protocol and the attachments (e.g., Manual of Procedures (MOP), package inserts), and provides the necessary assurances that this clinical study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and according to local legal and regulatory requirements and to the principles outlined in applicable U.S. and international regulations and ICH guidelines.

**Pediatric Trials Network Study Principal Investigator Name (Print or Type)**

**Pediatric Trials Network Study PI Signature** **Date**

**IND Sponsor (if different from above)**

**IND Sponsor's Signature** **Date**

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ABC | Aberrant Behavior Checklist |
| ABC-H | Aberrant Behavior Checklist Hyperactivity Subscale |
| ADHD | Attention-Deficit/Hyperactivity Disorder |
| AE | Adverse Event |
| ALCOA-C | Attributable, Legible, Contemporaneous, Original, Accurate, Complete |
| ALT | Alanine Transaminase |
| AR | Aortic Regurgitation |
| ASD | Autism Spectrum Disorder |
| asQ | Ask Suicide-Screening Questions |
| AST | Aspartate Transaminase |
| AUC | Area Under the Concentration Time Curve |
| AUCss/F | Apparent AUC Versus Time Curve at Steady State |
| BID | Twice Daily |
| BMI | Body Mass Index |
| BMP | Basic Metabolic Panel |
| BP | Blood Pressure |
| BPCA | Best Pharmaceuticals for Children Act |
| BUN | Blood Urea Nitrogen |
| CBC | Complete Blood Count |
| CFR | Code of Federal Regulations |
| CGI-I | Clinical Global Impression Improvement |
| CGI-S | Clinical Global Impression Severity |
| $CL_{ss}/F$ | Apparent Clearance |
| $C_{max,ss}$ | Steady State Peak Drug Concentration |
| $C_{min,ss}$ | Minimum Concentration |
| CMSU | Clinical Materials Services Unit |
| CNS | Central Nervous System |
| CoC | Certificate of Confidentiality |
| CPAP | Continuous Positive Airway Pressure |
| CSHQ | Child's Sleep Habits Questionnaire |
| DASH | NICHD's Data and Specimen Hub |
| DCC | Data Coordinating Center |
| DCRI | Duke Clinical Research Institute |
| DSMB | Data Safety Monitoring Board |
| DS | Down Syndrome |
| DUHS | Duke University Health System |
| eCRF | Electronic Case Report Form |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture e.g., Emmes Advantage eClinical® |
| ePRO | Electronic Participant Reported Outcomes |
| ER | Exposure-Response |
| ESI | Event of Special Interest |
| ESS-CHAD | Epworth Sleepiness Scale for Children and Adolescents |
| FDA | Food and Drug Administration |
| FWA | Federal-Wide Assurance |

| | |
|---|---|
| GCP | Good Clinical Practice |
| GER | Guanfacine Extended Release |
| GIR | Guanfacine Immediate Release |
| GMP | Good Manufacturing Practice |
| HCl | Hydrochloride |
| HDPE | High Density Polyethylene |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Heart rate |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| ICMJE | International Committee of Medical Journal Editors |
| ID | Identification |
| IDD | Intellectual or Developmental Disability |
| IEC | Independent or Institutional Ethics Committee |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ITT | Intent to Treat |
| Kg | Kilogram |
| LAR | Legally Authorized Representative |
| LFT | Liver Function Tests |
| MedDRA ® | Medical Dictionary for Regulatory Activities |
| Mg | Milligram |
| mL | Milliliter |
| MM | Medical Monitor |
| MOP | Manual of Procedures |
| NIH | National Institutes of Health |
| NICHD | National Institute of Child Health and Human Development |
| OAHI | Obstructive Apnea Hypopnea Index |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PO# | Masked Packaging Code |
| PP | Polypropylene |
| PTN | Pediatric Trials Network |
| q.h.s | Every night at bedtime |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event |
| SAR | Suspected Adverse Reaction |
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | Standard of Care |
| SUSAR | Suspected, Unexpected, Serious Adverse Reaction |
| $T_{max,ss}$ | Time at Peak Concentration |
| TORO | Transfer of Regulatory Obligations |
| TSH | Thyroid Stimulating Hormone |
| $t_{1/2}$ | Half-life |
| UIP | University of Iowa Pharmaceuticals |

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|---|---|
| ULN | Upper Limit of Normal |
| USP/NF | United States Pharmacopeia and National Formulary |
| V/F | Volume of Distribution |
| WBC | White Blood Cell |
| WGS | Whole Genome Sequencing |

# PROTOCOL HISTORY OF CHANGES

| Version | Date | Summary of Changes |
|---|---|---|
| v1.0 | 27FEB2023 | N/A Original protocol |
| v2.0 | 23MAY2023 | HR and BP assessment were added prior to each dose escalation.<br><br>Updated study design to indicate that participants will be given a FDA cleared device for parent/legal guardian to measure HR and BP remotely.<br><br>Added definition of HR and BP criteria that would prevent dose escalation.<br><br>Decreased HR and decreased BP were added as risks of Guanfacine Hydrochloride.<br><br>HR and BP criteria were initially listed as ESIs to only be assessed at in-persion visits (Week 4 and Week 8). They have now been moved to the general list of Safety ESIs.<br><br>References and Table of Contents (TOC) were updated accordingly. |
| v3.0 | 29AUG2023 | Added IND Number<br><br>Updated number of sites to approximately 17 sites.<br><br>Updated Exclusion Criteria to include any changes to another medication used to treat symptoms of hyperactivity, inattention and impulsivity within 2 weeks.<br><br>Updated to indicate that the HR/BP device would be distributed at Day 1 (randomization) instead of at Screening.<br><br>Added clarification that parents would need to complete the Study Diary during the bridge/taper period for those who are in the GIR arm. |

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| | | Updated definition of asQ from *Ask-Suicidal-Screening Questions* to *Ask Suicide-Screening Questions.*<br><br>Updated to indicate contraception is allowed but not required.<br><br>Specific references to *pharmacy* or *pharmacist* were removed and kept vague as *site* or clarified as *pharmacist (or designee).*<br><br>Changed *concomitant medications* to *concomitant medications of interest.*<br><br>Changed *Study Product Diary* to *Study Diary* since HR/BP was added to it.<br><br>Updated the definition of the efficacy population.<br><br>References and TOC were updated accordingly. |

# PROTOCOL SYNOPSIS

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|---|---|
| **Protocol Title:** | Guanfacine for Hyperactivity in Children with Down Syndrome (HYPEbeGONE_DS) |
| **NCT #:** | 06042257 |
| **Phase:** | Phase 2 |
| **Study Product(s) or Intervention:** | Guanfacine hydrochloride, Immediate Release |
| **Objectives:** | Primary:<br>1. Determine efficacy of guanfacine immediate release (GIR) for the treatment of hyperactivity/impulsivity and inattention in children with Down syndrome (DS) after 8 weeks of treatment.<br>Secondary:<br>1. Characterize the safety profile of GIR in children with DS.<br>Exploratory:<br>1. Characterize GIR exposure in children with DS.<br>2. Characterize the exposure-response relationship of GIR for the treatment of hyperactivity/impulsivity, inattention, and sleep quality in children with DS. |
| **Study Design:** | Prospective, multi-center, randomized, double-masked, placebo-controlled, flexibly-dosed trial |
| **Study Population:** | Children ages 6-12 years old with DS |
| **Inclusion Criteria:** | 1. Parent/Legal Guardian can understand the consent process and is willing to provide informed consent/HIPAA authorization prior to the conduct of any study related procedures. When applicable, the minor participant is willing to provide assent.<br>2. Participant has clinical diagnosis of non-mosaic DS.<br>3. Participant is between 6 and 12 years of age (inclusive) at time of consent.<br>4. Participant weight is ≥ 25 kg.<br>5. Participant has clinically significant symptoms of hyperactivity, inattention and impulsivity manifested as minimum scores on both of the following rating scales within 30 days of randomization:<br>a. A minimum score of 18 on the parent-reported Aberrant Behavior Checklist - Hyperactivity (ABC-H) subscale, AND<br>b. A minimum score of moderate or greater (≥ 4) on the clinician-reported Clinical Global Impression Severity |

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| | (CGI-S) score specific to hyperactivity, inattention, and impulsivity behaviors.<br>6. Participant has co-morbid medical screening and clearance to proceed with a non-stimulant medication trial with GIR within 30 days of randomization.<br>7. Participant is willing and able to comply with study procedures, including adherence to medication dosing schedule. |
| **Exclusion Criteria:** | 1. Participant has received guanfacine (any formulation) within 30 days of randomization.<br>2. Participant has received any of the following concomitant medication classes within 30 days of randomization:<br>a. Strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole)<br>b. Strong CYP3A4 inducers (e.g., avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort)<br>3. Participant has a psychiatric comorbidity, such as major depressive disorder, bipolar disorder, obsessive-compulsive disorder, or a psychotic disorder, that requires a pharmacological treatment other than guanfacine.<br>4. **For participants ≥ 8 years old at the time of consent**, participant has a history of suicidality or positive screen on Ask Suicide-Screening Questions (asQ) Tool.<br>5. Participant is currently in or plans to participate in another interventional study.<br>6. Participant has a known hypersensitivity to guanfacine.<br>7. Participant has had a previous guanfacine treatment failure, as determined by their primary treating physician.<br>8. Participant has had a change in another medication intended to treat symptoms of hyperactivity, inattention, and impulsivity within the last 2 weeks.<br>9. Participant has had a seizure within the last 6 months.<br>10. Participant has had a change in their anti-convulsant dose within the last 4 weeks.<br>11. Participant has a cardiac-related condition including:<br>a. Significant symptomatic bradycardia;<br>b. 2nd degree or 3rd degree (complete) heart block; |

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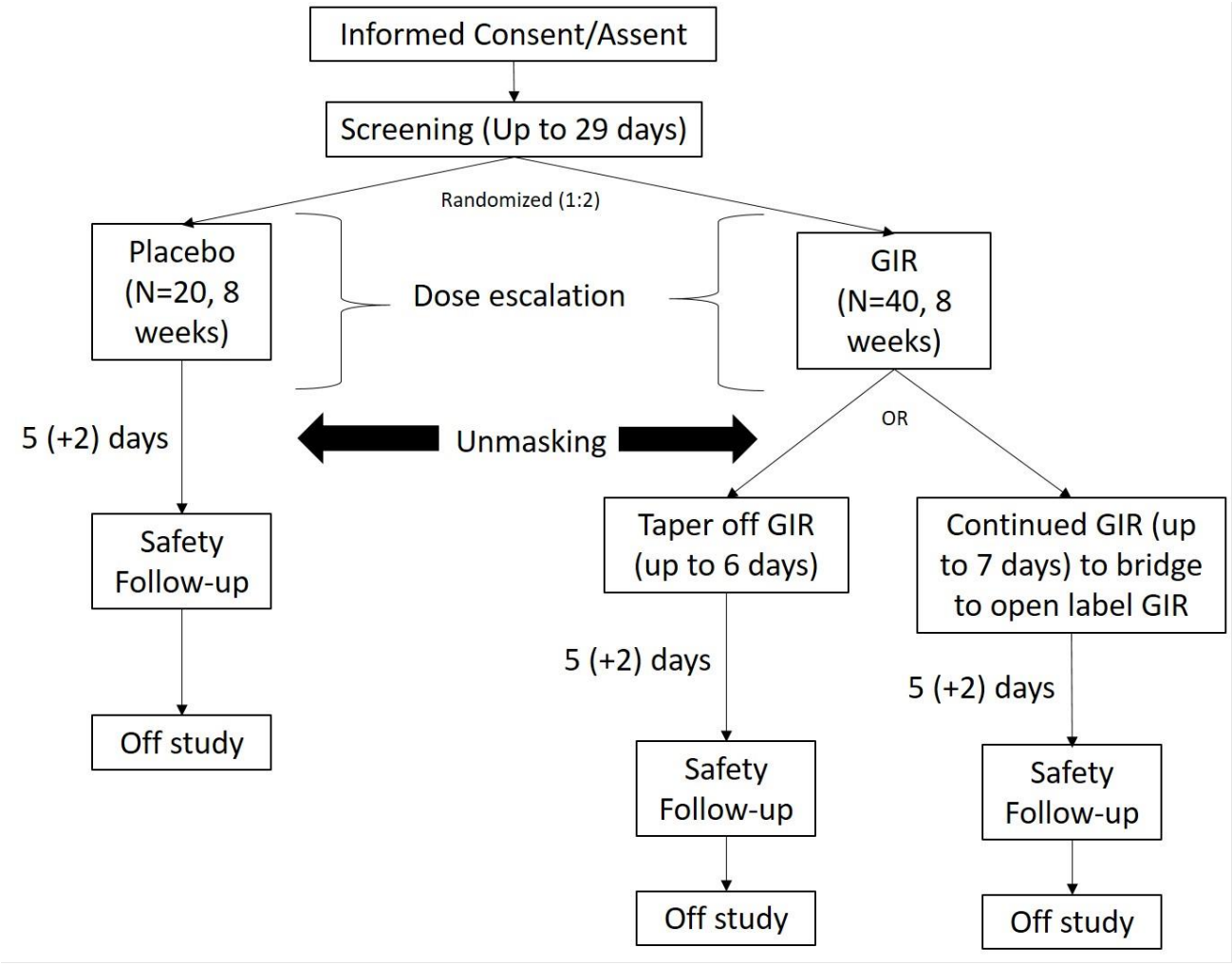
| | c. Baseline heart rate (HR) or systolic blood pressure (BP) > 2 standard deviations (SD) below mean for age as determined by medical examination;<br>d. History of aborted sudden cardiac death, unexplained syncope or near syncope, or historical use of a pacemaker as determined by medical history will require clearance by cardiology prior to enrollment;<br>e. Known history of congenital heart disease which requires ongoing care for monitoring or management will require clearance by cardiology prior to enrollment.<br>12. Participant has a history of untreated severe obstructive sleep apnea defined as obstructive apnea hypopnea index (OAHI) ≥ 10 events per hour or aortic regurgitation (AR). Participants with an OAHI index >10/hr are eligible if managed with continuous positive airway pressure (CPAP).<br>13. Participant has untreated thyroid disease.<br>14. Participant has a known hepatic impairment defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x the upper limit of normal (ULN) for age.<br>15. Participant has known impending or renal failure defined as:<br>a. Anuria diagnosed within 12 hours prior to enrollment;<br>b. Requiring renal replacement therapy.<br>16. Participant is pregnant.<br>17. Participant has any condition which would make the participant, in the opinion of the investigator, unsuitable for the study. |
| **Number of Participants:** | Approximately 60 participants, randomized 2:1 to GIR or placebo |
| **Number of Sites:** | Approximately 17 sites |
| **Duration of Participant Participation:** | A screening period of up to 29 days, followed by up to approximately 10 weeks of active study drug or placebo including follow-up |
| **Dose Schedule:** | Initiate dose at 0.5 mg at bedtime. Dose escalation of daily dose by 0.5 mg increments, on a BID schedule, as tolerated based on safety, HR, and BP assessments, no sooner than every 5 days up to a maximum dose of 3 mg/day (divided BID). |
| **Estimated Time to Complete Enrollment:** | Approximately 24 months |

# SCHEMATIC/DESCRIPTION OF STUDY DESIGN



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# 2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background Information

Section 409I of the Public Health Service Act, also known as The Best Pharmaceuticals for Children Act (BPCA) mandates the National Institutes of Health (NIH) to prioritize therapeutic areas in critical need for pediatric labeling; to sponsor pediatric clinical trials; and to submit these data to the Food and Drug Administration (FDA) for consideration for labeling changes. This study will be conducted in accordance with Section 409I of the Public Health Service Act; as such, the results from this research may be submitted to the FDA for review and use in negotiated labeling changes. This research study is contractually supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The NICHD awarded a contract to Duke University (Durham, NC), which established a Pediatric Trials Network (PTN) through its Duke Clinical Research Institute (DCRI) to facilitate trial design for studies supported by the NIH. The NICHD awarded a separate contract to The Emmes Company, LLC (Rockville, MD) to serve as the Data Coordinating Center (DCC).

See ICH E6 (R2) GCP, Section 6.2
(https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf)

### 2.1.1 Background of Attention-Deficit/Hyperactivity Disorder (ADHD) in Down Syndrome (DS)

**Clinical significance of ADHD in patients with Down syndrome:** Down syndrome (DS), caused by full or partial trisomy of chromosome 21, is the most frequent genetic cause of intellectual disability, occurring at an estimated prevalence of 12.9 per 10,000 individuals in the United States.[1,2] Children with DS are at risk for many comorbid conditions that require chronic medication therapies, and very little is known about drug disposition and effect in this population specifically.

Psychiatric and behavioral disorders are common in children with DS, with estimates of psychiatric comorbidity up to 38%.[3] Behavioral challenges, including hyperactivity and impulsivity, emerge as early as age 3, and it is estimated that between 10-45% of individuals with DS may be diagnosed with co-occurring ADHD[4,5] putting this population at high risk for other disruptive behaviors and comorbidities.[3,6-8] Hyperactivity and impulsivity place children with DS with baseline cognitive deficits at especially high risk for accidental injury and becoming lost or running away; and this becomes increasingly difficult to manage as they age into adulthood and other psychiatric comorbidities emerge.[3] Furthermore, there is a growing body of evidence suggesting that the diagnosis of DS itself confers a specific risk for ADHD compared to the general population, even more than other conditions associated with intellectual disability.[7,9]

**Outcome measures for ADHD in DS:** Identifying measures to evaluate cognition and behavior in children with intellectual or developmental disability (IDD) and DS specifically, within clinical trials has traditionally been challenging.[10] Leading clinician and scientific experts were assembled by the NIH to review existing measures and identify those that are appropriate for clinical trials in individuals with IDD and specifically DS.[11] The Aberrant Behavior Checklist (ABC) is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with IDD.[12] It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals with IDD across 5 domains: Irritability, Agitation, & Crying; Lethargy/Social Withdrawal; Stereotypic Behavior;

Hyperactivity/Noncompliance; and Inappropriate Speech, and it has been used extensively in pediatric and adult behavioral and psychiatric studies due to its high reliability and validity.[11,13] The ABC-hyperactivity (ABC-H) subscale has been the primary outcome measure in the only trial of Guanfacine Immediate Release (GIR) for ADHD and disruptive behaviors in children with DS, as well as in several trials of ADHD with and without Autism Spectrum Disorder (ASD) in children.[14-17] In addition to the ABC, the Clinical Global Impression (CGI) Scale will be utilized. The CGI was developed for use in National Institute of Mental Health-sponsored clinical trials to provide a brief, stand-alone clinician-determined summary measure prior to and after initiating a study medication that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function.[18] The CGI has two components – the CGI-Severity (CGI-S), which rates illness severity, and the CGI-Improvement (CGI-I), which rates change from the initiation (baseline) of treatment. The CGI is a widely used tool deemed appropriate for use in DS as identified by expert review. Previous studies have shown good concordance between parent/legal guardian and teacher ratings in neurotypical children[19] and children with ASD,[20] which supports the utility of this measure as a behavior outcome measurement in children with DS.

**Therapeutic options for treatment of ADHD in DS**: Recommended management of ADHD in neurotypically developing children, depending on age, includes a combination of medications and behavioral therapy in young children and medications alone in school age children and older. Medications approved by the FDA to treat ADHD in children include stimulants and non-stimulant classes of medications.[21] While stimulant medications (ex, methylphenidate, dexmethylphenidate, amphetamines) are very effective in the treatment of ADHD in neurotypically developing children, and are in fact considered the preferred first line therapy, studies in neurodevelopmental disorders, such as ASD, suggest that individuals with neurodevelopmental disorders respond differently to stimulant medications. Not only have they been shown to be less effective, but also have decreased tolerability and an unacceptable side effect profile specifically upon appetite and growth.[16,21] Furthermore, individuals with DS have an increased risk of congenital heart disease, which further limits the use of stimulant medications in this population.

Non-stimulant medications used for the treatment of ADHD include atomoxetine, clonidine, and guanfacine. Both clonidine and guanfacine are central alpha 2A-adrenergic receptor agonists thought to exert their actions through presynaptic stimulation and likely involve facilitation of both dopamine and noradrenaline neurotransmission, important in the pathophysiology of ADHD.[22] Although the effect size is reportedly slightly less than the stimulant medications, non-stimulant medications are well accepted and may be preferred when stimulant medications are ineffective or the side effects intolerable, which has been reported in up to 30-50% of children and adults.[23-25] Many thought leaders prefer guanfacine to clonidine in clinical practice because guanfacine has less sedation side effects than clonidine. Guanfacine IR (immediate release), or GIR, and Guanfacine Extended Release (GER) have been shown to be safe and effective in children with ASD and IDD,[14,15,17] and one study has shown that GIR is effective and well tolerated in children with DS.[6] However, only the extended release formulation, GER, is currently FDA approved for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children based on two clinical trials conducted in patients aged 6–17 years who met DSM-IV® criteria for ADHD.[26-28]

Prescribing guidelines report differences in pharmacokinetics and exposure between GIR and GER, and note that a dose substitution on a milligram for milligram basis will result in differences in exposure (INTUNIV® label);[26] GIR is 80% bioavailable and the relative bioavailability of GER tablets to GIR tablets is 58%. Compared to GIR, the Area Under the

Curve (AUC) and maximum serum concentration (Cmax) of GER tablets are 43% and 60% lower, respectively. Peak plasma concentrations occur 1 to 4 (average 2.6) hours after a single oral dose of GIR in adults and adolescents with hypertension and 5 hours after oral administration of extended-release tablets to children and adolescents with ADHD. However, studies have found that similar pharmacokinetics can be achieved between formulations. For example, plasma trough concentrations were similar in adults treated for smoking cessation with 3 mg/day administered BID of GIR and 4 mg/day of GER (3 mg/day GIR: M=3.40 ng/mL, standard error (SE) 0.34 vs. 4 mg/day GER: M=3.46 ng/mL, SE=0.67) with similar safety profiles between formulations.[29]

The GER formulation is a practical challenge to prescribe in children with DS because the pill cannot be crushed and must be swallowed whole, and children with DS are at a high risk for comorbid dysphagia and swallowing dysfunction that puts them at significant risk for aspiration.[30] Safely swallowing tablets is a challenge. Children with DS have also been shown to have high risk for sleep apnea and baseline diminished blood pressure profiles compared to age-matched controls,[31] thus this elevates the safety concerns for sedation and hypotension as known side effects that could be prolonged with an extended release formulation. As such, providers are using GIR to treat ADHD in children with DS in clinical practice with dosing strategies guided by the monitoring of side effects as doses are escalated. No formal dosing guidance exists for this population.

### 2.1.2 Pediatric Labeling of Guanfacine

**Adult:** Guanfacine immediate release (GIR) is FDA approved for the management of hypertension. It may be given alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

**Pediatric:** Included on the GIR label: Safety and effectiveness in children under 12 years of age have not been demonstrated. There is no specific information included regarding the use for ADHD/hyperactivity, inattention, or impulsivity. Adverse reactions noted with guanfacine hydrochloride are similar to those of other drugs of the central α2-adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing. Adverse events (AEs) reported in post marketing at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache, and nausea.[32]

There have been spontaneous post-marketing reports of mania and aggressive behavioral changes in pediatric patients with ADHD receiving GIR tablets. The reported cases were from a single center. All patients had medical or family risk factors for bipolar disorder. All patients recovered upon discontinuation of guanfacine tablets. Hallucinations have been reported in pediatric patients receiving guanfacine tablets for treatment of ADHD.

Included in the label for GER: INTUNIV® is indicated for the treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications. INTUNIV® was studied for the treatment of ADHD in three controlled monotherapy clinical trials (up to 8 weeks in duration) and one controlled adjunctive trial with psychostimulants (8 weeks in duration) in children and adolescents ages 6-17 who met DSM-IV® criteria for ADHD. The effectiveness of INTUNIV® for longer-term use (more than 8 weeks) has not been systematically evaluated in controlled trials.

## 2.2 Scientific Rationale

As mentioned in Section **2.1.1**, one study has shown that guanfacine is effective and tolerated in children with DS.[6] While the aforementioned study demonstrated preliminary data, it was limited by the fact that it was open-label, did not include a randomized placebo group, and did not

include scheduled dose increases or follow-ups. To date, there are no randomized, masked, placebo-controlled studies of any ADHD medication in children with DS. This is a significant gap in care for these individuals for a number of reasons: 1) This is a high-risk population for ADHD, with 2) inherent challenges using FDA-approved formulations, and 3) specific comorbidities that make them a uniquely vulnerable population for both the diagnosis and treatment of ADHD.[33] Trials to evaluate drug efficacy and safety coupled with drug exposure data are desperately needed to ensure safe and effective dosing in children with DS.

## 2.3 Potential Benefits

The use of GIR in this population may result in improved hyperactivity measures, including irritability in participants who are randomized to study drug; however, it is unknown if there will be a benefit to the participant for being in this study. Nonetheless, by sharing the study data and specimens (via NICHD's Data and Specimen Hub (DASH)), children in the future may benefit.

## 2.4 Known Potential Risks

### 2.4.1 Risks of Blood Drawing

It is possible that the participant will feel discomfort during the blood draw. It is also possible there will be bruising, swelling or bleeding where the needle enters the skin. The participant may also feel dizzy or a little light-headed when blood is drawn. Every effort should be made to avoid non-standard-of-care draw/sticks for this study and to time clinical blood draws with timed study specimens.

### 2.4.2 Risks of Guanfacine Hydrochloride

Adverse reactions associated with guanfacine hydrochloride include:

- Dry mouth
- Sedation (somnolence)
- Weakness (asthenia)
- Dizziness
- Constipation
- Impotence
- Decreased HR
- Decreased BP

Most reactions are mild and typically disappear after continued dosing.

### 2.4.3 Potential Risk of Loss of Confidentiality

There is a potential risk of loss of confidentiality. Every effort will be made to protect the participant's confidential medical information, but this cannot be guaranteed.

### 2.4.4 Unforeseen Risks

There may be other risks to the participant from this research that are not known or foreseeable at this time.

# 3 OBJECTIVES AND OUTCOME MEASURES

| | Objectives | Outcome Measure(s) | Endpoint(s) |
|---|---|---|---|
| Primary Objective: | Determine efficacy of GIR for the treatment of hyperactivity/impulsivity and inattention in children with DS after 8 weeks of treatment. | Primary Efficacy Outcome Measure: Parent-rated ABC-H subscale score<br><br>Secondary Efficacy Outcome Measure: CGI-I specific to hyperactivity, inattention and impulsivity behaviors | Primary Endpoint: Change from baseline to Week 8 of the ABC-H subscale score<br><br>Secondary Efficacy Endpoints: Change from baseline to Week 4 of the ABC-H subscale score. Proportion of participants with a CGI-I score of 2 or better at Week 4 and Week 8. |
| Secondary Objective: | Characterize the safety profile of GIR in children with DS. | • Adverse Events (AEs)<br>• Serious Adverse Events (SAEs)<br>• Safety Events of Special Interest (ESIs) | Incidence of AEs, SAEs, and safety ESIs through Week 8 |
| Exploratory Objective 1: | Characterize GIR exposure in children with DS. | Guanfacine HCl plasma concentration | Guanfacine HCl exposure at Week 4 and Week 8 as indicated by the following endpoints:<br>• Steady state peak drug concentration ($C_{max,ss}$)<br>• Time at peak concentration ($T_{max,ss}$)<br>• Minimum concentration ($C_{min,ss}$)<br>• Apparent area under the concentration versus time curve at steady state ($AUC_{ss}/F$)<br>• Apparent clearance ($CL_{ss}/F$)<br>• Volume of distribution (V/F)<br>• Half-life ($t_{1/2}$) |
| Exploratory Objective 2: | Characterize the exposure-response relationship of GIR for the treatment of hyperactivity/impulsivity, inattention, and sleep quality in children with DS. | • Guanfacine HCl plasma concentrations ($C_{max,ss}$ and $C_{min,ss}$)<br>• Area under the concentration time curve ($AUC_{ss}$)<br>• ABC-H subscale score<br>• CGI-I<br>• Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD)<br>• Child's Sleep Habits Questionnaire (CSHQ) | Change in behavioral and sleep scales (ABC-H, CGI-I, ESS-CHAD, and CSHQ) relative to Guanfacine HCl plasma concentration ($C_{max,ss}$ and $C_{min,ss}$) and $AUC_{ss}$ at Week 4 and Week 8 |

# 4 STUDY DESIGN

## 4.1 Overall Design

A prospective, multi-center, randomized, double-masked, placebo-controlled, flexibly-dosed trial.

## 4.2 Study Design

### 4.2.1 Randomization

Participants will be randomized 2:1 to GIR or placebo.

### 4.2.2 Masking/Unmasking

A masked pharmacist or designee will dispense study product according to randomization treatment assignments. All other site staff as well as participants and parents/legal guardians will also be masked for up to 8 weeks while the study participant is receiving study product. Participants, parents/legal guardians, site staff, and study administrators will be unmasked at the 8 week study visit. Emergency unmasking may occur at any time throughout the study in the event that knowledge of the actual treatment is absolutely essential for further management of the participant. Refer to Section **4.4** below and to the Manual of Procedures (MOP) for details.

Unmasking at the 8-week visit is necessary to maintain ethical practice as guanfacine is a commercially available product, and it would be unethical to wean a study participant off of guanfacine if they and their treating clinician determine that it is best for them to maintain treatment outside of the study.

## 4.3 Study Intervention

Investigational, non-marketed, guanfacine hydrochloride immediate release (GIR) 0.5 mg capsules and matching placebo capsules.

## 4.4 Duration of Participant Participation

Participants will undergo a screening period of up to 29 days. Eligible participants will receive GIR for up to 8 weeks plus a bridge or taper period, or placebo for up to 8 weeks. The treatment period will consist of study product administration from day 0 through day 56 with a masked dose-escalation period from day 0 through day 49. Unmasking of participant and site staff will occur after the week 8, in-person assessment, Day 56 (± 3 days).

After unmasking, participants who were randomized to receive placebo will have a final telephone safety assessment 5 (+ 2) days after final study dose is administered.

After unmasking, participants who were randomized to receive GIR will be given the option to 1) remain on GIR and to transition to open-label GIR per standard of care or 2) taper off of GIR. If the participant, in consultation with their clinical provider, chooses to remain on open-label GIR via standard of care, participants will have enough study product to allow for a 7-day bridge of manufactured GIR study drug to allow time to receive the routine clinical prescription of non-study provided GIR. A final telephone safety assessment will occur 5 (+ 2) days after final manufactured GIR study dose is administered. Alternatively, if the participant, in consultation with their clinical provider, chooses to discontinue GIR, a manufactured GIR taper will be instructed to proceed by a decrease of 1 mg every 3 days (maximum 6 day duration, depending on final study dose) to minimize rebound hypertension. A final telephone safety assessment will occur 5 (+ 2) days after the final manufactured GIR study dose is administered.

## 4.5 Biological Specimen Collection

Blood will be collected at the Week 4 and Week 8 visits for PK analysis and lab assessments.

## 4.6 Biological Specimen Retention Plan

See Section **11**.

## 4.7 Safety

All AEs, SAEs, and safety ESIs will be collected from the time of first study product administration through the end of study participation.

## 4.8 Scientific Rationale for Study Design

A randomized, double-masked, placebo-controlled trial will minimize bias and control for confounders. A 2:1 randomization will be used to improve recruitment capacity as parent representatives have indicated that it would be more desirable to enroll their children on a trial that has a greater probability of receiving study drug versus placebo. This was particularly important due to guanfacine being commercially available. Participants will be given an FDA cleared device for parent/legal guardian to measure HR and BP remotely. These assessments will be evaluated prior to each dose escalation. A guided dose-escalation will be used; however, investigators or their designee have flexibility to maintain or decrease a dose based on safety and/or efficacy assessments. Prior networks have utilized a guided dose escalation strategy based on clinical effect and tolerance, similar to dose escalation in clinical practice. This trial will prove the feasibility of masking and randomization, and obtain requisite plasma samples to allow measurement of drug exposure.

## 4.9 Rationale for Dose Selection

The recommended initial dose of GIR tablets for hypertension when given alone or in combination with another antihypertensive drug is 1 mg daily given at bedtime to minimize somnolence. If after 3 to 4 weeks of therapy 1 mg does not give a satisfactory result, a dose of 2 mg may be given. The current labeled dose range for GER is 0.05-0.08 mg/kg/day, with higher doses of 0.12 mg/kg once daily potentially offering additional benefit. A recommended dosing range for GER is 1 to 4 mg once daily.

Dose escalation plans were created for children ≥ 25 kg, based on previous studies in IDD children who were treated with guanfacine,[14] and were further refined by experts in the clinical care of children with DS. A starting dose of 0.5 mg at bedtime was determined to be the safest starting dose in children weighing ≥ 25 kg. Limiting the participants to children ≥ 25 kg was decided to allow for the safest dose-escalation plan of 0.5 mg increments. Details of the dose escalation plan are shown in **Table 3**. Prior to each dose escalation assessment, parent/legal guardian will be asked to measure HR and BP using the device given to them from the study team at the time of randomization. The maximum dose will be 3 mg daily, which is below the highest tolerated dose (4 mg daily for GER) in children aged 6-12 years old and ≥ 25 kg. This maximum dose was selected by experts in the field based on clinical practice, which dictates that if symptoms are not manageable with 3 mg daily, the patient is taken off GIR or an additional therapeutic agent is added. This dose range is within the dose range used in studies of neurotypical children aged 6-12 years of age as referenced on the INTUNIV® (GER) label.

Currently, there are no pharmacokinetic (PK) data for GIR specific to children with DS, and although significant differences in drug disposition are not expected, there is no evidence to confirm that the exposure of guanfacine in DS is similar to neurotypical children.

## 4.10 Study Definition of Enrollment into Active Study

Study enrollment into Active Study is defined as participant has provided informed consent, met all eligibility criteria, and is randomized.

## 4.11 Study Definition of Completion

Study completion is defined as the last enrolled participant has completed the Final Telephone Safety Assessment 5 (+ 2) days after completion of study product.

Each participant will reach study completion after they have completed the Final Telephone Safety Assessment 5 (+ 2) days after completion of study product or all assessments required for Early Study Withdrawal if they withdraw from the study early (Section **6.6**).

# 5 STUDY POPULATION

## 5.1 Selection of the Study Population

A total of 60 eligible participants will be enrolled on this study.

## 5.2 Inclusion/Exclusion Criteria

| | |
|---|---|
| **Inclusion Criteria** | 1. Parent/Legal Guardian can understand the consent process and is willing to provide informed consent/HIPAA authorization prior to the conduct of any study-related procedures. When applicable, the minor participant is willing to provide assent.<br>2. Participant has clinical diagnosis of non-mosaic DS.<br>3. Participant is between 6 and 12 years of age (inclusive) at time of consent.<br>4. Participant weight is ≥ 25 kg.<br>5. Participant has clinically significant symptoms of hyperactivity, inattention and impulsivity manifested as minimum scores of the following rating scales within 30 days of randomization:<br>a. A minimum score of 18 on the parent-reported ABC-H subscale, AND<br>b. A minimum score of moderate or greater (≥ 4) on the clinician reported Clinical Global Impression Severity (CGI-S) score specific to hyperactivity, inattention and impulsivity behaviors.<br>6. Participant has co-morbid medical screening and clearance to proceed with a non-stimulant medication trial with GIR within 30 days of randomization.<br>7. Participant is willing and able to comply with study procedures, including adherence to medication dosing schedule. |
| **Exclusion Criteria** | 1. Participant has received guanfacine (any formulation) within 30 days of randomization.<br>2. Participant has received any of the following concomitant medication classes within 30 days of randomization:<br>a. Strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole)<br>b. Strong CYP3A4 inducers (e.g., avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort)<br>3. Participant has a psychiatric comorbidity, such as major depressive disorder, bipolar disorder, obsessive-compulsive disorder, or a psychotic disorder, that requires a pharmacological treatment other than guanfacine. |

4. **For participants ≥ 8 years old at the time of consent,** participant has a history of suicidality or positive screen on Ask Suicide-Screening Questions (asQ) Tool.
5. Participant is currently in or plans to participate in another interventional study.
6. Participant has a known hypersensitivity to guanfacine.
7. Participant has had a previous guanfacine treatment failure, as determined by their primary treating physician.
8. Participant has had a change in another medication intended to treat symptoms of hyperactivity, inattention, and impulsivity within the last 2 weeks.
9. Participant has had a seizure within the last 6 months.
10. Participant has had a change in their anti-convulsant dose within the last 4 weeks.
11. Participant has a cardiac-related condition including:
    a. Significant symptomatic bradycardia;
    b. 2nd degree or 3rd degree (complete) heart block;
    c. Baseline heart rate (HR) or systolic blood pressure (BP) > 2 standard deviations (SD) below mean for age as determined by medical examination;
    d. History of aborted sudden cardiac death, unexplained syncope or near syncope, or historical use of a pacemaker as determined by medical history will require clearance by cardiology prior to enrollment;
    e. Known history of congenital heart disease which requires ongoing care for monitoring or management will require clearance by cardiology prior to enrollment.
12. Participant has a history of untreated severe obstructive sleep apnea defined as obstructive apnea hypopnea index (OAHI) ≥ 10 events per hour or aortic regurgitation (AR). Participants with an OAHI index > 10/hr are eligible if managed with continuous positive airway pressure (CPAP).
13. Participant has untreated thyroid disease.
14. Participant has a known hepatic impairment defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal (ULN) for age.
15. Participant has known impending or renal failure defined as:
    a. Anuria diagnosed within 12 hours prior to enrollment;
    b. Requiring renal replacement therapy.
16. Participant is pregnant (refer to Section **7.6.1**).
17. Participant has any condition which would make the participant, in the opinion of the investigator, unsuitable for the study.

## 5.3 Screen Failures

Participants who provide informed consent, but who are not ultimately randomized in the Active Study (Section **4.10**), will be considered screen failures and will remain in the screening segment of the data system. The reason for screen failure will be captured in the data system.

## 5.4 Treatment Assignment Procedures

### 5.4.1 Randomization Procedures

Eligible participants will be randomly assigned in a 2:1 ratio to either GIR or placebo. The participant's randomized treatment assignment will be obtained through the Advantage eClinical® enrollment module. In the event that Advantage eClinical® is not available at the time of randomization, a back-up system specified in the MOP will be used. Randomization will be stratified by study site. The randomization procedure will be conducted centrally through the study data system and randomization assignments will not be conveyed to participants or study sites. The DCC statistician will generate the randomization schedule using balanced blocks within site to ensure relative equality of assignment across treatment groups. A DCC statistician will review randomization data on a regular basis to ensure that the scheme is being implemented according to plan. A randomization assignment, once issued, will not be re-allocated. Details of the randomization process are described in a separate Randomization Plan.

## 5.5 Participant Discontinuation/Withdrawal

### 5.5.1 Participant/Parent/Legal Guardian Decides to Withdraw Consent

Participants or their parent/legal guardian may voluntarily withdraw consent to participate in the study at any time. Participants or their parent/legal guardian are not obligated to state the reason for withdrawal. The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator. No additional study procedures or data should be collected after consent has been withdrawn.

### 5.5.2 Participant/Parent/Legal Guardian Decides to Withdraw from Study Product

Participants or their parent/legal guardian may also withdraw from receiving the study product for any reason but continue to be followed for safety, including safety ESIs.

Participants or their parent/legal guardian are not obligated to state the reason for withdrawal.

At the time of withdrawal from study product, participants (and site staff) will be unmasked and asked to complete an electrocardiogram (ECG), as well as provide a PK blood sample. Participants, who were randomized to receive GIR, will be transitioned off of GIR according to the dose taper process described in Section **6.13.2** followed by a final telephone safety assessment 5 (+ 2) days after the final study dose administered. Participants who were randomized to receive placebo will have a final telephone safety assessment 5 (+ 2) days after final study dose administered. The parent/legal guardian will be asked to complete the Aberrant Behavior Checklist (ABC) and the treating clinician will be asked to perform a CGI-I. Unmasking should only occur following completion of the other Early Withdrawal / Termination Visit Assessments (Section **6.6**). Refer to the MOP for details.

### 5.5.3 Study Investigator/Sponsor Decides to Withdraw Participant

The study doctors or sponsor may decide to take the participant out of this study without consent if:

- Participant's condition changes and the study is no longer in their best interest
- Participant/parent/legal guardian non-compliance with the study protocol
- The entire study is stopped by the FDA or the sponsor

A participant may be withdrawn from receiving study product if they experience a clinically significant AE that requires discontinuation of treatment, at the discretion of the study doctor or sponsor.

If any of the above occurs, the participant/parent/legal guardian will be informed and the investigator will discuss other options.

## 5.6 Handling of Withdrawals

The reasons for withdrawal, or failure to provide a reason, must be documented by the investigator.

Reasons of withdrawal may include:

- Parents/legal guardians of participants who withdraw consent and request no further follow-up
- If minor participants decide not to remain in the study, they will be withdrawn even if the parent/legal guardian of the minor participant has not withdrawn consent.
- Study Investigator/Sponsor decision

### 5.6.1 Early Withdrawal/Discontinuation Assessments

Refer to Section **6.13.2** for study product taper requirements. The following assessments will be collected at the time of early termination/withdrawal: ABC, ECG, a PK blood sample, and CGI-I. If a participant/legal guardian withdraws consent, no further follow-up will occur following withdrawal of consent. Participants who are discontinued from study drug due to an AE, whether serious or non-serious, must be followed by the investigator until the AE is resolved or considered stable. The medical monitor (MM) or study investigator must be notified if the AE may relate to overdose of study treatment; the package insert should be consulted for details of any specific actions to be taken.

### 5.6.2 Replacements

In all cases of early withdrawal from study, a replacement participant may be enrolled.

# 6 STUDY PROCEDURES

## 6.1 Summary of Procedures

**Table 1. Schedule of Study Procedures and Assessments**

| | Screening | Study Intervention (Weeks 1-3) | Study Intervention (Week 4) | Study Intervention (Weeks 5-7) | Study Intervention (Week 8) | Taper/ Bridge | Follow-Up | Early With-drawal/ Discon-tinuation |
|---|---|---|---|---|---|---|---|---|
| | Day -29 to 0[1] | Day 1[1]-21 (± 1 day) | Day 22-28 (± 3 days) | Day 29-49 (± 1 day) | Day 50-56 (± 3 days) | | 5 (+ 2) days post final study dose | |
| Informed consent/assent | X | | | | | | | |
| Distribution of device for remote HR and BP assessment | | X[3] | | | | | | |
| Demographics | X | | | | | | | |
| Medical History | X | | | | | | | |
| Physical Exam | X | X[3] | | | | | | |
| Weight/height | | | X | | X | | | |
| Vital Signs | X | X[3] | X | | X | | | |
| Concomitant Medications of Interest | X | | X | | X | | | |
| ECG | X | | X | | X | | | X |
| Lab assessments | X | | X[11] | | | | | |
| Pregnancy test[13] | X | | | | | | | |
| Blood Collection for PK | | | X[2] | | X[2] | | | X[2] |
| Randomization | | X[3] | | | | | | |
| Dose escalation with HR and BP assessment | | X[4] | X[4] | X[4] | | | | |
| Study product administration | | X[5] | X | X | X | | | |
| Unmasking | | | | | X | | | X |
| Study drug taper/bridge | | | | | | X[6] | | X |
| Study Diary | | Continuous | | | | X[6] | X[6] | |
| CGI-S | X | | | | | | | |
| CGI-I | | X[7] | X | X[7] | X | | | X |
| ABC | X | | X | | X | | | X |
| asQ Tool[12] | X | | X | | X | | | |
| Sleep assessments | | X[3] | X | | X | | | |
| Safety Events[8] | X[9] | X | X | X | X | X | X[10] | X |

1 – Day 0 and Day 1 may be the same calendar day.
2 – Preferred sampling: within 60 minutes prior to study product dose or 30-120 minutes after study product dose.
3 – Randomization; distribution of device for remote HR and BP assessment; physical exam, including weight/height; vital signs; and sleep assessments occur only on Day 1 prior to study product administration.
4 – Just prior to dose escalation time point, every 5 (+ 2) days, parent/legal guardian will be asked to measure HR and BP.
5 – Initial dose occurs on Day 1, Day 0 and Day 1 may be the same calendar day. The initial dose will be administered before bedtime on Day 1. Subsequent doses occur according to Section **6.13.1**.
6 – For GIR arm only. Participants who choose to discontinue GIR will be tapered off study drug at 1 mg every 3 days. Participants who choose to transition to standard of care GIR will continue on up to 7 days of study drug to bridge to standard of care GIR. See Section **6.13.2**.
7 – Weekly CGI-I, beginning at first weekly telephone assessment.
8 – Includes AEs, SAEs, and safety ESIs, as described in Section **7.1.2**.
9 – Only AEs directly related to study procedures (e.g., blood collection) during the screening period will be collected.
10 – A final Telephone Safety Assessment, including all safety events, will occur at 5 (+ 2) days after final study product administration.
11 – In the rare event that blood cannot be collected for any reason at Week 4, blood for LFTs can be collected at the Week 8 visit.
12 – Only used in participants ≥ 8 years old, as described in Section **6.10**.
13 – For participants who have reached menarche only, either urine or blood test is acceptable.

## 6.2 Screening (Day -29 to 0)

The investigator will screen participants in accordance with the eligibility criteria detailed previously (Section **5.2**). The investigator will not exercise selectivity so that bias is prevented.

The following assessments/procedures will occur during the Screening period:

- Informed consent/assent
- Demographics, including identified gender, race, ethnicity, and date of birth
- Complete Medical history
- Physical exam, including weight and height
- Vital signs, including BP and HR
- Concomitant medications of interest
- ECG
- Lab assessments for baseline complete blood count (CBC) w/differential, basic metabolic panel (BMP), liver function tests (LFTs), Thyroid function studies (Thyroid Stimulating Hormone [TSH], free T4)
- For participants who have reached menarche only, pregnancy test (urine or blood test is acceptable)
- CGI-S for Eligibility (Section **6.9.3**)
- ABC for Eligibility (Section **0**)
- asQ for Eligibility, as appropriate, for participants ≥ 8 years old who do not have prior known suicidality (Section **6.10**)
- AEs directly related to study procedures

## 6.3 Study Intervention (Day 1 to 56 ± 3 days)

Day 1 (Day 0 and Day 1 may be the same calendar day):

- Randomization
- Physical exam, including weight and height
- Vital signs, including BP and HR
- Study product administration – single dose at bedtime on Day 1
- Study Diary completion training and provision
- Safety Events, including AEs, SAEs, and safety ESIs; collection of safety events will be initiated after the first study product administration
- Parent/legal guardian-completed sleep assessments (Section **6.9.2**)

Weeks 1-3 (Day 1-21 ± 1 day):

- Study-product administration
- Dose escalation with BP and HR assessment (Section **6.8**), prior to dose escalation time point, every 5 (+ 2) days.
- Safety Events, including AEs, SAEs, and safety ESIs

- Study Diary review
- Clinician completed weekly CGI-I, beginning at first weekly telephone assessment (approximately Day 5) (Section **6.9.3**)

Week 4 (Day 22-28 ± 3 days):

- Concomitant medications of interest
- Weight/height
- Vital signs, including HR and BP
- ECG
- Lab assessments for liver toxicity: LFTs
- Blood Collection for PK
- Dose-escalation assessment (Section **6.8**)
- Study-product administration
- Study Diary review
- Clinician-completed CGI-I (Section **6.9.3**)
- Parent/legal guardian-completed ABC (Section **0**)
- Parent/legal guardian-completed sleep assessments (Section **6.9.2**)
- asQ, as appropriate, for participants ≥ 8 years old (Section **6.10**)
- Safety Events, including AEs, SAEs, and safety ESIs

Weeks 5-7 (Day 29-49 ± 1 day):

- Dose-escalation with BP and HR assessment (Section **6.8**), prior to dose escalation time point, every 5 (+ 2) days
- Study-product administration
- Study Diary review
- Clinician-completed weekly CGI-I (Section **6.9.3**)
- Safety Events, including AEs, SAEs, and safety ESIs

Week 8 (Day 50-56 ± 3 days):

- Weight/height
- Vital signs, including HR and BP
- Concomitant medications of interest
- ECG
- Lab assessments for liver toxicity: LFTs, *only if unable to collect at the Week 4 visit*
- Blood Collection for PK
- Study-product administration
- Study Diary review

- Clinician-completed CGI-I (Section **6.9.3**)
- Parent/legal guardian-completed ABC (Section **0**)
- Parent/legal guardian-completed sleep assessments (Section **6.9.2**)
- asQ, as appropriate, for participants ≥ 8 years old (Section **6.10**)
- Safety Events, including AEs, SAEs, and safety ESIs
- Unmasking of participant to determine standard of care plan

## 6.4 GIR Taper/Bridge (Up to 6 days post last study product administration)

Procedures will vary for those participants who are randomized to receive study drug, depending on their decision for GIR treatment following unmasking.

- Participants randomized to receive study drug, who choose to discontinue GIR:
  - See Dose Discontinuation/Taper (Section **6.13.2**)
  - Study Diary completion
- Participants randomized to receive study drug, who choose to transition to open-label GIR per standard of care:
  - Participants will have enough study product to allow for a 7-day bridge of manufactured GIR and will be instructed to contact their heathcare provider in order to obtain a clinical prescription of GIR within 7 days.
  - Study Diary completion

Note: Participants randomized to receive placebo will proceed directly to the Telephone Safety Follow-up (Section **6.5**)

## 6.5 Telephone Safety Follow-up (5 + 2 days after final study product administration)

A Telephone Safety Assessment, including a Study Diary review will be conducted for all participants, at 5 (+2) days after final study-provided product administration.

## 6.6 Early Withdrawal / Termination Visit

If a participant withdraws from study product administration or terminates from the study early, the study team will attempt to collect the following at an in-person visit, if an in-person visit is not feasible, a telephone assessment will occur to obtain the following assessments/procedures:

- Safety Events, including AEs, SAEs, and safety ESIs
- ECG (in-person only)
- Parent/legal guardian-completed ABC (Section **0**)
- Clinician-completed CGI-I (Section **6.9.3**)
- Blood collection for PK analysis (in-person only)
- Unmasking of participant and manage GIR Taper/Bridge per Section **6.4**. Unmasking should only occur following completion of the other Early Withdrawal / Termination Visit Assessments above.

## 6.7 Laboratory Evaluations

### 6.7.1 Pharmacokinetic Specimens

Opportunistic blood collection for PK analysis will occur at the Week 4 and Week 8 visits. Samples will be derived from the plasma matrix.

**Collect study product information for up to 8 doses prior to the sampling dose (last dose prior to PK biological sample collection):**

- Exact date and time of previous study product dose administration
- Dose amount
- Dose number
- Dose frequency
- Dosing weight
- Actual weight from physical exam at corresponding week
- Height from physical exam at corresponding week
- Formulation (i.e., capsule swallowed or capsule contents mixed with food)
- Food intake [yes (fed); no (fasted)]
- If food intake yes, please enter what food was mixed with contents

**Sampling Information to be collected at time of blood draw:**

- Exact date and time the sample is drawn
- Exact date and time the sample is frozen/stored
- Sample volume (estimated)
- Sample type (i.e., plasma, whole blood, etc.)
- Source of blood sample (i.e., arterial vs. venous)
- Sampling site

**Concomitant Medications of Interest Information:**

- Presence of concomitant medications of interest* within 24 hours before and after the dose of study product closest to the time of biological sample collection
- Total dose amount (per day)
- Route of administration

*Only concomitant medications of interest (see Section **6.17**) for specific drugs will be recorded on the eCRF.

**Timing of Sample Collection: Preferred Sampling Windows for PK include:**

1) Peak sample: within 30 to 120 minutes *after* study product dose*
2) Trough sample: within 60 minutes *prior to* next study product dose*

*Samples obtained outside those windows are not protocol deviations.

### 6.7.2 Clinical Laboratory Determinations

The following hematologic values are required to be collected at screening: hematocrit, white blood cell (WBC) count, platelet count, and differential. The following serum chemistry values are required to be collected at screening: blood urea nitrogen (BUN), serum creatinine, potassium, sodium, AST, ALT, total bilirubin, and albumin. Thyroid function will be measured, including TSH and free thyroxine, T4. If these values were obtained via standard of care within 30 days of enrollment, these values can be used; otherwise, they must be obtained prior to enrollment.

At the Week 4 visit, clinical labs will be collected to assess for liver toxicity: LFTs. If the blood sample for LFTs cannot be drawn at the Week 4 visit for any reason (e.g., parent/legal guardian request to cease blood draw attempts, participant uncompliance, etc.), the clinical lab draw for LFTs may be collected at the Week 8 visit.

## 6.8 Dose Escalation Assessments

Every 5 (+ 2) days through Week 7, just prior to each dose escalation assessment, parent/legal guardian will be asked to measure HR and BP using the device given to them from the study team at the time of randomization. A telephone or in-person assessment by the treating clinician will occur to determine dose escalation. If the participant reaches the maximum dose of 3 mg/day, prior to Week 7, no dose escalation will occur. Alternatively, a CGI-I will be determined by the treating clinician and any score of 3 or worse (higher) will warrant dose escalation, provided no significant safety concerns exist. AEs and safety ESIs will be recorded to assess safety.

Clinically significant findings that would prevent dose escalation include, but are not limited to:

- CGI-I score of 2 or 1
- HR and BP values that are considered unsafe to dose escalate:
    - Clinically significant hypotension, defined as systolic BP percentile less than the 5th percentile.[31,34] This corresponds to systolic BP percentiles for neurotypical children under the 8th percentile for males and under the 10th percentile for females.
    - Clinically significant bradycardia, defined as HR > 2 SD below mean for age
- Any AEs or safety ESIs that make it unsafe to dose escalate, at the discretion of the treating clinician
- Any other finding that indicates it is not safe to dose escalate, at the discretion of the treating physician and/or principal investigator (PI).

## 6.9 Clinical Outcome Assessments

Identifying measures to evaluate cognition and behavior in children with IDD and DS specifically, within clinical trials has traditionally been challenging.[10] Leading clinician and scientist experts were assembled by the NIH to review existing measures and identify those that are appropriate for clinical trials in individuals with IDD and specifically DS.[11] The ABC, ESS-CHAD, and CSHQ will be collected using Electronic Participant Reported Outcomes (ePRO), see Section **15.3**. Details regarding which individual(s) complete(s) each measure at the various visits are included in **Table 2**.

**Table 2. Frequency of measures and who completes each measure.**

| Measure | Frequency Parent/ Legal Guardian Completes | Frequency Clinician Completes |
|---|---|---|
| ABC (Section **0**) | Screening, Week 4, Week 8, Early Withdrawal | N/A |
| Sleep Assessments (Section **6.9.2**) | Day 1, Week 4, Week 8 | N/A |
| CGI-I (Section **6.9.3**) | N/A | Weeks 1-8, Early Withdrawal |
| CGI-S (Section **6.9.3**) | N/A | Screening |

### 6.9.1 Aberrant Behavioral Checklist (ABC)

The ABC is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with IDD.[12] It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals with IDD across 5 domains: Irritability (Agitation, & Crying); Lethargy/Social Withdrawal; Stereotypic Behavior; Hyperactivity (Noncompliance); and Inappropriate Speech, and it has been used extensively in pediatric and adult behavioral and psychiatric studies due to its high reliability and validity.[11,13] The ABC-H subscale has been the primary outcome measure in the only trial of GIR for ADHD and disruptive behaviors in children with DS, as well as in several trials of ADHD with and without ASD in children.[14-17] For this study, the ABC will be completed by parent(s)/legal guardian(s).

### 6.9.2 Sleep Assessments

**Epworth Sleepiness Scale:** The ESS-CHAD is a self-administered 8–item questionnaire to assess daytime sleepiness. For this study, the parent/legal guardian will complete the assessment.

**Child's Sleep Habits Questionnaire (CSHQ):** The abbreviated CSHQ includes 35 items that are divided into the following sections: bedtime, sleep behavior, waking during the night, and morning wake up. For this study, the parent/legal guardian will complete the assessment.

### 6.9.3 CGI-Severity for Eligibility and CGI-Improvement for Improvement

The CGI is a well-established research rating tool that can be used in the context of any psychiatric disorder. It consists of two parts including a 7-item assessment of the severity of psychopathology (CGI-S) and a 7-item assessment on the change from initiation of treatment (CGI-I). The CGI-S asks raters to indicate the frequency and severity of symptoms over a 7 day rating timeframe and establishes a baseline for each participant.[18] The CGI-I is an objective measure of a single participant's change (improvement or worsening) compared to baseline. For this study, the CGI assessments will be completed by clinicians.

## 6.10 Ask Suicide-Screening Questions (asQ) Tool

The asQ Tool was created by the National Institute of Mental Health as a suicide risk screening tool for ages 8 years and above. Prior to initiating the asQ, the treating clinician will use their judgement to answer the following questions: does the participant (1) have the language skills

adequate to understand death and suicide and (2) the verbal ability to respond to “yes/no” and “how/when” questions about suicide.

- **If yes**, proceed to asQ. The participant should be excluded from the study if further clinical assessment and/or judgement are needed.
- **If no or < 8 years old,** do not screen for suicidal ideation.

The asQ tool uses 4 screening questions. If the participant answers “no” to all of the screening questions, they are not identified as a suicide risk and the screening is complete. If the participant answers “yes” to any of the questions, they are identified as a positive screen and are asked a 5th question to assess acuity of the suicidality. If the participant answers “yes” to the 5th question, they are identified as an acute positive screen, if they answer “no” they are identified as a non-acute positive screen.[35] All sites should follow local guidelines if a participant screens positive for suicidality. Per eligibility criteria, a participant who has an acute positive screen at Screening will be excluded from the study.

## 6.11 Specimen Preparation, Handling, Storage, and Shipping

Samples collected for the research will be labeled with a unique number via a study provided barcode label. Instructions for collection, labeling, preparation, handling, and storage of specimens will be detailed in the MOP.

## 6.12 Study Product Description

Guanfacine hydrochloride immediate release, brand name Tenex, is a centrally acting small molecule antihypertensive that comes in a tablet form for oral administration. Guanfacine hydrochloride is a white to off-white powder that is sparingly soluble in water and alcohol and slightly soluble in acetone. The tablets contain the following inactive ingredients: FD&C Red 40 aluminum lake (1 mg tablets only), lactose, microcrystalline cellulose, providone, and stearic acid.[32] United States commercially available guanfacine tablets will be purchased and used as the source for the manufactured 0.5 mg dose guanfacine capsules with matching placebo by the University of Iowa Pharmaceuticals (UIP) to be used in this study. Guanfacine tablets will be milled and placed into capsules of 0.5 mg of active product.

The placebo will be a study drug-matched capsule filled with microcrystalline cellulose.

## 6.13 Dosage and Study Drug Information

### 6.13.1 Dose Timing

**Dose escalation**

Study product will be administered once daily (q.h.s.) during the first 5 (+ 2) days of study product administration and then twice daily thereafter. Twice daily doses may be administered in uneven BID dosing; for example, a total daily dose of 2.0 mg can be divided into 0.5 mg in the morning and 1.5 mg in the evening, at the discretion of the clinical provider. Dose escalation will occur based on the details in **Table 3** with the highest dose being dose level 6. Participants in both the GIR and placebo arms will be evaluated for potential dose escalation every 5 (+ 2) days via a Dose Escalation Assessment (via telephone during Weeks 1-3 and 5-7 or in-person at Week 4) described in Section **6.8**. Parent/legal guardian will be asked to measure HR and BP prior to each dose escalation assessment. If there is a safety concern during the weekly Dose Escalation Assessments (via telephone during Weeks 1-3 and 5-7 or in-person at Week 4) as stated in Section **6.8**, or for any other reason, the sites will be instructed on the following:

1. Hold at current dose/schedule for 5 (+ 2) days (or advance directly to step #3 or step #5 below, if deemed appropriate by the clinical provider)

2. Reassess at next dose-escalation assessment
3. If sedation is a significant concern, divide the total daily dose and give higher dose proportion at bedtime (q.h.s); example: 2 mg totally daily dose split as 0.5 mg in the morning and 1.5 mg q.h.s and
4. Reassess at next dose-escalation assessment
5. If safety concern remains, reduce total daily dose to the lower dose previously tolerated

**Table 3. Dose Escalation Plan***

| Dose Level | Total daily dose for weight ≥ 25 kg (mg) |
|---|---|
| 1 | 0.5 |
| 2 | 1.0 |
| 3 | 1.5 |
| 4 | 2.0 |
| 5 | 2.5 |
| 6 | 3.0 |

* Parent/legal guardian will be asked to measure HR and BP prior to each dose escalation assessment.

### 6.13.2 Dose Discontinuation /Taper

If a participant randomized to receive GIR withdraws from study early or chooses not to continue treatment with GIR via standard of care at the end of Week 8 unmasking, a drug taper plan will be employed for all participants whose final drug dose is > 1 mg/day. The dose taper will be a decrease in increments of 1 mg every 3 days. The taper will last a maximum of 6 days, but may be shorter if starting taper dose is less than 3 mg/day. Study Diary will be completed during the discontinuation/taper period.

Participants receiving < 1 mg at the final study drug administration will stop study drug treatment and will follow procedures for early withdrawal/termination (as applicable) or will proceed to Telephone Safety Follow-up (Section **6.5**).

### 6.13.3 Formulation, Packaging, and Labeling

The University of Iowa will manufacture 0.5 mg GIR capsules and matching placebo capsules adhering to Good Manufacturing Practice (GMP) and United States Pharmacopeia and National Formulary (USP/NF) from the purchase of United States-marketed GIR uncoated tablets.

The study product will be packaged (80 capsules per bottle) into High Density Polyethylene (HDPE) bottles, with a length of polyester coil and desiccant pack, and sealed with polypropylene (PP) child-resistant induction-sealed closures.

The University of Rochester Clinical Materials Services Unit (CMSU) will package and label kits containing 4 bottles (80 capsules per bottle). The kit box label will include an unique Kit identification (ID) number and a masked packaging code (PO#). The four bottles inside each kit will include labels with the Kit ID Number (matching the Kit ID Number on the kit box), a PO#, and a bottle number (1 through 4). Each randomized participant will be assigned one 4-bottle kit box.

The study product will be distributed by the site to the participant. The site will provide enough study product per participant for weeks 1-4 (1 bottle) on the day of randomization and for weeks 5-9 (3 bottles) at the Week 4 visit. See MOP for more details.

### 6.13.4 Product Storage and Stability

The study products should be stored at a controlled temperature between 20°C and 25°C in a tight, light-resistant container. Upon receipt and quality audit release of the manufactured GIR and matching placebo, CMSU will store the GIR in an ambient warehouse storage space (between 20°C and 25°C) prior to distributing to the clinical study sites. The study product will ship to sites in a qualified, controlled room-temperature shipper, and include a temperature-monitoring device while in transit. The site must acknowledge receipt of the kits in order for them to be available for dispensing. See MOP for more details.

## 6.14 Preparation and Administration of Study Product

Study product will be packaged and shipped from University of Rochester's CMSU to local sites who will be masked to the study-treatment assignment. Description on the masking procedures will be provided in the MOP. Local sites will distribute the appropriate respective study product on 1) the day of randomization (Day 1), and 2) the Week 4 in-person clinical assessment.

Participants will self-administer each oral dose. If the participant is unable to swallow the capsule whole, instructions to open the capsule and mix with food will be provided.

## 6.15 Modification of Study Product for a Participant

Dose reduction may occur according to the details in Section **6.13.1**. See MOP for more details.

## 6.16 Accountability Procedures for the Study Product(s)

Refer to MOP for more details.

### 6.16.1 Replacement Kits

If a study product bottle or kit is broken or unusable, a replacement kit with a new unique Kit ID Number will be provided. Replacement kits may be requested via contact information provided in the MOP. Any missed or forgotten doses will be documented in the Study Diary, refer to the MOP for details.

### 6.16.2 Disposition of Study Products Upon Study Completion or Expiration

Following notification from the sponsor, upon completion of the study, or upon notice of the study products' expiration, the study product should be disposed of at the site, after the drug accountability logs have been reviewed by the monitors, pursuant to the ICH/GCP guidelines and the investigators' institutional policies.

## 6.17 Concomitant Medications of Interest/Treatments

Concomitant medications of interest include the following: central nervous system (CNS) depressants (example: benzodiazepines, barbiturates, opioids), anti convulsants (example: carbamazepine), CNS stimulants or non-stimulants to treat ADHD (e.g., methylphenidate, dexmethylphenidate, amphetamines, clonidine, atomoxetine, bupropion) and antibiotics (e.g., ciprofloxacin, clarithromyscin, erythromycin, fluconazole, itraconazole, voriconazole, rifampin).

# 7 ASSESSMENT OF SAFETY

## 7.1 Adverse Events

An **adverse event (AE)** is any untoward medical occurrence in humans, whether or not considered drug-related, which occurs during the conduct of a clinical trial. Any change in clinical status, ECGs, routine labs, x-rays, physical examinations, etc. that is considered clinically significant by the study investigator is considered an AE.

A **suspected adverse reaction (SAR)** is any AE for which there is a reasonable possibility that the drug caused the event. A reasonable possibility implies that there is evidence that the drug caused the event. An **adverse reaction** is any AE caused by the drug.

A **serious, unexpected, suspected adverse reaction (SUSAR)** is defined as a SAR that is both serious and unexpected for which a reasonable causal relationship with the drug use is suspected but not confirmed.

### 7.1.1 Unexpected Adverse Event

An Unexpected Adverse Event is defined as any AE, of which the nature, specificity or severity is not consistent with the applicable product information (e.g., package insert/approved label) or investigational plan.

### 7.1.2 Safety Events of Special Interest (ESIs)

A safety ESI is a select safety event that could be related to the study drug. Safety ESIs will be solicited for their occurrence (No or Yes) at weekly dose-escalation assessments, including in-person assessments (Week 4 and Week 8), and the final telephone safety assessment (5 + 2 days) after the final dose of study drug. The safety ESIs documented will be assessed by the investigator/delegate (defined as a clinician licensed to make a diagnosis) for intensity, causality, and association to provide uniform data collection of all events. Any reported ESIs should be managed, as needed, according to clinical judgement and local guidelines.

Safety ESIs include:

- Syncope/passing out
- Sedation
- Trouble falling asleep
- Trouble staying asleep
- Trouble waking up
- Drowsiness
- Decreased Energy/Fatigue
- Trouble concentrating
- Trouble breathing
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Skin rash
- Itching
- Change in appetite
- Anxious/fearful

- Sadness/depressed mood
- Self-injurious behavior
- Clinically significant hypotension, defined as systolic BP percentile less than the 5th percentile.[31,34] This corresponds to systolic BP percentiles for neurotypical children under the 8th percentile for males and under the 10th percentile for females.
- Clinically significant bradycardia, defined as HR > 2 SD below mean for age

The following safety ESIs will only be assessed at in-person visits (Week 4 and Week 8):

- Any clinically significant cardiac event (e.g., clinically significant changes on ECG)
- Suicidality via the asQ Tool (see Section **6.10**)

## 7.2 Guidelines for Determining Seriousness

A **serious adverse event** (SAE) or **serious suspected adverse reaction** or **serious adverse reaction or serious event of special interest** as determined by the investigator or the sponsor is any event that results in any of the following outcomes:

- Death
- Life-threatening AE ("life-threatening" means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital anomaly or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

## 7.3 Guidelines for Assessing Intensity

The investigator/delegate (defined as a clinician licensed to make a diagnosis) will use the following definitions when assessing intensity of an event:

- **Mild -** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required
- **Moderate** - Participant experiences enough symptoms or findings to require intervention
- **Severe -** Participant experiences symptoms or findings that require significant intervention

## 7.4 Guidelines for Assessing Causality

The investigator/delegate (defined as a clinician licensed to make a diagnosis) will use the following question when assessing causality of an event to study drug: Is there a reasonable possibility that the drug caused the event? "Reasonable possibility" means that there is evidence to suggest a causal relationship between the study drug and the AE. An affirmative answer designates the event as a SAR.

## 7.5 Collection Period and Reporting Procedures

AE information will be gained from direct monitoring of the study participants as well as from clinician observation and self-reporting by the study participants or their guardians. The investigator/delegate (defined as a clinician licensed to make a diagnosis) must document their

assessment of severity and causality in the participant records in a timely manner and submit safety reports as required by their institutional review board (IRB)/research ethics board (REB)/institutional ethics committee (IEC).

AEs, safety ESIs, SAEs and SUSARs will be collected for all participants, following the first study product administration through 5 (+ 2) days after the last study product dose. AEs directly related to study procedures (e.g., blood collection) during the screening period will also be collected.

Safety ESIs will be captured on the Dose Assessment Form electronic case report forms (eCRFs) to provide uniform data collection and will not be reported separately as AEs. As these are expected pre-specified safety ESIs, they will not be reported in an expedited manner but will be reviewed by the MM and the BPCA Data Safety Monitoring Board (DSMB) convened by NICHD and reported to the FDA in the annual report.

Safety ESIs that are associated with any of the criteria that define the event as an SAE will be reported on the AE/SAE CRF set.

Deaths occurring during the study participation, irrespective of causality will be reported on the AE/SAE CRF set.

## 7.6 Safety Event Follow up and Sponsor Reporting

AEs and SAEs directly related to study procedures will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic. If the event resolves during the study or follow-up period, a resolution date should be documented on the eCRF.

AEs directly related to study procedures and safety ESIs (that are not defined as an SAE) will be reported in the data system within 7 days of identification/site awareness.

SAEs, SUSARs, and safety ESIs that are associated with any of the criteria that define the event as an SAE will be reported in the data system within 24 hours of identification/site awareness. Upon entry in the Electronic Data Capture (EDC) system, these events will generate an automatic email notification to the DCC, DCC MM, and the sponsor. The investigator/delegate (defined as a clinician licensed to make a diagnosis) must document their assessment of severity and causality in the participant records in a timely manner and submit safety reports as required by their IRB/REB/IEC.

The DCC MM will review all events at the time they are reported. Any event that requires expedited reporting based on federal regulations (21CFR 312.32) will be forwarded to the IND sponsor or the in-country designee. The IND sponsor or its representative will submit expedited safety reports (e.g., IND safety reports) to the regulatory agencies as necessary.

For non-US sites, the sponsor investigator's in-country designee must comply with all local regulatory requirements related to submitting reportable events to a regulatory authority and IEC. Documentation of the submissions must be retained for each reported event (annual or expedited) and provided to the DCC. The sponsor-investigator (or designee) will inform the investigators of any SUSAR safety reports submitted to a regulatory authority.

### 7.6.1 Pregnancy

Contraception is allowed but will not be required for participants. Although not considered an AE, if a pregnancy occurs during the study, it must be reported immediately by the site. The participant will be allowed to continue in the study but will be withdrawn from study products,

given an appropriate referral, and followed until resolution of the pregnancy. At the time of study product discontinuation, the participant will be asked to complete an ECG and provide a PK blood sample and their parent(s)/legal guardian(s) will be asked to complete the ABC. No further procedures will be done. Participants will then be followed for safety for at least 5 (+ 2) days after the last study dose. The site must document that they have informed the Sponsor, advised the participant to obtain appropriate prenatal medical care, and referred the participant for such care.

The site may be required to inform parent(s)/legal guardian(s) about pregnancies according to local/state laws. In addition, per the consent, researchers will follow the participant for the duration of the pregnancy and to obtain information (via direct examination or medical record review) to determine whether the resulting fetus/newborn survived delivery or had any congenital abnormalities. If the fetus/newborn does not survive delivery or any congenital abnormalities are present, these must be reported as an SAE following the usual requirements for SAE reporting. Please note that if a pregnancy is reported, the participant's subsequent weight, vital sign, and laboratory data will not be included in analyses for these variables. If the pregnancy is terminated, elective or otherwise, within the first 12 weeks of the pregnancy, inclusion of the participant's subsequent weight/height, vital signs, and laboratory data in the analyses will be determined by the PTN study team.

## 7.7 Regulatory Reporting

Any event that requires expedited reporting based on federal regulations will be forwarded to the IND sponsor via reporting on the study specific eCRF. The IND sponsor or its representative as detailed in the Transfer of Regulatory Obligations (TORO) will submit expedited safety reports (e.g., IND safety reports) to the FDA and other regulatory agencies as necessary and will inform the investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB/REB/IEC. Documentation of the submission and receipt by the IRB/REB/IEC must be retained for each expedited safety report.

Any event that requires reporting to Regulatory Authorities (e.g., SUSARS) based on applicable national regulations will be forwarded to the IND sponsor in time to meet reporting requirements.

## 7.8 Data & Safety Oversight (Medical Monitor/Data Safety Monitoring Board)

The study will be monitored by the BPCA DSMB. The DSMB is chartered by NIH to support all research activities conducted under the PTN.

In addition, the study has designated a qualified and experienced physician not otherwise associated with this protocol to serve as the MM and review all SAEs at the time they are reported and/or updated. The MM may request additional information regarding a site reported SAE; the site PI is expected to provide requested information or materials to the MM in an expeditious manner to support the writing/submission of study safety reports. The MM will be available to study sites as needed. The study IND sponsor will also review all SAEs to determine regulatory reporting and will be available to sites as needed.

If safety concerns are identified, the MM may request a meeting of the DSMB to review safety data. The MM will also provide an initial report to the study PI/sponsor and an unbiased written report to the DSMB of the event per the DSMB charter/safety monitoring plan. At a minimum, the MM will comment on the outcomes of the SAE and the relationship of the SAE to the study product. The MM will also indicate whether they concur with the details of the report provided by the study site investigator. If no SAEs prompt review at an earlier time point, the DSMB will review AEs and SAEs per the DSMB charter.

The DSMB will convene and make recommendations on termination of the study based on review of safety reports and halting rules. The safety data will be compiled by the DCC. Based on the recommendations of the DSMB, PTN, and NIH/NICHD, the IND sponsor will make a decision to terminate or continue the study.

*Ad Hoc* Meetings of the DSMB: The DSMB may convene an *ad hoc* meeting to discuss any issue of data and safety raised by the site investigator, the MM, the IND sponsor, NICHD, or a member of the DSMB. At the discretion of the investigators, the IND sponsor, NICHD, and DSMB members, a non-serious AE that is associated with the product or procedures may be considered as a trigger for an *ad hoc* DSMB meeting to assess the safety of the product, without resulting in halting the enrollment of the trial.

# 8 STUDY HALTING/TERMINATION

## 8.1 Study or Site Halting Criteria/Termination Criteria

This study may be terminated at any time by NICHD, the IND sponsor, or via recommendations by the DSMB to NICHD.

Reasons for termination include, but are not limited to, if in their judgment, there are no further benefits to be achieved from the study or if the treatment presents an unreasonable and significant risk to participants. If the study is terminated, notifications will be made to the regulatory authorities (e.g., FDA), investigators, IRBs/REBs, or study participants, in accordance with all applicable regulations governing the study and site/investigator.

A participating site/investigator may be terminated at any time by the sponsor, regulatory authority or by a ruling of the IRB/REB. Possible reasons for termination of the study at a site include, but are not limited to:

- Non-compliance with signed agreements, statements, or undertakings
- Safety concerns
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

If the site/investigator is terminated, notifications will be made to regulatory authorities, IRBs/REBs, or other concerned parties in accordance with the applicable regulations governing the study and site/investigator.

## 8.2 Halting Rules

No halting rules are planned.

# 9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of study participants are protected, that the reported study data are attributable, legible, contemporaneous, original, accurate, complete (ALCOA-C), and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH GCP [E6 (R2)], and with applicable regulatory requirement(s), including 21 CFR 312 Subpart D Responsibilities of Sponsors and Investigators.

The PTN PI or the DCC as detailed in the TORO, or their designee will conduct site-monitoring visits. Site visits will be made at standard intervals as defined by the clinical site monitoring plan appendix but may be made more frequently as directed by the DCC, IND sponsor, and/or NICHD. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, data collection forms, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

The study-specific clinical site monitoring plan appendix will supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

# 10 STATISTICAL CONSIDERATIONS

Efficacy, PK, safety, and exploratory analyses will be conducted. Participant demographics will be summarized. In addition, the number of participants enrolled, completed or discontinued early from study, and the reasons for discontinuation will also be summarized.

Descriptive statistics, such as the number of observations, mean, median, 95% confidence interval, standard deviation (SD), standard error, minimum, and maximum, will be considered for continuous variables (e.g., age, weight, etc.). Other descriptive statistics, such as counts, proportions, and/or percentages, will be presented to summarize discrete variables (e.g., sex, race, etc.).

## 10.1 Study Hypotheses

Improvement in the ABC-H subscale from baseline over an 8-week trial will be greater with GIR compared to placebo in children with DS.

## 10.2 Study Endpoints

### 10.2.1 Primary Endpoint

Primary Endpoint:

- Change from baseline to Week 8 of the parent-rated ABC-H subscale score

The following will serve as the secondary efficacy endpoints:

- Change from baseline to Week 4 of the parent-rated ABC-H subscale score
- Proportion of participants with a CGI-I score of 2 or better at Week 4 and Week 8

### 10.2.2 Secondary Endpoints

The following safety endpoints will be collected throughout the Week-8 treatment period of the study:

- Incidence of SAEs
- Incidence of safety ESIs
- Incidence of AEs

### 10.2.3 Exploratory Endpoints

The following PK endpoints will be estimated at Week 4 and Week 8:

- Guanfacine HCl plasma concentrations ($C_{max,ss}$ and $C_{min,ss}$)
- Time at peak concentration ($T_{max,ss}$)
- Apparent area under the concentration versus time curve at steady state ($AUC_{ss}/F$)
- Apparent clearance ($CL_{ss}/F$)
- Volume of distribution (V/F)
- Half-life ($t_{1/2}$)

The following will be used to characterize the exposure-response relationship of GIR for the treatment of hyperactivity/impulsivity, inattention, and sleep quality in children with DS at Week 4 and Week 8:

- Guanfacine HCl plasma concentrations ($C_{max,ss}$ and $C_{min,ss}$)
- Area under the concentration time curve ($AUC_{ss}$)
- ABC-H subscale score
- CGI-I

- Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD)
- Child's Sleep Habits Questionnaire (CSHQ)

## 10.3 Analysis Population

### 10.3.1 Intention-to-Treat (ITT) Population

The ITT population consists of all randomized participants.

### 10.3.2 Per-Protocol Population

Analyses may be conducted for a per-protocol population that only considers participants who are at least 70% compliant in taking study product for the 8-week study period and who receive the correct randomized treatment.

### 10.3.3 PK Population

All participants enrolled with at least 1 evaluable PK sample will be included in the PK analysis.

### 10.3.4 Safety Population

The safety population includes all participants who consume at least one dose of study product. This population may be identical to the ITT population.

### 10.3.5 Efficacy Population

The efficacy population includes all ITT participants with at least 1 follow-up efficacy measurement at Week 4 or Week 8. This population may be identical to the ITT population.

## 10.4 Analysis Plan

Descriptive statistics, such as number of observations, mean, median, SD, standard error, minimum, and maximum, will be presented for continuous variables (e.g., age, weight, etc.). Other descriptive statistics, such as counts, proportions, and/or percentages, will be presented to summarize discrete variables (e.g., race, sex, etc.). All descriptive analyses will be presented by appropriate treatment group and overall. A 95% confidence level will be used for confidence intervals. A detailed description of statistical methods and secondary analyses will be prepared and presented in the statistical analysis plan prior to data lock for final analyses.

### 10.4.1 Primary Analysis

The primary objective of this study is to determine GIR efficacy for the treatment of hyperactivity, inattention, and impulsivity in children with DS using the ABC-H scale. This objective will be evaluated using the endpoint of change from baseline to Week 8 of the ABC-H subscale score. The ABC-H subscale is a continuous scale with a minimum score of zero to a maximum score of 48, so the primary analysis will be conducted assuming a normal distribution. A mixed effect model analysis will be conducted to compare the change in ABC-H subscale score from baseline. Analysis will be conducted in SAS statistical analysis software using a PROC MIXED procedure. Fixed effects in the model will include indicator for the treatment assignment (GIR vs. placebo), baseline ABC-H score, and assessment week. To account for the correlation of longitudinal scores collected at baseline, Week 4, and Week 8, a participant level random intercept will be included in the model. The primary endpoint (effect size, p-value, and 95% confidence interval) of difference in the change from baseline to Week 8 of the ABC-H subscale will be evaluated using a contrast statement in the model. Additional analysis to evaluate impact of other covariates, including age, sex, weight, comorbid diagnosis of ASD, use of alternative agents(s) to treat ADHD, site, cumulative dose, demographics, may also be conducted. A sensitivity analysis may also be performed to determine how the missing data mechanism affects the primary outcome results.

**Secondary efficacy outcome measures:** GIR effectiveness for the treatment of hyperactivity, impulsivity, and inattention in children with DS will also be assessed using change from baseline to Week 4 of the ABC-H subscale score and with the CGI-I specific to hyperactivity, inattention, and impulsivity behaviors. The change from baseline to Week 4 of the ABC-H subscale score will be analyzed using the mixed effects model described above. The CGI-I is measured on a 7 point Likert scale from “very much improved” to “very much worse.” The proportion of participants with a CGI-I of “1-very much improved” or “2-much improved” will be analyzed as a dichotomous outcome. These dichotomized outcomes will be analyzed using a generalized linear mixed model with binary distribution and logit link. All mixed models for secondary efficacy endpoints will include covariates identified above for the analysis of primary efficacy endpoint.

In addition to the modelling analysis to obtain the effect size, p-value, and 95% confidence intervals, summary statistics for continuous, nominal, and ordinal outcomes at each of the visits will be presented by treatment group (GIR vs. placebo) and overall.

**Table 4. Distribution of CGI-I for Secondary Efficacy Outcome Measure**

| Scale | Distribution of Outcome Scale | Outcome Values |
|---|---|---|
| The Clinical Global Impressions Scale - Improvement (CGI-I) | Ordinal | 0 = not assessed<br>1 = very much improved<br>2 = much improved<br>3 = minimally improved<br>4 = no change<br>5 = minimally worse<br>6 = much worse<br>7 = very much worse |

### 10.4.2 Secondary Analysis

Safety profile of GIR will be presented using AEs and solicited safety ESIs. Number of AEs, SAEs, and SUSARS will be summarized by treatment group (GIR vs. placebo) and overall, by severity, and by each Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term.

Incidence of safety ESIs will also be presented by treatment group (GIR vs. placebo) and overall. Additional model based analyses of safety ESIs will be performed to estimate treatment effect adjusted for baseline covariates and cumulative dose.

### 10.4.3 Exploratory Analysis

**Exploratory Analysis 1:** Characterize GIR exposure in children with DS.

The dosing, sampling, and demographic information collected by the study will be merged with bioanalytical information to create a PK dataset for GIR. Because a sparse sampling scheme will be employed in this study, population PK will be used to characterize GIR PK. If a relationship between exposure and response is observed, population PK or exposure-response models may be developed.

A detailed description of PK/PD analyses will be described in the PK Analysis Plan. Briefly, the following analyses are anticipated depending on the adequacy of the collected data:

Population PK Analysis

Pharmacokinetic (PK) models for the pooled concentration data of GIR will be explored by non-linear mixed effects modeling using NONMEM or Phoenix NLME software. Appropriate compartmental models will be examined, and between-participant variability on model parameters will be explored. Covariate analysis will examine the correlation between model parameters with demographic factors (e.g., weight, body mass index (BMI), sex, race, lab values, and obesity status) and co-administered medications. Appropriate covariates will be incorporated into the model using a standard forward-addition backward-elimination technique. Standard model diagnostic plots and procedures will be used to evaluate model appropriateness. Empiric Bayesian estimates of individual participant PK parameters will be generated from the final model. Model evaluation will be performed by visual predictive check and bootstrapping procedures, as needed.

As appropriate, the following apparent PK parameters may be estimated at steady state: systemic clearance ($CL_{ss}/F$), volume of distribution (V/F), maximum concentration ($C_{max,ss}$), minimum concentration ($C_{min,ss}$), half-life ($t_{1/2}$), and area under the curve ($AUC_{ss}/F$). Other PK parameters may be estimated according to the adequacy of sampling.

**Exploratory Analysis 2:** Characterize the exposure-response relationship of GIR for the treatment of hyperactivity/impulsivity, inattention, and sleep quality in children with DS.

Exposure-Response (ER) Analysis:

A population ER analysis may be performed to characterize the PK/ER relationship between GIR exposure (e.g., $C_{max,ss}$, $AUC_{ss}$) and selected safety and efficacy endpoints (e.g., hyperactivity, impulsivity, inattention, or sleep quality in children is observed). The sleep quality will be assessed via the CSHQ and ESS-CHAD (see **Table 5**). These are continuous outcomes that will be analyzed similar to the primary outcome using a mixed effects model. Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) will also be analyzed as a dichotomous outcome; scores ≥ 10 are “sleepy” and scores <10 are “normal” using a generalized linear mixed model with binary distribution and logit link.

**Table 5. Distribution of Scales for Exploratory Outcome Sleep Quality Measures (CSHQ and ESS-CHAD)**

| Scale | Distribution of Outcome Scale | Outcome Values |
|---|---|---|
| Child’s Sleep Habits Questionnaire (CSHQ, Abbreviated Version) | Continuous | Minimum Total Score: 33<br>Maximum Total Score: 99 |
| Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) | Continuous | Minimum Total Score: 0<br>Maximum Total Score: 24 |

Different PK/ER models, including logistic regression model for binary safety outcomes, efficacy outcomes, and linear, log-linear, and $E_{max}$ models for continuous safety/efficacy outcomes, may be explored. The ER model development, evaluation, and validation will be similar to that described above for population PK model.

## 10.5 Demographics and Baseline Characteristics

The number of participants who either completed or discontinued early from the study will be summarized. Demographic and baseline characteristics will be summarized and compared between the study drug and placebo arms. Study product administration will be summarized in terms of number of days of dosing.

## 10.6 Sample Size Considerations

The primary hypothesis is that change from baseline on ABC-H subscale over the 8-week trial will be greater in GIR compared to placebo. In a randomized clinical trial of GER in ASD,[15] the guanfacine group showed a 43.6% decline in scores on the ABC-H subscale (mean scores of 34.2 at baseline to 19.3 at week 8 visit) compared with a 13.2% decrease in the placebo group (mean scores of 34.2 at baseline to 29.7 at week 8 visit; effect size Cohen's d=1.67). Modal doses of GER in this trial were 3 mg/day (range 1 mg/day to 4 mg/day). In another single arm GIR trial,[6] Capone et al. reported a mean decline in ABC-H scores from baseline to follow-up of 25% (mean scores of 29 at baseline to 21.2 at follow-up visit, Cohen's d = 0.9) over an average of 21 weeks. Average doses of GIR in the Capone study were 1.1 (± 0.5) mg/day, reflecting the more conservative approach to dose escalation in this patient population with DS. A decline in the ABC-H scale scores in the guanfacine group ranged from 25% to 43% across these studies. Although there are no identified studies characterizing a "clinically meaningful change" in ABC-H scores, the open-label Capone study revealed a significant improvement in target behaviors characterized as "inattention" and "activity" with the associated 25% improvement in ABC-H scores.[6]

Based on these studies, a conservative effect size of Cohen's d = 0.9 was assumed for the current randomized trial, which will be equivalent to assuming a 31.3% decline in the guanfacine arm (mean scores of 30 at Baseline to 20.6 at Week 8, SD = 6) compared with a 13.3% decrease in the placebo arm (mean scores of 30 at Baseline to 26 at Week 8, SD = 6). A sample size of 48 will achieve greater than 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.90 and the significance level (alpha) is 0.050 using a two-sided two-sample equal-variance t-test. If a 20% dropout is assumed, N=60 participants will need to be enrolled.

# 11 FUTURE USE OF STUDY RECORDS AND BIOLOGICAL SPECIMENS

The medical data and study information entered in the participant's medical records will be kept per individual site policies for medical record retention. Other study records held at the study site will be kept until the FDA has completed any necessary review of the study results, or for a minimum of 2 years after the study has ended – whichever is longer. The research data collected in this study, and provided to the sponsor, will be kept indefinitely.

Information about this study, including study results, will be published without further permission from the participant as detailed in the informed consent form (ICF). Participants will not be identified in any publications or presentations made about the study.

After the study is completed, information about the study, including study data, will be submitted to the NIH data repository (https://dash.nichd.nih.gov and referred to below as "DASH"). With NIH approval, the data submitted to DASH may be used by other researchers for future research. The study data submitted to DASH will be de-identified, meaning it will not include any information that can identify the participant. The study team may also share the de-identified study data with other researchers. When the participant's de-identified study data are provided to other researchers for the purposes of future research, it will be done without obtaining additional permission from the participant.

Biological specimens collected for study-specific testing will be labeled at the site with a study-provided barcode label. The specimen labels will only contain a unique code number; it will not include protected health information (PHI) or any other information that could identify the study participant. Specimens will be stored at the site and then shipped to a central lab for study-specific testing. After analysis, specimens will be stored until the FDA completes review of the final research study report and proposed drug label changes. Once FDA review of the study results is complete, and after consent for future use of these specimens is confirmed, the specimens will be submitted to an NIH storage facility. With NIH approval, the de-identified study specimens may be made available to other researchers for future research without obtaining additional permission from the participant. Although whole genome sequencing (WGS) is not part of this study, study specimens containing genetic materials, may be made available to other researchers who may conduct WGS in the future. The participant's study specimens will not be sold to anyone; however, the use of these specimens may result in commercial profit. There is no provision to provide the participant with financial compensation beyond what is described in the ICF. Biological specimens may be stored indefinitely. If a participant decides to withdraw permission to use their study data or specimens, they will be instructed per the ICF to contact the site investigator. Study data and samples that have been recorded / collected prior to withdrawal will continue to be used, but no new data or specimens will be collected.

# 12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 (R2), Section 4.9 and 21 CFR 312.62, and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and, when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aid or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Data collection forms will be derived from the eCRFs and provided by DCC.

# 13 QUALITY CONTROL AND QUALITY ASSURANCE

The site PI will provide direct access to all trial-related sites, source data/documents, data collection forms, and reports for the purpose of monitoring and auditing by the sponsor and its designees, and inspection by local and regulatory authorities. The PI will ensure that all study personnel are appropriately trained and applicable documentations are maintained on site.

The BPCA-designated clinical monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Clinical monitoring reports will be submitted to the PI, PTN, and NIH/NICHD.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for prompt clarification and resolution.

# 14 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

## 14.1 Informed Consent Process

Informed consent is a process that is initiated prior to the participant/child's parent/legal guardian agreeing to participate in the study and continuing throughout the individual's study participation.

This study enrolls children. Per 21 CFR 50.3 (o) and 45 CFR 46.402 (a), "children" is defined as persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations (or the research), under the applicable law of the jurisdiction in which the clinical investigation (or the research) will be conducted and so the legal age for consent may be different in different jurisdictions. The process for requesting permission from parents/legal guardians, pediatric assent, and adult informed consent are described in the MOP.

### 14.1.1 Permission from Parents, Legal Guardians, or Legally Authorized Representatives

Under 21 CFR 50.3:

- "permission" means "the agreement of parent(s) or legal guardian to the participation of their child or ward in a clinical investigation";
- "parent" means "a child's biological or adoptive parent";
- "guardian" means "an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care"; and
- "legally authorized representative" (LAR) means "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participant in the procedure(s) involved in the research.

Per 21 CFR 50.55 and 45 CFR 46.408, where parental/legal guardian permission is to be obtained, the IRB of record at each site must determine whether permission from one parent or both parents is required.

Extensive discussion of risks and possible benefits of participation in this study will be provided to the participant's parent(s)/legal guardian(s). Consent forms describing in detail the study procedures and risks are given to the participant's parent(s)/legal guardian(s), and written documentation of informed consent is required prior to enrolling in the study. Consent forms will be IRB-approved, and the participant's parent(s)/legal guardian(s) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant's parent(s)/legal guardian(s) and answer any questions that may arise. The participant's parent(s)/legal guardian(s) will provide consent prior to being enrolled in the study.

The IND sponsor, or designee will provide the investigator, in writing, any new information that bears significantly on the participant's risk to participating in the study. This new information will be communicated by the investigator to participants who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated, and participants will be re-consented, if necessary. Site staff may employ IRB-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, an informed consent form must be executed. By providing informed consent, the participant agrees to complete all evaluations required by the trial, unless the participant withdraws voluntarily or is terminated from the trial for any reason.

Participants may be asked to authorize exchange of information between the study staff and their primary care provider and/or other significant medical providers.

### 14.1.2 Pediatric Assent

The participant should be informed about the study to the extent compatible with the participant's understanding. As required by local regulatory authorities, the participant should assent, sign, and personally date the written consent form. A separate IRB/REB/IEC-approved assent form, describing (in simplified terms) the details of the study, study procedures, and risks, may be used. Assent forms are not substitutes for the consent form signed by the participant's legally acceptable representative. Consult with the institution's policies regarding enrollment of participants who are unable to provide informed consent for themselves.

Under 21 CFR 50.52, and 50.55, and 45 CFR Part 46.405, the IRB of record is responsible for determining that adequate provisions are made for soliciting the assent of children.

## 14.2 Assent Process

This study includes minor participants who may be enrolled in the study only with the consent of their parent(s)/legal guardian(s). The minor participant should be informed about the study to the extent compatible with their neurodevelopmental abilities. Participants who are nonverbal or minimally verbal, have significant intellectual disability, are younger than seven to ten years old (depending on local standards), or have marked thought disorganization or positive psychotic symptoms are very unlikely to be considered developmentally able to provide assent. Sites should follow the minimal age requirements for assent, per their local standards. If the Site PI/designee, who is a clinician licensed to make a diagnosis, judges the participant to be developmentally able to understand the concepts of voluntary participation in research, the participant will be given a simplified, developmentally appropriate assent form to review, will be asked to share any questions they may have, and then will be asked to sign and personally date the assent form.

Assent does not substitute for the permission form signed by the participant's parent(s)/legal guardian(s). Sites should consult with their institution's policies regarding enrollment of participants who are unable to provide informed consent.

## 14.3 Documentation of Permission, Assent, and Consent

Permission, assent, and consent must be documented using forms and processes determined by the Duke University Health System (DUHS) IRB and the site's IRB of record.

Prior to enrollment of participants into this trial, the protocol, the applicable informed consent/assent template, and any materials or advertisements presented to participants will be reviewed and approved by the DUHS IRB. The consent/assent templates approved by DUHS IRB will then be provided to sites and revised as necessary to comply with local regulations and institutional requirements. Sites are required to submit all changes to the templates to the DCC, which ensures compliance with U.S. and international regulations and sponsor (NIH) policies, prior to submission and approval to the IRB/REB/IEC of record for each site. Notification of the IRB/REB/IEC's approval, its composition, and the institution's federal-wide assurance number (FWA) will be provided to the DCC.

Should amendments to the protocol and consent/assent documents be required, the amendments will be written by the sponsor, approved by the DUHS IRB, and provided to the site investigator for submission to the site's IRB/REB/IEC of record.

Participants may be compensated for their participation in this study. Compensation will be in accordance with the local IRB/REB/IEC's policies and procedures and requires IRB/REB/IEC approval, and must be documented in the permission/consent/assent forms.

The IRB of record will determine whether one or two parent signatures are required at each site, based on the risk level of study or local regulatory requirements, and the participant or the participant's parent, guardian, or LAR will be asked to read and review the document.

For non-English speakers, a fully translated consent or an oral presentation accompanied by a short form may be used to obtain informed consent. The fully translated consent and the short form must be approved by the site's IRB of record and executed according to local requirements.

As appropriate, children will have the study explained to them as well in an understandable way, and their refusal to take part will be honored. As required by local regulatory authorities, children may sign an assent form. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participant/parent(s)/legal guardian(s) should have the opportunity to discuss the study and to think about it prior to agreeing to participate. Participant/parent(s)/legal guardian(s) must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the executed informed consent document will be given to the participant/parent(s)/legal guardian(s) for their records.

Site staff may employ IRB/REB/IEC-approved recruitment efforts prior to the participant consenting; however, before any protocol-specific procedures are performed to determine protocol eligibility, informed consent or waiver of informed consent must be obtained. The informed consent process will be conducted and the form fully executed, e.g., signed and dated, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The IND sponsor, or designee, will provide the investigator in writing with any new information that bears significantly on the participants' risk to receive the investigational product. This new information will be communicated by the site investigator to participants who consent to participate in the trial in accordance with IRB/REB/IEC requirements. The informed consent document will be updated, and participants will be re-consented, if necessary.

## 14.4 Confidentiality and Privacy

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

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological specimens in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The PI will ensure that the use and disclosure of PHI obtained during a research study complies with the HIPAA Privacy Rule. The rule provides United States federal protection for the privacy of PHI by implementing standards to protect and guard against the misuse of individually identifiable health information of participants participating in clinical trials. Authorization is required from each research participant (i.e., specific permission granted by an individual to a covered entity for the use or disclosure of an individual's protected health information). A valid authorization must meet the implementation specifications under the HIPAA Privacy Rule. Authorization may be combined in the informed consent document (if approved by the IRB).

The study monitor, other authorized representatives of the sponsor, representatives of the IRB/REB/IEC, and regulatory agencies may inspect all documents and records required to be

maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/REB/IEC, Institutional policies, or sponsor requirements. Both the site PI and the Institution at which the study is contracted to be conducted will hold responsibility to maintain custody of all study records until the sponsor permits their destruction.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DCC. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the DCC research staff will be secured and password protected.

To further protect the privacy of study participants, this study is covered by a Certificate of Confidentiality (CoC) from the National Institutes of Health. The CoC limits the ability of courts and other agencies from forcing the study team to share participant information or body fluids during a legal or legislative action without the participant's permission. The CoC does not restrict the parents/legal guardian from sharing information voluntarily.

# 15 DATA HANDLING AND RECORD KEEPING

The investigator is obligated to conduct this study in accordance with U.S. Federal Regulation 21 CFR 312.60-68 as specified on the signed form FDA 1572, applicable state and federal laws, and the International Council for Harmonisation: Good Clinical Practice: Consolidation Guideline. The investigator is responsible for informing the IRB/REB/IEC of any safety issues related to the study and the study product, including reports of serious adverse events, and all IND safety reports, as required by their IRB/REB/IEC.

## 15.1 Data Handling

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Data collection forms will be derived from the eCRFs and provided by the DCC to the sites to record and maintain data for each participant enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Permanent ink is required to ensure clarity of reproduced copies. When making a change or correction, the original entry should be crossed out with a single line, and the change should be initialed and dated. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF should be consistent with the data collection form/source documents, or the discrepancies should be documented. The sponsor and/or its designee will provide guidance to investigators on making corrections to the data collection forms and eCRFs.

## 15.2 Data Management Responsibilities

All data collection forms and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse events must be graded, assessed for severity and causality by a licensed clinician, and reviewed by the site PI or designee. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. During the study, the investigator must maintain complete, current and accurate documentation for the study.

The DCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

## 15.3 Data Capture Methods

Clinical data (including AEs) will be entered into a 21 CFR Part 11-compliant web-based data capture system provided by the DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the data collection forms/source documents. Some data, including the ABC, ESS-CHAD, CSHQ, and Study Diary will be collected via ePRO, a web-based platform for collecting data. The ePRO system can be used with an electronic device (computer, tablet, or phone). Paper completion, as well as telephone, email or text communication with site staff are options as well. A detailed description of the ePRO system is available in the MOP and study website.

## 15.4 Types of Data

Data for this study will include behavioral/sleep quality/quality of life data, PK data, and safety. Details regarding specific data collected are described as endpoints in Sections **3** and **10.2**.

## 15.5 Timing/Reports

The DSMB will convene and make recommendations on study continuation based on the safety data collected periodically.

## 15.6 Study Records Retention

Study records and source documents will be kept until the FDA has completed any necessary review of the study results, or for a minimum of 2 years after the study has ended – whichever is longer. The research data collected in this study will be kept indefinitely.

The disposition date related to FDA application will be posted on the PTN website for the Investigator's reference.

## 15.7 Protocol Deviations

A protocol deviation is any noncompliance/unplanned excursion from approved investigational plan (e.g., protocol, MOP), or ICH GCP guidelines. The noncompliance may be on the part of the participant, investigator, or site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. For this study, participant/guardian refusal for blood collection or any missing Clinical Outcome Assessment (Section **6.9**), **except** ABC score at Week 8 and those that are required to confirm eligibility, will not be considered protocol deviations in order to facilitate retention of participants for later study assessments, but will be tracked and reported to the sponsor.

Each investigator must adhere to the investigational plan as detailed in the study protocol and/or associated study materials (e.g. MOPs, Forms Instructions, User Guides etc.). Each investigator will be responsible for the training of delegated staff and enrolling only those participants who have satisfied all protocol eligibility criteria.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor, via the DCC's EDC system.

All deviations from the protocol must be reported in the study records/data system. Protocol deviations must be submitted to the local IRB/REB/IEC per their guidelines. The site investigator and study staff are responsible for knowing and adhering to their IRB/REB/IEC requirements.

# 16 PUBLICATION POLICY

Following completion of the study, the investigator may publish the results of this research in a scientific journal under the oversight/approval of the Publication Committee of the PTN. The PTN Publication Committee comprises representatives of the network cores, thought-leaders, DCC, and PTN and is responsible for generation and coordination of the publications that report scientific findings of the network. All public presentations (abstracts, manuscripts, slides and text of oral or other presentations, and text of any transmission through any electronic media) by participating investigators, participating institutions, DCC, and PTN that use PTN data and are intended to represent the PTN or are supported by the PTN will be reviewed by the Publication Committee per the Publication Committee charter.

The Publication Committee guarantees that the study results are presented by experts in the field that have working knowledge of the study design, implementation, data synthesis/analysis, and interpretation. The committee goals are to ensure that any confidential or proprietary information is protected, and that all appropriate statistical analyses have been included.

The PTN Publication Committee will adhere to the trials registration policy adopted by the International Committee of Medical Journal Editors (ICMJE) member journal. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the IND sponsor to register this trial in an acceptable registry.

The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase I trials), would be exempt from this policy.

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH-funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

http://publicaccess.nih.gov/

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html

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