LIST OF ABBREVIATIONS (con't)

Abbreviation	Definition
ICMJE	International Committee of Medical Journal Editors
IEC	independent or institutional ethics committee
IND	Investigational New Drug Application
IRB	institutional review board
LDL-C	low-density lipoprotein cholesterol
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	manual of procedures
N	number (typically refers to participants)
NHLBI	National Heart, Lung, and Blood Institute
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
PD	pharmacodynamics
PedsQL	Pediatric Quality of Life Inventory
PHI	protected health information
PK	pharmacokinetics
PPPMP	personal psychotropic-prescribing medical provider
PTN	Pediatric Trials Network
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson-Angus Extrapyramidal Symptom Scale
SGA	second-generation antipsychotic
SLAES	Systematic Longitudinal Adverse Events Scale
SMC	study medical clinician (medical doctor, principal investigator, nurse practitioner)
SMURF	Safety Monitoring Uniform Reporting Form
SS	study staff (study coordinator, research assistant)
$T_{1/2}$	half-life
TD	tardive dyskinesia
Tmax	time of maximum concentration
Vineland	Vineland Adaptive Behavior Scales
Vss/F	apparent volume of distribution at steady state after non-intravenous administration
z-score	a numerical measurement of a value's relationship to the mean in a group of values

Outcome Measures	Primary Outcome Measure: Pathologic weight change as reflected by longitudinal assessment of modified body mass index (BMI) z-score from the start of study (M0) as defined in CDC growth charts. Secondary Outcome Measures: Secondary measures of weight change: Change in BMI category Modified BMI z-score increase of ≥1.0 unit from M0 Safety Outcomes of Special Interest: Metabolic measures associated with risk of diabetes and cardiovascular disease (e.g., fasting glucose and lipid panel; fasting insulin; high-sensitivity C-reactive protein [hs-CRP]; hemoglobin A1c [Hgb A1c]) Hyperprolactinemia - assessed by monitoring serum prolactin levels Neuromotor effects - assessed by physical exam and abnormal movement scale ratings (Abnormal Involuntary Movement Scale [AIMS], Simpson Angus Extrapyramidal Symptoms Scale [SAS], Barnes Akathisia Rating Scale [BARS]) AEs - elicited AEs, including AEs of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater and clinically significant changes in suicidality Benefits – relationship of risperidone or aripiprazole therapy to adaptive functioning and quality of life as assessed by the Vineland Adaptive Behavior Scale standard scores, Pediatric Quality of Life Inventory (PedsQL, 23 item), Delighted-Terrible Faces Scale (DTFS), Caregiver Strain Questionnaire (CSQ), and changes in the intensity or frequency of pre-existing behavioral problems indicated at M0 (baseline) Pharmacokinetics - CL/F, Vss/F, AUCss, Cmax, Tmax, and $T_{1/2}$ at steady state
Study Population	The study population will consist of two groups of children 3 – <18 years old at the time of the M0 visit: • Risperidone group, n=350, including 30 children 3 – <6 years old and 320 children 6 – <18 years old. Approximately 50% – 80% of the entire group will have ≤90 days of prior treatment with any antipsychotic. • Aripiprazole group, n=350, including 30 children 3 – <6 years old and 320 children 6 – <18 years old. Approximately 50% – 80% of the entire group will have ≤90 days of prior treatment with any antipsychotic. We will target participants within each treatment group to be distributed across the age range to permit analyses of age effects with: • ~30 being 3 – <6 years • ≥35% (n ≥123) being 6 – <12 years • ≥35% (n ≥123) being 12 – <18 years A sub-study for centers with PK expertise will collect steady-state PK samples (obtained at up to five time-points relative to taking risperidone or aripiprazole) from ~24 children, 12 in each of the two treatment groups. Within each treatment group, ~6 children who are 6 – <10 years old with normal weight, ~3 who are 6 – <13 years with obesity (BMI ≥95th percentile), and ~3 who are 13 – <18 years old with obesity will be studied.

2. Safety outcomes of special interest:
    a. Metabolic measures associated with risk of diabetes and cardiovascular disease (e.g., fasting glucose and lipid panel; fasting insulin; hs-CRP; Hgb A1c)
    b. Hyperprolactinemia - assessed by monitoring serum prolactin levels
    c. Neuromotor effects - assessed by physical exam and abnormal movement scale ratings (AIMS, SAS, BARS)

3. AEs - elicited AEs, including AEs of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater, and clinically significant changes in suicidality

4. Benefits - relationship of risperidone or aripiprazole therapy to adaptive functioning and quality of life as assessed by Vineland standard scores, PedsQL (23 item), Delighted-Terrible Faces Scale (DTFS), CSQ, and changes in the intensity or frequency of pre-existing behavioral problems

5. PK - CL/F, Vss/F, AUCss, Cmax, Tmax, and $T_{1/2}$ at steady state

5 STUDY POPULATION

5.1 Selection of the Study Population

Eligible participants ages 3 – <18 years will be enrolled in the risperidone and aripiprazole groups. The primary analyses of the study, which are intended to be submitted to the FDA to inform pediatric labeling of risperidone and aripiprazole, will be conducted only in subjects ages 6 – <18 years at the M0 visit (n=320 within each group). A smaller number (n=~30 in each group) of children 3 – <6 years are included because both medications are widely used off label in very young children with autism spectrum disorders and attention deficit hyperactivity disorder [1].

The participants within each treatment group will be distributed across the age range to permit analyses of age effects, with:

- n=~30 being 3 – <6 years
- ≥35% (n=≥123) being 6 – <12 years
- ≥35% (n=≥123) being 12 – <18 years

To increase feasibility, there are no defined proportions of the study population that are required to be normal weight, overweight, or obese upon entry into the study. However, the distribution of participants within these weight categories will be monitored over time.

Approximately 50% to 80% of the entire risperidone group, and approximately 50% to 80% of the entire aripiprazole group will be required to have ≤90 days exposure to any antipsychotic at the time of the M0 visit to ensure that it is possible to distinguish between type and magnitude of adverse health risks associated with initial risperidone and aripiprazole treatment, vs longer-term risperidone and aripiprazole treatment. This will provide between 175-280 participants per treatment group with minimal prior antipsychotic exposure. We expect more participants <6 years old to be “antipsychotic-naïve” than participants ≥6 years. Siblings will be allowed to participate.

5.2 Inclusion/Exclusion Criteria

Inclusion Criteria

1. Guardian is has provided informed consent
2. Participant has provided assent if developmentally appropriate and as required by the IRB
3. 3 – <18 years of age inclusive at time of the M0 visit
4. Participant, when developmentally appropriate, and guardian are:
    a. Able to understand and describe key aspects of study procedures and expect to be able to comply with them for the 36-month study period
    b. Willing to authorize exchange of information between the SS and the participant’s PPPMP and/or other significant medical provider
    c. Affirm participant’s use at screening visit of either risperidone or aripiprazole as prescribed by participant’s PPPMP

hour. The guardian and/or participant can complete the assessments electronically with ePRO or on paper.

Guardian (G):

- Update information on contact form and back-up contact form, if any changes
- Medical & behavioral follow-up checklist
- Changes in medication
- PedsQL

Participant (P) (if developmentally able):

- PedsQL
- Medical & behavioral follow-up checklist

ePRO system:

- Reminds guardian to contact participant's PPPMP to report any new or significantly increasing concerns about child's physical or emotional health and to contact the PPPMP or go to the nearest emergency department if concerned about child's safety.
- Notify SS if participant endorses one of the key safety questions (see MOP for complete list)
- Notify SS if participant has stopped prior antipsychotic and/or has begun treatment with a different antipsychotic

Study Staff (SS):

- Notify PPPMP if key safety questions have been endorsed
- Contact guardian if participant's prior antipsychotic medication has been stopped or changed, an additional antipsychotic has been added, or potential SAE has been reported to the site
    - Contact guardian and arrange in-person visit as soon as possible (as applicable) OR
    - Obtains any available additional information about weight, clinical laboratory evaluations, and clinical status (from other medical providers)
    - Updates medication log - SMC

6.5 Clinic Follow-up Visits

These visits will occur at months 6, 12, 18, 24, 30, and 36 with a +/- 4-week window. These procedures may also occur as a part of an unscheduled visit related to antipsychotic changes or SAEs. The following assessments will be performed and recorded. Re-consent/assent may occur as needed and following site-specific policies and procedures. Yearly visits (M12, M24, and M36) are expected to last approximately three hours each. Mid-year visits (M6, M18, and M30) are expected to last approximately two-and-a-half hours.

Guardian (G):

- The following are completed within two days prior to meeting with the SMC:
    - Update information on contact form and back-up contact form, if any changes
    - Medical & behavioral follow-up checklist
    - Tanner stage form, if able and form is unable to be completed by participant
    - Changes in medication
    - PedsQL, if possible
    - School and employment questions

- The following questionnaires are completed electronically or via hard copy. Additionally, they can be completed either at the visit or during the 14-day period following the visit:
    - Vineland Adaptive Behavior Scales 3 (only at M12, M24, and M36)
    - CSQ

Participant (P) (if developmentally able):

- Completes the following within two days prior to meeting with the SMC:
    - Medical & behavioral follow-up checklist, complete separate form from guardian unless participant prefers to do it together
    - PedsQL
    - Tanner scale form
- Completes the DTFS in clinic with assistance from SS as needed

Study Staff (SS):

- Vital signs (standing height, weight, sitting BP, and pulse)
- Collect clinical lab and results for evaluation (see section 6.11 and MOP)
- Administer DTFS to the child, assessing ability to understand faces (see MOP)
- After visit, contact participant's PPPMP if concerned about AEs or reports of significant clinical worsening since participant's last contact with PPPMP
- Provide PPPMP with copy of all lab results (regardless of clinical significance)
- May provide a copy of lab results directly to guardian at guardian's request
- Determine whether participant is willing to complete optional blood sampling for future unspecified genetic analyses during the visit, provided they have not yet completed the sampling but have given consent to collect it (see section 6.5.1)
- Determine whether participant is eligible for sub-study of PK sampling and willing to complete optional PK sampling, provided they have not yet completed the sampling but have given consent for it and have not yet taken risperidone or aripiprazole for the day (see section 6.5.2)

Study Medical Clinician (SMC):

- Review/complete, via verbal discussion with the guardian, the following:
    - Medical & behavioral follow-up checklist
    - Tanner stage form
    - Participant report of current medications and interval changes (completes medication log)
    - PedsQL for guardian and participant, if able to be completed prior to meeting with the SMC
    - School and employment questions, if able to be completed prior to meeting with the SMC
- BSAS
- Suicidality assessment and evaluation of acute safety concerns with referral, if needed
- Brief physical exam form, noting whether acanthosis nigricans or hirsutism (for females) is present
- BARS
- SAS (parkinsonian)
- AIMS (TD scale)
- Elicite AE assessment, any events of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater and record on AE form.

Strategies to maintain engagement with participants, particularly those who have missed scheduled assessments, are described in the MOP.

Missed study visits, assessments, or procedures within an assessment will be documented on the eCRF but will not be considered protocol deviations.

6.10 Assessments and Procedures

6.10.1 Diagnostic (to be completed by guardian / participant / study medical clinician)

The SMC will record the PPPMP assigned diagnosis for which the participant was prescribed risperidone or aripiprazole.

Medical and behavioral history checklist: This guardian/participant-completed questionnaire was designed to gather information about a large range of medical and behavioral problems at any point during the participant's life as well as during the two-month period preceding the assessment. The participant is also asked to complete his/her own version of the checklist if cognitively able. It is generally based on the areas of inquiry in the Safety Monitoring Uniform Reporting Form (SMURF) [59] and is designed to facilitate the study clinician's completion of the past medical history form and initial BSAS ratings [Sikich, personal communication].

Medical History form: Before the SMC completes this form, he/she must review the guardian-completed medical and behavioral history checklist, past and current medication forms, interview the guardian and participant, and examine the participant.

6.10.2 Medication Related (to be completed by guardian and/or study medical clinician)

Prior psychiatric medications: The SMC will query the participant's guardian (or participant) asking him/her to list prior medications. This information will be recorded with approximate start and stop dates in the medication log by the SMC.

Current medications and interval medication changes form: At the screening visit, the guardian will be asked to provide information about all medications, including alternative medications and nutritional supplements taken for more than 14 consecutive days during the prior three months. Prior to each subsequent in-person assessment, the participant's guardian will be asked to complete a form with current medications, the doses of antipsychotic medications, and any changes in medication since the last contact.

This form will also be completed by the guardian during the interim web-, phone-, or mail-based assessments.

Medication log: The SMC will record **all** antipsychotic medications with start and stop dates in the medication log, if known. In addition, at the screening visit, the SMC will record concomitant medications, including alternative medications and nutritional supplements taken for more than 14 consecutive days during the three months prior to the screening visit. Subsequently, the SMC will record medications taken for 14 consecutive days, during intervals between study visits, in the medication log. Doses of antipsychotics taken during the trial will be recorded

every six months. If the antipsychotic is discontinued, switched, or if another antipsychotic is added, this information will be recorded in the medication log as soon as possible. Recording the doses of other medications is not required. The approximate dates of starting and stopping medications will be recorded.

6.10.3 Adverse Health Risk or Adverse Event Related to: (to be completed by guardian / participant / study medical clinician)

Weight, height, and vital signs log: This will be maintained for each participant at the site by SS. The information in this log will be reported on the appropriate visit data collection forms (DCFs). This log is used to facilitate rapid, real-time recognition of erroneous measurements (so they can be redone) or significant changes from prior assessments (so they can be assessed by the SMC).

Vital signs (pulse and BP) will be measured a minimum of 3–5 minutes prior to phlebotomy using appropriately sized BP cuffs while the participant is sitting, and results will be added to the log.

Orthostatic vital signs will be obtained only if the participant or guardian reveals concerns about dizziness, tachycardia, or fainting during the AE elicitation or if the SMC feels it is medically indicated. An increase in pulse of >30 beats per minute or a decrease in systolic BP of >20 mmHG or in diastolic BP of ≥10 mmHG will be considered consistent with orthostatic hypotension and considered an AE, if not part of medical history.

Assessment of BMI: At each in-person visit, the participant will be weighed and his/her height will be measured three times using a calibrated stadiometer.

Laboratory assessments: Please see section 6.11 for details of sample collection. Alert values and values requiring assessment for clinical significance will be defined based using PTN guidelines .

Neuromotor assessments: Three validated, medical, clinician-rated assessments with defined examination procedures will be used in this study and performed by the SMC as listed below.

- **Abnormal Involuntary Movement Scale (AIMS):** The AIMS is composed of 12 items and used to assess TD. Items related to severity of orofacial, extremity, and trunk movements; global judgment about incapacitation; and patient awareness are rated using a 5-point scale (categorical). Overall AIMS scores range from 0–42. Treatment-emergent dyskinesia is often defined as, a score of 3 or more on any of the first seven AIMS items, or a score of 2 or more on any two of the first seven AIMS items. A score of 2 and above (categorical) in the global judgment item (severity of abnormal movement) can indicate a treatment-emergent dyskinesia. In this study, the last approach for identifying treatment-emergent dyskinesia will be utilized.
- **Simpson-Angus Extrapyramidal Rating Scale (SAS):** The SAS is composed of 10 items and used to assess pseudoparkinsonism. SAS scores can range from 0–40, and each item is assessed on a 5-point scale. Signs that are assessed include gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head

dropping, glabella tap, tremor, and salivation. Treatment-emergent parkinsonism can be defined as an SAS score of >3 at any time following a score of ≤3. The scores can also be further categorized into severity groups: total scores from 3-6 (minimum), 7-10 (moderate), and >10 (severe) [43].

- **Barnes Akathisia Rating Scale (BARS):** The BARS scale includes an objective rating of akathisia, a subjective rating of awareness of restlessness and distress, and a global clinical assessment of akathisia. The measure of global clinical assessment (summary score) can be utilized to assess treatment-emergent akathisia. This categorical summary item ranges from 0 (absent) to 5 (severe akathisia). A category 3 (moderate akathisia) or above is generally considered treatment-emergent akathisia [44].

Hypertension assessment: Sitting BP will be obtained at each visit using appropriately sized BP cuffs. Hypertension will be defined using the National Heart, Lung, and Blood Institute (NHLBI) normative data.

Brief physical examination: The examination should include listening to heart and lungs and examining the face, neck, back, extremities, and abdomen for acanthosis nigricans, hirsutism, and signs of self-injury.

Suicidality assessment: The clinician will make a clinical judgment as to whether the participant understands the concepts of death and suicide. If the participant is determined to be able to understand these concepts, both the participant and guardian will be queried at each visit, including screening, regarding the incidence of thoughts or statements or attempts by the participant to hurt or kill him/herself prior to the screening visit or in the interim between the last and current in-person assessments. All suicidal attempts will be reported on the suicidality assessment form.

Any acute concerns related to safety of the participant, including concerns about suicide, identified during in-person assessments will be evaluated by the SMC according to local standard of care and each site's standard procedures. The SMC will determine whether the participant is safe to leave the site or requires ongoing emergency care. In the latter case, the SMC will ensure that the participant receives the needed emergency care. Suicidal events requiring overnight hospitalization will be reported on an AE form as an SAE. Additional information will be provided as updates to the SAE when obtained.

AE Assessment: At clinic follow-up visits, the SMC will review the participant/guardian-completed **medical and behavioral follow-up checklist(s),** observe the participant, and systematically query the participant (if able to understand questions) and guardian regarding pregnancy (for girls who have experienced menarche), hospitalizations, new medical or behavioral problems, and changes in pre-existing medical or behavioral problems since the prior visit. The clinician will then determine the intensity/grade of any untoward medical occurrences and, to the extent possible, the relationship between the untoward medical occurrence and risperidone or aripiprazole. Potential AEs related to laboratory collections will be reviewed. All untoward medical occurrences of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater, that are not part of past medical history and are not captured on the BSAS (described below) would be recorded on the AE form in Advantage eClinical (the electronic data capture [EDC] system). All events that satisfy SAE criteria or involve pregnancy will be reported in an expedited fashion according to the procedures described in section 8.

In addition, if the participant is developmentally capable of understanding and completing the form, he/she will be asked to separately complete the self-report version. If the guardian and participant both complete reports on the participant's quality of life, both sets of data will be entered and analyzed since there are often discrepancies between guardian and participant reports.

Delighted-Terrible Faces Scale (DTFS) – SS administered, participant completed: The DTFS is a uni-dimensional, single item scale that will be used to assess the participant's perceived life quality. Faces expressing various feelings are depicted, and the participant is asked which face comes closest to expressing how he/she feels about his/her life over the past month. The participant can then select from the range of seven categorical faces depicting delighted to terrible expressions [45]. This scale is included because it can be easily completed by participants with limited verbal and cognitive abilities as well as by very young children.

The first time the scale is completed by young or developmentally disabled participants, the study coordinator will evaluate whether the participant understands the distinction between the various faces and the concept of "how do you feel about your life overall" using standard procedures described in the MOP for individuals with cognitive limitations. If the study coordinator does not feel that the participant understands these concepts or the facial expressions, this measure will be omitted for that participant and considered as missing data.

6.10.7 Caregiver Quality-of-Life Outcomes (to be completed by guardian)

Caregiver Strain Questionnaire (CSQ): This is a 21-item questionnaire with a categorical scale ranging from 1 (not at all a problem) to 5 (very much a problem) that assesses the caregiver's quality of life. It asks specifically about the caregiver's quality of life by assessing the impact of caring for a child with emotional and behavioral problems. The questions include information about disruption of family life and relationships; demands on time; negative, mental, and physical health effects for any family member; financial strain; feelings of sacrifice; disruption of social/community life; worry/guilt; fatigue/strain; and embarrassment. The questionnaire includes both an objective strain (items 1–10) and a subjective strain (items 11-21) [46].

6.11 Laboratory Evaluations

6.11.1 Clinical Laboratory Evaluations

The following laboratory evaluations will be conducted at each in-clinic visit. Participants will be instructed to fast for at least six hours prior to the blood draw, and the time of last caloric intake will be recorded on the sample collection form. Caution should be taken with participants who are treated with beta-blockers to minimize the duration of the fast and ensure that they have been well nourished prior to beginning the fast due to reports of propranolol-related hypoglycemia in young children who have significantly reduced food intake for extended periods. Food and drink should be provided to participants immediately after phlebotomy. The site may use per their standard of care, agents to reduce severe anxiety associated with phlebotomy. A central laboratory will be utilized, see MOP for details.

- Glucose, BUN (blood urea nitrogen), creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase), AST (aspartate amino transferase), fasting lipid panel: total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides

- Fasting insulin
- hs-CRP
- Prolactin
- Hgb A1c
- Complete blood count with differential (CBC-D)

6.11.2 Whole Blood Samples and Future Unspecified Genetic Analyses (optional)

Participation in whole blood sample collection for future unspecified genetic analyses is optional for all participants. A whole blood sample will be obtained from the participant and uniquely identified with a scannable bar code. The frozen samples will be sent to a central lab until they are sent to an NICHD-approved biorepository.

Future unspecified genetic analyses may focus on the identification of genetic factors that increase or decrease vulnerability to specific antipsychotic-associated adverse effects or likelihood of positive response to antipsychotics or other agents (e.g., metformin). Outside funding will be sought for these genetic analyses. No analyses will be undertaken prior to obtaining IRB approval.

Guardians of participants will not be informed of genetic results. Detailed information is in the MOP.

Participants/guardians who previously consented to this optional whole blood collection, including those who turn 18 years old during the course of the study, may withdraw their consent. His/her genetic sample will be destroyed; however, data resulting from any genetic analyses performed prior to the participant/guardian withdrawing consent will not be destroyed.

6.11.3 Whole Blood Samples for Pharmacokinetic Analysis and *CYP2D6* Genotyping (optional) *Sub-study at Selected Centers*

Intensive steady-state PK studies will be conducted in a subset of 24 children on stable doses of risperidone or aripiprazole). Children enrolled in the PK portion of the study must be prescribed risperidone or aripiprazole for an FDA-labeled indication at time of enrollment as detailed in Table 2.

Table 2. Target enrollment for PK analysis

	Normal weight 6 – <10 years		**Obese 6 – <13 years**		**Obese 13 – <18 years**	
	N	**Acceptable Indication**	**N**	**Acceptable Indication**	**N**	**Acceptable Indication**
Risperidone	6	Irritability in autism spectrum disorder	3	Irritability in autism spectrum disorder Bipolar Mania	3	Irritability in autism spectrum disorder Bipolar Mania Schizophrenia

The following adverse health risks will **not** be recorded on the AE form because they are captured elsewhere in the data.

- Weight gain (BMI assessment)
- Metabolic measures associated with risk of diabetes and cardiovascular disease
- Hyperprolactinemia (laboratory assessment of prolactin concentrations)
- Neuromotor effects (assessed via clinical exam, and quantitatively rated using the AIMS, SAS, and BARS)
- Suicidality that does not result in death/hospitalization (will be recorded on Suicidality Form)

8.3 Reporting of Pregnancy

Although not considered an AE, pregnancy must be reported on the specific pregnancy report form. If a pregnancy occurs during the study, it must be reported immediately by the SMC. The SMC must document that they have informed the PPPMP, advised the participant to obtain appropriate prenatal medical care, and referred the participant for such care. The SMC may be required to inform guardians/parents 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/baby 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 aborted 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.

8.4 Adverse Events Definitions

Taking into account the above reporting exclusions, an AE is any untoward medical occurrence considered clinically significant by the SMC, whether or not considered drug-related, which occurs during the conduct of this clinical trial. Untoward medical occurrences may be detected and reported in multiple ways, including through systematic elicitation of medical problems, abnormal laboratory results, x-rays, neuromotor assessments, BSAS, suicidality assessments, and physical examinations.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study pharmaceutical agent, referred to as the "study drug", was the cause. A "reasonable possibility" implies that there is evidence that the drug caused the event.

An adverse reaction is any AE caused by the study drug.

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

1. Death
2. 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)
3. Congenital anomaly
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Inpatient hospitalization or prolongation of existing hospitalization
6. 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

8.5 Methods and Timing for Assessing and Recording Adverse Events

AE assessment will begin at the time of the first study procedure conducted during the M0 visit and will continue until the last follow-up visit or resolution of pregnancy or an SAE. Except as described above in “Adverse Health Risks”, newly emergent AEs with mild (grade 1) and related to risperidone or aripiprazole and all AEs of moderate (grade 2) or greater and conditions not otherwise reported as part of the BSAS assessment which the SMC determines worsen in a clinically significant way and are (grade 2) moderateor greater severity, must be reported as AEs. New neuropsychiatric events that occur after the study start will be tracked longitudinally throughout the study using the BSAS. These events will not be reported separately as AEs unless they meet the SAE criteria.

8.5.1 Unexpected Adverse Event

This is defined as any AE for which the specificity or severity is not consistent with the package insert, investigational plan, or prior medical history or illness being treated.

8.5.2 Follow-up of Adverse Events

All events (study-related or not) must be followed until resolution or until the last study visit. All serious suspected adverse reactions and serious adverse reactions will be followed until resolution or until the participant is medically stable. All other events that are ongoing at the time of the final study visit will have the status of ongoing event recorded.

8.5.3 Elective Surgery

For the purpose of this protocol, the following conventions will apply for SAE reporting of elective surgery:

A pre-scheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the participant is hospitalized, provided the site stipulates that:

- The condition requiring the pre-scheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the participant’s consent to participate in the clinical study and the time of the procedure or treatment
- The pre-scheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention

- Any untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE

8.6 Guidelines for Assessing Intensity of an Adverse Event

The investigator should use the following definitions when assessing intensity of an AE:

1. **Mild (grade 1):** Participant is aware of symptoms or has minor findings but tolerates them well, and no or minimal intervention required; hospitalization usually not required.
2. **Moderate (grade 2):** Participant experiences enough symptoms or findings that a medical intervention would be appropriate and functioning is somewhat impaired; hospitalization occasionally may be required.
3. **Severe (grade 3):** Participant experiences symptoms or findings that require significant medical intervention; hospitalization usually required.

8.7 Guidelines for Determining Causality

The investigator will use the following question when assessing causality of an AE to risperidone or aripiprazole: “Is there a reasonable possibility that the study 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 suspected adverse reaction.

8.8 Discontinuation Due to Adverse Events

Due to the nature of the study, no participants will be discontinued from the study due to an AE, pregnancy, or change in treatment, including change in the dosing or indication for use of risperidone or aripiprazole, addition of a different antipsychotic medication or other concomitant medication, and/or discontinuation of risperidone or aripiprazole. The goal of the study is to continue to follow participants throughout the 36-month study period in order to comprehensively assess the long-term safety outcomes of treatment with risperidone or aripiprazole. Establishing the persistence and sequelae of AEs after the participant stops risperidone or aripiprazole is part of this goal.

8.9 Adverse Event Reporting Procedures

All reportable safety events that are mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greaterwill be entered into the safety data system within seven days of identification. SAEs will be entered into the data system within 24 hours of identification. If there are any technical difficulties, the SAE will be reported by fax communication.

8.9.1 Serious Adverse Events

Any SAE entered in the safety database will generate an automatic email notification to the IND sponsor, study protocol principal investigator, funding sponsor, and the DCC designated staff. The BPCA medical monitor will review all SAEs at the time that they are reported. Investigators must also submit safety reports locally as required by their IRB.

8.9.2 Regulatory Reporting

The Medical Monitor will notify the IND sponsor of any event that requires expedited reporting based on federal regulations. In accordance with the study Transfer of Regulatory Obligations (TORO), the IND sponsor will submit expedited safety reports (e.g., IND safety reports) to regulatory agencies as necessary and also will inform all investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB. Documentation of the submission and receipt by each IRB, which requires such reporting, must be retained for each expedited safety report.

All serious events, irrespective of their designation as “related” or “not related” to study product(s), will be reported to the FDA at least annually in a summary format within the annual report.

8.10 Type and Duration of Follow-up of Participants after Adverse Events

SAEs will be followed by the SMC in-person, by phone or email, by medical record review, and/or by contact with the participant’s PPPMP until the event is resolved or the participant is medically stable. If the participant/guardian provides consent for SS to collect information about pregnancy outcome, pregnancies will be followed using the same approaches until the pregnancy resolves and the fetus/newborn is delivered and its survival and the presence of congenital abnormalities has been assessed. All other AEs that have not resolved, except those identified at the M36 visit, will be followed-up at the next scheduled in-person visit (i.e., in ~6 months). Any AEs present at the M36 visit that are not SAEs or pregnancies will not be followed-up and will have the status of “ongoing event” recorded at that time.

8.11 Halting Rules

As this is an observational study and no treatments are being prescribed or discontinued as part of the study, there are no safety-based halting rules.

8.12 Safety Oversight

The study will be monitored by the BPCA DMC on a regular basis. The DMC is well established and aware of the mission of the BPCA and PTN. Specifically, the DMC will review data on changes in modified BMI z-score, secondary measures of pathological weight gain, laboratory assessments, neuromotor assessments, suicidality, AEs of mild (grade 1) and related to risperidone or aripiprazole and all AEs of moderate (grade 2) or greater and SAEs.

In addition, the study has a designated BPCA DCC medical monitor, who is otherwise independent of the study, and will review all SAEs at the time they are reported and/or updated. The BPCA DCC medical monitor will be available to study sites as needed. The study protocol chair will also review all SAEs and be available to study sites as needed.

On a monthly basis, the DMC will review a listing of SAEs, including the associated clinical narratives. DMC will also receive narratives for SAEs that are assessed by the BPCA DCC medical monitor related to risperidone or aripiprazole.

If safety concerns are identified, the medical monitor may request a meeting of the DMC to review safety data. At a minimum, the medical monitor will comment on the outcomes of the SAE and causal relationship of the SAE to the study drug. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator. If no SAEs prompt review at an earlier time point, the DMC will review AEs and SAEs at the next regularly scheduled meeting.

8.13 Reporting Adverse Events to the Participant's Personal Provider

The study site will share the participant's study laboratory results and medically concerning changes in AEs and in the participant's clinical presentation detected during an in-person assessment with the participant's PPPMP. If the SMC feels that a new or worsening AE or behavioral symptoms might be related to the antipsychotic dose, he/she will share this information with the participant's PPPMP.

In addition, if the guardian positively endorses any key safety questions on the interim web-, phone-, or mail-based assessments, the site will notify the PPPMP.

Finally, the guardian and participant will be encouraged to discuss any physical, behavioral, or safety concerns that they have with the participant's PPPMP as soon as possible.

8.14 Reporting Concerns or Abnormal Clinical Laboratory Results to the Guardian

Although all clinical laboratory results will be directly transferred to the database from the central laboratory, a copy of laboratory results will also be provided to the site after each in-person visit. If requested, the SS will provide the participant's guardian with a copy of clinical laboratory test results and the vital signs log.

If the SMC has medical concerns about laboratory tests, neuromotor assessments, AEs, dosing of the antipsychotic or another medication, or has general information about potential treatment strategies, the SMC will share these with the guardian during or after the study visit and encourage the guardian to discuss any concerns or alternatives with the participant's PPPMP.

9 CLINICAL MONITORING

Site monitoring will be conducted to ensure that human participant protection, study procedures, laboratory procedures, and data-collection processes are of high quality and meet GCP/ICH and regulatory guidelines. Site monitoring will also ensure that the study is conducted in accordance with the protocol and Emmes and DCRI standard operating procedures. The IND sponsor, or as detailed in the Transfer of Regulatory Obligations (TORO), the BPCA DCC, NIH/NICHD, or its designee will conduct site-monitoring visits as detailed in the monitoring plan or MOP.

Site visits will be made at standard intervals as defined by the site monitoring plan and may be made more frequently as directed by the IND sponsor and NICHD/NIH. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, DCFs, informed consent forms (ICFs), 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.

9.1 Site Monitoring Plan

A site monitoring plan will be designed for each study to supplement the BPCA project-wide clinical monitoring plan based on protocol risk assessments.

hs-CRP and prolactin, will also be measured. Data obtained after a participant becomes pregnant will not be included in these analyses.

Changes in neuromotor symptoms will be assessed at each study visit by physical exam and quantified using the AIMS, BARS, and SAS rating scales. Changes in suicidality over time will be examined. The study will also record the incidence of all SAEs, serious adverse reactions, and AEs mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater adverse reactions and/or AEs over the course of the study. Data for these analyses will include those obtained after a participant has become pregnant.

10.1.2.3 Developmental, Functioning, and Quality-of-Life Endpoints

Potential benefits or function adverse effects of multi-year risperidone or aripiprazole treatment will be assessed by examining change over time in key outcomes. These outcomes include: adaptive behavior (Vineland), behavioral problems (BSAS), and quality-of-life scales (PedsQL-G and PedsQL-C), reflecting the participant's quality of life and completed by the guardian and participant respectively; the DTFS, reflecting the participant's overall happiness; and the CSQ, reflecting the guardian's quality of life. Data for these analyses will include those obtained after a participant has become pregnant.

10.1.2.4 Pharmacokinetic Endpoints:

Clearance (CL), volume of distribution (V), area under the curve (AUC), elimination half-life ($T_{1/2}$), maximum concentration (Cmax), and time of maximum concentration (Tmax) for each drug and its metabolites within each PK sub-population within each treatment group will be estimated in the population PK analysis. Estimated parameters will be compared to those already available in the medications' labels.

10.2 Populations for Analysis

Primary analysis population will be defined as all enrolled participants in the age group of 6-18 years old with at least one follow-up visit and who are not pregnant (pre-pregnancy data for females who become pregnant will be included). Participants with doses that are changed to be outside the FDA-labled dose range will be included in the primary analysis as part of the treatment group.

All enrolled participants with at least one follow-up visit after M0 will be included in the safety population.

The PK population will include only the subset of ~24 participants who have been consented into the PK portion of the study and who have at least one PK sample.

Planned populations for exploratory sub-analyses to better understand factors associated with individualized risk include: 1) "quasi-naïve" participants who have ≤90 days exposure to any antipsychotic at the M0 visit, and 2) those with exposure only to the antipsychotic taken at the time of the M0 visit.

PROTOCOL SYNOPSIS

Protocol Title	Long-term Antipsychotic Pediatric Safety Trial (LAPS)
Phase	4
Products	risperidone, aripiprazole
Objectives	Primary: Evaluate the long-term pathologic weight changes associated with multi-year risperidone or aripiprazole therapy in 3 – <18-year-old children, who have varying durations of prior antipsychotic drug exposure from the start of study Month 0 (M0). This is critical because children appear to have greater vulnerability to antipsychotic-associated weight gain than adults, and obesity has significant effects on morbidity and mortality. The primary analysis will focus on children 6 – <18 years at M0 visit. Secondary: 1. Evaluate the overall safety of multi-year risperidone and aripiprazole therapy in 3 – <18-year-old children by assessing long-term changes in safety outcomes of special interest: 1) metabolic measures associated with risk of diabetes and cardiovascular disease; 2) serum prolactin; 3) neuromotor effects; 4) rates of adverse effects (AEs) of mild (grade 1) and related to risperidone or aripiprazole, and all AEs of moderate (grade 2) or greater; and 5) suicidality. 2. Evaluate the potential long-term benefits of risperidone and aripiprazole by assessing age-normed adaptive functioning, child and caregiver quality of life, and changes in the intensity and frequency of pre-existing behavioral problems. 3. Estimate pharmacokinetic (PK) parameters of risperidone and aripiprazole in normal-weight children aged 6 – <10 years and obese children aged 6 – <18 years.
Study Design	Prospective, multi-site, Phase 4, observational study designed to systematically collect longitudinal post-marketing safety data. Assessments will occur every 3 months for up to 36 months with in-person, clinic-based assessments at months 0, 6, 12, 18, 24, 30, and 36, alternating with remote interim visits occurring at months 3, 9, 15, 21, 27, and 33. The remote interim assessments may be collected using electronic patient-reported outcome (ePRO) via an electronic device, paper (returned to site), or a phone call with the site staff. Some assessments during the in-person visits may also be completed via ePRO. The participant, his/her guardian, and the participant's personal psychotropic-prescribing medical provider (PPPMP) will make any and all decisions related to antipsychotic medications; any other medications; and the participant's current mental state, developmental/psychiatric condition, and level of risk for potential harm to self or others independent of the study procedures and assessments. Study staff (SS) will share lab results, medically concerning changes in AEs and the participant's clinical presentation as assessed during in-person visits, and positive responses to key safety questions (see the manual of procedures [MOP]) for the remote interim assessments with the participant's PPPMP and guardian (at in-person assessments). If an emergency safety concern is evident during a clinic visit, the study medical clinician (SMC) will immediately assess the participant, following medical standard-of-care procedures, to determine whether the participant is safe to leave the clinic or requires additional emergency care. If new or worsening symptoms are reported by the participant or guardian during remote interim assessments, guardians will be instructed to contact their PPPMP directly.

Inclusion Criteria

1. Guardian has provided informed consent
2. Participant has provided assent if developmentally appropriate and as required by the institutional review board (IRB)
3. 3 – <18 years of age inclusive at time of M0 visit
4. Participant, when developmentally appropriate, and guardian are:
   a. Able to understand and describe key aspects of study procedures and expect to be able to comply with them for the 36-month study period
   b. Willing to authorize exchange of information between the SS and the PPPMP and/or other significant medical provider
   c. Affirm participant's use at M0 visit of either risperidone or aripiprazole as prescribed by participant's PPPMP
5. Based on their age at the time of M0 visit, participant is receiving aripiprazole or risperidone at the specified dose and for the diagnoses as listed below:
   a. Participants ages 3 – < 6 years can have any diagnosis and any dose
   b. Participants ages ≥ 6 – 17 years (see table below)

Drug	
Aripiprazole*	Risperidone*
Dose	
2 – 30 mg/day	0.25 – 6 mg/day
Indication Labeled indications (underlined) and *Closely Related Disorders (italicized)*	
Irritability associated with autistic disorder *Irritability in autism spectrum disorder*	Irritability associated with autistic disorder *Irritability in autism spectrum disorder*
Treatment of Tourette's disorder *Tourette's disorder, persistent (chronic) motor or vocal tic disorder*	N/A
Bipolar mania/acute treatment of manic and mixed episodes associated with Bipolar I disorder *Bipolar spectrum disorders including disruptive mood dysregulation disorder*	Bipolar Mania *Bipolar spectrum disorders including disruptive mood dysregulation disorder*
Schizophrenia *Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder*	Schizophrenia *Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder*
*MYCITE® (aripiprazole) and all forms of injectables are not permitted in this study	

6. Guardian anticipates risperidone or aripiprazole treatment will continue for ≥6 months

4 STUDY DESIGN

This study is designed to evaluate long-term weight changes associated with multi-year risperidone and aripiprazole therapy in children. This study will also provide insights into the overall long-term safety and the effects of both drugs on psychiatric and behavioral symptoms. It will further evaluate long-term development, functioning, and quality of life in children treated with these antipsychotics. Lastly, the sub-study will estimate PK parameters in subsets of young and obese children.

4.1 Study Design

This is a prospective, multi-site, Phase 4, observational study designed to systematically collect robust, longitudinal, post-marketing safety data about multi-year pediatric treatment with risperidone or aripiprazole. Screening may occur for < 37 days prior to enrollment; study assessments will occur every three months for a total of 36 months with in-person, clinic-based assessments at months 0, 6, 12, 18, 24, 30, and 36 alternating with remote interim assessments occurring at months 3, 9, 15, 21, 27, and 33. The remote interim assessments may be collected using ePRO via an electronic device or paper (mailed to site) or phone call with site staff. The study will enroll 350 children treated with risperidone mono-antipsychotic therapy at the time of the M0 visit and 350 children treated with aripiprazole mono-antipsychotic therapy at the time of the M0 visit. Approximately 30 of the participants in each group will be 3 - <6 years old at the M0 assessment, and the remaining 320 will be 6 – <18 years old.

The SMCs will not prescribe nor provide treatment for participants. Each participant's PPPMP will use his/her own best clinical judgment to prescribe the participant's medications over the course of the study. It is anticipated that some participants will remain on the same medication throughout the study, while some will change antipsychotic treatments and/or discontinue antipsychotic treatment at different points in the trial.

4.2 Study Duration

Each participant enrolled in the study will participate for up to 38 months. Enrollment is expected to be completed within 18 months.

5. Based on their age at the time of M0 visit, participant is receiving aripiprazole or risperidone at the dose and for the diagnoses as listed below:
    a. Participants ages 3 – < 6 years can have any diagnosis and any dose
    b. Participants ages ≥ 6 – 17 years (see table below)

Drug	
Aripiprazole*	Risperidone*
Dose	
2 – 30 mg/day	0.25 – 6 mg/day
Indication Labeled indications (underlined) and *Closely Related Disorders (italicized)*	
Irritability associated with autistic disorder *Irritability in autism spectrum disorder*	Irritability associated with autistic disorder *Irritability in autism spectrum disorder*
Treatment of Tourette's disorder *Tourette's disorder, persistent (chronic) motor or vocal tic disorder*	N/A
Bipolar mania/acute treatment of manic and mixed episodes associated with Bipolar I disorder *Bipolar spectrum disorders including disruptive mood dysregulation disorder*	Bipolar Mania *Bipolar spectrum disorders including disruptive mood dysregulation disorder*
Schizophrenia *Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder*	Schizophrenia *Schizophrenia spectrum disorders including schizoaffective disorder, psychosis not otherwise specified, and delusional disorder*
*MYCITE® (aripiprazole) and all forms of injectables are not permitted in this study	

6. Guardian anticipates risperidone or aripiprazole treatment will continue for ≥6 months

Exclusion Criteria

1. History of prior or current diagnosis of an eating disorder or meets diagnostic criteria for an eating disorder as described in the DSM-5 and determined by psychiatric exam
2. Pre-existing or suspected major medical, metabolic, or genetic condition that is expected to be associated with weight, cardiovascular, neuromotor, or endocrine problems
3. Known or self-reported pregnancy
4. Taking antipsychotic medication other than either risperidone or aripiprazole at the time of the M0 visit
5. Contraindications to participation in the study in the opinion of the SMC or the potential participant's PPPMP
6. Unwilling or unable to provide back-up family contact information

6.5.1 Optional Blood Sampling for Future Unspecified Genetic Analyses

If the guardian consents for the participant to participate in the optional, one-time collection of a whole blood sample for future unspecified genetic analyses, SS will complete the following:

Study Staff (SS):

- Verify consent/assent for future unspecified genetic analyses sample collection
- Collect whole blood sample (see MOP)

6.5.2 At Selected Centers: Optional Pharmacokinetic Sampling Sub-study

If the guardian consents for the participant to participate in the steady-state PK sampling and he/she meets the criteria for inclusion in the PK study, the following procedures will be performed during an in-person visit(s), which may be scheduled for a separate day from the other assessments. All possible efforts will be made to combine PK sampling with sample collection for future unspecified genetic analyses and/ or clinical assessment labs.

Study Staff (SS):

- Verify consent/assent for the optional PK study
- Verify participant has:
  - Taken the last five days of risperidone or aripiprazole as prescribed
  - Not taken the dose prior to the visit
  - Brought the dose that is due to be taken with him/her to the visit
- Confirm time of last meal
- Collect pre-dose PK sample
- Instruct participant to take scheduled dose of risperidone or aripiprazole
- Collect steady-state PK samples at four remaining scheduled time points relative to in-visit dosing of risperidone or aripiprazole (see MOP)
- Collect whole blood samples for *CYP2D6* genotype at time of PK sampling
- Collect all medications, including dosing and times for five days prior to PK sampling (record on the PK medication log)
- Record times of all PK blood sampling and ingestion of risperidone or aripiprazole dose

For participants in the PK sub-study ≥6 years of age at the time of PK sub-study collection, risperidone and/or aripiprazole is to be prescribed for acute or maintenance treatment of a disorder within the an FDA-labeled pediatric dose range indication and dose for the participant's age.

6.6 Month 36 Final Study Visit (+/- 4 Weeks or Early Study Withdrawal)

The assessments completed during the M36 or early study withdrawal visits are exactly the same as at other in-person follow-up visits (see section 6.5). However, at the final visit, every attempt should be made to have the participant and guardian complete all rating scales prior to or during the visit itself.

If a guardian or participant contacts SS between visits with thoughts about withdrawing from the study, all reasonable and non-coercive efforts should be made to encourage him/her to remain in the study. If a guardian/participant continues to feel that it is most appropriate to withdraw, SS

6.10.4 Behavioral Symptoms (to be completed by study medical clinician)

Behavioral Symptoms Assessment Scale (BSAS): The intensity of, pattern of, and any changes in pre-existing behavioral symptoms, and any new behavioral symptoms will be systematically tracked throughout the study using the BSAS. This scale is a modification of the SMURF [56] and the Systematic Longitudinal Adverse Events Scale (SLAES) [61], which have been used in prior studies of psychiatric illnesses in children. The study clinician completes this form after reviewing the guardian- and participant-completed medical and behavioral history checklist at screening and the medical and behavioral follow-up checklist at subsequent visits, observing the participant and asking the participant and guardian about significant changes in behavioral symptoms or emergent new behavioral problems. This scale has a listing of generalized prompts for the study clinician on the first page, with more detailed specification of significant behavioral symptoms, including preferred terms for the specific behaviors present, intensity, pattern, and changes since the last visit. If a problem has never been present, this is noted on the first page and the corresponding detailed information entry related to it is left blank. The BSAS will be used to track behavioral symptoms associated with the various psychiatric disorders being treated with antipsychotics in the study.

6.10.5 Developmental Outcomes (to be completed by guardian / participant / study medical clinician)

Developmental questions about school promotion and employment status: This brief questionnaire will be used to assess major milestones in the participants' lives. Specifically, school promotions and graduations, changes in school supports, type of living situations, romantic relationships, arrests, and types and extent of employment during the interval since the prior visit will be assessed. This is typically completed by the guardian, sometimes with the help of the participant.

Vineland Adaptive Behavior Scales 3 (Vineland-3): The Vineland is designed to measure adaptive behavior of individuals from birth to age 90. The Vineland-3 contains five overarching domains: communication, daily living skills, socialization, motor skills, and maladaptive behavior (optional). The domain scores yield an adaptive behavior composite score, which will be the main measure of functional change. Motor skills will not be analyzed since this domain is only valid in young (<5 years) children. Children who are continuing on a normal developmental trajectory would not be expected to show any change in standard scores in each of the domains, whereas those who had developmental delays related to an underlying mental illness may show increased standard scores if treatment allows them to begin to make greater developmental progress than prior to treatment. This is completed by the guardian.

6.10.6 Pediatric Quality of Life Inventory (to be completed by guardian and participant, if able)

Pediatric Quality of Life Inventory v4 (PedsQL): The 23-item PedsQL Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization in individuals aged 2 years and older [62]. There are separate forms for young adults (age 18–25), teens (age 13–18), children (age 8–12), young children (age 5–7), and toddlers (age 2–4) as well as forms for guardians of individuals at each age group. The main scales include physical functioning, emotional functioning, social functioning, and school functioning. Summary scores can also be utilized to measure change over time. The guardian will be asked to complete the parent version for reporting on their child's quality of life.

	Normal weight 6 – <10 years		Obese 6 – <13 years		Obese 13 – <18 years	
	N	**Acceptable Indication**	**N**	**Acceptable Indication**	**N**	**Acceptable Indication**
Aripiprazole	6	Irritability in autism spectrum disorder Tourette's Disorder	3	Irritability in autism spectrum disorder Tourette's Disorder, Bipolar Mania	3	Irritability in autism spectrum disorder Tourette's Disorder Bipolar Mania Schizophrenia

For participants in the PK sub-study: Risperidone and/or aripiprazole is prescribed for acute or maintenance treatment of a disorder within the FDA-labeled pediatric dose range

PK sampling can occur at any visit after M0 as long as the participant is currently on risperidone or aripiprazole and has taken the same dose of risperidone or aripiprazole as prescribed by the PPPMP over the 14 days prior to the PK sampling. The participant/guardian will be instructed to record the date, time, and amount of drug taken during the five days prior to the study visit. The participant will be instructed to refrain from taking that day's dose of study drug and to bring it with him/her to the study visit (see MOP). In addition, the date, time, route, and dose of all concomitant medications of interest (see Appendix 3) administered during the five days prior to administration of the PK dose and until the final PK sample is acquired will be recorded.

Up to five PK samples (approximately 2 ml per sample, or total about 2 teaspoons) per participant will be collected for plasma concentration determinations at specified times relative to in-visit antipsychotic administration (Table 3).

Table 3. Optimal PK sampling collection windows for study drugs

PK Sample #	Sample Collection Window
1	15–45 minutes prior to dose
2	1–2 hrs.
3	2.5–4 hrs.
4	4.5–6 hrs.
5	6.5–8 hrs.

All reasonable and non-coercive efforts possible should be made to collect all five PK samples for each participant enrolled in the PK study. All five samples do not need to be collected after the same dose (see MOP). Collection of PK samples should be timed with collection of other laboratory tests specified in the protocol to minimize blood draws when possible. Parent compound and active metabolite concentrations in plasma will be measured at a bioanalytical laboratory using a validated bioanalytical assay. Participants who have at least one PK sample

10 STATISTICAL CONSIDERATIONS

The general statistical analysis approach is outlined below. A more detailed description of the statistical methods will be provided in the separate statistical analysis plan (SAP), which will be finalized before database lock.

10.1 Statistical Endpoints

10.1.1 Primary Endpoint:

The primary endpoint is pathological weight change as reflected by longitudinal change in the modified BMI z-score from M0. BMI will be calculated within the database using the formula: weight in kg / (height in cm)^2. The modified BMI z-scores are calculated by adjusting for the appropriate population, age- and sex-specific levels for the normal population provided by 2000 CDC growth charts. The primary analysis will estimate change over the 36-month study period within each treatment group. Change from M0 to M36 will be estimated using 95% confidence intervals. No formal hypotheses will be tested. The primary analysis for the clinical study report will focus on children 6 – <18 years old at the M0 visit with at least one follow-up visit. BMI data obtained after a participant becomes pregnant will be eliminated from this analysis.

Exploratory analyses will include all age groups in the entire study sample. Change in participants who stay on the treatment from M0 to the end of study will be compared to change in participants who switch to another SGA treatment, who discontinue SGA treatment, and who are taking specific concomitant medications (e.g., metformin or multiple SGAs simultaneously) as part of the exploratory analyses.

10.1.2 Secondary Endpoints:

All secondary endpoints, other than the PK endpoints, are primarily descriptive or exploratory in nature. Event rates and longitudinal change will be evaluated within and between groups using 95% confidence intervals. No formal hypotheses will be tested. PK endpoints will be evaluated using population PK methods as described in section 10.1.2.4. Key secondary endpoints are listed below.

10.1.2.1 Additional Weight Change Endpoints

Other measures of pathological weight change will also be analyzed to complement the primary outcome measure: 1) change in BMI category (underweight, normal, overweight, obese, severely obese [≥99th percentile]) over specific time intervals; and 2) modified BMI z-score increase of ≥1.0 unit from M0. Data obtained after a participant becomes pregnant will not be included in these analyses.

10.1.2.2 Additional Safety Endpoints

Secondary safety endpoints of special interest are 1) metabolic measures associated with risk of diabetes and cardiovascular disease, 2) hyperprolactinemia, and 3) neuromotor effects. Metabolic risks will be assessed by measuring laboratory values such as fasting insulin, fasting lipid profile, and Hgb A1c at each study visit. Additional laboratory values of interest, including

10.3 Analysis Plan

In this prospective, multi-site, Phase 4, observational study, participants who switch treatment from what they were receiving at enrollment will remain in the study. Separate analyses will be performed using the treatment group at enrollment and the treatment group at the time of the specific outcome event. Participants who have switched off risperidone or aripiprazole to another SGA or who have discontinued SGA treatment or have taken multiple SGAs will be summarized separately. Data from participants after they have become pregnant will not be included in the primary weight, vital sign, and metabolic lab analyses. Only the PK sub-study population will be included in the PK analyses.

Event rates and longitudinal changes will be analyzed using both descriptive summaries and modeling approaches. Descriptive statistics will be calculated by treatment and age groups (3 - <6 and 6 – 18 years). Statistics such as number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. Counts and proportions or percentages will be calculated for summaries of discrete variables. Confidence intervals will be calculated using the 95% confidence level.

No interim analysis is planned other than the DMC's monthly review of related and unexpected SAEs and the DMC's regularly scheduled reviews of AEs, all SAEs, the proportion of participants with clinically meaningful weight change (defined as modified BMI z-score ≥1.0 unit from M0), and changes in key safety outcome measures including labs, neuromotor assessments, and suicidality.

Descriptive summaries and the primary analysis will be performed using SAS software version 9.4 or later. The PK analysis will be performed using NONMEM software.

10.3.1 Baseline Descriptive Statistics and Participant Disposition

Descriptive statistics will be calculated to summarize demographic and other variables from the initial M0 visit by treatment group. Baseline weight and height measured before antipsychotic and risperidone/aripiprazole initiation as well as duration of any prior antipsychotic treatment and duration of current risperidone/aripiprazole treatment will be summarized when possible. Pre-treatment baseline data is unlikely to be available from a large minority of participants.

Participant disposition will be summarized. The number of participants who complete all scheduled study assessments, the number who complete the M0 and M36 assessments, but do not complete all interim assessments, and the number who do not complete the M36 assessment will be reported. The number of participants who discontinue the M0 antipsychotic treatment prior to the M36 visit and their reasons for discontinuation will be tabulated. Treated participants who switch to the other study treatment (aripiprazole or risperidone) or alternative therapies (SGA or non-SGA) will be summarized. The duration of each participant's treatment on each antipsychotic medication during the study period, as well as the total duration of any antipsychotic treatment during the study period, will be summarized based on the participant/guardian reporting of current medications and interval changes. If information about duration and/or type of prior antipsychotic treatment is available for at least one-third of participants within a treatment group, that information will be consolidated with their on-study antipsychotic treatment information and analyzed in an exploratory fashion. The proportion of participants who are antipsychotic-naïve (≤90 days of prior treatment with any antipsychotic)