

**A randomized, placebo controlled trial of metformin for the treatment of overweight induced by antipsychotic medication in young people with ASD**

# **Master Clinical Trial Protocol and Summary of Amendments**

**Protocol Title:** Treatment of Overweight Induced by Antipsychotic Medication in Young People with ASD

**Trial Sponsor and Principal Investigator:** Dr. Evdokia Anagnostou

## **TABLE OF CONTENTS**

- 1. SUMMARY OF PROTOCOL AMENDMENTS**
- 2. MASTER CLINICAL TRIAL PROTOCOL AND APPENDIX**

## 1. SUMMARY OF PROTOCOL AMENDMENTS

Please note that for the purposes of readability and tracking, changes have been color coded based on the version of the protocol in which they were implemented. All changes are tracked from the original approved clinical trial Protocol [V.2] 01Oct12.

- Changes implemented in Protocol [V.3] 02May13 are highlighted in **yellow**
- Changes implemented in Protocol [V.4] 22Oct13 are highlighted in **green**
- Changes implemented in Protocol [V.5] 04Feb14 are highlighted in **fuchsia**
- Changes implemented in Protocol [V.6] 05Aug14 are highlighted in **blue**. Please note that this is the final, approved clinical trial protocol.

Version	Submitted to IRB	Summary of Amendment Areas	Approved by IRB
Protocol [V.2] 01Oct12	19-Dec-2012	<ul style="list-style-type: none"> <li>Originally approved protocol</li> </ul>	16-Apr-2013
Protocol [V.3] 02May13	10-May-2013	<ul style="list-style-type: none"> <li>Dr. Eric Butter, of Nationwide Children's Hospital/Ohio State University has been added as a Co-Investigator, as Dr. Butter is the main collaborator at Nationwide Children's Hospital in collaboration with Dr. Aman at Ohio State University.</li> <li>In order to facilitate recruitment efforts, inclusion criteria was revised as follows: potential participants must have a documented <math>\geq 7\%</math> increase in BMI since starting atypical antipsychotic therapy (as opposed to 10%) or, if BMI is greater than or equal to 85th percentile corrected for age and sex (as opposed to 80th), then a greater than 5% body weight increase per year; BMI participants must be on a stable atypical antipsychotic dose for a minimum of one month (as opposed to two months); screening visits will be completed within 14 days (as opposed to 7).</li> <li>Clarification made to exclusion criteria regarding psychotropic concomitant medications to communicate that dose changes during the course of the trial are not permitted.</li> <li>Participants will not be required to complete an ADOS if they have previously completed one at any point in their lifetime (as opposed to within the past two years), a full copy of the protocol will also not be required (only proof that the assessment was completed); participants will not be required to complete cognitive testing if they have had a cognitive assessment within the past two years (as opposed to within the past year); finally, previous assessments can also be clinical as opposed to only being completed by personnel who are research-reliable.</li> <li>Additional collection/processing information regarding blood sampling for DNA extraction has been added to the protocol.</li> <li>An additional assessment has been added to the assessment battery for the study (inclusion of the Modified Children's Verbal Learning Test, an assessment adapted from the California Verbal Learning Test – Children's Edition).</li> <li>Removed language pertaining to the Data Coordinating Center (DCC) providing training and certification in the use of a specimen tracking system, as it is not required.</li> <li>All sections pertaining to safety reporting to the FDA have been revised, as this study is under an IND exemption; as a result of the IND exemption, the safety reporting sections have also been revised using ICH definitions to comply with Health Canada reporting requirements.</li> <li>Responsibilities of the site PIs and the sponsor have been clarified with regards to safety reporting, documentation, data management, and follow up.</li> <li>Additional information has been added to the protocol regarding safety precautions if a participant undergoes a radiologic procedure.</li> <li>Minor administrative revisions including formatting, glossary additions, clarification of terms and grammatical corrections have been made to the protocol.</li> </ul>	05-Jun-2013
Protocol [V.4]	18-Dec-2013	<ul style="list-style-type: none"> <li>The AIR-P Network, under which the study is funded, is in the process of transferring data coordination and monitoring responsibilities from the EMMES Corporation/AdvantageEDC</li> </ul>	16-Jan-2014

22Oct13		<p>database to the MGH Biostatistics Center/StudyTrax Database. In light of this transition, the protocol has been revised to remove specific mention of the EMMES Corporation and Advantage EDC. Terms have been revised to indicate that data will be entered/monitored in an electronic database.</p> <ul style="list-style-type: none"> <li>• The text of Section 7.4 (Analysis Populations) has been revised to clarify each group (Safety, ITT Efficacy, and MITT Efficacy), and to specify that analysis of baseline characteristics and efficacy will be performed for the safety ITT and the MITT populations. Efficacy analyses based upon the ITT population will be regarded as the primary analyses.</li> <li>• Upon the recommendation of the study's Data Safety Monitoring Board (DSMB), protocol text has been revised to indicate that information regarding family history of diabetes/related disorders and obesity will be included as part of the medical history during the Screening Visit (Section 5.1).</li> <li>• A minor change was made to ordering of Co-Investigator Dr. Aman's title.</li> </ul>	
Protocol [V.5] 04Feb14	14-Feb-2014	<ul style="list-style-type: none"> <li>• Based on site reports regarding the increasing difficulty in recruiting/retaining participants due to the number of blood draws for safety laboratory measures, the protocol has been revised to decrease the number of blood draws. Safety laboratory measures are currently taken at Screening, Week 8, Week 16, Week 24, and Week 32; this will be reduced to Screening, Week 16 9 (end of RCT phase), and Week 32 (end of open-label phase), reducing the total number of draws from 5 to 3. In order to determine the safety of reducing the laboratory measures, the Principal Investigator has reviewed the product monograph and investigational brochure for Riomet (current and past). There is no recommendation for blood monitoring at the frequency that is currently scheduled in the protocol. The only time that the product monograph suggests monitoring blood work every three months is to monitor the efficacy for glucose control in diabetics. A consultation with the research team's endocrinology consultant, has confirmed that there is no reason for any greater frequency than every 6 months.</li> </ul>	13-Mar-2014
Protocol [V.6] 05Aug14	11-Aug-2014	<ul style="list-style-type: none"> <li>• Changes were made to the Co-PIs in the study. Specifically, Kevin Sanders was added as a PI at Vanderbilt University and Jeremy Veenstra-VanderWeele's affiliation was changed from Vanderbilt University to Columbia University. Additionally, the IND Sponsor was changed to reflect the current IND exemption of the study in the United States.</li> <li>• Details regarding breaking the study blind were clarified to specify that the unblinding is not mandatory and is only offered upon the family's request.</li> <li>• Capturing adverse events at baseline were removed from the table in Appendix A to reflect current practice.</li> <li>• Addition of a parent satisfaction survey to the protocol. This survey will be utilized at the Week 32 or end visit in order to assess participant's satisfaction with various aspects of the study, including the use of the study drug and value of study procedures.</li> </ul>	22-Sep-2014

## 2. MASTER CLINICAL TRIAL PROTOCOL AND APPENDIX

### Treatment of Overweight Induced by Antipsychotic Medication in Young People with ASD

#### Study Chair:

Evdokia Anagnostou, M.D., FRCPC  
Child Neurologist, Child Neurodevelopmentalist  
Bloorview Research Institute and University of Toronto

#### Co-PIs:

~~Kevin Sanders~~ ~~Jeremy Veenstra-VanderWeele, M.D.~~  
Autism Translational Medicine Program, Vanderbilt University [Medical Center](#)

Benjamin Handen, Ph.D.  
Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center

[Eric Butter, Ph.D.](#)  
[Nationwide Children's Hospital of Columbus, in Collaboration with](#)  
[Ohio State University's Nisonger Center, UCEDD](#)

Michael G. Aman, Ph.D.  
[Ohio State University's Nisonger Center, UCEDD](#)  
[In Collaboration with Nationwide Children's Hospital of Columbus, in Collaboration with](#)  
[Ohio State University's Nisonger Center, UCEDD](#)

[Jeremy Veenstra-VanderWeele, M.D.](#)  
[New York State Psychiatric Institute, Columbia University](#)

#### Supported by:

Health Resources and Services Administration

Grant Number: UA3MC11054

#### Study Intervention Provided by:

Ranbaxy Pharmaceuticals, Inc.

#### Sponsor of IND (United States):

[N/A \(Under IND exemption\)](#)  
~~Dr. Jeremy Veenstra-VanderWeele~~  
~~IND # TBA, 116714~~

#### Sponsor of CTA (Canada):

Dr. Evdokia Anagnostou  
CTA# MET-10-2012

## TABLE OF CONTENTS

<b>1. STUDY OBJECTIVES .....</b>	<b>11</b>
1.1 PRIMARY OBJECTIVE .....	11
1.2 SECONDARY OBJECTIVES .....	11
<b>2. BACKGROUND .....</b>	<b>12</b>
2.1 RATIONALE AND SUPPORTING DATA .....	12
<b>3. STUDY DESIGN.....</b>	<b>13</b>
3.1 RESEARCH DESIGN AND METHODS .....	13
3.1.1 <i>The Autism Treatment Network</i> .....	13
3.1.2 <i>Recruitment of Subjects</i> .....	14
<b>4. SELECTION AND ENROLLMENT OF SUBJECTS.....</b>	<b>15</b>
4.1 INCLUSION CRITERIA .....	15
4.2 EXCLUSION CRITERIA .....	15
4.3 CONSENT PROCEDURES.....	15
<b>5. STUDY INTERVENTIONS .....</b>	<b>17</b>
5.1 INTERVENTIONS, ADMINISTRATION AND DURATION .....	17
5.1.1 <i>Handling of Study Interventions</i> .....	17
5.1.2 <i>Dose Titration</i> .....	18
5.1.3 <i>BLINDING</i> .....	18
5.1.4 <i>Concomitant Interventions</i> .....	18
5.1.5 <i>Concomitant Non-Medical Treatments</i> .....	19
<b>6. STUDY EVALUATORS .....</b>	<b>20</b>
6.1 CLINICAL AND LABORATORY EVALUATIONS .....	20
6.1.1 <i>ASD Diagnoses</i> .....	20
6.1.2 <i>DSM-IV Clinical Diagnosis</i> <sup>23</sup> .....	20
6.1.3 <i>Assessment of IQ</i> .....	20
6.1.4 <i>Aberrant Behavior Checklist (ABC) (Parent)</i> <sup>26</sup> .....	20
6.1.5 <i>The Clinical Global Impressions Scale (CGI) (Clinician)</i> <sup>28</sup> .....	20
6.1.6 <i>Comprehensive Medical and Developmental Assessment, Physical Examination</i> .....	21
6.1.7 <i>Clinical Laboratory Analysis</i> .....	21
6.1.8 <i>Blood Sample for DNA Extraction</i> .....	21
6.1.9 <i>Safety Monitoring Uniform Report Form (SMURF)</i> <sup>30</sup> .....	21
6.1.10 <i>Measures of diet and exercise</i> .....	22
6.1.11 <i>Spatial <u>and Verbal</u> Memory</i> .....	22
6.2 STUDY PROCEDURES .....	22
6.2.1 <i>Part I: Double-blinded Efficacy Phase (16 weeks)</i> .....	23
6.2.2 <i>Part II: Open Label Continuation Phase (16 weeks)</i> .....	23
6.2.3 <i>Intervention Discontinuation Evaluations</i> .....	24
<i>Premature Withdrawal from drug</i> .....	24
<b>7. STATISTICAL CONSIDERATIONS .....</b>	<b>25</b>
7.1 GENERAL DESIGN ISSUES.....	25
7.2 OUTCOMES.....	25
7.3 SAMPLE SIZE CONSIDERATIONS.....	25
7.4 ANALYSIS POPULATIONS .....	26
7.5 RANDOMIZATION .....	27
7.6 SUBJECT DISPOSITION .....	27
7.7 STATISTICAL ANALYSES.....	27
7.7.1 <i>Demographics and Baseline Characteristics</i> .....	27
7.7.2 <i>Efficacy phase analyses</i> .....	28

7.7.3	16-week continuation phase analyses .....	28
7.8	SAFETY ANALYSIS .....	28
7.8.1	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation .....	28
7.8.2	Serious Treatment Emergent Adverse Events .....	29
7.9	STATISTICAL AND ANALYTICAL ISSUES .....	29
7.9.1	Adjustment for Covariates .....	29
7.9.2	Handling of Dropouts or Missing Data .....	29
7.9.3	Multiple Comparisons / Multiplicity .....	29
7.9.4	Use of an Efficacy Subset of Subjects .....	29
7.9.5	Criteria for Unblinding the Results .....	29
<b>8.</b>	<b>DATA COLLECTION AND SITE MONITORING .....</b>	<b>30</b>
8.1	SOURCE DOCUMENTS .....	30
8.2	WEB-BASED DATA COLLECTION AND MANAGEMENT SYSTEM .....	30
8.3	CERTIFICATION IN THE USE OF WEB-BASED DATA ENTRY SYSTEM .....	30
8.4	DATA STORAGE AND QUALITY CONTROL .....	30
8.5	DATA QUALITY CONTROL AND ASSURANCE .....	30
8.6	DATA PROCESSING AND DATA MANAGEMENT .....	31
<b>9.</b>	<b>SAFETY MONITORING .....</b>	<b>32</b>
9.1	DEFINITIONS .....	32
9.1.1	Adverse Event .....	27
9.1.2	Adverse Drug Reaction .....	33
9.1.3	Treatment Emergent Adverse Event .....	33
9.1.4	Serious Adverse Event .....	28
9.1.5	Adverse Drug Reaction Event .....	33
9.2	PROCEDURES AND MONITORING .....	33
9.2.1	Relationship to Study Drug Definitions .....	33
9.2.2	Severity of Adverse Events .....	29
9.3	SITE ADVERSE EVENTS COLLECTION AND REPORTING PROCEDURES .....	34
9.3.1	Recording and Summarizing Adverse Events .....	34
9.3.2	Study and Individual Stopping .....	36
9.4	SERIOUS ADVERSE EVENT NOTIFICATION .....	37
9.4.1	Notifying Health Canada .....	37
9.4.2	Notifying the Data and Safety Monitoring Board (DSMB) and the Institutional Review Board (IRB) or Research Ethics Board (REB) .....	38
<b>10.</b>	<b>HUMAN SUBJECTS .....</b>	<b>39</b>
10.1	DATA AND SAFETY MONITORING BOARD (DSMB) .....	39
10.2	INSTITUTIONAL REVIEW BOARD, RESEARCH ETHICS BOARD (IRB/REB) REVIEW AND INFORMED CONSENT .....	39
10.3	SUBJECT CONFIDENTIALITY .....	40
10.4	STUDY MODIFICATION/DISCONTINUATION .....	40
10.5	STATEMENT REGARDING SCIENTIFIC MISCONDUCT .....	41
<b>11.</b>	<b>PUBLICATION OF RESEARCH FINDINGS .....</b>	<b>42</b>
<b>12.</b>	<b>REFERENCES .....</b>	<b>43</b>



### PROTOCOL SYNOPSIS

Study Title	Treatment of Overweight Induced by Antipsychotic Medication in Young People with ASD.
Objectives	Evaluate the safety and efficacy of treatment with oral metformin vs. placebo to decrease weight or weight gain associated with atypical antipsychotic medication in children (ages 6-17 years, 4 months) with ASD.  Evaluate the long-term safety and efficacy of metformin by offering 16 weeks of open-label treatment with metformin to all subjects after Part I.
Design and Outcomes	This is a double-blind, placebo-controlled, multi-site randomized trial to evaluate oral fixed dose metformin treatment in children ages 6-17 years, 4 months with ASD who are currently taking atypical antipsychotic medication. The primary efficacy endpoint for the efficacy phase is the change from baseline to the end of Part I (Week 16) in BMI age- and gender-standardized z-scores using Year 2000 Center for Disease Control and Prevention norms.
Intervention and Duration	Children will be randomized to treatment with metformin or placebo. If the metformin is well tolerated for 2 weeks, the dose will be increased as per schedule and based on age. The randomized phase (efficacy phase) will last 16 weeks followed by an optional 16 week open-label phase (continuation phase). A liquid preparation will be used because some children with ASD have difficulty swallowing pills.
Sample Size and Population	Up to 90 children (21-24 per site), ages 6-17 years, 4 months, with ASD whose BMI has increased $\geq 740\%$ within the past 12 months on an atypical antipsychotic or, if BMI is $\geq$ to 850th percentile corrected for age and sex, who gained greater than 5% body weight per year (and prorated at greater than 5% body weight increase if medicated for longer than a year), will be recruited and randomized from each of four sites: Ohio State University's Nisonger Center, Vanderbilt University, Bloorview Research Institute (University of Toronto), and Western Psychiatric Institute and Clinic (University of Pittsburgh Medical Center).

### Glossary of Abbreviations

<b>ABC</b>	Aberrant Behavior Checklist
<b>ADOS</b>	Autism Diagnostic Observation Schedule
<b>ADI-R</b>	Autism Diagnostic Interview - Revised
<b><u>ADR</u></b>	<u>Adverse Drug Reaction</u>
<b>AE</b>	Adverse Event
<b>AIR-P</b>	Autism Intervention Research Network on Physical Health
<b>ASD</b>	Autism Spectrum Disorders
<b>ATN</b>	Autism Treatment Network
<b>BMI</b>	Body Mass Index
<b>CFR</b>	Code of Federal Regulations
<b>CGI</b>	Clinical Global Impressions Scale
<b>CS</b>	Clinically Significant
<b>DCC</b>	Data Coordinating Center
<b>DSMB</b>	Data and Safety Monitoring Board
<b>DSMP</b>	Data and Safety Monitoring Plan
<b>EC</b>	Ethics Committee
<b>FDA</b>	Food and Drug Administration
<b>GCP</b>	Good Clinical Practice
<b>ICH</b>	International Conference on Harmonization
<b>IDS</b>	Investigation Drug Services
<b>IMFAR</b>	International Meeting for Autism Research
<b>IRB</b>	Institutional Review Board
<b>ITT</b>	Intent-to-Treat
<b>MITT</b>	Modified Intent-to-Treat
<b>PP</b>	Per-protocol
<b>REB</b>	Research Ethics Board
<b>RUPP</b>	Research Unit on Pediatric Psychopharmacology
<b>SAE</b>	Serious Adverse Event
<b>SD</b>	Standard Deviation
<b>SMURF</b>	Safety Monitoring Uniform Report Form
<b>SOC</b>	System Organ Class
<b>TEAE</b>	Treatment Emergent Adverse Event

## 1. STUDY OBJECTIVES

### 1.1 *Primary Objective*

The primary aim of the current proposal is to assess the safety and efficacy of metformin (Riomet<sup>®</sup>) to decrease weight or weight gain associated with atypical antipsychotic medication in children with ASD. A 16-week, double-blind, placebo-controlled randomized trial of metformin with dose guided by age will be conducted. Following a screening visit, subjects will return at baseline, 2, 4, 8, 12, and 16 weeks. There will also be a phone call at week 1. A secondary study aim will be to assess the long-term safety and efficacy of metformin by conducting a 16-week open label continuation. Throughout both the double-blind and open label trials, we will note and report the rate of adverse events.

**Aim 1:** To assess the safety and efficacy of metformin to decrease weight or weight gain associated with atypical antipsychotic medication in children with ASD.

Hypothesis 1: At the end of 16 weeks, subjects receiving metformin will experience significantly less weight or weight gain than subjects receiving placebo.

Hypothesis 2: At the end of 16 weeks, subjects receiving metformin will not experience significant deterioration to commonly observed problem behaviors (defined as worsening of the ABC irritability score of 0.6 SD great than among subjects receiving placebo).

### 1.2 *Secondary Objectives*

**Aim 2:** To assess the long-term (32 week) safety and efficacy of metformin to decrease weight or weight gain associated with atypical antipsychotic medication in children with ASD.

Hypothesis 1: At the end of the 16-week extension, “responders” to metformin will continue to maintain their weight reductions (in comparison to the double-blind study baseline scores).

Hypothesis 2: At the end of the 16-week extension, those who have been on metformin will exhibit no change in rate and severity of adverse events judged by the investigator/study physician to be related to drug.

Hypothesis 3: At the end of the 16-week extension, “nonresponders” to placebo during the double-blind trial will evidence statistically significant decreases in weight and demonstrate no significant deterioration to commonly observed problem behaviors (as defined in Aim 1, Hypothesis 2).

**Aim 3:** To describe frequency and severity of adverse events in the metformin and placebo groups at 16 and 32 weeks.

## 2. BACKGROUND

### 2.1 *Rationale and Supporting Data*

Atypical antipsychotics are the only medications approved by the FDA for use in children with autism. Both risperidone and aripiprazole show significant benefit for a number of symptom domains in children from 6-17 years old, including irritability/agitation and repetitive behavior<sup>1-6</sup>. Unfortunately, several studies also show troubling increases in weight in children with autism treated with these medications. For example, Martin et al. (2004) followed 63 children with autism and witnessed peak weight gain at 5 months of treatment of about 6 kg; at 6 months, BMI increased by an average of 10.6%<sup>7</sup>. Aman et al. (2005) reported excessive appetite for 49% to 62% of subjects receiving risperidone following 8 to 24 months of treatment<sup>8</sup>. Although weight gain may be reversible<sup>9</sup>, simply stopping these medicines is not often an option for children with autism. When the RUPP study tried to do so in the context of a blinded withdrawal study, the prior irritable/agitated behavior returned for 62.5% of children<sup>10</sup>. No controlled studies have examined options for combating this weight gain in children with autism.

In adult populations, multiple studies have found that metformin may stop or reverse weight gain from atypical antipsychotics<sup>11,12</sup>. Metformin is a biguanide anti-diabetic drug that acts by increasing insulin sensitivity and decreasing intestinal glucose absorption and hepatic glucose production. Adverse events are typically mild except when patients have predisposing medical conditions<sup>12</sup>. Studies suggest that metformin is safe and effective in children and adolescents; although it has not been tested in autism. A randomized, placebo-controlled trial of metformin versus placebo added on to atypical antipsychotics in children and adolescents (age 10-17 years) showed a significant benefit, with a decrease in body mass index (BMI) in the metformin group and an increase in the placebo group<sup>13</sup>, similar to two open label trials<sup>14,15</sup>. A study of metformin versus placebo in 100 obese, insulin-resistant children (age 6-12 years) showed safety and efficacy for weight loss in this younger age range<sup>16</sup>. Gastrointestinal adverse events, including diarrhea and nausea, were reported in children taking 2000 mg daily of metformin but were less common at lower doses, with no serious adverse events<sup>16</sup>. Headaches were also reported. Rarely, lactic acidosis or hypoglycemia may occur<sup>17, 18, 19</sup>.

Since atypical antipsychotic medications are commonly used and effective in children with autism, there is a pressing need to test whether metformin can ameliorate the weight or weight gain and metabolic symptoms commonly associated with these drugs in children with autism. Our study will add to the published literature in a number of significant ways. First, we extend into a younger age group that has not been previously studied and which is most relevant to the autism population, in contrast to the larger population of children with bipolar disorder, schizophrenia, or disruptive behavior disorders. We set a lower limit of age at 6 years old given that safety has not previously been assessed in the pediatric population below this age<sup>16</sup>. Second, we focus exclusively on the ASD population. Children with ASD are less able to communicate potential adverse events, which merits a separate assessment of safety in this population. Children with ASD are also more likely than the general population to have gastrointestinal symptoms at baseline<sup>20</sup>. This coincides with gastrointestinal symptoms, including nausea and diarrhea, being the most common adverse events described with metformin<sup>16</sup>, raising the possibility that this medication will show a different tolerability in the ASD population. Finally, since the large ongoing study is single-blinded and lacks a placebo comparator, our study will be only the second pediatric randomized, placebo-controlled trial to test metformin for treatment of weight gain due to atypical antipsychotic medications.

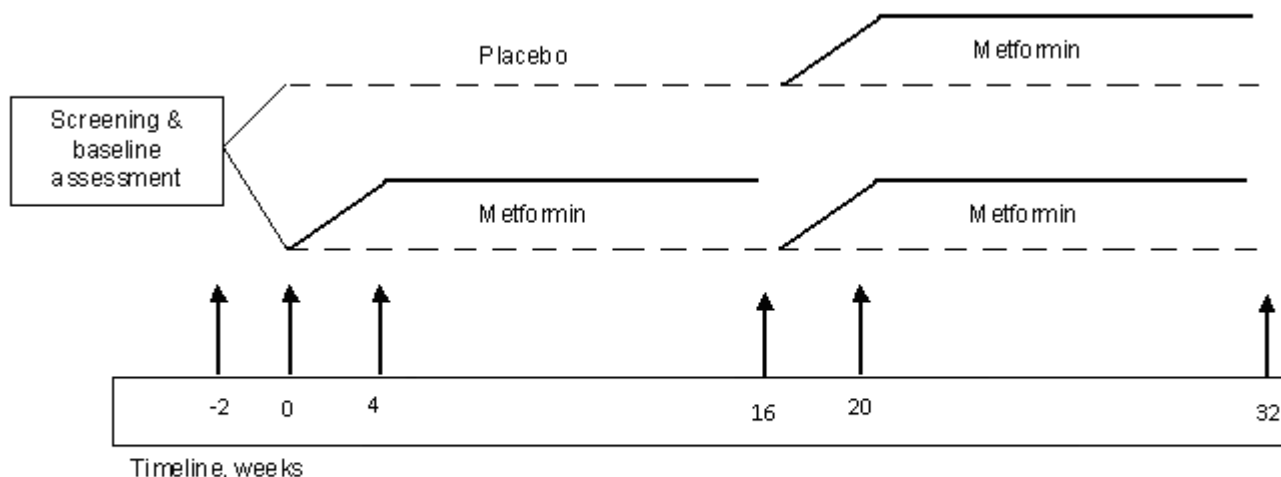
### 3. STUDY DESIGN

#### 3.1 Research Design and Methods

This study has two parts as illustrated in Figure 1.

- Part I (Efficacy Phase) is a 16-week, randomized, double-blinded, placebo-controlled trial of metformin in children and adolescents with ASD who have experienced  $\geq 7.4\%$  increase in BMI since starting an atypical antipsychotic, or in those with BMI greater or equal to 85th percentile corrected for age and sex, greater than 5% body weight increase per year (and prorated at greater than 5% body weight increase if medicated for longer than a year).
- Part II (Continuation Phase) is a 16-week open-label continuation phase on metformin for all subjects whether originally randomized to active drug or placebo.

**Figure 1. Time Line for Metformin Protocol**



Note: baseline represented by dashed line, administered Metformin dose represented by solid line

#### 3.1.1 The Autism Treatment Network:

The Autism Treatment Network (ATN) is collaboration between 17 academic centers around the country. The goal of the ATN Registry is to provide data to ultimately inform the development of standards of medical care for children with autism. The Registry was designed as a multi-center observational study to collect both retrospective and prospective data on patients with ASD in a standard format. All ATN subject identification numbers are assigned through an enrollment utility as part of the AdvantageEDC software suite. The EMMES Corporation (ATN Data Coordinating Center) owns and operates on their premises a system of server and client computers that meet all requirements for Internet-based and centralized data collection, data management, data analysis, collaborative research, corporate and project administration and software development. Client nodes operate in either a Microsoft Windows NT or Windows 2000 environment, giving authorized users access to selected features of the system. Systems are deployed in a secure Application Service Provider environment. Communications between users and the hosting site are protected using the highest levels of encryption commercially available (SSL). The EMMES Corporation Application

and Database Servers sit behind a multi-level firewall. Access to these servers is highly restricted. All servers have been placed behind multiple firewalls. ATN users are assigned unique usernames and passwords.

### 3.1.2 Recruitment of Subjects

A total of 90 subjects with a DSM-IV ASD diagnosis of Autism, Asperger's Disorder, or PDD-NOS will be recruited from the ATN registry and other research/clinical databases at the four individual sites. Each of the four sites will enroll 7-8 subjects per year over three years.

Recruitment planning is essential for sites to meet this goal. The sponsor will be assisting sites with recruitment efforts and each site will be required to track recruitment efforts on the Screening and Recruitment Log which will be periodically reviewed by the DCC and the CCC Study Coordinator. The spreadsheet is meant to be a working document and can be modified and updated as needed. Study Coordinators should track all recruitment efforts on this spreadsheet and may be periodically asked to send this to the DCC or the CCC Study Coordinator prior to a Study Team conference call.

Since advertising funds are limited, sites are encouraged to recruit within their offices and institutions before advertising outside their institutions. Recruitment will be a regular agenda item on bi-weekly Study Team calls and will be periodically discussed on AIR-P Research calls as well. Study Coordinators are encouraged to share recruitment ideas and best practices with other coordinators. The PI at each site will ultimately be responsible for ensuring that a sufficient number of subjects are recruited into this study. Therefore, in order to facilitate recruitment, it is anticipated that the PI will make frequent presentations in the community about the study and its potential benefits and risks.

The sponsor will follow up with sites if contractual recruitment goals are not met. Enrollment is competitive across all sites, so additional subjects may be randomized at a site if recruitment at other sites is below the projected goal.

## 4. SELECTION AND ENROLLMENT OF SUBJECTS

### 4.1 Inclusion Criteria

To receive randomized treatment in this study, subjects must have all of the following characteristics:

- Diagnosis of Autism Spectrum Disorder (autistic disorder, pervasive developmental disorder NOS, Asperger's disorder) based upon an ADOS and DSM-IV interview.
- Minimum of 12 months on a stable atypical antipsychotic dose with no plans to change the dose for the next 4 months.
- A documented  $\geq 7.40\%$  increase in BMI since starting atypical antipsychotic therapy (within the last going back as far as prior 12 months); or, if BMI is greater or equal to 85<sup>th</sup> percentile corrected for age and sex, then a greater than 5% body weight increase per year (prorated at greater than 5% body weight increase if medicated for longer than a year).
- Age 6 years to 17 years, 4 months.
- Subjects and their parents (guardians) must be judged reliable for medication compliance and must agree to keep appointments for study visits and tests as outlined in the protocol.
- Prior to the conduct of any study-specific procedures, the subject must provide assent to participate in the study (if developmentally appropriate), and their parents (guardians) must provide written informed consent.

### 4.2 Exclusion Criteria

Subjects who have any of the following characteristics will not be assigned to randomized treatment and will be declared ineligible:

- History of intolerable adverse effects with metformin.
- Prior history of an exposure to metformin of sufficient dose or duration to determine response status.
- History of liver disease, renal impairment, congestive heart failure, pernicious anemia, any other condition increasing the risk for lactic acidosis, or any serious medical illness requiring treatment.
- Use of cationic drugs excreted by the kidneys.
- Planned surgery or procedure requiring contrast.
- Pregnant at screening contact.
- On other psychotropic concomitant medications for less than 12 months; any plans to change the dose during the course of the trial.
- Treatment or planned treatment with concomitant medications with unacceptable interactions with metformin, including topiramate, levetiracetam, beta blockers, ACE inhibitors, diuretics, or histamine H<sub>2</sub> receptor antagonists.
- Unable to tolerate blood work.
- Current use of medication for target symptoms of appetite or weight loss.
- Planned change of medication, medication dose, or behavioral treatment targeting weight loss during the study period.

### 4.3 Consent Procedures

Consent will be obtained as per the Declaration of Helsinki/Tri-Council Policy Statement according to institutional guidelines. If the subject is not able to consent, their parent/non-parent caregiver will sign the consent form and they will be assented as per institutional guidelines.

All procedures will be explained to the subjects, and all reasonable efforts will be made to help the child understand the study procedures and their purpose. During the consent process, subjects will be asked if they agree to have a letter sent to their primary care and prescribing physicians if they have one to inform them that the individual is taking part in a clinical trial. The physician will be asked to respond within 7 days of the time the letter was sent if there is a reason that the subject should not participate. The investigating team may also choose to call the physicians' office. Subjects will also be asked if they give permission for the ~~treating clinician~~ investigator/study physician to access their hospital medical chart if available.



## 5. STUDY INTERVENTIONS

### 5.1 *Interventions, Administration and Duration*

#### **Screening Assessments**

Subjects and their caregivers will participate in a screening process to establish relevant medical, developmental and psychiatric diagnoses, and to assess current symptomatology. The screening assessments are to be completed within a 147 day period across 1 to 2 visits.

The following measures will be obtained: a) Diagnostic assessment including ADOS and DSM-IV interview; b) Cognitive assessment via the Stanford-Binet 5<sup>th</sup> Edition Abbreviated Battery or Mullen Scales of Early Learning; c) Caregiver-completed Aberrant Behavior Checklist (ABC); d) Comprehensive medical and developmental assessment to confirm study eligibility; e) Vital signs, height, weight, physical examination, review of medical and psychiatric history including SMURF, review of concomitant therapies; and f) clinical laboratory tests (Liver function tests, BUN, creatinine, electrolytes, bicarbonate, serum lactate, fasting glucose, HgbA1C, insulin, vitamin B12, total cholesterol, LDL, HDL, triglycerides, and CBC). Urine or blood pregnancy testing will be conducted for girls of child-bearing potential (i.e., post menarche); and g) information on phrase speech as measured by Item #10 of the ADI-R<sup>21</sup>.

#### **Baseline Visit**

The schedule of assessments that will be completed is listed in Appendix A. The baseline visit is to occur +/- 30 days of the last Screening assessment visit, across 1 to 2 visits (within +/- 14 days). The research pharmacy will be notified by research staff to dispense study medication according to the subject's randomization assignment.

The subject will be administered a spatial and verbal memory task, and the parent, guardian, or other caregiver will complete the Aberrant Behavior Checklist (ABC). For Screening and Baseline, the ABC will be completed to reflect the previous 4 weeks; thereafter, the ABC will be completed to reflect the time since the previous visit.

In addition, general advice about healthy habits related to diet and exercise will be reviewed at this point, as part of standard clinical care.

#### **Weekly Study Visits**

The study visits from Week 2 onwards are to occur at the appropriate week, +/- 4 days of the most recent baseline visit, ~~or, the first day in which the subject received metformin/placebo.~~

#### 5.1.1 **Handling of Study Interventions**

Riomet<sup>®</sup> (metformin) and matching placebo is donated to the study by Ranbaxy Pharmaceuticals Inc. The same lot of metformin will be used for the study, or if multiple lots, the lot numbers will be tracked at each IDS and as part of the Study Product Administration form.

Returned study product will be accounted for by the study staff to ensure compliance to the dosing regimen and again by the IDS staff prior to destruction following the institution's destruction policy.

### 5.1.2 Dose Titration

Metformin will be dispensed in a liquid suspension of 100 mg/mL, with placebo prepared to match the appearance, smell and taste of the metformin as closely as possible. For children from 6-9 years of age, metformin will be started at 250 mg at their evening meal for 1 week, followed by the addition of a 250 mg dose at breakfast for 1 week. At the Week 2 visit, if metformin is well-tolerated, the dose will be increased to 500 mg twice daily. For children from 10-17 years of age, metformin will be started at 250 mg at their evening meal for 1 week, followed by the addition of a 250 mg dose at breakfast for 1 week. At the Week 2 visit, if metformin is well-tolerated, the dose will be increased to 500 mg twice daily. At the Week 4 visit, if metformin is well-tolerated, the dose will be increased to 850 mg twice daily. In the case of adverse events, the treating clinician investigator/study physician may decrease the dose in multiples of 50 mg and can also re-challenge the subjects with higher doses in multiples of 50 mg units, not to exceed 500 mg twice daily for children 6-9 years of age, and 850 mg twice daily for children 10-17 years of age, once the adverse event has resolved. We will encourage families to give the subjects a daily multivitamin containing cyanocobalamin (Vitamin B12) over the course of the study. After Week 16 assessments, all subjects will be offered open-label metformin.

### 5.1.3 Blinding

All treatment received during Part I (Efficacy Phase) will be double-blinded. None of the subjects, their guardians or the research staff involved in adjusting study treatments or evaluating treatment response will know whether the subject is receiving metformin or placebo. However, the IDS at each site will maintain records of medication assignment which are accessible to authorized staff only.

All subjects will be offered open treatment with metformin upon completion of Part I. For subjects who complete 16 weeks on the assigned drug in the efficacy phase, open label treatment will be offered right after. We will encourage subjects to not find out about their randomization status until Week 32, but if they insist on knowing what they have been on, a staff member independent of this study will disclose randomization status to the family after Week 16 is completed, to help with future planning. If a subject experiences an adverse event during the efficacy phase that necessitates their withdrawal from the active drug, the independent staff member will also disclose randomization status. For those randomized to placebo who wish to try metformin, open label treatment will be offered at that point. We recognize that allowing this may provide some information to the investigators about how the drug is behaving in the group, but given that 1) the primary outcome measure is BMI and therefore not affected by investigator's impressions and 2) the paucity of safety data for metformin in this population, we believe this to be an appropriate compromise.

### 5.1.4 Concomitant Interventions

***We shall allow stable psychotropic medications (provided that no change in dose has occurred within the prior ~~two~~ months).*** Subjects may also require new pharmacologic intervention for routine pediatric illnesses at various time points during the study, given that study duration may be up to 32 weeks. Given that concomitant medications could interact with metformin pharmacokinetically and/or pharmacodynamically, we will take special precaution in instructing parents/legal guardians on the importance of recording and reporting use of all medications both prior to and during study participation. The more common pediatric medications will be classified as acceptable or unacceptable, and this list will be given to all research staff as well as parents/legal guardians. Medications not on the list will be discussed between

the ~~treating clinician~~ investigatory/study physician and parent/legal guardian and/or subject's pediatrician prior to administration. Special attention will be given to non-psychotropic drugs with known interactions with metformin (diuretics, ACE inhibitors, beta blockers, quinolones, topiramate, nifedipine, cationic drugs, or drugs eliminated by active tubular secretion, including levetiracetam, aspirin, or histamine H<sub>2</sub> receptor antagonists).

#### 5.1.5 Concomitant Non-Medical Treatments

Continuation of non-pharmacologic treatments will be permitted if begun at least one month s prior to participation in the study. These treatments include vitamin and diet therapy, educational/socialization therapy, and behavioral modification. A careful review of non-pharmacologic treatments will be discussed with the subject's parent/legal guardian at screening, at each subsequent study visit, and will be documented on a separate form. This will include a question about changes in educational and other services received. Initiation of new behavioral or non-medical therapies aimed at weight loss and feeding behavior during the study may confound the results of the study and, therefore, will be flagged for potential ancillary statistical analysis.

## 6. STUDY EVALUATORS

### 6.1 Clinical and Laboratory Evaluations

#### 6.1.1 ASD Diagnoses

The diagnosis of ASD will be confirmed using the ADOS<sup>22</sup>. The ADOS is a standardized, interactive protocol for direct observation (45 minutes) of social and communicative behavior associated with ASD, and consists of structured and semi-structured methods for interaction<sup>22</sup>. This assessment tool is designed to assess a wide range of children and adolescents, from nonverbal/barely verbal children to adolescents and adults with fluent speech. If an ADOS was done ~~done by a research reliable clinician~~ at any time in the subject's life, we will accept those scores or proof that it was done and that the child met criteria, as long as we are provided a copy of the full protocol.

#### 6.1.2 DSM-IV Clinical Diagnosis<sup>23</sup>

All subjects must also meet ASD diagnostic criteria based upon a clinical evaluation using DSM-IV criteria. This evaluation will be conducted by a psychologist, psychiatrist, or developmental pediatrician at each of the sites.

#### 6.1.3 Assessment of IQ

All subjects will have an updated assessment of full IQ at the time of initial screening using either the Stanford-Binet V<sup>24</sup> or Mullen Scales of Early Learning AGS Edition<sup>25</sup>. For subjects whose IQ falls below 40, the Mullen Scales of Early Learning AGS Edition will be used. If a child has had a full-scale IQ test done within 24 years (e.g., Stanford-Binet, Mullen Scales, Wechsler Scales, DAS,), this will be accepted in place of the Stanford-Binet or Mullen Scales. The Mullen is a measure of cognitive functioning for infants and preschool children from birth through 68 months. It provides standardized scores across five domains: Visual Reception (nonverbal problem-solving skills), Receptive Language, Expressive Language, Fine Motor skills, and Gross Motor skills. The Mullen was standardized on 1,849 young children and has highly acceptable reliability. A mental age (IQ estimate) will be derived. Consistent with the Autism RUPP Protocol, only three of the five Mullen subscales will be used to determine mental age: Fine Motor Skills, Receptive Language and Visual Reception. The Expressive Language subscale is not used because many subjects do not have expressive language and the use of this subscale would artificially lower the overall assessment of mental age.

#### 6.1.4 Aberrant Behavior Checklist (ABC) (Parent)<sup>26</sup>

The ABC is a standardized scale comprising 58 items for assessing problem behavior in subjects with developmental disabilities. The ABC was empirically derived from ratings on approximately 1,000 subjects, and the items resolve onto five subscales: (I) Irritability (15 items), (II) Lethargy/Social Withdrawal (16 items), (III) Stereotypic Behavior (7 items), (IV) Hyperactivity (16 items), and (V) Inappropriate Speech (4 items). There is considerable research on the psychometric characteristics of the ABC, which appear to be very sound<sup>27</sup>. The primary caregiver will rate the subject.

#### 6.1.5 The Clinical Global Impressions Scale (CGI) (Clinician)<sup>28</sup>

This clinician rating scale includes a severity of illness and global improvement subscales. The severity of the illness is scored from 1= normal to 7= extremely ill. The patient's improvement is scored on a 7-point scale which ranges from "very much improved" (1), through "no change" (4), to "very much worse" (7). The CGI has been widely used in psychopharmacological studies, and it is highly sensitive to medication effects<sup>29</sup>. The scores on the *Severity of illness* and *Improvement* scale will be based upon primary

caregiver interview, primary caregiver completed behavior problem checklists, and direct observation of the child. The CGI score will be based upon severity and improvement of global symptoms related to behavioral, emotional, and physical functioning. **In other words, has this medication improved the child's overall clinical status, while taking into account any impairment in his or her behavioral/emotional status and/or adverse event profile?** This tool will be given at baseline, Week 16, and Week 32 (Severity assessment) and at all clinic visits after baseline (Improvement assessment). The CGI will be completed by a study team member who has established reliability.

#### 6.1.6 Comprehensive Medical and Developmental Assessment, Physical Examination

This includes a physical exam as well as the collection of vital signs, height, and weight, abdominal and hip circumference. The PI or study staff will also review the subject's medical, psychiatric, and concomitant therapy histories.

#### 6.1.7 Clinical Laboratory Analysis

The analysis includes fasting (10 hours) liver function tests, BUN, creatinine, electrolytes, bicarbonate, serum lactate, fasting glucose, HgbA1C, insulin, vitamin B12, total cholesterol, LDL, HDL, triglycerides, and CBC. Urine or blood pregnancy testing will be conducted for girls of childbearing potential (i.e., post menarche). Given the population, we recognize that there will be circumstances when we cannot take a blood sample. If this takes place at screening, we will not enroll the patient. Every effort will be made to obtain all scheduled subsequent blood draws but recognize that we may need to accept a failed attempt for some individuals.

#### 6.1.8 Blood Sample for DNA Extraction

At the time of screening or at the time of a subsequent blood draw, one additional 3 mL blood sample for each subject may be collected in a lavender top tube for later genetic analyses. After gentle mixing by 5-6 inversions, the sample will be transferred to a plastic, screw-top storage tube. This sample will be labeled with the study subject number the date of the draw only and will be stored at  $-80^{\circ}\text{C}$  prior to shipment to the Veenstra-VanderWeele laboratory, where DNA will be extracted and stored at  $-80^{\circ}\text{C}$ . DNA tubes will be labeled with study subject numbers and the date of the draw only. Once the full study has been completed for all subjects and results have been analyzed, investigators will evaluate which follow-up pharmacogenetic analyses should be performed. Results of any subsequent genetic analyses will be deposited in the ATN biorepository database using study subject identifiers only. Results of genetic testing will be used for research only and individual results will not be shared with study subjects.

#### 6.1.9 Safety Monitoring Uniform Report Form (SMURF)<sup>30</sup>

The SMURF, slightly modified to assess metformin-specific adverse events (including fatigue, difficulty breathing, dizziness, irregular heartbeat, sweating, and changes in vision, coordination, confusion and seizures), will be administered by the clinician on every visit. In addition, families will be counseled at the beginning of the study regarding these potential AEs and asked to call the study doctor on call pager if they experience any of these. For each AE, the clinician will record: 1) date and time of onset; 2) severity; 3) serious risk status; 4) attribution; 5) action taken; 6) outcome and 7) date and time resolved. Additionally, any clinically significant changes noted during interim or final physical examinations and laboratory sampling will be recorded (e.g. vital signs, weight).

### 6.1.10 Measures of diet and exercise

We will use the Block Questionnaire for Ages 8-17 – 2004 FFQ and the Child's Physical Activity Questionnaire at baseline, week 16 and week 32. The Block Questionnaire includes 77 food items, individual portion size, and pictures are provided to facilitate accuracy of quantification<sup>31</sup>. This diet questionnaire takes approximately 25 minutes for the primary caregiver to rate. The Child's Physical Activity Questionnaire is a 7-day recall instrument for the primary caregiver to complete<sup>32, 33, 34</sup>. It assesses the subject's general levels of physical activity and provides a summary physical activity score.

Our consultant endocrinologist and local ATN nutrition support will assist with this endeavor.

### 6.1.11 Spatial and Verbal Memory

We will use the NEPSY-II memory for designs and memory for designs delayed subtests<sup>35</sup> at baseline, week 16 and week 32 to assess spatial memory<sup>36</sup>. The memory for designs involves showing the subject a grid of four to ten designs on a page and then removing the grid from the subject's view. The subject is then asked to select the designs from a set of cards and place the cards on a grid in the same location as previously shown. This task is meant to assess spatial and content memory for novel visual material. The memory for designs delayed task will then be administered 15-25 minutes later and requires the subject to select eight to ten designs from a set of cards and place the cards on a grid in the same location previously; this second task assesses long-term visuospatial memory.

We will also use the Modified Children's Verbal Learning Test (MCVLT) an adaptation of the California Children's Verbal Learning Test<sup>37</sup>, to assess verbal memory at baseline, week 16 and week 32. The MCVLT requires subjects to listen to a series of common nouns taken from basic levels of the Peabody Picture Vocabulary Test (PPVT) and then to repeat as many of the words as possible. There are five immediate recall trials, in which the subject repeats words immediately after hearing the word list. Then there is a delay of 10 minutes, in which the subject is engaged in some other activity unrelated to the MCVLT. This is followed by one long delay recall trial (trial 6). Finally, the subject is presented with 20 nouns (10 previously heard and 10 new ones), and the subject is asked to categorize these as previously heard ("yes" response) or not previously heard ("no" response). The task provides scores for (a) the Immediate Free Recall portion (trials 1-5), (b) the Long Delay Free Recall portion (trial 6), and (c) the Recognition portion. The possible ranges of scores are as follows: a) Immediate Free Recall portion, 0-50; (b) Long Delay Free Recall portion, 0-10; and (c) the Recognition portion, 0-20.

If a subject encounters great difficulty in the first two trials (score of 4 or less), then the examiner starts the test again, but this time the trials are accompanied by pictures of the stimuli using a flip chart. Past experience with this task has shown that even subjects with significant developmental delays are usually able to perform the MCVLT when the stimuli are presented both aurally and visually. The task has been used successfully in multisite pharmacological trials<sup>38, 39, 40</sup>, and regular gains are evident with greater maturity. The MCVLT is readily mastered by investigators across multiple sites.

## 6.2 Study Procedures

The study visits and procedures are summarized in Appendix A. Once the screening evaluation is complete, there are two parts to the study: 1) Efficacy Phase (Part I), and 2) Continuation Phase (Part II).

### 6.2.1 Part I: Randomized Efficacy Phase (16 weeks)

Study procedures and visits are summarized in Appendix A. During the efficacy phase (baseline through Week 16), subjects will have a phone call with the clinical research team at Week 1, and then meet with the clinical research team every 2 weeks at first (Weeks 2 and 4) and four weeks after that to monitor therapeutic maintenance and adverse events. Adverse events, concomitant medications, non-pharmacological treatments, vital signs, height and weight will be recorded at each visit. Unplanned visits will be permitted if there are any concerns about AEs. The study physician will determine if the dose titration can continue as scheduled (or if the dose needs to be lessened due to AEs). Furthermore, the ABC and CGI will be completed as indicated in Appendix A. Compliance/accountability with study medication will be assessed by measuring the weight of the bottle before dispensing and upon return as well as the number of missed doses as reported by the parent. A written drug log for parents will be given every week. At Week 16, determination of study response will be made. Subjects/ parent/non-parent caregiver will be asked to complete a Blinding Assessment at this time as indicated in Appendix A to assess whether they thought they received metformin or placebo during this part of the study.

Efficacy Variables. The primary efficacy measure will be change in body mass index z-score calculated from Year 2000 Centers for Disease Control and Prevention age- and gender-normed growth charts. Secondary outcomes will include (a) changes in additional body composition parameters (absolute and relative change in weight, absolute BMI, and abdominal and hip circumference); (b) changes in fasting metabolic parameters (total cholesterol, LDL, HDL, triglycerides, glucose and insulin) at 16 weeks; and (c) changes in ABC scores.

Safety Measures: The Safety Monitoring Uniform Report Form (SMURF) and vitals will be administered at each visit. Safety laboratory measures will be obtained at Weeks 8 and 16.

Responder Definition. A “responder” will be defined as a subject whose BMI z-score does not increase over the course of the 16-week treatment period.

### 6.2.2 Part II: Open Label Continuation Phase (16 weeks)

All subjects will be offered open label metformin treatment at the end of taking the assigned drug in Part I. **if the family requests.** The blind will be broken by staff members independent of the study at the point of the child’s exit from the study (Week 32 or end visit) but may be broken earlier if 1) an adverse event necessitating withdrawal from active drug is evident or 2) if the family requests at the end of Week 16.

**At the Week 32 or end visit, parents will be asked to fill out a Parent Satisfaction Survey as indicated on Appendix A to assess their satisfaction of the study.**

*Study procedures and visits are summarized in Appendix A. During the continuation phase (Weeks 16 through 32), subjects will have a phone call with the clinical research team at Week 17, and then meet with the clinical research team every 2 weeks at first (Weeks 18 and 20) and four weeks after that to monitor therapeutic maintenance and adverse events. Subjects will be evaluated by the same clinical research team as in the efficacy phase. Additional monitoring visits or phone calls with the **treating clinician investigator/study physician** will be scheduled as needed. Adverse events, concomitant medications, non-pharmacological treatments, vital signs, height and weight will be recorded at each visit. Laboratory measurements may be repeated if clinically indicated*

by the investigator/study physician. A final safety check phone call with the clinical research team will occur 45 days (+/- 14 days) after the Week 32 visit.

### 6.2.3 Intervention Discontinuation Evaluations

#### *Premature Withdrawal from Drug*

If at any point during the study, a subject experiences intolerable adverse events which cannot be controlled adequately with dose reduction, or are so severe as to preclude a trial of dose reduction, the subject will stop study drug.

If a subject experiences a significant deterioration in functioning as reflected by a CGI-I score of "6- much worse" or "7- very much worse," the blinded ~~treating clinician~~ investigator/study physician will evaluate whether the subject should be immediately removed from the study or whether interventions such as changing the dose or adding interim visits are indicated. If a subject has two consecutive CGI-I ratings of 6 or 7, he/she will discontinue dosing and be followed to 16 weeks. For safety, subjects who are felt to require additional psychotropic medication during the study will be withdrawn from metformin if the new medication is known to interact significantly with metformin and another non-interacting agent cannot be found.

If a subject withdraws from drug prematurely, irrespective of what decisions have been made regarding participation in trials or other treatments, we will do all termination assessments and will ask the subject to come back for either the week 16 or week 32 assessments (dependent on whether the subject withdraws during Part I or Part II of the study), for measurement of the primary outcome measure. The research team will continue to provide clinical care for former subjects until their first visit with another provider.



## 7. STATISTICAL CONSIDERATIONS

### 7.1 *General Design Issues*

Summaries of efficacy will be presented separately for each study phase, i.e. the efficacy phase and the continuation phase. Generally, safety data will be presented across both study phases; safety data will be summarized separately by study phase for the majority of safety parameters as well.

Descriptive statistics for continuous data will be summarized using N, mean, SD, median and range. Summaries of changes from baseline will also be provided, whenever appropriate. Categorical data will be presented as frequencies and percentages. Shift tables for changes from baseline of categorical outcomes may be produced, whenever appropriate.

Body mass index and weight will be transformed to standardized z-scores using anthropometric indices based on the 2000 Centers for Disease Control and Prevention age- and gender-normed growth charts.

All statistical tests will be two-sided using an alpha level of 0.05 in order to declare significance, if not otherwise noted. For secondary and tertiary efficacy parameters, there is no pre-specified hierarchical order for assessment, and no adjustments of the significance level for multiple testing will be performed. All analyses will be performed using SAS, version 9 or higher.

### 7.2 *Outcomes*

Primary outcome (including definition): The primary efficacy measure will be change in body mass index z-score.

Secondary outcomes: Secondary outcomes will include changes in additional body composition parameters (absolute and relative change in weight, absolute BMI, and abdominal and hip circumference) and changes in fasting metabolic parameters (total cholesterol, LDL, HDL, triglycerides, glucose and insulin) at 16 weeks.

### 7.3 *Sample Size Considerations*

The sample size and power estimate was conducted first and foremost to determine the sample size needed for the efficacy (randomization) phase of the study. Given the single arm, open label design of the 16-week continuation phase, formal sample size estimates and power calculations were not conducted for this phase.

The sample size for the efficacy phase was determined based on the number of subjects required to demonstrate a statistically significant difference in the mean change from baseline to Week 16 in BMI z-scores in the two treatment arms. The null and alternative hypotheses for the primary efficacy endpoint are as follows:

Ho: There is no difference in mean change from baseline to Week 16 BMI standardized z-scores between subjects randomized to metformin and subjects randomized to placebo.

Ha: There is a difference in mean change from baseline to Week 16 BMI standardized z-scores between subjects randomized to metformin and subjects randomized to placebo.

Sample size estimates were based primarily on the following considerations. The study is powered to detect a 0.5 SD difference between metformin and placebo in mean change from baseline standardized z-score after 16 weeks of treatment during the efficacy phase, assuming a common SD of 0.6 and a Student's t-distribution. With a two-sided significance level of 5% ( $\alpha = 0.05$ ) and a 1:1 (metformin:placebo) allocation ratio, and assuming approximately 15% of the subjects ~~will not meet the modified intent-to-treat (MITT) definition~~ ~~are lost to follow-up~~, a total of 90 subjects (45 subjects in each arm with 39 in each arm ~~ultimately meeting the MITT definition~~ ~~with follow-up~~) will provide at least 90% power (actual type II error  $\beta = 0.07$ ) to reject the null hypothesis of no difference between metformin and placebo in mean change from baseline BMI standardized z-score after 16 weeks of treatment.

#### 7.4 Analysis Populations

The following analysis populations will be defined for each study phase:

- a) ~~Intent-to-Treat (ITT) Safety~~: The ITT safety population for a given study phase ~~will~~ ~~consist~~ of all consented subjects who were randomized ~~and received at least one dose of study drug~~. Subjects will be analyzed according to ~~the~~ treatment actually received.
- b) ~~ITT Efficacy~~: ~~The Intent-to-Treat (All ITT safety subjects who are evaluated for efficacy (i.e., subjects who have at least one post-baseline efficacy assessment) for a given phase are included in the ITT)~~ efficacy population for ~~a given study phase will consist of all consented subjects who were randomized and received at least one dose of study drug~~. ~~That phase—All~~ subjects will be analyzed according to the treatment to which they were randomized, regardless of ~~the~~ treatment actually received.
- c) ~~MITT Efficacy~~: ~~The modified ITT (MITT) efficacy population for a given study phase will consist of all consented~~ ~~All randomized~~ subjects who ~~were randomized, received at least one dose of study drug, and~~ continued their underlying atypical antipsychotic medication during the entire efficacy phase.

In addition, the following analysis population will be defined for the Efficacy ~~and Continuation~~ Phases only:

- d) ~~Per-protocol (PP) Efficacy~~: ~~The PP efficacy population for the Efficacy Phase will consist of all~~ ~~All~~ MITT efficacy subjects who have no major protocol deviations ~~will be included in the PP efficacy population for the Efficacy Phase~~. Major protocol deviations will be defined prior to study unblinding.

The analysis of baseline characteristics and efficacy will be performed for the ~~safety~~ ITT ~~population~~ and the MITT population. Efficacy analyses based upon the ITT population will be regarded as the primary analyses for statistical inference regarding efficacy for the trial.

~~The primary analysis will be based on ITT cohorts~~

## 7.5 Randomization

Subjects will be randomized after written consent is obtained and they are determined to be eligible. A computer generated randomization schedule that assigns subjects equally to the metformin and placebo treatment arms will be created by the Clinical Coordinating Center (for each site-by-stratum combination). ~~The investigational drug pharmacy will receive an auto generated email with the treatment assignment once a subject is enrolled into the randomization segment at the participating site by the study coordinator. Subjects who meet all criteria for randomization will be formally randomized during the baseline visit. Randomization ID will be sent to the site once a subject has been successfully screened and enrolled into the study. The Study Coordinator will coordinate the randomization visit with the pharmacist. Only the investigational drug pharmacy at each site and unblinded staff at the DCC will have access to the actual treatment assignment.~~

A total of 90 subjects will be randomized during the baseline visit according to a computer-generated randomization schedule that assigns subjects equally (1:1) to the metformin and placebo treatment arms. The randomization will be via permuted blocks stratified by age group (6-9 vs. 10-17) and clinical center using ~~alternating~~ random block sizes of 2 and 4. The randomization list will be created by the AIR-P DCC.

~~If the subject is eligible for the screening segment the study coordinator will enter enrollment information into the Electronic Data Capture (AdvantageEDC<sup>SM</sup>) system to obtain the study identification number. If a subject is eligible to be randomized into the efficacy phase the Study Coordinator will enroll the subject into the Randomization segment in AdvantageEDC<sup>SM</sup> to obtain the treatment assignment using the same study identification number. The Study Coordinator will coordinate the randomization visit with the pharmacist. The pharmacist will receive an email with the subject's treatment code (metformin or placebo). The investigational drug pharmacy at each site will log the treatment assignment in their study pharmacy binder and only they will have access to the actual treatment assignment.~~

Since the subjects will be treated with open-label metformin during the continuation phase, there will be no randomization scheme used during this phase.

## 7.6 Subject Disposition

All subjects who provide informed consent and are randomized will be accounted for. Summaries will be provided for the overall population entering each study phase, and in addition will be provided by treatment group for the efficacy and continuation phases. Entries will include the number of subjects who are qualified for each analysis population (~~ITT~~ Safety, ITT Efficacy, MITT Efficacy, and PP Efficacy if applicable). Overall study completion status, and by phase completion status will be summarized; for subjects who discontinued in any phase, the primary reason for discontinuation will be summarized.

## 7.7 Statistical Analyses

### 7.7.1 Demographics and Baseline Characteristics

Descriptive summaries of demographic characteristics (age, gender, race and ASD Type) for both study phases will be provided for the ~~ITT~~ Safety population. A summary of baseline disease characteristics will be provided overall for the ~~ITT~~ Safety population entering the Efficacy Phase.

### 7.7.2 Efficacy phase analyses

The primary efficacy endpoint for the efficacy phase is the change from baseline to the end of phase (Week 16) BMI standardized z-scores. The null hypothesis of no difference between treatment groups in mean change from baseline to Week 16 BMI standardized z-scores will be assessed using a mixed effects model, with baseline BMI z-score as a covariate, treatment group as a factor, and their interactions with time from treatment initiation. All observations will be included in the analysis with covariance among repeated measures accounted for using random subject-specific intercepts and slopes.

Additional efficacy analyses will be conducted for the ITT and MITT efficacy analysis population. Generally, covariate adjusted mixed effects models of additional efficacy endpoints will include baseline score as a covariate and treatment group as a factor.

We will also assess change in commonly observed problem behaviors as measured by the ABC and change in laboratory measures. As above, the analyses will be conducted using adjusted mixed effects models with the baseline subscale score/laboratory measure as a covariate and treatment group as a factor.

### 7.7.3 16-week continuation phase analyses

The primary efficacy endpoint for the continuation phase is change from baseline to end of phase (Week 32) BMI standardized z-score in “responders” to metformin and change from Week 16 to end of phase in “placebo-nonresponders.” Estimates of change from baseline for metformin “responders” and change from Week 16 for “placebo-nonresponders” will be obtained from mixed-effect change-point models.

## 7.8 Safety Analysis

The evaluation of safety for the **ITT** safety population will be based upon the following:

- Adverse events (AEs), treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to study drug discontinuation
- Any deaths
- Clinically significant (CS) laboratory findings

Generally, safety summaries will be provided for each phase separately. For summaries descriptive statistics will be provided overall and by treatment group during the Efficacy Phase and by cohort (metformin “responders” and “placebo nonresponders”) for the Continuation Phase. The proportion of subjects experiencing TEAEs during the Efficacy Phase will be compared between treatment groups by Fisher's exact test for each category of TEAE and for overall rate by negative binomial regression. The proportion of TEAEs occurring during the Continuation Phase for each cohort tested using a one-sample test of proportions to determine whether the proportion of TEAEs differs from zero.

Non-inferiority of metformin vs. placebo with respect to problem behaviors will be inferred from Wald confidence intervals obtained from analysis of Part I data by mixed model ANCOVA.

### 7.8.1 Treatment Emergent Adverse Events Leading to Study Drug Discontinuation

A summary of the number and percentage of subjects with TEAEs leading to study drug discontinuation will be prepared across study phases and for each phase separately. A data listing of TEAEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the **eCRF**.

### 7.8.2 Serious Treatment Emergent Adverse Events

A summary of the number and percentage of subjects with serious TEAEs will be prepared across study phases and for each phase separately. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the eCRF.

## 7.9 Statistical and Analytical Issues

### 7.9.1 Adjustment for Covariates

The primary efficacy analysis for the Efficacy Phase will be adjusted for age, gender, and baseline weight. The primary efficacy analysis for the Continuation Phase will be adjusted for age, gender and baseline weight. Similar adjustments will be made for secondary efficacy endpoints.

Exploratory multivariate analyses will be conducted to assess the potential contribution of a number of baseline and treatment-related risk factors on efficacy outcomes (e.g. which atypical medication, length of treatment, IQ etc).

### 7.9.2 Handling of Dropouts or Missing Data

Subjects without post-baseline values for a given efficacy assessment will be excluded from analyses based upon that assessment. If a subject is missing a response for any item needed for the computation of efficacy scores or subscores, the corresponding total score or subscore will be calculated as per instrument guidelines. Efficacy outcomes will be censored at the time of discontinuation of a subject's atypical antipsychotic.

Subjects who withdraw or are withdrawn will not be replaced under this protocol.

### 7.9.3 Multiple Comparisons / Multiplicity

The primary efficacy hypotheses associated with the Efficacy Phase and the Continuation Phase are independent hypothesis tests, and consequently will be analyzed using an overall significance level of 0.05 ( $\alpha = 0.05$ ) for each primary efficacy endpoint for each study phase.

The secondary efficacy endpoints are considered supportive of the primary efficacy endpoint. A significance level of 0.05 will be used for these analyses also; no adjustments for multiplicity will be made.

### 7.9.4 Use of an Efficacy Subset of Subjects

The PP (per protocol) efficacy population will be used to confirm the results of the primary efficacy analyses conducted for the ITT and MITT efficacy populations in the Efficacy Phase.

### 7.9.5 Criteria for Unblinding the Results

A pre-analysis meeting will take place before breaking the study blind, to decide how to deal with problems in subjects' data (missing values, withdrawals, drop outs, protocol violations, etc.), to refine definitions of the analysis populations, and to consider changes to the analysis plan.

After the pre-analysis meeting and documentation of all decisions, and approval and locking of the database, the data will be unblinded and analyzed.

## 8. DATA COLLECTION AND SITE MONITORING

### 8.1 *Source Documents*

Source documents are defined as original documents, data and records. They may include hospital records, clinical and/or office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media and x-rays. Study staff will clearly define the various source documents used to support the study as part of their local data management support.

The investigators will permit study-related monitoring, audits, IRB/REB review, FDA/Health Canada inspection, and will provide direct access to all source data documents at the time of monitoring and/or upon request by the AIR-P DCC.

### 8.2 *Web-Based Data Collection and Management System*

Data collection will occur via a web-based data entry system (AdvantageEDC for study specific needs such as enrollment and subject ID assignment) provided by the Data Coordinating Center (DCC) of the ATN to allow easy access to enrollment 24 hours a day, seven days a week, and the Internet System for Assessing Autistic Children (ISAAC) system for copyrighted assessments. Upon enrollment in AdvantageEDC, a form submission schedule is generated for each subject, and displayed as a grid of forms by study visit that permits direct access to each eCRF for data entry. As data are entered, they are validated through range and within-form consistency checks.

### 8.3 *Certification in the Use of Web-Based Data Entry System*

The DCC will provide training and certification of study staff in the use of the data entry and specimen tracking systems. Once certified, users are permitted to enter data into the production system. Access is password controlled. Certification for use of the web-based data entry system will be completed via individual practicum assessment.

### 8.4 *Data Storage and Quality Control*

Data for individual subjects will be recorded on electronic case report forms (eCRF) in the AdvantageEDC system. All subjects screened for the study, including the screen failures, must be entered into AdvantageEDC. Subjects will be randomized in the AdvantageEDC system and the eCRFs must be current to reflect subject status at each phase during the course of the study. Subjects will not be identified on the eCRFs by name or initials; the system will generate a study identification number once a subject is entered into the system. Investigators are required to keep a separate log of subject names and addresses. If requested as part of an FDA/Health Canada inspection, this log may be shown to the FDA/Health Canada investigator, but no copy should be provided so that confidentiality is protected.

Because of the potential for errors and inaccuracies in entering data into eCRFs, laboratory and other test results must be kept on file with the subject's study dossier. Study records should be maintained for 25 years post completion of the final study report or publication of the primary endpoints.

### 8.5 *Data Quality Control and Assurance*

Prior to the initiation of the study, an investigator's meeting will be held with the AIR-P CCC, AIR-P DCC, the investigators and their study coordinators. This meeting will include a detailed discussion of the protocol, performance of study procedures, safety reporting requirements, AdvantageEDC training and eCRF completion and simulation of study procedures, as applicable. Study staff that is responsible for the collection and

submission of the study data will be required to pass AdvantageEDC training for certification prior to use of the production system for submission of the data. The study Manual of Procedures will be reviewed during training for site personnel and should be utilized to reference key details regarding study processes.

After completion of the entry process, computer logic checks or Integrity reports will be executed to assess data inconsistencies (e.g., inconsistent study dates or out of range laboratory values). A response to these reports is required from site personnel by the defined report date. In addition, data modifications to the data field(s) must be made in AdvantageEDC which tracks the audit history of all data entered and modified.

#### **8.6 *Data Processing and Data Management***

Clinical data processing and management will be employed based on the procedures developed in conjunction with the AIR-P DCC. All of the data entered into the AdvantageEDC system will be checked for valid values and ranges, between item logical consistency, and within-subject variation. Prior to any analyses the distributions of the measures will be examined to aid in selecting appropriate statistical techniques and data transformations. Data transformations (e.g., log transformations) will be used in an attempt to normalize non-normally distributed data so as to still be able to use statistical techniques appropriate for normal data. In addition, nonparametric and semi-parametric techniques may be used with non-normally distributed data.

#### **8.7 *Data Plan for Subjects with Incomplete Data***

Subjects will be included in the data analysis provided that they complete the testing procedures listed and have completed at least one treatment visit, and do not receive additional interacting medications. The DCC will work with site staff to ensure that the study records for all subjects who terminate early are as up to date and as possible, with field and form exceptions reviewed and accepted to account for all required data.

## 9. SAFETY MONITORING

This section defines the types of AEs to report and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Please note that as this study is under an IND exemption, we will use ICH definitions to comply with Health Canada reporting requirements.

This study involves slightly greater than minimal risk. Metformin is a medication used in adults and adolescents for the treatment of type 2 diabetes. It has also been used in pilot studies in children and adolescents for weight management. In addition, the drug has a high index of safety and is rarely associated with serious adverse events. The study also involves placebo-control and blood tests for research purposes.

To minimize the risk, subjects will be systematically monitored for symptom severity, adverse events, out of range vital signs, and changes in weight through the Efficacy Phase (Part I) and Continuation Phase (Part II). When the ~~treating clinician~~ investigator/study physician is informed of ~~elicits~~ an adverse event (AE), it is documented, regardless of suspected relationship to the study drug. For all AEs, the investigator/study physician will obtain sufficient information to determine the onset, course, and outcome of the AE.

Though radiologic studies requiring contrast are not anticipated during the course of the study, if an emergency procedure is required, the study product (metformin or placebo) will be stopped for two days after the radiologic procedure requiring contrast. The subject will be appropriately hydrated and the medication may be resumed. This will not require unblinding and will provide an appropriate safety margin with the use of metformin.

***The research team is available 24 hours per day in the case of medical emergency or serious adverse events.***

### 9.1 Definitions

~~9.1.1 An AE is a new, undesirable medical event or occurrence or worsening of an existing condition (including an abnormal laboratory finding that is considered clinically significant) in a subject that occurs throughout the study, whether or not it is considered to be study related.~~ **Adverse Event:** An adverse event (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. (Any change from baseline in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the investigator/study physician are considered AEs.)

~~9.1.1.2 Adverse Drug Reaction: An adverse drug reaction (ADR) is any noxious and unintended response to a medicinal product related to any dose. ~~is any adverse event caused by the study drug/intervention.~~~~

~~Treatment Emergent Adverse Event: A treatment emergent adverse event (TEAE) is defined as any untoward event reported either on/after the first dose of study medication or represents an exacerbation of a pre-existing condition. ~~AEs or medical events and toxicities occurring after initiation of treatment are treatment emergent adverse events (TEAEs).~~~~



**9.1.4 Serious Adverse Event (SAE):** A **serious adverse event (SAE)** is defined as any adverse therapy experience occurring at any dose that suggests a significant hazard, contraindication, adverse event, or precaution. This includes, but is not limited to, any of the following events: (For a copy of the current MedWatch Form 3500, see the list of PDF forms on the web at: <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>)

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy whether or not considered treatment-related must be reported.
2. Life-threatening: Any adverse therapy experience that places the subject or subjects, in the view of the investigator/study physician, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that had it occurred in a more serious form, might have caused death).
3. In-patient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions~~Persistent or significant disability or incapacity.~~
5. Congenital anomaly/birth defect.
6. ~~An event that required intervention to prevent permanent impairment or damage.~~

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

**9.1.5 Unexpected Adverse Event/Drug Reaction:** An **adverse reaction/AE** is considered “unexpected” when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the Investigator’s Brochure (IB) or product monograph.

## 9.2 Procedures and Monitoring

In order to report the occurrence of an AE associated with oral metformin/placebo dosing, the physician will complete a Safety Monitoring Uniform Research Form (SMURF) at each visit to document physical and/or behavioral symptoms in discussion with the child and their parent. If a subject has experienced an adverse event, the subject may return to the site at the PI’s discretion. If any of these events are serious **and/or unexpected**, as defined above, the site PI will contact the sponsor within 24 hours of becoming aware of the event.

### 9.2.1 Relationship to **Procedure Study Drug** Definitions

Causality assessment is required for clinical investigation cases. All AEs judged by either the physician or the sponsor as having a reasonable suspected causal relationship to the study drug qualify as ADRs.

For all AEs, the physician must attribute the AE to the study drug using the following classification:

- **Definite:** AE is clearly related to study drug
- **Probable:** AE is likely to be related to the study drug
- **Possible:** AE may be related to study drug
- **Unlikely:** AE is doubtfully related to the study drug

- **Unrelated:** AE is clearly not related to the study drug

An AE that is suspected to be related to test product or procedures will be reported as a suspected adverse reaction (SAR). An AE that is believed to be related to test product or procedure will be reported as an adverse reaction (AR).  
<http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf>

### 9.2.2 **Classification Severity of Adverse Events**

- **Mild:** Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain). ~~AE poses no interference and no intervention is required.~~
- **Moderate:** Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible. ~~AE poses some interference OR requires some intervention — e.g., lowering the dose of the medication.~~
- **Severe:** Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible. ~~AE poses some interference AND requires intervention.~~

### 9.3 **Site Adverse Events Collection and Recording Procedures**

Adverse events will be systematically reviewed at each visit by the treating clinician investigator/study physician. This review will include a general inquiry about health, other medications, and visits to medical providers since the last visit. The treating clinician investigator/study physician will administer the SMURF with the parent and child. This rating covers a range of behavioral and physical adverse effects that are relevant to this class of medications. Worsening on the SMURF from baseline will in general be considered adverse events and reported on the adverse event eCRF. Vital signs (pulse, blood pressure) and weight will be measured at each visit. Standardized procedures will be used for all physical measurements. Vital signs will be assessed with the subject seated. Height and weight will be assessed with all outer-wear and shoes removed and using a wall-mounted stadiometer, and with shoulders and rump placed snugly to the wall. Hip and waist measurements will be assessed in centimeters, to the nearest 0.5 cm, with the tape placed snugly over the child's under garments. Circumferences will be measured three times, and the mean will be recorded. At the initial multi-site meeting, the use of the measuring tape will be illustrated by a "gold standard" clinician, who will demonstrate the appropriate "tension" to be used when employing the measuring tape.

All SAEs must be reported to the sponsor by the site PI within 24 hours of their occurrence and/or the site's knowledge of the event. The sponsor is responsible for notifying the DSMB as per their guidelines, and sites are responsible for reporting to their IRB/REB

Sites are required to enter reportable AEs and SAEs into the AdvantageEDC system. Additional information may need to be gathered to evaluate the SAE and to complete the appropriate eCRFs. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type of records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stabilized at the time of initial reporting,

or if new information becomes available, follow-up information must be submitted as soon as possible.

Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow up will continue through 30 days post last study visit. Research personnel will obtain as much information as possible about the reportable AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting serious events to their IRB, per their IRB's guidelines.

Sites are required to enter reportable AEs and SAEs in to the study's data capture system. Additional information may need to be gathered to evaluate the SAE and to complete the appropriate CRFs. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stabilized at the time of initial reporting or if new information becomes available, follow up information must be submitted as soon as possible.

Reportable AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study.

### 9.3.1 Recording and Reporting Procedures Recording and Summarizing Adverse Events

The investigator/study physician treats subjects experiencing AEs appropriately and observes them at suitable intervals until their symptoms resolve or their status stabilizes.

A clear description of how Adverse Events are to be coded and summarized is required by ICH E3 and ICH E9. The incidence of adverse events is usually expressed in the form of a proportion relating the number of subjects experiencing events to the number of subjects at risk. The number of subjects at risk is usually the number of subjects in each treatment group, and overall treatment groups.

However, other methods such as risk ratios for an adverse event, survival analysis methods, or cumulative adverse event rates should be considered when long-term safety assessment is planned and a large proportion of the subjects will withdraw or die during the course of the study.

All AEs are collected using the SMURF. If an AE is indicated on the SMURF the incident will also be recorded on an Adverse Event (AE) form and will be presented in subject listings. Treatment emergent adverse events (TEAEs) are defined as any untoward events reported either on/after the first dose of study medication or represent an exacerbation of a pre-existing condition. Non-serious adverse events are reported if the onset date is within 7 days of the last study procedure and within 30 of the last study procedure for serious adverse events.

All AEs will be coded using MEDRA (Medical Dictionary of Regulatory Activities). An overall tolerability summary will include the number and percentage of subjects:

- With at least one TEAE
- With TEAEs by severity and relationship to study drug
- Receiving rescue medication/psychotherapy
- With serious TEAEs
- With TEAEs leading to study drug discontinuation
- With an outcome of death

Additionally, the total number of TEAEs, SAEs, and ADRs adverse reactions (AR) and suspected adverse reactions (SAR) will be provided. Summaries of overall tolerability will be provided across both study phases and for each phase separately.

Summaries of the number and percentage of subjects with TEAEs will be organized by System Organ Class (SOC) and Preferred Term. Summaries of TEAEs across study phases and for each phase separately will be prepared for any TEAE, TEAEs by intensity, and TEAEs by relationship to study drug.

Each subject will be counted only once within each preferred term for each study phase. If a subject experiences more than one TEAE within a preferred term for the same phase, only the TEAE with the strongest relationship or the greatest intensity, as appropriate, will be included in the summaries of relationship and intensity.

### 9.3.2 9.3.2 Serious Adverse Event Recording and Reporting Procedures Study and Individual Stopping

~~The PI at each site will apply clinical judgment to determine whether an AE is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator will suspend any trial procedures and refer to appropriate medical care. The PI at each site will report serious AEs to the local IRB/REB and the overall PI who will then report to the DSMB.~~

#### DSMB:

~~AEs will be summarized on the appropriate form for the IRB/REB on an annual basis and reviewed by the DSMB every six months or more frequently if requested. Correspondence between the sites and the DSMB will be copied and distributed to each of the local IRB/REBs.~~

#### Study Stopping:

After ~~subsequent~~ review by the FDA, Health Canada, DSMB, and the IRB/REB, the sponsor may suspend further trial treatment or procedures at a site. The sponsor, FDA, Health Canada, IRB/REB, and DSMB retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

#### Individual Stopping:

The investigator/study physician at each site will apply clinical judgment to determine whether an AE is of sufficient severity to require that the subject be removed from treatment. If necessary, an investigator/study physician will suspend any trial procedures and refer to appropriate medical care.

A subject may voluntarily withdraw from treatment due to what the subject perceives as an intolerable AE, or for any other reason. If a subject voluntarily withdraws, the subject will be requested to continue (at least limited) scheduled evaluations, have a study termination assessments completed, and receive appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

Additionally, clinically significant abnormal findings on laboratory results at study end will be recorded as adverse events, as will clinically significant changes in physical examination findings and vital signs.

A summary of the number and percentage of subjects with TEAEs leading to study drug discontinuation will be prepared across study phases and for each phase separately. A data listing of TEAEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the eCRF.

#### **Reporting Decisions for Adverse Events**

1. Notify the site's investigator.
2. Record the information regarding a SAE report in the subject's study or medical chart.
3. SAE follow-up reports will include hospital admittance notes, hospital discharge summary, clinical notes, resolution date, treatment, and any other pertinent information regarding the event. Do not delay reporting in order to provide these documents.
4. In the event of a death, you must complete the Death Form and transmit it along with other supporting data (e.g., death certificate, medical notes, etc.).

#### **Adverse Events Leading to Study Drug Discontinuation**

A summary of the number and percentage of subjects with TEAEs leading to study drug discontinuation will be prepared across study phases and for each phase separately. A data listing of TEAEs leading to withdrawal of study drug will also be provided, displaying details of the event(s) captured on the CRF.

## **9.4 Serious Adverse Event Notification**

### **9.4.1 Notifying the Sponsor and the FDA / Health Canada**

~~The site PIs are responsible for notifying the sponsor with the reporting of the event to the clinical database (i.e., SMURF form, Hematology form, Chemistry form, etc.) As noted above, the site will report a SAE within 24 hours of awareness of the event.~~

The sponsor will review each SAE report and will determine whether the SAE must be reported to ~~the FDA~~ Health Canada on an expedited basis. The final decision for disposition regarding reporting rests with the sponsor.

The FDA / Health Canada requires that all SAEs that are serious, unexpected and ~~potentially~~ related to the study intervention must be reported to the ~~FDA~~ Health Canada in writing within 15 calendar days of notification to the sponsor. SAEs that are unexpected and related to the study intervention that meet the criteria for death or immediately life-threatening also require the sponsor to notify the regulatory agencies as soon as possible but no later than 7 calendar days, with a follow-up written report within 15 calendar days.

#### 9.4.2 Notifying the Data and Safety Monitoring Board (DSMB) and the Institutional Review Board (IRB) or Research Ethics Board (REB)

The sponsor is responsible for informing the DSMB. The study DSMB is provided with listings of all AEs and SAEs ~~by the DCC~~ on an ongoing basis. The DSMB will review all reported safety information every six months or more frequently if requested. Correspondence between the sites and the DSMB will be copied and distributed to each of the local IRB/REBs.

The investigators will ensure the timely dissemination of all AE information, including expedited reports, to the IRB/REB in accordance with applicable local regulations and guidelines. AEs will be summarized on the appropriate form for the IRB/REB on an annual basis.

## 10 HUMAN SUBJECTS

### 10.1 *Data and Safety Monitoring Board (DSMB)*

This study will be overseen by a DSMB. The AIR-P DCC will assist in the preparation of reports for the DSMB that include tables of all the AEs, enrollment and randomization figures, and descriptions of subject flow. Quarterly or more often if requested, adverse events will be categorized as to prevalence and severity as reported. The DSMB will also receive reports regarding site data currency, protocol deviations and changes in safety measures. The DSMB will review these reports twice a year, determine if any additional information or protocol changes are needed, and provide a summary of their assessment and make recommendations to the PI, will communicate the summary of the DSMB findings to the AIR-P DCC and the AIR-P DCC will send a summary to each site to share with their own IRB/REB. Recommendations from the DSMB will be promptly implemented, and those requiring a change to the protocol or consent will be submitted to the IRB/REB as a protocol or consent amendment.

Members of the DSMB will not participate in ratings or in the clinical care of the subjects in this study in order to maintain their independence from the study sponsor, the study faculty and staff. The DSMB will receive tabulated data relating to safety and confidentiality of study subjects. This evaluation will also assess data quality and timeliness, subject recruitment, accrual, and retention. These reviews will allow the DSMB to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation. These reviews will also allow the DSMB to determine whether the study should: 1) continue as originally designed, 2) implement a protocol change, or 3) be terminated. If a recommendation is made to change the research study design, an adequate rationale for this decision must be provided. In addition, members of the DSMB will review data from individual study subjects on a quarterly basis to evaluate the progress of the study and the safety and confidentiality of study subjects. Any serious adverse events (SAEs) or breaches in confidentiality will be reviewed by the AIR-P DCC and reported immediately to the DSMB for review throughout the study.

### 10.2 *Institutional Review Board, Research Ethics Board (IRB/REB) Review and Informed Consent*

This protocol, the informed consent document, any applicable recruitment/advertising materials, and any subsequent modifications will be reviewed and approved by the IRB/REB responsible for oversight of the study (IRB/REB at the collaborating institutions at the University of Pittsburgh, Vanderbilt University, Oregon Health and Sciences University, and the University of Toronto). A signed consent form will be obtained from the subject. For subjects who cannot consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this will be documented in the subject's document.

All investigators will have completed the federally required training in research ethics and will emphasize the voluntary nature of this study. Treatment through the participating site will not be altered by the decision to participate or not participate. Approval from the IRB/REB will be in place prior to beginning recruitment. The four collaborating sites will each have a weekly staff meeting and a monthly conference call to review recruitment and problem-solve. For the first three months, there will be a

weekly conference call as needed to establish procedures and ensure training of all staff in the measures.

### 10.3 **Subject Confidentiality**

Raw data will be stored in locked cabinets in a locked office. De-identified data will be submitted to a central database designed by The EMMES Corporation, the DCC. The database will be password protected. All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB/REB, the FDA/Health Canada, HRSA, the OHRP, the sponsor, or the sponsor's designee. Any information uncovered through the interviews that might indicate abuse or neglect requires the investigators to inform appropriate local agencies in accordance with State law. Otherwise, all information will remain confidential.

A site and subject number will be assigned for each subject. Data forms will only be identified by subject number. The database will not contain any personal identifiers other than subject number. The results of these assessments will be kept strictly confidential unless an appropriate written release of information is provided by the subject's parent/legal guardian(s).

The research team will do everything possible to keep others from learning about the subject's participation in this research study. Each subject will be assigned a sequential identification number and these numbers rather than names will be used to collect, store, and report subject information.

*Inclusion of Females:* Since the ratio of males to females in autism is 4-5:1, we anticipate that there will be a preponderance of males in this sample of children with ASD.

*Inclusion of Minorities:* We will not restrict enrollment on the basis of race or ethnicity. We will attempt to have representation in the sample to reflect the clinical population served at the four ATN sites collaborating in this initial study. Across the four participating sites, we expect that the distribution will be representative of the US and Canadian population.

*Inclusion of Children:* Our proposal focuses on children ages 6 to 17 years, 4 months of age.

*Importance of Knowledge to be Gained:* Benefit may not be realized for the individual subject. The overall benefit of this study is the improved understanding of the safety and efficacy of use of metformin to treat weight or weight gain in children taking atypical antipsychotic medication(s).

### 10.4 **Study Modification/Discontinuation**

The study may be modified or discontinued at any time by the IRB/REB, HRSA, the sponsor, the OHRP, the FDA/Health Canada, or the DSMB as part of their duties to ensure that research subjects are protected.



**10.5 Statement Regarding Scientific Misconduct**

This study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB/REB. Any amendments to the protocol or to the consent materials must also be approved before they are implemented.

Compliance with 42 CFR Part 93, Public Health Service (PHS) Policies on Scientific Misconduct is implicit in the application for this proposal. The academic institutions participating in the ATN and this proposal have approved assurances and required renewals on file with the Office of Research Integrity (ORI) and compliance with these policies and procedures and the requirements of part 93 are in place. We understand and abide by the definitions of research misconduct per PHS policies (fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results).

## 11 PUBLICATION OF RESEARCH FINDINGS

The investigators will disseminate the results of this proposal through written and oral presentation to colleagues at other ATN sites as the data is collected and analyzed. This will take place in the monthly lead autism clinician calls and ATN annual meeting. A Webinar is proposed for ATN collaborators who would not be in attendance at the annual meeting since this topic is of general interest to all involved specialties and feedback from all ATN collaborators will be valuable. Abstract presentation at international meetings such as IMFAR (International Meeting for Autism Research) and PAS (Pediatric Academic Societies) will be planned in advance of publication of the results in peer reviewed journals that will have high impact for readers for whom this information is clinically important. Information relevant to primary care will be disseminated by the above academic routes and to practicing health care providers in partnership with professional organizations such as the American Academy of Pediatrics as well as nonprofit organizations interested in the health of children with ASD. Dissemination to families: This will be done through the ATN website and through talks at community oriented conferences sponsored by our institutions, regional Autism Speaks and other advocacy group meetings.

Inclusion of 4 ATN sites spread across regions of North America with urban, suburban, and rural populations with ethnic and racial distribution was planned so that the results of these studies may be generalized to the North American population and should be replicable.

## 12 REFERENCES

1. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D. Risperidone in children with autism and serious behavioral problems. *N Engl J Med.* 2002;347(5):314-321.
2. McDougle CJ, Scahill L, Aman MG, McCracken JT, Tierney E, Davies M, Arnold LE, Posey DJ, Martin A, Ghuman JK, Shah B, Chuang SZ, Swiezy NB, Gonzalez NM, Hollway J, Koenig K, McGough JJ, Ritz L, Vitiello B. Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *Am J Psychiatry.* 2005;162(6):1142-1148.
3. Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, Aman MG. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry.* 2009;48(11):1110-1119.
4. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, Carson WH, Findling RL. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics.* 2009;124(6):1533-1540.
5. Aman MG, Kasper W, Manos G, Mathew S, Marcus R, Owen R, Mankoski R. Line-item analysis of the Aberrant Behavior Checklist: results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. *J Child Adolesc Psychopharmacol.* 2010;20(5):415-422.
6. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, Dunbar F. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics.* 2004;114(5):e634-641.
7. Martin A, Scahill L, Anderson GM, Aman M, Arnold LE, McCracken J, McDougle CJ, Tierney E, Chuang S, Vitiello B. Weight and leptin changes among risperidone-treated youths with autism: 6-month prospective data. *Am J Psychiatry.* 2004;161(6):1125-1127.
8. Aman MG, Arnold LE, McDougle CJ, Vitiello B, Scahill L, Davies M, McCracken JT, Tierney E, Nash PL, Posey DJ, Chuang S, Martin A, Shah B, Gonzalez NM, Swiezy NB, Ritz L, Koenig K, McGough J, Ghuman JK, Lindsay RL. Acute and long-term safety and tolerability of risperidone in children with autism. *J Child Adolesc Psychopharmacol.* 2005;15(6):869-884.
9. Lindsay RL, Leone S, Aman MG. Discontinuation of risperidone and reversibility of weight gain in children with disruptive behavior disorders. *Clin Pediatr (Phila).* 2004;43(5):437-444.
10. Network RUoPPA. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry.* 2005;162(7):1361-1369.
11. Bjorkhem-Bergman L, Asplund AB, Lindh JD. Metformin for weight reduction in non-diabetic patients on antipsychotic drugs: a systematic review and meta-analysis. *J Psychopharmacol.* 2010.
12. Bushe CJ, Bradley AJ, Doshi S, Karagianis J. Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. *Int J Clin Pract.* 2009;63(12):1743-1761.
13. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *Am J Psychiatry.* 2006;163(12):2072-2079.

14. Shin L, Bregman H, Breeze JL, Noyes N, Frazier JA. Metformin for weight control in pediatric patients on atypical antipsychotic medication. *J Child Adolesc Psychopharmacol.* 2009;19(3):275-279.
15. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiatry.* 2002;159(4):655-657.
16. Yanovski JA, Krakoff J, Salaita CG, McDuffie JR, Kozlosky M, Sebring NG, Reynolds JC, Brady SM, Calis KA. Effects of metformin on body weight and body composition in obese insulin-resistant children: a randomized clinical trial. *Diabetes.* 2011;60(2):477-485.
17. Freemark, M. (2007). Pharmacotherapy of Childhood Obesity: An evidence-based, conceptual approach. *Diabetes Care,* 30(2), 395-402.
18. Stang, M., Wysowski, D. K., & Butler-Jones, D. (1999). Incidence of Lactic Acidosis in Metformin Users. *Diabetes Care,* 22(6), 925-927.
19. Riomet<sup>®</sup>, product monograph, Ranbaxy Laboratories, Inc. June 2011.
20. Ibrahim SH, Voigt RG, Katusic SK, Weaver AL, Barbaresi WJ. Incidence of gastrointestinal symptoms in children with autism: a population-based study. *Pediatrics.* 2009;124(2):680-6.
21. Lord, C., M. Rutter, and A. Le Couteur, Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord,* 1994. 24(5): p. 659-85.
22. Lord, C., Rutter, M., DiLavore, P. C., and Risi, S. (1999). Autism diagnostic observation schedule: A standardized observation of communicative and social behavior. Los Angeles: Western Psychological Services.
23. American Psychiatric Association (1994). *Diagnostic and statistical manual of mental health disorders* (4th ed). Washington DC: Author.
24. Roid GH (2003). *Stanford-Binet Intelligence Scales* (5th ed.). Itasca, IL: Riverside Publishing.
25. Mullen EJ (1989). *Mullen Scales of Early Learning.* Bloomington, MN: Pearson Assessments.
26. Aman MG, Singh NN, Stewart AW, Field, CJ (1985a). The Aberrant Behavior Checklist: A behavior rating scale for the assessment of treatment effects. *American Journal of Mental Deficiency,* 89, 485-491.
27. Aman MG, Singh NN, Stewart AW, Field CJ. (1985b). Psychometric characteristics of the Aberrant Behavior Checklist. *American Journal of Mental Deficiency,* 89, 492-502.
28. Guy, W. (1976). *ECDEU Assessment Manual of Psychopharmacology.* Rockville, Md.: National Institute of Mental Health US Dept. of Health, Education, and Welfare publication (ADM), Psychopharmacology Research Branch, 76-338. Guy, W. (1976). *Dosage Record and Treatment Emergent Symptoms Scale,* ECDEU Assessment Manual for Psychopharmacology (Revised). US Department of Health, Education and Human Welfare publication (ADM)(pp. 223-244), 76-338.
29. Aman, M.G. & Pearson, D.A. 1999. Monitoring and measuring drug effects. II. Behavioral, emotional, and cognitive effects. In *Practitioner's guide to psychoactive drugs for children and adolescents.* Edited by J.S. Werry & M.G. Aman. New York: Plenum Press. 2nd ed 99-164.
30. Greenhill LL, Vitiello B, Fisher P, Levine J, Davies M, Abikoff H, Chrisman AK, Chuang S, Findling RL, March J, Scahill L, Walkup J, Riddle MA. Comparison of increasingly detailed elicitation methods for the assessment of adverse events in pediatric psychopharmacology. *J Am Acad Child Adolesc Psychiatry.* 2004 Dec;43(12):1488-96
31. Weber Cullen, K., Watson, K., & Zakeri, I. (2008). Relative Reliability and Validity of the Block Kids Questionnaire among Youth Aged 10 to 17 Years. *Journal of the American Dietetic Association,* 108(5), 862-866.

32. Crocker, P. R. E., Bailey, D. A., Faulkner, R. A., Kowalski, K. C., & McGrath, R. (1997). Measuring general levels of physical activity: Preliminary evidence for the Physical Activity Questionnaire for Older Children. *Medicine and Science in Sports and Exercise*, 29, 1344-1349.
33. Kowalski, K. C., Crocker, P. R. E., & Faulkner, R. A. (1997). Validation of the Physical Activity Questionnaire for Older Children. *Pediatric Exercise Science*, 9, 174-186.
34. Kowalski, K. C., Crocker, P. R. E., & Kowalski, N. P. (1997). Convergent validity of the Physical Activity Questionnaire for Adolescents. *Pediatric Exercise Science*, 9, 342-352.
35. Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY—Second Edition (NEPSY-II)*. San Antonio, TX: Harcourt Assessment *Journal of Psychoeducational Assessment* April 2010 28: 175-182.
36. Wang, J., Gallagher, D., DeVito, L. M., Cancino, G. I., Tsui, D., He, L., Keller, G. M., Frankland, P. W., Kaplan, D. R., & Miller, F. D. (2012). Metformin Activates an Atypical PKC-CBP Pathway to Promote Neurogenesis and Enhance Spatial Memory Formation. *Cell Stem Cell*, 11(23-35), 23-35.
37. [Delis DC, Kramer JH, Kaplan E, Ober BA: California Verbal Learning Test, Children's Version, Manual. Orlando, Fla. Psychological Corp/Harcourt, Brace, 1998.](#)
38. [Aman, M. G., De Smedt, G., Derivan, A., Lyons, B., Findling, R.L., & The Risperidone Disruptive Behavior Study Group. \(2002\). Risperidone treatment of children with disruptive behavior disorders and subaverage IQ: A double-blind, placebo-controlled study. \*American Journal of Psychiatry\*, 159, 1337-1346.](#)
39. [Snyder, R., Turgay, A., Aman, M. G., Binder, C., Fisman, S., Carroll, A., & The Risperidone Conduct Study Group. \(2002\) Effects of risperidone on conduct and disruptive behavior disorders in children with subaverage IQs. \*Journal of the American Academy of Child and Adolescent Psychiatry\*, 41, 1026-1036.](#)
40. [Pandina, G., Bilder R., Harvey P.D., Keefe R., Aman, M., & Gharabawi G. \(2007\). Risperidone and cognitive function in children with disruptive behavior disorders. \*Biological Psychiatry\*, e-pub ahead of print. doi:10.1016/j.biopsych.2006.09.036.](#)

Appendix A

Schedule of Assessments

<b>Forms</b>	V i s i t 0 0	V i s i t 0 1	P h o n e c a l l	V i s i t 0 2	V i s i t 0 3	V i s i t 0 4	V i s i t 0 5	V i s i t 0 6	P h o n e c a l l	V i s i t 0 7	V i s i t 0 8	V i s i t 0 9	V i s i t 1 0	V i s i t 1 1	P h o n e c a l l
	<b>S c r e e n i n g</b> (c o m p l e t e i n 1- 2 v i s i t s w i t h i n +/ - 3 d a y s o f S c r e e n i n g; c o m m		<b>Part I: Efficacy Phase</b>						<b>Part II: Continuation Phase</b>						
<b>Week Number (End of Week)</b>	W e e k 0 /	W e e k 1	W e e k 2	W e e k 4	W e e k 8	W e e k 1 1	W e e k 1 2	W e e k 1 6	W e e k 1 7	W e e k 1 8	W e e k 2 0	W e e k 2 4	W e e k 2 8	W e e k 3 2	<b>F i n a l S a f e t y C h e c k</b>
	Must be booked within X weeks and +/- 4 days after the final baseline visit or first day of receiving medication (e.g., Week 2 visit must be booked 2 weeks and +/- 4 days after the final baseline visit or first day of receiving medication; Week 4 visit must be booked 4 weeks and +/- 4 days after the final baseline visit or first day of receiving medication; and so on)														4 5 d a y s + / - 1 4 d a y

Metformin

Version 23456.0

October 1, 2012 May 02, 2013 October 22, 2013 February 04, 2014 August 05, 2014



Exam														
Laboratory Analysis	X					X					X			X
Blood sample for DNA Extraction	X													
<b>Symptom Evaluation Done by Evaluating Clinician:</b>														
Height and Weight	X	X		X	X	X	X	X		X	X	X	X	X
Vital Signs	X	X		X	X	X	X	X		X	X	X	X	X
Hip and Waist Measure		X				X		X				X		X
Clinical Global Impression (CGI) -Severity		X						X						X
Clinical Global Impression (CGI) - Improvement				X	X	X	X	X		X	X	X	X	X
SMURF	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Treatment Review	X	X		X	X	X	X	X		X	X	X	X	X
Dose Management		X	X	X	X	X	X	X	X	X	X	X	X	X

Metformin



Log															
Spatial and Verbal Memory Tasks		X						X							X
<b>Done by Parent:</b>															
Aberrant Behavior Checklist	X	X					X	X				X			X
Diet and exercise Surveys		X						X							X
Blinding assessment								X							
Medication Diary		X	X	X	X	X	X	X	X	X	X	X	X	X	
Parent Satisfaction Survey															X

\*\* If never done before by a research reliable person and their team \*\*\* If not previously done within 24 years by research trained personnel