Protocol Cover Page for ClinicalTrials.Gov Record

Official Study Title: Impact of combined medication and behavioral treatment in young children with comorbid ASD and ADHD

NCT #: NCT03242772

Duke University Health System (DUHS) Protocol #: Pro00085179

Document Version Date (DUHS IRB Approval of Protocol): 16-DEC-2021

Document Name: Main Study Protocol

A+ Treatment: ACE Project 3

A pilot study of the impact of combination medication and behavioral treatment in young children with comorbid ASD and ADHD.

Duke IRB Protocol Number: Pro00085179

National Clinical Trial (NCT) Identified Number: NCT03242772

Principal Investigator: Dr. Lauren Franz

IND Exemption Received by Dr. Linmarie Sikich

Funded by: National Institute of Child Health and Human Development

Version Number: v.4.6

13 DEC 2021

APPROVED 16 DEC 2021

Proposed Changes in this IRB amendment from protocol v 1.0		
Version/Date	**Change**	**Brief Rationale**
4.6/ December 13, 2021	Corrected and clarified designation of outcomes Table in section 3 and Schedule of Activities and other language to reflect Aims (Section 2.3) and protocol.	Wanted to ensure that the outcomes table and schedule of activities correctly reflects primary outcome, secondary outcome, and exploratory outcomes per the specific aims.
4.5/ April 16, 2021	Changed PI from Dr. Geraldine Dawson to Dr. Lauren Franz	Dr. Franz has valuable experience to take on the role and this change helps balance other PI transitions across the ACE program.
4.4/October 8, 2020	Clarified that Intervention history form at 10 weeks will ask about interventions over the past 10 weeks, and the study staff may ask participants about interventions during the course of treatment as well. Added Stimulant Washout Confirmation Form and Condensed Medical History Form at Screening. Added instance of CGI I&S at Week 24. Parenting Sense of Competence form (baseline and week 10)	Stimulant Washout Form will be used to document stimulant washout in a standardized fashion, to continue to document this has been done prior to medication start; CGI I& S will help capture changes in participant symptoms/behaviors up through Week 24, and Parenting Sense of Competence will provide indication of changes in caregiver's sense of efficacy and satisfaction related to parenting role during intervention.
4.3/October 22, 2019	• Removed Intervention Log mention in the protocol • Removal of Selective Serotonin Reuptake Inhibitors as prohibited concomitant medications • Clarified visit windows through the screening and baseline portion of the study.	• This is to reflect changes already put in place and to represent the Schedule of Activities • With the expansion of the age group we predict more children will be taking prescription medications. This removal should improve enrollment. • This will allow for a more steady stream of participants and the ESDM portion of the study will be better able to accommodate participant schedules
4.2/September 12, 2019	• Removed blood chemistries at baseline visit • Rearranged the timing of physician visits • Changed the timing of the AE follow-up visit • Clarified that all conmeds will be collected even if PRN and taken less than 14 days	• Removal will allow more subjects to participate due to major obstacle in collecting blood in this population • This will allow for an in-person visit within a week of reaching target dose and allow the physician to make dose adjustments more readily. • This will allow an evaluation of any ongoing AEs much sooner and may facilitate resolution of AEs • This is more in-line with the industry standard of collecting ALL conmeds to address any potential AE's in general inquiry prompt • This is dependent on the type of visit in this study and was depicted in the SoA

	• Clarified when a participant would be lost to follow-up • Clarified that at baseline and end of assessment time point the ADHD-RS would continue to be collected	previously but was also added to the text and refers to the SoA for clarity • It was inadvertently left out due to some confusion on when the caregiver form and the clinician form would be administered but has now been clarified in the text
4.1/August 08, 2019	• Removed lower limit Inclusion Criteria of General Conceptual Ability Score having to be higher than 60 • Removed the PAERS form and will replace with general AE inquiry • Removed CGI-S and I parent form and added new Impairment Rating Scale-Parent Form (IRS)	• Removal of lower IQ limit in hopes of broadening eligible population for recruitment • Removal of this form will better streamline the safety monitoring process • The new Impairment Rating Scale-Parent Form is a more parent-friendly form than the CGI-S
4.0/ July 03, 2019	• Changed Inclusion Criteria to expand age range to include children 36 months to <132 months of age • Removed criteria based on receptive language age equivalent • Added lower IQ limit of 60 • • Switched primary and secondary end points. Primary end point is PCI Jeri Rating to measure joint engagement. Secondary end point is Vineland Adaptive Behavior Scale – socialization subscale and communication subscale. • Updated language on exclusion criteria for other psychiatric conditions and/or elevated symptoms to allow for clinical case review and PI decision • Updated language on medication inclusion / exclusion to allow for meds that address sleep disturbances and irritability; and to exclude other stimulants and anti-depressants • Shortened medication phase 10 weeks. • Restructured study visits to allow 2 weeks of titration prior to starting behavioral intervention • Change study visit schedule to o Diagnostic evaluation o Med screen and baseline assessments o 2 weeks of med/placebo titration followed by 8 weeks of continued titration/optimal dose of med/placebo and behavioral intervention sessions o End point assessments the visit	• Increased age range is to broaden eligible population for recruitment • Removing receptive language age equivalent and setting lower IQ requirement is designed to facilitate diagnosis of ADHD in children who do not have severe developmental disabilities • Direct observational measure (PCI) will be a better indicator of the effects of COMB vs. BEH treatment in this study timeframe • Keeping VABS-3 as key secondary and using remote follow-up to allow sufficient time to observe change in response and improvement • Broadened language on criteria associated with other psychiatric conditions allows PI and study team to assess individual circumstances and whether conditions confound assessments • Shortened medication phase is aligned with stimulant trials, accommodates participant engagement, and allows unblinding directly following treatment phase • Restructured visit schedule encompasses all safety precautions in medical exams and med titration, in addition to collecting assessment data, without overburdening family or participant on any given visit

	following last ESDM-informed parent coaching session o 30 day AE follow-up o Remote follow-up at 24 weeks • Changed behavioral intervention from 12 weekly sessions of P-ESDM including curriculum assessment to 8 weekly sessions of ESDM-informed parent coaching model • Changed Schedule of Activities to accommodate shorter study duration and remove midpoint assessments while preserving baseline, end point and follow-up assessments • Changed AE reporting to use PAERS system for reporting and tracking • AE reporting must occur at each visit and may be completed with MD or study coordinator • Changed study intervention to include unblinding of participants to med/placebo group immediately following completion of end point assessments • Added optional follow-up phase for remote assessments at 24 weeks after baseline assessments • Reduced n to 48 participants • Remove CPT • Add CGI S&I parent report form • Adjust compensation for new visit schedule. This increases total potential compensation to $600.	• 8 sessions of behavioral intervention cover of all principles of ESDM model without extending medication treatment phase unnecessarily • SOA includes all baseline and endpoint assessments. Requirement for midpoint assessments is no longer relevant as there is no need to "re-baseline" following medication ramp. • PAERS reporting tools are commonly used in pediatric clinical drug trials and allows for reporting at every visit – both physician and therapy led visits. • Remote 24 week follow-up creates opportunity for additional administration of VABS-3 to address secondary aim. • Reduced number of participants is selected to accommodate remaining grant period. • Removed CPT as it no longer aligns with primary, secondary or exploratory aims. • Added CGI S&I parent forms to enable tracking at visits that do not include physician • Increased compensation to adequately compensate families for length and number of visits
3.0/ Oct. 30,2018	• Changed Inclusion Criteria to include children --55-72 months with receptive language age equivalent of = or < 72 months, --changed exclusion for amount of child therapy outside of study to be no time limit but stable in amount and dose for 8 weeks prior to enrollment • Will provide transportation to those children and their families who would not otherwise be able to obtain consistent transportation. • Built in assessment of caregiver fidelity to the P-ESDM model within the P-ESDM coaching sessions. zzzz	• Increase feasibility of recruiting full sample size to provide P-ESDM to broader array of children, to children receiving more intensive therapies not specifically focused on reciprocal social interactions and attention. • Increase recruitment by making study accessible to indigent families who may not have access to reliable transportation • Provide a measure of parent responsiveness to coping which we expect to be a major component of child response to P-ESDM • Compliance with DEA requests and changes in how study investigational

	• Provided more clarification of blinding and drug accountability procedures a • Moved measures obtained at Week 0 only to 1st section of Schedule of Assessments • Made visit windows broader • Increased initial rate of study drug titration	materials were supplied. • Increase clarity • To reduce burden on participants. • DSMB suggestion • Increase coordination of grant &protocol • Changed to reflect specific functional areas targeted by P-ESDM.
2.0/ Sep. 21, 2018	• Added Specific Aims Section • Changed the primary outcome measure to the mean of the VABS socialization and communication subscale standard scores • Changed key secondary outcomes to include JERI ratings joint attention and engagement. • Eliminated the week 10 EEG measures. • Changed timing and length of P-ESDM curriculum assessment and coaching sessions. • Added Sluggish Cognitive Tempo questionnaire weeks 0, 10,24,& 52. • Removed ASSIST/READY, added Sense to Know • Changed exclusion criteria, Leiter guidelines & deleted post baseline Leiters, & added home videos, childhood behavior inventory, sensory experiences questionnaire and preschool executive function battery to week 0 • Changed FDA reporting to reflect IND exemption; provided more detail about safety reporting, documentation of TEAEs, and drug accountability procedures • Updated references & corrected clerical errors	• Increased sensitivity vs duration coding & alignment across Duke ACE center. • Reduce burden & cost. • Prevent overlap with week 10, reduce burden & assess parent fidelity. • Advisory board suggested given potential overlap with ASD & ADHD • Unable to agree on contract • To standardize week 0 assessments with A+ Development facilitate centerwide comparisons. • Revisions necessary as gathered new regulatory information & developed database & drug blinding procedures. • Clerical

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

A+ Treatment: Impact of combined medication and behavioral treatment for young children with Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD); Duke Autism Center of Excellence (Duke ACE), Project 3; Protocol Pro00085179, v1.1 20 August 2018)

Study Description: This randomized, placebo-controlled, phase 2, pilot study will evaluate the developmental impact of combined medication and behavioral treatment (COMB) versus placebo and behavioral treatment (BEH) in children with comorbid ASD and ADHD, who are between 36 and <132 months of age. The active medication treatment will be an orally dissolvable, extended release amphetamine preparation (Adzenys-XR-ODT, (2)) administered following baseline assessments for 10 weeks and titrated to the optimal dose. The provided behavioral treatment will be eight ~60-minute sessions in ESDM-informed parent coaching delivered weekly, beginning 2 weeks after medication/placebo administration begins and continuing for 8 consecutive weeks. The implicit behavioral treatment is Early Start Denver Model (ESDM)-informed parent coaching implemented within the child's daily schedule by the parent/caregiver.

Objectives: The overarching goal of A+ Treatment is to evaluate whether combined medication and behavioral treatment improves quality of sustained joint engagement at 10 weeks after medication baseline.

Other important objectives are to determine whether the COMB treatment improves ADHD ratings and results in greater social communicative developmental progress than the behavioral intervention alone.

Exploratory objectives are to identify potential assessments of overall attention, social attention/engagement and/or neurophysiologic biomarkers that correlate with greater improvements in social communicative development independent of medication group assignment; and to determine if there is a difference in social communicative functioning and ADHD symptoms in treatment groups 24 weeks after beginning treatment.

Primary Endpoint: Change in the amount and quality of joint engagement between the child and the parent/guardian during a semi-structured 6 minute parent child interaction task using the Joint Engagement Rating Inventory (JERI(4)).

Key Secondary Endpoints Change in the Mean of the Vineland Adaptive Behavior Scale - 3rd edition (VABS(3)) Socialization subscale standard score and Communication subscale standard score (aka Vineland -2DC).

Preschool and School age ADHD Rating Scale(5) – parent report and MD report

Multiple other assessments will be obtained to provide supportive information related to the child's functioning, general attention, social attention, executive functioning, safety, and potential neurophysiologic indices of improved social and general attention.

Study Population: ~ 48 participants who are between 36 months and <132 months of age with comorbid ASD and ADHD.

Inclusion criteria

- Provision of a parent/guardian signed and dated informed consent form.
- Stated willingness to comply with all study procedures and availability for the duration of the study.
- Aged 36 months and <132 months of age at baseline.
- Diagnosed with *both* ASD and ADHD based on consensus diagnosis informed by results of the Autism Diagnostic Observation Schedule 2nd edition (ADOS-2(7)), Autism Diagnostic Interview - Revised (ADI-R(8)), a standardized ADHD Diagnostic Interview (9), and the MINI psychiatric diagnostic interview.
- In good general health as evidenced by medical history, physical exam and review of safety labs and electrocardiogram.

Exclusion Criteria

- Recent use of prohibited psychoactive medication in close proximity of baseline assessments. See MOP for specific medications that are prohibited and washout procedures.) Use of a monoamine oxidase

inhibitor is prohibited within 14 days of baseline.
- Known allergic reactions to amphetamines or components of Adzenys-XR-ODT.
- Known history of sudden non-ischemic cardiac death in a first or second degree family member (sibling, parent, aunt, uncle, cousin or grandparent).
- Personal history of significant cardiac abnormalities or disease, particularly rhythm abnormalities.
- Significant visual, auditory or motor impairments that would preclude participation in ESDM-informed parent coaching or completion of key assessments (see MOP for details).
- Inability of the caregiver participating in ESDM-informed parent coaching and responding to questionnaires to fluently speak English.
- Parent's participation in another parent coaching intervention on more than a monthly basis that may affect ESDM-informed parent coaching as deemed by the PI or clinician.
- Presence of any psychiatric conditions or psychiatric symptoms in addition to ASD and ADHD that would confound assessments and/or affect participation in the study as deemed by the PI or clinician. See MOP for procedures for senior clinician review of psychiatric conditions and/or symptoms.
- Known genetic (e.g. Fragile X) or neurological syndrome or condition with established link to autism, but not events in which the link to ASD is less well known/established (e.g., 16p11.2 CNVs, CHD8 mutations, Trisomy 21, 22q deletion syndrome).
- History of epilepsy or seizure disorder (*except* for history of simple febrile seizures or if the child is seizure free - regardless of seizure type - for the past year)
- History of neonatal brain damage. (e.g., with diagnoses of hypoxic or ischemic event)
- Any known environmental circumstances that is likely to account for the clinical presentation of autism in the proband (severe nutritional or psychological deprivation etc.)
- Study clinician judgment that it is not in the best interests of the participant and/or the study for the child to participate.

Phase: This is a phase 2 pilot study.

Description of Sites Enrolling Participants: Single academic center site in US.

Description of Study Intervention: All participants will be randomized to receive flexible dose (1.55 mg to 18.6 mg/day) Adzenys-XR-ODT extended release, orally dissolvable tablets or matched placebo for ~10 weeks following baseline assessments until the end

of treatment assessments are completed. Adzenys-XR-ODT or placebo treatment will be initiated at 1 tablet (3.1/0 mg/day) for participants 36 to <72 months of age, and 2 tablets (6.2/0 mg/day) for participants 72 to < 132 months of age. Dose will be flexibly titrated upward to reach a target dose of 4 tablets (12.4/0 mg) daily. If necessary, the dose may be decreased to as little as ½ tablet (1.55/0 mg) daily or increased to as many as 6 tablets (18.6/0 mg) daily using procedures described in the MOP. The study drug may also be stopped if there are intolerable adverse events.

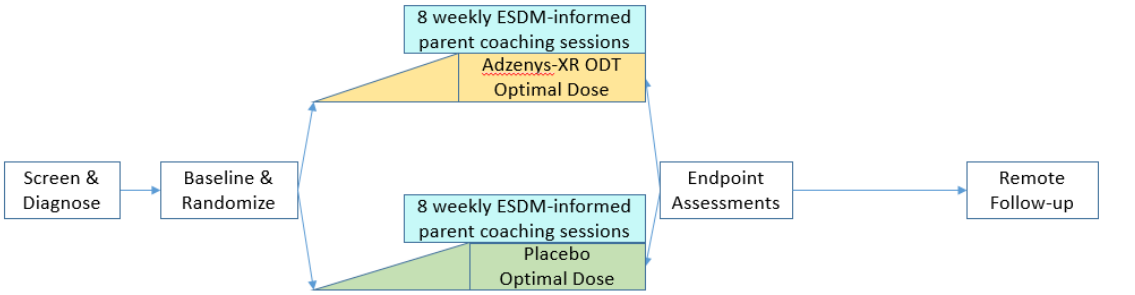
In addition, all participants will receive eight consecutive weekly ~60-minute ESDM-informed parent coaching sessions following 2 weeks of medication titration.

The two randomized intervention groups will be:

- **COMB** in which participants receive flexibly dosed Adzenys-XR-ODT (1.55mg – 18.6 mg) each morning between day1 (day following completion of baseline and completion of endpoint assessment(10 weeks) plus eight consecutive weekly ~60 minute ESDM-informed parent coaching sessions between day 14 and day 63 of study drug treatment. .
- **BEH** in which participants receive flexibly dosed Placebo each morning between day1 (day following completion of baseline and completion of endpoint assessment(10 weeks) plus eight consecutive weekly ~60 minute ESDM-informed parent coaching sessions between day 14 and day 63 of study drug treatment..

Participant Duration: Total participation is expected to require 30 weeks, including optional remote follow-up at 24 weeks after start of medication treatment. The A+ Treatment diagnostic and screening visits will generally occur between 1 and 6 weeks prior to baseline. After randomization, study-provided medication and ESDM-informed parent coaching will be delivered per the Schedule of Activities (SOA) for 10 weeks. Following the endpoint assessment participants and parents/guardians will be free to obtain medication or behavioral intervention outside of the study, but none will be provided by the study team. The final assessment will be obtained at 24 weeks after baseline when the parent will be contacted remotely to conduct caregiver-report assessments of child behavior.

1.2 Schema



Visits 1-4	Visits 5-6	Visits 7-8	Visits 8 – 15	Visit 16		Visit 18
Screen & Diagnose	Baseline	Titration	Med/Placebo + ESDM Sessions	Endpoint Assessments		Remote Follow-up
	Joint engagement Social communication ADHD symptoms EEG/EGT Biomarkers Safety			Joint engagement Social communication ADHD symptoms EEG/EGT Biomarkers Safety		Social communication ADHD symptoms

Figure 1: A+ Treatment Schema A+ treatment staff will meet with parents/caregivers to explain the study and to review the informed consent document with them. Eligibility in the A+ Treatment study will include meeting diagnostic, cognitive and age criteria. A+ Treatment staff will obtain an electrocardiogram (ECG)and perform other medical assessments necessary to determine eligibility, ESDM-informed parent coaching beginning after 2 weeks of study drug titration. Adverse events will be evaluated weekly with dose titration as needed. The primary outcome assessments will evaluate change between baseline assessments and endpoint assessments, following 10 weeks of study drug and ESDM-informed parent coaching. In addition, parents will be contacted remotely (via phone/internet) at 24 weeks following baseline to conduct caregiver-report assessments, to obtain information about the course of subsequent developmental and behavioral changes.

1.3 Schedule Of Activities (SoA)

Part of Study	Screening#				Baseline#		Study Intervention Period									Endpt	FU	
Visits	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Type	ADI-R	Consent and Diagnostic	Diagnostic	Med Screen and Feedback	Baseline 1	Baseline 2 and Medication	Titration	Titration and ESDM Week 1	ESDM Week 2**	ESDM Week 3	ESDM Week 4	ESDM Week 5	ESDM Week 6	ESDM Week 7	ESDM Week 8	Endpoint Assessments	2 week AE Follow-up	Remote Follow-up
Typical Week offset from med baseline	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	12	24
Window	n/a	n/a	Within 6 months				+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 1 wk	+/- 1 wk
					Within 30 days													
Consent/ Diagnostic Procedures																		
Informed consent	A	A																
ADI-R	A																	
Demographics		A																
ACE Subject Med History		A																
ACE Family History		A																
Intervention History		A																
Vineland-3 parent report		A																
ADOS		A																
Cognitive testing DAS-2		A																
CBCL		A																
ADHD-RS-parent,		A																

teacher (optional)																		
SRS-2		A																
MINI Kid 7.0.2			A															
Spence			A															
Diagnostic Feedback				A														
Additional Screening																		
Family Hx Cardiac Disease				X														
Recent & Current Meds				X		X	X	X	X	X	X	X	X	X	X	X	X	X
Intervention History				X												X		X
PMH, Psychiatric History				X														
Electrocardiogram				X														
Physical Exam, focused				X		X		X		X			X			X		
Vital signs, height, weight				X		X	X	X	X	X	X	X	X	X	X	X		
Condensed Medical History Form				X														
Stimulant Washout Confirmation Form				X														
Visits	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Type	ADI-R	Consent and Diagnostic	Diagnostic	Med Screen and Feedback	Baseline 1	Baseline 2 and Medication	Titration	Titration and ESDM Week 1	ESDM Week 2	ESDM Week 3	ESDM Week 4	ESDM Week 5	ESDM Week 6	ESDM Week 7	ESDM Week 8	Endpoint Assessments	2 week AE Follow-up	Remote Follow-up
Week offset from med baseline	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	12	24
Window	n/a	n/a	within 6 months		Within 30 days		+/- 3days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 1 wk	+/- 1 wk
RANDOMIZATION to COMB/BEH						X												

MD Dispense study pills						X				X			X					
Participant takes study pills						X	X	X	X	X	X	X	X	X	X	X		
ESDM-informed parent coaching								X	X	X	X	X	X	X	X			
Monitor																		
AE Monitoring						X	X	X	X	X	X	X	X	X	X	X	X	
Suicidality Assessment						X				X			X			X	X	
Prescribed dose record						X	X	X	X	X	X	X	X	X	X	X		
Medication Accountability							X	X	X	X	X	X	X	X	X	X		
ESDM parent eng rating								X	X	X	X	X	X	X	X			
ESDM coaching fidelity								*	*	*	*	*	*	*	*			
PRIMARY OUTOME																		
PCIT-(allows JERI & Activity Video)					X											X		
SECONDARY/Exploratory OUTCOMES																		
ADHD-RS parent/clinician report						X	X	X	X	X	X	X	X	X	X	X		X
Vineland 3-interview					X											X		X
CBCL																X		X
Eye Gaze Tracking & Sense to Know$_B$					X											X		
ABC					X							X				X		
SRS-2					X											X		
Childhood Behavior Questionnaire					X													
Leiter –executive function					X													
Sensory Experiences					X													

Questionnaire																		
Visits	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Type	ADI-R	Consent and Diagnostic	Diagnostic	Med Screen and Feedback	Baseline 1	Baseline 2 and Medication	Titration	Titration and ESDM Week 1	ESDM Week 2**	ESDM Week 3	ESDM Week 4	ESDM Week 5	ESDM Week 6	ESDM Week 7	ESDM Week 8	Endpoint Assessments	2 week AE Follow-up	Remote Follow-up
Week offset from med baseline	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9	10	12	24
Window	n/a	n/a	Within 6 months				+/- 3days	+/- 3 dsys	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 1 wk	+/- 1 wk
					Within 30 days													
SECONDARY/Exploratory OUTCOMES																		
Home Video					X													
Sluggish Cognitive Tempo Rating						X										X		
BRIEF						X										X		
Child Sleep Health Questionnaire						X										X		
CGI-S&I clinician report						S	S,I	S,I		S,I			S, I			S,I		S,I
Impairment Rating Scale						XB	F	F	F	F	F	F	F	F	F	F		
Caregiver Strain Questionnaire						X										X		
Parent Satisfaction Questions																X		
Treatment Guess																X		
Parenting Sense of Competence Form					X											X		
EEG OUTCOMES																		

Regional Coherence						X									X		
Interphase Coherence						X									X		
Evoked response to social						X									X		

#=Portions of visits may be completed in the context of A+ Assessment or A+ Development in advance of signing consent for A+ Treatment. If this is the case, medical screening would be done after A+ Treatment consent is signed. In addition, outcome assessments for A+ Treatment may need to be repeated from A+ Development if they have occurred more than 3 months previously for EEG,EGT, PCI and more than 1 month previously for parent questionnaires.

A=Assessments performed as part of eligibility evaluation and diagnostics. Source documents are submitted and IRB-approved under the A+ Assessment protocol.

X=Assessments performed as part of the A+ Treatment protocol

XB=IRS baseline form

F=IRS follow-up form

* ESDM coaching fidelity is completed by the clinician for one session for each participant. The session is selected at random.

**Physician may attend this visit if deemed necessary.

S= CGI-S form completed

I= CGI-I form completed

2 INTRODUCTION: SCIENTIFIC RATIONALE AND BACKGROUND INFORMATION

2.1 Rationale

The Significance on the Comorbidity of ASD and ADHD

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are highly comorbid, with ~40-60% of children with ASD having co-occurring ADHD and ~18% of children with ADHD exhibiting social communication deficits similar to those observed in ASD(11, 12). Multiple studies have shown that youth with ASD+ADHD often receive a delayed diagnosis of ASD, have worse clinical outcomes, require more restrictive environments and have caregivers experiencing higher levels of stress than those without ADHD(13-16). Studies that have examined the shared and distinguishing features of ASD and ADHD in school-age children suggest that each disorder is associated with a unique profile of attentional, behavioral, affective and cognitive processing problems that impact social communication and long term outcomes(17, 18). Specifically, ASD has been associated with difficulties in disengaging attention, reduced attention to social stimuli, reduced expression of positive affect and deficient early stage neural processing of social information. In contrast, ADHD has been associated with difficulties in selective and sustained attention and inhibitory control, challenging behaviors such as hyperactivity, increased negative affect, and deficient neural processing of higher order social information. Older children with comorbid ASD and ADHD have greater impairments than those with either ASD or ADHD alone. Thus, the difficulties typically associated with ADHD are likely to exacerbate the attentional, social, affective and neural processing impairments generally associated with ASD, leading to significantly greater initial and long-term impairments in children with ASD+ADHD. We posit that co-occurring ADHD symptoms also significantly impair the ability of children with ASD to respond to and fully benefit from ASD behavioral interventions, further increasing the functional gap between them and their peers with ASD alone throughout development. This idea is supported by a recent study reporting decreased efficacy of a social skills intervention for children with ASD+ADHD vs. peers with ASD alone or with ASD and comorbid anxiety(16).

Treatment Gaps for Young Children with ASD + ADHD

The impact of co-occurring ADHD symptoms on response to ASD behavioral intervention has not been studied. However, clinical observations suggest that ADHD behaviors significantly slow the pace of progress during intervention. Successful treatment depends upon increasing children's attention to social and nonsocial (e.g., toys) stimuli and sustained social engagement, both of which can be disrupted by inattention, hyperactivity, and negative affect, all of which are associated with ADHD. In addition, there is little information about the efficacy and tolerability of various medications to treat ADHD in children with ASD + ADHD. Finally there are few ADHD medications available for children who are not able to swallow pills or capsules.

2.2 Background

Prevalence

Approximately half of children with autism spectrum disorder (ASD) have co-occurring attention deficit hyperactivity disorder (ADHD)(11, 12). Unfortunately, the long-term outcomes of individuals with comorbid ASD and ADHD (ASD+ADHD) are significantly worse than individuals with ASD or ADHD. Those with ASD+ADHD are often diagnosed with ASD significantly later and exhibit more behavioral problems,

poorer peer relationships and increased use of restricted educational settings(13-15). As described in the Duke ACE Overall Research Plan, we hypothesize that these negative outcomes in individuals with ASD+ADHD are, in part, the consequence of ADHD symptoms compromising the individual's ability to fully benefit from behavioral interventions for ASD, which all require the interventionist to acquire and sustain the child's attention. Consequently, we hypothesize that effective treatment of co-occurring ADHD symptoms will improve developmental and functional outcomes for children with ASD+ADHD.

ADHD Comorbidity with ASD Related to Impaired Verbal Working Memory and Verbal Delayed Recall

The main manifestations of ASD include impaired social interaction, communication, and restricted and repetitive patterns of behaviors. Although ASD is typically an exclusion criteria for ADHD according the DSM-5, several studies have reported ADHD symptoms co-occurring in subjects with ASD. A study by Andersen et al (19) studied 38 children with high functioning autism (HFA) with (+) and without (-) "attention problems" according to the Child Behavior Checklist, 79 with ADHD alone and 50 typically developing children. The children were administered a Letter-Number Sequencing test (LNS) where children are required to listen to a presentation of alternating letters and digits and afterwards asked to recall the numbers in ascending order and the letter in alphabetical order (19). It was found that children with HFA+ displayed significant impairment compared to other typically developing children in all three neurocognitive measures while those with HFA- only had greater impairments with working memory and acquisition measures. In addition, the HFA+ group scored significantly lower than the HFA- group and the ADHD group on verbal working memory and delayed recall measures.

Background and Justification for the Interventions and Neural Correlates to be Examined

Early Start Denver Model (ESDM(20)). ESDM is an empirically-validated, naturalistic, developmental, behavioral intervention for children with ASD who have mental ages between 12 and 60 months. Intervention strategies are delivered in the context of affectively- and socially-engaged joint activities between the child and adult. A key goal is to promote social attention and social engagement as a platform for teaching joint attention, imitation, language, motor, cognitive and social skills, and for reducing maladaptive, disruptive behaviors. Thus, this intervention provides an ideal context in which to evaluate our overall conceptual framework, which posits that ADHD symptoms impede the ability of children with ASD to acquire and improve sustained social attention and social engagement. ESDM was co-developed by Sally Rogers and Duke ACE Center PI Geraldine Dawson. An RCT demonstrated that, when delivered intensively by trained therapists, ESDM results in significant improvements in IQ, language, social abilities, and adaptive behavior. It was also found that children who received ESDM showed normalized brain activity, reflected in measures of EEG activity during viewing of social stimuli(21). ESDM also has been associated with significant reductions in clinician-rated maladaptive behaviors, with 68% of children showing reductions by 12 weeks and 79% after ~ 1 year(22).

Parent-delivered ESDM (P-ESDM) A parent delivered version of ESDM, parts of which will be used in this project, also has been developed, manualized, and evaluated. After the coach has assessed parent goals for their child, the therapist coaches that child's parents on ESDM strategies to increase social attention and motivation, social

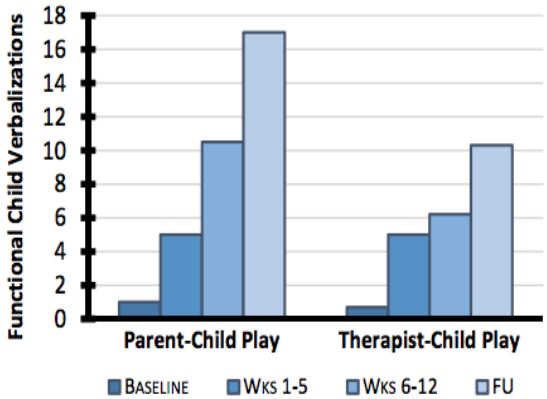


Figure 2: P-ESDM effect on communication[40]

routines, joint activity routines, nonverbal communication, imitation, joint attention, speech development, functional and symbolic play skills, and management of challenging behavior in the context of parent identified social communication goals. The first study of P-ESDM evaluated the benefits of 1 hour/week of parent-coaching for 12 weeks in 8 children with ASD. Parents acquired the strategies and achieved fidelity by the 6th week(23). Children demonstrated sustained increases in joint attention, social engagement, social initiation, imitation and functional communicative behaviors (Figure 2).

Next, a larger (N = 98), NIH-funded RCT was conducted, evaluating the same brief 12-week, 1 hour/week of P-ESDM parent coaching vs. treatment-as-usual (TAU) in the community(21). The TAU group received significantly more hours of intervention, many of which were delivered by trained professionals. Both groups demonstrated similar statistically significant improvements in social symptoms and communication abilities, as measured by the ADOS social affect score and the Mullen Scales of Early Learning respectively. Parents in the P-ESDM group demonstrated significantly lower levels of parenting stress. A+ Treatment will utilize principles derived from P-ESDM for 8 caregiver coaching sessions.

Zhou et al. (24) evaluated the effects of a more intense version of P-ESDM that provided 1.5 hours/week of parent coaching for 6 months vs. treatment-as-usual in the community. The control group was comprised of children with ASD who did not live near the university where the study was being conducted, and, thus, could not feasibly attend weekly treatment. At baseline, there were no group differences in gender, birth history, parental education and income, parental age, or number of siblings. With appropriate controls for baseline scores and intervention hours received, the P-ESDM group showed significantly greater improvements on the Griffiths Mental Development Scales T-scores in the Social ($M = 5.4$ vs. -4.4; $p = 0.001$) and Receptive/Expressive Language ($M = 20.3$ vs. -6.6; $p < 0.001$) domains.

Research on the developmental impact of the intervention after parent coaching is relatively more limited, although the impact of therapist delivered ESDM is typically assessed after 1-2 years and benefits appear to increase over time.

Treatment of ADHD. Multiple treatment guidelines focused on ADHD in children recommend that initial treatment include behavioral management. In preschool children, behavioral treatment alone is recommended, while in school-aged children combined treatment with a stimulant medication and, if there is inadequate response, behavioral treatment is recommended(25). Although no specific form of behavioral treatment is recommended, general principles include: 1) modifying the environment to reduce distractions, facilitate organization (a specific logical place for each thing), and increase predictability; 2) setting small attainable goals, 3) providing visual tools for assessing progress and on task behaviors, 4) rewarding positive behaviors, 5) minimizing reinforcement of negative behaviors and 6) calm non-punitive discipline. Although behavioral interventions typically improve problem behaviors often associated with ADHD, there is no indication that they directly impact ADHD symptoms.

Multiple pharmacological treatments for ADHD have been demonstrated to have efficacy. These medications typically fall into the following categories: 1) stimulants within the methylphenidate class or the amphetamine class, 2) alpha adrenergic agents which seem especially helpful for hyperactivity, 3) norepinephrine reuptake inhibitors (atomoxetine, a selective norepinephrine reuptake inhibitor with a specific indication or venlaflaxine, which inhibits both norepinephrine and serotonin reuptake and does not have a specific ADHD indication), and other agents with theoretical actions that might increase dopaminergic tone. Stimulant medications are the mainstay of treatment because they act very quickly, have a well-established safety profile and their impact is readily apparent. Multiple different formulations of stimulants have been developed that vary primarily in terms of their formulations (liquid, tablet, capsule, transdermal) and their pharmacokinetic properties, generally with the goal of

consistent benefit throughout the day with minimal on off periods. For any given stimulant medication, approximately 70% of treated children with ADHD alone will respond. In the definitive clinical trial of methylphenidate and behavioral treatment of ADHD in school-age children the effect size of methylphenidate was 0.66 for parents and 1.33 for teachers (26, 27). Further, ~ 85% of school-aged children with ADHD alone will respond to some stimulant medication, suggesting the benefit of trying the other stimulant class or a different formulation if the initial stimulant medication is not beneficial. Methylphenidate preparations and amphetamine preparations have similar adverse effects, although one meta-analysis suggested that amphetamine preparations may be slightly better tolerated (28). However, more information is available about the use of methylphenidate preparations in very young children and in children with ADHD.

Adverse effects frequently seen during stimulant treatment include: reduced appetite, insomnia, emotional lability, increased anxiety and dysphoria, and weight loss. In trials of Adderall XR (an extended release formulation of mixed amphetamine salts that the FDA views as generally equivalent to Adzenys-XR-ODT), 2.4% of Adderall treated school-aged children (n=425) with ADHD alone withdrew from treatment due to adverse effects compared to 2.7% of placebo treated children (n=259). Overall, in school age children treated with Adderall XR loss of appetite, gastrointestinal distress and insomnia are reported in approximately 20% with emotional lability, nervousness, fever, vomiting, nausea, and weight loss reported in 4-10%. Tics are seen infrequently (2). Long-term follow-up of children with ADHD treated with methylphenidate from the NIH funded MTA study has also shown that children who remain on stimulant treatment for many years are about 1 inch shorter than their untreated peers (29). Infrequent adverse events include seizures, palpitations, increased heart rate, increased blood pressure, bad taste in one's mouth, tiredness, rash, blurred vision, hair loss, prolonged erections and Raynaud's phenomena (pain and vascular constriction in fingers with cold exposure). Highly significant but rare to isolated adverse events include possible new or worsening psychosis and/or bipolar disorder, muscle breakdown, cardiomyopathy, and sudden cardiac death. A large FDA funded study examining the rates of sudden cardiac death in children treated with stimulants did not find any association of sudden cardiac death and stimulant use (30-32). However, treatment guidelines suggest careful assessment of cardiac health prior to stimulant treatment and avoidance of stimulant use in individuals in whom tachycardia or increases in blood pressure could be dangerous.

Mixed amphetamine salts, including Adzenys-XR-ODT, are typically metabolized more quickly in younger children than in older children or adults (2). The rate of metabolism appears to depend upon the weight of individuals with metabolism slowing as individuals weigh less. This is in contrast to methylphenidate preparations where older individuals typically metabolize the drug more quickly. In pharmacokinetic studies of Adzenys-XR-ODT 3.1 mg (1 tablet) has dose equivalence to 5mg of mixed amphetamine salts and is metabolized in the same way with a peak in adults after a single dose at about 3 hours and return to non-detectible levels by ~ 60 hours. Please see Appendix 1 containing the package inserts for Adderall XR and Adzenys-XR-ODT for more detailed information.

Pharmacological treatment of ADHD in preschool-age children. The only large trial of ADHD medications for preschool children with ADHD was the PATS study (33). This study, in which the dose range was limited by the DSMB, showed that all but the lowest dose of methylphenidate was significantly better than placebo at reducing parent and teacher ratings of ADHD with effect sizes of 0.54 and 0.66 respectively, which is reduced considerably from the effect sizes seen in the MTA, particularly for teachers. In addition, about 10% of the preschool children could not tolerate methylphenidate and withdrew. The most frequent adverse event associated with withdrawal was emotionality or irritability.

While appetite loss, stomachaches and insomnia occurred at similar rates as in older children, the preschool children also showed high rates of social withdrawal and lethargy (dull/tired/listless) compared to periods of placebo treatment. Further only about 20% showed complete remission of ADHD symptoms.

ADHD Medications in children with ASD + ADHD. Similar to preschool children with ADHD alone, school-aged children with ASD+ADHD demonstrate lower rates of response and more frequent adverse effects to methylphenidate (34-37). Again mood adverse effects were particularly common and approximately 20% of children with ASD +ADHD could not tolerate any of the studied doses. Further, the optimal dose was lower among school-aged children with ASD+ADHD than among similar children with ADHD alone. Subsequently, trials have also shown benefit of atomoxetine and guanfacine extended release in school age children with ASD + ADHD(38-42). In each of these trials the same general pattern has been observed. Specifically, children with ASD+ADHD appear to have more frequent adverse events, particularly related to mood stability/irritability, and are modestly less likely to respond.

To date no adequately powered, randomized controlled trials have examined the impact of an ADHD medication in preschool children with ASD + ADHD. However, a small study of 12 preschool children with ASD+ADHD using a similar cross-over design as the RUPP MPH study, found that MPH significantly reduced ADHD symptoms, with a response rate similar that seen in older children with ASD+ADHD(43). Surprisingly, there were fewer dropouts due to intolerable adverse effects among the preschool children than the older children with ASD+ADHD.

Impact of ADHD treatment of school-aged children with ASD+ADHD on Core ASD Symptoms. Relevant to the aims of the A+ Treatment study, Jahromi et al.(44) evaluated a subset of 33 school-aged children with ASD+ADHD from the pivotal RUPP MPH study using an objective assessment of social communication functioning (the Joint Attention Measure from the Early Social Communication Scales, known as the JAMES). Optimal dose MPH, compared to placebo, resulted in significantly more joint attention initiations and responses during the assessment. In addition, the children demonstrated less negative affect during parent-child interactions while treated with MPH compared to treatment with placebo. These findings with school-age children provide support for our conceptual model and hypotheses for A+ Treatment.

We will examine stimulants due to 1) established efficacy, 2) practice guidelines to use stimulants as the first medication option and 3) most importantly, evidence of positive effects on social communication (joint attention) in school-age children with ASD+ADHD.

Neural correlates of attentional problems in ADHD and ASD and response to intervention. A growing body of evidence suggests that altered neural synchronization is a defining feature of both ADHD and ASD(29, 45-50). Studies of EEG connectivity (e.g., EEG coherence)(45) suggest that altered (hyper- or hypo) neural connectivity is associated with ADHD and ASD, and characterized by atypical long-range connectivity, especially between the frontal and other brain regions. This pattern also has been identified via fMRI studies. In addition, individuals with ADHD and those with ASD have been shown to exhibit increased variability of neural transmission, a neural signature that has been correlated with attentional control(51, 52). Variability in neural transmission can be evaluated via intertrial phase coherence (ITPC), a measure of the degree to which the phase (or timing) of the frequency-domain

event related component of the EEG signal aligns across trials, independently of amplitude. Using measures of ITPC, studies have demonstrated that the event-related brain potential (ERP) responses of individuals with ASD and ADHD are less consistent when compared to typically developing controls(51). However, some evidence suggests that, in the ASD group, this might be explained by the subgroup of individuals with ASD with co-occurring ADHD. Finally, substantial evidence from studies of infants through adults conducted by Dawson and Murias, as well as by others, indicates that ASD is associated with reduced neurophysiological responses to social stimuli (e.g., faces), as reflected in altered ERPs and spectral power(53, 54). Evidence is accumulating that changes in neurophysiologic activity are associated with symptomatic responses to pharmacologic, behavioral, and device-related interventions. For example, increases in neural connectivity, measured by resting state fMRI, have been demonstrated in children with ADHD who were treated with MPH, and also were associated with reductions in ADHD symptoms(51). In an RCT, Dawson et al. demonstrated that preschool-age children receiving ESDM intervention exhibited normalized neural activity (faster ERP responses, and decreased alpha and increased theta spectral power) when viewing social stimuli after receiving intervention(21). Improvements in social communication correlated significantly with measures of alpha and theta spectral power while viewing faces. Finally, there is evidence of treatment-related changes in intertrial phase coherence in children with hearing loss and cochlear implants (55). Specifically, reduced variability in neural transmission - increased ITPC - correlated with the amount of time the cochlear implant was present and, consequently, the duration of the ability to perceive auditory stimuli. In the present study, we will examine whether improvements in ASD and ADHD symptoms (i.e., joint attention, social communication functioning, and ADHD-RS scores) are correlated with enhanced (1) long range neural connectivity assessed by EEG coherence, (2) neural stability reflected by intertrial phase coherence, and (3) neural responsiveness while viewing social (face) stimuli (i.e., shorter ERP latency and increased cortical activation reflected in alpha and theta spectral power). Such neurophysiologic changes in response to interventions may reflect an underlying neural mechanism of treatment response and demonstrate target engagement, as well as a focus for the development of new treatments.

2.3 Specific Aims

Approximately half of children with autism spectrum disorder (ASD) have co-occurring attention deficit hyperactivity disorder (ADHD)(11, 12). Unfortunately, the long-term outcomes of individuals with comorbid ASD and ADHD (ASD+ADHD) are significantly worse than individuals with ASD or ADHD. Those with ASD+ADHD are often diagnosed with ASD significantly later and exhibit more behavioral problems, poorer peer relationships and increased use of restricted educational settings(13-15). We hypothesize that these negative outcomes in individuals with ASD+ADHD are, in part, the consequence of ADHD symptoms compromising the individual's ability to fully benefit from behavioral interventions for ASD, which all require the interventionist to acquire and sustain the child's attention. Consequently, we hypothesize that effective treatment of co-occurring ADHD symptoms while receiving ASD behavioral intervention will improve developmental and functional outcomes for children with ASD+ADHD.

The overarching goals of Project 3 are to (1) evaluate a novel behavioral intervention model personalized for children with ASD+ADHD that involves pharmacologically addressing ADHD symptoms while receiving behavioral intervention, and (2) identify changes in patterns of social attention, social interaction, and neurophysiology that may underlie improved treatment outcomes in children with ASD+ADHD. We will accomplish these goals by conducting a randomized controlled trial (RCT) evaluating whether stimulant treatment augments the benefits of ESDM-informed parent coaching (23, 24). Children with ASD+ADHD will be randomized to receive either an extended-release amphetamine

product (Adzenys-XR-ODT; AMP) or placebo prior to initiating ESDM-informed parent coaching. The flexibly- dosed AMP or placebo will be provided for 10 weeks under double-blind conditions. ESDM-informed parent coaching will consist of individual parent coaching provided weekly for 8 weeks beginning 2 weeks after AMP or placebo is initiated. We will achieve our overall goals with the following specific aims:

Aim 1. **Determine whether stimulant medication combined with a parent-delivered behavioral intervention (COMB) is more efficacious than behavioral intervention alone (BEH) for improving social communication functioning in children with ASD+ADHD**. We hypothesize that degree of change of child's joint engagement during parent-child interaction (assessed via the JERI coding rating scale) will increase to a greater extent in children receiving COMB compared to those receiving BEH. Key secondary outcomes will be the changes in the mean of the Vineland Adaptive Behavior Scales-3rd edition Socialization subscale standard score and Communication subscale standard score.

Aim 2. **Evaluate the efficacy of AMP vs. placebo for reducing ADHD symptoms in children with comorbid ASD+ADHD**. We hypothesize that ADHD symptom reduction (assessed via the clinician administered Preschool or School age ADHD Rating Scale[10, 11]) will be greater in children receiving AMP than placebo.

Aim 3 (descriptive). Determine the association between pre- to post-treatment changes in behavioral outcomes (social communication functioning - VABS-3 and ADHD symptoms), without regard to treatment group, and changes in objective measures of children's social attention (assessed via an eye-gaze tracking biomarker) and social engagement (assessed during a semi-structured parent-child interaction). We hypothesize that increases in social communication functioning and/or reductions in ADHD symptoms will be correlated with a) increases in objectively measured attention to social stimuli in eye gaze tracking tasks and b) increases in amount, quality and fluency of parent-child joint attention and engagement.

Aim 4 (exploratory). Determine the association between pre- to post-treatment changes in behavioral outcomes (social communication functioning and ADHD symptoms) and changes in neuro-physiological activity, as reflected in a) neural connectivity (EEG coherence), b) neural stability (inter-trial phase coherence; ITPC), and c) neural responsiveness to social information (event-related brain potentials [ERP] to social stimuli). We hypothesize that each of the following – increases in social communication functioning and reductions in ADHD symptoms – will be positively correlated with enhanced long-range EEG coherence and ITPC, and shorter ERP latency and increased cortical activation (reduced alpha and increased theta spectral power) in response to social stimuli.

A+Treatment will provide essential information about the impact of treating co-occurring ADHD on response to behavioral intervention which may influence the priority that practitioners place on early identification and treatment of ADHD in young children with ASD. By combining the results of Projects 1, 2, and 3, the Duke ACE Center research program will offer a comprehensive understanding of the impact of co-occurring ADHD symptoms on early detection, trajectory, functional outcomes, neural mechanisms, and treatment response in young children with ASD.

2.4 Risk/Benefit Assessment

2.4.1 Known potential risks

Study Drug:

The potential risks of participating in this study are primarily related to the use of the active medication – **Adzenys-XR-ODT.** As stated above in section 2.2, these risks are well known from the prolonged use of mixed amphetamine salts. Specifically, adverse effects frequently seen during stimulant treatment include: reduced appetite, insomnia, emotional lability, increased anxiety and dysphoria, and weight loss. In trials of Adderall XR (an extended release formulation of mixed amphetamine salts that the FDA views as generally equivalent to Adzenys-XR-ODT)(2), 2.4% of Adderall treated school-aged children (n=425) with ADHD alone withdrew from treatment due to adverse effects compared to 2.7% of placebo treated children (n=259). Overall, in school age children treated with Adderall XR loss of appetite, gastrointestinal distress and insomnia are reported in approximately 20% and emotional lability, nervousness, fever, vomiting, nausea, and weight loss reported in 4-10%. Tics are seen infrequently. Long-term follow-up of children with ADHD treated with methylphenidate from the NIH funded MTA study (ref) has also shown that children who remain on stimulant treatment for many years are about 1 inch shorter than their untreated peers. Infrequent adverse events include seizures, palpitations, increased heart rate, increased blood pressure, bad taste in one's mouth, tiredness, rash, blurred vision, hair loss, prolonged erections and Raynaud's phenomena (pain and vascular constriction in fingers with cold exposure). Highly significant but rare to isolated adverse events include possible new or worsening psychosis and/or bipolar disorder, muscle breakdown, cardiomyopathy, and sudden cardiac death. A large FDA funded study examining the rates of sudden cardiac death in children treated with stimulants did not find any association of sudden cardiac death and stimulant use. However, treatment guidelines suggest careful assessment of cardiac health prior to stimulant treatment and avoidance of stimulant use in individuals in whom tachycardia or increases in blood pressure could be dangerous. We would anticipate that the children in this trial may be more likely to have mood regulation, social withdrawal and listlessness adverse effects compared to the school age sample described in the Adzenys-XR-ODT label due to their young age and the presence of comorbid ASD. In clinical practice many of these adverse effects are dose related, so the use of a flexible dosing strategy should be beneficial.

In addition, the active pharmaceutical ingredient – amphetamine salts – can be abused and diverted by adults for their own use and thus is a controlled substance. However, it is extremely unlikely that the participants in this trial would abuse the medication due to their young age and high levels of supervision.

Rescue Medications:

Melatonin _Studies of melatonin use for durations up to four years have failed to demonstrate significant adverse effects in a variety of pediatric populations(56-58). However, potential side effects include suppression of the hypothalamic–gonadal axis (triggering precocious puberty on discontinuation) and increased reactivity of the immune system in children on immunosuppressants (i.e., corticosteroids) or with immune disorders. Melatonin has been demonstrated to have benefits on sleep latency in children with ASD(56, 57, 59, 60).

Clonidine Clonidine's label (*www.accessdata.fda.gov/drugsatfda_docs/label/2012/017407s037lbl.pdf*) (2) indicates most adverse effects are mild and tend to diminish with continued therapy. The most frequent, which appear to be dose-related, are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in

100. Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100. The following less frequent adverse experiences have also been reported in patients receiving clonidine tablets, but in many cases patients were receiving concomitant medication and a causal relationship has not been established: fatigue, fever, headache, pallor, weakness, withdrawal syndrome, a weakly positive Coombs' test and increased sensitivity to alcohol. Cardiovascular adverse events include bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, sinus bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Central nervous system events include agitation, anxiety, delirium, delusions, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares. Dermatological events include alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria. Gastrointestinal events include abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, and vomiting. Genitourinary symptoms include difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention. Hematologic events include thrombocytopenia. Endocrine and metabolic events include gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, and weight gain. Musculoskeletal events include leg cramps and muscle or joint pain. Dryness of the nasal mucosa has been reported. Ophthalmological symptoms include accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of eyes.

Diphenhydramine Diphenhydramine is usually well tolerated but has been associated with paradoxical effects in some young children. Up to date (61) lists its adverse effects as: Cardiovascular: Chest tightness, extrasystoles, hypotension, palpitations, tachycardia; Central nervous system: Ataxia, chills, confusion, dizziness, drowsiness, euphoria, excitement, fatigue, headache, insomnia, irritability, nervousness, neuritis, paradoxical excitation, paresthesia, restlessness, sedation, seizure, vertigo; Dermatologic: Diaphoresis; Endocrine & metabolic: Menstrual disease (early menses); Gastrointestinal: Anorexia, constipation, diarrhea, dry mucous membranes, epigastric distress, nausea, vomiting, xerostomia; Genitourinary: Difficulty in micturition, urinary frequency, urinary retention; Hematologic & oncologic: Agranulocytosis, hemolytic anemia, thrombocytopenia; Hypersensitivity: Anaphylactic shock; Neuromuscular & skeletal: Tremor; Ophthalmic: Blurred vision, diplopia; Otic: Labyrinthitis (acute), tinnitus, Respiratory: Constriction of the pharynx, nasal congestion, thickening of bronchial secretions, wheezing.

2.4.2 Known potential benefits

All participants in this trial will receive 8 sessions of ESDM-informed parent coaching, a well-accepted parent coaching behavioral intervention from expert providers free of charge. The ESDM-informed parent coaching is expected to facilitate the parents' use of ESDM behavioral intervention strategies in multiple daily living contexts on a daily basis for an extended period. The parent implementation of these strategies and techniques is expected to promote the development of participants and to provide a sense of self efficacy for participating caregivers. Such therapy is currently often hard to access in the community so immediate access may be of benefit. In addition, participants will have their ADHD symptoms carefully monitored and some will receive a medication that is likely to reduce ADHD

symptoms. It is hypothesized that reduction of ADHD symptoms will improve the participant's receptivity to ESDM-informed parent coaching. Finally, the Vineland Assessments may be useful in further treatment and/or educational planning. However there is no guarantee that any one participant will benefit from participation.

2.4.3 Assessment of potential risks and benefits

The purpose of this trial is to determine whether the benefits of a parent-delivered behavioral intervention in children with ASD + ADHD can be improved by providing carefully monitored and flexibly dosed stimulant medication (Adzenys-XR-ODT). If the trial provides evidence that the response to behavioral intervention in children with ASD+ADHD is improved by concurrent treatment with ADHD medications, it will allow us to personalize treatment for this comorbid population, which typically does not benefit as much from behavioral treatment as same aged children with ASD alone. Further we would be able to provide additional guidance regarding the frequency and severity of adverse events in this vulnerable population and about the typical medication doses to which they respond. The exploratory eye tracking and neurophysiologic measures may help us further personalize treatment or identify potential ways to more objectively assess the benefit from combined medication and behavioral treatment.

The primary risks are time-limited adverse events that typically resolve shortly after medication discontinuation in children with ADHD alone and in older children with ASD+ADHD. There is no reason to believe that they would be more persistent in this population. The study's titration schedule and flexible dosing should reduce the likelihood of a participant experiencing an adverse event for a prolonged period. In addition, study doctors will be reachable 24 hours a day for emergencies.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION
Aim 1: Determine whether stimulant medication combined with a parent-delivered behavioral intervention (COMB) is more efficacious than the same behavioral intervention alone (BEH) for improving a core ASD symptom - social communication functioning.	Primary Outcome: Change in JERI ratings of joint attention and social engagement (fluency and connectedness) during a 6 minute, semi-structured parent child interaction task, assessed at Baseline and 10 weeks later at Endpoint assessments. *Key* Secondary Outcome: Change in mean of VABS 3 Socialization and Communication subscale Standard scores assessed at Baseline and 10 weeks later. Additional completion at	ESDM is designed to improve core symptoms of ASD and thus lead to improved overall functioning of the child. The JERI ratings provide for objective ratings of parent and child engagement that consider both duration and quality of behaviors. They have been demonstrated to distinguish between diagnostic groups and to change with typical development. Joint engagement is a critical aspect of social communication, which is impaired in ASD. The VABS 3(3) provides standardized measures of the child's actual functioning as reported by the caregiver. Clinically

OBJECTIVES	ENDPOINTS	JUSTIFICATION
	remote follow-up 24 weeks after baseline (exploratory time point).	meaningful changes in VABS have determined a sample of >9000 individuals with ASD(62).
Aim 2: Evaluate the efficacy of COMB vs. BEH for reducing ADHD symptoms in children with comorbid ASD+ADHD.	Secondary Outcome: Parent/clinician completed ADHD Rating Scale (ADHD-RS)(5, 63) at diagnostic assessment (clinician), baseline (clinician), and weekly during treatment phase. Additional completion at remote follow-up 24 weeks (exploratory time point) after baseline.	Validated scale with parent rating. Week 24 visit is remote so clinician rated ADHD-RS is not feasible but will be administered at baseline and end of study assessments visits.
Aim 3: Determine the association between changes in behavioral outcomes (social communication functioning and ADHD symptoms) without regard to treatment group, and changes in objective measures of social attention and social engagement.	Secondary Outcome: Eye Gaze Tracking (EGT) measures during presentation of social and nonsocial stimuli at baseline (visit 6) and endpoint (visit 16)	EGT(63) is highly objective and quantitative and relatively efficient to administer. Changes have been detected in other treatment studies.
Aim 4 (Exploratory): Determine the association between changes in behavioral outcomes (social and ADHD symptoms) independent of treatment group and changes in neuro-physiological activity.	*Exploratory Outcomes* • SenseToKnow app with presentation of social and novel stimuli at baseline (visit 6) and endpoint (visit 16) • JERI ratings of coordinated joint attention and fluency and coordination during PCIT(4, 64). • Video activity monitoring during PCIT and structured free play assessment. • Neural connectivity (EEG coherence). • Neural stability (intertrial phase coherence; ITPC).	• SenseToKnow is quantifiable measure and relatively easy to administer to children at a young age. • JERI ratings are more sensitive to diagnostic differences than duration of joint attention and reflects a key ESDM-informed parent coaching goal. • Noldus monitoring provides precise quantitative measures of approach and proximity.(70) • EEG provides an objective, noninvasive way to assess neural functioning in response to specific stimuli. It may provide a marker for prediction of

OBJECTIVES	ENDPOINTS	JUSTIFICATION
	• Neural response to social stimuli (evoked response potentials; ERP).	response. Well regulated activity between different cortical regions and relative stability in responses to repeated stimuli during a trial are hypothesized to reflect increased sustained attention during task. Extent of response to social vs. nonsocial stimuli likely reflects social attention.
Other supportive behavioral outcomes (exploratory)		
Assess core ASD social functions	• Social Responsiveness Scale-2 (SRS-2)(66-68) • Aberrant Behavior Checklist-2 (ABC)(69, 70) • Clinical Global Impression (CGI)(71) • Impairment Rating Scale (IRS)	• Community-normed parent completed scale evaluating social function • Parent rating of functions often impaired in ASD and widely used in ASD pharmacologic trials • Clinician rating of overall severity of all problematic behaviors and of improvement since baseline • Parent rating of overall severity of all problematic behaviors and of improvement since last time point.
Assess other aspects of attention and executive function	• Behavioral Rating Inventory of Executive Function (BRIEF)(77, 78) • Sluggish Cognitive Tempo Questionnaire (REF).	• Parent report measure of executive functioning • Questionnaire assesses the rate with which the child responds cognitively, which may be misinterpreted as inattention.
Other Relevant Behaviors	• Child Behavior Checklist (CBCL)(79)	• Parent report measure that assesses a wide variety of behaviors in children including problematic internalizing and externalizing symptoms. The measure has been validated and normed in a large US sample and yield a T score with thresholds for potential and definite clinical concerns in several different domains including atypical behavior and attentional problems

OBJECTIVES	ENDPOINTS	JUSTIFICATION
	• Children's Sleep Habits Questionnaire(80-82)	• Validated parent report of children's sleep issues
Caregiver functioning & attitudes toward treatment	• Caregiver strain questionnaire (CSQ)(83, 84) • Treatment satisfaction • Treatment guess	• Parent report measure validated in parents of children with ASD and other developmental disorders. • Measures of parent perception of treatment
Safety assessments	• Adverse effects assessed based on 1) spontaneous report from parent/caregiver; and 2) General AE Inquiry from coordinator or study physician ECG • Suicidality assessment	• Standard approach for evaluating adverse events in stimulant medication trials • Routine assessment of cardiac functioning • Assess child safety and suicidality in conjunction with AE monitoring.

Several other measures will be obtained at baseline only to allow comparison between our sample and that of other groups in the A+ Development study. These include the Leiter attention and memory scales in children with IQ ≥ 70, the Childhood Behavior Questionnaire, the Sensory Experiences Questionnaire and upload of early home videos if available.

4 STUDY DESIGN

4.1 Overall Design

The overall study design and key outcomes and assessments are shown in the Schema in the synopsis. This randomized, placebo-controlled, Phase 2, single site, pilot study will evaluate the developmental impact of combined medication and behavioral treatment (COMB) versus placebo and behavioral treatment (BEH) in children with comorbid ASD +ADHD, who are 36 and <132 months of age. The active medication treatment will be an orally dissolvable, extended release amphetamine preparation (Adzenys-XR-ODT) administered from following baseline assessments for 10 weeks (visit 6 – 16) and carefully titrated to the optimal dose using an algorithm (see MOP) that considers adverse events and improvement in attention symptoms with a flexible dose range of 1.55mg – 18.6mg/day. The target dose is 12.4mg/day. A placebo, matched to the active medication, will be titrated and adjusted using the same algorithm in the BEH arm. The provided behavioral treatment will be eight consecutive weekly ~60-minute coaching sessions in ESDM-informed parent coaching delivered beginning after 2 weeks of

study drug treatment.. The implicit behavioral intervention is the parent-delivered behavioral intervention provided during interactions with the child at home and in the community. The ESDM-informed parent coaching is a modification of the evidence-based behavioral treatment of ESDM, which is typically delivered as 20 hrs/week of 1:1 interaction between the child and a trained therapist over a 2-year period. The ESDM-informed parent coaching modification reduces rigid time demands on families and is more likely to be sustainable and available in the current healthcare environment.

Forty-eight participants will be randomly assigned to either the COMB or BEH treatment arms. To account for possible differences in attrition due to potential poor tolerability of Adzenys-XR-ODT, participants will be randomized in a 7 COMB to 6 BEH ratio. Treatment assignment will be provided by the Data Management and Analysis Core (DMAC) using computer generated algorithms.

The primary analyses will compare changes in outcomes between baseline assessments and endpoint assessments, study visits 6 and 16, (a planned duration of ~10 weeks). Exploratory analyses will evaluate changes between baseline assessments and remote follow-up with caregivers, study visits 6 and 18, (a planned duration of ~ 24 weeks).4.

The primary outcome measure will be changes in objective JERI ratings made by blinded coders of parent-child joint engagement during the semi-structured parent child interaction task (PCIT) and clinician ratings of ADHD symptoms. The JERI ratings use a 7 point ordinal scale that considers both amount and quality of joint attention and engagement. The amount of time spent in coordinated joint attention has shown significant differences between two different parent interventions for ASD(Kasari et al 2014). The ratings have been shown to correlate well with time measures but to be more sensitive in distinguishing ASD from Down syndrome and typical development and in distinguishing between children with increased ASD interventions over time (Adamson 2017; Suma 2016).

Our key secondary outcome is a change in the mean of the interview version of the VABS-3 Socialization subscale and Communication subscale standard scores. These standardized scores have real clinical significance, account for the variable rates of change observed developmentally, and reflect the core symptom domain targeted by ESDM-informed parent coaching: social communication.

We also will examine several other supportive behavioral outcomes including parent ratings of social functioning (SRS-2), several aberrant behaviors including social withdrawal, attention, irritability, repetitive behavior, and abnormal speech (ABC), executive function (BRIEF), parental ratings of ADHD symptoms (ADHD-RS-parent) and sluggish cognitive tempo, and caregiver strain (CSQ). We will also assess the safety and tolerability of Adzenys-XR-ODT compared to placebo.

In subsequent aims, we will examine the relationship between changes in behavioral outcomes (independent of treatment group) and more objective measures of attention (eye gaze tracking to social stimuli, JERI and video activity measures of overall activity and attention, and parent child interactions such as time spent near parent, latency to approach parent). Finally, we will examine whether improvements in ASD and ADHD symptoms are associated with changes in electroencephalographic (EEG) neural functioning measures related to enhanced neural connectivity (EEG coherence), neural stability (ITPC) and social processing (evoked response potentials (ERPs) and spectral power to faces vs. objects).

4.2 Scientific Rationale for Study Design

This study is limited to a single site and to comparison of two treatment groups due to the amount of funding available. The intention of the study is *not* to evaluate the efficacy of the behavioral intervention, which is informed by a widely accepted, clinical intervention that has demonstrated efficacy compared to usual care treatment that did not include ESDM at the time. Instead, we are testing whether addition of a pharmacological treatment for ADHD alongside ASD specific behavioral treatment improves social communicative functioning, a core ASD symptom domain, to a greater extent than the ASD behavioral treatment alone in children with both ASD and ADHD. Our hypothesis, shown below, is that children with ASD+ADHD have poorer outcomes than those with ASD alone because their ADHD symptoms interfere with their engagement in ASD behavioral interventions.

Medication treatment is chosen rather than behavioral treatment for ADHD in these children for three reasons. First, the behavioral intervention for ASD –ESDM-informed parent coaching – already incorporates the key elements of behavioral treatment for ADHD. Secondly, behavioral intervention for ADHD reduces problem behaviors associated with ADHD, but does not reduce core ADHD symptoms. Thirdly, we hypothesize that ADHD symptoms significantly impair the ability of children with ASD + ADHD to respond to behavioral interventions as shown below. The choice of medication to be studied was based on four factors. First, ADHD medication treatment guidelines suggest use of a stimulant prior to use of other classes of ADHD medications. Secondly, the orally dissolvable formulation was well suited to the age of the population being studied in contrast to tablets or capsules. Thirdly, well matched placebo was available. Fourth, examination of an amphetamine preparation would provide novel information about a different class of stimulants in children with ASD + ADHD, rather than extending existing studies of methylphenidate to a younger population.

All key assessments will be performed by evaluators who are blinded to treatment assignment and who do not observe the parent coaching sessions. The control group is rigorously designed by providing a matched placebo so that parental expectations of medication response are minimized. Prior studies in both children with ADHD alone and in children with ASD + ADHD have shown that children treated with placebo also show relatively high rates of adverse effects and treatment discontinuation due to adverse effects, so it is not likely that the blind will be broken by observation of adverse events. In addition, more objective secondary measures are included.

4.3 Justification for Dose

Choice of medication Many young children are unable to swallow tablets or capsules, so it was necessary to choose an ADHD medication that could be readily taken by the youngest children in the study. Such formulations include liquids, transdermal patches that are often poorly tolerated by children with ASD due to sensory issues, or orally dissolvable tablets. We were fortunate to partner with a commercial company who agreed to provide matched placebo at no charge, allowing the study to be conducted within available funding limits and to be initiated as quickly as possible without requiring

additional time to formulate the placebo. The use of an extended release formulation is expected to minimize rebound effects and to provide more consistent coverage throughout the day, which is particularly important since young children with ASD + ADHD are likely to be developing social communication skills throughout the day rather than only during specific, time limited structured educational activities. However, we are aware that use of an extended release product may be associated with higher rates of insomnia.

Titration schedule Overall, dosing will be flexible and guided by safety and efficacy considerations. Dosing will be initiated at 3.1 / 0 mg (1 pill; active/placebo assigned groups) daily for participants <72 months of age, and 6.2 / 0 mg (2 pills; active/placebo assigned groups) for participants 72 months of age or older. Dosage will be increased by 3.1 / 0mg weekly up to the target dose of 12.4 mg/0 mg daily by week 4, as tolerated provided there is insufficient benefit at a lower dose (see MOP for more detail). Once the target dose has been reached and tolerated for at least 2 weeks, dose increases above the target dose may be considered using the same criteria as above. These dose adjustments may be made during unscheduled visits. The maximal dose is 18.6 / 0 mg daily. The dose can be reduced at any time if there are issues with tolerability or if attention and hyperactivity appeared to be reduced to greater extent on a lower dose. The study allows use of ½ a pill in those children who are unable to tolerate a 3.1 / 0 mg dose. If 1.55 / 0 mg is not tolerated, the participant will discontinue medication but continue to receive ESDM-informed parent coaching. Since younger children metabolize Adzenys-XR-ODT more quickly than older children, we do not anticipate that they will require lower doses than are currently planned.

This is a similar strategy to what is recommended in the label for Adzenys-XR-ODT, which suggests initiating dosing with 6.3 mg and increasing the dose increments of 3.1 mg or 6.3 mg at weekly intervals. Our target dose of 12.4 mg is less than the recommended maximum dose of 18.8 mg in children 6 to 12 years old(2). The study is pursuing a more conservative strategy for the maximum dose due to the increased vulnerability of children with ASD + ADHD to adverse effects with other ADHD agents, the general observation that most children with ASD + ADHD require lower doses of ADHD medications than children with ADHD alone, and the challenges in assessing clinical response in younger children who are less often in settings requiring high levels of sustained attention. In addition, we are more interested in the effects of medication treatment on ASD-related outcomes, rather than efficacy of the medication alone for treating ADHD symptoms.

This study utilizes only 3.1 / 0 mg tablets to facilitate dose adjustments and simplify medication dispensing.

FDA Regulatory Activities The investigators have received an Investigational New Drug (IND) exemption for the study since the results of the study are not intended to change labeling of Adzenys-XR-ODT and the use of Adzenys-XR-ODT is not expected to pose a significantly greater risk in this study than when used clinically. Further, the population participating in the trial is not significantly different from that indicated in the label, which makes no statement about the presence of comorbid ASD. The label of Adderall, which uses an identical active pharmaceutical ingredient, implies indicated use in children as young as 3 years old:

> *"***Pediatric Use:** Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit," https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011522s043lbl.pdf.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed the endpoint assessments all phases of the study including visit 16 – endpoint assessments or has been withdrawn from both treatment and assessments in the study. If a participant wishes to stop medication and/or behavioral treatment in the study before endpoint assessments, he or she will be requested to complete them on schedule if at all possible. The remote follow-up call at 24 weeks following baseline is optional.

5 STUDY POPULATION

The planned sample size is 48 children. There are no limitations related to sex, race or ethnicity.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of a parent/guardian signed and dated informed consent form.
2. Stated willingness to comply with all study procedures and availability for the duration of the study.
3. Aged 36 months and <132 months of age at baseline.
4. Diagnosed with *both* ASD and ADHD based on consensus diagnosis informed by results of the Autism Diagnostic Observation Schedule 2nd edition (ADOS-2(7)), Autism Diagnostic Interview - Revised (ADI-R(8)), a standardized ADHD Diagnostic Interview (9), and the MINI psychiatric diagnostic interview.
5. In good general health as evidenced by medical history, physical exam and review of safety labs and electrocardiogram.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Recent use of prohibited psychoactive medication in close proximity of baseline assessments. See MOP for specific medications that are prohibited and washout procedures.) Use of a monoamine oxidase inhibitor is prohibited within 14 days of baseline.
2. Known allergic reactions to amphetamines or components of Adzenys-XR-ODT.
3. Known history of sudden non-ischemic cardiac death in a first or second degree family member (sibling, parent, aunt, uncle, cousin or grandparent).
4. Personal history of significant cardiac abnormalities or disease, particularly rhythm abnormalities.
5. Significant visual, auditory or motor impairments that would preclude participation in ESDM-informed parent coaching or completion of key assessments (see MOP for details).
6. Inability of the caregiver participating in ESDM-informed parent coaching and responding to questionnaires to fluently speak English.
7. Parent's participation in another parent coaching intervention on more than a monthly basis that may affect ESDM-informed parent coaching as deemed by the PI or clinician.
8. Presence of any psychiatric conditions or psychiatric symptoms in addition to ASD and ADHD that would confound assessments and/or affect participation in the study as deemed by the PI or clinician. See MOP for procedures for senior clinician review of psychiatric conditions and/or symptoms.
9. Known genetic (e.g. Fragile X) or neurological syndrome or condition with established link to autism, but not events in which the link to ASD is less well known/established (e.g., 16p11.2 CNVs, CHD8 mutations, Trisomy 21, 22q deletion syndrome).
10. History of epilepsy or seizure disorder (*except* for history of simple febrile seizures or if the child is seizure

free - regardless of seizure type - for the past year)
11. History of neonatal brain damage. (e.g., with diagnoses of hypoxic or ischemic event)
12. Any known environmental circumstances that is likely to account for the clinical presentation of autism in the proband (severe nutritional or psychological deprivation etc.)
13. Study clinician judgment that it is not in the best interests of the participant and/or the study for the child to participate.

5.3 Lifestyle Considerations

None applicable.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or included in the modified intent to treat analyses. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. The following information will be collected for all screen failures: demography, reason for screen failure details and any serious adverse event (SAE) that occurred while enrolled in the trial.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of concurrent pharmacological or behavioral treatments, a nonfebrile seizure within the six months prior to randomization, or a participating caregiver's inability to fluently speak English may be rescreened when the exclusionary criteria has resolved. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

The target sample size is 48. We anticipate that 20% or less of the sample will be female due to the lower prevalence of both ASD and ADHD among females. We expect that Caucasians will be modestly overrepresented in the sample due to increased historical comfort with clinical trials than minorities. Further, among minorities we anticipate that Hispanic individuals will be most underrepresented in the sample due to requirements that the parent participating in ESDM-informed parent coaching be fluent in English. We expect to enroll 2participants per month and a total of 24 per 12 month period; we anticipate that 18-22 of these will be randomized and have at least one post baseline assessment.

Participants will be recruited from A+ Assessment, A+ Health, A+ Development, community advertisements and physician contacts. Recruitment strategies include: developing radio and newspaper ads and brochures, using social media, attending community events, delivering community talks, meeting with various agencies who provide clinical and educational services for children, developing and maintaining active relationships with local autism and ADHD advocacy and support groups, and reaching out to community pediatricians, family practice doctors, child psychiatrists and psychologists, early intervention programs, and schools to make them aware of the treatment needs of children with ASD+ADHD and the availability of A+ Treatment. We will also approach churches and cultural institutions that serve primarily African American, Hispanic and/or Asian populations about giving informational talks and providing informational materials to increase minority recruitment.

Retention: A+ Treatment staff including behavioral therapists will maintain regular ongoing contact with all participants and their families to facilitate retention and discuss any concerns that may arise. We anticipate that any concerns will be adequately addressed during the frequent medication visits and the weekly ESDM-informed parent coaching visits. Every effort will be made to coordinate assessment procedures with parent coaching sessions so that families do not have to make additional trips to the center. If necessary, some parts of the diagnostic and major assessment visits can be split into 2 visits up to one week apart if the family prefers. Randomization will not occur until all baseline assessments have been completed. All treatment and follow-up visits will be scheduled as an offset of completion of baseline visits and the start of medication. Additional visits with an MD may be scheduled at any time if medication concerns arise. In addition, the recruitment core will send birthday/holiday cards, distribute newsletters, and e-blasts; provide diagnostic reports that summarize testing results; provide clinical referrals; and give regular updates about Duke ACE Center and DCABD research and activities.

Incentives for Participation: We will provide participants with $50 for completing each physician visit and its associated assessments, for each coaching session, and for the remote follow-up assessment completion for a maximum of $600 to help compensate for parental time off work, transportation costs and meals during the assessments. We will provide transportation to those children and their families who would not otherwise be able to obtain consistent transportation up to 90 miles. We will also provide incentives for children during assessments and provide each child with a certificate when he/she completes the study. In addition, the opportunity to receive ESDM-informed parent coaching as part of the study without extensive waiting and free of charge is anticipated to be an incentive. We will also provide reports of Vineland and diagnostic assessments to schools and other providers if requested. Finally, we will facilitate transfer of care after each participant completes the study.

Rationale for Selection Criteria: We have included children between 36 months and < 132 months in order to facilitate recruitment. We excluded children below 36 months chronological age in order to ensure that ADHD can be reliably diagnosed. We excluded children with known cardiac disease, neurodevelopmental, genetic or environmental factors that are likely the etiology of their ASD, uncontrolled seizures, or family history of relevant cardiac disease to reduce risk of adverse events associated with stimulant treatment. We review those with >1 comorbid psychiatric conditions in addition to ASD+ADHD for inclusion / exclusion because the PATS trial, which examined the response of preschool children to methylphenidate, found poorer response was associated with having > 2 diagnoses in addition to ADHD. We are allowing one additional comorbid diagnosis because studies suggest that a substantial percentage of children with ASD+ADHD will have a third psychiatric diagnosis, and we would not be able to reach our recruitment goals if these children were excluded. All children will be administered the Child Behavior Checklist (CBCL), which is a widely-used, well-normed, and empirically validated tool to facilitate diagnosis of other psychiatric problems. If a child has clinically elevated scores, this will be followed up with a semi-structured diagnostic interview by an expert clinician.

Attrition: We conservatively estimate that ~15% will not be able to tolerate the lowest dose of stimulant medication. However, we will encourage these children to continue in the study and will include them in the modified intent to treat analyses. To compensate for potential differences in attrition in the COMB group compared to the BEH group, 7 participants will be randomized to COMB for every 6 participants randomized to BEH. We expect this to yield very similar sample sizes (~24) in the two treatment arms for a per protocol sensitivity analysis. We expect our low starting dose, slow titration schedule and flexible dose strategy to reduce withdrawals due to medication intolerance. We will continue to provide ESDM-informed parent coaching and obtain outcome assessments in children

who discontinue study medication treatment. We will not replace any participants due to medication discontinuation.

We acknowledge that some participants may not be able to cooperate sufficiently to acquire usable EGT and EEG data. However, based on our extensive past research with severely affected preschool children with ASD (some of whom had ADHD), we estimate no more than 10% attrition on these secondary and exploratory outcomes due to lack of compliance and expect to have >20 in each group with usable biomarker data.

6 STUDY INTERVENTION

6.1 Study Interventions Administration

6.1.1 Study medication intervention description

Active Agent: Adzenys-XR-ODT is an orange flavored, orally disintegrating tablet form of Adderall XR (mixed salts of a single-entity amphetamine product extended-release capsules referred to as MAS ER). Each 3.1 mg. tablet of Adzenys-XR-ODT contains mixed amphetamine salts equivalent to those in a 5 mg. capsule of Adderall XR. Each lozenge is packaged in a tamper resistant foil package and designed to be dissolved on top of the tongue. The lozenge should not be chewed or crushed. It should be swallowed after dissolving.

When the New Drug Application (NDA) for Adzenys-XR-ODT was submitted, the FDA permitted the manufacturer to rely on efficacy and adverse event data previously submitted in support of the Adderall XR NDA and only required demonstration of overlapping pharmacokinetics and animal studies to demonstrate an absence of toxicity of the formulation. Adzenys-XR-ODT has an FDA indication for the treatment of ADHD in patients 6 years and older. Two studies in 4-6 year old children are currently underway and anticipated to be completed during 2018. The FDA has indicated that it does not feel trials in 3 year olds are feasible due to challenges in diagnosis. The U.S. labels for both Adzenys-XR-ODT and Adderall XR are included in Appendix 1.

We are using this commercially available medication in a manner that is consistent with its labeled indication, i.e., for the treatment of ADHD. Some of our participants may be younger than stated on the label, but this is consistent with general clinical practice and we will provide updated information for use in younger children from the ongoing trials when it becomes available. We have received an IND exemption for use of Adzenys-XR-ODT in this study.

Control Agent: The manufacturer of Adzenys-XR-ODT is supplying us with a matched placebo orally disintegrating tablet identical in appearance, disintegration characteristics and taste to the active medication. The same low starting dose, slow titration schedule and flexible dosing paradigm will be used for placebo as for the active medication.

6.1.2 Medication dosing and administration

Medication Dosing . Treatment will be initiated according to the following algorithm according to the child's age.

Children ages 3- 5 years, 11 mo: start at 1 tablet = 3.1 mg or 0 mg of mixed amphetamine daily. Doses will be flexibly titrated upward by 1 tablet (3.1 mg or 0 mg) weekly up to a target dose of 4 tablets= 12.4 mg or 0 mg of Adzenys-XR-ODT unless there are intolerable adverse events or great improvement in ADHD symptoms. Doses may be reduced at any point during the trial (typically in 0.5-1 tablet increments) but may be increased only once every week in order to fully assess potential benefits and adverse events of the current dose.

Children ages 6-10 years 11 mo: start at 2 tablets = 6.2 mg or 0 mg of mixed amphetamine daily. Doses will be flexibly titrated upward by 1 tablet (3.1 mg or 0 mg) weekly up to a target dose of 4 tablets= 12.4 mg or 0 mg of Adzenys-XR-ODT unless there are intolerable adverse events or great improvement in ADHD symptoms. Doses may be reduced at any point during the trial (typically in 0.5-1 tablet increments) but, after the first two weeks, may be increased only once every week in order to fully assess potential benefits and adverse events of the current dose.

The allowable dose will range from 1.55/0 mg (1/2 tablet) to 18.6/0 mg (6 tablets) for both groups based on clinical improvement and/or judgment of adverse events.

Study drug will be administered in the morning. If a participant has not taken the day's dose by noon, the dose should be skipped. Handouts providing directions for opening the foil packages and placing the tablet on the tongue will be provided to each participant's caregiver. The 3.1 mg AMP dose has been demonstrated to be bioequivalent to, and to have the same pharmacokinetic profile as, 5 mg Adderall XR. The 12.4 mg dose is smaller than recommended for children 6-12 years, consistent with what is known about tolerability of ADHD medications in young children with ADHD alone and in older children with ASD+ADHD.

Medication discontinuation If a participant cannot tolerate the lowest dose of study drug (1/2 tablet) or has an adverse event that the study physician feels precludes ongoing treatment, the participant will discontinue study medication, but will continue to receive ESDM-informed parent coaching and to participate in study assessments. Participants who have taken fewer than 6 doses of medication during the first 2 weeks of the study will be replaced if possible.

Medication Adherence Medication adherence will be based on pill counts conducted by unblinded staff at each physician visit in which the participant's family remembers to bring in dispensed cartons and unblinded staff is available. If unblinded staff is not available or the family does not return the study investigational drug treatments and is unable to estimate the number of unused tablets/cards remaining, study physician will assume the maximum number of tablets have been used and prescribe the corresponding number of cartons. If unblinded staff were not available at a visit, adherence will be determined at the next medication visit when both the cartons are returned and unblinded staff are available.

See section 4.3 for Justification of Medication Dose**.**

6.1.3 Study Behavioral Intervention Description

All participants and their caregivers will receive the same behavioral intervention. The therapist will discuss and identify appropriate goals for the participant in the first treatment session. Coaching sessions are a modification of the evidence-based behavioral treatment known as ESDM(20), which is typically delivered as 20 hrs/week of 1:1 interaction between the child and a trained therapist for a 2 year period. ESDM-informed parent coaching modification reduces demands on families and is more likely to be available and sustainable in the current healthcare environment. Each participant and his/her caregiver(s) will meet with the behavioral therapist for eight ~60 minute consecutive weekly

sessions. During these sessions, the therapist will coach the parent in developing specific skills and strategies to engage the child and promote the child's social, communicative and cognitive development. Sessions will begin with a free play session in which the therapist will assess parent fidelity to and comfort with previously taught strategies. Then the therapist will check-in with the caregiver regarding any issues or successes during the prior week and will review the new technique/strategy to be learned and practiced during the session. Subsequently, the caregiver will practice of the technique with his/her child with feedback and suggestions as needed from the therapist. At the end of the coaching session, the therapist and the caregiver will discuss potential opportunities for utilizing the strategy and other strategies presented in earlier sessions during the coming week (homework). The caregiver will also be provided with a book that describes some strategies used in ESDM-informed parent coaching. The caregiver is expected to utilize the strategies when interacting with his/her child in naturalistic situations on a daily basis. More than one caregiver may attend one or more coaching sessions, but the same caregiver is expected to commit to attending all coaching sessions. The therapists will have been trained in ESDM-informed parent coaching by a certified ESDM trainer.

The therapist will not participate in study physician visits or in the majority of assessments. If the therapist becomes aware of a concern or has feedback for the study physician, this may be provided. If the caregiver has concerns about adverse effects, he/she will be directed to the study coordinator to facilitate contact with the study MD. If a parent coaching visit is missed, it can be rescheduled within the session window of +/- 3 days. The total number of parent coaching visits attended will be tracked, the parent's use of ESDM techniques will be assessed at coaching sessions 1-8 by the therapist, and the therapist's fidelity to the parent coaching model will be assessed from a video recording of one random sessions during the course of each participant's treatment by an independent rater.

Participants who choose to discontinue parent coaching sessions prematurely will be included in the modified intent to treat analysis. Those who do not attend any parent coaching sessions will be included in the intent to treat analysis but not in the per protocol sensitivity analysis. Such participants will not be replaced.

6.1.4 Study intervention groups

The two randomized intervention groups will be:

- **COMB** in which participants receive flexibly dosed Adzenys-XR-ODT (1.55mg – 18.6 mg) each morning between Visit 6 – Visit 16 (10 weeks) plus eight consecutive weekly ~60 minute ESDM-informed parent coaching sessions during Visit 8 through Visit 15.
- **BEH** in which participants receive flexibly dosed Placebo each morning between Visit 6 – Visit 16 (10 weeks) plus eight consecutive weekly ~60 minute ESDM-informed parent coaching sessions during Visit 8 through Visit 15.

Treatment will be provided in a double-blind fashion such that none of the study staff whom interact with participants and caregivers, therapists who provide parent coaching or the participant's caregivers will be aware of whether the participant is receiving active or placebo study medication. All involved in the study will know the family is receiving ESDM-informed parent coaching.

6.2 Clinical Trial Supplies Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

See Pharmacy Manual for further details. Prior to receiving any clinical trial supplies, the Duke ACE Center Data Management and Analysis Core (DMAC) will prepare a random, nonsequential list of 6000 carton #s, each of which is linked to treatment assignment (COMB or BEH).

Acquisition: After receiving an appropriately completed DEA 222 form from the study principal investigator, Neos Therapeutics will ship specially manufactured lots of Adzenys-XR-ODT 3.1 mg tablets and of matched placebo in sealed, plain white cartons containing 12 blister cards of 6 tablets (for a total of 72 tablets/carton). The cartons will be marked only with the lot number and expiration date. The individual tablets are packaged in a child-resistant manner, with the lot number printed on the packaging of each tablet. The clinical trial supplies are expected to have an expiration date that is at least 24 months after the initial manufacturing date.

Neos expects to ship clinical trial supplies on at least an annual basis. The DMAC team and/or unblinded research staff will notify the principal investigator when ~30% of the original inventory of either active or placebo cartons remains, so that there is sufficient time for NEOS to manufacture new supplies and distribute them to the research site upon receiving a DEA 222 form. Both the DMAC and the unblinded research staff will track the inventory and expiration dates of clinical trial supplies. Separate drawers in the locked storage file will be reserved for cartons that expire in 8 weeks, which could be dispensed at weeks 0, 6, and 10 weeks, and in 12 weeks, which could be dispensed at week 16.

When Neos therapeutics sends clinical trial supplies, they will also provide a shipping manifest documenting the lot #, information about whether the lot contains active or placebo, and the number of cartons in each lot shipped. We anticipate that they will ship two lots simultaneously. The shipping manifest from NEOS will be stored in a separate binder in a locked location accessible only to unblinded staff. When Neos notifies the PI of the maximum number of cartons per lot that will be shipped, the PI will notify the DMAC of this number. The DMAC will refer to the list they prepared prior to the site receiving any clinical trial supplies and provide a list of potential carton # labels to the unblinded study staff, so that they can prepare the necessary labels.

Accountability and Blinding:

Overview: Since the active clinical trial supply (Adzenys XR-ODT/ adderall/ DEA # 1100) is a schedule IIN drug, it will be stored in a locked steel file cabinet with no other investigational drug supplies to limit access in the Department of Psychiatry, Lakeview Pavillion East Investigation Drug Supplies storage room. This room is behind a locked door requiring an ID badge swipe for entry. The door the storage room is triple locked requiring an ID badge swipe, key (not included as part of the floor master key), and individual specific pin # to open. Only authorized staff participating in this study will have access to the key to the file cabinet containing the clinical trial supplies for this study. Placebo and Active supplies will be mixed together and stored in sequential order within the file cabinet after initial labeling. Separate Blinded and Unblinded Inventory Logs, an Unblinded Accountability Log and a Blinded Dispensing Log will be maintained. All entries into any of the logs will require that two staff with the appropriate credentials (unblinded or blinded) sign off at the same time. Blinded inventories will be done on a monthly basis. Unblinded inventories will be done every six months or more frequently if needed. Only unblinded study staff and select Duke ACE Center Data Management and Analyses Core (DMAC) staff will have access to Unblinded documents. Only the unblinded A+ Treatment and DMAC staff will be aware of the linkages between specific carton numbers, lot numbers and active/placebo substance identities. Only the unblinded DMAC staff will have access to the file linking subject ID to treatment group assignment. DMAC staff have developed a program that will allow them to monitor the inventory

of clinical trial supplies on an ongoing basis and assign the appropriate carton #'s when study staff input the subject's ID number and the number of carton's prescribed by the study physician. Once a carton has been assigned by the DMAC program, it will be removed from the DMAC inventory. There will be triple accountability and inventory of the clinical trial supplies by the DMAC, unblinded study staff and blinded study staff (who will have access only to carton #'s, and not to lot #'s, expiration dates or treatment assignment).

Initial receipt: When each lot of active and placebo clinical trial supplies arrives, the DMAC will provide the unblinded staff with 2 tables assigning each carton in each lot a unique carton # based on the DMAC table linking carton #'s to treatment assignment. Then the unblinded staff will prepare one carton label containing study information and a unique carton ID # (carton # label) and a set of labelmaker labels containing only the unique carton # to facilitate tracking and accountability of the clinical trial supplies.

After receiving the DMAC tables assigning carton #'s to specific lots, two unblinded staff will verify the lot # on the each carton against the DMAC table assigning carton #'s to the lot, then place the carton # label over the lot # and expiration date imprinted on the carton. Two-three of the labels with only the unique carton # will be partially taped onto the carton for removal and placement in the Blinded Dispensing Log when the carton is dispensed by MD and later when returned by the participant

At the same time, labels with only the carton # will be placed generally as follows (See Pharmacy Manual for details):

- 1 on the Unblinded DMAC document assigning carton #'s to the specific lot,
- 1 in the Unblinded Inventory Log received column,
- 1 in the Blinded Inventory Log received column, and
- 1 in the Blinded Dispensing Log received column

The remaining label with only the carton # will be placed in the Unblinded Inventory Log Binder, to be used when the carton and any remaining tablets within it are destroyed.

Minimizing the amount of clinical trial supplies dispensed: The participant's caregiver will be instructed to bring all unused tablets in their original carton and any cartons in which all the tablets have been used to the next medication visit, so that staff can be sure they are taking the medication correctly. When the caregivers do so, the caregiver and an unblinded staff member will count the number of tablets available for ongoing use. The caregiver will retain control of all opened cartons containing unused tablets; cartons that have no unused tablets will be logged on the Blinded Dispensing Log and Unblinded Accountability Log as noted below. Study staff will calculate the percentage of the expected number of used tablets and will notify the study physician. The study physician will address any issues related to use of too many or too few tablets and will subtract the number of remaining tablets from the number to be dispensed, so that the minimal number of cartons are dispensed.

Dispensing: At the time of dispensing, study staff will start the DMAC dispensing program, enter the subject ID and the number of cartons prescribed by the study physician. The program will provide a printable document with the subject ID, date and the unique carton #'s to be dispensed. Only full sealed cartons will be dispensed; no cartons will be redispensed. Two study staff will pull the cartons specified by the DMAC dispensing program and will verify the carton #'s pulled agree with the DMAC assignment sheet. The printed DMAC assignment, the physician's order and carton # only labels for each dispensed box will be maintained in the subject's source documentation. In addition, one of the duplicate carton # only labels will be placed in the Blinded Dispensing Log and the date and study ID number of the subject to whom it is to be dispensed will be noted and both staff will sign off on the log.

Subject Return of Used Cartons: Participants' caregivers will be instructed to return the study drug cartons to the site after they have used all the tablets in the carton or at the week 249 visit, whichever comes first. When the used carton is returned to the site, another carton # only label will be placed in the Blinded Dispensing Log, along with the date it is returned and sign off by two staff members. As soon as possible after return, two unblinded staff will examine the returned cartons, determine whether there are remaining unused tablets, document the number of returned unused tables, date returned and counted and both will sign off on the Blinded Dispensing Log and the Unblinded Inventory Log. Returned clinical trial supplies will be stored in the investigational drug storage room in a locked drawer, separate from the drawers containing clinical trial supplies that have not yet been dispensed.

Clinical Trial Supply Destruction: Two unblinded staff will be responsible for removing expired or returned clinical trial supplies from the active clinical supply stock, documenting the removal in the Blinded Dispensing Log and Unblinded Destruction Log, and preparing the supplies for destruction.

The unblinded staff will identify which expired/returned tablets contain active medication and transfer those materials to a locked safe in the investigational drug storage room prior to transfer to a reverse distributor for DEA approved destruction at least one time per year. Empty cartons and blister cards and expired and returned placebo supplies will be disposed of according to Duke University policies for biomedical waste. A carton # only label for each carton destroyed, indicating the number if any unused tablets from the carton destroyed or awaiting destruction by the Reverse Distributor will be placed on the Unblinded Destruction Log, along with the date of destruction or of transfer to the locked safe. When the contents of the locked safe are transferred to the reverse distributor, the total number of active tablets transferred will be recorded and the Unblinded Destruction Log updated with documentation of receipt by the reverse distributor.

6.2.2 Formulation, appearance, packaging, and labeling

Formulation and Appearance:

Adzenys-XR-ODT (amphetamine extended-release orally disintegrating tablet) contains a 3 to 1 ratio of d-to l-amphetamine, a central nervous system stimulant. The labeled strengths reflect the amount of amphetamine base in Adzenys-XR-ODT whereas the strengths of the (mixed salts of a single-entity amphetamine) products are in terms of the amount of amphetamine salts. Adzenys-XR-ODT is an extended-release orally disintegrating tablet containing 50% immediate release and 50% delayed-release amphetamine for once daily dosing. ADZENYS-XR-ODT also contains the following inactive ingredients: Mannitol, Crospovidone, Microcrystalline Cellulose, Methacrylic Acid Copolymer Type A, Sodium Polystyrene Sulfonate, Citric Acid, Fructose, Orange Flavor, Colloidal Silicon Dioxide, Triethyl Citrate, Sucralose, Lake Blend Orange, Magnesium Stearate, and Polyethylene Glycol.

Packaging:

Adzenys-XR-ODT is packaged in child-proof blister packages with a fold line for each tablet that permits opening the foil blister containing the tablet. Twelve blister cards containing 6 tablets each are provided in a white carton ~3 inches x 6 inches x 2 inches, which is initially imprinted with a lot number and expiration date. In addition, each tablet containing blister pack has an imprinted lot number on it.

Labeling:

Carton number labels: Upon receipt at Duke, the DMAC will assign each carton in the lot with a unique nonsequential carton number as described in 6.2.1. Then, the unblinded A+ Treatment medication coordinator and supervising, unblinded physician will place a unique, nonsequential carton number label over the lot number and expiration date of each carton in the lot. The following information will be included:

Duke Center for Autism and Brain Development
2608 Erwin Rd, Suite 300 Durham, NC 27705
Protocol# Pro00085179 **NCT**03242772 **A+Treatment**
LIMITED BY US FEDERAL LAW TO INVESTIGATIONAL USE ONLY
CARTON #:_____

Participant labels: After the study physician prescribes a specific number of cartons for the specific participant and the DMAC program provides the unique carton number(s) to be dispensed, the A+ Treatment staff will place a participant label on the carton that includes the dispensing date, the participant's name, the statement that the carton contains Adzenys-XR-ODT 3.1 mg OR 0 mg for investigational use only in the A+ Treatment study, the instructions for use, an expiration date for the participant's use (generally within 2-7 months of dispensing, and never longer than the actual expiration date of the lot from which it comes) and the study emergency phone number to call for urgent concerns and the name of the Study Principal Investigator. The Participant Label will be similar to that shown to the right.

Duke Center for Autism and Brain Development
Pavilion East at Lakeview 2608 Erwin Rd, Suite 300 Durham, NC 27705
919 681 0017 M-F 9-5; All other times 347-927-7473
Protocol# Pro00085179 **NCT**03242772 **A+Treatment, PI: Lin Sikich, MD**
LIMITED BY US FEDERAL LAW TO INVESTIGATIONAL USE ONLY
Date:_____ **Expiration:_____**
Name:_____ **DOB:_____**
DIRECTIONS:

RETURN TO CLINIC after use or at Week 24

6.2.3 Product storage and stability

The product tablets are individually packaged in foil blisters of six blisters per blister card. The blister cards protect from light, humidity and crushing. Additional protection from crushing is provided by the storage carton. Clinical trial supplies will be stored in a triple-locked, limited access, temperature regulated (20°C - 25 °C) investigational drug storage room, in a locked steel cabinet until the blinded A+ Treatment physician orders a specific number of cartons be prepared for dispensing to a specific participant. The temperature in the drug storage room will be monitored daily. The drug storage room is located off a hallway that requires a key card for access. The room itself is triple locked and can't be opened using a master key. The Access to the drug storage room is limited to fewer than 20 staff members within the Duke Psychiatry Department, each of whom must use their badge, a unique pin number for the keypad and a key to open the investigational drug storage room. A separate key (which is kept in a locked storage box in a separate location) is required to open the A+ treatment clinical supplies storage cabinet. Other research teams that also utilize the investigational drug storage room will not have access to keys for the cabinet in which the A+ Treatment clinical trial supplies are stored. Storage will be in accordance with established SOPs and Duke, NC Pharmacy Board, NC DEA and US Drug Enforcement Administration regulations for a regulated Schedule IIN drug. All Duke SOP's for storage and use of controlled substances in outpatient clinical trials will be followed precisely.

6.2.4 Preparation

The unblinded A+ Treatment medication coordinator will label each carton as above. Either blinded or unblinded staff can utilize the DMAC program to link a specific subject's ID number with specific carton numbers to be dispensed at the visit after receiving the study physician's prescription. Once the carton numbers are determined, the cartons are pulled and labeled for the specific subject according to the study physician's prescription as described above, the cartons will be given to the study physician for dispensing to the subject's caregiver. This will be done in accordance with the study physician's orders using established Duke Center for Autism and Brain Development dispensing policies and procedures that have been developed in accordance with the Duke Investigational Drug Service. The blinded study coordinator will provide the participant's caregiver with visual instructions on opening the blister packages and letting the tablets dissolve on the participant's tongue.

6.3 Measures to Minimize Bias: Randomization And Blinding

6.3.1 Randomization

Participants will be randomly assigned to COMB or BEH in a 7:6 ratio using blocks of 13 or 26 participants. The DMAC will be responsible for the randomization assignment and linking the subject ID and randomization assignment within the DMAC drug inventory program. The randomization schedule will be stratified by chronological age ([36 to 72 months] or [73 to <132 months]) and by nonverbal IQ ([less than or equal to 69] or [equal to or greater than 70]). The DMAC will maintain a table linking the treatment group to individual medication lot numbers and subsequently to unique carton numbers, which will be accessible only to the DMAC unblinded staff member and the unblinded A+ Treatment staff. The DMAC program will provide unique, random, nonsequential carton numbers for dispensation to specific participants according to their treatment assignment and the study physician's prescription each time medications are dispensed.

Participants will be randomized at the week 0 visit after all inclusion/exclusion criteria are confirmed and all baseline assessments have been completed. At that time, the study physician will prescribe the initial carton of study medications and the study staff will utilize the DMAC program to obtain a specific carton number to dispense. Two staff members will verify that appropriate carton of study medication has been pulled from the inventory, labeled appropriately for the participant and entered into the blinded drug accountability log. A similar process will be followed at subsequent visits with the exception that the unblinded A+ Treatment staff will determine the number of unused tablets remaining in the carton to assess compliance and ensure that excessive amounts of study drug are not dispensed.

6.3.2 Blinding

Blinding of Study Medications:

The placebo used in this study is manufactured by NEOS Therapeutics, the maker of Adzenys-XR-ODT, and appears identical in appearance and taste to the active Adzenys-XR-ODT. NEOS Therapeutics will ship both the active and placebo tablets, which will be identifiable by their unique lot numbers as indicated on the shipping inventory form, directly to the unblinded A+ Treatment Clinical Supply Manager, who will be responsible for labeling each carton with a unique non-sequential carton number prior to storing them in our existing temperature-controlled, triple-locked drug storage room in accordance with established SOPs and Duke, NC Pharmacy Board and US Drug Enforcement Administration Regulations for a regulated Schedule IIN drug.

Limited Unblinded Staff:

Only two to three designated unblinded staff members (one person from the Data Analysis and Management Core [DMAC] and the Project 3 unblinded Clinical Supply Manager and supervising unblinded physician) will know whether a given lot contains placebo or active tablets. The lot number will be covered after verification by two unblinded staff members with a unique carton number to reduce the potential of accidental unblinding. PDFs of the shipping manifests reporting the active or placebo contents of specific cartons will be stored in a password protected file on a separate computer drive from all other study files and the originals will be stored in a locked cabinet accessible only by the unblinded Clinical Supply Manager.

These unblinded staff will have no interaction with participants and will be thoroughly trained in the importance of maintaining the blind by not discussing any subject-specific information with other staff members, including the study coordinator, EGT/ EEG assistants, study staff involved in coding of the Parent Child Interaction Task, behavioral therapists, and study physicians.

Potential Unblinding Due to Adverse Effects:

Prior trials of Adderall XR have demonstrated fairly similar rates of the most common adverse events among active and placebo groups. The frequent adverse events of insomnia, stomach upset or pain, decreased appetite, anxiety and mood lability are even more frequently seen in young children with ASD than in children with ADHD. Because these adverse events are so common in preschool children with ASD who are not treated with medications, it is unlikely that occurrence of an adverse event would unblind the study clinician. Further the collection of multiple different types of outcome measures (clinician rated, parent rated, observed during structured interactions and rated by evaluators not involved in the interaction, and objective and neural measures) should minimize the likelihood of results being skewed by adverse events. Further, behavioral treatments like those provided in ESDM-informed parent coaching contain the elements of behavioral treatments that are sometimes beneficial in ADHD treatment. Thus an improvement in symptoms would be unlikely to be ascribed to the medication alone.

Situations When Blinded Treatment Assignment Would Be Revealed:

Most emergency medical situations would not necessitate revelation of the study treatment assignment because there is not a specific antidote to the active study medication and the active study medication could simply be held due to the relatively short half-life. If the emergency medical situation might be related to study medication (e.g. anaphylactic reaction), the study medication treatment would be stopped regardless of whether the treatment contained active or placebo treatment while parent coaching would continue. However, if the treating clinician for the medical emergency felt that it was absolutely essential to determine whether the participant was taking active medication, the study physician would call the unblinded A+ Treatment Clinical Supply manager and request that the clinical supply manager reveal the treatment assignment directly to the outside clinician responding to the medical emergency. In such cases, medication treatment would be discontinued for the remainder of the trial although parent coaching would continue. The outside clinician would be requested not to reveal the identity of study medication treatment to the family and the family would be asked not to discuss their suspicions about the treatment identity with the A+ Treatment staff.

Approximately 2 weeks after the endpoint assessments all participants' caregivers will be notified of their child's treatment assignment. Those who wish to continue medication treatment will be referred to a physician who is not involved in the study for ongoing medication treatment.

6.4 Study Intervention Compliance

Study drug compliance will be determined by comparing the number of tablets that should have been taken with the difference between the number of tablets dispensed less the number of tablets the caregiver reports were wasted (spit out, dropped etc.) and the number of tablets unopened in the blister packs. This will be expressed as percent compliance.

$$\% \text{ compliance} = \frac{\text{Number dispensed} - (\text{number reported wasted} + \text{number remaining in blister package unopened})}{\text{Number of pills prescribed per day} * \text{Number of days since dispensing}}$$

Parent coaching session compliance will be assessed by determining the number of sessions attended.

We will not measure the amount of time the caregiver spends engaged in using ESDM strategies due to burden on caregivers and expected low quality of the data.

6.5 Concomitant Therapy

6.5.1 Prohibited concomitant therapies

Participants will be asked to refrain from taking any of the following medications throughout the course of the trial. Those who do take such medications will be excluded from the per protocol population.

- Monoamine oxidase inhibitors including rasagiline (Azilect), selegiline (Eldepryl, Zelapar), isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate).
- Other medication treatments for ADHD including any other sort of stimulant MAS ER salts, lis-dexamphetamine(Vyvanse), methylphenidate products, atomoxetine (Strattera), amantadine (Symmetrel), memantine, buproprion (Wellbutrin), venlaflaxine (Effexor), omega 3 fatty acids, Vayarin.
- Participants will be asked to refrain from changing the type or intensity of other behavioral interventions obtained during the eight weeks preceding Week 0 of the study through the Week 9 assessment in the study. The amount and type of other behavioral interventions will not be restricted in order to increase feasibility of recruiting the full sample.
- Participant's caregivers will be asked to refrain from more than one other parent coaching intervention provided no more than 1x per month. Those participants whose caretakers do engage in more than one other parent coaching session per month will be excluded from the study per protocol population.

6.5.2 Permitted concomitant therapies

Participants may receive the following therapies and still be considered as complying with the study protocol. The study physician will determine if any additional monitoring is required if a permitted concomitant medication is used.

- Aripiprazole (Abilify) or risperidone (Risperdal) prescribed for the treatment of irritability in ASD
- Melatonin or immediate release clonidine prescribed for the treatment of insomnia
- Special diets
- Antibiotics for treatment of acute infections
- Antipyretics such as acetaminophen and ibuprofen
- Antianxiety medications for medical procedures such as phlebotomy, but not within 2 hours prior to outcome assessments other than safety labs. (In such cases all of the behavioral and neural assessments should be performed prior to the safety blood draw or the blood draw should be performed at a separate time.
- Asthma medications
- Gastrointestinal medications
- Any behavioral intervention delivered to the participant inside a school or daycare setting or that is provided outside a school or daycare setting that has been of the same type and intensity for 8 weeks prior to the Week 0 assessments.
- Any behavioral intervention changes for either the parent or child during the first 9 weeks of the study are discouraged, but are not prohibited.

The concomitant medication Case Report Form (CRF) will report all those prescription medications, over-the-counter medications and supplements taken. Doses will not be reported. The Intervention History CRF will track hours and types of behavioral interventions received. Intervention history form at 10 weeks will ask about interventions over the past 10 weeks, and the study staff may ask participants about interventions during the course of treatment as well.

6.5.3 Rescue medicine

Insomnia The study physician will be permitted to prescribe melatonin ≤ 6mg/night, immediate release clonidine ≤ 0.2mg/night or diphenhydramine ≤ 12.5mg/night for insomnia that is not responsive to reductions in the dose of study medication and behavioral interventions, if desired by the participant's caregivers. This medication will be recorded on the case report form.

These rescue medications will not be provided or paid for by the study. The rescue medications will be recorded on the case report forms.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

7.1 Study Halting Rules

The DSMB may choose to halt the study at any time they feel there is significant risk to participants as a result of study procedures or as a result of the safety profile of the study medication treatments (active Adzenys-XR-ODT or placebo), study behavioral treatment (ESDM-informed parent coaching), or of specific study assessments. Of these situations, concerns about the safety profile of study medication treatments is most likely to occur, since the behavioral treatment is well accepted in the community and does not appear to have specific safety concerns and the assessments are used in a wide variety of

studies of young children with ASD and have never been shown previously to result in significant safety risks.

In addition, we will place the study on hold and request DSMB review for safety concerns if we note that the proportion of participants withdrawing from active medication treatment in either treatment arm is greater than 40% and more than 3x that of the other treatment arm. This is a study interruption rule – "halting" rule –, although the final decision to stop the study or change study procedures will be made by the DSMB and/or IRB.

7.2 Rules for Individual Participant Discontinuation in Study Interventions

Participants' caregivers may choose to discontinue the study drug intervention and/or the behavioral parent coaching intervention at any time for any reason. Similarly the study physician or therapist may choose to withdraw the participant at any time if the physician or therapist feels that it is not in the participant's best interest to continue.

In addition, if the participant has intolerable adverse events that have not sufficiently resolved even on the lowest available dose of study medication (1/2 tablet daily = 1.55 mg / 0 mg Adzenys-XR-ODT) or are so medically serious that dose reduction is not in the best interests of the child in the study physician's or caregiver's opinion, the participant will be withdrawn from study medication treatment., In any of these cases, every effort will be made to encourage the participant and his/her caregiver to complete the outcome assessments according to the study schedule. A+ Treatment staff will continue to assess safety and adverse events for up to 30 days following discontinuation or until the adverse event has resolved or stabilized.

7.3 Participant Discontinuation/Withdrawal from the Study

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

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

- Significant study intervention non-compliance,
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant,
- The entire study has been halted.

The reason for participant discontinuation or withdrawal from the study will be recorded on the End of Study CRF. Participants who are randomized but do not receive the study intervention may be replaced if feasible. Participants who receive at least one component of the study intervention (medication or behavioral) and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.4 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to attend planned study visits over the time period described in the SoA under window and is unable to be contacted by the study site staff after 3 attempts by 2 methods including email and phone.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant by phone, email and/or regular return receipt mail at least 3 separate times over the period window (see SOA). These contacts will be recorded on the appropriate study CRF.
- If the study staff is able to reach the participant's caregiver, staff will counsel the participant's caregiver on the importance of maintaining the assigned visit schedule and ascertain if the participant's caregiver wishes to and is able to continue in the study. If the caregiver is willing to continue, study medication visits will be rescheduled as soon as possible. Study behavioral parent coaching visits will be resumed as soon as possible. Missed sessions will not be rescheduled outside the session window of +/- 3 days.
- If the study staff is able to reach the caregiver, every effort will be made to encourage the participant's caregiver to participate in the final outcome assessment.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

8.1.1 Primary efficacy assessment

Procedures:

We will utilize a semi-structured Parent Child Interaction Task (PCIT) modified by DeVito et al., 2016, personal communication) to assess several key behaviors using a standard set of materials in a naturalistic setting. Children and their parents are observed during a series of 2-6 minute scenarios that include 1) staff instructions to the child to not touch a particular toy that is placed separately from other toys, 2) child independent play while parent is busy, 3) a six minute parent-child free play session, and 4) a parent structured "clean up" period at the end. These specific scenarios will allow assessment of the child's ability to attend to directions, inhibit impulses, attend to and comply with requested tasks, hyperactivity, and child approach to the parent and to rate child, parent and dyadic behavior. All sessions will be video taped using two research assistant-controlled cameras in the room designed to capture as much of the child and parent's behaviors simultaneously as possible and a fixed, ceiling-mounted, wide angle camera (Ethovision) that inputs the resulting video into an automatic analysis program (Noldus software) to track child and parent proximity and the child's movements within regions of interest in the room across time. Many ratings and objective measures from the PCIT will be derived, but we will only analyze two ratings from the **Joint Engagement Rating Inventory (JERI) Ratings of parent child joint attention and engagement** developed by Adamson and colleagues (164) and adapted as needed for the study in collaboration with her group as key primary outcomes.

The JERI rating system considers both duration and quality of behaviors. It correlates well with time spent in specific engagement states and appears to be more sensitive in distinguishing diagnostic groups and change than simply determining the total time spent in particular engagement states (Adamson 2012; Suma 2017). Raters blinded to treatment status will be trained to reliability by a trainer from Adamson's group and Dr. Devito. In addition, ~15% of videos from each rater will be coded by another rater and the gold standard rater on an ongoing basis to ensure that interrater reliability is maintained. We are focusing on two specific JERI ratings, but there are several other ratings from the JERI that may be of interest in the future.

Social related measures from the Noldus system include the time until the child approaches the parent, proportion of time spent in proximity of the parent, percent of time spent neither in proximity of toys or parent and compliance with instructions during the clean-up activity including latency to help and percent of time spent helping with clean-up.

Multiple ADHD related measures can be derived from the Noldus system during PCIT. Physical activity measures include total minutes in physical activity and total distance traveled. Inhibition control measures are based on Noldus tracking of interactions with the forbidden toy, and will include the latency to first touch of toy, number of touches of toy, and total proportion of time spent touching the forbidden toy.

Two JERI ratings of social communication will be considered as the primary outcome measures. One of these will focus on joint attention. The other will focus on the coordination and fluency of parent child joint engagement.

8.1.2 Secondary efficacy procedures and assessments

Key Secondary Efficacy Assessments:

Vineland Adaptive Behavior Scale (VABS) Mean of the Standard Scores of the socialization and communication subscales is a key secondary outcome. This measure will assess how the participant actually has been functioning over the preceding month with regard to communication and social behaviors. The VABS-3(3) comprehensive form will be administered as a semi-structured interview by a trained and research reliable staff member according to the specifications in the Manual of Procedures (MOP). The standard score is based on the participant's age and is normed from a large sample of typically developing children. The standard score has a mean of 100 and a standard deviation of 15. The minimally clinically significant change on the VABS adaptive behavior composite and standard scores for each of the subscales within individuals with ASD has recently been determined (Chatham et al., 2017).

In addition, the **Preschool or School age ADHD Rating Scale – clinician rating (P-ADHD- RS-C)** will be used as the measure to assess ADHD symptoms in aim 2. It will be based on all information available to the clinician including review of parent ratings, parent interview, participant exam and unstructured observations during the visit. At the remote follow-up assessment (24 weeks following baseline), the parent rating of the P-ADHD-RS will be used to assess ADHD symptoms since the visit is conducted remotely. The parent version of the P-ADHD-RS contains the same questions as the clinician rating.

8.1.3 Exploratory objective outcome assessments

Objective Measures of Social Attention during Eye Gaze Tracking. These will include time in seconds and percent of total looking time spent looking at social stimuli. Eye gaze tracking (EGT) will be recorded using a Tobii system. The system utilizes near-infrared illumination to create reflections on the eyes that can be tracked with high accuracy. Near-infrared light can be found in our natural environment, for instance in candle lights, fires, and in the sun where the IR light is invisible or viewed as white light. All Tobii Eye Trackers have been tested and approved by certified labs according to the European standard for optical radiation hazards of different lamps and lamp systems, IEC/EN 62471. Light emission that meets this standard is not harmful to the human eye. Eye-tracking systems are completely non-intrusive, and do not require the subject to wear any equipment (such as a helmet, eyeglasses or facial markers). No apparatus is connected to the participants. The participants will be shown videos of

various social and non-social stimuli as well as dynamic videos that contain both socially relevant and non-socially relevant stimuli. Regions of interest will be used to define the social and nonsocial stimuli. The total amount of time looking at the screen, looking at the social stimuli, looking at nonsocial stimuli, latency to looking at each type of stimuli for the first time and number of fixations on each type of stimuli will be recorded. The analyzed variables will reflect change between baseline and final outcome / endpoint assessments (10 weeks apart).

SenseToKnow. Children may complete this task which is delivered on a mobile device which uses computer vision analysis to code visual attention and affective expressions in response to brief videos presented on the device. Stimuli consist of a series of video clips including toys that make noise, a man blowing bubbles, bubbles cascading and popping, and a puppy video with unexpected events. Children will sit on the parent's/guardian's lap or a chair with the mobile device at eye level for the child. Children will watch videos and play games that are presented on the mobile device. Overall, the entire task will take approximately 10-15 minutes. Children will be allowed to take breaks between videos and games as needed. A research assistant will be present at all times to answer questions.

EEG Measures of Neurophysiologic Activity. Brain activity will be examined using high-density EEG recordings. We will record EEGs in the neurophysiology laboratory at the Duke Center for Autism and Brain Development. The technique of measuring brain activity with EEG is completely non-invasive and involves the use of a light net of damp electrodes (128 Ag/AgCl electrodes encased in soft sponges and soaked in a saline solution). Before EEG testing begins, participants are familiarized with the laboratory and equipment. Participants will be seated in a comfortable chair, and the elastic net will be place over their head and secured with a chinstrap. Preparation (placing of the net and ensuring that electrodes are properly aligned) takes approximately 5 minutes. All participants will be given an appropriate explanation of the procedure before it takes place and will be given an opportunity to examine the materials and equipment. The experimenter, as well as parent if desired, will remain in the room with the participant at all times. A second experimenter will monitor the EEG recording and behavior of the participant via a video link from an adjoining room. We will record EEG continuously while the participant watches various videos (e.g. of brightly colored geometric shapes, models displaying emotional faces, an hour glass), or listens to sounds. The session will be videotaped to monitor the participant's affect during the EEG. The EEG will be preprocessed to remove artifacts. We will examine regional connectivity, interphase stability and total spectral power during evoked electrical responses to social stimuli. Due to the intensive time and staff demands of the EEG assessments, they will be obtained only at baseline and endpoint.

8.1.4 OTHER SUPPORTING BEHAVIORAL OUTCOME ASSESSMENTS

- **Aberrant Behavior Checklist – 2nd Edition Community Version (ABC)** is a parent report measure that was initially developed for use with intellectually disabled children and adults in residential settings but has been validated for use with individuals with ASD living in the community. Reference values are available from large samples of individuals with ASD. The ABC includes 5 subscales: irritability, attention, lethargy/social withdrawal, repetitive behaviors, and abnormal language. Each of the 40 items is rated from 0 – not at all a problem to 3 – very much a problem. Respondents are asked to rate behaviors in comparison to typically developing individuals. The ABC will be obtained at baseline and endpoint.
- **Behavior Rating Inventory of Executive Function (BRIEF)** The BRIEF is a caregiver report measure that assesses age appropriate executive function behaviors for children. The preschool BREIF is for children between 3 years and 5 years 11 months and the BREIF 2 is designed for children 6 and

older. The same version of the BRIEF will be used at baseline and endpoint to assess changes over time. The following domains will be examined: inhibition, shifting, emotional control, working memory and planning.

- **Caregiver Strain Questionnaire (CSQ)** The CSQ is a caregiver completed measure with 21 questions assessing the impact of a child with a developmental disorder or behavioral disorder on the caregiver and the rest of the family. Questions are rated on a 5 point scale from not at all a problem to very much a problem. In the original version one item relating to your child is reverse scored. We will use a version in which the question is rephrased to avoid reverse scoring. The scale has 3 subscales: objective, internalizing and externalizing. It takes about 5 minutes to complete.
- **Child Behavior Checklist (CBCL)** The CBCL is a caregiver- completed scale that assesses problem behaviors using a 3 point scale (*not true*, *somewhat or sometimes true*, and *very true or often true*) over the prior two months. The preschool version is designed for children 1.5 to 5 years and contains 99 items. The school age version is designed for children 6-17 and contains 118 items. The behavioral domains that are assessed include Emotionally Reactive; Anxious/Depressed; Somatic Complaints; Withdrawn; Attention Problems; Aggressive Behavior and, in the older version, sleep problems. There are also DSM-oriented scales that are consistent with DSM-5 diagnostic categories. Depressive Problems; Anxiety Problems; Autism Spectrum Problems; Attention Deficit/Hyperactivity Problems; Oppositional Defiant Problems. The scale is standardized to provide a mean T score of 50 with a standard deviation of 10. Higher scores reflect more impairment. It has been studied in samples of both school-aged and preschool children with ASD, other psychiatric disorders and typical development(85, 86). It takes about 15 min to complete. http://www.aseba.org/preschool.html
- **Children's Sleep Habits Questionnaire abbreviated (CSHQ)** This caregiver report measure assesses the sleep habits of children 4-10 years old. 33 items are rated on a three point scale. The scale reports on sleep domain scale scores: (1) bedtime resistance, (2) sleep duration, (3) parasomnias, (4) sleep-disordered breathing, (5) night awakenings, (6) daytime sleepiness, (7) sleep anxiety, and (8) sleep onset delay. It takes about 5 min to complete.
- **Clinical Global Impressions Scale** (CGI) is a clinician rated measure of overall clinical severity and improvement that compares to typically developing individuals of a similar age using anchored descriptions. The severity score (CGI-S) ranges from 1- no clinical problem to 7- among the most severely ill; the improvement score (CGI-I) ranges from 1- very much improved to 7 – very much worse, both as compared to baseline. Four CGI measures will be used focusing on 1) overall functioning that includes the impact of the child's ASD + ADHD as well all associated and comorbid problems, Social communication behaviors, 2) ADHD symptoms only, 3) social communication behaviors, and 4) restricted and repetitive behaviors and interests. The CGI will be assessed by the study physician at physician and at the endpoint visit. The CGI raters will be trained by the PI and reliability will be established using a set of vignettes. Raters will be considered to be reliable if they are in exact agreement with half of the gold standard ratings and within 1 point of the gold standard on the other half of the ratings. Reliability will be reassessed annually by coding additional vignettes or double coding observed or taped participant visits.
- **Impairment Rating** Scale (IRS) is a parent reported measure that quantifies impairment present in a child's life in both school and non-school settings. The scale ranges from 1 – No challenge; definitely does not need treatment/special services to 7 – Extreme challenge; definitely needs treatment/special services. The IRS will be assessed at the ESDM informed coaching visits during weeks 2-8.

- **Satisfaction Questionnaire** The satisfaction questionnaire includes 4 questions asking about the caregiver's impression of the quality of treatment received during the study, the extent to which the caregiver believes her/his child and she/he as the caregiver benefited from the study treatment, and the caregiver's impression of participating in research assessments. It takes about 2 minutes to complete and will be done with the endpoint assessments.
- **Sluggish Cognitive Tempo Questionnaire** is a caregiver completed questionnaire that assesses 15 items (Becker et al 2017) that reflect daydreaming, low physical and cognitive energy and challenges in maintaining focus on ones thoughts, which have been conceptualized as sluggish cognitive tempo historically. These symptoms, which are highly comorbid with the inattention symptoms of ADHD, can be reliably distinguished from nine key symptoms of inattention within ADHD on the Child Adolescent Behavior Inventory. Some of these symptoms also overlap with symptoms sometimes associated with ASD such as stares blankly into space, gets lost in own thoughts and spaces out. However, studies have suggested that when ADHD symptoms and ASD symptoms are statistically controlled, SCT is independently associated with greater social dysfunction and more internalizing symptoms. The questionnaire will be completed at baseline and endpoint.
- **Social Responsiveness Scale- Revised (SRS-2)** is a parent report version characterizing various social and repetitive behaviors associated with ASD. The scale's 65 items are rated between 1 and 4 and typically can be completed within 10 minutes. It is designed for use in children between the ages of 2 ½ – 18 years. It contains subscales assessing social awareness, social cognition, social communication, social motivation, and restricted and repetitive behaviors. The measure has been standardized on a large sample including individuals with typical development and demonstrated to be distributed along a continuum. Threshold scores suggestive of ASD have been determined separately for boys and girls. Participants between ages 2.5 and <4 years will receive the Preschool SRS-2, and those ages 4 and above will be asked to complete SRS-2 School age version. The SRS will be obtained at baseline and endpoint.
- **Treatment guess questionnaire** The caregiver, parent coach and study doctor will indicate whether s/he thinks the child was receiving active medication during the trial at the endpoint assessment before unblinding.

8.1.5 Other descriptive measures obtained only at baseline

- **Children's Behavior Questionnaire Short Form** (Rothbart, 2000; Rothbart et al 2001,) is a caregiver report measure designed to provide a detailed assessment of temperament in children 3 to 7 years of age. Individual differences are assessed on 15 primary temperament characteristics indicating three broad dimensions of temperament: Extraversion/Surgency, Negative Affectivity, and Effortful Control. Temperment characteristics on the CBQ have been linked with subsequent psychopathology, including negative affectivity and ADHD.
- **Home Video Tape Upload**, typically of the child's first birthday or an occasion that involves clear social expectations and interactions with others, will be requested at baseline.
- **Leiter Attention and Memory Scales** (Roid et al. 2013) The Leiter is a standardized nonverbal assessment with 3 subscales: cognition, attention and memory and examiner ratings of various aspects of the child's behaviors (not standardized). The attention and memory component includes five subtests: two measure nonverbal attention; two measure memory; and one measures cognitive interference (nonverbal Stroop test). It takes about 30 minutes to administer and will be obtained in participants with IQ' ≥ 70, only at baseline.

- **The Sensory Experiences Questionnaire, version 3.0** (Baranek 1999, 2006) is a 105 item caregiver report measure designed to characterize sensory features in children 2-12 years old. It has been shown to have good discriminate validity between children with ASD, intellectual disability and typical development and also has good test-retest reliability. (Baranek et al., 2006; Little et al., 2011).
- **The Parenting Sense of Competence scale** (Gibaud-Wallston & Wandersman, 1978) measures parental competence along two dimensions: Satisfaction and Efficacy. It is a 17 item Likert-scale questionnaire (on a 6 point scale ranging from strongly agree [1] to strongly disagree [6]), with ten questions under Satisfaction (examining the caregiver's anxiety, motivation and frustration) and seven under Efficacy (which looks at the caregiver's competence, capability levels, and problem-solving abilities in their role). The scale can also be scored as a 16-point scale (where the last question isn't used). This measure will examine changes in participant's parental competence before and after the study and will be administered at baseline and week 10.

8.2 Safety and Other Assessments

- **ACE Medical and family history forms**-Caregivers will be administered the ACE Subject Medical History Questionnaire, and the ACE Family Medical History Questionnaire at the screening visit. These forms collect medical history and current status so that our physicians can have a basis for on-going questions as needed. The ACE Subject Medical History Questionnaire will provide a detailed developmental history and systematic review of problems in each body system using a standardized data dictionary shared across all ACE funded projects. The ACE Family Medical History Questionnaire elicits the developmental and neuropsychiatric history of parents, full- and half-siblings in a similar standardized and shared format. The study physician will review the ACE Subject Medical History and ACE Family Medical History forms completed by the A+ Assessment Core prior to interviewing and examining the participant and his/her parents.
- **Cardiovascular History Form-** The study physician will ask the caregivers about family medical history of cardiovascular problems or malformations and subject history of cardiac congenital malformations, hypertension, arrhythmia, fainting spells and chest pain to get an idea of cardiac history or current issues that could be problematic.
- **Electocardiogram (ECG)**-The child will be administered an ECG at Screening, which will be read by a pediatric cardiologist at screening only to rule out any heart complications prior to randomization. The physician may decide to request additional ECGs, if warranted at any point of the study.
- **Physical examination** The ACE Physical Exam form containing standardized data elements will be completed at baseline and endpoint. At subsequent physician visits, a more targeted brief physical exam will be performed.
- **Vital signs** Vital signs including height, weight, pulse, and blood pressure will be taken at each in-person visit and reviewed by the study physician. Recognition of clinically relevant changes, patterns, or trends in vital signs and growth indices will be facilitated by use of a "vital signs log" that contains all measurements over the study for a particular participant.
- **Assessment of adverse events** At each visit, the participant's caregiver will be asked an open-ended question about new medical/behavioral problems or significant worsening of existing problems. Responses to these will be reviewed by study staff and the study physician to determine whether any further action is necessary to mitigate risks. Any treatment emergent adverse events (i.e. events

not included in past medical history or present at baseline or events that significantly increase in intensity rating from the intensity at baseline or in the PMH) will be recorded. Upon resolution of the AE or at the end of the study, each problems relatedness to the study interventions is assessed. The adverse event form will include information about intensity, start and stop dates, action taken, relatedness to study and status of AE when it resolves or at the endpoint assessment.

- **Suicidality Assessment** At each physician visit, a child suicidality assessment form will be given. A clinician/physician will assess the appropriateness of directing the questions to the participant based on age, verbal ability, cognitive functioning, overall functioning, behavior, willingness, etc.

  Concomitant Medication Log: At the first visit, the physician will make a list of any medications the subject is currently taking. The physician or study staff will record ANY changes to the subjects' medications and dietary supplements throughout the course of the study.

8.3 Adverse Events and Serious Adverse Events

8.3.1 Definition of adverse events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32a). Adverse events will be specifically elicited using the open ended queries. Adverse events may also include abnormal medically concerning laboratory or ECG findings obtained during the course of the study as the result of the participant's routine medical care or study assessments.

In this trial we are eliciting all AE's using open-ended queries, but analyses will focus only on Treatment Emergent AE's (TEAE's). Medical and behavioral conditions that are present at screening and/or baseline will only be considered treatment emergent adverse events if their severity increases significantly after the participant has taken at least one dose of study treatment. Intermittent conditions such as seasonal allergies will only be considered TEAEs, if the severity or frequency is significantly greater than at their most intense during the previous two years.

If a TEAE occurs, its relationship to study product (assessed only by those with the training and authority to make a diagnosis, which would include MD, DDS, DMD, PA, Nurse, Nurse Practitioner or DO), and resolution/stabilization will be coded at the resolution of the event or end of the subject's participation through week 24 of the study. All TEAEs occurring while on study must be documented appropriately regardless of relationship. If a TEAE is a severe adverse event rating of "Severe" and an Unexpected Problem (UP-no prior history of issue/not commonly seen in autistic patients and not described as a risk of the treatment), the UP form must be completed. If a TEAE is a Serious Adverse Event (SAE - see below), but not an UP, the SAE description completed.

8.3.2 Definition of serious adverse events (SAE)

An adverse event (AE) is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, imminent threat of death, inpatient overnight hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 Classification of an adverse event

Intensity of Event:

- **Mild:** Mild events require minimal or no treatment and do not significantly interfere with the subject's daily activities for more than a day or two.
- **Moderate:** Moderate events lead to consideration of medical evaluation or treatment and typically cause some significant interference with functioning for multiple days.
- **Severe:** Severe events prevent a subject's usual daily activity for an extending period of time and are usually incapacitating. Medical evaluation and treatment are generally required if such treatment exists.
- **Extreme**: Life threatening events pose imminent and substantial risk of dying or require urgent intervention to prevent risk of dying.

Relationship to Study Intervention:

The study physician will assess the relationship between each TEAE to the study interventions and procedures based on his/her knowledge of similar medical events, the study procedures and the temporal relationship between the study treatment/procedure and emergence of the TEAE. All TEAEs regardless of the relationship between the AE and study treatment will be reported. The degree of certainty about relatedness will be graded using the categories below.

- **Yes/Definitely related (certainly related)**: The adverse event and administration of the study drug are related in time, and a direct association can be demonstrated. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The AE, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other exposures. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **No (unrelated)**: The AE is clearly explained by another cause not related to the study intervention. The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology.

Expectedness:

The study PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention or procedure or with typical experiences of children. See package insert for detailed information pertaining to what AEs may be expected with Adzenys-XR-ODT extended release, orally dissolvable tablets.

8.3.4 Time period and frequency for event assessment and follow-up

The occurrence of a treatment emergent adverse event (TEAE) or serious adverse event (SAE) may come to the attention of study personnel during study visits or contacts with other medical providers caring for the study participant, or in the context of other contacts between the participant, his/her caregivers and study staff. All non-serious TEAEs will be followed up until satisfactory resolution, the site investigator determines the TEAE to be chronic or the child completes participation in week 9 of the study. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

8.3.5 Adverse event reporting

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured in the through a general AE inquiry. Information to be collected includes event description, clinician's assessment of intensity, relationship to study product (assessed only by those with the training and authority to make a diagnosis) AEs will be followed to adequate resolution or the completion of the child's week 9 visit in the study. Any medical condition that is present at the time that the participant is screened or at the week 0 visit will be considered as past medical history and not reported as a treatment emergent AE. However, if the study participant's condition deteriorates at any time during the study, that is, there is an increase in the condition's intensity rating, it will be considered a TEAE.

8.3.6 Serious ADVERSE EVENT REPORTING

An SAE is defined as an AE that meets certain conditions as defined in section 8.3.2. As soon as study staff become aware of a possible SAE, they will notify the study physician or study PI.

The study physician or PI will review and evaluate the potential SAE, obtaining external medical records and requesting the participant attend an unscheduled physician visit as needed to determine whether or not the event is an SAE.

If the event is an SAE:,

- The study PI and ACE Center PIs will be notified within 24 hours.
- The study medical monitor will be notified within 14 days
- Record event on the appropriate SAE CRF
- follow through resolution (study clinician), updating as needed

Timeline for reporting of SAEs is:

- Medical Monitor: The PI will report all SAEs to the medical monitor within 14 days of becoming aware of the SAE and receive acknowledgment that she/he has reviewed them.
- DSMB: The PI will report SAEs that are considered possibly related to study treatment to the DSMB within 14 days of being made aware of their occurrence.
- IRB: SAEs will be reported to the IRB in the context of the annual report or within 14 days of being made aware of the SAE's occurrence if it is considered related and unexpected or results in death.

- FDA: This study has received an IND exemption, so there is no mandated reporting required. However, if the SAE results in death, is related and unexpected the SAE will be reported using FDA's public Adverse Event Reporting System (FAERS) within 7 days. If the SAE does not result in death, but is both related and unexpected it will be reported using FAERS within 14 days of becoming aware of the SAE.
- NICHD: The ACE center co-PIs and study PI will report SAES that result in death to the NICHD program officer within 48 hours of becoming aware of the event, regardless of whether the SAE was related or expected. If SAE does not result in death or permanent disability, but is considered related and unexpected, we will report it to the NICHD program officer within 14days of becoming aware of the SAE. SAEs that are not considered related or unexpected will be reported in annual progress reports.

- Neos Therapeutics: within 7 days if the SAE results in death and is considered related to treatment and within 14 days if the SAE does not result in death and is considered related to treatment.

8.3.7 Reporting events to participants

If any information emerges that the DSMB or IRB concludes significantly changes the risk: benefit profile of participation in the study, the information will be incorporated into a revised informed consent document for approval by the IRB and the caregivers of participants who are still active in the study will be reconsented with IRB approved revised consent at the earliest possible opportunity.

8.3.8 Events of special interest

Cardiac Monitoring. Based on the patient's age, gender, and height percentile, we have adapted blood pressure parameters where blood pressures above or below the set threshold will prompt the PI or study physician to consider doing a repeat ECG. These parameters were derived from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents(88). We have likewise adapted parameters from Pediatric cardiology for practitioners(50) and Normal ECG standards for infants and children (89) to establish heart rate guidelines where patients whose heart rate is above or below these thresholds will be considered for an ECG at every visit. Finally, we will incorporate clinical signs and symptoms of cardiac risk into our clinical medical assessment. The SLAES also specifically queries for the presence of syncope, dizziness, palpitations, shortness of breath, and bradycardia or tachycardia. Family cardiac history will also be collected and assessed by a physician before starting the study.

8.3.9 Reporting of pregnancy

Not-applicable due to age of participants.

8.3.10 Reporting of suspected child abuse or neglect

If any member of the study staff has significant concerns that a participant may be being abused or neglected, they will discuss it with the study PI. The study PI will attempt to obtain any additional information felt necessary to clarify the situation. If after this there is still concern about abuse or neglect, the PI will contact child protective services and file a report.

8.4 Unanticipated Problems

8.4.1 Definition of unanticipated problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given both the research procedures that are described in the protocol-related documents, and the characteristics of the participant population being studied;
- Related or possibly related to participation in the research and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated problem (UP) reporting

The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

Timelines for reporting the UP are listed below. The FDA and IRB require different reporting based on the characteristics of the UP as noted below.

- Study PI within 24 hours of staff suspecting a UP
- ACE Center co-PIs within 7 days of the Study PI confirming a UP has occurred.
- Medical Monitor: The study PI will report all UPs to the medical monitor within 14 days and receive acknowledgment that she/he has reviewed them.
- DSMB: The ACE co-PIs and the study PI will report UPs that are considered possibly related to study treatment to the DSMB within 14 days of being made aware of their occurrence.
- FDA: Only those UP's that are also SAEs will be reported to the FDA using the FAERS. Timelines for reporting to the FDA follow.
    - Fatal or life threatening unanticipated problems in 7 days
    - Non-fatal/non-life threatening unanticipated problem in 14 days
- IRB: The PI is responsible for reporting unanticipated problems according to the time frames below.
    - Unanticipated Problems that are also SAEs within 7 days of becoming aware of the event.
    - Any other Unanticipated Problem within 14 days of becoming aware of the problem.

- Neos Therapeutics: within 14 days of becoming aware of the UP.

8.4.3 Reporting unanticipated problems to participants

The informed consent document for the study will be revised to reflect the UP. After IRB approval of the revised informed consent document is received, all participants who are continuing to be treated within A+ Treatment will be reconsented. In addition, all participants who do not have a previously scheduled appointment within 2 weeks of the approval of the revised informed consent document will be notified by phone, email or mail that the UP has occurred and that a revised consent form now exists. They will be asked to contact study staff if they wish to discuss the event prior to the next scheduled study visit

8.5 Overall Plan to Protect Patient Safety

Frequent monitoring by study physician Participant safety will be monitored at an individual level by the treating study physician through review of the caregiver medical and behavioral checklist, vital signs and labs, as well as systematic interview elicitation of potential medical and behavioral problems via the SLAES and regular physical and psychiatric exams during scheduled visits, which are more frequent than is typical with community care. In addition, caregivers will have access to a study physician 24hrs/day by contacting the study coordinator during regular business hours and using the emergency phone number after business hours. Additional appointments and laboratory or ECG assessments can be provided at any time according to the treating study doctor's clinical judgment.

Flexible dosing, which includes a 1.55mg dose, is allowed to address dosing-related adverse effects. In addition, participants who are not able to tolerate this small dose are allowed to completely discontinue study medication while continuing participation in assessments and parent coaching.

Rescue medication is provided for significant insomnia, which is one of the most common and problematic adverse effects of stimulant medications.

Medical Monitor The study will also provide for additional oversight via a medical monitor who reviews SAEs and unexpected problems and who will be available to the study clinicians upon request to discuss safety concerns.

Data Safety and Monitoring Board (DSMB) The study will have a three person data and safety monitoring board that reviews the initial protocol prior to any participant being enrolled. After the first participant has been randomized until the last participant has completed the week 24 visit, the DSMB will meet a minimum of two times a year to review the study's progress and the safety of randomized participants. Specifically, the following will be reviewed at each meeting:

1. enrollment and randomization as compared to proposed enrollment and randomization,
2. SAEs and UPs with any resulting changes in study procedures or consents,
3. participant discontinuation of study medication, study withdrawals, and study completions

4. adverse events separated by system organ class, severity and relatedness,
5. changes in laboratory and ECG assessments between screen and week 24 and TEAE related laboratory and ECG assessments,
6. protocol deviations and
7. status of data entry.

Reports related to participant safety will be separated into two groups but the treatment identity of each group will not be disclosed by the unblinded statistician/programmer unless requested by the DSMB. The DSMB may also request additional reports or additional meetings. The membership of the DSMB includes two child psychiatrists who are experts in psychopharmacological treatments for ASD and conducting clinical trials in ASD and a statistician. The DSMB will determine at each meeting whether there are any concerns, especially with regard to safety, that lead the board to conclude that the study should be suspended or that the protocol should be amended to provide greater protections for subjects. The DSMB may also raise concerns or provide suggestions to improve recruitment or procedures for the trial. The DSMB charter, which lists its current members, is included as a appendix.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Primary Analysis: ***Efficacy of COMB vs BEH:*** We hypothesize that, in children 36 to <132 months old with comorbid ASD+ADHD, COMB – stimulant medication provided during 10 weeks, including 8 weeks of ESDM-informed parent coaching – will demonstrate greater improvements in **the degree of child joint attention and fluency and coordination of parent child joint engagement as measured by the JERI coding rating scale and the mean of the VABS Socialization and Communication domain standard scores** than BEH – placebo medication provided during 10 weeks, including 8 weeks of ESDM-informed parent coaching. The significance level will be set at $p < 0.05$. An exploratory analysis will explore changes between week 0 and week 24.

Secondary Analysis: ***Efficacy of Adzenys-XR-ODT vs Placebo:*** We hypothesize that in 36 to <132 month old children with ASD + ADHD, ADHD symptom reduction (assessed via changes in the clinician-administered **preschool or school age ADHD Rating Scale** will be significantly greater in children receiving Adzenys-XR-ODT than in children receiving matched placebo in the 24 week duration between baseline and remote follow-up assessments..

Exploratory Hypotheses are primarily descriptive and will not be corrected for multiple comparisons**.**

- ***Determine the Efficacy of COMB vs BEH on supportive measures of ASD related symptoms*****:** We will compare the COMB and BEH groups with regard to changes between baseline and endpoint assessments (an 10 week duration) in the following outcomes: JERI ratings of coordinated joint attention and of fluency and coordination of engagement during the PCIT free play task, proportion of time spent near caregiver in the PCIT video activity recording, social attention assessed via EGT and via ERP to social stimuli, SRS-2 total, ABC-social withdrawal and repetitive behavior subscale scores, and CGI scores for overall functioning, social communication and

repetitive behaviors. We will also compare week 24 scores controlling for baseline on the following parent report measures: SRS-2, ABC, and VABS (caregiver report form).

- ***Determine the Efficacy of COMB vs BEH on supportive measures of ADHD, sluggish cognitive tempo and executive functioning:*** We will compare the COMB and BEH groups with regard to changes between baseline and endpoint assessments (an 10 week duration) in the parent rated ADHD-RS, SCT questionnaire, the inattention subscale of the ABC and the CBCL, , and time spent moving during the video activity monitoring. We will examine changes in the BRIEF, ABC and parent rated ADHD-RS between baseline and endpoint assessments (an 10 week duration).
- ***Determine the Efficacy of COMB vs BEH on supportive measures of caregiver strain and treatment satisfaction*** between baseline and endpoint assessments (an 10 week duration)..
- ***Determine if there is a correlation between reductions in ADHD symptoms measured by the ADHD-RS and measures of social communication and executive functioning.*** We will initially focus on the changes in the VABS adaptive behavior composite standard score, objective measures from the PCIT as a function of changes in the ADHD-RS. We will subsequently examine changes across the study period or the SRS-2 and the BRIEF.
- ***Determine if there is a correlation between changes in VABS mean Socialization and Communication standard scores, JERI ratings of parent child joint attention and coordination and fluency of engagement and ADHD-RS scores and changes in neural connectivity, neural stability and neural response to social stimuli between weeks 0 and 10 and weeks 0 and 24.*** We hypothesize that each of the following – increases in social communication functioning, increases in ratings of coordinated joint attention and fluency and coordination of engagement, and reductions in ADHD symptoms – will be positively correlated with increases in EEG coherence and ITPC, and with shorter ERP latency and increased cortical activation (reduced alpha and increased theta spectral power) in response to social stimuli.

9.2 Sample Size Determination

The power calculation is based on the primary hypothesis that COMB treatment will result in improvement in the degree of child joint attention and fluency and coordination of parent child joint engagement as measured by the JERI coding rating scale at week 9 that is significantly greater than the change seen in the BEH treatment group. A moderate effect size (ES) of 0.50 is estimated. This estimate is based on prior information about the impact of P-ESDM on VABS Adaptive Behavior Composite in toddlers at risk for ASD after 12 weeks of active parent coaching(21), the benefits of ESDM on young children with ASD(20), and the interfering impact of ADHD on response to social skills interventions in older children with ASD + ADHD(16). Specifically in the study of toddlers at risk for ASD, who would be expected to be more likely to show improvement than young children who actually have ASD, the improvement in the VABS Adaptive Behavior Composite was less than one point after 12 weeks of P-ESDM. In the pivotal study of ESDM in children with ASD who were ~ 2 years old when starting intervention, both the intervention and the community control groups showed a reduction in the VABS Adaptive Behavior Composite after one year, though the reduction in the ESDM group was about 50% that of the control group. Further by year 2, the ESDM group's score was reversing whereas the control group's score continued to worsen. Finally, we expect that ESDM-informed parent coaching will have limited impact in children with comorbid ASD + ADHD due to the interference with engagement in treatment related to ADHD symptoms.

Power estimates were derived empirically via simulation in SAS 9.4. We modeled the VABS Adaptive Behavior Composite for simplicity rather than the mean of the standard scores for the Socialization and Communication domain scores. A mean baseline composite score of 72.0 was assumed for both treatment groups (based on data from Chatham et al 2017(62)), with an improvement in control group of 2.0 points by week 52. For the active treatment group, an improvement of 4.5 additional points was assumed by week 52, for an estimated ES of 0.50. Attrition by week 52 was estimated at 10%, and incorporated missing values in the simulated data based on a uniform pattern of 5% missing by week 12, 5% by week 24, and 10% missing by week 52. In sample size calculations for longitudinal studies, it is also necessary to include information about the correlation structure both between patients and within patients over time. The variance components were conservatively estimated assuming a total standard deviation of 9.0 and a within-individual correlation of 0.75 among repeated ABC Composite scores. After generating 1,000 simulated datasets under these assumptions, a longitudinal regression model (described in section 9.4 below) was fit to each simulated dataset and assessed the effect of interest using two-sided tests with a Type I error rate of 0.05. For a total sample size of 76 and within-individual correlation of 0.75, the empirical power estimate is 92.7%.

9.3 Populations for Analyses

The Primary Analysis Population will include all randomized participants who have taken at least one dose of study medication and have completed at least one post-baseline ADHD-RS assessment. This is a modified intent to treat analysis dataset.

The Safety Population will include all randomized participants who have taken at least one dose of study medication and whose caregiver has provided adverse events information at least one time after randomization.

The Per Protocol Population will include all participants who have continued to take study medication throughout the 10 weeks, who have completed 6 of 8 parent coaching sessions and have completed the Vineland and ADHD-RS assessments at baseline and remote-followup assessment.

9.4 Statistical Analyses

9.4.1 General approach

We will conduct preliminary checks to identify potential outliers and missing data that will guide the choice of models for our formal analyses. We then will address the primary and secondary analyses using the general linear model (GLM), which includes linear, logistic, and Poisson regression models, which allow random effects models. We will turn then to the other aims, which examine whether changes in biomarkers (EGT and EEG) are associated with changes in behavioral functioning. We also will examine clinically meaningful and potentially useful subgroupings such as age, gender, and IQ. We plan to do extensive exploratory data analysis which includes the use of dimensionality reduction techniques, such as factor analysis and principal components analysis, model selection procedures to identify the most appropriate covariates to include, and the use of modern clustering methods to try to identify homogeneous subgroups that warrant further study of their characteristics. As part of the study design, efforts will be made to collect all outcomes on all randomized participants, even when treatment is prematurely terminated.

A final statistical analysis plan will be developed and signed prior to final database lock.

9.4.2 Analysis of the primary efficacy endpoint

JERI ratings The primary endpoints are the JERI ratings of parent child joint attention and fluency and coordination of parent child joint engagement. They will be analyzed using a similar approach to the primary outcome measure. Tests will be two-sided, and a P value of less than 0.05 will be considered to indicate statistical significance, even though we anticipate some correlation between the two ratings.

9.4.3 Analysis of the secondary endpoints

The analyses of the secondary endpoints will be independent of the results of the primary endpoint.

The mean of the VABS Socialization and Communication Subscale standard scores will be derived from the age standardized scores for the Socialization and Communication subscales, calculated from the Vineland Manual or, for the caregiver report at 24 weeks after baseline, by Q-data. The age standardized score has a mean of 100 and a standard deviation of 15. The VABS has predefined rules for data imputation such that if there are more than 2 missing values in a subdomain, the subdomain is considered invalid, and if there are two or fewer missing values they are converted to scores of 1.

The VABS standard scores are continuous scales. In this study, we will examine the co-efficients of change over time with repeated measures using time as a continuous variable across the period from 0-10 weeks). The minimal clinically important difference in children has been determined to be between 2.3 and 2.7 by Chatham et al. 2017(62).

The analyses will compare the COMB group and the BEH group. The primary analysis will utilize the primary analysis group; a sensitivity analysis will utilize the per protocol data set. Exploratory analyses will also consider the effects of age, sex and IQ.

Longitudinal regression models will be used to examine mean differences in the continuous outcomes including the VABS between the two randomized treatment groups at each assessment visit. Each regression model includes indicators of time (assessment visit), group assignment, sex and all time-by-group interaction terms. Residual error terms will be assumed to follow a mean-zero, normal distribution with an unstructured covariance structure used to capture the within-person correlation over time. The fitted models will be used to report mean scores at each assessment visit and make inferences about between-groups comparisons at the final assessment visits (week 24 – in person visit, and week 52 – remote assessment- primary). Tests will be two-sided, and a P value of less than 0.05 will be considered to indicate statistical significance. The sequential Dunnett test will be used to control the overall (familywise) error rate. Longitudinal models will be fit using PROC MIXED in SAS Statistical Software, Version 9.4 (SAS Institute, Cary, NC).

Presentation of results will include p-values and 95% confidence intervals for the least mean square values at weeks 0, 10, 24. To enhance interpretation of the results, we will calculate the number needed to treat (NNT) using a binary indicator of response. For the continuous outcomes, we will calculate standardized between-group mean differences at the week 10, 24 and 52 visits.

ADHD-RS Is a continuous measure which consists of the sum of scores on each of 18 questions within the scale, ranging between 0 (not at all) and 3 (very often). The instructions for the measure will be adjusted to report on the prior week rather than the prior 6 months as in the initial measure. Different normative values are utilized with boys and girls. Clinically significant scores in boys are 14 for

inattention items (odd numbered items) and 17 for hyperactivity/impulsivity items (even numbered items). Clinically significant thresholds in girls are 12 for inattention items and 14 for hyperactivity/impulsivity items. A supportive exploratory analysis will examine change to a nonclinically significant score at 24 weeks after baseline.

The statistical approach will be similar to that for the primary outcome variable with the exception of a categorical presentation of above and below ADHD criteria in the supportive exploratory analyses. Specifically, longitudinal regression models will be used to examine mean differences in the continuous outcome of ADHD-RS scores between the two randomized treatment groups at each assessment visit. Each regression model includes indicators of time (assessment visit), group assignment, sex and all time-by-group interaction terms. Residual error terms will be assumed to follow a mean-zero, normal distribution with an unstructured covariance structure used to capture the within-person correlation over time. The fitted models will be used to report mean scores at each assessment visit and make inferences about between-groups comparisons at the final assessment visits (visit 16 – in person visit, and visit 18 – remote assessment). Tests will be two-sided, and a P value of less than 0.05 will be considered to indicate statistical significance. The sequential Dunnett test will be used to control the overall (familywise) error rate. Longitudinal models will be fit using PROC MIXED in SAS Statistical Software, Version 9.4 (SAS Institute, Cary, NC).

Presentation of results will include p-values and 95% confidence intervals for the least mean square values at baseline, endpoint, and remote follow-up timepoints (visit 6, 10 weeks later at visit 16, and 24 weeks after baseline at visit 18). To enhance interpretation of the results, we will calculate the number needed to treat (NNT) using a binary indicator of response.

Since ADHD-RS ratings are considered to be independent of the mean of the VABS standard scores for the Socialization and Communication domains and we will separately examine the correlation between changes in each of these two measures with other more objective measures of social communication and attention in Aim 3, we will not correct for multiple comparisons in the analysis of the ADHD-RS.

Finally, for children who complete the SenseToKnow application, data collected will include: audio and video recordings tracking movement, facial expressions, vocalizations, and device information which includes accelerometer, gyroscope and tactile response data.

9.4.4 Safety analyses

We will report the percent of participants who have vital sign abnormalities in the two treatment groups. The specific thresholds for reporting are presented in the MOP. In addition, we will present the mean and standard deviation of changes between baseline and endpoint in BMI percentile for age and gender, blood pressure percentiles, and absolute values of each laboratory value studied.

All AE's will be coded to MedDRA terms by the project staff and physician. Each AE will be counted once only for a given participant. TEAEs will be presented by System Organ Class (SOC) and preferred term groupings, severity, proportion of group experiencing the TEAE, and % of each TEAE that was judged to be related to treatment. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented as a listing by treatment group.

9.4.5 Baseline descriptive statistics

Intervention groups will be compared on baseline characteristics, including demographics, ADOS severity scores, cognitive function, adaptive behavior scores, ADHD-RS scores using descriptive statistics of mean value, standard deviation and range. Inferential statistics will be used.

9.4.6 Planned interim analyses

No interim analyses are planned.

For each DSMB report, we will determine the proportion of participants in the COMB group and in the BEH group who withdraw due to adverse events and lack of efficacy. We will also present a tabulation of TEAEs within each of the treatment groups by severity and system organ class.

9.4.7 Sub-group analyses

We will not conduct any inferential subgroup analyses. If subgroup analyses are done, they will be purely non-inferential and hypotheses generating, given that this is a pilot study with a small sample size that is unlikely to have subgroups of sufficient size to draw meaningful conclusions.

9.4.8 Tabulation of individual participant data

Individual participant data will not be tabulated.

9.4.9 Exploratory analyses

Overall, exploratory endpoints focusing on supportive behavioral measures of autism symptoms, ADHD symptoms, and caregiver perceptions will be analyzed using the above methods for the primary and secondary analyses.

However, relationships between changes in EGT and EEG biomarkers and changes in outcomes will be analyzed slightly differently. The general framework for addressing the relationship between changes in biomarkers (e.g. EGT, EEG) and changes in outcome (VABS standard scores, ADHD symptoms) in children with ASD+ADHD (Aims 3 and 4) also will be the GLM. GLMs handle group comparisons and correlational analyses using a common framework while controlling for important sources of heterogeneity in our design, such as age, gender, and IQ. The primary variables of interest, EGT variables (e.g., % time gazing at actress) and EEG (e.g., amplitudes, latencies, power, coherence and ITPC), will be modeled as a function of task condition and treatment group, controlling for relevant covariates. By using standardized versions of the measures, we will be able to interpret model coefficients as partial correlations. A similar approach will be used to examine relationships between changes in social engagement measured via PCIT coding and video activity monitoring, and outcomes.

These outcomes are primarily descriptive and will not be subject to multiple comparison corrections or strict p value criteria to assess significance.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical and Study Oversight Considerations

10.1.1 Informed consent process

Consent/Assent Provided to Participants. Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant's caregiver and documentation of informed consent is required prior to starting intervention/administering study intervention. Informed assent is not required of the participants due to their developmental status. The informed consent document for the preliminary screening study (A+ Assessment) and this study (A+ Treatment) are included in the appendices. These materials will be provided to the participants' caregivers when they express interest in the study and will be discussed with them as described below.

Consent Procedures and Documentation: Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms and consent procedures will be Institutional Review Board (IRB)-approved. The participant's caregiver(s) will be asked to read and review the document with sufficient time allowed prior to meeting with study staff. If the caregiver is still interested in participating or has questions that may influence his/her willingness to participate, the study coordinator and/or co-investigator or one of the study physicians will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the caregiver's comprehension of the purposes, procedures, and potential risks of the study and of their and their child's rights as research participants. A study physician will always be available to potential participants' caregivers to answer any questions. The caregiver will be encouraged to discuss the study with their family or their child's current providers prior to agreeing to participate.

If the potential participant's caregivers want the child to participate in the study, the caregiver(s) will sign the informed consent document prior to any procedures being done specifically for the study. Participants and their caregivers will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed informed consent document will be given to the participants for their records. The informed consent process, including the date the documents are signed, will be conducted as per existing Standard Operating Procedures (SOPs) and documented in the source documents, before the participant undergoes any study-specific procedures.

10.1.2 Study discontinuation and closure

Individual Participant Discontinuation Please see section 7 for a full description of situations in which an individual might discontinue participation in the trial and for reasons why the entire study might be stopped. Briefly, individual participants may discontinue study treatment and/or participation in study assessments at any time without providing any reason for doing so. If participants/participant caregivers wish to discontinue participation in study interventions, they will be strongly encouraged to continue participation in other aspects of study interventions (e.g. discontinue study medication treatment but continue parent coaching) and/or study assessments. Similarly, if the study physicians feel it is in the best interests of the participant to discontinue some aspect of the study treatments or study assessments, they will be encouraged to have the participant continue other aspects of the study. If a participant is discontinued from the trial, the study team will provide and facilitate referrals to other appropriate clinicians for ongoing treatment.

Suspension of the entire study This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. *We plan to suspend enrollment of new participants, if the proportion of participants withdrawing from one treatment arm is greater than 40% and more than 3x that of the other treatment arm*, until the DSMB reaches a decision regarding continuation of the study.

In addition, the study might be interrupted or prematurely terminated in the following situations or other as yet unanticipated situations.

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Withdrawal of financial support of the trial
- Determination that a sufficient sample can't be recruited.

If the concerns leading to study interruption can be satisfactorily addressed, the study may resume with the consent of the sponsor, IRB and/or Food and Drug Administration (FDA).]

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator and, if applicable, funding agency or DSMB. Subsequently, the study PI will provide written notification documenting the reason for study suspension or termination to the study participants, funding agency or DSMB as applicable, FDA, drug manufacturer and IRB. If possible and if there are not safety concerns, the active participants in the study will complete their participation. Study participants will have the opportunity to contact the PI and other study staff to further discuss the decision to suspend the trial if they wish.

10.1.3 Confidentiality and privacy

Participant confidentiality and privacy is strictly held in trust by the study team, the sponsor and regulatory authorities. Confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. All research activities will be conducted in as private a setting as possible.

In this study, a strict separation will be maintained between information that contains information that is personally identifiable (such as the study consent form and information used to obtain a GUID) and the data that will be analyzed from the study. In all data, participants will be identified by a unique subject ID. Some derived data required in this study requires information about the participant's age (birthdate) and gender but will not be linked to other potentially identifying information such as initials or address. All data will be housed in secure locations, that are double password protected.

The study monitor, other authorized representatives of Duke University and/or the National Institute of Child Health and Human Development (study sponsor), representatives of the Institutional Review Board (IRB), FDA or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, study source documents, medical records and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored at the site for internal use during the study and until the final results of the study have been shared with the participants and/or their caregivers. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

In this study, data identified only by the participant's globally unique identifier (GUID) will be uploaded into the National Database for Autism Research (NDAR) to facilitate additional analyses and discoveries to improve the understanding and care of individuals with ASD.

Mobile devices will be used to deliver/use the applications developed for this study. The mobile devices

Principal Investigator	Medical Monitor	Center PI	Center Co-PI

(SenseToKnow app) assigned to each study for use during the visits are Duke-owned. Participant data will be stored on the study device(s), which will be handled by trained study staff.

Data that is collected by the SenseToKnow app will be stored locally on the devices until data is securely moved to Fileshare. PHI stored on the device will be automatically erased immediately after data transfer to the secure database is completed by a trained staff member.

The devices will be hardened according to guidelines from the Office of IT Security. For additional security we will add a user password to this application so that no one other than those that were given the password set on the device can have access to this data through the device itself.

Security for the mobile device-based application will be taken care of by using 'iOS Keychain' security features. This will enable the storage of video and test data on device in a space that only the application has access to. No other application will be able to access this data including the camera roll or video viewer. Video and test files will be saved in the application directory and not with the rest of the multimedia. For device offloading, all the data saved will be encrypted so that only agents with the correct decryption will be able to view the test data and videos located in the folder after downloading the encrypted files. Data will be transferred every night when the mobile device is charging to a local Duke server using native iOS SSL features, which will enable us to securely transfer files over the internet and data will be deleted once uploaded to the Duke server.

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 Future use of stored specimens and data

We do not plan to collect any specimens that will used in the future. The data collected in this study will be transferred to NDAR as described above, but will not be able to linked to a specific individual.

10.1.1 Safety oversight

There will be a medical monitor and DSMB to oversee the safety of participants in the study as described in section 8.5. All of these individuals are independent of Duke University and of the study. In addition, the study will be reviewed annually and more often if needed by the IRB and the FDA.

10.1.2 Key roles and study governance

Dr. Lauren Franz, MBChB, MPH	Laura Politte, MD	Geraldine Dawson, PhD	Scott Kollins, PhD
Duke University School of Medicine	Wake Med	Duke University School of Medicine	Duke University School of Medicine
2608 Erwin Rd, suite 300 Durham, NC 27705		2608 Erwin Rd, suite 300 Durham, NC 27705	2608 Erwin Rd, suite 300 Durham, NC 27705
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lauren.franz@duke.edu	*lpolitte@gmail.com*	Geraldine.dawson@duke.edu	Scott.kollins@duke.edu

10.1.3 Clinical monitoring

The Duke ACE center Data Management and Analysis Core (DMAC) will undertake monitoring of this study using multiple procedures. First, data that is directly entered into the database will be checked for completeness by study staff during the in person visit related to the caregiver report. If items are left blank or are inconsistent the caregiver will be asked to clarify and complete the items in question. Caregivers will be urged not to leave any questions unanswered.

Data generated by study staff on paper forms will be double data entered. The DMAC will identify any inconsistencies in the doubly entered data points and a third person will resolve discrepancies and/or contact the appropriate study staff to clarify the data.

The Duke ACE Center DMAC will implement many data validation rules ((e.g., blank but required entries, out-of-range values, and skip patterns), that will be enforced by the EDC system during data entry. Other, more complex error conditions will be checked using custom error-check programs. Inconsistencies in data patterns across forms will be used to identify complex errors or confirm validity of data. For example, values on the spontaneous language item on the ADI-R are compared to ADOS-2 module to ensure validity of measures employed with each subject. The DMAC will continually monitor data quality as data are entered using a module named the Data Anomaly Detection and Resolution Module (DAD-RM), which we have successfully deployed in other studies. The DAD-RM system integrates built-in EDC data validity rules with external rules of arbitrary complexity to produce a database of potential data problems ("logical queries") that must be resolved by study staff and approved and documented by the DMAC. Using the DAD-RM system, project coordinators and the DMAC will be able to review all data query records via the Portal website. Each record must be annotated and marked as either resolved by data update, approved as an extreme value, or unrecoverable. The DAD-RM error checks and database update will be run daily, providing studies the opportunity to address data issues early when the probability of resolution is highest. We will resolve individual and recurring problems with the data entry system during DMAC weekly staff meetings. These meetings will be used to discuss and resolve issues and answer operational concerns, such as data entry questions, use of technologies, and EDC. Dr. Compton will manage the data resolution process and host training sessions as needed. Procedures regarding QC will be performed to address inconsistencies that emerge following data validation processes and work with study staff to address data quality issues and to refine the data collection and reporting process.

In addition, the Duke ACE Center Regulatory Coordinator will conduct periodic audits during the course of the trial. During these audits, she will monitor all regulatory documents, documentation of protocol deviations and violations, and correlations between randomly chosen source documents and the data base.

10.1.4 Quality assurance and quality control

All entered data will be subject to Quality Assurance (QA) Measures. QA processes will be overseen by the Administrative Core, in collaboration with Dr. Dawson. All study staff will be trained on center-wide Standard Operating Procedures (SOPs), approving and tracking SOP deviations, Good Clinical Practice (GCP) and human subjects research training. The Data Management and Analysis Core will provide the Administrative Core with information regarding timeliness of data submission from the study, protocol deviations and missing data, and NDAR submissions. This information will help identify areas of deficiency, aspects of GCP that need reinforcement, or additional training that may be required. If these steps do not correct deficits or GCP concerns, steps may be taken to discipline, relocate, or replace a staff member or modify study procedures. The Administrative Core staff will work closely with the DMAC, which will oversee consistent application of scientific standards and methodological rigor for data collection, processing, entry, cleaning, and analytics. The DMAC will be responsible for study specific QC for all behavioral, questionnaire, EEG, EGT, and biosample data. This will be accomplished by the development of well-defined procedures, intensive training of staff, and Manual of Procedures (MOPs) with detailed instructions for procedures involved in data acquisition, processing, and upload to the Data Management and Analysis Core. Fidelity to research procedures will be accomplished by the development of well-defined protocols, intensive reliability training, regular in-person meetings to avoid drift, and internal audits. Protocol-specific training will be based on the delegated role of investigators and staff as defined in delegation of responsibility logs.

10.1.5 Data handling and record keeping

Data Collection and Management Responsibilities. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the project lead, Dr. Dawson. Dr. Dawson is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Hardcopies of the study visit worksheets will be used as source document worksheets for recording data obtained by study staff for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the redcap database designed and provided by the Duke ACE Center DMAC, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be double entered directly from the source documents.

The participants' caregivers will receive emails from the study team/DMAC notifying them when they should complete rating scales online via RedCAP or Q-global. If a caregiver does not wish to utilize the electronic rating scales, study staff will either complete the rating scale with them over the phone or provide them with a paper copy of the rating scale to complete.

At each assessment point, the study staff will document whether any assessments were not completed and the reason for noncompletion.

The Duke Autism Center DMAC will provide Dr. Dawson with a listing of expected but not entered data at least monthly.

Study Records Retention: All records will be retained for at least 2 years following publication of the final manuscript related to the study or for at least 3 years after submission of the study's Federal Financial Report submission.

10.1.6 Protocol deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

The study staff will record any deviations as they happen and/or as they become aware of the deviation. Such deviations will include assessments occurring outside the allowed windows, failure to complete scheduled assessments, study medication dosing that is not consistent with the protocol, and issues with documenting consent. Study staff will also document the reason(s) for the deviation and the corrective actions that will be put into place to prevent future deviations. In addition, the DMAC will provide a listing of all study visits that occur outside of specified study windows, any medication doses that are outside the allowed range (0 tablets to 6 tablets), and any increases in study medication that are made prior to the prescribed schedule (eg. within less than 14 days of the most recent dose increase unless there has been an interruption in dosing or a dose decrease due to concerns about a TEAE). All protocol deviations during the prior year will be reported to the IRB in the annual report.

Protocol violations will consist of inclusion of ineligible participants, medication dispensing errors (eg. the wrong study treatment), and unblinding of participants or blinded study staff. Protocol violations will be reported to Dr. Dawson, the DMAC and the Duke Center for Autism Administrative Core within 14 days of becoming aware of the event. Subsequently, procedures must be put into place as soon as possible and within an additional 14 days to prevent similar events in the future. The IRB and DSMB will be notified of all protocol deviations at the time of the next scheduled report or sooner if there are safety concerns associated with the deviation.

10.1.7 Publication and data sharing policy

Every effort will be made to publish the results of this study in a peer reviewed journal as soon as possible after completion of the study. Authorship of resulting papers will be as inclusive as possible. If there are confilicts about authorship, the Duke ACE Center Executive committee will resolve the conflicts in accordance with the center's publication policies.

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers 3 years after the completion of the primary endpoint by contacting Dr. Dawson or the Duke Center of Autism. Further, all data will be uploaded into the National Database for Autism Research (NDAR) for use by other investigators according to the specific agreement between NDAR and the Duke ACE Center.

Genomic data will not be generated by this study.

10.1.8 Conflict of interest policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Duke ACE Center Administrative Core, in conjunction with the NICHD and Duke University School of Medicine, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 Abbreviations

The list below includes abbreviations utilized in this protocol.

ABC	Aberrant Behavior Checklist
ACE	Autism Center of Excellence
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	Preschool Attention Deficit Hyperactivity Disorder Rating Scale
ADI-R	Autism Diagnostic Interview - Revised
ADOS	Autism Diagnostic Observation Schedule
AE	Adverse Event
ASD	Autism Spectrum Disorder
BRIEF	Behavior Rating Inventory of Executive Function
CBCL	Child Behavior Checklist
CFR	Code of Federal Regulations
CGI	Clinical Global Impressions Scale
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSHQ	Children's Sleep Habits Questionnaire
CSQ	Caregiver Strain Questionnaire

DAS	Differential Abilities Scale
DMAC	Data Management and Analysis Core
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
IRS	Impairment Rating Scale
ITT	Intention-To-Treat
JERI	Joint Engagement Rating Inventory
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NICHD	National Institutes of Child Health & Human Development
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SCT	Sluggish Cognitive Tempo Questionnaire
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SRS-2	Social Responsiveness Scale – 2nd edition
TEAE	Treatment Emergent Adverse Event
UP	Unanticipated Problem
US	United States
VABS	Vineland Adaptive Behavior Scales – 3rd edition

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A copy of Summary of Changes table for the current amendment follows the Protocol Title Page.

Version/Date	Change	Brief Rationale
1.1/Aug. 30, 2018	• Added Specific Aims section • Changed the primary outcome measure to the mean of the VABS socialization and communication subscale standard scores • Changed key secondary outcomes to include JERI ratings coordinated joint attention and fluency and coordination of engagement. • Eliminated the week 10 EEG measures. • Changed timing and length of P-ESDM curriculum assessment and coaching sessions. • Added Sluggish Cognitive Tempo questionnaire weeks 0, 10,24,& 52. • Removed ASSIST/READY; added Sense to Know • Changed exclusion criteria, Leiter guidelines & deleted post baseline Leiters, & added home videos, childhood behavior inventory, sensory experiences questionnaire preschool executive function battery,& to week 0 • Changed FDA reporting to reflect IND exemption; provided more detail about safety reporting, documentation of TEAEs, and drug accountability procedures • Updated references & corrected clerical errors	• Increase concordance between grant and protocol. • Changed to reflect specific functional areas targeted by P-ESDM. • Increased sensitivity vs duration coding & alignment across ACE centers. • Reduce burden & cost. • Prevent overlap with week 10 assessments, reduce burden & assess parent fidelity. • Advisory board suggested given potential overlap with ASD & ADHD • Unable to work out contract • To standardize week 0 assessments with A+ Development facilitate centerwide comparisons. • Revisions necessary as obtained new regulatory information & developed database & drug blinding procedures

11 APPENDIX 1: CONMED SHEET WITH WASHOUT INSTRUCTIONS

A+ STUDY CONCOMITANT MEDICATIONS

Medication	A+ Treatment	A+ Development Only
Clonidine (Kapvay, Catapres)	Allowed	Prohibited unless only taking at night for sleep. (May wean down to night-time use only in order to participate.)
Guanfacine (Intuniv (XR), Tenex (IR))	Allowed	Washout for 24 hours
Aripiprazole (Abilify)	Allowed	Allowed
Atomoxetine (Stratterra)	Up to 3 weeks (10-14 days to wean off high doses, followed by 1 week to see if tolerable if not can continue.)	PI/clinician judgement on a case by case basis.
Amphetamine (Adzenys ER, Adzenys XR-ODT, Dynavel XR, Mydayis)	Washout 1 week for immediate release (IR).	Washout for 24 hours.
Dexmethylphenidate (Focalin IR & LA)		
Dextroamphetamine/amphetamine salt (Adderall IR & XR)		
Dextroamphetamine, damphetamine (Dexedrine, Dextrosta, Procentrat, Zenzedi)		
Lisdexamphetamine (Vyvanse)		
Methylphenidate (Aptensio XR, Concerta, Cotempla XR-ODT, Daytrana, Desoxyn, Metadate, Methylin, Quillichew, Quillivant, Ritalin, Ritalin LA)		

Pemoline (Cylert)		
Risperidone (Risperdal)	Allowed	Allowed

The following medications will be assessed on a case by case basis: Wellbutrin (bupropion), Effexor (venlaflaxine), Desipramine, Amitriptyline, Nortriptyline, Amantadine (Symmetrel), Memantine (Namenda),

MAO-I's require 14 day washout prior to A+ Treatment Baseline: Isocarboxazid (Marplan), Phenelzine (Nardil), Selegiline (Emsam), Tranylcypromine (Parnate)

12 REFERENCES

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