Angelman Syndrome Video Assessment (ASVA)

Source Material Study

CAS-CAS006-01 v2.0

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1 Synopsis

Study Title:	Angelman Syndrome Video Assessment (ASVA) Source Material Study (SMS)
Protocol ID:	CAS-CAS006-01
Study Design:	This is a longitudinal, observational, nonrandomized, fully remote study enrolling approximately 55 participant-caregiver dyads. The study includes no treatments or interventions, and participants will not be asked to change their current treatments.
Objectives:	The objective of this study is to gather sufficient source material videos to develop a scoring system for ASVA and to perform preliminary validation of that scoring system.
Endpoints:	• ASVA videos collected at baseline, baseline re-test, and again at a 12-week visit. • Vineland Adaptive Behavior Scale-Third Edition (VABS-3) scores collected at baseline and again at the 12-week visit. • Caregiver Global Impression of Change (CGIC) in each domain at the 12-week visit
Target Population & Sample Size:	40 participants with Angelman Syndrome (AS) and their caregivers (AS-caregiver dyads) and up to 15 neurotypically (NT) developing children and their caregivers (NT-caregiver dyads) for a total of up to 55 participant-caregiver dyads.
Key Inclusion/Exclusion Criteria:	AS-caregiver dyads will be enrolled if the caregiver reports a laboratory confirmed diagnosis of AS, the participating individual with AS is at least 1 years old, and the caregiver is comfortable reading and speaking English. NT-caregiver dyads will be enrolled if the child is between 1 and 8 years old and the caregiver is comfortable reading and speaking English.
Schedule of Assessments:	ASVA videos will be captured 3 times (baseline, baseline re-test, and at a 12-week visit). VABS-3 will be administered 2 times (baseline and at a 12-week visit) as an interview with caregivers. CGIC will be captured in the study app for each of 4 domains at the 12-week visit.
Data Analysis:	Videos will be reviewed and analyzed to develop an ASVA scoring/rating system. Videos captured of neurotypical children will be used as a qualitative comparator to ensure the ASVA scoring system is sufficiently specific to physical and behavioral manifestations of AS. VABS-3 and CGIC data will be used as comparators for validation analyses of ASVA.

2 Introduction & Background

Angelman syndrome (AS) was first described in 1965 as a neurodevelopmental disorder characterized by global developmental delay leading to severe intellectual disability, lack of expressive language, ataxia, tremors, unique behavioral features including a happy predisposition, easy laughter, mouthing of objects, fascination with water, as well as maladaptive behaviors such as hair-pulling and other aggressive behaviors. It was subsequently found to be caused by a lack of expression of the *UBE3A* gene, which may be due to a deletion of the critical segment from the maternally-inherited copy of chromosome 15q11q13 that encompasses *UBE3A* (in about 70 – 75% of affected individuals), a pathogenic variant in the maternally-inherited copy of *UBE3A* (in about 10%), paternal uniparental disomy (UPD) of chromosome 15 (in about 5 – 10%), or an imprinting defect (in about 5 – 10%) Estimates of prevalence are approximately 1 in 20,000 to 1 in 50,000.[1–3]

Individuals with AS present with moderate to severe degrees of cognitive deficits and neurological manifestations, with deletion-type AS typically having more severe deficits.[4] Epilepsy is common.[5,6] Most individuals with AS use few spoken words, if any, and possess better receptive than expressive communication skills.[7] AS is also marked by some common physical features (e.g., microcephaly, thin vermilion of upper lip) and a high prevalence of scoliosis. Behaviorally, individuals with AS commonly have a decreased need for sleep or other sleep-related issues, are easily excitable and/or are prone to hyperactivity, and have a happy demeanor.[5] Developmental delays typically appear within the first year of life.[5] Life expectancy is near normal, and individuals with AS require functional support throughout their life span.[1,5] Current treatments for AS are, therefore, generally supportive in nature.[5]

Therapeutic interventions that target the underlying genetic causes of AS are in development. Any therapy aimed at modifying the neural substrates of the disorder may affect multiple functional domains if they result in improved neuronal functioning. To date, outcome measures available for use in therapeutic trials for AS focus on specific, individual functional domains often using in-clinic standardized neurodevelopmental assessments that may be insufficiently sensitive to identify changes in habitual function.

Thus, the Angelman Syndrome Video Assessment (ASVA) is being developed by Casimir, LLC (Casimir) in collaboration with Boston Children's Hospital and Ionis Pharmaceuticals to capture observable behaviors and functioning of individuals with AS while in their typical home environment. ASVA is intended to measure changes in relevant functional domains. Results of a previously conducted feasibility study informed a refined list of activities and improved caregiver instructions for the video capture.

The ASVA Source Material Study will be conducted by Casimir, with full funding provided by Ionis Pharmaceuticals, to perform the next phase of development of the ASVA outcome measure. Videos collected as part of the ASVA Source Material Study will be used to develop the scoring system for ASVA and perform preliminary validation of the newly developed scoring system. Videos for pre-specified activities will be captured for individuals with AS across a range of ages and abilities and for neurotypically developing children. The videos will provide sufficient information to devise a scoring system and ensure that the system is tailored to differentiate AS-specific difficulties from neurotypical development.

3 Study Design

This is a longitudinal, observational, nonrandomized study enrolling up to 40 participants with AS and their caregiver (AS-caregiver dyads) and up to 15 neurotypically (NT) developing children and their caregiver (NT-caregiver dyads) for a total of up to 55 participant-caregiver dyads. ASVA videos will be captured 3 times (baseline, baseline re-test, and at a 12-week visit). Vineland Adaptive Behavior Scale v3 (VABS-3) will be remotely administered 2 times (baseline and 12 weeks) as an interview with the caregiver. The study includes no treatments or interventions, and participants will not be asked to change their current treatments.

The study will be remotely conducted (all visits and captures performed at-home). Participant-caregiver dyads that meet inclusion criteria may be enrolled, regardless of their location of residence.

3.1 Objectives

The objective of this study is to gather sufficient source material videos to develop a scoring system for ASVA and to perform preliminary validation of that scoring system.

3.2 Endpoints

- ASVA videos collected at baseline, baseline re-test, and again at 12-week visit.
- VABS-3 scores collected at baseline and again at 12-week visit.
- Caregiver Global Impression of Change (CGIC) at 12 weeks for physical ability, activities of daily living, communication, and attention/focus.

3.3 Measures Taken to Minimize Bias

As an observational study intended to gather source material for outcome measure development, no randomization or blinding will be employed.

4 Participants

Up to 40 AS-caregiver dyads and up to 15 NT-caregiver dyads will be enrolled.

4.1 Inclusion/Exclusion Criteria

AS-Caregiver dyads are eligible for inclusion if the:

- Caregiver reports that the individual with AS has a laboratory-confirmed diagnosis of Angelman syndrome
- Individual with AS is at least 1 year old
- Caregiver is willing and able to provide informed consent for themselves and oversee study participation
- Caregiver or legal guardian is willing to provide informed consent on behalf of the individual with AS
- Caregiver is comfortable reading and speaking in English
- Caregiver has access to a smartphone or tablet that is compatible with the study app OR caregiver has internet access and is willing to use a wi-fi only device to record and upload videos

NT-Caregiver dyads will be eligible for inclusion if the:

- Neurotypical individual is between 1 and 8 years of age
- Caregiver is willing and able to provide informed consent and oversee study participation and NT individual is willing and able to provide assent, as applicable
- Caregiver is comfortable reading and speaking in English
- Caregiver has access to a smartphone or tablet that is compatible with the study app OR caregiver has internet access and is willing to use a wi-fi only device to record and upload videos

Participant-Caregiver dyads will be excluded from the study only if they do not meet the inclusion criteria above.

4.2 Recruitment

AS-caregiver dyads will be recruited for this study through referrals from collaborators and advocacy groups as well as through direct marketing via social media. Boston Children's Hospital's Department of Neurology (BCH) and advocacy groups will not be responsible for direct recruitment of the study participants. Rather, BCH and advocacy will facilitate recruitment by making available to interested caregivers Institutional Review Board (IRB) approved recruitment materials. If caregivers provide written or verbal consent to be contacted by Casimir study staff, BCH may share their contact information with Casimir study staff via a secure channel. Potential participants may also share their contact information directly with Casimir via a secure, online form.

Additionally, recruitment for the study may also occur through postings with patient advocacy groups and on social media. Casimir will supply the advocacy groups with IRB-approved language for website postings and group emails. All contact information will be obtained using a secure web form that is compliant with Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulation (GDPR).

4.3 Informed Consent

Casimir study staff will explain the study and answer any questions on an initial call. Casimir will obtain verbal consent prior to the official electronic consent (e-consent) process that takes place. If interested, Casimir study staff will conduct e-consent/assent using the following process:

- Casimir study staff will schedule a phone call/web-conference with potential participant-caregiver dyads and send the informed consent form (ICF) and any applicable assents.
- Casimir staff will review the ICF and any applicable assents with the potential participant-caregiver dyad.
- Casimir study staff will provide the potential participant and caregiver with the opportunity to ask questions.
- If the participant and caregiver verbally consents/assents during the phone call/web-conference, Casimir study staff send the appropriate ICF and/or assent forms to participants to be signed electronically using a web-based signatory system and in accordance with applicable Casimir Standard Operating Procedure and applicable study specific plans and/or Work Instructions

If the caregiver in a participant-caregiver dyad is unable to legally provide informed consent for the participant, a legal guardian of the participant who can provide consent will also be included in the consent process described above.

Copies of the signed informed consent and any applicable assent form will be provided to the caregiver and/or legal guardian once signatures are completed. Study staff will also maintain a copy of the electronically signed consent and applicable assent form. Appropriate IRB-approved informed consent and/or assent forms will be used based on the age and mental capacity of the participant.

4.4 Eligibility Determination

Eligibility will be established if the potential participant-caregiver dyad meets all the inclusion criteria.

4.5 Discontinuation Criteria

Casimir, in coordination with the funder, Ionis, may elect to discontinue this study at their discretion. Participant-caregiver dyads may elect to withdraw from the study at any time.

5 Study Procedures

5.1 Schedule of Visits & Assessments

Following informed consent and during the baseline period, caregivers will participate in a remote administration of the Vineland Adaptive Behavior Scales (VABS-3) conducted as an interview. After the Baseline VABS-3, a Training Call will be scheduled by phone or secure web conference to train participating caregivers for video capture and orient them to the study supply kit. After the Training Call, caregivers will capture Baseline ASVA videos, which includes capturing 2 sets of videos (baseline and re-test captures). Approximately 12 weeks later, VABS-3 will be remotely administered again, and the participant-caregiver dyad will capture an additional set of ASVA videos and complete CGIC in the study app before exiting the study.

5.1.1 Baseline Visit Window

The baseline visit window may span approximately 5 weeks. Caregivers will have approximately 2 weeks to complete the baseline VABS-3. Then, participant-caregiver dyads will have approximately 3 subsequent weeks to complete the Baseline Video capture. Visit windows may be extended at the discretion of the investigator.

5.1.2 12-Week Visit

Approximately 12 weeks after the baseline VABS-3 was administered, the 12-week visit window will open and may span approximately 4 weeks. The 12-week interview will be conducted during the first 2 weeks of the window after which participant-caregiver dyads will have approximately 2 additional weeks to complete the final video capture. Visit windows may be extended at the discretion of the investigator.

The table below summarizes the data to be collected at each visit.

Data to be Collected/Assessments	**Data Captured at Remote Visits^**		
	Consent Call	**Baseline**	**12 Weeks Visit**
Contact Information (PII)	X		
Demographics & Medical History (PHI)	X		
ASVA		X*	X**

Data to be Collected/Assessments	Data Captured at Remote Visits^		
	Consent Call	Baseline	12 Weeks Visit
VABS-3		X	X
CGIC			X

*Baseline ASVA will be captured twice (test-retest) over a 3-week window.
**Participant-caregiver dyads will have approximately 2 weeks after completion of the VABS-3 to complete the video submissions for ASVA (12-week visit)
^No data is collected at the Training Call.
PII=Personal Identifiable Information; PHI=Protected Health Information; ASVA=Angelman Syndrome Video Assessment; VABS-3 = Vineland Adaptive Behavior Scales v3; CGIC = Caregiver Impression of Change

5.2 Description of Remote Visits & Assessments

5.2.1 Consent Call

Study Coordinators will conduct e-consent via phone or web-conferencing platform. After consent is obtained, the caregiver's shipping address and other contact information will be confirmed. Study coordinators will also ask the caregiver for demographics and medical history information about the participant. The participant-caregiver dyad will then be sent a study kit of supplies needed to perform the at-home assessments. Study kits will be shipped to the caregivers in accordance with Casimir Standard Operating Procedures (SOPs). The contents of the study kit will be explicitly outlined in the Caregiver Manual and approved by the IRB.

5.2.1.1 Demographics & Medical History

For each participant, name, age, and sex will be obtained. For individuals with AS, caregivers will also be asked to report the participant's age at diagnosis and to report the mutation/deletion type of the participant's diagnosis.

5.2.2 Training Call

Once participants have received their study supply kit, a Training Call (approximately 1h duration) will be conducted via telephone or web-conference platform. Participants will be helped with download, registration, and use of the smartphone/tablet application (study app), and the Study Coordinator will orient the participant to the assessment materials and study kit.

5.2.3 ASVA

Caregivers will capture videos of the participant doing activities in the home using a smartphone or tablet. All videos will be submitted via a HIPAA- and GDPR-compliant smartphone/tablet application (study app).

All activities are similar to usual behaviors for individuals with AS and NT children, like looking at a book, communicating yes or no, and walking or crawling. Activities were designed to capture the following relevant functional domains:

- Gross motor function
- Fine motor function
- Communication/Cognition
- Activities of daily living

Caregivers will be provided instructions and training for setting up, performing, and submitting the ASVA videos in an IRB-approved Video Capture Manual and through training videos that can be viewed in-app.

Depending on the functional ability of the participant, participant-caregiver dyads will capture and submit between 11 and 14 different activities. Caregivers have the option to skip any assigned activities. Videos will vary in length between 30 s to about 5 min in duration.

At baseline, participant-caregiver dyads will have 3 weeks to capture each assigned ASVA video twice (baseline and re-test). Once the first capture of a task is submitted and approved, caregivers will have the ability to collect the re-test capture of that same activity. Caregivers may collect activity videos in any order during the baseline period as long as 2 captures of each task are completed.

5.2.3.1 Video Re-shoots

Caregivers may be asked to re-record videos if Casimir study staff determine that the quality of the video is compromised.

5.2.3.2 Study Kit

A study kit will be supplied to each participating family and will contain materials intended to support the caregiver in capturing the tasks outlined in the Caregiver Manual. At the close of the study, the caregivers may keep or dispose of the study kit materials; they will not be asked to return any supplies to Casimir.

5.2.4 Vineland Adaptive Behavior Scales (VABS) 3rd Edition

Vineland Adaptive Behavior Scales (VABS-3)[8,9] is a validated tool for assessing adaptive functioning in daily living, socialization, communication, and motor skills, as well as maladaptive behaviors through a standardized questionnaire administered to caregivers. At baseline and again at the 12-week visit, trained VABS administrators will conduct the interviews with caregivers by using a secure web-conferencing platform and complete the standardized VABS form. Interviews will last approximately 1.5h and will be recorded.

5.2.5 Caregiver Impression of Change (CGIC)

Caregivers will be asked to answer 4 questions in the study app after they have completed the final video capture for the 12-week visit. Caregivers will rate their impression of change during the study for each of the 4 functional domains captured by ASVA. They will rate change using IRB-approved questions on a 5-point Likert scale ranging from 1 = much worse to 5 = much better, with 3 = no change.

5.3 Safety Reporting

Since this is a minimal risk, non-interventional study, Casimir study staff will not be actively monitoring for potential adverse events. If a study-related adverse event is reported, Casimir will report the event to the IRB in accordance with the requirements of the IRB, provide appropriate referrals for care, if applicable, and track the adverse event through its resolution.

5.4 Participant Withdrawal

If, at any time, a participant or caregiver notifies Casimir study staff of a desire to withdraw from participation in the study, Casimir study staff will coordinate any final compensation(s) due for activities completed and no additional data collection will be performed for that participant. All data collected prior to withdrawal will be retained as part of the study data unless a participant resides in a country that affords them rights under GDPR. For participants who are afforded GDPR protections, they will retain their "right to forget" and previously captured study data may be deleted upon written request by the participant or legal guardian of a minor participant.

5.5 Compensation

Participant-Caregiver dyads will be provided up to $300 USD as stipend for their time and internet expenses that may be incurred during participation. After participant-caregiver dyads complete the baseline activities, they will be provided a $200 USD gift card. After participant-caregiver dyads complete the Week 12 activities, they will be provided a $100 USD gift card.

If a participant elects to withdraw prior to completing all study activities, they will be provided the stipend for the timepoint completed up to the date of withdrawal.

5.6 Study Personnel

All study procedures described above will be performed by personnel with adequate training and experience to perform the duties to which they are assigned. Documentation of training and experience will be kept on file.

6 Data Management

6.1 Data Storage

All electronic data, including, but not limited to, participant contact information, emails, audio/video data, and scores will be stored in a secure location in accordance with applicable privacy regulations. Videos will be collected via a secure, authenticated mobile application. All videos are transmitted and encrypted using a secure web service to the mobile application database. All media files received within the platform are stored in an encrypted format. All data will be kept in a secure location until it is destroyed.

6.2 Record Retention

Data obtained from this study, including participant identity information, will be handled, processed, stored, and retained in accordance with applicable laws, regulations, and guidance. As per Casimir SOP for Record Retention (CAS-SOP-020), we will keep study-related data for at least 3 years.

6.3 Confidentiality

All ASVA videos will be filmed and submitted through a secure platform, and the application will only be accessible to the caregiver by a unique QR code. Videos submitted and recorded interviews will not be de-identified with facial blurring or voice masking.

Government staff sometimes review studies to make sure they are being conducted safely and legally. The U.S. Food and Drug Administration (FDA), other regulatory authorities, patient advocacy groups, and

the Institutional Review Board (IRB) may review participant study data that may contain identifying information.

The following research collaborators will be provided access to identifiable study data using secure and HIPAA/GDPR-compliant data sharing methods:

- Clinician Researchers at Boston Children's Hospital
- Research Collaborators who have signed a confidentiality agreement with Casimir

In the event of breach of electronic data storage for personally identifiable information (PII) or protected health information (PHI), participants and/or caregivers will be notified per Casimir SOP for Handling PHI and/or Identifiable Information (CAS-SOP-063).

7 Data Analysis

This study is intended to capture source material for the development of a scoring system for the activity videos. The videos will be qualitatively reviewed by Casimir and its collaborators to identify quantifiable aspects of behavior that can be included in the scoring system. Once the draft of the scoring system is complete, all videos will be scored using the newly developed scoring system. Subsequently, ASVA and VABS scores will be used to perform preliminary validation analyses for ASVA. The measurement properties for the ASVA scoring system are unknown until after data collection, and, as such, validation analyses cannot be specifically defined *a priori*. Generally, validation analyses will examine the relationships between ASVA domain and activity scores in relation to VABS domain and sub-scale scores. A Statistical Analysis Plan (SAP) will be created at such time as analyses can be specified.

8 Ethical Considerations

Prospective participants will be provided an informed consent form or age-appropriate assent form, as applicable, that describes the study and provides sufficient information to make an informed decision about participation. Potential participants will be given adequate time to review the participant information in the informed consent and assent forms, given the opportunity to ask questions, and understand that, if they decline to participate in the study, their future care will not change. The informed consent form must be signed by the adult participant and the assent form must be signed by the minor participant unless a waiver of consent is granted by the IRB. Participants may elect to withdraw from the study at any time without consequence.

8.1 Risks, Stress or Discomfort

Being videotaped doing activities may cause psychological distress for participants and their caregivers. Participants may experience physical stress while doing the movement activities. There are no other risks expected to occur due to participation in this study.

8.2 Benefits

Participants and their caregivers will not directly benefit from this study, but participation in the study may help to develop an outcome measure that can be used to assess changes in signs and symptoms of AS.

9 Publications & Future Use of Data

The data, information, documentation, reports, and/or other products resulting from this project are the property of Casimir. Casimir will publicly report the results of the study using de-identified data in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings or published in professional journals. Any public dissemination of the data collected as part of this study will include only de-identified data unless express written release from the participant is obtained.

Videos collected as part of this study may be used for future research to further develop and validate ASVA or to facilitate training research personnel on the use of ASVA. Videos will only be used for other research and training purposes if caregivers expressly opt-in during the consent process.

10 Financial Disclosure

This study is being funded by Ionis Pharmaceuticals, Inc.

11 References

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Protocol Signature Page

I have read and understand the below identified protocol. I agree to conduct this research study according to the protocol, including all statements regarding confidentiality, ethical conduct, protection of human subjects, informed consent, management and reporting of adverse events, and according to federal and local legal and regulatory requirements and regulations.

Study Information	
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Protocol Version:	V2.0
Site and Principal Investigator Information	
Site Name/Number:	Casimir/CAS-CAS006
Principal Investigator Name:	Mindy Leffler
Principal Investigator Signature:	
Date:	May 2, 2022

CAS-CAS006-01_ASVA SMS Protocol_v2.0

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