Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study Investigating the Efficacy, Safety, and Tolerability of JNJ-42165279 in Adolescent and Adult Subjects with Autism Spectrum Disorder

Protocol 42165279AUT2001; Phase 2a

JNJ-42165279

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	22 Jan 2021	Not Applicable	Initial release
Amendment 1	Xx Nov 2022	Fixed formatting errors Section 1.5: Clarified how QD or BID treatment groups are assigned Section 2.1: Minor edits to the analysis windows Section 2.3.2.3: Added a modified FAS-BID analysis set Section 5.2.3: Added a sensitivity analysis using the modified FAS-BID analysis set. Section 5.3.2.1: Corrections made to ABI-S item table Section 5.3.4.2: Removed frequency of change from baseline in CGI-S. Added MMRM analysis Section 5.3.5: Added MMRM analysis Section 5.3.9.1: Clarification made to SRS-2 scoring Section 5.3.10.2: Removed frequency of change from baseline in Caregiver GI-S. Added MMRM analysis Section 5.4.2.1.2: Corrections made to analysis of Daily Tracker features. Section 5.4.2.2.2: Corrections made to analysis of Mood Report features. Section 5.4.3.1.2: Corrections made to analysis of Actigraph features. Section 6.5.2: Added definition and analysis for the Aberrant Behavior Inventory-Irritability Scale Section 7: Added summary analysis for Pharmacokinetics results. Section 8:Added correlation analyses for plasma concentrations of CCI and efficacy measures.	Made the analysis plan consistent with the protocol objectives and reflect the change in dose regimen from Protocol Amendment 5.

ABBREVIATIONS

ABC	Aberrant Behavior Checklist
ABC-I	Aberrant Behavior Checklist-Irritability Subscale
ABI	Autism Behavior Inventory (Caregiver, full version)
ABI-C	Autism Behavior Inventory-Clinician interview
ABI–S	Autism Behavior Inventory-Short Form
ADOS-2	Autism Diagnostic Observation Schedule, Second edition
ASD	Autism Spectrum Disorder
AE	adverse event
AEA	N-arachidonoylethanolamine
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR[1]	autoregressive order 1
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
Caregiver GI-S	Caregiver Global Impression of Severity
CASI-Anx	Child Adolescent Symptom Inventory – Anxiety
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CI	confidence interval
CRF	case report form
CSS	Calibrated severity score
C-SSRS	Columbia Suicide Severity Rating Scale
DB	Double blind
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EEG	electroencephalogram
ERP	event-related potential
FAA	fatty acid amide
FAAH	fatty acid amide hydrolase
FACET	Facial Expression Analysis
FAS	full analysis set
F/U	Follow-up
HAI	high autism interest
IWRS	interactive web response system
JAKE	Janssen Autism Knowledge Engine
K-BIT	Kaufman Brief Intelligence Test
LAI	low autism interest
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
OEA	N-oleoylethanolamide
PEA	N-palmitoylethanolamide
PI	principal investigator
PK	pharmacokinetic(s)
RBS-R	Repetitive Behavior Scale – Revised
RRB	Repetitive/Restrictive Behavior
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
Self GI-I	Self Global Impression of Improvement
SRS-2	Social Responsiveness Scale 2
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
ULN	upper limit of normal

US	United States
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
ZBI	Zarit Burden Interview

DEFINITIONS OF TERMS

Autism Behavior Inventory	(or "ABI") - A module of My JAKE; a series of 62 questions related to the core and associated symptoms of ASD
Autism Behavior Inventory-Short	(or "ABI-S") - A shorter version of the ABI with 24 questions
Autism Behavior Inventory-Clinician	(or "ABI-C") - A14-item version of the ABI to be completed by the clinician following an interview
Continuous Biosensor(s)	A wearable wrist-based biosensor worn over extended periods of time throughout the day and during sleep
JAKE	Janssen Autism Knowledge Engine. Refers generally to the set of tools and technologies developed by Janssen Research & Development, LLC, for the purpose of tracking outcomes and enabling research of new treatments in autism spectrum disorders.
JAKE Sense	A component of the JAKE System; all biosensors (Continuous and Periodic) used by the JAKE System. JAKE Sense (and its hosted biosensors) are used solely for exploratory, proof-of-concept research.
JAKE Sense Data Pipeline	(or "JSDP") - a component of the JAKE System; the JAKE Sense Data Pipeline refers to all feature extraction methods, processes, and procedures, as well as the study data archive for maintaining traceability of all JAKE Sense datasets. Data collected and archived via the JSDP may contain limited personal identifiers. This data is available only to employees and contractors of Janssen Research & Development, and its affiliates.
My JAKE Data Pipeline	(or "JDP") - a component of the JAKE System; the My JAKE Data Pipeline refers to all feature extraction methods, processes, and procedures, as well as the study data archive for maintaining traceability of all My JAKE datasets. Data collected and archived via the JDP may contain limited personal identifiers. This data is available only to employees and contractors of Janssen Research & Development, and its affiliates.
My JAKE	A component of the JAKE System; the web and mobile based platform used by caregivers and study participants to interact with the JAKE System
JAKE System	The core elements of JAKE: My JAKE, JAKE Sense, My JAKE Data Pipeline, and JAKE Sense Data Pipeline.
JAKE Task Battery	(or "Task Battery") - A set of challenge tasks and stimuli, approximately 30 minutes in length, used in conjunction with Periodic Biosensors
Mentis	An internally-used project codename used to label activities and research studies related to JAKE
Periodic Biosensors	A set of wearable and stationary biosensors used during a discrete period of assessment at a study visit; representative devices include EEG, ECG, eye tracking, and video

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for Study 42165279AUT2001.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of JNJ-42165279 compared with placebo in the improvement of symptoms of Autism Spectrum Disorder (ASD) during 12 weeks of treatment on the following parameters:

- Autism Behavior Inventory (ABI) Core Domain Score (Social Communication and Repetitive/Restrictive Behavior [RRB]).
- ABI Social Communication Domain Score.
- ABI RRB Domain Score.

Secondary Objectives

- To assess the safety and tolerability of JNJ-42165279 compared to placebo.
- To assess the effect of JNJ-42165279 compared with placebo on the following parameters in subjects with ASD:
  - ABI Mood & Anxiety, Challenging Behavior, Self-Regulation domains.
  - Aberrant Behavior Checklist (ABC), Autism Behavior Inventory-Short Form (ABI-S), Autism Behavior Inventory-Clinician interview (ABI-C), Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I), Repetitive Behavior Scale-Revised (RBS-R), Zarit Burden Interview (ZBI), Child Adolescent Symptom Inventory-Anxiety (CASI-Anx), Social Responsiveness Scale 2 (SRS-2), Caregiver Global Impression of Severity (Caregiver GI-S), Caregiver Assessment of Treatment, and Self Global Impression of Improvement (Self GI-I) scales.
- To correlate changes in the ABI with changes in biosensors, Janssen Autism Knowledge Engine (JAKE®) components and standard scales (ABC, CGI-S, RBS-R, ZBI, CASI-Anx, and SRS-2).
- To compare the performance of the ABI with that of the ABC.
- To compare the effect of JNJ-42165279 to placebo using the JAKE Task Battery biosensor data.
- To assess the pharmacokinetics (PK) of JNJ-42165279 in subjects with ASD using a population PK approach, and explore its relationship with efficacy and safety parameters where appropriate.
- To evaluate the relationship between plasma concentrations of CCI and efficacy.

Exploratory Objectives

The exploratory objectives are:

CCI

[redacted]

1.2. Trial Design

This is a randomized, multi-center, double-blind, placebo-controlled, parallel group, outpatient study assessing the efficacy, safety, and tolerability of JNJ-42165279 during 12 weeks of treatment in adolescent and adult subjects with ASD.

Approximately 80 adolescent and adult subjects (between 13 and 35 years of age, inclusive) will be randomized in a 1:1 ratio to receive double-blind treatment of either JNJ-42165279 or placebo. The randomization will be stratified by gender and age (13 - 17 years and 18 – 35 years). Subjects enrolled prior to Protocol Amendment 5 were randomized to receive once daily dosing of placebo or 25 mg JNJ-42165279 throughout the treatment period. All other subjects will receive twice daily (BID) dosing of placebo or 25 mg JNJ-42165279 (total daily dose of 50 mg).

Study procedures include safety and efficacy evaluations and blood sample collections for pharmacogenomic assessment, pharmacokinetics, and biomarkers of treatment activity.

This study consists of a 26-day eligibility screening period, a 12-week double-blind treatment period and a follow up examination (to occur 14 days [±1 week] after last dose of study drug). The study duration for each subject will be approximately 4 months.

The study design scheme is described in Figure 1.

Figure 1: Subject-specific Trial Scheme

Abbreviations: ASD=Autism Spectrum Disorder.

Screening (Day -26 to Day -1)

Subjects will be screened within 26 days prior to Day 1 of the double-blind period to assess their eligibility for the study, according to the inclusion and exclusion criteria. Caregivers will return for a second screening visit for set up and training for the caregiver reporting tool (My JAKE/My JAKE Mobile Medical App v 1.0 [My JAKE MMApp]), and for completion of select scales.

Double-Blind Treatment Phase

Subjects who successfully complete the screening phase will visit the clinical site/unit to be randomized on Day 1 (Baseline visit) of the double-blind phase.

Subjects will visit the study site with their caregiver at 2, 4, 8, and 12 weeks after the start of treatment. Throughout the treatment period, caregivers will record information in the caregiver reporting tool and subjects will wear a continuous biosensor wristband that measures activity.

If a subject withdraws from the study before the end of the double-blind phase, an early withdrawal visit should be conducted within 1 week of the date of discontinuation, followed by the follow up phase.

Follow Up Phase

Subjects will return to the clinical site for a safety follow up visit at 14 days (±1 week) following the last dose of study drug (Day 85).

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis for this study is that JNJ-42165279 is superior to placebo in reducing the core symptoms associated with ASD as assessed by the ABI Core Domain (Social Communication and Restrictive Behavior), Social Communication Domain, or Restrictive Behavior Domain.

The study will be deemed positive if any of the primary efficacy endpoints are statistically superior to placebo using a 1-sided 0.10 significance level.

1.4. Sample Size Justification

The sample size for the study is based on all subjects who are enrolled under BID dosing. The assumption used in the determination of sample size was a treatment effect size of 0.63 for the difference between the JNJ-42165279 treatment group and placebo, calculated as the mean change in the primary endpoints from baseline to Day 85. To detect the treatment effect size of 0.63 in any of the primary endpoints with a power of 90% at an overall 1-sided significance level of 0.10, 25 subjects in each group are required. When adjusted for a drop-out rate of approximately 15% of subjects, this will require 60 subjects to be randomly assigned to treatment in a 1:1 ratio (30 per group).

The treatment difference effect size is based on results of a previous meta-analysis showing that applied behavior analysis interventions lead to medium-to-large effects in a variety of symptomatic rating scales for children with autism (Virues-Ortega 2010). Additionally, previous studies of selective serotonin reuptake inhibitors (SSRIs), antipsychotics and antiepileptic drugs were reviewed. The sample size calculation is based on simulated multivariate normal data with the additional assumption that there is a correlation of 0.75 between the ABI Social Communication and Restrictive Behavior domains and 0.90 between each of the domains and the ABI Core Domain score.

1.5. Randomization and Blinding

Randomization

Central randomization will be implemented in this study. At the start of the double-blind phase, subjects will be randomly assigned to 1 of 2 treatment groups (JNJ-42165279 or placebo) based on the computer-generated randomization schedule prepared before the study by, or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by gender (male and female) and age at time of first consent (13-17 years and 18-35 years), with an allocation ratio of 1:1 to placebo and JNJ-42165279.

The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Subjects will be assigned to either QD or BID treatment groups programmatically by comparing the randomization date to the issue date of the protocol the subject consented to at study enrollment.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject for reasons related to the subject's safety.

Data that may potentially unblind the treatment assignment (eg, study medication plasma concentrations, plasma biomarkers) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner.

Subjects who have had their treatment assignment unblinded should continue to return for required follow up evaluations.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an interim data review by the Data Monitoring Committee (DMC) is specified, the randomization codes and, if required, the translation of randomization codes into treatment and control groups will be disclosed to those authorized and only for those subjects included in the interim review.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses but they can be used for determination of clinically important end points. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the end point. Listed below (Table 1) are the visit windows and the target days for each visit defined in the protocol.

The My JAKE Daily Tracker and Mood Report, along with the JAKE Sense Continuous Biosensor, will not be windowed since these are intended to be collected on a daily or continuous basis.

Table 1: Visit Windows

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
ABI, ABC	Screening	2	Screening	<1	-21 to -1
	DB	3	Baseline	<=1	1
		5	Day 29	2 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
ABI-S	DB	4	Day 15	2 to 29	15
		--	Day 43	30 to 57	43
		--	Day 71	58 to end of DB	71
		DB final visit	End Point (DB)	2 to end of DB	
ABI-C, JAKE Sense Periodic Biosensors	DB	3	Baseline	<=1	1
		5	Day 29	2 to 57	29
		7	Day 85	58 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
CASI-Anx, RBS-R, SRS-2	Screening	2	Screening	<1	-21 to -1
	DB	3	Baseline	<=1	1
		5	Day 29	2 to 57	29
		7	Day 85	58 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
ZBI	DB	3	Baseline	<=1	1
		7	Day 85	2 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
Caregiver GI-S, CGI-S	DB	3	Baseline	<=1	1
		5	Day 29	2 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
CGI-I	DB	5	Day 29	2 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
Caregiver Assessment of Treatment, Evaluation of JAKE, Self GI-I	DB	7	Day 85	2 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
C-SSRS	Screening	1	Screening	<1	-30 to -3
	DB	3	Baseline	<=1	1
		4	Day 15	2 to 22	15
		5	Day 29	23 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)
	F/U	8	Follow-up	End of DB + 1 to end of F/U	99
ABC-I	Screening	1	Screening (1)	<1	-30 to -3
		2	Screening (2)	<1	-21 to -1
	DB	3	Baseline	<=1	1
		4	Day 15	2 to 22	15
	F/U	8	Follow-up	End of DB + 1 to end of F/U	99
Vital signs	Screening	1	Screening	<1	-30 to -3
	DB	3	Baseline	<=1	1
		4	Day 15	2 to 22	15
		5	Day 29	23 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
	F/U	8	Follow-up	End of DB + 1 to end of F/U	99
Body weight	Screening	1	Screening	<1	-30 to -3
	DB	3	Baseline	<=1	1
		5	Day 29	2 to 57	29
		7	Day 85	58 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
	F/U	8	Follow-up	End of DB + 1 to end of F/U	99
Height	DB	1	Baseline	<=1	-30 to -3
Clinical laboratory assessment	DB	1	Baseline	<=1	-30 to -3
		4	Day 15	2 to 22	15
		5	Day 29	23 to 43	29
		6	Day 57	44 to 71	57
		7	Day 85	72 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
ECG	DB	1	Baseline	<=1	-30 to -3
		7	Day 85	2 to end of DB	85
		DB final visit	End Point (DB)	2 to end of DB	
	F/U	8	Follow-up	End of DB + 1 to end of F/U	99

*Relative to Study Day 1. DB=double-blind. F/U=Follow-up

2.2. Pooling Algorithm for Analysis Centers

All subjects will be enrolled at sites in the United States (US). No pooling of sites will be carried out.

2.3. Analysis Sets

2.3.1. All Randomized Analysis Set

The all randomized analysis set includes all subjects who were randomized in the study (ie, subjects who reported a randomization date or were assigned a randomization number) regardless of whether treatment was received. This analysis set will be used for summarizing the overall study completion/withdrawal information.

2.3.2. Efficacy Analysis Set

2.3.2.1. FAS-BID Analysis Set

The full analysis set (FAS-BID) includes all randomized subjects who received at least 1 dose of study agent at the BID dose and have both a baseline and at least 1 postbaseline efficacy assessment. This analysis set will be used for all efficacy analyses.

2.3.2.2. FAS Analysis Set

The FAS analysis set includes all randomized subjects who received at least 1 dose of study agent at either dose and have both a baseline and at least 1 postbaseline efficacy assessment. This analysis set will be used for summaries of efficacy data and efficacy sensitivity analyses.

2.3.2.3. Modified FAS-BID Analysis Set

The modified FAS-BID analysis set includes subjects who meet the same criteria for the FAS-BID analysis set described above but excludes subjects who were non-compliant with study medication. Non-compliance will be determined from PK samples at the Day 85/Early Withdrawal Visit with < 1 ng/ml detected.

2.3.3. Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 dose of study agent. This analysis set will be used for all safety analyses.

2.3.4. Pharmacokinetics Analysis Set

The PK analysis set is defined as subjects who received at least 1 dose of study agent and have at least 1 valid blood sample drawn for PK analysis.

2.4. Study Reference Start and End Dates

The overall reference start date for the study is defined as the date of the first dose of study agent (the date is missing for screened subjects who did not receive a dose of study agent). The overall reference end date for the study is the end of trial date including the last follow-up visit.

2.5. Analysis Phases

There are 3 analysis phases defined in this study: Screening, Double-blind, and Posttreatment (Follow-up). Each analysis phase has its own analysis reference start date.

2.5.1. Start and End Dates of Analysis Phases

Screening

The analysis reference start date of the screening phase is the date informed consent is obtained. The analysis reference end date of the screening phase ends 1 day prior to the date of the first dose of study drug in the double-blind treatment phase. The screening phase end date is left missing for those subjects who did not receive study drug. Note, however, that for Height, Clinical

Laboratory Assessments, and ECG, the results taken at Screening will be used as the baseline, given that there is not a scheduled assessment on Day 1 (see Table 1).

Double-Blind Treatment Phase

The analysis reference start date of the double-blind phase is the date of the first study agent administration. The analysis reference end date of the double-blind phase (except for Adverse Events and Concomitant Medications) is the maximum of the date of the last visit in the double-blind phase and the date of early treatment termination. For Adverse Events and Concomitant Medications, the analysis reference end date of the double-blind phase is the date of the last dose of study drug plus 6 days. For randomized subjects who did not receive any medication in the double-blind phase, both analysis reference start and end dates are missing for the double-blind analysis phase.

Posttreatment (Follow-up) Phase

Start and end dates for the follow-up phase are only defined for subjects who continued into the follow-up phase. The start date of the follow-up phase is the day after the double-blind end date. The follow-up phase end date is the last follow-up visit date.

2.6. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

2.7. Baseline and End Point

Baseline is defined as the last observation prior to the start of the first study agent administration. Baseline is defined for each parameter/assessment.

End point is defined as the last available postbaseline result within the double-blind treatment phase and is referred to as ‘End Point (DB)’. Unscheduled visit results are included in this definition and will be considered as the end point value if the unscheduled visit result is the last postbaseline result available within the double-blind treatment phase.

2.8. Imputation Rules for Missing Adverse Event (AE) Date of Onset/Resolution

Partial AE onset dates will be imputed as follows:

- If the onset date of an AE is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start

  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an AE is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the day of the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

2.9. Imputation Rules for Determining Prior or Concomitant Medication and other ASD Therapy When Missing Dates

2.9.1. Prior Medications or other ASD Therapy

Prior medications or therapy are those taken by subjects before the start of dosing of first study agent. Medications will be classified as prior if the medication start date is complete and prior to the date of first dose of study agent or the medication end date is complete and prior to the date of first dose of study agent.

If the medication start day is missing, and the month and year of the medication start date are not missing, then if:

- The month and year of the start date of medication is earlier than the month and year of the initial study agent administration; or
- The case report form (CRF) indicates the medication was taken prior (prior medication flag=Yes) and the month and year of the start date of medication is the same as the month and year of the initial study agent administration

then the medication will be considered prior.

If the medication start month and day are missing, and the year of the medication start date is not missing, then if:

- The year of the start date of medication is earlier than the year of the initial study agent administration; or
- The CRF indicates the medication was taken prior when the year of the start date of medication is the same as the year of the initial study agent administration

then it will also be considered prior.

If the medication start date is completely missing, and the CRF indicates it was taken prior, it will also be considered prior.

2.9.2. Concomitant Medications or other ASD Therapy Taken During the Double-blind Phase

Concomitant medications taken during the double-blind phase are those that started on the same day as the first dose or after the start of dosing or those continuing from predose (prior medication flag=Yes) and the CRF indicates the medication is ongoing or the medication stop date is on or after the first dose of study agent. Medications that start on or after the date of the last dose of study agent plus 7 days are not considered concomitant medications taken during the double-blind phase, but will be included as concomitant medications taken during the follow-up phase (see Section 2.5.1).

If the medication start date is missing the day, but the medication month and year are complete, then if the month and year of the medication start date are on or prior to the month and year of the last dose of study agent plus 6 days and:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or
- The stop date of the medication is on or after the initial study agent administration, or
- The stop date month and year (day is missing) of the medication is on or after the initial study agent administration, or
- The stop date year (day and month are missing) of the medication is on or after the initial study agent administration

then the medication is classified as concomitant during the double-blind phase.

If the medication start date is missing the month and day, but the year is complete, then if the year of the start date is the same as or prior to the year of the last dose of study agent plus 6 days and:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or

- The stop date of the medication is on or after the initial study agent administration, or
- The stop date month and year (day is missing) of the medication is on or after the initial study agent administration, or
- The stop date year (day and month are missing) of the medication is on or after the initial study agent administration

then the medication is classified as concomitant during the double-blind phase.

If the medication start date is completely missing then if:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or
- The stop date of the medication is on or after the initial study agent administration, or
- The stop date month and year (day is missing) of the medication is on or after the initial study agent administration, or
- The stop date year (day and month are missing) of the medication is on or after the initial study agent administration

then the medication is classified as concomitant during the double-blind phase.

2.9.3. Concomitant Medications or other ASD Therapy Taken During the Follow-up Phase

Follow-up medications are those medications that started on or after the last dose of study agent plus 7 days, or that started prior to the last dose of study agent plus 7 days, but continue on or after the last dose of study agent plus 7 days.

If the medication start date is complete and the medication started on or after the last dose of study agent plus 7 days, then the medication is classified as concomitant during the follow-up phase.

If the medication start date is complete and the medication started prior to the last dose of study agent plus 7 days or the medication start date is a partial date (missing day or missing month and day) or the medication start date is completely missing, then if:

- The CRF indicates that the medication is ongoing, or
- The stop date of the medication is missing, or
- The stop date of the medication is on or after the last dose of study agent plus 7 days, or
- The stop date month and year (day is missing) of the medication is on or after the last dose of study agent plus 7 days, or
- The stop date year (day and month are missing) of the medication is on or after the last dose of study agent plus 7 days

then the medication is classified as concomitant during the follow-up phase.

2.10. Definition of Subgroups

Descriptive statistics will be provided for the primary efficacy endpoints by the following subgroups:

Subgroup	Definition
IQ (based on K-BIT IQ composite standard score)	• <85 • 85 to 115 • ≥116
Autism Severity (based on ABI Core Domain score)	• <0.91 • ≥0.91 to <1.44 • ≥1.44
Age Group	• 13 - 17 years • 18 - 35 years

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An internal DMC, with 1 external expert, will be established to monitor data to ensure the continuing safety of the subjects enrolled in this study. The committee will meet at least once to review interim data. After the review, the DMC will make recommendations regarding the safety and continuation of the study. The details will be provided in a separate DMC charter and DMC SAP.

4. SUBJECT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group and dose and overall. In addition, the distribution of subjects by site ID will be presented.

4.1. Demographics and Baseline Characteristics

Table 2 presents a list of the demographic variables that will be summarized by treatment group and dose and overall for the FAS analysis set.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body mass index (BMI) (kg/m^2)	
Categorical Variables	
Age (13-17 years, 18-35 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese ≥30 kg/m^2)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Since only month and year will be collected on the CRF for date of birth, age will be calculated assuming the day of the date of birth is the first day of the month (ie, day = 1). Age at the time of informed consent will be calculated out to 1 decimal place.

Table 3 presents a list of the baseline disease characteristics variables that will be summarized by treatment group and dose and overall for the FAS analysis set.

Table 3: Baseline Disease Characteristics

Continuous Variables	**Summary Type**
Kaufman Brief Intelligence Test (K-BIT) verbal standard score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
K-BIT nonverbal standard score	
K-BIT IQ composite standard score	
Autism Diagnostic Observation Schedule, Second edition (ADOS-2) total score and CSS total score	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
ASD therapy ongoing (Yes/No)	
Neurodevelopmental conditions (Yes/No)	

Listings of the demographic and baseline characteristics, as well as medical history and neurodevelopmental conditions, will be provided.

4.2. Disposition Information

Screened subjects and reason for screen failures will be summarized overall.

The number of subjects in the following disposition categories will be summarized throughout the study by treatment group and dose and overall:

- Subjects randomized
- Subjects receiving study agent
- Subjects completing the study
- Subjects who terminated study prematurely
- Reasons for termination of study

Listings of subjects will be provided for the following categories:

- Subjects who terminated study prematurely
- Subjects who were unblinded during the study period
- Subjects who were randomized yet did not receive study agent.

4.3. Treatment Compliance

Study agent compliance will be calculated as follows:

Study agent compliance (%) = 100 x number of days taking study medication at planned dose/total treatment duration (including days off study agent)

The total treatment duration will be based on the date of the last dose recorded in the CRF.

Descriptive statistics on the percent (%) compliance will be summarized by treatment group for the safety analysis set. In addition, percent compliance will be categorized as <60%, 60%-<80%, 80%-≤100%, and the number and percentage of subjects in each category will be summarized.

4.4. Extent of Exposure

Total duration of exposure (including days off study agent) is defined as (date of last dose of study agent – date of first dose of study agent) +1.

Total dose days of exposure is defined as the total number of days that study agent was administered to the subject (excluding days of study agent interruption).

Descriptive statistics (N, mean, SD, median, minimum, and maximum) for total duration of exposure (including days off study agent) and for total dose days of exposure (excluding days off study agent) will be presented by treatment group and dose for the safety analysis set.

A listing of study drug administration will be provided.

4.5. Protocol Deviations

Subjects with major protocol deviations will be summarized by category for the full analysis set.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

In addition, protocol deviations related to COVID-19 including missing visits and remote visits due to COVID will be summarized; corresponding listing will be provided.

4.6. Prior and Concomitant Medications and ASD Therapy

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue after the first dose of study agent.

Prior medications will be summarized by treatment group and standardized medication name for the safety analysis set. The proportion of subjects who receive each prior medication will be summarized as well as the proportion of subjects who receive at least one prior medication.

Summaries of concomitant medications will be presented by treatment group and standardized medication name for the safety analysis set, for those medications used during the double-blind

phase and for those used during the follow-up phase separately. Definitions for concomitant medications used during the double-blind phase and those used during the follow-up phase are provided in Section 2.9.2 and 2.9.3, respectively. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication.

A by-subject listing of all prior and concomitant medications will also be provided.

5. EFFICACY

The efficacy variables for the primary endpoint ABI, as well as the ABI- Short form and ABI-Clinician, and other standard scales used in this study are listed in Table 4.

Table 4: Efficacy Variables for ABI and Standard Scales

Efficacy Variable		Endpoint
ABI	• Change from baseline to Day 85 in the ABI Core Domain score (Social Communication and Restrictive Behavior)	Primary
	• Change from baseline to Day 85 in the ABI Social Communication Domain score	Primary
	• Change from baseline to Day 85 in the ABI Restrictive Behavior Domain score	Primary
	• Change from baseline to Day 85 in the ABI Mood & Anxiety Domain score	Secondary
	• Change from baseline to Day 85 in the ABI Challenging Behavior Domain score	Secondary
	• Change from baseline to Day 85 in the ABI Self-regulation Domain score	Secondary
	• Change from baseline to Day 85 in the ABI Reciprocity Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Non-verbal Communication Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Verbal Communication Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Resistance to Change Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Stereotypical Behavior Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Hypersensitivity Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Impulsivity Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Irritability Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Hyperactivity Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Anxiety Subdomain score	Secondary
	• Change from baseline to Day 85 in the ABI Agression Subdomain score	Secondary

Table 4: Efficacy Variables for ABI and Standard Scales

Efficacy Variable		Endpoint
ABC	• Change from baseline to Day 85 in ABC Irritability subscale score	Secondary
	• Change from baseline to Day 85 in ABC Lethargy/Social Withdrawal subscale score	Secondary
	• Change from baseline to Day 85 in ABC Stereotypic Behavior subscale score	Secondary
	• Change from baseline to Day 85 in ABC Hyperactivity/ Noncompliance subscale score	Secondary
	• Change from baseline to Day 85 in ABC Inappropriate Speech subscale score	Secondary
ABI-S	• Change from baseline to Day 85 in the ABI-S Core Domain score (Social Communication and Restrictive Behavior)	Secondary
	• Change from baseline to Day 85 in the ABI-S Social Communication Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-S Restrictive Behavior Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-S Mood & Anxiety Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-S Challenging Behavior Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-S Self-regulation Domain score	Secondary
ABI-C	• Change from baseline to Day 85 in the ABI-C Core Domain score (Social Communication and Restrictive Behavior)	Secondary
	• Change from baseline to Day 85 in the ABI-C Social Communication Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-C Restrictive Behavior Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-C Mood & Anxiety Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-C Challenging Behavior Domain score	Secondary
	• Change from baseline to Day 85 in the ABI-C Self-regulation Domain score	Secondary
CGI-S	• Change from baseline to Day 85 in CGI-S	Secondary
CGI-I	• Improvement at Day 85 in CGI-I	Secondary
RBS-R	• Change from baseline to Day 85 in the Overall score	Secondary
	• Change from baseline to Day 85 in the Stereotyped Behavior subscale score	Secondary
	• Change from baseline to Day 85 in the Self-injurious Behavior subscale score	Secondary
	• Change from baseline to Day 85 in the Compulsive Behavior subscale score,	Secondary
	• Change from baseline to Day 85 in the Ritualistic Behavior subscale score	Secondary
	• Change from baseline to Day 85 in the Sameness Behavior subscale score	Secondary

Table 4: Efficacy Variables for ABI and Standard Scales

Efficacy Variable		Endpoint
	• Change from baseline to Day 85 in the Restricted Behavior subscale score	Secondary
ZBI	• Change from baseline to Day 85 in ZBI global score	Secondary
CASI-Anx	• Change from baseline to Day 85 in CASI-Anx Symptom Severity score	Secondary
SRS-2	• Change from baseline to Day 85 in SRS-2 total score T-score	Secondary
	• Change from baseline to Day 85 in SRS-2 Social Awareness subscale T-score	Secondary
	• Change from baseline to Day 85 in SRS-2 Social Cognition subscale T-score	Secondary
	• Change from baseline to Day 85 in SRS-2 Social Communication subscale T-score	Secondary
	• Change from baseline to Day 85 in SRS-2 Social Motivation subscale T-score	Secondary
	• Change from baseline to Day 85 in SRS-2 Restricted Interests and Repetitive Behavior subscale T-score	Secondary
	• Change from baseline to Day 85 in SRS-2 Social Communication and Interaction subscale T-score	Secondary
Caregiver GI-S	• Change from baseline to Day 85 in Caregiver GI-S	Secondary
Caregiver Assessment of Treatment	• Responses to each of the questions at Day 85	Secondary
Self GI-I	• Value at Day 85 in Self GI-I	Secondary

The efficacy variables based on the JAKE System are listed in Table 5.

Table 5: Efficacy Variables Based on the JAKE System

Efficacy Variable		Endpoint
My JAKE JAKE Sense	CCI [redacted]	
	• Various features from the Periodic Biosensors (see Section 5.4.3.2)	Secondary

5.1. Analysis Specifications

5.1.1. Level of Significance

The primary efficacy endpoints will be evaluated at a 1-sided significance level of 0.10 based on the mixed effects model for repeated measures (MMRM) analysis. For all other analyses of the primary efficacy endpoints and for all other efficacy endpoints, nominal 1-sided p-values will be

presented, for signal finding purposes. Two-sided 80% confidence intervals will be presented. No adjustments for multiplicity will be made.

5.1.2. Data Handling Rules

Imputation of missing individual item scores will apply to each of the standard scales according to the methods described in their manuals.

5.2. Primary Efficacy Endpoints

5.2.1. Definition

The primary efficacy endpoints are the changes from baseline to Day 85 in the ABI Core Domain score, ABI Social Communication Domain score, and ABI Restrictive Behavior Domain score. The ABI is a series of 62 questions related to the core and associated symptoms of ASD and is completed by the caregiver at screening, baseline, Day 29, Day 57, and Day 85. It has 5 domains: Social Communication, Restrictive Behavior, Mood & Anxiety, Self-regulation, and Challenging Behavior. Questions are answered on 1 of 2 possible dimensions, quality (how well a person carries out a particular behavior) or frequency (how often a particular behavior occurs). The response options for items rated on the Quality dimension include: “Not at all”, “With support”, “With some reminders”, and “Without help”, along with an option of “I don’t know.” The response options for items rated on the Frequency dimension include: “Never”, “Sometimes”, “Often”, and “Very often”, along with an option of “I don’t know.”

For the ABI, the following dimensions are used:

- Items 1-13 are assessed using Quality dimension
- Items 14-62 are assessed using the Frequency dimension

The steps below outline the steps needed to calculate the ABI domain and subdomain scores.

Score Individual Items

The individual items in the ABI should be scored based on the following algorithm.

For items assessed on the Quality dimension, scores are given as follows:

Not at all = 3
With support = 2
With some reminders = 1
Without help = 0

For all items assessed on the Frequency dimension, with the exception of ABI items 14, 15, 16, 17, and 18, scores are given as follows:

Never = 0
Sometimes = 1
Often = 2

Very often = 3

For ABI items 14, 15, 16, 17, and 18, scores are given as follows:

Never = 3
Sometimes = 2
Often = 1
Very often = 0

Calculate ABI Domain Scores

The items from the ABI that are included in each domain and subdomain for the ABI are shown in Table 6. In addition, an ABI Core Domain score is created from the items in the ABI Social Communication and ABI Restrictive Behavior Domains. In order to calculate a score for a given domain or subdomain, at least 50% of items must be non-missing and not "I don't know". The domain and subdomain scores are calculated as the average of the non-missing items (ie, sum of all non-missing items divided by the number of non-missing items). If more than 50% of items for a given domain or subdomain are missing or "I don't know", then no score for that domain or subdomain is calculated.

For all domains and subdomains, scores range from 0 to 3 with higher scores indicating more severe symptoms of ASD. Negative changes in ABI domain and subdomain scores indicate improvement.

CCI

CCI

[redacted]

CCI

[redacted]

5.2.2. Estimand

The primary estimands, the main clinical quantities of interest to be estimated in the study, are defined by the following 5 components:

Treatment:

- Experimental: JNJ-42165279 dose of 50mg
- Control: Placebo

Population: subjects with a diagnosis of ASD, as defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population;

Variable: changes from baseline to Day 85 in the ABI Core Domain score, ABI Social Communication Domain score, and ABI Restrictive Behavior Domain score had all subjects remained on randomized treatment;

Intercurrent event: captured through the variable definition;

Population-level Summary Measure: the difference in variable least squares (LS) means between placebo and JNJ-42165279.

The primary analysis will be based on the FAS-BID analysis set and the ABI scores collected during the double-blind phase.

5.2.3. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for the ABI Core Domain score, ABI Social Communication Domain score, and ABI Restrictive Behavior Domain score by treatment group and dose.

Each of the primary efficacy endpoints (changes from baseline to Day 85 in the ABI Core Domain score, ABI Social Communication Domain score, and ABI Restrictive Behavior Domain score) will be analyzed using an MMRM, with time (scheduled Day), treatment (placebo, JNJ-42165279), time-by-treatment interaction, age group as randomized (13-17 years, 18-35 years), and gender (male, female) as factors, and baseline score as a continuous covariate. An unstructured variance-covariance matrix will be used. In case of convergence problems, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and autoregressive order 1 (AR[1]) with separate subject random effect. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. The treatment effects will be estimated using LS means. A point estimate and 80% confidence interval for the treatment difference, along with the associated p-value will be provided.

The MMRM, as described above, will also be used to analyze all other post baseline time points for the ABI Core Domain score, ABI Social Communication Domain score, and ABI Restrictive Behavior Domain score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Descriptive statistics of the actual values and changes from baseline at each scheduled time point and end point will be presented for the other ABI domain scores (ABI Mood & Anxiety, ABI Self-regulation, and ABI Challenging Behavior) and the ABI subdomain scores by treatment group and dose. The other ABI domain scores (ABI Mood & Anxiety, ABI Self-regulation, and ABI Challenging Behavior) will be analyzed using the MMRM as described above. Point estimates

and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the ABI domain scores.

ANCOVA

To assess the sensitivity of the results of the MMRM analysis of the primary endpoints, an analysis of covariance (ANCOVA) model for the change from baseline to end point in ABI Core Domain score, ABI Social Communication Domain score, and ABI Restrictive Behavior Domain score will be carried out. The ANCOVA model will include factors for treatment (placebo, JNJ-42165279), age group as randomized (13-17 years, 18-35 years), and gender (male, female) as factors, and baseline score as a continuous covariate. In addition, the same ANCOVA model will also be performed on observed case data at Day 85. The estimates of treatment differences based on the LS means and 80% CIs will be provided for each model, along with the 1-sided p-values.

Sensitivity

To take into consideration all subjects enrolled prior to the dose regimen change from once daily to BID, the MMRM analyses described above will also be conducted for the full analysis set for the ABI Domain Scores.

In addition, the MMRM analyses described above will be conducted for the modified FAS-BID analysis set for all 6 ABI Domain Scores.

5.3. Secondary Endpoints

5.3.1. Aberrant Behavior Checklist (ABC)

5.3.1.1. Definition

The ABC is a 58-item behavior rating scale used to measure behavior problems across 5 subscales: Irritability, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance, and Inappropriate Speech. Items are rated on a 4-point Likert scale (ranging from 0 [not at all a problem] to 3 [the problem is severe in degree]), with higher scores indicating more severe problems.

The items related to each subscale are given below.

Irritability items: 2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57

Lethargy/Social Withdrawal items: 3, 5, 12, 16, 20, 23, 26, 30, 32, 37, 40, 42, 43, 53, 55, 58

Stereotypic Behavior items: 6, 11, 17, 27, 35, 45, 49

Hyperactivity/Noncompliance items: 1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 51, 54, 56

Inappropriate Speech items: 9, 22, 33, 46

To score the ABC, the individual items for each subscale are simply summed to their respective totals. Thus, the scale renders five subscale scores. The Irritability subscale score ranges from 0 to 45; the Lethargy/Social Withdrawal subscale score ranges from 0 to 48; the Stereotypic Behavior subscale score ranges from 0 to 21; the Hyperactivity/Noncompliance subscale score ranges from 0 to 48; and the Inappropriate Speech subscale score ranges from 0 to 12. The use of a total of the five subscales is inappropriate and should not be considered.

The recommended maximum amount of missing data that can be tolerated varies by subscale. The upper limits (ie, number of missing items tolerated for each subscale before discarding the data for the subscale) are as follows: Irritability (15-item scale): 3 items, Lethargy/Social Withdrawal (16-item scale): 3 items, Stereotypic Behavior (7-item scale): 2 items, Hyperactivity/Noncompliance (16-item scale): 3 items, and Inappropriate Speech (4-item scale): 1 item. If more items than the stated upper limit are missing for a subscale, the subscale score will not be calculated.

If the amount of missing data is within the upper limits described above, the subscale score will be prorated as follows: (a) Take the total number of items on the subscale and divide this be the number of completed items. (b) Multiply that number by the total score for that subscale. (c) This becomes the new total score for this subscale for the given subject.

For all ABC subscales, higher scores indicate more severe problems. Negative changes in ABC subscale scores indicate improvement.

5.3.1.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for each of the 5 ABC subscales by treatment group and dose.

The change from baseline to Days 15 (Irritability subscale only), 29, 57, and 85 in each of the 5 ABC subscale scores will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective baseline ABC subscale score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the ABC subscale scores.

5.3.2. Autism Behavior Inventory-Short Form (ABI-S)

5.3.2.1. Definition

The ABI-S is a shorter version of the ABI with 24 questions that is completed by the caregiver on Week 2, Week 6, and Week 10. The baseline ABI-S score will be calculated from the full version of the ABI completed at Day 1.

Each item is assessed on 1 of 2 dimensions that target the quality or frequency of the given behavior as described in 5.2.1.

For the ABI-S (and the corresponding items from the ABI), the following dimensions are used:

- Items 1-3 are assessed using Quality dimension
- Items 4-24 are assessed using the Frequency dimension

The steps below outline the steps needed to calculate the ABI-S domain scores.

Score Individual Items

The individual items in the ABI-S should be scored based on the following algorithm.

For items assessed on the Quality dimension, scores are given as follows:

Not at all = 3
With support = 2
With some reminders = 1
Without help = 0

For all items assessed on the Frequency dimension, with the exception of ABI-S items 4 and 5 (corresponding ABI items 17 and 18), scores are given as follows:

Never = 0
Sometimes = 1
Often = 2
Very often = 3

For ABI-S items 4 and 5 (corresponding ABI items 17 and 18), scores are given as follows:

Never = 3
Sometimes = 2
Often = 1
Very often = 0

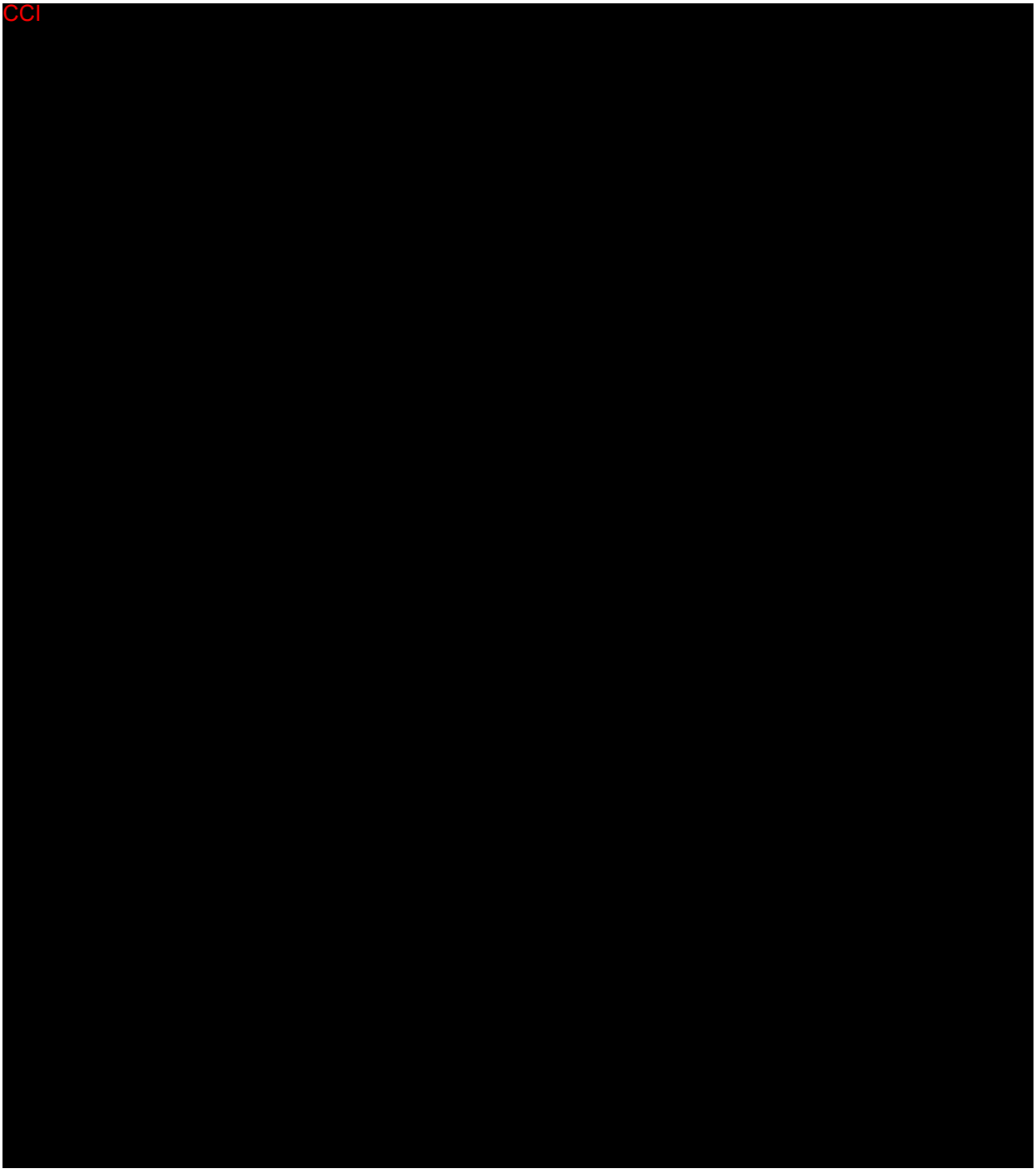
Calculate ABI-S Domain Scores

The items from the ABI-S and the ABI that are included in each domain for the ABI-S are shown in Table 7. In addition, an ABI-S Core Domain score is created from the items in the Social

Communication and Restrictive Behavior Domains. In order to calculate a score for a given domain, at least 50% of items must be non-missing and not "I don't know". The domain score is calculated as the average of the non-missing items (ie, sum of all non-missing items divided by the number of non-missing items). If more than 50% of items for a given domain are missing or "I don't know", then no score for that domain is calculated.

For all domains and subdomains, scores range from 0 to 3 with higher scores indicating more severe symptoms of ASD. Negative changes in ABI-S domain and subdomain scores indicate improvement

CCI



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[redacted]

5.3.2.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for each of the 5 ABI-S domains by treatment group and dose.

The change from baseline to Days 15, 43 and 71 in each of the 5 ABI-S domain scores will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective baseline ABI-S domain score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the ABI-S domain scores.

5.3.3. Autism Behavior Inventory-Clinician interview (ABI-C)

5.3.3.1. Definition

The ABI-C covers the domains of the ABI and is intended for completion by the clinician following an interview with the caregiver and observation or interview with the individual with ASD, as appropriate. The clinician is required to rate the severity of behaviors or level of impairment observed or described on a scale of 1 to 7, where 1 indicates no impairment of behavior and 7 indicates very severe difficulties with an area of functioning. There are 14 items across the 5 domains of Social Communication, Restrictive Behavior, Mood & Anxiety, Self-regulation and Challenging Behavior.

The items from the ABI-C that are included in each domain are shown in Table 8. In addition, an ABI-C Core Domain score is created from the items in the ABI-C Social Communication and Restrictive Behavior Domains. In order to calculate a score for a given domain, at least 50% of items must be non-missing. The domain score is calculated as the average of the non-missing items (ie, sum of all non-missing items divided by the number of non-missing items). If more than 50% of items for a given domain are missing, then no score for that domain is calculated.

For all domains, scores range from 0 to 7 with higher scores indicating more severe symptoms of ASD. Negative changes in ABI-C domain and subdomain scores indicate improvement

Table 8: ABI-C Domains	
Domain	**ABI-C Items**
Social Communication (3 items; 2 items must be non-missing to calculate)	1. Social attention 2. Turn taking in social interaction 3. Non-verbal communication
Restrictive Behavior (5 items; 3 items must be non-missing to calculate)	4. Resistance to change 5. Restricted interests 6. Stereotypical behaviors 7. Self-harm 8. Hypersensitivity
Mood & Anxiety (2 items; 1 item must be non-missing to calculate)	9. Anxiety 10. Sleep
Self-regulation (2 items; 1 item must be non-missing to calculate)	11. Impulsivity 12. Hyperactivity
Challenging Behavior (2 items; 1 item must be non-missing to calculate)	13. Aggression 14. Temper tantrums
Core Domain (includes all items from the Social Communication and Restrictive Behavior Domains; 8 items; 4 items must be non-missing to calculate)	1, 2, 3, 4, 5, 6, 7, 8 (ie, items 1-8)

5.3.3.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for each of the 5 ABI-C domains by treatment group and dose.

The change from baseline to Days 29 and 85 in each of the 5 ABI-C domain scores will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective baseline ABI-C domain score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the ABI-C domain scores.

5.3.4. Clinical Global Impression–Severity (CGI-S)

5.3.4.1. Definition

The CGI-S scale assesses the severity of all illness. The CGI-S is a 7-point scale that requires the clinician to assess the severity of the subject's illness from 1 to 7, with higher scores indicating more severe illness.

5.3.4.2. Analysis Methods

A frequency distribution of the CGI-S score at baseline, Day 29, Day 57, and Day 85 will be provided by treatment group and dose. In addition, descriptive statistics (N, median, minimum, and maximum) of the actual values and the change from baseline will be presented by treatment group and dose for observed case data. Hodges-Lehmann estimates and the corresponding 80% CI for the treatment differences in the FAS-BID analysis set will be provided for each time point.

In addition, the change from baseline in CGI-S score at each postbaseline timepoint will be analyzed using an MMRM model with baseline CGI-S score as a covariate.

Frequency distributions of the CGI-S score will be presented graphically using stacked bar charts for each time point.

5.3.5. Clinical Global Impression – Improvement (CGI-I)

5.3.5.1. Definition

The CGI-I is a 7-point scale to measure improvement in illness [(1=very much improved, 2=much improved, 3=minimally improved, 4=no change from baseline, 5=minimally worse, 6=much worse, 7=very much worse)].

5.3.5.2. Analysis

Descriptive statistics of the actual values will be presented by treatment group and dose for observed case data.

A frequency distribution of the CGI-I score at Day 29, Day 57, and Day 85 will be provided by treatment group and dose. In addition, descriptive statistics (N, median, minimum, and maximum) of the actual values will be presented by treatment group and dose for observed case data. Hodges-Lehmann estimates and the corresponding 80% CI for the treatment differences in the FAS-BID analysis set will be provided for each time point.

In addition, the CGI-I score at each postbaseline timepoint will be analyzed using an MMRM model with baseline CGI-S score as a covariate.

Frequency distributions of the CGI-I score will be presented graphically using stacked bar charts for each time point.

5.3.6. Repetitive Behavior Scale – Revised (RBS-R)

5.3.6.1. Definition

The RBS-R is a 43-item report scale to indicate occurrence of repetitive behaviors and degree to which a behavior is a problem on a range between 0 (behavior does not occur) and 3 (behavior is a severe problem). There are 6 subscale scores: Stereotyped Behavior, Self-injurious Behavior, Compulsive Behavior, Ritualistic Behavior, Sameness Behavior, and Restricted Behavior.

The items related to each subscale are given below.

Stereotyped Behavior: items 1 to 6

Self-injurious Behavior: items 7 through 14

Compulsive Behavior: items 15 through 22

Ritualistic Behavior: items 23 through 28

Sameness Behavior: items 29 through 39

Restricted Behavior: items 40 through 43

To score the RBS-R, the individual items for each subscale are summed to their respective totals. Thus, the scale renders six subscale scores. If 2 or more items are missing within a subscale, no imputation will be performed, and the score will be left missing. Otherwise, the score will be calculated as the sum of the non-missing items multiplied by the ratio of the maximum number of items (i.e., 6 for Stereotyped Behavior) to the number of non-missing items.

The Stereotyped Behavior subscale score ranges from 0 to 18; the Self-injurious Behavior subscale score ranges from 0 to 24; the Compulsive Behavior subscale score ranges from 0 to 24; the Ritualistic Behavior subscale score ranges from 0 to 18; the Sameness Behavior subscale score ranges from 0 to 33; and the Restricted Behavior subscale score ranges from 0 to 12. An overall score is also calculated as the sum of all 43 items and ranges from 0 to 129.

For all subscales, as well as the overall score, higher scores indicate more severe problems. Negative changes in subscale and overall scores indicate improvement.

5.3.6.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for each of the 6 RBS-R subscales and the overall score by treatment group and dose.

The change from baseline to Days 29 and 85 in each of the 6 RBS-R subscale scores and the overall score will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective baseline RBS-R subscale or overall score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the RBS-R subscale and overall scores.

5.3.7. Zarit Burden Interview (ZBI)

5.3.7.1. Definition

The ZBI - short version is a scale of 22 items designed to assess the psychological burden experienced by a caregiver. Items ask how the caregiver feels and responses range from 0 (never) to 4 (nearly always). The ZBI global score is the sum of all item scores and can range from 0 to 88, with a higher score representing a higher burden. A negative change in the ZBI global score indicates improvement.

If at least 16 items have been completed, a prorated score will be calculated as follows:

- Sum the items that were answered.
- Divide the sum by the number of items that were answered to yield the mean (average) response per item.
- Multiply the mean response per item by 22 (the total items in the scale).

The ZBI global score will also be categorized into the following burden categories: Little or no burden (0-20), Mild to moderate burden (21-40), Moderate to severe burden (41-60), Severe burden (61-88).

5.3.7.2. Analysis Methods

Descriptive statistics of the actual values at baseline and Day 85 and the change from baseline to Days 85 will be presented for the ZBI global score by treatment group and dose.

The change in ZBI global score from baseline to Day 85 will be analyzed using an ANCOVA model. The ANCOVA model will include factors for treatment (placebo, JNJ-42165279), age group as randomized (13-17 years, 18-35 years), and gender (male, female) as factors, and baseline score as a continuous covariate. The estimate of treatment difference based on the LS means and 80% CIs will be provided, along with the 1-sided p-value.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for the ZBI global score.

A frequency distribution of the ZBI burden categories at baseline and Day 85 will be provided by treatment group and dose.

5.3.8. Child Adolescent Symptom Inventory – Anxiety (CASI-Anx)

5.3.8.1. Definition

The CASI assesses symptoms of the following disorders: attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, generalized anxiety disorder, social phobia, separation anxiety disorder, disruptive mood dysregulation disorder, major depressive episode,

manic episode, dysthymic disorder, schizophrenia, autistic/Asperger's disorder, anorexia, and bulimia.

This study will use a 21-item anxiety scale (CASI-Anx) and responses range from 0 (never) to 3 (very often), with higher scores indicating more severe anxiety.

The Symptom Severity score is the sum of the response values for each item. If 2 or more items are missing, no imputation will be performed, and the score will be left missing. Otherwise, the score will be calculated as sum of the non-missing items multiplied by the ratio of the maximum number of items (i.e., 21) to the number of non-missing items.

The Symptom Severity score ranges from 0 to 63, with higher scores indicating more severe anxiety. Negative changes in Symptom Severity scores indicate improvement.

5.3.8.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for the CASI-Anx Symptom Severity score by treatment group and dose.

The change from baseline to Days 29 and 85 in the CASI-Anx Symptom Severity score will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the baseline CASI-Anx Symptom Severity score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time the CASI-Anx Symptom Severity score.

5.3.9. Social Responsiveness Scale 2 (SRS-2)

5.3.9.1. Definition

The SRS-2 is a 65-item scale that distinguishes autism spectrum conditions from other child psychiatric conditions by identifying the presence and extent of autistic social impairment. The SRS-2 comes in 3 versions- for preschool, school age, and adult. The principal investigator (PI) will choose whether the school age or adult version is most appropriate for each subject in this study using the instructions in the SRS-2 manuals.

General scoring instructions for the scale are below. The specific algorithm for each version of the form is given in Attachment 1.

Each of the 65 items has 4 possible responses: "Not True", "Sometimes True", "Often True", and "Almost Always True". The scoring value for each item is 0 to 3 based on the appropriate Scoring Worksheet. If a response to an item is missing, then the pre-defined median value for the item (0 or 1) is imputed. The SRS-2 will not be scored if 7 or more item responses are missing.

The total raw score is the sum of the item response values. Tables for each form are provided to convert the total raw score to a standardized T-score. For the School-Age Form, the conversion depends on the gender of the individual and whether the rater was a parent or teacher. In this study, it will always be the parent (caregiver) as the rater. The T-score can be categorized into one of four severity ranges to help interpret the results (Within normal limits, Mild, Moderate, Severe).

The SRS-2 also has 5 subscales: Social Awareness (Awr), Social Cognition (Cog), Social Communication (Com), Social Motivation (Mot), and Restricted Interests and Repetitive Behavior (RRB). The raw score for each subscale is obtained by adding the response values from the Scoring Worksheet for the items associated with the subscale. The sum of the subscales excluding the RRB raw score creates the Social Communication and Interaction (SCI) raw score. The raw scores for each subscale can be converted to a T-score using the appropriate table for the form.

All analyses of the SRS-2 will use the derived T-scores. For each of the subscale T-scores and the total score T-score, higher scores indicate more severe symptoms. Negative changes in T-scores indicate improvement.

5.3.9.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for each of the SRS-2 subscale T-scores and the total score T-score by treatment group. In addition, a frequency distribution of the SRS-2 total score severity category at each scheduled time point and end point will be provided by treatment group and dose.

The change from baseline to Days 29 and 85 in each of the subscale T-scores and the total score T-score will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective baseline SRS-2 subscale or total T-score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the SRS-2 subscale T-scores and the total score T-score.

5.3.10. Caregiver Global Impression of Severity (Caregiver GI-S)

5.3.10.1. Definition

The Caregiver GI-S is a single-item instrument that asks caregivers to rate their overall impression of the severity of their child's ASD symptoms. The scale ranges from 1 (none) to 7 (severe), with higher scores indicating more severe symptoms.

5.3.10.2. Analysis Methods

A frequency distribution of the Caregiver GI-S score at baseline, Day 29, Day 57, and Day 85 will be provided by treatment group and dose. In addition, descriptive statistics (N, median, minimum, and maximum) of the actual values and the change from baseline will be presented by treatment

group and dose for observed case data. Hodges-Lehmann estimates and the corresponding 80% CI for the treatment differences will be provided for each time point.

In addition, the change from baseline of the Caregiver GI-S score at each postbaseline timepoint will be analyzed using an MMRM model with baseline Caregiver GI-S score as a covariate.

Frequency distributions of the Caregiver GI-S score will be presented graphically using stacked bar charts for each time point.

5.3.11. Caregiver Assessment of Treatment

5.3.11.1. Definition

The Caregiver Assessment of Treatment is a 3-item questionnaire completed at the end of the treatment period.

- The first question asks caregivers to rate their overall impression of improvement in their child's autism since starting the study medication, with 7 response options ranging from 1 "Very much improved" to 7 "Very much worse" with higher scores indicating worsening of symptoms.

- The second question asks caregivers whether there was improvement in 9 specific symptoms, with responses options of "Yes" or "No".

- The third question asks caregivers their interest in having their child continue the study medication. There are 5 response options ranging from "Not at all interested" to "Extremely interested".

5.3.11.2. Analysis Methods

Frequency distributions of the responses for each of the questions will be provided by treatment group and dose. In addition, descriptive statistics (N, median, minimum, and maximum) of the actual values of question 1 will be presented by treatment group and dose for observed case data. Hodges-Lehmann estimates and the corresponding 80% CI for the treatment differences in the FAS-BID analysis set will be provided

5.3.12. Self Global Impression of Improvement (Self GI-I)

5.3.12.1. Definition

At the end of the treatment period, the subject will be asked to give his/her impression of overall improvement in ASD symptoms using a single-item instrument, the Self GI-I. The scale ranges from 1 (very much better) to 7 (very much worse), with higher scores indicating worsening of symptoms.

5.3.12.2. Analysis Methods

A frequency distribution of the Self GI-I score will be provided by treatment group and dose. In addition, descriptive statistics (N, median, minimum, and maximum) of the actual values will be

presented by treatment group and dose for observed case data. Hodges-Lehmann estimates and the corresponding 80% CI for the treatment differences in the FAS-BID analysis set will be provided.

5.4. Janssen Autism Knowledge Engine (JAKE)

The primary and secondary endpoints for this study are derived from caregiver or clinician-reported measures.

In addition to standard outcome measures, this study utilizes JAKE to collect daily caregiver reports and continuous and periodic biosensor measures, which may be useful as clinical endpoints. Key representative features from the daily caregiver reports and the biosensors were selected for the CSR to examine treatment differences. The selection was based on reported findings in the literature and/or performance in previous non-interventional studies which have utilized JAKE.

An addendum to the CSR, the Exploratory Biosensor Study Report, will contain both the key representative features and the larger set of features. This report will include the relationship of these features to other endpoints, in addition to analyses of the change over time and between treatment groups, with the purpose of developing a set of biosensor features and report measures which are sensitive to change.

In this SAP, only the analyses of the key representative features that will be included in the CSR are described.

5.4.1. Evaluation of JAKE

5.4.1.1. Definition

At the end of the treatment period, caregivers will provide feedback on their experience with the JAKE system using a questionnaire. This is not a part of the evaluation of treatment, but may provide useful feedback for future use of the JAKE system.

- The question “How interested would you be in continuing to use the MY JAKE system?” has 5 response options ranging from “Not at all interested” to “Extremely interested”.

- The question “How easy or difficult was it to complete the following parts of My JAKE during the study?” has 5 response options ranging from “Very difficult” to “Very easy” for 4 JAKE components Daily Tracker, Mood Report, ABI, ABI-S

There are additional questions asking for free-form text responses which will not be analyzed.

5.4.1.2. Analysis

Frequency distributions of the responses for each of the questions will be provided.

5.4.2. My JAKE

My JAKE encompasses various modules for use by clinicians, caregivers and the sponsor.

5.4.2.1. Daily Tracker

Each day caregivers are asked to report on sleep quality in the morning and 'overall type of day' after 6 pm using an 8-point scale, ranging from 0 ('troubling') to 7 ('encouraging').

In addition, the caregivers are required to select 3 items to track on a daily basis. These items are chosen from a subset of items presented, based on the caregiver's response in the ABI. Following completion of the ABI at the screening visit, a clinician at the site will discuss possible items to track with the parents and help them with their selection. Parents will have opportunity to change the behaviors they track at the baseline visit. After this point they are required to track the same behaviors for the duration of the study. After 6 pm each day, caregivers are required to report on these behaviors, using an 8-point scale, ranging from 0 ('troubling') to 7 ('encouraging').

For analysis purposes, only data from primary caregivers will be used.

5.4.2.1.1. Definition

The key representative features chosen to evaluate the daily tracker are given in Table 9:

Table 9: Key Representative Daily Tracker Features

Task	Feature	Direction that Indicates Improvement (or two.sided if no hypothesis)	Derived in Analysis Datasets?
Daily Tracker	DAILY TRACKER | SLEEP TODAY	increase	
	DAILY TRACKER | TYPE OF DAY TODAY	increase	
	DAILY TRACKER | AVERAGE SLEEP RATING	increase	Yes
	DAILY TRACKER | AVERAGE TYPE OF DAY	increase	Yes

For both the sleep quality and type of day, the actual daily values over time will be used in the analyses (ie, the features of "Sleep Today" and "Type of Day Today"). In addition, the daily values for the seven days following the baseline visit, the seven days prior to the Day 29 visit, the seven days prior to the Day 57 visit, and the seven days prior to the Day 85 visit will be averaged (ie, "Average Sleep Rating" and "Average Type of Day"). A minimum of three valid daily values are required to compute the given weekly average for each feature.

If a subject reports more than one response in a day, the last assessment will be used.

5.4.2.1.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline of the daily values over time will be presented by treatment group and dose for "Sleep Today" and "Type of Day Today". Descriptive statistics of the average values at baseline, Day 29, Day 57, and Day 85 and the change from the baseline average to the average values at Days 29, 57, and 85 will also be presented by treatment group and dose for "Average Sleep Rating" and "Average Type of Day".

For "Average Sleep Rating" and "Average Type of Day ", the change from average baseline to each average postbaseline time point will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective average baseline rating. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the averaged values over time for "Average Sleep Rating" and "Average Type of Day".

5.4.2.2. Mood Report

The 'mood' report allows the caregiver an opportunity to report the subject's state, in terms of valence (mood) and arousal (activity) levels. This can be completed at any time through the event tracker. In addition, it is presented following the daily tracker completion in the evening, once for overall mood and once for most extreme mood, requiring parents to report: 1) subject's overall mood for that day and 2) subject's most extreme mood for that day. For all analyses, only the values from the mood report (not values from the event tracker) will be used. Valence and arousal levels range from -1 to +1.

For analysis purposes, only data from primary caregivers will be used.

5.4.2.2.1. Definition

The key representative features chosen to evaluate the mood report are given in Table 10:

Table 10: Key Representative Mood Report Features

Task	Feature	Direction that Indicates Improvement (or two.sided if no hypothesis)	Derived in Analysis Datasets?
Mood Report	MOOD REPORT | OVERALL MOOD | VALENCE	increase	
	MOOD REPORT | OVERALL MOOD | AVERAGE VALENCE	increase	Yes
	MOOD REPORT | OVERALL MOOD | AVERAGE POSITIVE VALENCE %	increase	Yes

For the "Overall Mood \| Valence" feature, the actual daily values over time will be used in the analyses. Since the daily percent positive valence will be either 0% or 100% for each subject, this feature will not be analyzed using the daily values.

The daily values for the seven days following the baseline visit, the seven days prior to the Day 29 visit, the seven days prior to the Day 57 visit, and the seven days prior to the Day 85 visit will be averaged to compare the mood report features (ie, the features of "Overall Mood \| Average Valence" and "Overall Mood \| Average Positive Valence %") to the standard scales performed at the clinic visits. A minimum of three valid daily values are required to compute the given weekly average for each feature.

If a subject reports more than one response in a day, the last assessment will be used.

5.4.2.2.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline of the daily values over time will be presented by treatment group and dose for the "Overall Mood | Valence" feature. Descriptive statistics of the average values at baseline, Day 29, Day 57, and Day 85 and the change from the baseline average to the average values at Days 29, 57, and 85 will be presented by treatment group and dose for "Overall Mood | Average Valence" and "Overall Mood | Average Positive Valence %".

For the "Overall Mood | Average Valence" and "Overall Mood | Average Positive Valence %" features, the change from baseline to each average postbaseline time point will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to average baseline feature. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the averaged values over time for "Overall Mood | Average Valence" and "Overall Mood | Average Positive Valence %".

5.4.3. JAKE Sense

5.4.3.1. Continuous Biosensor

The Continuous Biosensor is the ActiGraph GT9X Link Wristband. The ActiGraph Link is a wireless wristband biosensor that measures activity. This sensor should be worn continuously except when necessary to remove it for charging or other reasons.

5.4.3.1.1. Definition

The key representative features chosen to evaluate the continuous biosensor are given in Table 11:

Table 11: Key Representative Daily Tracker Features

Task	Feature	Direction that Indicates Improvement (or two.sided if no hypothesis)	Derived in Analysis Datasets?
ActiGraph Link	ACC | ADJUSTED SLEEP | ALL DAYS	increase	Yes
	ACC | AVERAGE ADJUSTED SLEEP | ALL DAYS | 7 DAYS	increase	Yes
	ACC | SD ADJUSTED SLEEP | ALL DAYS | 7 DAYS	decrease	Yes
	ACC | NUMBER AWAKENINGS | ALL DAYS	decrease	
	ACC | AVERAGE NUMBER AWAKENINGS | ALL DAYS | 7 DAYS	decrease	Yes
	ACC | SD NUMBER AWAKENINGS | ALL DAYS | 7 DAYS	decrease	Yes

Adjusted sleep duration is calculated by subtracting the recommended sleep duration for the age group from actual sleep duration as measured by the actigraph 'average sleep' extracted feature. The recommended sleep duration by age group is listed below:

Age Group (years)	Recommended Sleep
6-13	600 min (10 hours)
14-17	540 min (9 hours)
18+	480 min (8 hours)

For both adjusted sleep and number awakenings, the actual nightly values over time will be used in the analyses (ie, the features of "Adjusted Sleep | All Days" and "Number Awakenings | All Days"). In addition, the nightly values for the seven nights following the baseline visit, the seven nights prior to the Day 29 visit, the seven nights prior to the Day 57 visit, and the seven nights prior to the Day 85 visit will be averaged to compare the continuous biosensor features that are averages (ie, the features of "Average Adjusted Sleep | All Days | 7 Days" and "Average Number Awakenings | All Days | 7 Days") to the standard scales performed at the clinic visits. The corresponding SD of these 7-nightly averages for each subject will be computed for the features of "SD Adjusted Sleep | All Days | 7 Days" and "SD Number Awakenings | All Days | 7 Days". A minimum of three valid nightly values are required to compute the given weekly average for each feature.

5.4.3.1.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline of the nightly values over time will be presented by treatment group and dose for "Adjusted Sleep | All Days" and "Number Awakenings | All Days".

Descriptive statistics of the average values at baseline, Day 29, Day 57, and Day 85 and the change from the baseline average to the average values at Days 29, 57, and 85 will also be presented by treatment group and dose for "Average Adjusted Sleep | All Days | 7 Days" and "Average Number Awakenings | All Days | 7 Days".

Likewise, descriptive statistics of the values at baseline, Day 29, Day 57, and Day 85 and the change from baseline to Day 29, Day 57, and Day 85 will be presented by treatment group and dose for "SD Adjusted Sleep | All Days | 7 Days" and "SD Number Awakenings | All Days | 7 Days".

For "Average Adjusted Sleep | All Days | 7 Days" and "Average Number Awakenings | All Days | 7 Days", the change from average baseline to each average postbaseline time point will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the respective average baseline feature as a covariate. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values. Likewise, the change from baseline to each postbaseline time point will be analyzed using an MMRM for "SD Adjusted Sleep | All Days | 7 Days" and "SD Number Awakenings | All Days | 7 Days".

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the averaged values over time for "Average Adjusted Sleep | All Days | 7 Days" and "Average Number Awakenings | All Days | 7 Days".

5.4.3.2. Periodic Biosensors

Periodic Biosensors will only be worn or used for a discrete period of assessment at a study visit. As opposed to the Continuous Biosensors, which will also be worn during normal daily activities, Periodic Biosensors will be assessed during the time that the subject is exposed to specific visual and auditory tasks or stimuli via a computer interface (the JAKE Task Battery).

The JAKE Task Battery for use with Periodic Biosensors will comprise a battery of tests approximately 30 minutes in duration. The tasks and the associated biosensors are given below.

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Abbreviations: ECG=electrocardiogram, EEG=electroencephalogram, ERP=event-related potential, FACET=Facial Expression Analysis, HAI=high autism interest, LAI=low autism interest.

5.4.3.2.1. Definition

The key representative biosensor features chosen to evaluate the periodic biosensors are given in Table 12:

Table 12: Key Representative Periodic Biosensor Features

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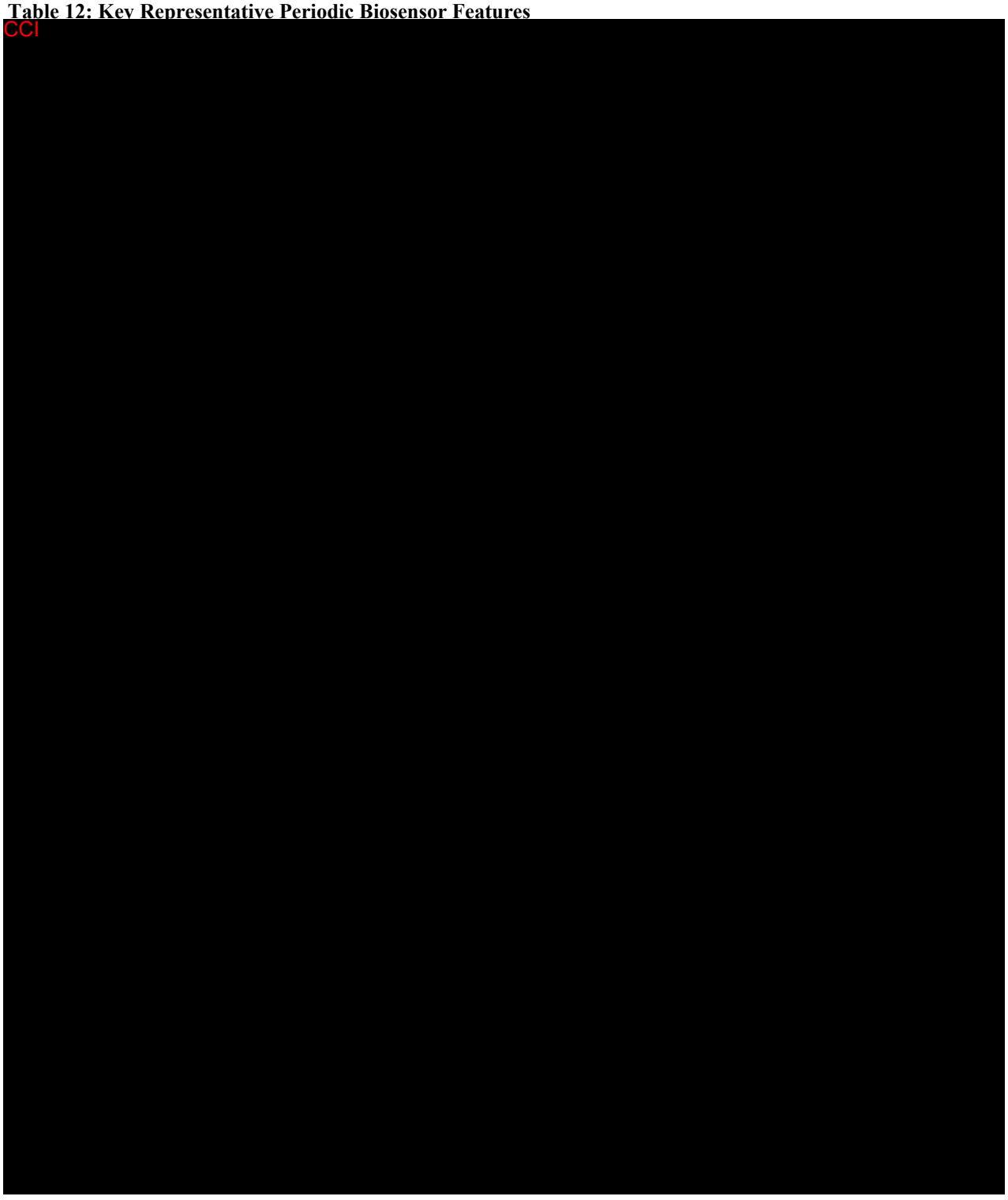

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The recordings from the biosensors will be preprocessed by applying appropriate corrections and algorithms to classify the data. As part of the preprocessing, measurement values from the periodic biosensors that are +/- 5 standard deviations from the mean value for that parameter will be considered extreme outliers due to measurement error. These outliers will be excluded from the analysis.

For the derived periodic biosensor features, the calculation is either dividing the result of one feature by another or subtracting one feature from another, as given in the feature name.

5.4.3.2.2. Analysis Methods

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes from baseline at each scheduled time point and end point will be presented for each of the periodic biosensor features by treatment group and dose.

The change from baseline to Days 29 and 85 in each of the periodic biosensor features will be analyzed using the same MMRM as described in Section 5.2.3 for the primary efficacy endpoint, with the continuous covariate for baseline ABI domain score changed to the respective baseline periodic biosensor feature score. Point estimates and 80% confidence intervals for the treatment differences at each time point will be provided, along with 1-sided p-values.

Means (±standard error [SE]), mean changes (±SE) from baseline, and LS mean changes (±SE) from baseline will be presented graphically for the observed values over time for each of the periodic biosensor features.

In case of data deemed questionable due to issues during testing, analysis may be repeated on a subset of evaluable data. Determination of what is considered evaluable will occur prior to database lock.

6. SAFETY

All safety analyses will be based on the safety analysis set based on actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent through the day of last dose plus 6 days is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events (TEAEs) will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group and dose.

Summary tables will be provided for:

- TEAEs
- TEAEs occurring in ≥10% of subjects in either combined dose treatment group
- Treatment-emergent serious AEs (SAEs)
- TEAEs leading to discontinuation of study agent
- TEAEs leading to termination of study participation
- TEAEs by severity
- TEAEs by relationship to study agent
- TEAEs leading to dose interruption

For the summaries of TEAEs by severity/relationship to study drug, the observation with the most severe occurrence/closest relationship to study agent will be chosen if there is more than one incident of the same TEAE for the subject.

The incidence of TEAEs of special interest will be summarized by preferred term and treatment group and dose. These include diplopia, vision impairment, gait disturbance, and severe headache. The preferred terms of the AEs to be included in the summary of TEAEs of special interest are marked as such on the AE CRF.

In addition to the summary tables, listings will be provided for subjects who:

- Died

- Had SAEs
- Had AEs leading to discontinuation of study agent
- Had AEs leading to termination of study participation

6.2. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set.

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis (pH and specific gravity) laboratory tests at scheduled time points. In addition, change from baseline to all postbaseline time points will be summarized for chemistry, hematology, and urinalysis (pH and specific gravity) tests and displayed by treatment group and dose.

The number and percentage of subjects with treatment-emergent postbaseline markedly abnormal values will be presented by treatment group and dose. Clinical laboratory test values will be considered "treatment-emergent markedly abnormal" (TEMA) using the criteria defined by the sponsor listed in Attachment 2. The identification of TEMA laboratory values is based on the postbaseline value being out of range while the baseline value is either missing or within the range given in Attachment 2. If postbaseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the postbaseline abnormality will also be considered TEMA. The same applies to the postbaseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of subjects with treatment-emergent alanine aminotransferase (ALT) values >3*upper limit of normal (ULN), ALT values >5*ULN, aspartate aminotransferase (AST) values >3*ULN, AST values >5*ULN, total bilirubin values >2*ULN, and INR values >1.5 will be presented for the double-blind phase.

Additionally, incidence of treatment-emergent hepatic toxicity (suspected Hy's Law (US Dept Health 2009) cases) defined as (ALT values >3*ULN or AST values > 3*ULN) AND total bilirubin values >2*ULN will be presented for the double-blind phase. Similar to the markedly abnormal analysis, only subjects with baseline (ALT values ≤3*ULN or AST values ≤3*ULN) (AND baseline total bilirubin values ≤2*ULN for hepatic toxicity) (or if baseline value is missing) will be eligible for these analyses.

The incidence of subjects with (ALT values >3*ULN or AST values >3*ULN) AND (total bilirubin values >2*ULN or INR >1.5) will be presented for the double-blind phase. As above, only subjects with baseline (ALT values ≤3*ULN or AST values ≤3*ULN) (AND baseline total bilirubin values ≤2*ULN or INR ≤1.5) (or if baseline value is missing) will be eligible for these analyses.

A listing of TEMA laboratory values will be provided, along with a listing of all laboratory values.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, weight, pulse, blood pressure (systolic and diastolic), and BMI will be summarized at each assessment time point. BMI will be calculated as weight (kg)/(height (m))^2, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation.

Change from baseline will be summarized for the treatment and follow-up periods. Descriptive statistics (mean, SD, median, minimum and maximum) will be presented.

Incidence of treatment-emergent clinically important vital signs while on treatment, as defined in Table 13, will be summarized for subjects who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table 13: Clinically Important Vital Signs

Vital Sign	Criteria
Pulse	>120 bpm and with >30 bpm increase from baseline
	<50 bpm and with >20 bpm decrease from baseline
Systolic blood pressure	>165 mm Hg and with >30 mm Hg increase from baseline
	<90 mm Hg and with >30 mm Hg decrease from baseline
Diastolic blood pressure	>105 mm Hg and with >30 mm Hg increase from baseline
	<50 mm Hg and with >20 mm Hg decrease from baseline
Temperature	>38°C and with ≥1°C increase from baseline
Weight	increase 10% from baseline
	decrease 10% from baseline

A listing of subjects with treatment-emergent clinically important vital signs will be presented, along with a listing of all vital sign measurements.

In addition, listings will be provided for physical examination and neurological examination results.

6.4. Electrocardiogram

All electrocardiogram (ECG) parameters will be displayed for the subjects included in the safety analysis set. No statistical testing will be performed.

Triplicate 12-lead electrocardiograms (ECGs) will be performed at the site and reviewed by the clinical investigator. There will not be a central ECG reader.

The ECG parameters that will be analyzed are heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc using Fridericia's formula (QTcF) correction method:

Fridericia's formula: QTcF (msec) = QT (msec) / RR$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$.

For each visit, the triplicate results for each parameter will be averaged. The averaged value will be considered the 'Visit' ECG result for that parameter and will be used for all of the analyses below.

Descriptive statistics will be presented by treatment group and dose for the above ECG parameters at each scheduled time point. In addition, change from baseline to each scheduled time point, will be descriptively summarized by treatment group and dose.

A treatment-emergent abnormal ECG is defined as an ECG assessed as normal at baseline and abnormal postbaseline.

The number and percentage of subjects with treatment-emergent ECG values outside the predefined normal limits defined below will be presented by treatment group and dose:

- Heart Rate (50-100 bpm)
- PR interval (120-200 msec)
- QRS interval (up to 120 msec)

The number and percentage of subjects with QTc interval increases from baseline to the maximum postbaseline value will be summarized at each scheduled time point. Refer to the following Table 14 for summary categories.

Table 14: Criteria for Abnormal QTc Values and Changes From Baseline

QTc value (msec)	Normal QTc	≤450 for male, ≤470 for female
	>450-480 >470-480	>450 to ≤480 for male, >470 to ≤480 for female
	>480-500	>480 to ≤500
	>500	>500
QTc change from baseline (msec)	No concern	≤30
	Concern	>30-60
	Clear concern	>60

The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of subjects having an abnormal ECG at each time point.

A listing of treatment-emergent potentially clinically important ECGs (either meeting the above criteria or having an abnormal ECG interpretation) will be presented, along with a listing of all ECG data.

6.5. Other Safety Parameters

6.5.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Columbia Suicide Severity Rating Scale) is a low-burden measure of the spectrum of suicidal ideation and behavior to assess severity and track suicidal events through any treatment. It is a semi-structured clinician-administered questionnaire designed to solicit the occurrence, severity, and frequency of suicide-related ideation and behaviors during the assessment period.

Using the C-SSRS, potentially suicide-related events will be categorized using the following scores:

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no event that can be assessed on the basis of C-SSRS"). Higher scores indicate greater severity.

A frequency distribution at each time point by treatment group and dose will be provided for the safety analysis set. Shifts from baseline to the maximum postbaseline score during the double-blind phase will be summarized by treatment group and dose.

The maximum postbaseline score during the double-blind phase assigned for each subject will be summarized into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from baseline to the maximum category during the double-blind phase will be summarized by treatment group and dose.

A listing of all C-SSRS results will be provided.

6.5.2. Aberrant Behavior Checklist-Irritability Subscale (ABC-I)

The Aberrant Behavior Checklist (ABC) is a 58-item behavior rating scale used to measure behavior problems across 5 subscales: Irritability, Lethargy (Social Withdrawal), Stereotypy, Hyperactivity, and Inappropriate Speech. Items are rated on a 4-point Likert scale (ranging from 0 [not at all a problem] to 3 [the problem is severe in degree]), with higher scores indicating more severe problems. The ABC-I is a subscale of the ABC focusing on irritability, aggression and self-injurious behavior and consists of 15 items:

If 2 or fewer items are missing, the missing items will be given a score of 0. The ABC-I score will then be calculated by summing the scores of the 15 items and will range from 0 to 45. If 3 or more items are missing, the ABC-I score will not be calculated.

The ABC-I was collected at Screening Visit 1, Day 15 and at the follow-up visit. The full ABC was collected at all other visits and the ABC-I subscale will be derived from the full scale.

Descriptive statistics for the ABC-I score will be presented at each time point by treatment group and dose for the safety analysis set. In addition, descriptive statistics for the change from baseline for the ABC-I score will be presented.

A listing of all ABC-I results will be provided.

7. PHARMACOKINETICS/PHARMACODYNAMICS

PK analyses will be performed on the PK analysis set, defined as subjects who have received at least 1 dose of JNJ-42165279 and have at least 1 valid blood sample drawn for PK analysis.

Descriptive statistics (N, mean, SD, median, range and CV (%)) will be used to summarize JNJ-42165279 concentrations at each sampling time point. Summary outputs will be provided by each combination of age group (adolescents or adults) and dosing (QD or BID).

Listed below (Table 15) are the visit windows and the target times for each visit defined in the protocol for blood sample collection for JNJ-42165279 and CCI. Samples collected outside the intervals will be excluded from the summary outputs but included in a listing.

Table 15: Visit Windows for Blood Sample Collection

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval (label on output)	Time Interval (Time)*	Target Time Point (Time)
Blood sample collection for JNJ-42165279	DB	3	Day 1: 0.5-1h	20 mins – 70 mins postdose	45 mins postdose
		4	Day 15: predose	>0 mins predose	predose
		4	Day 15: 0.5-1h #	20 mins – 70 mins postdose	45 mins postdose
		4	Day 15: 2.0-2.5h	110 mins – 160 mins postdose	135 mins postdose
		7	Day 85/EW: predose	>0 mins predose	predose
		7	Day 85/EW: 2.0-2.5h #	110 mins – 160 mins postdose	135 mins postdose
Blood sample collection for CCI	Screening	1	Screening		
	DB	4	Day 15: predose	>0 mins predose	predose
		4	Day 15: 0.5-1h #	20 mins – 70 mins postdose	45 mins postdose
		4	Day 15: 2.0-2.5h	110 mins – 160 mins postdose	135 mins postdose
		7	Day 85/EW: predose	>0 mins predose	predose
		7	Day 85/EW: 2.0-2.5h #	110 mins – 160 mins postdose	135 mins postdose

***** Time interval and target time point are relative to each day dose time.
# Note that for subjects enrolled prior to protocol amendment 3, the collection time was 0.5-1.0h postdose.

Additional details of the population pharmacokinetic and concentration-effect analyses (if conducted) will be provided in a separate document.

8. BLOOD / PLASMA BASED BIOMARKERS

The analyses of the plasma concentrations of CCI will be based on the FAS analysis set. The plasma concentrations are collected at screening, Day 15, and Day 85/early withdrawal.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of the actual values and changes and percent changes from baseline for concentrations of CCI at each scheduled time point and end point will be provided by age group (adolescents or adults), treatment group and dose.

Samples collected outside the intervals listed in Table 15 will be excluded from the summary outputs but included in a listing.

Means (±standard error [SE]) and mean changes (±SE) from baseline will be presented graphically for the observed values over time for CCI.

Exploratory biomarker and DNA sample analyses may be conducted to identify patient sub-types and/or predict response to treatments. Findings are reported separately to the clinical team.

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Other efficacy measures may be explored.

REFERENCES

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). [2009] Guidance for industry drug induced liver injury: premarketing clinical evaluation. Available: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Virues-Ortega J. Applied behavior analytic intervention for autism in early childhood: meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. Clin Psychol Rev. 2010: 30(4): 387-399.

ATTACHMENTS

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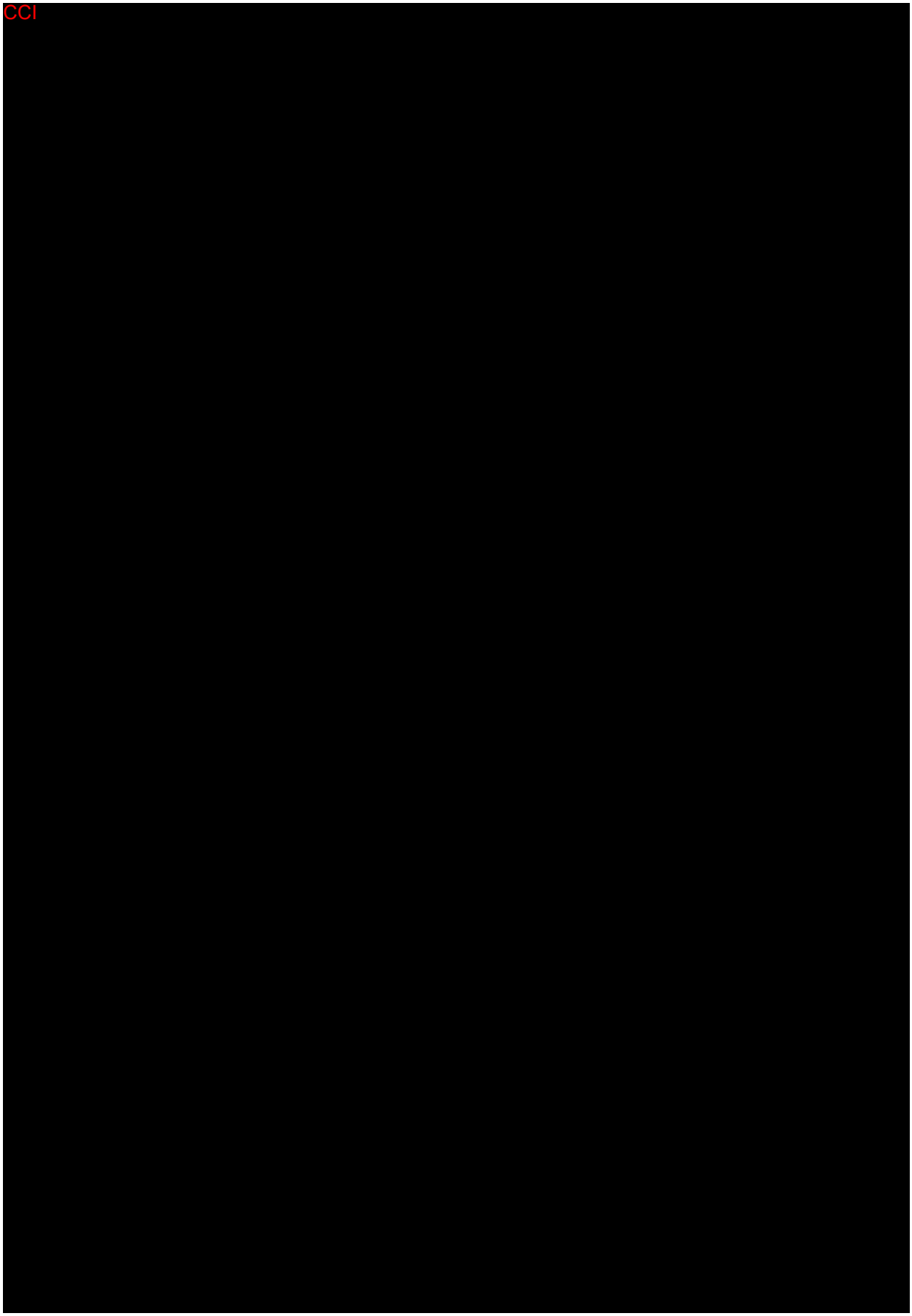

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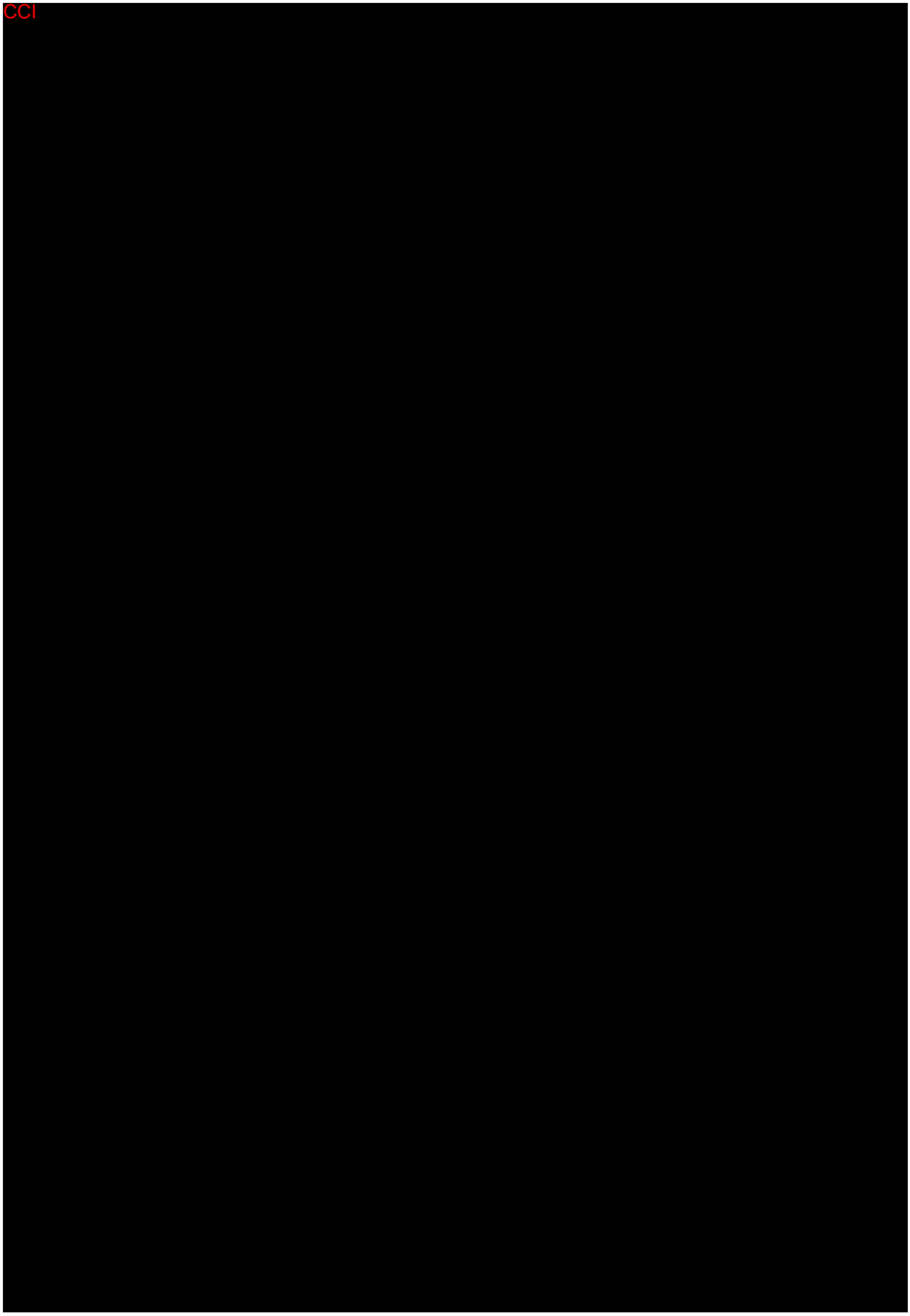

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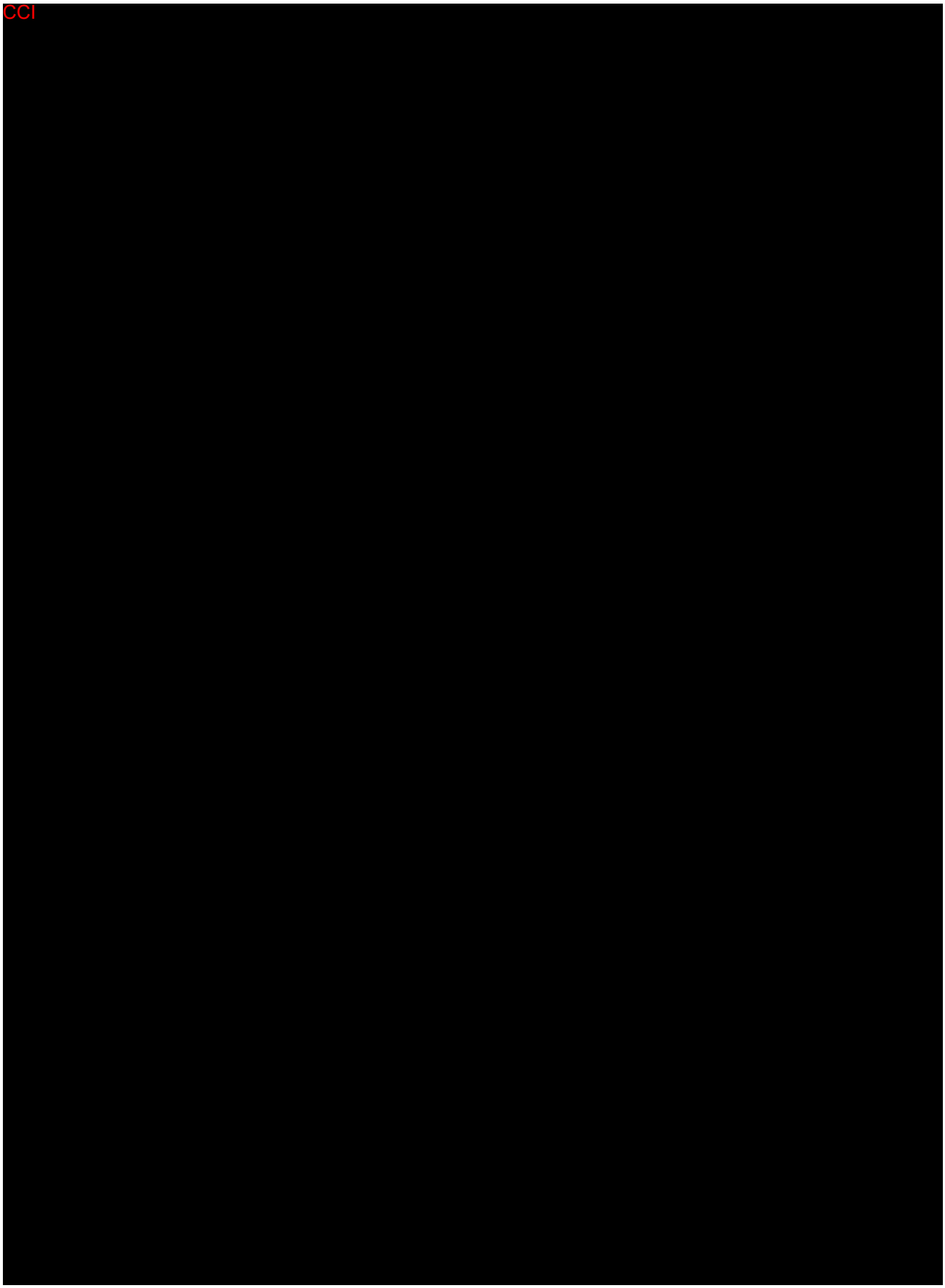

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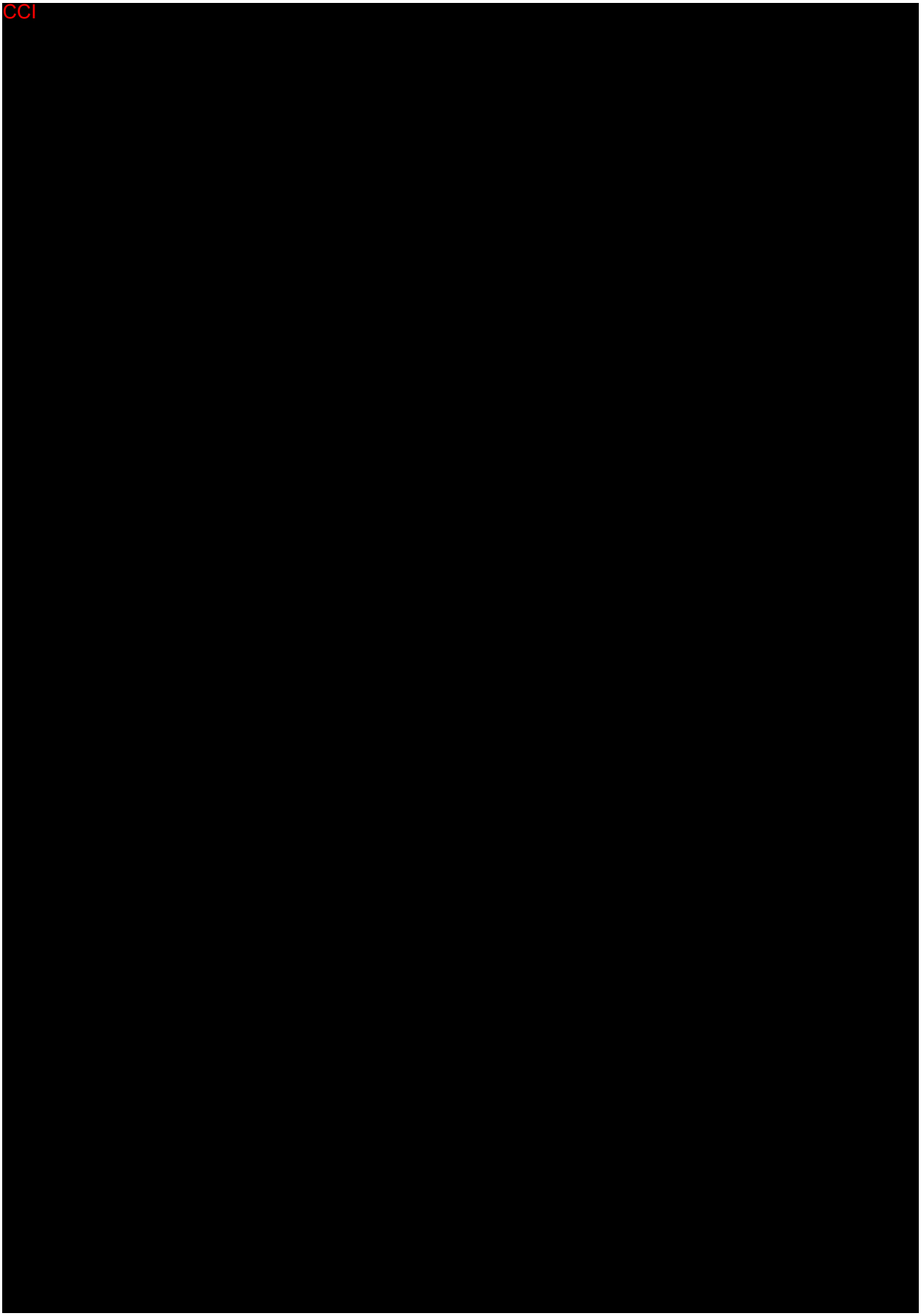

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ATTACHMENT 2 CRITERIA FOR TREATMENT-EMERGENT MARKEDLY ABNORMAL LABORATORY VALUES

	Markedly Abnormal Limits	
Laboratory Parameter	Low	High
Alanine aminotransferase (ALT) (SGPT) [U/L]	N/A	200
Albumin [g/L]	24	60
Alkaline phosphatase [U/L]	N/A	250
Aspartate aminotransferase (AST) (SGOT) [U/L]	N/A	250
Basophils [%]	N/A	6
Bicarbonate [mmol/L]	15.1	34.9
Bilirubin, total [µmol/L]	N/A	51.3
Blood urea nitrogen [mmol/L]	N/A	17.9
Calcium [mmol/L]	1.5	3
Chloride [mmol/L]	94	112
Creatine kinase (U/L)	N/A	990
Creatinine [µmol/L]	N/A	265.2
Eosinophils [%]	N/A	10
Erythrocytes (RBC) [x1012/L] -- female	3.0	5.5
-- male	3.0	6.4
Gamma glutamyl transferase [U/L]	N/A	300
Glucose [mmol/L]	2.2	16.7
Hemoglobin [g/L]	80	190
Hematocrit [fraction] -- female	0.28	0.50
-- male	0.24	0.55
INR (unitless)	N/A	2
Lactate Dehydrogenase [U/L]	N/A	500
Leukocytes(WBC) [x109/L]	2.5	15.0
Lymphocytes [%]	10	60
Magnesium [mmol/L]	0.41	2.02
Monocytes [%]	N/A	20
Neutrophils, segmented [%]	30	90
(activated) Partial thromboplastin time [seconds]	N/A	70
Phosphate [mmol/L]	0.7	2.6
Platelet count [x109/L]	100	600
Potassium [mmol/L]	3.0	5.8
Protein, total [g/L]	50	N/A
Sodium [mmol/L]	125	155
TSH [mIU/L]	<0.1	>5
Urate [µmol/L]	89.2	594.8
Urine pH	N/A	8.0

Note: The same limits apply to both males and females unless gender is indicated;
N/A = Not applicable.