Janssen Research & Development *

Clinical Protocol

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

AMENDMENT 6

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
Date: 29 September 2020
Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	14 September 2016
Amendment 1	9 March 2017
Amendment 2	17 July 2018
Amendment 3	26 September 2019
Amendment 4	9 December 2019
Amendment 5	13 April 2020
Amendment 6	29 September 2020

Amendments below are listed beginning with the most recent amendment.

Amendment 6 (29 September 2020)

The overall reason for the amendment: The overall reason for the amendment is to provide options for study-related participant management in the event of disruption to the conduct of the study due to the Coronavirus 2019 (COVID-19) pandemic, remove alcohol breath test screening, extend the allowable time window for administration of the ADOS-2, change the version of the suicidality evaluation instrument used at screening, and modify the exclusion criterion regarding CYP3A4 inducers and inhibitors.

Applicable Section(s)	Description of Change(s)
Rationale: Modifications to study conduct may be needed due to the COVID-19 pandemic.	
9.1.1 Study Overview	Added reference to Attachment 16 for COVID-19 related guidance.
Attachments	Added Attachment 16 for guidance on study conduct during the COVID-19 pandemic.
Rationale: The risk of alcohol consumption on the day of a study visit is believed to be low in this patient population. Compliance with protocol-defined alcohol restrictions can be adequately assessed via verbal confirmation with subject and/or caregiver and general appraisal by site staff for signs of acute intoxication.	
Time & Events; 9.1.2 Screening Phase	Removed alcohol breath test.
4.2. Exclusion Criteria	Removed positive tests for alcohol from Exclusion Criterion 9.
15.Materials	Removed breathalyzers.
Rationale: To broaden the allowable time window for ADOS-2 administration prior to the screening visit. ADOS-2 scores are expected to be relatively stable within a 2-year period.	
4.1 Inclusion Criteria; 9.2.2.6 Standard Instruments & Scales	Changed the allowable period for the ADOS-2 administration in Inclusion Criterion 2 from 12 months to 24 months prior to the screening visit.
Rationale: Removed requirement for investigators to consult with sponsor for all stable medical conditions given the burden and possible delay such a requirement poses and limited utility for well-managed, stable conditions. Investigators may continue to consult the sponsor should a subject's concurrent medical diagnosis raise.	
4.2 Exclusion Criteria	Modified Exclusion Criterion 3 to indicate that the investigator, with consultation with the sponsor, if warranted, will determine whether patients with stable conditions can be enrolled in the study.

Applicable Section(s)	Description of Change(s)
Rationale: To more precisely define length of time for which moderate/strong CYP3A4 inhibitors or inducers are prohibited during the study, call attention to non-drug supplements to which the prohibition also applies, and clarify that Attachment 2 comprises a non-exhaustive list of CYP3A4 inhibitors and inducers.	
4.2 Exclusion Criteria	Modified Exclusion Criterion 5 regarding moderate/strong CYP3A4 inhibitors or inducers: 1) included supplements, 2) removed ambiguous language from the intended prohibited period and added additional language to account for CYP3A4 inhibitors or inducers with unusually long half-lives by changing the period for restriction from one month to 30 days or 5 half-lives (whichever is longer) prior to Day 1, and 3) indicated that the Attachment 2 list of medications includes some examples of CYP3A4 inhibitors or inducers.
Rationale: A different version of the C-SSRS is needed at screening to capture suicidal ideation and behavior during the periods defined in the exclusion criterion. The current version only captures lifetime suicidality.	
9.6.2 Suicidality Evaluation	Changed the version of the C-SSRS to be used at screening from the Baseline version to the Baseline/Screening version.
Attachments	Replaced representative pages of the C-SSRS used at screening in Attachment 12.
Rationale:	To clarify the description of qualified study site personnel.
16.1 Design Considerations	Modified the description of qualified personnel to indicate that safety assessments will be performed by experienced and medically-qualified study site personnel.

Amendment 5 (13 April 2020)

The overall reason for the amendment: The overall reason for the amendment is to update the JNJ-42165279 clinical background information, change the dosing regimen/dose, increase the sample size, and remove the cap on the number of adult patients to be enrolled.

Applicable Section(s)	Description of Change(s)
Rationale: Recent analyses of Phase 2 data with JNJ-42165279 indicate that AEA levels are not sufficiently sustained in all patients over a 24-hour dosing interval with 25 mg once daily dosing. Subjects with higher trough AEA levels showed superior efficacy than those with lower AEA levels in measures of depression and anxiety. PK/PD modeling predicts that higher trough drug exposure and AEA levels can be achieved with twice daily (BID) administration of JNJ-42165279 25 mg (50 mg total daily dose) while maintaining good safety margins.	
Time & Events	Changed the dosing regimen from once daily to twice daily, and changed "bottle" to "bottles."
Time & Events; 6. Dosage; 9.1.3 Treatment Phase	Added that dosing in the clinic should be the subject's first dose of the day.
Synopsis; Time & Events; 6. Dosage; 9.4.1. PK Evaluations	Modified the description of which study drug administrations should have the date and time recorded.
Synopsis; 3.1 Overview of Design	Described that subjects enrolled prior to Protocol Amendment 5 were randomized to receive once daily dosing of placebo or 25 mg JNJ-42165279 and all other subjects will receive twice daily (BID) dosing of placebo or 25 mg JNJ-42165279 (total daily dose of 50 mg).

Applicable Section(s)	Description of Change(s)
Synopsis; 2.1 Objectives; 9.1.3. Treatment Phase	Removed the reference to once daily dosing.
1.1. Background	Added information on the estimated drug exposure and safety margins of adolescents compared to adults, as well as the estimated impact of the change to BID dosing on C_{max} and AUC in adults.
1.1 Background; 3.2.2.1 Rationale for including adolescents	Replaced the safety margins associated with once daily dosing of JNJ-42165279 25 mg to those associated with 25 mg BID.
3.2.3. Rationale for Dose	Modified the rationale for dose selection to reflect the change from once daily to BID dosing.
6. Dosage; 9.1.3. Treatment Phase	Indicated that treatment phase visits should be scheduled for mornings.
6. Dosage	Added information regarding dosing, including recommended and required dosing intervals for BID dosing. Changed the definition of noncompliance to be recorded on diaries from >1 pill to >2 pills.
9.1.1. Overview	Removed information regarding the time of day for scheduled visits.
11.1. Subject Information	Changed the primary analysis set from Intent-to-Treat (ITT) to ITT-BID, which includes only subjects who are enrolled under BID dosing.
Synopsis; 11.2. Sample Size	Indicated that the sample size is based on the number of subjects to receive BID dosing.
11.3. Efficacy Analyses	Deleted statement that all efficacy analyses will be based on the ITT analysis set.
11.3.1. Primary efficacy endpoints	Added that primary efficacy analysis will be based on the ITT-BID analysis set. Added that additional sensitivity analyses for the primary efficacy endpoints may be specified in the SAP. Removed the subgroups to be included in the descriptive statistics and indicated that this will be specified in the SAP.
11.6. Safety Analysis	Added “by dose level” to the summaries of adverse events and clinical laboratory tests.
16.1. Study-Specific Design Considerations	Changed the dose from 25 mg to 25 mg BID (total daily dose of 50 mg).
Rationale: As some subjects have been enrolled under once daily dosing prior to Protocol Amendment 5, the total sample size needs to be increased to have adequate power for the comparison of placebo BID and JNJ-42165279 25 mg BID.	
Synopsis; 3.1. Overview of Design	The number of subjects to be randomized in the study was changed from 60 to 80.
Rationale: Data are now available from one Phase 1 study in healthy Japanese subjects and two Phase 2 studies with JNJ-42165279.	
Synopsis; Introduction	Updated the brief description of Phase 1 and Phase 2 studies.

Applicable Section(s)	Description of Change(s)
1.1. Background	Added a summary of results of the Phase 1 study in healthy Japanese subjects (Study 42165279EDI1007), the Phase 2 study in patients with severe social anxiety disorder (Study 42165279SAX2001), and the Phase 2 study in patients with major depressive disorder with anxiety symptoms (42165279MDD2001).
Rationale: The restriction to enroll no more than 50% adult subjects is being removed due to low adolescent enrollment to date. There is no expected impact on evaluation of treatment efficacy in this Proof-Of-Concept study.	
Synopsis; 3.1 Overview of Design; 4.1. Inclusion Criteria; 5. Treatment Allocation	Removed statement that at least 50% of subjects will be adolescents.
Rationale: Recent analyses of Phase 2 data indicate that assessing the relationship between plasma AEA levels and efficacy measures can aid in the understanding of treatment efficacy.	
Synopsis; 2.1.1. Objectives	Added a secondary objective to evaluate the relationship between plasma concentrations of CCI and efficacy.
Synopsis; 3.2.5. Rationale for Biomarker Evaluations 11.4. Biomarker Analysis	Modified the description to state that CCI levels will be correlated with efficacy and other clinical evaluations.
Rationale: The length of contraception usage by female subjects, as well as the period in which eggs (ova, oocytes) should not be donated, is intended to reflect the period of time JNJ-42165279 may exert an effect on female reproductive cells. The time frame has been shortened to be consistent with the average menstrual cycle length. Additionally, clarification was needed on the length of contraception usage for female partners of male subjects.	
4.1 Inclusion Criteria	Added the duration for use of contraception by female partners of male subjects (mirroring the male subject's duration of contraception use) to Criterion 4. Changed the duration of contraception use for female subjects in Criterion 19 from 90 to 30 days after the last dose. Changed the duration for female subjects to avoid donation of eggs in Criterion 20 from 90 to 30 days after the last dose.
Rationale: To allow for revisions to the Evaluation of JAKE questionnaire during the study, the representative pages of this questionnaire were removed.	
9.2.2.6.12. Evaluation of JAKE	Removed "4-item" from description of the Evaluation of JAKE questionnaire and removed cross-reference to the corresponding attachment of representative pages.
12.3.1. All Adverse Events; Attachments	Renumbered the Attachment of Anticipated Events
Attachments	Removed representative pages of the Evaluation of JAKE questionnaire.
Rationale: Minor changes were made to improve clarity or readability, correct errors and inconsistencies, repeat text in other applicable sections, and remove unnecessary information.	
Synopsis	Removed text considered unnecessary for a study synopsis.
Synopsis; 2.1.2. Endpoints	Indicated that the endpoints lists are efficacy endpoints.
Synopsis; 3.1 Overview of Design; 5. Treatment Allocation	Added information regarding the timing of the interim PK analysis that was included in Section 11.5.

Applicable Section(s)	Description of Change(s)
Synopsis; 3.1. Overview of Design	Indicated that the continuous biosensor is a wristband that measures activity.
3.2.2.1. Rationale for Inclusion of Adolescents	Corrected the percent reduction in sperm motility observed in the 3-mos GLP rat study to 25%.
3.2.5. Rationale for Pharmacogenetic; 11.5. Pharmacokinetic	Removed CCI [redacted]
9.1.3. Treatment Phase	Modified section to be more concise.
9.2.2.7. JAKE Help/Manuals	Deleted information regarding the format and timing of training on the JAKE system.
11.6. Safety Analysis	Changed the QTcF intervals to be used for reporting to be consistent with the exclusion criterion (>450 msec for males and >470 msec for females).
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 4 (9 December 2019)

The overall reason for the amendment: The overall reason for the amendment is to modify the list of examples of prohibited cytochrome P450 (CYP) 3A4 inhibitors and inducers.

Applicable Section(s)	Description of Change(s)
Rationale: Errors and omissions were identified in the list of examples of prohibited CYP3A4 inhibitors and inducers.	
8. Concomitant Therapies	Added description of Attachment 2, and that the investigator should evaluate all prestudy and concomitant medications to assess whether they are moderate or strong inducers or inhibitors of CYP3A4 and consult with the Sponsor if unsure.
Attachment 2	Modified attachment title to specify CYP3A4, and added statement that this is not a comprehensive list of all moderate and strong CYP3A4 inhibitors and inducers. Modified the list of inducers and inhibitors.

Amendment 3 (26 September 2019)

The overall reason for the amendment: The overall reason for the amendment is to add a description of a new application containing the caregiver reporting tool, My JAKE MMApp, modify eligibility criteria considered unnecessarily restrictive, modify the blood sampling schedule to enhance exposure/response analyses, and include a clinician rating of disease improvement.

Applicable Section(s)	Description of Change(s)
Rationale: A new caregiver reporting application (App) is needed due to a decision by Microsoft to discontinue Microsoft Health Vault, which stores the data collected in the current application, My JAKE. Some components of My JAKE will not be available in the new application, and there may be periods when neither application is available.	

Applicable Section(s)	Description of Change(s)
Abbreviations; Definitions	Added abbreviation and definition of the new application containing the caregiver reporting tool, My JAKE Mobile Medical Application v 1.0, and updated the definition of My JAKE.
Throughout the protocol	Replaced term "My JAKE" with "caregiver reporting tool" in statements that are applicable to both applications (My JAKE and My JAKE MMApp). Added "My JAKE Mobile Medical App v 1.0" and/or the abbreviation "My JAKE MMApp" where applicable
T&E	Modified the description of the caregiver reporting tool account set up in footnote e.
Synopsis; T&E; 3.2.6.1 My JAKE; 9.2.2 Evaluations; 9.2.2.1 Caregiver Reporting Tool	Indicated which components of the caregiver reporting tool are available in My JAKE and My JAKE MMApp.
T&E; 3.2.6.1 My JAKE; 9.2.2.1 Caregiver Reporting Tool	Indicated the components of the caregiver reporting tool which will be collected on paper if My JAKE and My JAKE MMApp are not available.
3.2.6 JAKE System; 9.2.2.1 My JAKE	Described that there are 2 applications containing the caregiver reporting tool, My JAKE and My JAKE MMApp, and that caregivers will use the application that is available during their participation in the study.
3.2.6 JAKE System	Added Figure 3 schematic of My JAKE MMApp.
9.2.2.1 Caregiver Reporting Tool	Stated that My JAKE MMApp is for use by caregivers and the sponsor.
9.2.2.4 Caregiver Reporting Tool: Data Processing	Revised title of Section 9.2.2.4 from "My JAKE Data Pipeline" to "Caregiver Reporting Tool: Data Processing." Modified description of data processing for the caregiver reporting tool.
9.2.2.7 JAKE Help/Manuals	Revised description of help information available to clinical sites and caregivers for the caregiver reporting tool to reflect differences between My JAKE and My JAKE MMApp.
15 Materials	Added paper versions of ABI, ABI-S and Daily Tracker to list of study-specific materials.
16.1 Design Considerations	Removed statement regarding potential benefit to caregivers of having HealthVault information available after the completion of the study.
17.4 Source Documentation	Added statement that if paper forms are used for the Daily Tracker, ABI, or ABI-S, they will be considered source data.
Attachment 15	Modified the representative page of the Evaluation of JAKE scale to include a "NA" option for ratings of JAKE components not available in My JAKE MMApp or paper versions. Added the description "(Behaviors, Sleep)" to the Daily Tracker component, and removed a redundant scale definition.

Rationale: To add a clinician rating of subjects' global improvement to augment outcome assessments. A clinician evaluation of both severity and improvement may be more sensitive in detecting changes with treatment than a severity rating alone.

Applicable Section(s)	Description of Change(s)
Abbreviations	Added abbreviation for the Clinical Global Impression of Improvement scale (CGI-I)
T&E	Added the CGI-I to table, footnote, and abbreviations.
Synopsis; 2.1.1 Objectives	Added the assessment of CGI-I to the secondary objectives.
Synopsis; 2.1.2 Endpoints; 9.2.1 Endpoints	Added the assessment of CGI-I at Day 85 to the secondary endpoints.
Synopsis; 9.2.2 Evaluations	Added clinicians' global impressions of disease improvement to efficacy evaluations.
9.2.2.6.8 Clinical Global Impression	Added description of CGI-I scale.
15 Materials	Added the CGI-I to the list of study-specific materials.
Attachment 11	Added a representative page for the CGI-I scale.
Rationale: To increase the upper age limit of eligible subjects from 30 to 35 years. The upper limit of 30 years was considered unnecessarily restrictive, as the study endpoints are unlikely to differ between a 30- and 35-year-old subject.	
Synopsis; 3.1 Study Design; 3.2.2 Study Population; 4 Subject Population; 4.1 Inclusion Criteria;	Changed the upper age limit for eligibility from 30 years to 35 years.
3.1 Study Design	Removed age range in Figure 1.
Synopsis; 3.1 Study Design; 3.2.1 Randomization; 5 Treatment Allocation; 11.3.1 Primary Efficacy Endpoints	Revised the second randomization stratum from 18 – 30 years to 18 - 35 years of age.
Rationale: To broaden the allowable time window for ADOS-2 administration prior to the screening visit. ADOS-2 scores are expected to be stable within a 1-year period.	
4.1 Inclusion Criteria; 9.2.2.6 Standard Instruments	Changed the allowable period for the ADOS-2 administration from 6 months to 12 months prior to the screening visit.
Rationale: To obtain predose and postdose PK and CCI samples at Weeks 2 and 12 to 1) enable evaluation of the relationship between exposure/pharmacodynamics and efficacy, 2) confirm subject compliance with dosing, and 3) assess change in drug exposure and pharmacodynamics from 2 to 12 weeks. In order to collect predose samples at Week 12, dosing will need to occur at the clinic.	

Applicable Section(s)	Description of Change(s)
T&E	Moved information regarding time points for PK and CCI samples from footnotes to T&E Table. Changed the PK postdose sample time point at the Week 2 visit from 0.5-1h to 2.0-2.5h postdose. Added PK samples at the Week 12 visit at predose and 2.0-2.5h postdose. Add a CCI sample at Week 2 at 2.0-2.5h postdose. Added a Week 12 predose CCI sample and specified that the postdose time point for the CCI sample at Week 12 will be 2.0-2.5h. Modified footnote "k" to state that safety laboratories at the Week 2 and 12 visits will be collected predose.
T&E; 6 Dosage & Administration	Changed the visits in which dosing will occur in the clinic from Visits 3-6 to all visits in the treatment phase.
T&E; 6 Dosage & Administration; 9.1.3 Treatment Phase	Changed the dosing time at Week 12 from approximately 3 hours prior to the visit to dosing in the clinic.
Synopsis; T&E; 9.4.1 PK Evaluations	Changed the days in which accurate recording of dosing time is needed from Days 1, 14, and 15 to Day 1, Week 2, and Week 12 visits, and the day prior to the Week 2 and 12 visits.
9.1.1 Overview	Modified Table 1 blood volume information to reflect changes in PK and CCI sample collection. Added Week 12 to the statement regarding blood sample collection before and after dosing. In the description of the order of procedures involving the JAKE Task Battery, added that the JAKE Task Battery must be completed prior to blood draws and removed the reference to Day 1 and Week 4 visits.
Rationale: Minor changes were made to improve clarity or readability, or to correct errors, inconsistencies, or omissions and remove unnecessarily redundant information.	
T&E	Moved dosing-related information from the previous footnote regarding PK samples to footnote e. Removed "Mood Report" from table and added mood report to description of Daily Tracker in footnote "u."
Synopsis; 9.2.2 Evaluations	Added clinicians' global impressions of disease severity to efficacy evaluations.
Synopsis; 11.5 PK and PK/PD	Changed "Day 15" to "the Week 2 visit."
3.2.2.1 Rationale for Including Adolescents	Changed the age in the Section title from "13 to 18 years" to "13 to 17 years"

Applicable Section(s)	Description of Change(s)
3.2.6. JAKE System	Removed the previous Section 3.2.6.3, My JAKE Data Pipeline, and moved the information not already included elsewhere to Section 9.2.2.4. Removed the previous Section 3.2.6.4, JAKE Sense Data Pipeline Added cross-references to Sections 9.2.2.4 and 9.2.2.5 for information on data processing.
3.2.6.1 My JAKE/My JAKE MMApp	Moved description of Mood Report to bullet for Daily Tracker.
6 Dosage and Administration	Added sentence regarding dosing diaries provided to subjects/caregivers.
Definitions; 9.2.2.1 Caregiver Reporting Tool	Removed "subjects" or "study participants" in statements regarding users of My JAKE.
9.2.2.1 Caregiver Reporting Tool	Changed period in which caregivers should not revoke access to My JAKE and Microsoft Health Vault from "until told to do so at the time of database lock" to "without investigator approval." Removed previous Section 9.2.2.1.3, Mood Report.
9.2.2.1.1 ABI	Added sentence "The ABI-C is completed on paper."
9.2.2.1.2 Daily Tracker	Revised description of Daily Tracker to include the Mood Report. Added that caregivers will report on subjects' overall type of day. Removed sentence "These items are chosen from a subset of items presented, based on the caregiver's response in the ABI." Changed "parents" to "caregivers."
9.2.2.6.5 CASI-Anx	Corrected the range of values for the CASI-Anx scale.
Attachment 16	Deleted the following text in the description of anticipated events: "based on reports by healthy subjects in Phase 1 studies."
Throughout the protocol	Minor grammatical, formatting, or punctuation changes were made.

Amendment 2 (17 July 2018)

The overall reason for the amendment: To allow females to participate in this study, including women of childbearing potential under conditions of pregnancy testing and use of contraception. Additionally, to update the description of the ABI and the JAKE system and assessments, to modify the eligibility criteria, to modify time points of procedures, and to add or modify assessments of caregiver and subject global impressions.

Applicable Section(s)	Description of Change(s)
Rationale: To allow females to participate in this study, due to notification of health authority approval for women of childbearing potential to participate in clinical trials with JNJ-42165279.	
Protocol front page; Synopsis	Changed protocol title to remove the word "male."
4.1 Inclusion	Removed requirement for subjects to be male in Inclusion Criterion #1.

Applicable Section(s)	Description of Change(s)
Throughout the protocol	Modified text to reflect that participation in the trial is not limited to males.
Rationale: To add requirements that will minimize the chance of pregnancy in female subjects and female partners of male subjects and avoid possible exposure of an embryo or fetus to study drug, add pregnancy testing, and include pregnancy reporting information. Additionally, to remove the requirement for male subjects to use contraception when there is no potential for pregnancy, move restriction for donation of sperm to a separate criterion, and move rationale for contraception for male subjects to a different section.	
Synopsis: Safety Evaluation; Time & Events; 9.6.6 Laboratory	Added serum pregnancy test at screening for all female subjects and urine pregnancy test at all other subject visits for women of childbearing potential (WOCBP).
3.2.2 Study Population	Added rationale for pregnancy testing and use of contraception for female subjects.
4.1 Inclusion	The following changes were made: • Added Inclusion Criterion #17 requiring female subjects to have negative pregnancy tests at screening and, for WOCBP, at Day 1 before randomization. • Added Inclusion Criterion #18 requiring female subjects using oral contraceptives to also use a barrier method of contraception with spermicide. • Added Inclusion Criterion #19 requiring female subjects to either be of non-childbearing potential or to use a highly effective method of contraception during the study and for 90 days after the last dose. • Added Inclusion Criterion #20 restricting donation of eggs for female subjects during the study and within 90 days after the last dose. • Modified Inclusion Criterion #4 to: A male subject who has not had a vasectomy must agree to use a condom when having sex with a female partner of childbearing potential (See Attachment 1) during the study and for 3 months after receiving the last dose of study drug. The condom must have a spermicide or the partner must use a spermicide. A male subject should also be advised to inform their female partner to use a highly effective method of contraception, as condoms may break or leak. • Moved restriction for donation of sperm to a separate criterion (#16).
4.1 Inclusion; 3.2.2.1 Rationale for Adolescents	Moved rationale for male contraception (previously included as part of Inclusion Criterion #4) to Section 3.2.2.1 regarding rationale for inclusion of adolescents.
4.2 Exclusion	• Added Exclusion Criterion #21 for male subjects who are sexually active, or plan to be sexually active during the trial, with a female who is pregnant. • Added Exclusion Criterion #22 for female subjects who are pregnant or breastfeeding, or plan to become pregnant or breastfeed during the trial or within 3 months after the last dose.
9.1.1 Overview	Added description of possible additional pregnancy testing during the study. Added serum pregnancy test to blood volume table.
10.2 Discontinuation	Added subject becoming pregnant as a reason for discontinuation from study.
12.3 Adverse Event Procedures	Added Section 12.3.3 with information on pregnancy reporting.
16.1 Design Considerations	Added that females will be of nonchildbearing potential or using contraception, and that pregnancy testing will be performed.
Attachments	Added Attachment 1 with further information on contraception requirements. Renumbered all subsequent Attachments.

Applicable Section(s)	Description of Change(s)
Rationale: To amend the description of ABI assessments based on health authority feedback and the decision not use a structured interview guide for the ABI-C, and to allow for possible revisions to these instruments or the JAKE Daily Tracker prior to study start.	
Synopsis Objectives, Endpoints; Time & Events; Definition of Terms; 2.1.1. Objectives; 2.1.2. Endpoints; 3.2.6.1. My JAKE; 3.2.7.2. Instruments for Measuring Change; 9.2.2.1.1. ABI	The description of the ABI (full version, ABI-S, ABI-C) was amended, including a change in approximate number of items, removal of a second anchor, renaming of the Mental Health Domain as "Mood & Anxiety," and removing "structured" in descriptions of the ABI-C interview.
Attachments	Replaced previous Attachment 2 (now Attachment 3) to remove the ABI full version, ABI-S, and Daily Tracker and replace the ABI-C with a new version.
Rationale: To modify or clarify details of the JAKE system, including data collection and processing, due to recent updates.	
Throughout the protocol	Changed the name of the JAKE portal, JAKE Biosensor Array, and other components of the JAKE system.
Abbreviations; 3.2.6.2 JAKE Sense; 3.2.6.4 JAKE Sense Data Pipeline; 9.2.2.5 JAKE Sense Data Pipeline	Indicated that JAKE Sense biosensors are used solely for exploratory, proof-of-concept research, and removed text regarding their validation.
3.2.6 JAKE System; 3.2.6.2.3 Workbench	Indicated that data from My JAKE and JAKE Sense are separated.
Abbreviations; 3.2.6.1 My JAKE; 9.2.2.1.4 Therapy Tracker	Removed medication, diet, and illness as items tracked in Therapy tracker.
3.2.6.2.2 Periodic Biosensors; 9.2.2.2.2.2 Actiwave	Added distinction between the ECG used for the JAKE Task Battery from the 12-lead ECG for safety assessment.
3.2.6. JAKE System	Replaced JAKE schematic.
3.2.6.4. JAKE Sense Data Pipeline	Replaced all text with new description.
3.2.6.2.2. Periodic Biosensors	Changed period for continuous biosensors from during normal daily activities to throughout the treatment period.
9.2.2. Evaluations	• Indicated that the journal and therapy tracker are encouraged but optional. • Added information on actigraphy, EEGs, and ECGs used as part of JAKE system. • Modified description of personal information to be collected and shared in My JAKE Pipeline and JAKE Sense Data Pipeline. • Indicated that breaks within a set of the JAKE Task Battery are discouraged. • Modified description of JAKE help and manuals. • Modified task durations of the JAKE Task Battery. • Copied text from Time and Events Schedule regarding performance of the Task Battery at approximately the same time of day for an individual subject.

Applicable Section(s)	Description of Change(s)
15 Materials	Modified list of equipment related to JAKE system.
Throughout the protocol	Minor changes were made to the description of the JAKE system.
Rationale: To identify subjects taking drugs of abuse during the study and exclude subjects with alcohol intake at study visits prior to enrollment, as drug and alcohol use may impact study endpoints. Additionally, to modify the allowed use of alcohol to be gender-specific, based on current dietary guidelines, and to include 2 additional drugs of abuse in urine drug test.	
Time & Events	Added urine drug test at all treatment period visits, and alcohol breath test at Screening Visit 1 and Day 1.
4.2 Exclusion	Modified Exclusion Criterion #9 to exclude subjects with a positive drug or alcohol test at screening or Day 1.
4.2 Exclusion (Criterion 9); 9.6.6 Laboratories	Added phencyclidine and 3,4-methylenedioxy-methamphetamine (MDMA) to list of drugs included in urine drug testing.
4.3 Prohibitions	Indicated that alcohol use should be avoided on study visit days, prior to the time of a visit, and modified recommended limit to 2 drinks/day for males and 1 drink/day for females.
Rationale: Eye-tracker calibration can be subject to environment factors in the equipment or room set up, rather than the intended purpose of evaluating subject characteristics. Thus, allowing calibration to be repeated to determine eligibility is considered appropriate.	
Time & Events; 4.1 Inclusion (Criterion 14); 9.1.2 Screening	Indicated that the eye-tracker calibration can be repeated during the screening period to meet the criterion of "good" calibration.
Rationale: To assure that only individuals who spend some time every week with their parent/primary caregiver are enrolled in the study. The period of reporting for some study evaluations is over the past week.	
4.1 Inclusion	Inclusion Criterion #7: Changed the required period for individuals to spend with their parent/caregiver (if not living with them) to: "during each week they must either (A) spend at least 3 hours a day for at least 4 days or, (B) spend the weekend with a parent or primary caregiver."
Rationale: To change the QTc interval used for eligibility and reporting of abnormal intervals to be gender-specific, given the gender difference in QTc normal ranges. Additionally, to modify how changes in QTc intervals from baseline are summarized.	
4.2 Exclusion Criteria	Modified the QTc interval in Exclusion Criterion #2 to indicate that QTcF >450 msec applies to males and added QTC interval >470 msec for females.
11.6 Safety Analysis	Modified the reporting of QTc intervals to include QTcF >450 msec for males and >470 for females. Modified the change from baseline description from 30-60 msec to >30 msec.
Rationale: To use the same minimum IQ criterion for eligibility as that used in the previous studies for the development and validation of the JAKE system. Additionally, to assure that the KBIT-2 scale is completed for determination of eligibility.	
4.1 Inclusion; 4.2 Exclusion; 3.2.7.1 Diagnostic and Classification Instruments	Changed the eligibility criterion regarding the KBIT-2 scale from an exclusion criterion (previous Criterion #20.1) to an inclusion criterion (Criterion #15). Also changed the minimum KBIT-2 composite score from at least 50 to at least 60.
Rationale: To provide greater clarity on informed consent requirements, and add requirement for signing of a caregiver consent form to address caregivers' responsibilities during the study.	

Applicable Section(s)	Description of Change(s)
4.1 Inclusion; 9.1.2 Screening; 16.2.3 Informed Consent	Modified description of informed consent requirements, including additional requirement for caregivers of all subjects to sign a separate caregiver consent form.
Rationale: To exclude individuals with incomplete vaccination status, as this may be applicable to the study population, and clarify eligibility criteria for abnormal renal or liver function.	
4.1 Inclusion	Modified Inclusion Criterion #6 to clarify that subjects with an AST or ALT >1.5 times the upper limit of normal cannot be enrolled.
4.2. Exclusion	Modified Exclusion Criterion #3 to exclude subjects with incomplete vaccination status. Changed "renal or liver insufficiency" to "evidence of abnormal liver or renal function."
Rationale: To modify the exclusion criterion regarding planned surgery.	
4.2 Exclusion	Exclusion Criterion #16: Added entry into a major body cavity and significant blood loss as examples of major surgery. Modified note regarding allowed surgery to specify "minor" surgery, and added requirement for approval by sponsor.
Rationale: To correct an error in the exclusion criterion regarding use of drugs with CYP3A4 activity. Correct information was included elsewhere in the protocol.	
4.2 Exclusion	Modified Exclusion Criterion #5 to include CYP3A4 inducers as well as inhibitors.
Rationale: To clarify the exclusion criterion regarding employees of the investigator or study site.	
4.2 Exclusion	Modified description of Exclusion Criterion #19 regarding employees of investigator or study site or their family members.
Rationale: To exclude subjects who are unable to perform or comply with all study requirements.	
4.2 Exclusion	Added Exclusion Criterion #23 for subjects who are judged by the investigator to be unable to perform or comply with all study-specific requirements.
Rationale: To provide additional information regarding determination of eligibility and circumstances in which repeat of procedures is allowed.	
Time and Events	Modified footnotes to 1) remove statement regarding repeat of safety labs if >28 days have elapsed since the screening labs and 2) refer to screening section of protocol for information regarding retesting.
4.1 Inclusion; 4.2 Exclusion	Modified criterion regarding safety laboratory tests (Inclusion Criterion #6 and Exclusion Criterion #3) to indicate that they can be repeated once at the discretion of the investigator.
4.1 Inclusion	Added note to clarify that the parent or primary caretaker referenced in the inclusion criteria (except Inclusion Criterion #8) is the designated caretaker for the study.
4.2 Exclusion	Added information at the end of the exclusion criteria section regarding evaluation of eligibility and referenced other sections for additional information regarding retesting.
9.1.2 Screening	Allowed one rescreening and circumstances in which this would be allowed. Allowed one retest for abnormal safety laboratory tests or positive drug or alcohol test. Copied text from inclusion criterion regarding abnormal labs.
Rationale: To add measurement of CCI at a time point when a PK sample is collected for evaluation of the PK/biomarker relationship.	

Applicable Section(s)	Description of Change(s)
Time & Events; 9.1.1 Overview	Added blood sample collection for CCI [redacted] on Day 15 (predose) and updated the blood volume collection table.
Rationale: To measure CCI at approximately the time of expected peak CCI levels after dosing.	
Time & Events; 6. Dosage; 9.1.3 Treatment Phase	The time of dosing on the last dosing day (Week 12 visit) was changed from during the study visit to 3 hours prior to the scheduled time of the visit.
Rationale: To add a physical examination immediately prior to enrollment.	
Time & Events	A physical examination was added at Day 1.
Rationale: To require completion of the ABC-I in addition to the C-SSRS after screening, regardless of whether administration of the C-SSRS is feasible. This was requested by the Health Authority in order to have ABC-I data for comparison across time points, in the event that the C-SSRS cannot be completed throughout the trial. In addition, the description regarding the timing of these 2 assessments was revised for greater clarity.	
Time & Events; 9.6.2 Suicidality	Information regarding the ABC-I and C-SSRS was removed from the footnote of the Time and Events Schedule and added to the body of the protocol. The time points in the Time and Events table for these assessments was revised. Instructions regarding when the C-SSRS and ABC-I should be administered was revised.
Rationale: To correct the time points for collection of continuous biosensor data.	
Time & Events	Changed time points for collection of continuous biosensor data to Weeks 2, 4, 8, and 12.
Rationale: To change the scale to be used for caregivers' global assessment of disease severity to one more appropriate for non-clinicians.	
Time & Events	Added a single-item Caregiver Global Impression of Severity (Caregiver GI-S) scale at the Day 1, Week 4, Week 8, and Week 12 visits. Removed statement regarding completion of the CGI-S by caregiver.
9.2.2.6 Standard Instruments	Added Subsection 9.2.2.6.9 with description of Caregiver GI-S.
15 Materials	Added Caregiver GI-S to list of materials.
Rationale: To correct an error in the time points for drug accountability.	
Time & Events	Removed the Day 15 time point for drug accountability.
Rationale: To divide the **"**Self-Assessment of Treatment Experience" into 2 instruments, as the content includes 2 diverse subject areas (the evaluation of study treatment and the JAKE system). Additionally, to change the title of instrument to reflect completion by caregiver rather than the subject.	
Time & Events	Deleted the row "Self-Assessment of Treatment Experience" and added 2 new rows: "Caregiver Assessment of Treatment" and "Evaluation of JAKE."
9.2.2.6 Standard Instruments	Added descriptions of both instruments (new Subsections 9.2.2.6.10 and 9.2.2.6.12)
15 Materials	Added both instruments to list of materials.
Attachments	Split previous Attachment 14, Self-Caregiver Assessment of Treatment Experience, into 2 Attachments (Attachments 14 and 15 with new titles of questionnaires).

Applicable Section(s)	Description of Change(s)
Rationale: To obtain subjects' impressions of improvement in their disorder.	
Time & Events; 15 Materials	Added a single-item scale entitled "Self-Global Impression of Improvement (Self GI-I) at the Week 12 visit.
9.2.2.6 Standard Instruments	Added description of Self GI-I (new Subsection 9.2.2.6.11)
Rationale: To include assessment of 3 additional scales in secondary objectives, evaluations, and endpoints.	
Synopsis Objectives, Endpoints, Efficacy; 2.1. Objectives & Endpoints; 9.2.1 Endpoints; 9.2.2 Evaluations	Added the Caregiver GI-S, Caregiver Assessment of Treatment, and Self GI-I to secondary objectives, evaluations, and endpoints.
Rationale: To update study background information with new information.	
1. Introduction; 1.1 Background; 3.2.2. Study Population	Updated the summary of data on JNJ-42165279 based on the current version of the Investigator's Brochure (Edition 5), and modified the summary of Mentis-HV-001 and Mentis-ASD-002 study results.
Rationale: To provide a more detailed description of the exploratory objective regarding pharmacogenomic data and to modify the purpose for collection of the pharmacogenomic sample. Additionally, to describe the rationale for collection of pharmacogenomic and biomarker data in the Study Design Rationale section.	
Synopsis Objectives; 2.1.1. Objectives	Revised description of exploratory objective regarding correlations between pharmacogenomic data and treatment outcomes.
3.2 Study Design Rationale; 9.2.2 Evaluations	Added new Section 3.2.5 describing the rationale for pharmacogenomic and biomarker evaluations; included information moved or copied from other sections. Removed Subsection 9.2.2.7, Genomic Assessments, that was a part of Section 9.2.2, Efficacy Evaluations.
9.5 Pharmacogenomic	Added "efficacy" to the list of outcomes that might be influenced by genetic factors.
Rationale: To assure a balance in treatment assignment by gender and include gender as a factor in analyses due to potential gender differences that may impact treatment endpoints. Additionally, to clarify the time point for determination of age for stratification.	
Synopsis Overview; 3.1 Overview; 3.2.1. Randomization; 5. Treatment Allocation	Substituted study center with gender as a stratification factor. Indicated that the age at the time of first consent will be used for stratification of randomization.
Synopsis Overview, Efficacy Analysis; 11.3.1. Primary Efficacy Endpoint	Replaced study center with gender as a factor in the primary efficacy analyses.
Rationale: To increase consistency in time of visits and type of day (weekday vs weekend) for visits during the treatment period, to reduce potential confounding effect of these on treatment endpoints.	
Time & Events; 9.1.1 Overview	Added recommendation for study visits to occur on the same type of day and same period of the day for each subject.

Applicable Section(s)	Description of Change(s)
Rationale: To remove the requirement for study visits to occur in the morning to accommodate subject and caregiver schedules.	
Time & Events; 6 Dosage; 9.1.1 Overview; 9.1.3 Treatment Phase; 9.4 Pharmacokinetics	Removed "morning," or changed to indicate that morning is preferred, from description of visits and dosing on day of visits.
Rationale: To clarify the visit window for the first screening visit and accommodate caregiver schedules by allowing a longer visit window for the second screening visit.	
Synopsis Overview; Time & Events; 3.1. Study Design; 9.1.1 Overview; 9.1.2 Screening	The maximum time between the first screening visit and Day 1 was changed from 21 days to 26 days. Removed screening visit window of ±5 days. The maximum time between the second screening visit and Day 1 was changed from 7 days to 14 days.
Rationale: The prohibitions and restrictions list did not include all applicable restrictions specified in the eligibility criteria.	
4.3 Prohibitions	Replaced the first restriction regarding contraception use with one that states that subjects must follow all requirements that must be met during the study as noted in the eligibility criteria.
Rationale: To add information regarding the order of procedures at study visits.	
Time & Events; 6 Dosage; 9.1.1 Overview; 9.1.3 Treatment Phase	Added or replaced information regarding the order of study procedures, and provided further information regarding the timing of study drug administration at study visits and at home.
Rationale: To add dosing instructions in the event of a missed dose.	
6. Dosage	Added statement that a missed morning dose can be taken later in the day, as long as 12 hours remain until the next dose.
Rationale: For consistency in ECG evaluations across study visits, the Follow Up Visit ECG was changed to a triplicate ECG.	
Time & Events; 9.6.4 Electrocardiogram	Indicated that triplicate ECGs are required at all ECG time points.
Rationale: The subject's position for collection of vital signs was changed from supine to sitting, as sitting is most appropriate for outpatient studies. Additionally, there was an erroneous statement regarding collection of standing blood pressure.	
Synopsis Safety Analysis; Time & Events; 9.6.3 Vital signs; 11.6 Safety analysis	Changed the subject's position for collection of vital signs to sitting.
Rationale: To change restriction durations on days of biomarker collection to be relative to a time that the subject can know (time of visits), rather than time of blood draws. Additionally, to add a specific duration for following a low-fat diet and simplify description of information collected on restrictions for biomarker collection.	
Time & Events; 4.3 Prohibitions; 8 Concomitant Therapy; 9.3 Biomarkers	Modified durations for restrictions on biomarker collection days to advise subjects to follow a low-fat diet for at least 8 hours prior to their scheduled visit. Also revised text to indicate that restrictions on strenuous exercise and NSAIDs are relative to *time of study visits*. Simplified the description of recording compliance to these restrictions.

Applicable Section(s)	Description of Change(s)
4.3 Prohibitions	Removed rationale for restriction on NSAIDs.
Rationale: JAKE Tablets will not be provided to caregivers; they will use their own devices to access the JAKE system at home.	
Definition of Terms; 15. Materials; 9.2.2.1. JAKE Portal	Removed provision of small personal computer or tablet (JAKE Tablet).
Rationale: Due to a recent change in sponsor privacy policy, the sponsor will not collect the full data of birth.	
Definitions; 3.2.6.3 JAKE Pipeline; 9.2.2.4 My JAKE Pipeline; 17.3 Subject identification	Removed date of birth or changed to either age at time of first informed consent or month and year of birth.
Rationale: Measurement of QTcF alone is considered sufficient for evaluation of QT prolongation.	
11.6 Safety Analysis	Removed QTcB from ECG data to be summarized.
Rationale: To remove requirement for clinical safety laboratory tests to be collected under fasted conditions in order to avoid unnecessary fasting. Safety can be monitored with samples collected under fed or fasted conditions.	
9.6.6 Laboratory Tests	Removed “under fasted conditions whenever feasible.”
Rationale: Samples collected for future research will not be anonymized and will not be permanently stored.	
10.2 Discontinuation; 16.2.5 Retention of Samples	Removed statement regarding possible anonymization of samples used for future research, and changed period for long-term storage to up to 15 years.
Rationale: Collection of vital signs from the opposite arm as blood sample collection is unnecessary, as the procedures will be performed at different times.	
9.1.1 Overview	Removed statement regarding vital signs collection from opposite arm from which blood samples are collected.
Rationale: To specify documentation of a thorough baseline neurological examination at screening, and subsequently permit more abbreviated/directed examinations if appropriate, to limit patient fatigue.	
9.6.5 Examinations	Indicated that the description of the neurological examination was for the screening examination, and added that examinations subsequent to screening may be more abbreviated and directed for follow up of abnormalities.
Rationale: To remove summaries of C-SSRS data that may not be performed; the planned analyses will be described in a separate Statistical Analysis Plan.	
11.6 Safety Analysis	Removed C-SSRS shift tables and reporting of separate endpoints for suicidal ideation and behavior.
Rationale: To provide additional instruction on reporting and evaluation of anticipated adverse events.	
12.3.1. Adverse Events	Added information regarding reporting and assessment of anticipated events.
Rationale: To specify the time period for reporting of product quality complaints (PQCs).	
13.1 PQC Procedures	Changed the time period for reporting of PQCs for the site to the sponsor from “as soon as possible” to within 24 hours after awareness of the event.
Rationale: To change the number of pills per bottle of study drug, to have sufficient supply to cover the visit windows.	
14.1 Study Drug	The number of pills per bottle was changed from 31 to 33.

Applicable Section(s)	Description of Change(s)
Rationale: Minor changes were made to improve clarity or readability, correct errors and inconsistencies, repeat or move text to other applicable sections, and remove unnecessarily redundant information.	
Time & Events	Modified several footnotes to improve clarity, remove redundant information, add or change references to sections of the protocol, or reflect protocol changes that are described elsewhere.
Time & Events	Added collection of background information at screening to row with medical history and demographics.
Synopsis PK; Time & Events; 9.4.1 PK Evaluations	Specified that the dosing on Day 15 will be after the "first" PK sample collection.
1. Introduction	Indicated that BIA 10-2474 is a FAAH inhibitor. Clarified that some references to "study" are referring to the Platform study/protocol.
Synopsis Objectives; 2.1 Objectives	Modified the description of the secondary objective regarding the biosensors to indicate that comparison will be made between treatments.
Synopsis Overview; 3.1 Overview	Modified the study design description, including addition of information included elsewhere in the protocol.
3.2.2.1 Rationale for Adolescents	Clarified the results of the Pacey et al (2016) study.
9.1.1 Overview	Added information regarding the designated caregiver being responsible for all caregiver-related activities.
4.3 Prohibitions; 8. Concomitant Medications	Clarified that the period for prohibition for inducers or inhibitors of CYP3A4 is from Day 1 through the end of the posttreatment period.
Time & Events; 4.3 Prohibitions	Changed "medications" to "therapy" in the description of information provided in Section 8.
5 Treatment Allocation	Added statement to clarify that the investigator is solely responsible for breaking the intervention code in emergency situations.
6 Dosage; 9.1.1 Overview; 9.1.3 Treatment Phase	Stated that dosing must occur after confirmation of eligibility and subjects' baseline safety assessments on Day 1 and after administration of the JAKE Task Battery at the Day 1 and Week 4 visits.
Synopsis Overview; 3.1 Overview; 6. Dosage; 9.1.3 Treatment Phase	Clarified that the baseline assessments at Day 1 are the baseline safety assessments, and that the Baseline Visit is the Day 1 visit.
Synopsis; 6. Dosage	Changed description of tablets (JNJ-42165279/placebo) from physically identical to identical in appearance.
Synopsis Efficacy; 9.2.2 Evaluations	Removed genomic measurements from list of efficacy evaluations.
9.2.2.1.1 ABI	Clarified a statement regarding the same caregiver or same site personnel completing the ABI. Deleted statement regarding completion of the ABI on the same days as completion of the caregiver and clinician-rated scales.
9.2.2.6.4 SRS-2; Attachments	Removed the Preschool version of the SRS-2 as an option for use in the study. Replaced the SRS-2 representative page with the School Age version.
11 Statistical Methods	Deleted subsection entitled "Pharmacodynamic Analysis," and moved section text to Section 11.5, PK and PK/PD Analysis.

Applicable Section(s)	Description of Change(s)
11.4 Biomarker and Pharmacogenomic Analysis	Indicated that the baseline biomarkers are collected at screening.
15. Materials	Updated list of materials to be provided.
16.1 Design Considerations	Corrected inconsistency with Section 10.2 by replacing specific liver function criteria for stopping treatment with general statement regarding elevated liver function analytes.
17.4 Source Documentation	Removed description of source documents for the JAKE system (to avoid confusion regarding available source documents) and revised description of the instruments and scales.
References	Deleted 2 references that were removed from body of protocol.
Throughout protocol	Indicated that attachments with questionnaires are representative examples.
Throughout protocol	Other minor changes in text were made.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 1 (9 March 2017)

The overall reason for the amendment: The overall reason for the amendment is to revise the eligibility age group of subjects in the study, add an interim PK analysis that will be conducted after randomization of at least 8 subjects (aged 13-17 years) on the active drug, include additional assessment visits for neurological examination and ABC, and to add ABC-I among safety assessments that will be performed for patients for whom C-SSRS is not feasible.

Applicable Section(s)	Description of Change(s)
Rationale: In order to ascertain the robustness of the ABI, a new secondary objective was included that examined its performance with that of the ABC.	
Synopsis; 2.1.1 Objectives	The following secondary objective was added: • To compare the performance of the ABI with that of the ABC.
Rationale: Based on health authority feedback, the eligibility age group of subjects enrolled in the study was revised from between 12 and 30 years (inclusive) to between 13 and 30 years (inclusive).	
Throughout protocol	The eligibility age group of subjects enrolled in the study was updated from between 12 and 30 years (inclusive) to between 13 and 30 years (inclusive).
4.1 Inclusion Criteria	Inclusion criterion 1 was revised to read: Subject must be a male between 13 and 30 years of age, inclusive. At least 50% of subjects in the study should be between 13 and 17 years of age, inclusive. Inclusion criterion 3 was revised to read: Subjects (18 years of age or older) must have a body mass index (BMI=weight/height^2) between 18 and 35 kg/m^2, inclusive, at screening. Subjects (between 13 and 17 years of age, inclusive) must have a BMI $\geq 5^{th}$ percentile and $<95^{th}$ percentile on the Centers for Disease Control and Prevention BMI-for-age percentile growth charts.

Applicable Section(s)	Description of Change(s)
Rationale: Neurological safety examinations were defined, and additional assessment visits for neurological examination were included in the Time and Events Schedule for clarity.	
Time and Events Schedule	In the Time and Events Schedule, additional assessment visits for neurological examination were added for Day 1, Week 4, and Week 8. Also, a new footnote f was included and subsequent footnotes were renumbered: f. A neurological examination should be conducted in the event of any adverse events of special interest as described in Section 9.6.6.
9.6.6 Physical and Neurological Examination	Section 9.6.6 was revised to include criteria for neurological safety examinations: The neurological examination can be adapted as necessary but should include mental status (orientation and memory); oculomotor motion and vision for cranial nerve testing; limb strength and abnormal movements for motor function; and tests of cerebellar function: gait, finger-to-nose, heel-to-shin, and rapid alternating movements. Tests of sensation (eg, pain, vibration, etc) should be included only if indicated by clinical history/symptoms.
Rationale: Based on health authority feedback, it was determined that ABC-I would be performed for patients for whom C-SSRS was not feasible. As such, ABC-I was included as a safety assessment that would be performed consistently throughout the study for patients for whom C-SSRS was not feasible.	
Time and Events Schedule	In the Time and Events Schedule, specified that ABC-I would be performed consistently throughout the study for patients for whom C-SSRS was not feasible. In addition, footnote g was revised to reflect the addition of ABC-I.
4.2 Exclusion Criteria	Exclusion criterion 1 was modified in order to include that ABC-I would be performed consistently throughout the study for patients for whom C-SSRS was not feasible.
9.6.3 Aberrant Behavior Checklist-Irritability Subscale	A new Section 9.6.3 Aberrant Behavior Checklist-Irritability Subscale was added (subsequent sections were renumbered).
Synopsis; 11.7 Safety Analysis	In the Synopsis and Section 11.7 Safety Analysis, a new subsection Aberrant Behavior Checklist-Irritability Subscale was included.
Rationale: In the JAKE Portal procedures, ABI (Caregiver) and ABI-S (Caregiver) assessment visits were revised for accuracy. Also, abbreviation for ABI (Clinician structured interview) was revised for clarity.	
Time and Events Schedule; 9.2.2.1.1 ABI	In the Time and Events Schedule and Section 9.2.2.1.1 ABI, an additional assessment visit for ABI (Caregiver) was added for Week 8. ABI-S (Caregiver) assessment visits were updated to be completed on Week 2 (site), Week 6 (home), and Week 10 (home). Accompanying footnote q was updated to read: q. The full ABI will be completed by the primary caregiver at screening, Day 1, Week 4, Week 8, and Week 12. The ABI must be completed at the site. The ABI-S will be completed by the primary caregiver on Week 2 (site), Week 6 (home), and Week 10 (home). The ABI-C will be completed by the PI or delegate at Day 1, Week 4, and Week 12. The Daily Tracker is completed twice daily by the caregiver. The caregivers are required to select 3 items to track on a daily basis. 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. See Section 9.2.2.1.1 for details on ABI administration.
Throughout protocol	Abbreviation for ABI (Clinician structured interview) was updated from ABI-SI to ABI-C for consistency.

Applicable Section(s)	Description of Change(s)
Rationale: The assessment visits for completing ABC were updated for alignment with that of ABI.	
Time and Events Schedule	Additional assessment visits for completing ABC were included for Screening (Days -7 to 1), Week 4, and Week 8.
Rationale: The assessment visits for completing CGI-S and CGI-I were revised for clarity.	
Time and Events Schedule	An additional assessment visit for completing CGI-S was included for Week 8. CGI-I was deleted from the Time and Events Schedule.
Rationale: Assessment visits for collection of venous blood samples for measurement of plasma JNJ-42165279 concentrations were revised for specificity.	
Time and Events Schedule	In the Time and Events Schedule, blood sample collection for JNJ-42165279 was revised to occur on Day 1 and Day 15. In addition, associated footnote s was updated: s. A venous blood sample will be collected for measurement of plasma JNJ-42165279 concentrations between 0.5 to 1 hour postdose (Day 1 and Day 15) and prior to the morning dose (Day 15 only). The date and time of study drug administration on Day 1, Day 14, and Day 15 must be accurately recorded. Subjects will be instructed to take the morning dose of study drug on Day 15 at the clinical site after collection of the PK blood sample.
Rationale: Definitions of terms was updated to include ABI-S and ABI-C for accuracy.	
Definitions of Terms	Added definitions for ABI-S and ABI-C.
Rationale: Added text describing study being intended as the first cohort in a planned platform study of autism using the JAKE system and ABI for clarity.	
1 Introduction	Paragraph was revised to read: The current study will be conducted to assess the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of treatment with JNJ-42165279 using the Janssen Autism Knowledge Engine (JAKE®) system in adolescent and adult male subjects with ASD. This study is intended as the first cohort in a planned 'Platform' study of autism using the JAKE system and the Autism Behavior Inventory (ABI). Additional cohorts, using different investigational compounds may be added, either one at a time or even in parallel over the course of the study. Additional cohorts may be added through 'Intervention Specific Appendices' to the protocol. Information may be shared between cohorts particularly on placebo subjects enabling fewer placebo subjects in later cohorts. The study would thus not be considered completed until the final cohort completes. The results from the study will afford a more comprehensive understanding of ASD, and will support the development of JNJ-42165279 as a potential treatment for the core and/or associated symptoms of ASD.
Rationale: Secondary objectives and secondary endpoints were updated to include ABI-C and CGI-S rating scales for accuracy.	
Synopsis; 2.1.1 Objectives	The following secondary objective was updated to include ABI-C and CGI-S: • Aberrant Behavior Checklist (ABC), Autism Behavior Inventory-Short Form (ABI-S), Autism Behavior Inventory-Clinician structured interview (ABI-C), Clinical Global Impression-Severity (CGI-S), Repetitive Behavior Scale-Revised (RBS-R), Zarit Burden Interview (ZBI), Child Adolescent Symptom Inventory-Anxiety (CASI-Anx), and Social Responsiveness Scale 2 (SRS-2) scales.

Applicable Section(s)	Description of Change(s)
Synopsis; 2.1.2 Endpoints; 9.2.1 Endpoints	The following secondary endpoint was updated to include ABI-C and CGI-S: • The change from baseline to Day 85 in the ABC, ABI-S, ABI-C, CGI-S, RBS-R, ZBI, CASI-Anx, and SRS-2 scales.
Rationale: Study design section was revised to specify the collection of a PK blood sample from eligible subjects on Day 1, and conducting an interim PK analysis following randomization of at least 8 subjects (aged 13-17 years) on active drug.	
Synopsis; 3.1 Overview of Study Design	In the Double-Blind Treatment Phase section, paragraph was revised to read: A pharmacogenomic blood sample will be collected from all eligible subjects at the time point described in the Time and Events Schedule. Participation in the pharmacogenomic research component is requested for the identification of genetic factors that may influence PK, pharmacodynamics (PD), safety and/or tolerability of JNJ-42165279. Subjects (aged 13-17 years) will be randomized until at least 8 subjects are on the active drug, following which screening of subjects of that age range will be temporarily paused while an interim PK analysis is conducted.
Rationale: In the rationale for dose selection section, text pertaining to use of allometric scaling to predict concentration-time profiles of 25 mg q.d. doses in adolescent subjects was revised for accuracy.	
3.2.3 Rationale for Dose Selection	Paragraph was updated to read: Allometric scaling was applied to predict the concentration-time profiles produced by 25 mg q.d. doses in adolescent subjects (12-17 years). Based on these simulations, exposures (ie, plasma C_{max} and AUC) up to 1.5 fold higher than in adults can be expected in subjects who are 12 years of age. Exposures up to 1.2 fold higher than in adults can be expected in subjects who are 15 years of age. Exposures in the 17 years age group are expected to be very similar to exposures observed in adults. Based on these results, no dose adjustments are recommended for adolescent subjects. Based on FDA age classification, enrollment will include subjects 13 years of age and older.
Rationale: A new section on the rationale for pharmacokinetic evaluations was added for clarity.	
3.2.4 Rationale for Pharmacokinetic Evaluations	In the new section, the following text was added: If warranted at the time of the interim analysis and after completion of the study, the plasma concentration-time data of JNJ-42165279 will be analyzed using population PK modeling. Concentration-time data will allow estimation of individual PK parameters for JNJ-42165279. It will also help to understand potential differences between ASD subjects treated with JNJ-42165279 and those treated with placebo. Time and days of JNJ-42165279 plasma concentration assessment were chosen to gather maximal information about the PK properties of JNJ-42165279 while minimizing subject burden regarding blood sampling.
Rationale: Descriptions of the components of the JAKE Portal were revised for accuracy.	
3.2.5.1 JAKE Portal	Descriptions of the components of the JAKE Portal were revised.
Rationale: The tasks and stimuli for use with the Periodic Biosensors were clarified for accuracy.	
3.2.5.2.2 Periodic Biosensors and JAKE Task Battery	Descriptions of tasks and stimuli for use with the Periodic Biosensors were clarified.

Applicable Section(s)	Description of Change(s)
Rationale: The Periodic Biosensor of Interest: Electroencephalogram Portion section was updated for better readability.	
3.2.5.2.2.1 Periodic Biosensor of Interest: Electroencephalogram Portion	Sections on Kanwisher Videos and Event Related Potentials to Direct/Averted Gaze Facial Stimuli were deleted. Section on NimStim Emotional was re-titled Event-related Potential Faces Compared to High Autism Interest Objects, and associated text was updated.
Rationale: Chawarska Videos was renamed Social Information Processing Task.	
3.2.5.2.2.2 Periodic Biosensor of Interest: Eye Tracking Portion	Chawarska Videos was replaced with Social Information Processing Task throughout.
Rationale: Section on FACET Portion was renamed Affect Detection Portion for clarity.	
3.2.5.2.2.3 Affect Detection Portion	FACET Portion was re-titled Affect Detection Portion.
Rationale: Section on Instruments for Measuring Change and Validating the ABI was renamed Instruments for Measuring Change for accuracy.	
3.2.6.2 Instruments for Measuring Change	Instruments for Measuring Change and Validating the ABI was re-titled Instruments for Measuring Change.
Rationale: Inclusion criterion 2 was modified to specify that an ADOS-2 completed by a trained professional within 6 months prior to screening visit would be acceptable if the item responses were available for entry into the eCRF as opposed to database.	
4.1 Inclusion Criteria	Inclusion criterion 2 was modified to read: Diagnosis of ASD in subjects must be according to DSM-5 criteria and made or confirmed using the ADOS-2 (minimum score of 8 [autism spectrum]). (An ADOS-2 completed by an adequately trained professional within the 6 months prior to screening visit will be acceptable if the item responses are available for entry into the electronic case report form [eCRF].)
Rationale: In order to promote subject eligibility and participation in the study, inclusion criterion 10 was revised to indicate that primary caregivers must have a means of obtaining internet connectivity for a desktop, laptop or tablet computer as opposed to possessing a portable electronic device capable of running the JAKE mobile applications.	
4.1 Inclusion Criteria	Inclusion criterion 10 was modified to read: Primary caregivers must have a reliable means of obtaining internet connectivity for a desktop, laptop or tablet computer.
Rationale: A new exclusion criterion was added to specify exclusion of subjects currently taking or those who have taken within the past month recreational or medically prescribed cannabis.	
4.2 Exclusion Criteria	A new exclusion criterion 7 was added (subsequent criteria were renumbered): Subject is currently taking or has taken within the past month recreational or medically prescribed cannabis.

Applicable Section(s)	Description of Change(s)
Rationale: Exclusion criterion 20 was updated to specify that a KBIT-2 conducted within the past 6 months was acceptable, as opposed to any IQ test.	
4.2 Exclusion Criteria	Exclusion criterion 20 was revised to read: Subject has a measured composite score on KBIT-2 of less than 50. A KBIT-2 conducted within the past 6 months is also acceptable provided the scores are available for entry into the eCRF.
Rationale: Prohibitions and Restrictions 2 was updated to specify that subjects must abstain from using recreational or medically prescribed cannabis, in addition to illegal drugs, from screening through the end of the posttreatment phase of the study.	
4.3 Prohibitions and Restrictions	Prohibitions and Restrictions 2 was modified to read: Subjects must abstain from using illegal drugs or recreational or medically prescribed cannabis from screening through the end of the posttreatment phase.
Rationale: In Prohibitions and Restrictions 6, replaced test battery with Task Battery for clarity.	
4.3 Prohibitions and Restrictions	Prohibitions and Restrictions 6 was modified to read: Subjects must not take any sedating medications on the day of the Task Battery (other than any preexisting daily medications) and must not consume caffeine within 2 hours prior to the battery.
Rationale: In the randomization section of Treatment Allocation and Blinding, text pertaining to conducting an interim PK analysis following randomization of at least 8 subjects (aged 13-17 years) on the active drug, was added for clarity.	
5 Treatment Allocation and Blinding	A new paragraph was added to the randomization section.
Rationale: In Section 9.2.2.1.1 ABI, created a new heading on ABI-C with a description of the assessment for clarity.	
9.2.2.1.1 ABI	A new heading on ABI-C was added: **ABI-C** The ABI-C is an abbreviated version of the ABI-S for completion by the clinician following a semi-structured interview with the caregiver or 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 severe difficulties with an area of functioning. There are 14 items across each of the 5 domains.
Rationale: Section Recording Mood was renamed Mood Report for consistency with the rest of the protocol.	
9.2.2.1.3 Mood Report	Section Recording Mood was re-titled Mood Report.
Rationale: Section 9.2.2.1.7 Other Sections was deleted for accuracy.	
9.2.2.1.7 Other Sections	Section was deleted.

Applicable Section(s)	Description of Change(s)
Rationale: Section Continuous Biosensors was renamed Continuous Biosensor. Content was revised to reflect a truly continuous plan.	
9.2.2.2.1 Continuous Biosensor	Section Continuous Biosensors was re-titled Continuous Biosensor. Paragraph on use of the biosensor was revised to read: The Continuous Biosensor is the Actigraph GT9X Link Wristband. The Actigraph 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.
Rationale: Section iMotions Attention Tool: FACET Module was renamed iMotions Biometric Research Platform: Emotient FACET Module. Content was updated for accuracy.	
9.2.2.2.2.4 iMotions Biometric Research Platform: Emotient FACET Module	Section iMotions Attention Tool: FACET Module was re-titled iMotions Biometric Research Platform: Emotient FACET Module. Paragraph was revised to read: iMotions® Biometric Research Platform: Emotient™ FACET Module (https://imotions.com/blog/facial-expression-analysis/) will be used for affect detection via computer recognition of subject affect. Facial recognition will take place throughout the administration of the JAKE Task Battery using a standard computer web camera.
Rationale: Content in JAKE Task Battery section was revised for accuracy.	
9.2.2.3 JAKE Task Battery: Tasks and Stimuli for use With Periodic Biosensor	Section was revised for accuracy.
Rationale: Content from subsections of the JAKE Task Battery was consolidated and described in tabular format for better readability.	
9.2.2.3 JAKE Task Battery: Tasks and Stimuli for use With Periodic Biosensor	Sections 9.2.2.3.1, 9.2.2.3.1.1, 9.2.2.3.1.2, 9.2.2.3.1.3, 9.2.2.3.1.4, 9.2.2.3.1.5, 9.2.2.3.2, 9.2.2.3.2.1, 9.2.2.3.2.2, 9.2.2.3.2.3, 9.2.2.3.2.4, 9.2.2.3.3, 9.2.2.3.3.1, 9.2.2.3.3.2, and 9.2.2.3.4 were deleted. Content from deleted sections were consolidated and described in tabular format.
Rationale: In the Child Adolescent Symptom Inventory Anxiety section, specified the range of responses in the scale for clarity.	
9.2.2.5.5 Child Adolescent Symptom Inventory Anxiety	Paragraph was revised to read: This study will use only the 21-point anxiety scale (CASI-Anx) which was recommended as a possible outcome measure for autism.[65] Responses will range from 0 (never) to 4 (very often).
Rationale: In the Repetitive Behavior Scale-Revised (parent) section, defined the range of responses in the scale for clarity.	
9.2.2.5.6 Repetitive Behavior Scale-Revised (parent)	Section was revised to read: The RBS-R (Attachment 8) 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).

Applicable Section(s)	Description of Change(s)
Rationale: Section Clinical Global Impression-Improvement was renamed Clinical Global Impression-Severity for accuracy. Content was updated to specify that the scale will be completed by both the clinician and caregiver for clarity.	
9.2.2.5.8 Clinical Global Impression-Severity	Section Clinical Global Impression-Improvement was re-titled Clinical Global Impression-Severity. Section was revised to read: The CGI-S scale assesses the severity of all illness. The CGI-S is a 7-point scale that requires the clinician and caregiver to assess the severity of the subject's illness at baseline and other visits as per the Time and Events Schedule. Versions of this scale used in this study are provided in Attachment 10.
Rationale: With regards to pharmacokinetic evaluations, added text to indicate that date and time of study drug administration must be recorded for accuracy. Also, included instructions on taking the morning dose of the study drug on Day 15 after collection of the PK blood sample on that day, for clarity.	
Synopsis; 9.4.1 Evaluations	Added a new paragraph: The date and time of study drug administration on Day 1, Day 14, and Day 15 must be accurately recorded. Subjects will be instructed to take the morning dose of study drug on Day 15 at the clinical site after collection of the PK blood sample on that day.
Rationale: Erroneously placed text pertaining to rationale was removed from the analytical procedures.	
9.4.2 Analytical Procedures	The following text was removed: Concentration time data will allow estimation of individual PK parameters for JNJ-42165279 using a population PK modeling approach. It will also help to understand potential differences between ASD subjects treated with JNJ-42165279 and those treated with placebo. Time and days of JNJ-42165279 plasma concentration assessment were chosen to gather maximal information about the PK properties of JNJ-42165279 while minimizing subject burden regarding blood sampling
Rationale: Section on PK parameters that will be evaluated was revised for accuracy.	
9.4.3 Pharmacokinetic Parameters	Section was revised for accuracy.
Rationale: Section on PK and PK/PD analysis was updated to describe conducting an interim PK analysis after at least 8 subjects (aged 13-17 years) were randomized to the active drug, for clarity.	
Synopsis; 11.6 Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis	Section was updated to describe conducting an interim PK analysis after at least 8 subjects (aged 13-17 years) were randomized to the active drug.
Rationale: Attachment 1 was re-titled Examples of Prohibited Cytochrome P450 Inhibitors and Inducers for clarity.	
Attachment 1: Examples of Prohibited Cytochrome P450 Inhibitors and Inducers	Attachment title was updated.

Applicable Section(s)	Description of Change(s)
Rationale: Attachment 2 was re-titled Janssen Autism Knowledge Engine (JAKE) ABI (Long Form, ABI-S, and ABI-C) and Daily Tracker for accuracy. Updated representative pages of scales were added.	
Attachment 2: Janssen Autism Knowledge Engine (JAKE) ABI (Long Form, ABI-S, and ABI-C) and Daily Tracker	Attachment title was updated, and revised representative pages of scales were added.
Rationale: Included representative pages of C-SSRS scales (children version, and adults and adolescents version) in Attachments 11 and 12 for accuracy.	
Attachment 11: Columbia Suicide Severity Rating Scale – BASELINE; Attachment 12: Columbia Suicide Severity Rating Scale – Since Last Visit	Included representative pages of C-SSRS scales (children version, and adults and adolescents version).
Rationale: List of anticipated events was updated in Attachment 13 for clarity.	
Attachment 13: Anticipated Events	List of anticipated events, based on reports by healthy subjects in Phase 1 studies, was updated to include: • anxiety • depression • self-injurious behavior • disruptive/challenging behavior
Rationale: Attachment 14 was re-titled Self/Caregiver-Assessment of Treatment Experience for accuracy. Revised pages of scale were added.	
Attachment 14: Self/Caregiver-Assessment of Treatment Experience	Attachment title was updated. Revised pages of scale were added.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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

JNJ-42165279 is a potent, selective, and orally bioavailable inhibitor of the enzyme fatty acid amide hydrolase (FAAH). This enzyme is primarily responsible for the degradation of a variety of fatty acid amides (FAAs), including the endocannabinoid N-arachidonoylethanolamine, or anandamide (AEA), the first identified endogenous cannabinoid receptor agonist. The endocannabinoid system is believed to play important roles in the regulation of the immune system, pain perception, affect, motivation, emotion, fear and anxiety responses. As such, the endocannabinoid system and FAAH inhibition could modulate the core symptoms associated with social communication deficits, and restrictive and repetitive behaviors (RRB). Evidence has demonstrated that the endocannabinoid system is involved in behavior and emotion directly relevant to Autism Spectrum Disorder (ASD). Modulation of behavior and emotion related to ASD is the basis for testing JNJ-42165279 for therapeutic effect in adolescent and adult subjects with ASD.

JNJ-42165279 has been studied in 7 Phase 1 studies and 2 Phase 2a studies. The Phase 1 studies included a single ascending dose regimen up to 250 mg and a multiple dose regimen of 100 mg once daily in healthy males, a study with healthy Japanese males administered a single dose and multiple dose regimen of 25 mg once daily for 10 days, a multiple dose study with cohorts receiving 10, 25, 75 or 100 mg for 10 days, a brain FAAH occupancy study using positron emission tomography (PET), a drug-drug interaction study (DDI), an oral bioavailability study, and a functional magnetic resonance imaging (fMRI) study with a dose of 100 mg once daily over 4 days to healthy males. Both Phase 2a studies evaluated the safety and efficacy of once daily dosing of JNJ-42165279 25 mg using a double-blind, randomized, placebo-controlled design. One of the Phase 2 studies included patients with severe social anxiety disorder, while the other evaluated patients with major depressive disorder with anxious distress.

OBJECTIVES AND HYPOTHESIS

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 ASD during 12 weeks of treatment on the following parameters:

- Autism Behavior Inventory (ABI) Core Domain Score (Social Communication and 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

Endpoints

Primary Endpoint

The primary endpoints will be measured as follows:

- Change from baseline to Day 85 in the ABI Core Domain Score (Social Communication and RRB).
- Change from baseline to Day 85 in the ABI Social Communication Domain Score.
- Change from baseline to Day 85 in the ABI RRB Domain Score.

Secondary Endpoints

The secondary efficacy endpoints are:

- The change from baseline to Day 85 in the ABI Mood & Anxiety, Challenging Behavior, and Self-Regulation domains.
- The change from baseline to Day 85 in the ABC, ABI-S, ABI-C, CGI-S, RBS-R, ZBI, CASI-Anx, SRS-2, and Caregiver GI-S.
- Caregiver Assessment of Treatment, Self GI-I, and CGI-I at Day 85.

Hypothesis

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 Domains (Social Communication and RRB), Social Communication Domain, or RRB 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.

OVERVIEW OF STUDY 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. An interim PK analysis is planned following Week 2 PK sample collection from approximately 8 adolescent subjects randomized to active drug.

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.

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.

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).

SUBJECT POPULATION

Subjects (13 to 35 years of age) with a definitive diagnosis of ASD using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), who have an IQ as measured by the KBIT-2 of ≥60, and who are capable of completing and complying with all study-specific requirements will be enrolled.

DOSAGE AND ADMINISTRATION

Following Protocol Amendment 5, subjects will self-administer double-blind study medication twice daily for 12 weeks. Study medication will be provided as JNJ-42165279 25 mg tablets, or matching placebo, packaged in bottles. All tablets (JNJ-42165279 /placebo) are identical in appearance.

EFFICACY EVALUATIONS

Evaluations throughout the study will encompass several categories:

- My JAKE/My JAKE MMApp, including the ABI, ABI-S, and Daily Tracker, as well as system components available only in My JAKE (Journal and Event Tracker, Therapy Tracker, and Medical/Development History), to be completed periodically as instructed.
- The ABI-C, to be completed periodically by the PI or delegate as instructed.
- The JAKE Sense Continuous Biosensor, with training and manuals to guide appropriate use.
- The JAKE Task Battery with the JAKE Sense Periodic Biosensors.
- Standard assessment instruments and rating scales for evaluating ASD core and related symptoms, functioning, clinicians' global impressions of disease severity and improvement, and caregiver stress.
- Caregivers' and subjects' global impressions (Caregiver GI-S, Caregiver Assessment of Treatment, Self GI-I).

PHARMACOKINETIC EVALUATIONS

Venous blood samples for analysis of JNJ-42165279 in plasma will be collected at the time points indicated in the Time and Events Schedule.

BIOMARKER EVALUATIONS

During the study, the following PD evaluations will be performed at the time points indicated in the Time and Events schedule: plasma concentrations of CCI [redacted].

Additionally, blood biomarkers related to autism (including but not limited to cytokines and miRNAs) will be investigated to allow for exploratory immunophenotyping and for an exploratory PD evaluation. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

The biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between ASD and phenotypes and biomarkers.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected from all eligible subjects. Deoxyribonucleic acid (DNA) samples will be analyzed for FAAH gene variants. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data. DNA samples may also be used for the identification of genetic and/or epigenetic factors that may influence the PK, PD, efficacy, safety and/or tolerability of JNJ-42165279, and for exploratory genetic and/or epigenetic analyses, including of autism.

DNA samples will be used for research related to JNJ-42165279 or ASD. They may also be used to develop tests/assays related to JNJ-42165279 or ASD. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to JNJ-42165279 or ASD clinical endpoints.

The pharmacogenomics data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between ASD and phenotypes and biomarkers.

SAFETY EVALUATIONS

During the study, regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to: vital signs, electrocardiogram (ECG), physical examination, adverse events, Columbia Suicide Severity Rating Scale (C-SSRS), Aberrant Behavior Checklist-Irritability Subscale (ABC-I), and clinical laboratory tests.

STATISTICAL METHODS

Sample Size Determination

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 (under BID dosing) to be randomly assigned to treatment in a 1:1 ratio (30 per group).

Efficacy Analysis

The primary efficacy analysis will be based on the ITT-BID analysis set. 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 RRB Domain Score during the double-blind treatment phase. Each will be analyzed using a mixed effects model for repeated measures (MMRM). The model will include time, treatment, time-by-treatment interaction, age group (13-17 years and 18-35 years, inclusive), and gender (male and female) as factors, and baseline score as a continuous covariate. An unstructured variance-covariance matrix will be used. In case of convergence problems, simpler variance-covariance structures such as Toeplitz or autoregressive order 1 (AR[1]) will be considered. 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.

For the secondary efficacy endpoints, comparisons between JNJ-42165279 and placebo will be performed by means of an MMRM model as described for the primary efficacy endpoints. Relationships between select biosensors and scales will be measured with the appropriate correlation analyses.

Biomarker and Pharmacogenomic Analysis

Baseline biomarker values (collected during screening) and changes from baseline to the time points specified in the Time and Events Schedule will be assessed. Biomarker values will be tabulated by treatment group over time points and summary statistics will be calculated. Associations between biomarkers and clinical endpoints will be explored. Correlations between CCI values with efficacy and other clinical evaluations will be assessed.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response.

Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis

An interim analysis will be conducted to evaluate the concentrations of JNJ-42165279 in plasma of adolescent subjects. The analysis would be performed after approximately 16 adolescent subjects (ie, 8 adolescent subjects randomized to active drug) have been randomized and participated in the PK sampling at the Week 2 visit.

The individual plasma JNJ-42165279 concentration-time values will be listed and summarized descriptively.

A population PK modeling of plasma concentrations of JNJ-42165279 will be undertaken, if warranted at the time of the interim analysis and after completion of the study.

Where appropriate, the relationship between plasma concentrations of JNJ-42165279 and corresponding plasma concentrations of CCI will be plotted to evaluate the relationships graphically.

Population PK/PD analysis of biomarkers and/or efficacy markers may also be performed, and a suitable dose- and/or exposure-response model may be developed.

Safety Analysis

All randomized subjects who receive at least 1 dose of study medication will be included in the safety analysis set. Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the double-blind treatment phase (ie, treatment-emergent adverse events [TEAEs], and adverse events that have worsened since baseline) will be included in the analysis. For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group and dose level. Serious adverse events will be summarized separately.

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline, and for observed values and changes from baseline at each scheduled time point.

Descriptive statistics of pulse, blood pressure (systolic and diastolic), temperature, and body weight values and changes from baseline will be summarized at each scheduled time point.

Subjects with abnormal findings in ECG will be listed.

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence tables.

Irritability, aggression, and self-injurious behavior based on the ABC-I will be summarized descriptively at each scheduled visit by treatment group.

TIME AND EVENTS SCHEDULE

Phase	Screening		Double-Blind Treatment [a]					Posttreatment [a,b] (Follow up)
							ET/EW [b]	
Visit Number	**1**	**2 [c]**	**3**	**4**	**5**	**6**	**7**	**8**
Week (end of)	**-**	**-**	**-**	**2**	**4**	**8**	**12**	
Day	**-26 to -3**	**-14 to -1**	**1**	**15**	**29**	**57**	**85**	**14 Days (±1 Week) After Last Dose**
Clinic Visit (C)	C	C	C	C	C	C	C	C
Study Procedures								
Screening/Administrative								
Informed consent (and assent, if applicable)	X							
Inclusion/exclusion criteria	X		X					
Medical history, demographics, and background information	X							
Prestudy therapy [d]	X							
Preplanned surgery/procedure(s)	X							
ADOS-2/Diagnosis of ASD	X							
KBIT-2	X							
My JAKE/My JAKE MMApp account set-up [e]		X						
GUID Generation		X						
Study Drug Administration								
Randomization			X					
Dispense bottles of JNJ-42165279 or placebo			X		X	X		
Oral dose of study medication [f]			*Twice daily from Days 1 to 85*					
Drug accountability					X	X	X	
Safety Assessments								
Physical examination	X		X				X	X
Neurological examination [g]	X		X		X	X	X	X
C-SSRS (if feasible) [h]	X		X	X	X	X	X	X
ABC-I [h]	X			X				X
Vital signs [i]	X		X	X	X	X	X	X
Body weight [j]	X		X		X		X	X
Height	X							
Clinical laboratory assessments [k]	X [l]			X	X	X	X [m]	
Serology [n]	X							
12-lead ECG (triplicate)	X						X	X
Urine drug screen	X [l]		X [l]	X	X	X	X	

Phase	**Screening**		**Double-Blind Treatment** [a]					**Posttreatment** [a,b] **(Follow up)**
							ET/EW [b]	
Visit Number	**1**	**2** [c]	**3**	**4**	**5**	**6**	**7**	**8**
Week (end of)	**-**	**-**	**-**	**2**	**4**	**8**	**12**	
Day	**-26 to -3**	**-14 to -1**	**1**	**15**	**29**	**57**	**85**	**14 Days (±1 Week) After Last Dose**
Clinic Visit (C)	C	C	C	C	C	C	C	C
Serum pregnancy test (β-hCG) (all women)	X							
Urine pregnancy test (WOCBP) [o]			X	X	X	X	X	X
My JAKE /My JAKE MMApp Procedures [p]								
ABI (Caregiver, full version) [q,r]		X	X		X	X	X	
ABI-S (Caregiver) [r,s]			Completed on Week 2 (site), Week 6 (home), and Week 10 (home)					
ABI-C (Clinician interview) [t]			X		X		X	
Daily Tracker [r,u]		*Continuous (twice daily)*						
Therapy Tracker [v]		*Continuous (as items are identified)*						
Medical/Developmental History [v]	*Continuous*							
Journal and Event Tracker [v]		*Continuous (3 events per week)*						
Other Rating Scales[w]								
CASI-Anx		X	X		X		X	
RBS-R		X	X		X		X	
SRS-2		X	X		X		X	
ZBI			X				X	
ABC [h]		X	X		X	X	X	
Caregiver GI-S			X		X	X	X	
CGI-S			X		X	X	X	
CGI-I					X	X	X	
Caregiver Assessment of Treatment							X	
Evaluation of JAKE							X	
Self GI-I							X	
JAKE Sense								
Eye Tracker Calibration Check [x]	X							
JAKE Task Battery with periodic Biosensors (counterbalanced for order) [y]			X		X		X	
Continuous Biosensor training (caregiver)		X	X					
Wear Continuous Biosensor (subject) [p]			*Continuous*					
Continuous Biosensor data collection (subject)				X	X	X	X	

Phase	Screening		Double-Blind Treatment [a]					Posttreatment [a,b] (Follow up)
							ET/EW [b]	
Visit Number	**1**	**2 [c]**	**3**	**4**	**5**	**6**	**7**	**8**
Week (end of)	**-**	**-**	**-**	**2**	**4**	**8**	**12**	
Day	**-26 to -3**	**-14 to -1**	**1**	**15**	**29**	**57**	**85**	**14 Days (±1 Week) After Last Dose**
Clinic Visit (C)	C	C	C	C	C	C	C	C
Pharmacokinetics								
Blood sample collection for JNJ-42165279			0.5–1.0h postdose	predose, 2.0-2.5h postdose			predose, 2.0-2.5h postdose	
Pharmacogenomics (DNA)								
Blood sample collection for pharmacogenomics [z]	X							
Biomarkers [aa]								
Blood sample collection for CCI	X			predose, 2.0-2.5h postdose			predose, 2.0-2.5h postdose	
Exploratory biomarkers (cytokines and miRNAs)	X						X	
Ongoing Subject Review								
Concomitant therapy [bb]	*Continuous*							
Adverse events	*Continuous*							

Footnotes:

a. Visits after Day 1 should be conducted within ±3 days of the scheduled visit day, except where otherwise specified. For each subject, treatment period visits should occur on the same type of day (weekday or weekend) and same period of the day (morning, afternoon; mornings are preferable), when possible.

b. If a subject discontinues treatment before the end of the double-blind treatment phase, early withdrawal (EW) assessments should be obtained. Follow up visit will take place 14 days (±1 week) after the early withdrawal visit.

c. Should not take place until all laboratory results become available. Only primary caregivers are required to attend; subject attendance is optional.

d. Prestudy therapy will include all medications taken within the 3 months before screening.

e. This includes set up of various accounts necessary for the study, including caregiver's Microsoft Account (for login authentication) and Microsoft HealthVault account for My JAKE users, or set up of My JAKE MMApp account.

f. Dosing on all treatment phase visit days will occur at the clinic. The in-clinic dose should be the subject's first dose for the day. The date and time of study drug administration in the clinic must be accurately recorded on Day 1, Week 2 and Week 12 visits, and the day immediately prior to the Week 2 and 12 visits (both morning and evening doses). Subjects will be instructed to take the study drug at the clinical site on Weeks 2 and 12 after collection of the first blood sample.

g. In addition to the time points indicated, a neurological examination should be conducted in the event of any adverse events of special interest as described in Section 12.2.

h. See Sections 9.6.2 and 9.6.2.1 for details on evaluation of suicidality, including when the C-SSRS and ABC-I will be administered and versions of the C-SSRS to be used. The irritability subscale (ABC-I) is part of the ABC; thus, the table above includes only ABC-I time points other than those in which the full ABC is administered.

i. Sitting blood pressure, pulse, and oral temperature.

j. Body weight will be measured with subjects lightly clothed.
k. Serum chemistry, hematology, and urinalysis. Samples at the Week 2 and 12 visits will be collected predose.
l. See Section 9.1.2 for circumstances in which repeat testing during screening is allowed.
m. Any clinically significant abnormalities observed at Week 12 or at EW should be repeated at follow up.
n. Including thyroid-stimulating hormone.
o. If the urine pregnancy test is positive, a serum β-hCG test will be performed. Investigators may perform additional pregnancy testing at their discretion, as clinically needed.
p. Continuous Biosensors and My JAKE/My JAKE MMApp components (other than the ABI) are used throughout the study and not restricted to discrete study visits.
q. The full ABI will be completed by the primary caregiver. The ABI must be completed at the site.
r. Paper versions are available for participants to use in the event that My JAKE and My JAKE MMApp are not available.
s. The ABI-S will be completed by the primary caregiver at the Week 2 visit (site), at home at the end of Week 6 (Day 43 ± 3 days), and at home at the end of Week 10 (Day 71 ±3 days).
t. The ABI-C will be completed by the PI or delegate.
u. The Daily Tracker will be completed twice daily by the caregiver (sleep quality rating each morning, tracking 3 behaviors and mood report in the evening). Following completion of the ABI at the screening visit, a clinician at the site will discuss possible behaviors to track with the caregiver and help them with their selection.
v. The Therapy Tracker, Medical and Developmental History, and Journal & Events are only available for participants who are using My JAKE and not My JAKE MMApp.
w. The CGI-S and CGI-I rating scales will be completed by the clinician. The Self GI-I will be completed by the subject. The remaining rating scales will be completed by the caregiver.
x. Eye tracker calibration can be repeated during the screening period, either at the Screening Visit 2 or at unscheduled visits, in order to meet the eligibility criterion.
y. Sites should make every effort to perform the Task Battery at approximately the same time of day for an individual subject throughout the study.
z. The pharmacogenomics (DNA) sample should be collected at the specified time point. However, if necessary, it may be collected at a later time point without constituting a protocol violation.
aa. A venous blood sample will be collected for multi-analyte biomarkers and for CCI analysis. Subjects should be advised to follow a low-fat diet for at least 8 hours prior to their scheduled visit. Subjects should be advised to refrain from strenuous exercise and use of NSAID medications for 24 hours before their scheduled visit.
bb. Concomitant therapies must be recorded throughout the study beginning with the signing of the informed consent to the final follow up visit (Visit 8).

Notes:
See Section 9.1.1 for the recommended order of procedures at study visits.

Abbreviations: ABC=Aberrant Behavior Checklist; ABC-I=Aberrant Behavior Checklist-Irritability Subscale; ABI=Autism Behavior Inventory; 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; Caregiver GI-S=Caregiver Global Impression-Severity; CASI-Anx=Child Adolescent Symptom Inventory-Anxiety; CGI-I=Clinical Global Impression-Improvement; CGI-S=Clinical Global Impression–Severity; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=Electrocardiogram; ET=End of Treatment; EW=Early Withdrawal; CCI ; GUID=globally unique identifier; JAKE=Janssen Autism Knowledge Engine; KBIT-2=Kaufman Brief Intelligence Test, Second Edition; MMApp= Mobile Medical App; NSAID=nonsteroidal anti-inflammatory drug; PI=principal investigator; PK=pharmacokinetics; RBS-R=Repetitive Behavior Scale–Revised; Self GI-I=Self Global Impression-Improvement; SRS-2=Social Responsiveness Scale 2; WOCBP=women of childbearing potential; ZBI=Zarit Burden Interview.

ABBREVIATIONS

ABA	applied behavior analysis
ABC	Aberrant Behavior Checklist
ABC-I	Aberrant Behavior Checklist-Irritability Subscale
ABI	Autism Behavior Inventory
ABI-C	Autism Behavior Inventory-Clinician interview
ABI–S	Autism Behavior Inventory-Short Form
ADI-R	Autism Diagnostic Interview-Revised
ADOS-2	Autism Diagnostic Observation Schedule, Second edition
AEA	N-arachidonoylethanolamine
anti-HCV	hepatitis C antibody
ASD	Autism Spectrum Disorder
BID	twice daily
BMI	body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
CASI-Anx	Child Adolescent Symptom Inventory – Anxiety
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression–Severity
CRF	case report form (paper or electronic as appropriate for this study)
CSF	cerebrospinal fluid
CYP	cytochrome P450
DDI	drug-drug interaction
DIF	Differential Item Functioning
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - 5th Edition
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EEG	electroencephalogram
EFA	Exploratory Factor Analysis
EMG	electromyogram
EOG	electrooculogram
ERP	event-related potential
FAA	fatty acid amide
FAAH	fatty acid amide hydrolase
FACET	Facial Expression Analysis
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GMR	geometric mean ratio
GSR	galvanic skin response
GUID	globally unique identifier
HAI	high autism interest
HBsAg	hepatitis B surface antigen
HR	heart rate
HRV	heart rate variability
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISI	interstimulus interval
IWRS	interactive web response system
JAKE	Janssen Autism Knowledge Engine
JDP	My JAKE Data Pipeline
JSW	JAKE Sense Workbench

KBIT-2	Kaufman Brief Intelligence Test, Second Edition
LAI	low autism interest
MDMA	3,4 methylenedioxy methamphetamine
My JAKE MMApp	My JAKE Mobile Medical App
MMRM	mixed effects model for repeated measures
NDAR	National Database for Autism Research
NIH	National Institute of Health
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
OEA	N-oleoylethanolamide
PD	pharmacodynamics
PEA	N-palmitoylethanolamide
PET	positron emission tomography
PHI	protected health information
PI	principal investigator
PK	pharmacokinetics
PQC	product quality complaint
PRT	Pivotal Response Training
RBS-R	Repetitive Behavior Scale – Revised
RDI	Relationship Development Intervention
RRB	Repetitive/Restrictive Behavior
SAE	serious adverse event
SAP	Statistical Analysis Plan
SRS-2	Social Responsiveness Scale 2
TBL	total bilirubin level
TD	typically-developing
TEACCH	Treatment and Education of Autistic and related Communication Handicapped Children
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential
ZBI	Zarit Burden Interview

DEFINITIONS OF TERMS

Autism Behavior Inventory	(or “ABI”) - A module of My JAKE; a series of approximately 65 questions related to the core and associated symptoms of ASD
Autism Behavior Inventory-Short	(or “ABI-S”) - A shorter version of the ABI with approximately 20 questions
Autism Behavior Inventory-Clinician	(or “ABI-C”) - Approximately 14-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.

JAKE Sense Workbench PC (JBW PC)	(or "JSW LAB PC") - The laptop / desktop computer used for administration of the JAKE Task Battery and configuration / synchronization of Periodic Biosensors
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 Event Tracker	(or "Event Tracker") - A module of My JAKE; an interface for tracking both positive and negative events (tantrum, stereotypy, social interaction, etc.) as they occur.
My JAKE Journal	(or "Journal") - A module of My JAKE; an interface for ad hoc free-text entry by caregivers and members of a subject's extended care team.
My JAKE Mobile	The mobile-based view of My JAKE/My JAKE MMApp. The My JAKE Mobile interface is available for 2 platforms: Android and iOS (v7+).
My JAKE	The original caregiver reporting application used in this study. A component of the JAKE System; the web and mobile based platform used by caregivers to interact with the JAKE System.
My JAKE Mobile Medical Application	A redesigned caregiver reporting application for use in this study. My JAKE Mobile Medical Application V1.0. MMApp is a web and mobile system used to collect caregiver information about the individual with autism spectrum disorder (ASD), or symptoms of ASD, for monitoring and outcomes assessment. My JAKE MMApp is not to be used as a standalone diagnostic tool.
JAKE System	The core elements of JAKE: My JAKE/My JAKE MMApp, 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
My JAKE Therapy Tracker	(or "Therapy Tracker") – A module of My JAKE; an interface for tracking a subject's various medical and other treatments and therapies.
JAKE Uploader	An internally-developed application used on the JSW LAB PC to facilitate the secure transfer of data collected by JAKE Sense. The JAKE Uploader organizes and encrypts submissions before sending them to the sponsor's secure file transfer protocol (SFTP) server.
My JAKE Web	The web-based view of My JAKE/My JAKE MMApp. The My JAKE Web interface is supported by most modern Internet browser programs.
Mentis	An internally-used project codename used to label activities and research studies (described in Section 1.1, Background).
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
PHI	Protected health information. PHI is 18 classes of information defined by United States law and regulation (45 CFR 164.514) that can be used to identify an individual.
RAVE	sponsor's eCRF system

1. INTRODUCTION

There is a growing interest in developing novel medicines for the treatment of Autism Spectrum Disorder (ASD). The emerging evidence from genomics, neuroimaging, and neurobiologic research is elucidating new molecular targets with the potential for clinical benefit. Given the high incidence of ASD (1 in 68 births in the United States of America [USA]), the significant unmet medical need, and long-term associated morbidity, there are multiple facets of the disorder that could benefit from novel treatments. There are currently no medications approved for the treatment of core symptoms of ASD.

JNJ-42165279 is a potent, selective, and orally bioavailable inhibitor of the enzyme fatty acid amide hydrolase (FAAH). This enzyme is primarily responsible for the degradation of a variety of fatty acid amides (FAAs), including the endocannabinoid N-arachidonoylethanolamine, or anandamide (AEA), the first identified endogenous cannabinoid receptor agonist. The endocannabinoid system is believed to play important roles in the regulation of the immune system, pain perception, affect, motivation, emotion, fear and anxiety responses. As such, the endocannabinoid system and FAAH inhibition could modulate the core symptoms associated with social communication deficits, and restrictive and repetitive behaviors (RRB). Evidence has demonstrated that the endocannabinoid system is involved in behavior and emotion directly relevant to Autism Spectrum Disorder (ASD).[122] Modulation of behavior and emotion related to ASD is the basis for testing JNJ-42165279 for therapeutic effect in adolescent and adult subjects with ASD.

JNJ-42165279 has been studied in 7 Phase 1 studies and 2 Phase 2a studies. The Phase 1 studies included a single ascending dose regimen up to 250 mg and a multiple dose regimen of 100 mg once daily in healthy males, a study with healthy Japanese males administered a single dose and multiple dose regimen of 25 mg once daily for 10 days, a multiple dose study with cohorts receiving 10, 25, 75 or 100 mg for 10 days, a brain FAAH occupancy study using positron emission tomography (PET), a drug-drug interaction study (DDI), an oral bioavailability study, and a functional magnetic resonance imaging (fMRI) study with a dose of 100 mg once daily over 4 days to healthy males. Both Phase 2a studies evaluated the safety and efficacy of once daily dosing of JNJ-42165279 25 mg using a double-blind, randomized, placebo-controlled design. One of the Phase 2 studies included patients with severe social anxiety disorder, while the other evaluated patients with major depressive disorder with anxious distress.

The participation, dosing, and enrollment in the Phase 2a studies was voluntarily suspended by Janssen on 16 January 2016 following the report of serious adverse events (SAEs) occurring in a Phase 1 clinical study conducted by Biotrial, Rennes, France while evaluating BIA 10-2474, a FAAH inhibitor from Bial Pharmaceutical company, Trofa, Portugal. Janssen received formal notification from the US FDA of the full clinical hold of 3 active Investigational New Drug Applications (INDs) related to JNJ-42165279, pending further investigation into the cause of the Bial trial's serious adverse events. Investigations were completed by European and US health authorities and the hold placed by the FDA was removed on 22 September 2016.

Results from preclinical studies on ASD have determined that variation/mutation/disruption of the endocannabinoid system is associated with behavioral and electroencephalogram (EEG) changes.[45,59,132] Specifically, the CB_1 cannabinoid receptors and their endogenous ligands (AEA and 2-arachidonoyl-*sn*-glycerol [2-AG]) have been associated with modulating social play and social anxiety, 2 pivotal facets of social behavior.[14,49,96,131] In a study that examined genes with abnormal expression levels in the cerebella of subjects with autism compared with control subjects, it was determined that the *CB1* gene demonstrated a 30% down-regulation in subjects with autism.[98] Furthermore, *CB1* gene variations contributed to regulating the perception of signals of social reward, such as happy faces, suggesting that *CB1* is a critical component in the molecular perception of social behavior.[25] FAAH inhibitors and other endocannabinoid modulators reverse core ASD behaviors and comorbidities in preclinical models.[59,132] For instance, a recent study in mice has demonstrated that AEA signaling at CB_1 receptors modulates the incentive salience of social interactions, and this was independent of AEA's ability to regulate anxiety.[141] Oxytocin receptor activation by endogenous oxytocin enhances AEA mobilization in the mouse nucleus accumbens. This indicates that oxytocin functions as a social reinforcement signal within this limbic region. Furthermore, heightened AEA signaling (via FAAH inhibition) stimulates social reward and occludes the prosocial effects of oxytocin. These results suggest that pharmacologic modulation of oxytocin-driven AEA signaling via a FAAH inhibitor (such as JNJ-42165279) may be beneficial in the treatment of social impairment in ASD. Overall, these findings support the hypothesis that modulation of the endocannabinoid system by a FAAH inhibitor may improve the core symptoms of ASD.

The current study will be conducted to assess the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of treatment with JNJ-42165279 using the Janssen Autism Knowledge Engine (JAKE®) system in adolescent and adult subjects with ASD. This study is intended as the first cohort in a planned 'Platform' study of autism using the JAKE system and the Autism Behavior Inventory (ABI). Additional cohorts, using different investigational compounds may be added to the Platform study, either one at a time or even in parallel over the course of the study. Additional cohorts may be added through 'Intervention Specific Appendices' to the Platform protocol. Information may be shared between cohorts, particularly data from placebo subjects, enabling fewer placebo subjects in later cohorts. The Platform study would thus not be considered completed until the final cohort completes. The results from the study will afford a more comprehensive understanding of ASD, and is intended to support the development of JNJ-42165279 as a potential treatment for the core and/or associated symptoms of ASD.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of JNJ-42165279, refer to the latest version of the Investigator's Brochure (IB) for JNJ-42165279.

Nonclinical Studies

Nonclinical Pharmacology

JNJ-42165279 is a mechanism-based inhibitor of FAAH (IC_{50s} of 26 ±4.9 nM [human] and 500 ± 70 nM [rat] at native FAAH) with behavior consistent with a slowly turned-over enzyme substrate. Extensive in vitro profiling, including CEREP and kinase panels, radioligand binding, functional assays, and proteomics studies, has shown this compound to be highly selective.

Nonclinical effects of JNJ-42165279 have been demonstrated in 3 in vivo pain models in rats: the mild thermal injury model of acute burn pain, the formalin paw model of tonic pain, and the spinal nerve ligation model of neuropathic pain. Doses that produced maximal FAAH enzyme inhibition in white blood cells (WBCs) and brain corresponded to doses that produced maximal efficacy in the spinal nerve ligation model of neuropathic pain. CCI

CCI

Therefore, safety margins in adolescents are expected to be very similar to those in adults. CCI

CCI

These exposures have been used to calculate safety margins from the preclinical study data.

Safety Pharmacology

CCI

Pharmacokinetics and Product Metabolism in Animals

CCI

During pregnancy, rat and rabbit fetuses were well exposed to JNJ-42165279 and the drug distributed to the eyes of both species. In concert with the substantially higher (4-fold) plasma exposures in rabbit compared to rat dams, the rabbit fetus also had higher exposure (2 to 4 –fold comparing plasma and whole fetus exposure in rats and rabbits) to JNJ-42165279. In addition, the exposure in rabbit fetal eyes was 3-fold higher than that in rat fetal eyes. Comparing total radioactivity to JNJ-42165279 levels, it is evident that JNJ-42165279 was more extensively metabolized in rats than rabbits leading to a higher metabolite burden in the rat fetuses (fetal eye, plasma, and whole) than in rabbits despite the generally higher exposures in rabbits.

No information is currently available about any pharmacology of any metabolites of JNJ-42165279.

Toxicology

The oral toxicity of JNJ-42165279 was characterized in GLP 2-week and 3-month toxicity studies in rats and dogs. In the GLP 3-month studies, adverse effects on coagulation parameters (increased prothrombin time [PT] and activated partial thromboplastin time [aPTT]) and the reproductive organs (decreased sperm motility and abnormal sperm morphology) were observed in male rats at all doses. In female rats, microscopic changes were observed in the kidney (mineralization and vacuolar degeneration) at ≥25 mg/kg, while there were no findings at the low dose of 5 mg/kg. Based on these findings, the no observed adverse effect level (NOAEL) could not be established in male rats and was 5 mg/kg in female rats. Relative to exposures at the intended clinical dose of 25 mg BID (C_{max}= 273 ng/mL and AUC = 3886 ng.h/mL), C_{max} and AUC exposures in the female rats provide 8-fold and 3-fold margins respectively. In dogs, doses of 5 and 15 mg/kg were well tolerated, while adverse effects at 100→50 mg/kg were noted in the

liver and gall bladder (vacuolation with cellular degeneration or necrosis that correlated with mild increases in aspartate transaminase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], and gamma-glutamyltransferase [GGT]), thymus (atrophy), bone (hypercellularity of the erythroid cell line in sternal bone marrow), and epididymis/testis (decreased sperm numbers and secondary spermatid degeneration/depletion). Based on these findings, the NOAEL in dogs was 15 mg/kg, providing C_{max} and AUC margins of at least 21-fold and 20-fold over those at the anticipated human exposures.

Reproductive and embryo-fetal safety was evaluated in rats and rabbits. Male rats treated with JNJ-42165279 for 4 weeks had significantly reduced sperm motility and increased number of abnormal sperm at doses of 100 and 200 mg/kg but not at 25 mg/kg; these changes were fully reversible following a 4-week recovery period and are considered exaggerated effects of FAAH inhibition. JNJ-42165279 at the high dose of 100 mg/kg, but not at ≤30 mg/kg, induced changes in female rat oestrus cycling (regularity and cycle length), which is also likely an exaggerated effect of FAAH inhibition. The C_{max} (3,280 ng/mL) and AUC (9280 ng.h/mL) exposures in male rats at 25 mg/kg (the NOAEL for fertility findings) provide margins of 12- and 2.4-fold over the anticipated human effective levels. In pregnant rats and rabbits, JNJ-42165279 induced minimal maternal toxicity in both species (decreased food consumption and body weight gain). There were no fetal changes in rabbits. In rabbits, the NOAEL for fetal toxicity was the highest dose tested, offering C_{max} and AUC margins of over 64-fold. Rat fetuses at the high dose of 100 mg/kg showed a significant increase in incidence of background primary lens fiber swelling and degeneration with or without fragmentation on histological evaluation. When offspring of pregnant rats dosed with JNJ-42165279 were allowed to grow to maturity, ophthalmoscopy revealed a significant increase in the incidence of nuclear cataracts at the high dose of 100 mg/kg with a slight trend at 30 mg/kg. Primary lens fiber swelling, focal degeneration and nuclear cataracts are common background findings in rats, but these were exacerbated by treatment with JNJ-42165279. Following an integrated assessment of the lens findings in 3 rat studies, the NOAEL for fetal toxicity was 10 mg/kg. At this dose, C_{max} and AUC exposures (3,660 ng/mL and 19,200 ng.h/mL) provide 13-fold and 5-fold margins over anticipated mean human exposures at the dose of 25 mg BID. Adjusting for plasma protein binding (6.4% free in humans vs 9.1% free in rats), the C_{max} and AUC margins are 19- and 7-fold, respectively. No treatment related changes were noted in adult eyes exposed to JNJ-42165279 for up to 3 months.

JNJ-42165279 was not genotoxic in the in vitro bacterial/microsomal activation assay, the mouse lymphoma assay, or the in vivo chromosome aberration test in rats.

Clinical Studies

JNJ-42165279

This will be the tenth study (7 Phase 1 studies completed, 2 Phase 2a studies completed, and this study) involving the administration of JNJ-42165279 to humans.

A double-blind Phase 1 study (Study 42165279EDI1001) was completed with 29 healthy male subjects to evaluate the safety, tolerability, PK, and PD activity of JNJ-42165279 after single and repeated oral dosing. In Part 1, 2 cohorts (both n=9) received single ascending doses of

JNJ-42165279 or placebo during each of 3 or 4 dosing periods, separated by washout periods, using an alternating panel design. Two additional subjects participated in Panel 1 but withdrew from the study after the first dosing for reasons unrelated to safety or tolerability; 1 received placebo and 1 received JNJ-42165279.

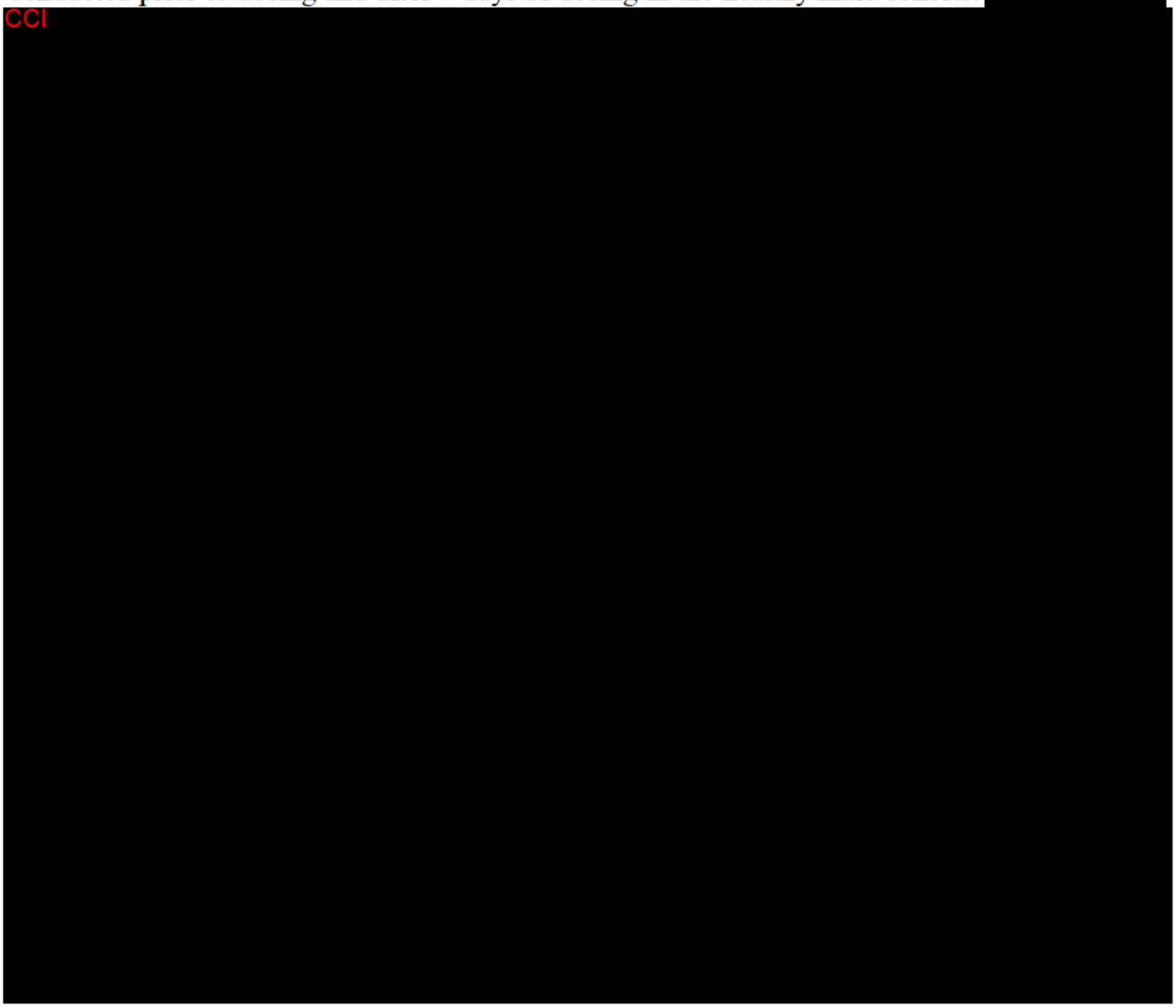
Doses studied in a fasted state were 2.5, 10, 30, 100, 175, and 250 mg. An additional 30-mg dose was also administered after intake of a regular meal. In Part 2, a separate cohort of 9 subjects received either 100 mg JNJ-42165279 (n=6) or placebo (n=3) once-daily for 6 consecutive days in a fed state. JNJ-42165279 was administered as an oral suspension (5 mg/mL or 50 mg/mL) throughout the study.

After a single dose, systemic exposure to JNJ-42165279, expressed as C_{max}, AUC_{last}, and AUC_{∞}, increased with increasing dose. CCI

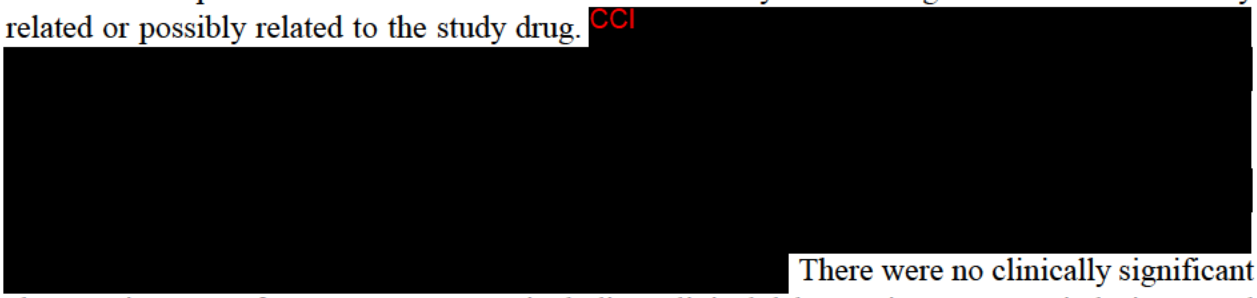
JNJ-42165279 was found to be well tolerated. There were no clinically significant changes in any safety measurements, including clinical laboratories, ECGs, vital signs, and physical and neurological examinations. There were no changes or abnormal findings in blood coagulation parameters. There were no deaths, SAEs, or discontinuations due to adverse events. All adverse events reported were mild in severity and had resolved by the time of the follow up visit. The most frequently reported adverse events for subjects receiving JNJ-42165279 were headache, nasal congestion, and dizziness.

In the second multiple ascending dose (MAD) study 42165279EDI1002, 5 cohorts were studied: healthy males at 10 mg, 25 mg, and 75 mg; healthy females (non-child-bearing potential) at

100 mg, and healthy elders at 100 mg. Six subjects were on active and 2 on placebo in each cohort. All subjects were dosed for 10 days and cerebrospinal fluid (CSF) sampling was conducted prior to dosing and after 7 days of dosing in the healthy male cohorts. CCI



The most common TEAEs (≥3 subjects per dose group) in subjects dosed with JNJ-42165279 were headache, dizziness, and fatigue. Overall, more TEAEs were reported with JNJ-42165279 compared with placebo. All the TEAEs were either mild or moderate in intensity. None of the TEAEs was reported as severe and all were considered by the investigator as either doubtfully related or possibly related to the study drug. CCI



There were no clinically significant changes in any safety measurements, including clinical laboratories, ECGs, vital signs, and physical and neurological examinations. There were no changes or abnormal findings in blood

coagulation parameters. There were no deaths, SAEs, or discontinuations due to adverse events. Subjects receiving 100 mg reported slight similarity to sedatives and dissimilarity to stimulants on the Addiction Research Center Inventory-53; no groups reported similarity to cannabinoids. No subjective effects were reported in any of the cohorts by Bond-Lader visual analogue scales.

During the DDI study 42165279EDI1004 16 subjects received a single 30 mg JNJ-42165279 dose on Day 1. Thereafter, they received single oral doses of 200 mg itraconazole from Day 4 to Day 10 (inclusive). Subjects also received a dose of 30 mg JNJ-42165279 along with 200 mg itraconazole on Day 8.

CCI [redacted]

In the safety analysis, the most frequently reported TEAEs (n=2) were dry throat (JNJ-42165279), rhinitis (itraconazole), and erythema (JNJ-42165279 and itraconazole). All other TEAEs were reported as a single incident. All the TEAEs were mild in intensity except for 2 TEAEs (dry throat after JNJ-42165279, and bone contusion after JNJ-42165279 and itraconazole treatments) which were moderate in intensity. None of the TEAEs were reported as severe and all of the TEAEs resolved at the end of the study. None of the TEAEs were probably or very likely related to the study drug. Two subjects had TEAEs of elevated ALT. However, both events were mild in intensity and were considered possibly related to itraconazole by the investigator.

An analysis of brain FAAH occupancy by JNJ-42165279 using PET of ^{11}C-MK-3168 has been conducted (study 42165279EDI1003). CCI [redacted] From the analysis of safety data, it was determined that all TEAEs reported in the study were mild in severity and all TEAEs were considered to be not related to the study agent, except for the event of headache, which was reported as possibly related to the study agent.

CCI [redacted]

CCI

Study 42165279ANX1001 examined whether JNJ-42165279 (100 mg administered once daily over 4 days) affected blood oxygen level dependent (BOLD) fMRI signals in the amygdala elicited by an Emotional Face Processing Task, in healthy young male subjects. In the safety analysis, no deaths or other SAEs were reported. A total of 14 (63.6%) subjects in the JNJ-42165279 group and 9 (42.9%) subjects in the placebo group reported at least 1 TEAE. The most frequently reported TEAE in the JNJ-42165279 group was headache (reported in 4 subjects [18.2%]), followed by fatigue, nasal congestion, and nasopharyngitis (each reported in 2 subjects [9.1%]). The most frequently reported TEAEs in the placebo group were headache, fatigue, dizziness, nausea (each reported in 2 subjects [9.5%]). All TEAEs were mild in severity, with the exception of 1 moderate TEAE (blood creatine phosphokinase increased, in a subject assigned to placebo). Most TEAEs were considered to be unrelated or of doubtful relationship to study agent by the investigator. Five subjects in the JNJ-42165279 group and 5 subjects in the placebo group had a TEAE that was considered possibly or probably related to study agent by the investigator; no subject had a TEAE that was considered by the investigator to be very likely related to study agent. TEAEs considered possibly or probably related were headache, dizziness, fatigue, nausea, palpitations, migraine, energy increased, nasal congestion, and insomnia. All TEAEs had resolved by the end of the study. No suicidal ideation or suicidal behavior was reported based on the results of the Columbia Suicide Severity Rating Scale (C-SSRS). No clinically relevant changes in mean vital sign parameters and mean laboratory parameters were observed in the JNJ-42165279 or placebo group. There were no clinically relevant changes observed in liver

function tests. In light of the reports from the Biotrial study, T1 weighted scans obtained during the Day 4 MRI session were evaluated by an independent neuroradiologist, and no findings of concern were noted.

The clinical effects of JNJ-42165279 in patients with severe social anxiety disorder were investigated in a double-blind, parallel-group, Phase 2a study (42165279SAX2001). A total of 149 patients were randomized to receive once daily treatment with either JNJ-42165279 25 mg or placebo for 12 weeks. The treatment groups did not significantly differ in improvement in the Liebowitz Social Anxiety Scale (LSAS) total score (primary endpoint), nor in other measures of anxiety and depression. The percentage of subjects with ≥ 30% improvement on the LSAS total score was significantly higher in subjects treated with JNJ-42165279. Additionally, the percentage of subjects much improved or very much improved on the CGI was also significantly higher in subjects treated with JNJ-42165279. The occurrence of TEAEs was similar across the 2 treatment groups (62.2% JNJ-42165279 versus 56% placebo). The most frequent TEAEs in subjects treated with JNJ-42165279 were headache, fatigue, upper respiratory infection, diarrhea, and nasopharyngitis. There were 2 SAEs reported in the JNJ-42165279 treatment group: anaphylaxis due to accidental egg ingestion in a subject with known allergy, considered unrelated to study drug, and alcohol use disorder considered doubtfully related to study drug. There were no SAEs reported in the placebo group.

Another Phase 2a study, 42165279MDD2001, investigated the effects of JNJ-42165279 in patients diagnosed with major depressive disorder with anxiety symptoms who were not receiving adequate control with their SSRI/SNRI treatment. In this randomized, double-blind, parallel-group study, patients received once daily treatment with JNJ-42165279 25 mg or placebo for 6 weeks after a placebo lead-in period. There were no significant treatment differences in the primary endpoint, the Hamilton Depression Rating Scale ($HDRS_{17}$), or in other efficacy measures. The proportion of patients experiencing TEAEs was 23.4% in the JNJ-42165279 group and 36.8% in the placebo group. TEAEs occurring in 2 or more subjects treated with JNJ-42165279 were headache and nasopharyngitis (3 subjects each), and neutropenia (2 subjects). There were 2 SAEs experienced by subjects in the JNJ-42165279 treatment arm: a bunion resulting in elective/corrective surgery and an anaphylactic reaction due to accidental shrimp ingestion by a subject with known shellfish allergy, which occurred 14 days into the withdrawal period. One placebo subject experienced an SAE of gastroenteritis during the treatment period. See Section 3.2.3 for information on PK/PD analyses performed for this study.

For more details about the clinical data please refer to the IB.

JAKE System

A series of studies have been conducted leading up to the present study to test and assess various components of the overall JAKE System.

MENTIS-HV-001

The primary objective of this study was to assess the functionality of preliminary, testable components of JAKE, for use as a digital health data capture system in adult subjects without

autism. The secondary objective was to assess the feasibility of deployment and in-home use of JAKE for up to 24 weeks. This included an examination of use patterns of preliminary, testable JAKE components. The exploratory objective was to explore the relationship between biosensor data and self-reported information on health, mood, and activity.

The JAKE preliminary, testable components included in the study were the following:

1. A pre-production-environment (PPE) version of Microsoft HealthVault
2. The web-based JAKE User Interface (UI)
3. The JAKE smart phone application (App) that prompted participants for information about mood, sleep, and activity throughout the day (available on Android and iOS devices)
4. FitBit®Flex™, a wrist band biosensor that measures activity and sleep
5. Affectiva Q™, a wrist band biosensor that measures skin conductance
6. FitBit®Aria™ WiFi Scale to measure body weight
7. A confidential, private database where information collected through JAKE and biosensors was stored
8. Cerora MindReader™, a portable, single-lead wireless EEG device (OPTIONAL COMPONENT).

A total of 25 subjects (17 males, 8 females) were screened and enrolled in the trial. Of those, 21 subjects completed the trial.

In general, the results of the System Usability Scale suggested that subjects had a favorable view of the system. Scores on individual items generally improved between Visit 2 and Visit 3, as subjects gained more experience with the system. Examples of items that were more favorably rated included: “I think I would like to use this website frequently” (median=agree), “I thought the website was easy to use” (median=agree), and “I found the various functions in this website were well integrated” (median=agree). Less favorably rated included: “learning how to use it required a little / no time” (median=agree somewhat), “after using it for a while you can’t imagine not having it” (median=neither agree nor disagree), and “makes me feel in control when managing various aspects of Autism” (median=neither agree nor disagree). Some of the less favorable items, however, were more oriented towards a clinical population ie, ASD, rather than a healthy volunteer population, and this may have affected subjects’ ability to respond appropriately.

Several system problems and software bugs were identified, including scaling problems with items on the phone application, registration difficulties and problems with initial application downloads, and difficulties with visualization of data from symptom ratings. These were fixed during the course of the trial, and retested with a successful outcome.

Subjects entered a large amount of presumed fictitious medical history information, ranging from vital signs (blood pressure example provided below), to family history, to medical conditions and medications. As an example, 17 subjects provided hypothetical blood pressure ratings (not from actual sphygmomanometer measurements), with a total of 35 observations. This demonstrates

the feasibility of transferring dynamic measures of vital signs from HealthVault (in this case, a fictitious PPE account) into the research data warehouse. In the future, these data could be generated from automated devices, from medical records obtained directly from physicians' offices, or self-entered data.

Subjects were also able to successfully utilize the Affectiva Q sensor band, and data from this band were uploaded for further analysis showing readings of activity/movement, sleep (in some cases), and galvanic skin response within expected levels for healthy adults. A large proportion of subjects were able to complete the voluntary EEG portion of the study, and a total of n=11 participants completed at-home administration of the EEG battery. Data demonstrated that it is feasible to conduct home-based self-administration of EEG and computer-based tasks. This was true across the various tasks included in the approximately 20-minute EEG battery. Several data discrepancies were noted which suggest that careful instruction and training may still result in minor inaccuracies that could have an impact on data quality, particularly in a clinical population (ie, individuals with ASD, with tests administered by a parent).

Of the 21 subjects who completed, a total of 3 subjects reported adverse events. All 3 adverse events were related to the Affectiva Q sensor: all events were skin irritation and itching (2 mild, 1 moderate severity).

Results of this study confirmed the feasibility of utilizing a web-and-mobile system, as well as home and lab-based biosensors, for use in clinical trials. Important information was gleaned about the registration process, other procedures including connection and synchronization of devices, system bugs, and on the form factor of the MLE. The system itself was deemed to be easy to use once registration and linking of devices was complete. Further, connection of the MLE to, and biosensor data transfer into, Microsoft HealthVault was successful, as was data extraction from the HealthVault PPE to the Janssen Research Data Warehouse. Feedback provided on the MLE resulted in identification of pain points, as well as myriad constructive suggestions for how to improve the system.

Overall, the frequency and severity of adverse device effects was limited, resolved without intervention, and did not result in any long-term consequences to subjects.

MENTIS-AUT-0001

This Investigator Initiated pilot research study helped to evaluate how well-established JAKE System features would work in an applied setting, as well as informed future directions for JAKE System development.

This study utilized the Affectiva Q sensor device and a prototype web interface and personal health record platform developed by ilumivu, Inc. (the ilumivu Platform).

The following specific aims guided the pilot study:

1. Evaluate the usability and feasibility of stakeholders (ie, healthcare professionals) using the ilumivu Platform to collect behavioral and physiological data from individuals with ASD multiple times per day over several days.
2. Learn what elements of the ilumivu Platform will make multimodal data collection easy, useful, and compelling for stakeholders to use.
3. Assess the functionality of specific components of the ilumivu Platform, including:
   A. Symptom ratings (both routine and momentary);
   B. Biosensor data collection;
   C. Stakeholder journaling;
   D. Charting/visually displaying obtained information; and
   E. Communicating between parents, school staff, and researchers.

From February 1, 2014 through April 25, 2014 (82 days), 91 Center for Discovery (CfD) staff members and parents used the ilumivu Platform to record information about 20 children in their care.

The trial successfully accomplished its goal by providing the research team with a clear understanding of what the JAKE System will be required to do in order to be clinically useful in a real-world setting. Responses from participants were critical in helping to determine clinical use and research needs while shaping the system into an effective tool for these particular stakeholder groups. Many new features and ideas were gained from talking to the staff and parents who used the system. A rich multi-user dataset was created to help inform both the Center for Discovery's clinical practice and their staff management policies.

MENTIS-HV-002

This study, conducted across 3 laboratories at Northeastern University, aimed to compare the usability, sensitivity, and accuracy of various experimental biosensors to that of their gold-standard, laboratory instrumentation counterparts. Feedback from this study informed decisions on future development of the JAKE Biosensor Array.

The study was conducted in healthy, adult subjects and utilized tasks and stimuli to test the full-range of sensing capabilities of the various sensors in a single session.

The sensors modalities tested were actigraphy, galvanic skin response (GSR), ECG, EEG, and eye tracking.

Ten subjects were tested with EEG, 10 with eye tracking and 20 with actigraphy, GSR and ECG.

The study demonstrated that mid-range actigraph, eye tracking and EEG equipment were logistically feasible to use and provided data quality sufficient for the intended analyses in future studies.

The mid-range ECG device was superior to the lab instrumentation.

The GSR devices tested were not comparable to the lab instrumentation, likely due to the lack of wet electrodes and to the placement on the wrist rather than the palm or fingertips. It is questionable whether these devices would provide adequate data.

MENTIS-ASD-001

MENTIS-ASD-001 was the first study conducted in subjects with ASD utilizing the complete JAKE System. Thirty-five subjects were enrolled; with approximately 15 of those undergoing the JAKE Task Battery and the remainder using only the JAKE Portal. Subjects in Stage 1 participated for 1 week, while those in Stage 2 participated for 4 weeks. This study began the process of validating and optimizing the JAKE System, enabling the sponsor to optimize platform components such as the JAKE Task Battery, JAKE Biosensor Array, and JAKE Portal (including its subcomponents, such as the JAKE Symptom Tracker, later renamed ABI).

Based on scale correlations for the ABI, it was determined that most correlations were statistically significant ($p<0.001$). Also, most of the standard scale correlation values between the baseline and endpoint visit were statistically significant ($p<0.001$). Most of the estimated correlations for the scales between the baseline and endpoint were >0.7. Correlations between the total ABI and domains of the ABI with the standard scale total and domain scores with which they might be expected to correlate were generally high (>0.7) and statistically significant ($p<0.001$).

The overall correlations between the key biosensor features with some standard scales such as SRS Social Communication and Child Adolescent Symptom Inventory-Total Score and Symptom Tracker, measured using Pearson's correlations were strongly positive ($r= \geq 0.70$) and considered significant ($p<0.001$) for ASD subjects. However, due to limited data available and small sample size during each stage, no definitive conclusions could be reached.

The experiences in this study led to many improvements, both in the biosensor devices used, the JAKE Portal software and processes, the Task Battery, and the Janssen Research Data Warehouse. As a whole, the System appeared to be a viable platform to be used in clinical studies of ASD. There were no safety issues observed with any components of the overall system.

MENTIS-ASD-002

This was a non-interventional study that aimed to continue from MENTIS-ASD-001, and tested and validated the final JAKE System. The testing and validation of the final JAKE System included the subcomponents of the JAKE Portal (later renamed My JAKE), as well as the selected biosensors and procedures for biosensor testing that will be used for objective measurement of core and associated symptoms of ASD in a population of children, adolescents, and adults. The study also examined the JAKE Task Battery and selected components of the JAKE Biosensor Array (later renamed JAKE Sense) on a cohort of typically-developing (TD) children and adults in order to obtain comparative data. Feedback on both the My JAKE interface and JAKE Sense biosensors were obtained, and data obtained via the interface and biosensors were compared to symptom measures commonly used in clinical research.

The study consisted of children and adults with ASD and a TD group for comparison. A total of 185 participants (ASD, 144; TD, 41) were enrolled in this observational study. The majority of participants were male (ASD, 77.8%; TD, 65.9%); the mean (SD) age of participants was 14.6 (7.83) years (ASD group) and 16.3 (13.18) (TD group). The ASD group participated in the JAKE Task Battery 3 times at approximately 4-week intervals. TD participants had a single visit wherein they underwent a single session with the JAKE Task Battery and biosensors.

The results demonstrated support for the utility of the ABI in measuring the clinical symptoms of ASD. The results supported the usability of the JAKE System (including subcomponents of My JAKE and selected JAKE Sense biosensors) for monitoring clinical outcomes in ASD. Key sensor variables of Periodic and Continuous Biosensors were identified using data mining approaches. Examination of sensor variables as change measures in the full dataset was performed.

At the end of this study the sponsor validated the ABI, completed computer system validation on My JAKE and all of its subcomponents, developed the algorithms to extract meaningful features from My JAKE and JAKE Sense input, and identified the combination of biosensors and task/stimuli most likely to be able to detect changes in response to treatment.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. 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 ASD during 12 weeks of treatment on the following parameters:

- Autism Behavior Inventory (ABI) Core Domain Score (Social Communication and 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:

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2.1.2. Endpoints

Primary Endpoint

The primary endpoints will be measured as follows:

- Change from baseline to Day 85 in the ABI Core Domain Score (Social Communication and RRB).
- Change from baseline to Day 85 in the ABI Social Communication Domain Score.
- Change from baseline to Day 85 in the ABI RRB Domain Score.

Secondary Endpoints

The secondary efficacy endpoints are:

- The change from baseline to Day 85 in the ABI Mood & Anxiety, Challenging Behavior, and Self-Regulation domains.
- The change from baseline to Day 85 in the ABC, ABI-S, ABI-C, CGI-S, RBS-R, ZBI, CASI-Anx, SRS-2, and Caregiver GI-S.
- Caregiver Assessment of Treatment, Self GI-I, and CGI-I at Day 85.

2.2. Hypothesis

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 Domains (Social Communication and RRB), Social Communication Domain, or RRB 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.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study 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). See Section 3.2.3 for the rationale for the change in dose of JNJ-42165279 during the study.

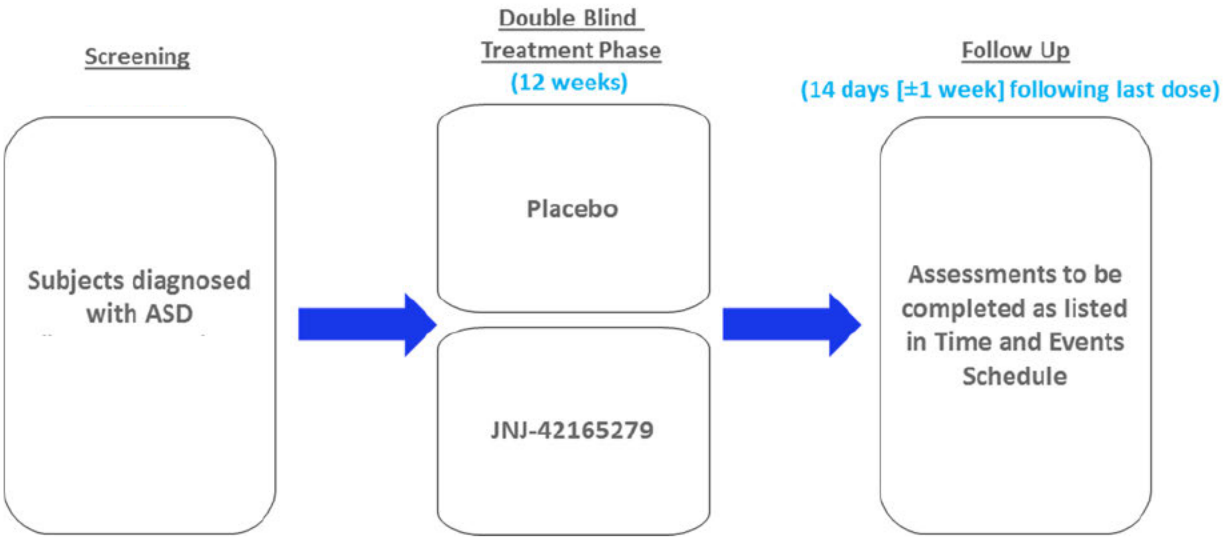
Study procedures include safety and efficacy evaluations and blood sample collections for pharmacogenomic assessment, pharmacokinetics, and biomarkers of treatment activity. An

interim PK analysis is planned following Week 2 PK sample collection from approximately 8 adolescent subjects randomized to active drug.

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.

The Time and Events Schedule summarizes the visits as well as the frequency and timing of assessments applicable to this study.

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).

Study Extension

No extension is planned for this study.

3.2. Study Design Rationale

3.2.1. Randomization, Blinding, and Control

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Stratified randomization will be used for gender (male and female) and age (13-17 years and 18-35 years). Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints as well as adverse events. A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

3.2.2. Study Population

ASD is a neurodevelopmental disorder consisting of the core symptoms of social communication deficits and RRB. Associated symptoms include deficits in self-regulation, irritability, anxiety, depression, problems with attention, and challenging behaviors such as aggression. These criteria are laid out in the Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5) and are widely accepted in the field.

The overall goal of subject selection is to identify subjects, aged 13 to 35 years old (inclusive), with a definitive diagnosis of ASD using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), who have an IQ as measured by the KBIT-2 of ≥60, and are capable of completing and complying with all study-specific requirements.

Given observations in the rat reproductive toxicology studies (see Section 1.1), women of childbearing potential (WOCBP) will only be included if they agree to ongoing use of a highly effective method of contraception (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly). Pregnancy testing will be done at screening and at each study visit during the treatment phase. Safety and efficacy data in this population are important for future clinical studies.

3.2.2.1. Rationale for Including Adolescent Subjects, Aged 13 to 17 Years

JNJ-42165279 has been evaluated for general toxicity in rat and dog studies of up to 3 months in duration. Evaluation of embryo-fetal toxicity has been completed in rats and rabbits, while fertility performance has been assessed in rats. Cardiovascular safety was evaluated in dogs and acute neurobehavioral effects assessed in rats. Animals used in the multiple dose toxicology studies straddled early to late reproductive maturity at study start. Specifically, animals used in

the rat 2-week and 3-month studies were at least 8 weeks old, and therefore considered at the top end of adolescence, while those used in the neurobehavioral study were 6 weeks old (at start of adolescence). In dog studies, those for the 2-week study were 7 months old (adolescents), while those in the 3-month study were 10 months old at start of dosing (considered young adults). Several target organs were identified, mostly in the 3 month and reproductive safety studies. These included changes in kidneys of female rats only, coagulopathy in male rats only, liver changes in dogs only, testicular changes in both rats and dogs, and lens fiber swelling and fragmentation in fetuses of pregnant rats treated with JNJ-42165279 during the period of organogenesis.

A key consideration in assessing the potential risk to human adolescents in a clinical trial is whether the target organs identified in the general and reproductive toxicity studies continue to undergo significant growth and development, which may not have been evaluated in young adult or adult animals used in the toxicity studies. In general, most human organs are fully developed by the age of 13 years with the notable exception of the brain cortex, the reproductive and skeletal systems. The endocannabinoid system is integral to brain development and reproductive function but has not been linked with skeletal development.

Reproductive function: Endocannabinoids are known to control multiple reproductive functions in both males and females through precisely orchestrated steps and levels requiring either up- or down regulation of various endocannabinoids particularly anandamide. Changes in anandamide levels play an integral role in sperm viability, acquisition of motility, and capacitation ability, amongst others.[11,66,126] FAAH inhibition has also been demonstrated in preclinical models to modulate male fertility in a manner similar to exogenous CB1 agonists such as tetrahydrocannabinol (THC).[65,66,126] Mating wild-type female mice with FAAH knockout male mice had only a minimal effect on litter size while the effect was more significant when FAAH $^{-/-}$ males were mated with FAAH $^{-/-}$ females. Sperm motility was also reported to be reduced in FAAH $^{-/-}$ males and this correlated with increased anandamide levels. In a study looking at endocannabinoid levels in sperm from fertile and infertile men, Lewis et al (2012) reported a substantial modulation of AEA metabolism in infertile men.[66] Anandamide biosynthesis (3-fold lower) and to a lesser extent FAAH activity (2-fold lower) were significantly impaired in infertile versus fertile sperm plasma. In a case reference study by Pacey et al (2014), recent cannabis use emerged as a modifiable risk factor for <4% normal sperm morphology (criterion for significant infertility).[91] Although FAAH inhibition is expected to represent a selective stimulation of the CB1 receptors in specific regions as opposed to the broad and nonselective effects of exogenous CB1 agonists such as THC, the testicular effects in JNJ-42165729-treated rats and dogs appear to mirror those of THC administration. Therefore, in the absence of human data from FAAH inhibitors, it is reasonable to consider data on reproductive effects of cannabis use as the maximal possible pharmacological expression of FAAH inhibition. Treatment with JNJ-42165279 resulting in increased levels of anandamide is therefore expected to modulate sperm motility and possibly fertility. However, these effects were shown in the studies in rats and dogs to be dose dependent and reversible on treatment cessation as they are limited to spermatids, the last phase in spermatogenesis. In the GLP 3-month study in dogs, testicular effects were not seen at NOAEL AUC exposures 26-fold over the anticipated clinical AUC

exposure. In the GLP rat 3-month study, sperm motility was reduced by 25%, and 39% of the spermatozoa were abnormal at the lowest dose tested (2.4-fold exposure ratio over the human exposures) but this level of change was shown to have no impact on pregnancy rates in the rat fertility study. In conclusion, FAAH inhibition through dosing with JNJ-42165279 has the potential to modulate sperm and fertility parameters in adolescents and adults but these effects at the clinical dose are expected to be minimal and reversible based upon preclinical studies and the known effects of CB1 agonists in humans.

Based on these observations, male subjects must use a condom and spermicide during the study and for a minimum of 1 spermatogenesis cycle after the last dose of study drug.

Neurobehavioral effects: There is limited literature data on the effects of FAAH inhibition on the developing brain and behavior. In the 3-month studies in rats and dogs, central nervous system-related clinical signs were mostly seen in dogs and limited to the high dose group. They included ataxia, excessive licking, salivation, tremors, and uncoordinated movement. In the Modified Irwin assay in rats, behavioral changes were limited to reduced muscle tone and reduced body temperature, well-recognized cannabimimetic effects. FAAH inhibition represents tonic activation of the endocannabinoid system. Although there is a growing body of evidence suggesting that chronic use of exogenous CB1 agonists such as cannabis (as distinct from FAAH inhibition) during adolescence could have deleterious neurocognitive effects, preclinical and clinical data have not reported any neurocognitive effects with JNJ-42165279. There is also evidence that CB1 activation including via heightened AEA signaling as a result of FAAH inhibition may be beneficial in the treatment of social impairment in ASD. Moreover, subjects with ASD have been shown to have altered expression levels of the *CB1* gene, suggesting that intervention outcomes with FAAH inhibition could be different relative to normal subjects exposed to cannabis.

3.2.3. Rationale for Dose Selection

Based on preclinical models of JNJ-42165279 efficacy with adjustment for differences in affinity of JNJ-42165279 for human FAAH, a 25 mg once daily regimen was chosen as the dose to carry forward into the Phase 2 proof of concept studies. CCI [redacted] However, a post-hoc analysis of the Phase 2 studies 42165279SAX2001 and 42165279MDD2001 found that the AEA concentrations observed in the JNJ-42165279 treatment group were only about 3-fold greater than the pre-drug concentrations. AEA trough concentrations in these 2 studies exhibited a high degree of variability, and the distribution of AEA trough concentrations in the JNJ-42165279 treatment group was found to overlap with that in the placebo group. These findings suggest that elevated AEA levels and FAAH inhibition associated with 25 mg JNJ-42165279 administered once daily was not sufficiently sustained for all subjects throughout the 24-hour dosage interval.

The relationship between AEA trough concentrations and clinical outcomes was explored using the data from these Phase 2 studies. In the MDD2001 study, subjects with higher trough AEA concentrations after 6 weeks of treatment exhibited greater reductions in anxiety (measured by

the Hamilton Anxiety Rating Scale) and depression (measured by the $HDRS_{17}$) than subjects with lower trough AEA levels.

CCI [redacted] See Section 1.1, Background, for information on safety margins.

In view of these analyses CCI [redacted] the dose in the 42165279AUT2001 study will be changed to 25 mg BID (50 mg total daily dose).

CYP3A4 plays an important role in the metabolic elimination of JNJ-42165279. In the presence of the strong CYP3A4 inhibitor itraconazole, CCI [redacted] respectively (Study 42165279EDI1004). CYP3A4 inhibitors will be restricted in this study.

3.2.4. Rationale for Pharmacokinetic Evaluations

If warranted at the time of the interim analysis and after completion of the study, the plasma concentration-time data of JNJ-42165279 will be analyzed using population PK modeling. Concentration-time data will allow estimation of individual PK parameters for JNJ-42165279. It will also help to understand potential differences between ASD subjects treated with JNJ-42165279 and those treated with placebo. Time and days of JNJ-42165279 plasma concentration assessment were chosen to gather maximal information about the PK properties of JNJ-42165279 while minimizing subject burden regarding blood sampling.

3.2.5. Rationale for Pharmacogenomic and Biomarker Evaluations

A blood sample will be collected from all eligible subjects. Participation in the genomics research component is required to assess whether the subject is carrier of the A-allele variant for *FAAH* and to identify genetic factors that may influence the PK, PD, efficacy, safety and/or tolerability of JNJ-42165279.

Plasma concentrations of CCI [redacted] will be used as biomarkers of JNJ-42165279 activity. Correlations between CCI [redacted] values with efficacy and other clinical evaluations will be assessed. Blood biomarkers related to autism (including but not limited to cytokines and miRNAs) will allow for exploratory immunophenotyping and for an exploratory PD evaluation. The biomarker data obtained from this study may also contribute to an ongoing cross-study analysis to investigate the relationship between ASD and phenotypes and biomarkers.

3.2.6. JAKE System

The JAKE system is an integrated system of tools and technologies designed to optimize clinical trials for ASD. The JAKE System includes JAKE Sense, which collects biosensor data, and a reporting tool which collects caregivers' reports on the behavior and mood of the subjects.

Caregivers will use 1 of 2 versions of a caregiver reporting tool: My JAKE (the first application used in this study) or My JAKE MMApp (the second application used in this study). Caregivers will use the application which is operational during the time of their participation.

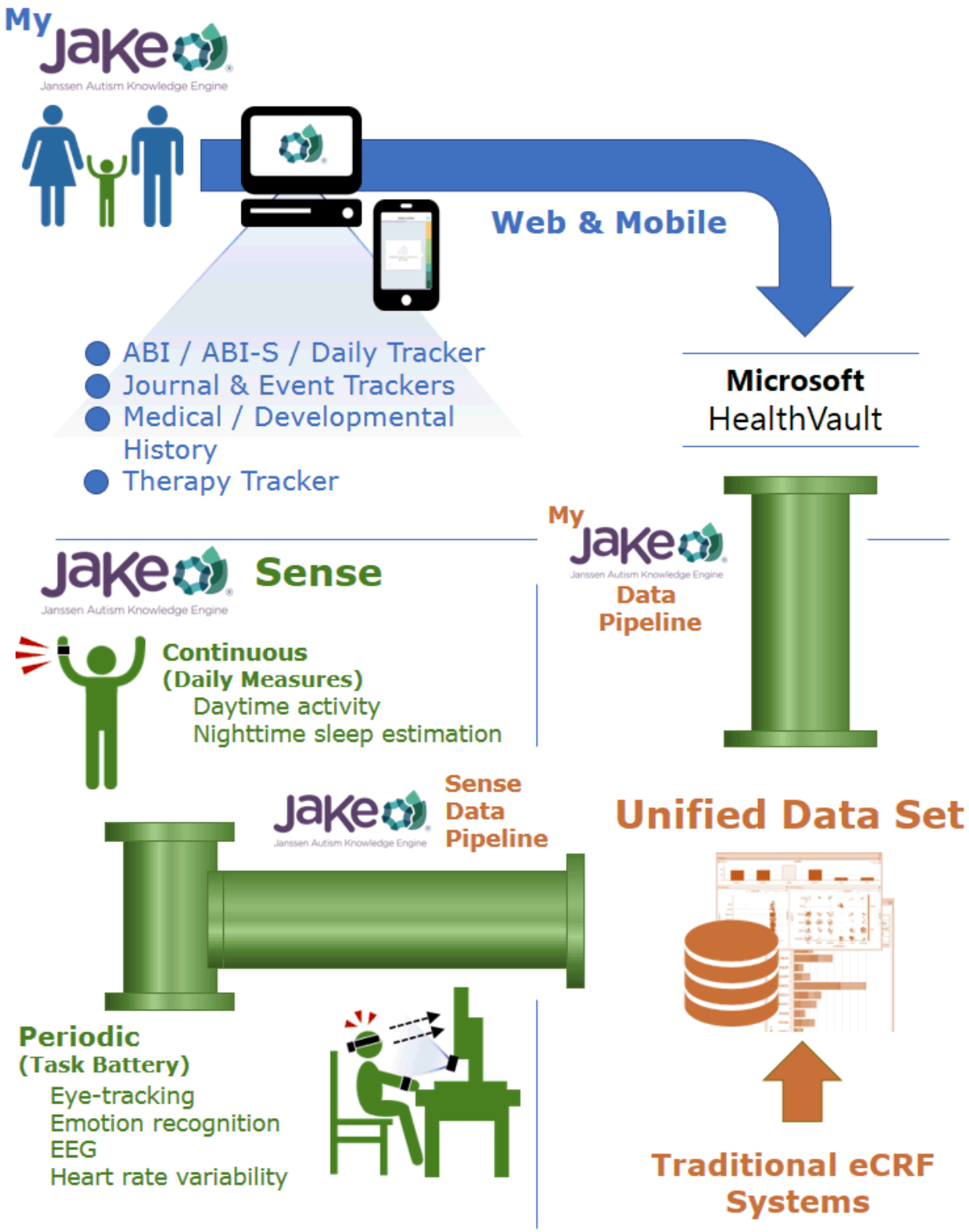
The input from My JAKE/My JAKE MMApp (which includes the ABI) and JAKE Sense will be processed separately. Additionally, case report form (CRF) data (study events, concomitant medications, demographics, etc) and data from the standard caregiver and clinician rating scales will be incorporated in the analysis.

See Sections 9.2.2.4 and 9.2.2.5 for information on data processing for the caregiver reporting tool and JAKE Sense, respectively.

It should be noted that the JAKE Sense and the individual sensors and components working as part of the array have been qualified for signal and processing compatibility but have not yet undergone full Computer Systems Validation. As such, any data derived from them should be considered exploratory. JAKE Sense (and its relevant processing and storage systems) are virtually isolated from the My JAKE/My JAKE MMApp system to ensure integrity of the primary endpoint measurement.

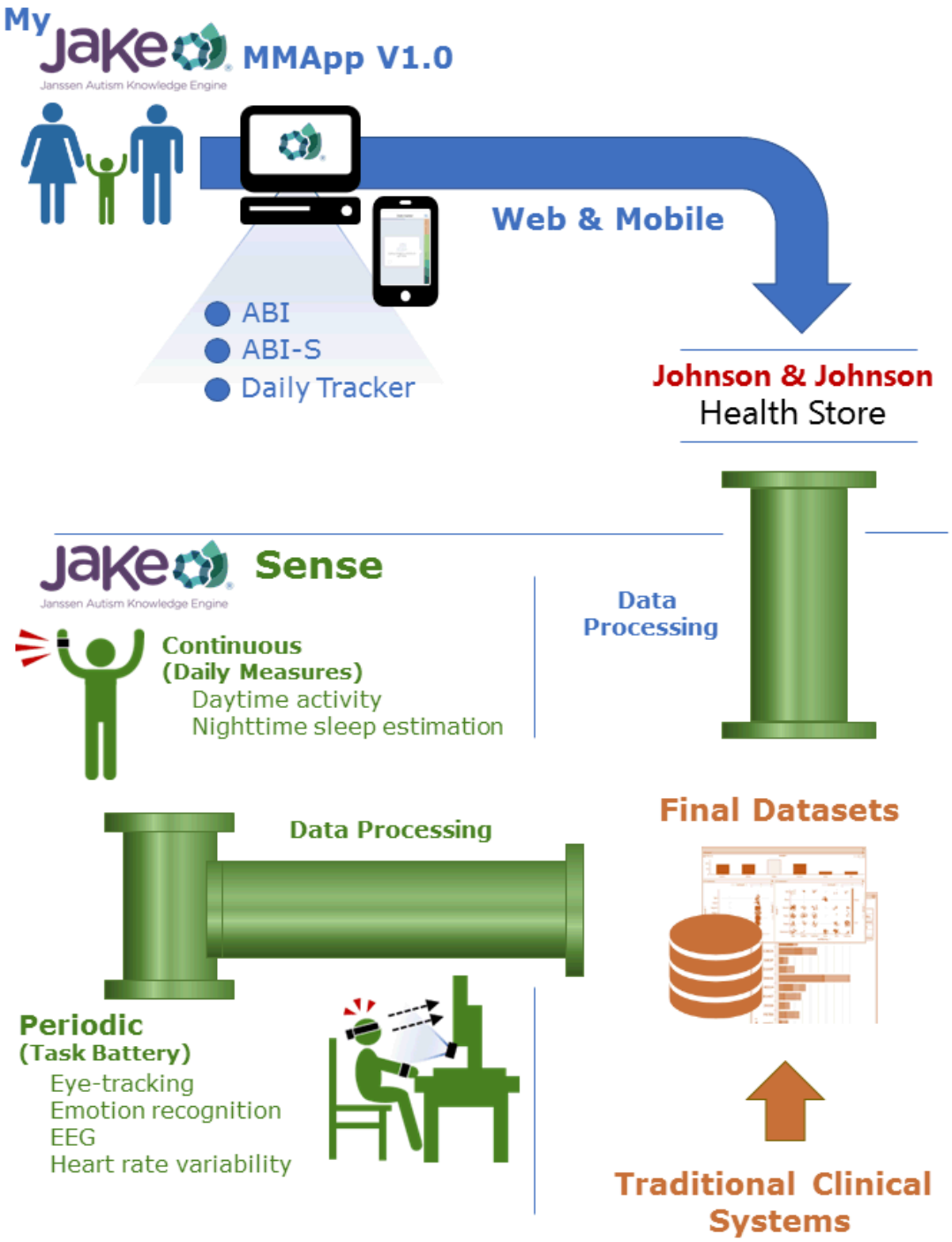
The following schematics show the overall structure of the JAKE System and its data flows for My JAKE (Figure 2) and My JAKE MMApp (Figure 3).

Figure 2: My JAKE System



Abbreviations: ABI=Autism Behavior Inventory; ABI-S=Autism Behavior Inventory-Short Form; eCRF=electronic case report form; EEG=electroencephalogram; JAKE=Janssen Autism Knowledge Engine.

Figure 3: My JAKE MMApp



Abbreviations: ABI=Autism Behavior Inventory; ABI-S=Autism Behavior Inventory-Short Form; EEG=electroencephalogram; JAKE=Janssen Autism Knowledge Engine

3.2.6.1. My JAKE /My JAKE MMApp

All of the following components are included in My JAKE:

- ABI: A rating scale consisting of approximately 65 questions related to the core and associated symptoms of ASD.
- ABI-S: A shorter version of the ABI, consisting of approximately 20 questions.
- Daily Tracker: In the morning, the caregiver will be asked to report on their dependent's quality of sleep the night before. Additionally, the caregiver will be required to select 3 behaviors related to ASD to track on a daily basis. After 6 PM each day, the caregiver is required to report on these behaviors, on their dependent's overall type of day, and on their dependent's mood, in terms of emotion and energy levels.
- Journal and Event Trackers: A tracking system that allows caregivers to quickly log key 'events' and information as they happen – such as a bad night's sleep or a positive improvement. This can be in the form of free-text journal entries or common ASD events from a pick-list.
- Therapy Tracker: A calendar-like 'therapy tracker' that allows caregivers to keep track of their dependent's care-related appointments, organized in weekly or monthly views. In addition, it can keep track of treatments, and other therapies. It can also be used to set up and schedule study visits.
- Medical/Developmental History: A detailed medical and developmental history form designed to construct a picture of the subject's ASD including treatments and other information, and personalize the caregiver's view of this information.

My Jake MMApp includes only the ABI, ABI-S, and Daily Tracker. If My JAKE and My JAKE MMApp are not available, paper versions of the ABI, ABI-S, and Daily Tracker will be used.

Currently there are no measures which have been specifically designed to measure change in behavior in ASD. This impacts the development of new treatments for autism, since effectiveness cannot be established and compared across interventions. Many of the existing scales, such as the ADOS and SRS have been developed to diagnose and classify, rather than detect change over time. They are limited in their use as change indicators by their long recall periods, or lack of variability in response options. This has led to the prevalence of use of outcome measures such as changes in IQ, adaptive behavior, and language, which are often unrelated to the main focus of treatment, and/or rely on measures which are developed for individuals without intellectual or developmental disabilities.[19]

Therefore, the pressing need for research in autism is around more systematized measures, developed for the ASD population, which are sensitive to change over time and capable of capturing the heterogeneity of presentations. The ABI, its short form the ABI-S, and accompanying components of the JAKE System are designed to capture sufficiently variable presentations across all the key domains, while providing a high level of utility – effectively making it simple for caregivers and other observers to record critical information on improvement or worsening of symptoms and behaviors.

3.2.6.2. JAKE Sense

The literature has shown that differences between TD children and autistic children can be detected by various physiologic and cognitive biomarkers. These modalities were chosen to detect differences between TD subjects and ASD subjects as well as potentially to detect differences between ASD subjects, treatment-induced changes and changes over time. As subjects improve on treatment, it is expected that biosensor signals will be more like TD individuals.

The following sections describe the rationale for the various sensor-experimental modalities used in this study, while subjects are monitored continuously (see Section 3.2.6.2.1) or assessed through a periodic experimental battery (see Section 3.2.6.2.2).

JAKE Sense (and its hosted biosensors) are used solely for exploratory, proof-of-concept research. While JAKE Sense may host medical devices, and while these devices are being used in compliance with their intended use, no portion of JAKE Sense is being used in such a way as to diagnose, treat, or prevent any disease or disorder, nor is the output being used in (or in support of) any regulatory filing (now or in the future).

3.2.6.2.1. Continuous Biosensor

Continuous Biosensors can be worn over extended periods of time such as throughout the day or during sleep. They will also be worn and assessed during study visits as with the Periodic Biosensors below. It is expected that biosensors will provide more direct characteristics of the ASD population than indirect assessment via questionnaires filled in by caregivers. It is also expected that changes in features extracted from the biosensors will be detected prior to changes observed in scales.

During day/night time, recordings will be done with an actigraphy device to monitor activity. All biosensors were reported to have been successfully used in children (including those under 10 years old) previously, including cohorts of individuals with ASD.[1,78,134]

3.2.6.2.1.1. Actigraphy/Accelerometry

An actigraph measures activity while worn on a subject's wrist like a watch. Based on data recorded during the day, time periods of child involvement in sedentary, light, moderate, and moderate-to-vigorous activities are expected to correlate with disease severity, where an ASD population is expected to spend more time in sedentary activity, with less time in light, moderate and moderate-to-vigorous activity than TD children of the same age.[134] At the same time it was reported that the prevalence of sleep problems ranges from around 50% to 80% for children with ASD compared with 9% to 50% for a TD group.[101] The use of an actigraph for sleep monitoring provides an easy-to-use way (in comparison to polysomnography) of sleep monitoring with about 90% sensitivity of sleep estimation.[78]

ASD is characterized by repetitive behaviors (which are included in gold standard diagnostic tools such as the ADOS-2 and the Autism Diagnostic Interview-Revised [ADI-R]), which includes body rocking, hand flapping and others.[105,106,133] The frequency and durations of such

activity are usually estimated via caregivers' reports. CCI [redacted]

3.2.6.2.2. Periodic Biosensors and JAKE Task Battery

Periodic Biosensors will only be worn or used for a discrete period of assessment during a study visit. As opposed to the Continuous Biosensor, which will be worn continuously throughout the treatment period, Periodic Biosensors will be assessed only 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 Periodic Biosensor array consists of an EEG, an eye-tracker and a device for ECG recordings (different from the medical ECG used for drug safety evaluation). These devices have been extensively used in child and adolescent populations.[8,23,35,37,56,115,138] In addition, the subject's affect (apparent emotion) will be measured with the use of a standard web camera and the iMotions® Biometric Research Platform Emotient™ Facial Expression Analysis (FACET) module. The FACET module will analyze facial expressions across all task presentations, with particular focus on the analysis of the funny videos task.

The JAKE Task Battery includes a number of different experiments which aim to detect changes in core symptoms of ASD (description and rationale provided below). The experiments are distributed across 2 sets. Some of the experiments were developed for specific biosensors, but all of the biosensors are used throughout the Task Battery in order to identify new biomarkers across different biosensor modalities.

ECG will be monitored during the entire battery and will provide assessment of such characteristics as HR and HRV to study potential impairments in the autonomic nervous system associated with ASD.[35] In addition, change in HR response to auditory stimuli will be measured specifically during an auditory task and a short physical challenge task. Since emerging ASD literature associates autonomic nervous system activity with social function, ECG recordings could provide a link between measurable biological activity and both social behavior and cognitive function.[8,72,92,135]

The tasks and stimuli for use with the Periodic Biosensors were chosen based on the literature and scientific advice to elicit physiologic and behavioral differences between ASD and TD populations using the various sensor modalities, and the battery was adapted following the ASD-002 study preliminary results. CCI [redacted] The battery encompasses both static and dynamic stimuli in an attempt to elicit the broadest range of responses.

The tasks are divided across 2 sets. Each set includes a variety of tasks which induce behaviors measured by EEG, eye tracking, FACET, and HR changes, which are associated with symptom severity in ASD.

The entire Periodic Biosensor array will be used during each portion of the Task Battery in order to look for new biomarkers which could provide added value to the primary sensor for a particular modality. Literature suggests that some tasks have utility beyond the individual sensor. As such, data from all sensors on a particular task may be highly informative.

Though not part of the Periodic Biosensor array, subjects are required to wear the Continuous Biosensor during administration of the Task Battery.

3.2.6.2.2.1. Periodic Biosensor of Interest: Electroencephalogram Portion

While the primary biosensor is an EEG recording device, changes in biomarkers derived from other modalities are also expected. This portion of the JAKE Task Battery consists of the following experiments:

Resting State

ASD populations exhibit an increase in brain white matter activity, which is evident from magnetic resonance studies.[31,50] White matter reflects myelinated axons that transmit signals between neurons within 1 or several cortical areas. EEG recorded from electrodes on the scalp reflects synchronous activity among thousands of neurons in the tissue underlying a particular location. Thus, changes in local neural connectivity will influence changes in EEG from single electrodes. At the same time, EEG coherence reflects functional cortical connectivity, which could serve as an index of changes in long range connectivity, which could be altered due to changes in white matter. Those EEG indexes are best assessed during resting state in order to exclude EEG changes induced by any task or stimuli.

ASD subjects have memory problems: some show severely impaired memory, while others fall into the other extreme with 'savant' memory.[83,89] Executive control of memory processing is mediated by the frontal cortex and also involves the integrated actions of multiple brain areas.[20,40,44, 90,112,123] As such, abnormalities in neural connectivity may underlie memory deficits in ASD.[102] This is especially so in theta waves in EEG during rest, which relate to memory processing.[62]

ASD subjects have increased attention to details. It was found that resting state alpha power of EEG recordings is linked to attention.[63] As such, we may expect abnormal alpha in an ASD population during resting state.

ASD subjects have abnormalities in processing, perceiving and showing emotions. ASD is also associated with depression and anxiety. There is evidence that the frontal lobe is involved in emotional processing with a difference in lobes (right vs. left) for different emotions.[36,46] Thus patterns of frontal EEG (asymmetry) may serve as an index of abnormalities in emotion processing and emotionally-related problems, as depression and anxiety.

ASD is also related to abnormal functioning of gamma-aminobutyric acid (GABA)-ergic tone in inhibitory circuitry, which influences the functioning and development of the brain.[140] Abnormal functioning of GABA-ergic tone is thought to modulate power at high-frequency and low-frequency EEG bands while increasing power of middle range frequencies (alpha band).[140]

Event-related Potential: Faces Compared to High Autism Interest Objects

The study will use event-related potentials (ERPs) to investigate brain activity related to the presentation of faces (social) or objects determined to be high autism interest (HAI; non-social).[42]

According to the social motivation hypothesis, disrupted social motivation mechanisms may represent a primary deficit in ASD. This could include a decreased preference for social images and/or an increased preference for certain classes of non-social information, known as HAI objects.[42,109]

ERP studies have demonstrated differences in P300 (stimulus evaluation, novelty detection) and N170 (facial recognition response) between TD and ASD. Longer latency and reduced amplitude to faces, but not objects, have been seen in ASD.[33,34,38,41,70,77]

These differences may be seen in amplitudes and latencies of ERP components (especially the face-sensitive adult N170 component) and their hemispheric asymmetry relation, and changes in amplitude and latency responses may correlate with changes in symptoms.

Recently the response of the last positive potential – a centro-parietal ERP positive component at approximately 300 ms after stimulus onset and lasting to 1500 ms, has been found to be greater for HAI relative to faces in ASD, when compared with TD.[13]

In addition, attention to key facial features, especially the eye and mouth region, may relate to ASD symptoms.[56] Fixation features estimated from eye-tracker data (number of fixations, total time spent in gazing) on key facial features, CCI [redacted], will also be measured.

3.2.6.2.2.2. Periodic Biosensor of Interest: Eye Tracking Portion

The eye tracking portion of the periodic biosensor array consists of following tasks:

Social Information Processing Task

The Social Information Processing Task involves actors engaging in child-directed speech and includes a bid for joint attention (the shared focus of 2 individuals on an object).

Visual information processing in TD subjects is reinforced with additional speech information, which shows TD children's ability to integrate multimodal input for faster encoding and recognition of faces.[6,21,48,67,107,127] There is evidence that face detection is facilitated when it is combined with directed speech in TD infants.[61,137] At the same time, ASD children are characterized by their limited attention to faces combined with under-responsivity to speech.[23,26,28,87,93] Limitation in attention to faces in ASD subjects is mainly prominent for

dynamic (videos) face stimuli, when they are presented in complex naturalistic context.[55,129] It is possible that limited attention to faces is a direct result of increased salience of objects, which are of high autism interest (HAI).[110,111] CCI [redacted] ASD subjects will show diminished attention assessed with the eye-tracker to the entire scene and spend less time monitoring the speaker's face in general and mouth in particular. Instead, they will direct their attention toward the toys as well as the hand/action area.

Visual Search

ASD is characterized by interests that are restricted to some particular things (so-called HAI objects), social difficulties and stereotyped repetitive behavior.[105,106,133] CCI [redacted]

Biological Motion

TD subjects show a preference for biological motion from birth.[120] At the same time, children and adults with ASD do not show such preferences.[4,86] CCI [redacted]

It is also known that in TD individuals the mirror neuron system activates when they either watch someone perform a task or perform the task themselves.[103] Response of this system is characterized via suppression of mu waves in EEG.[103] In contrast,, in an ASD population, mirror neurons become active (and consequently mu waves are suppressed) only when the individual performs the task him- or herself.[15,1] CCI [redacted]

Activity Monitoring

It is known that the ability to understand intentional and goal-directed actions of others arises early in infancy in a TD population.[5,117,129] Attention to the actions and activities of others is a critical component of the learning and development of cognitive and social skills.[117] Attention to others and their actions facilitates learning about affordances, is a pre-requisite for imitation and emulation, and is crucial to the development of higher-level cognitive skills such as joint attention, social play, and the comprehension of intentions, goals, and motivations.[1,7,24,47,51,52,69,79,81] The fact that skills such as affordance learning, imitation, and joint

attention emerge in a regular fashion, together with their relationships with later development of language and theory of mind skills, argue for mutual interdependencies and suggest that common requirements, such as activity monitoring, may evolve together with the skills themselves.[117] At the same time, many of the skills outlined above have been found to be impaired in the ASD population.[117,125,133,142]

CCI [redacted]

3.2.6.2.2.3. Affect Detection Portion

It has been found that facial expressions activated via automatic or intentional mimicry influence corresponding emotions in controls, but that the influence of facial expressions is impaired in the ASD population.[124] Consequently it is expected that ASD individuals will show fewer facial emotional responses (less variance in emotion) in response to funny videos than TD individuals. A more neutral flatness of affect has also been found in the activated facial expressions of autistic children.[144] CCI [redacted]

It is known that humans automatically mimic a variety of behaviors, including but not limited to emotional facial expressions.[76] ASD individuals have been found not to automatically mimic facial expressions presented to them whereas TD individuals do.[76] CCI [redacted]

When asked to produce a specific emotion, ASD individuals are also known to produce more ambiguous or "bizarre" expressions, a behavior that is not apparent in the TD population.[68,144]
CCI [redacted]

3.2.6.2.2.4. HRV Portion

A review of the literature on physiological reactivity to sensory and social and emotional stimuli indicates that abnormalities exist for some individuals with ASD.[71]

In addition to looking at patterns of autonomic nervous system activity across portions of the Task Battery, the Auditory Processing task is designed to measure HR responsivity to auditory stimuli, and the physical task measures HR responsivity to change in posture from sitting to standing.

The toilet flush and ticking clock are presented as examples of non-biological, ecologically valid stimuli. They are similar to those rated in the IADs Affective Ratings of sounds. They were selected as they elicited similar medium level values of valence and arousal in TD adults and are therefore considered 'neutral' and non-aversive.[17]

Parents report increased sensory sensitivity in children with ASD and there is evidence that these atypical sensitivities are particularly present in the auditory domain.[58,75] There are indications that differences in sensitivity in ASD subjects are related to underlying differences in autonomic nervous system responsivity, as measured by, for example, HRV.

It is also thought that these differences may be related to other behavioral differences in ASD, such a repetitive behaviors and anxiety.

CCI [redacted]

There could also be different patterns observed within ASD and these differences may correspond with other ASD symptoms.[16]

3.2.6.2.3. JAKE Sense Workbench

The JAKE Sense Workbench is a platform that will link together and synchronize all components of the Periodic Biosensor collection (as well as the Continuous Biosensor) while presenting the JAKE Task Battery. Data collected through the JAKE Sense Workbench (JSW) is transmitted directly to the JAKE Sense Data Pipeline via the secure file transfer protocol application CCI [redacted] – permitting comprehensive analysis of all biosensor data inputs and integration with the separately-processed manually-entered data from the caregiver reporting tool.

3.2.7. Standard Instruments and Rating Scales

Throughout the study, data collected from the caregiver reporting tool and JAKE Sense will be compared and correlated with standard instruments and scales. The scales form a selection of the secondary outcome measures, in addition to contributing to the process of validation of the JAKE System as a tool for measuring clinical outcomes in ASD.

3.2.7.1. Diagnostic and Classification Instruments

These instruments will be given a single time to establish the diagnosis of autism or help rule it out, to help classify subjects by IQ, or to rule out or rule in the presence of other psychiatric disorders in subjects.

Autism Diagnostic Observation Schedule, Second Edition

The ADOS-2 is a diagnostic measurement tied to the inclusion criteria.

Kaufman Brief Intelligence Test, Second Edition

The KBIT-2 is a diagnostic measurement tied to the inclusion criteria.

3.2.7.2. Instruments for Measuring Change

The scales have been selected based on their ability to detect changes over time in the ASD population. As described in Section 3.2.6.1, there are no existing scales which are specifically designed for measuring changes in behavior in ASD. Therefore, instruments were selected based

on input from scientific advisors and current use as outcome measures in ASD interventional studies.

Autism Speaks commissioned 3 reports on current scales for Social Communication, Restrictive Repetitive Behaviors, and Anxiety, which were suitable for use in clinical trials for Autism.[3,64,113] The findings of these reports, compiled by experts in the field, were influential in the consideration of scales for comparison.

Scales were selected to ensure comparisons across all 5 domains measured by the ABI. The scales to be used in this study and the rationale for their use are described in the table below:

CCI

3.2.7.2.1. Zarit Burden Interview

In addition to the behavioral scales, a measure of parent burden is also included in order to assess the impact of behaviors and the impact of behavioral change on the caregiver and family life. There are no specific scales developed to measure this aspect. The ZBI was originally developed to assess burden of care for dementia patients, but has also been used to assess burden in those who care for children and adults with ASD.[22]

3.2.8. National Database for Autism Research/Global Unique ID

The National Database for Autism Research / Globally Unique Identifier (NDAR GUID) system was established as a mechanism to share data on individual subjects among the research community without sharing subjects' protected health information (PHI).

More information on NDAR can be found at http://ndar.nih.gov/.

4. SUBJECT POPULATION

Subjects (13 to 35 years of age) with a definitive diagnosis of ASD using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), who have an IQ as measured by the KBIT-2 of ≥60, and who are capable of completing and complying with all study-specific requirements will be enrolled.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study unless otherwise specified:

1. Criterion modified per Amendment 1.

    1.1. Criterion modified per Amendment 2.
    1.2. Criterion modified by Amendment 3.
    1.3. Criterion modified per Amendment 5.
    1.4. Subject must be between 13 and 35 years of age, inclusive..

2. Criterion modified per Amendment 1.

    2.1. Criterion modified per Amendment 3.

    2.2. Criterion modified per Amendment 6.

    2.3. Diagnosis of ASD in subjects must be according to DSM-5 criteria and made or confirmed using the ADOS-2 (minimum score of 8 [autism spectrum]). (An ADOS-2 completed by an adequately trained professional within the 24 months prior to screening visit will be acceptable if the item responses are available for entry into the electronic case report form [eCRF].)

3. Criterion modified per Amendment 1.

   3.1. Subjects (18 years of age or older) must have a body mass index (BMI=weight/height^2) between 18 and 35 kg/m^2, inclusive, at screening. Subjects (between 13 and 17 years of age, inclusive) must have a BMI $\geq 5^{th}$ percentile and $<95^{th}$ percentile on the Centers for Disease Control and Prevention BMI-for-age percentile growth charts.

4. Criterion modified per Amendment 2.

   4.1. Criterion modified per Amendment 5.

   4.2. A male subject who has not had a vasectomy must agree to use a condom when having sex with a female partner of childbearing potential (see Attachment 1) during the study and for 3 months after receiving the last dose of study drug. The condom must have a spermicide or the partner must use a spermicide. A male subject should also be advised to inform their female partner to use a highly effective method of contraception over the same time period, as condoms may break or leak.

5. Subjects must be otherwise healthy for their age group or medically stable with or without medication on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population with written concurrence with the sponsor's medical monitor.

6. Criterion modified per Amendment 2.

   6.1. Subject must be otherwise healthy or medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant. This determination must be recorded in the subject’s source documents and initialed by the investigator. However, subjects with an AST or ALT >1.5x ULN cannot be enrolled. These tests may be repeated once during the screening period at the discretion of the investigator.

7. Criterion Modified per Amendment 2.

   7.1. Subject must live with a parent or primary caregiver or, if not, during each week they must either (A) spend at least 3 hours a day for at least 4 days or, (B) spend the weekend with a parent or primary caregiver.

8. Subject must be able to be compliant with self-administration of medication if living independently or have a parent or caregiver be able to administer medication.

9. Subject and primary caregiver must speak and understand English.

10. Criterion modified per Amendment 1.

    10.1. Primary caregivers must have a reliable means of obtaining internet connectivity for a desktop, laptop or tablet computer.

11. Subject must be able to swallow the study medication whole with aid of water.

12. Criterion modified per Amendment 2.

    12.1. A subject ≥18 years of age must sign an informed consent document (and/or their legally acceptable representative must sign) indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study, is willing to attend all site visits, and is willing and able to adhere to the prohibitions and restrictions specified in this protocol. For a subject <18 years of age, parent(s) (preferably both if available or as per local requirements) (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to allow the child to participate in the study. Assent is also required of adolescents (<18 years of age) capable of understanding the nature of the study as described in Section 16.2.3, Informed Consent. The subject's caregiver must also sign a caregiver consent form indicating that he or she understands and is willing and able to adhere to the caregiver's responsibilities in the study.

13. Any pharmacologic, diet, or behavioral intervention for the core or associated symptoms of ASD such as, but not limited to, an applied behavior analysis (ABA) program, Pivotal Response Training (PRT), Treatment and Education of Autistic and related Communication Handicapped Children (TEACCH), Floor Time and DIR, Relationship Development Intervention (RDI), Early Start Denver Model, Discrete Trial Training or a social skills program whether school-based or not must:

    A) Have begun at least 1 month prior to the baseline visit and continue unchanged through the double-blind period, or;

    B) Have ended at least 1 month prior to the baseline visit.

    If such therapy is started, discontinued or changed substantially during the course of the double-blind study the subject should be discontinued.

14. Criterion modified per Amendment 2.

    14.1. Subject must achieve at least 'GOOD' calibration on the eye-tracker in no more than 4 attempts/visit, at any time during the screening period.

15. Subject has a measured composite score on KBIT-2 of at least 60. A KBIT-2 conducted within the past 6 months is also acceptable provided the scores are available for entry into the eCRF.

16. A male subject must agree not to donate sperm during the study and for a minimum of 90 days after receiving the last dose of study drug.

17. A female subject must have a negative highly sensitive serum pregnancy test (β-hCG) at screening and, for women of childbearing potential, a negative urine pregnancy test on Day 1 before randomization.

18. A female subject using oral contraceptives must also use a barrier method of contraceptive (a male or female condom, diaphragm, or cervical cap) with spermicide (above that required in Inclusion Criterion 19).

19. Criterion modified per Amendment 5.

    19.1. A female subject must be (as defined in Attachment 1, Contraceptive Guidance and Collection of Pregnancy Information):

    a. Not of childbearing potential; or

    b. Of childbearing potential and:

    - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose. Examples of highly effective methods of contraception are described in Attachment 1, Contraceptive Guidance and Collection of Pregnancy Information.

20. Criterion modified per Amendment 5.

    20.1. A female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 30 days after receiving the last dose of study drug.

NOTE: All references to a caregiver in the inclusion criteria, except Criterion #8, should be the designated caregiver for this study, fulfilling all of the caregiver responsibilities as described throughout the protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study unless otherwise specified:

1. Criterion modified per Amendment 1.

    1.1. Subject has a current or recent history of clinically significant suicidal ideation within the past 6 months, corresponding to a score of 4 (active suicidal ideation with some intent to act, without specific plan) or 5 (active suicidal ideation with specific plan and intent) for ideation on the C-SSRS, or a history of suicidal behavior within the past year, as validated by the C-SSRS at screening or Day 1. Subjects with a prior suicide attempt, or prior serious suicidal ideation/plan ≥ 6 months ago, should be carefully screened for current suicidal ideation and only included at the discretion of the investigator. If the C-SSRS is unable to be administered, the principal investigator (PI) must document that there is no evidence of suicidality based on history and the Aberrant Behavior Checklist-Irritability Subscale (ABC-I).

2. Criterion modified per Amendment 2.

    2.1. Subject has a clinically significant abnormal physical examination or clinically relevant abnormal neurological examination, vital signs or 12-lead ECG (including QTcF >450 msec for males and >470 msec for females, Left Bundle Branch Block, AV Block second degree or higher, permanent pacemaker or implantable cardioverter defibrillator [ICD]) at screening or baseline (Day 1 predose), which in the opinion of the investigator is not appropriate and reasonable for the population under study. ECG recordings and vital signs may be repeated once and if in question, a cardiologist should be consulted.

3. Criterion modified per Amendment 2.

    3.1. Criterion modified per Amendment 6.

    3.2. Subject has a history of or current evidence of abnormal liver or renal function; incomplete vaccination status, has relevant clinically significant and/or unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic (including seizures), hematologic, rheumatologic, immunologic, or metabolic disturbances (eg, unstable situations needing monitoring or regular dose adaptations). Stable conditions (eg, epilepsy, attention deficit hyperactivity disorder, certain neurodevelopmental or psychiatric conditions) are permitted at the discretion of the investigator, and with consultation with the sponsor, if warranted. Any clinically relevant medical condition that could potentially alter the absorption, metabolism, or excretion of the study drug is exclusionary. Subjects with liver function analytes higher than the ULN at screening should be reviewed with the sponsor. If the subject has ALT or AST >1.5 times the ULN, he/she should not be

enrolled. Any test may be repeated once at the discretion of the investigator.

4. Subject has a history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with written concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

5. Criterion modified per Amendment 2.

   5.1. Criterion modified per Amendment 6.

   5.2. If a subject is using a drug or supplement with moderate/strong CYP3A4 inhibiting or inducing properties at, or prior to, screening, it must be discontinued at least 30 days or five half-lives (whichever is longer) prior to Day 1. Note: an existing medication should not be stopped solely for the purpose of the subject entering the study. Moderate and strong inducers or inhibitors of CYP3A4 are prohibited during the study (See some examples in Attachment 2).

6. Subject has a history of positive tests for hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV), or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at screening.

7. Subject is currently taking or has taken within the past month recreational or medically prescribed cannabis.

8. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at screening.

9. Criterion modified per Amendment 2.

   9.1. Criterion modified per Amendment 6.

   9.2. Subject has a history of drug or alcohol use disorder according to DSM-5 criteria within 6 months before screening or positive test result(s) for drugs of abuse (including barbiturates, opiates, cocaine, cannabinoids, amphetamines, benzodiazepines, phencyclidine, and 3,4 methylenedioxy methamphetamine [MDMA]) at screening or Day 1 (except if related to current treatment; eg, benzodiazepines).

10. Subject has a clinically significant acute illness within 7 days prior to study drug administration.

11. Subject has known allergies, hypersensitivity, or intolerance to JNJ-42165279 or its excipients (refer to Investigator's Brochure).

12. Subject has received an investigational drug or used an investigational medical device within 3 months before the planned start of study or is currently enrolled in an investigational study.

13. It has been less than 6 months since the subject was previously enrolled in another Mentis program study (endpoint visit of that study) to the screening visit of the current study.

14. Subject is a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.

15. Subject has any condition (eg, vision abnormalities such as ptosis) for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

16. Criterion modified per Amendment 2.

    16.1. Subject has had major surgery, (eg, requiring general anesthesia, entry into a major body cavity, or significant blood loss) within 8 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 4 weeks after the last dose of study drug administration.

    Note: subjects with planned minor surgical procedures to be conducted under local anesthesia may participate, with approval of sponsor.

17. Subject has a history of spontaneous, prolonged or severe bleeding.

18. Subject has donated 1 or more units (approximately 450 mL) of blood or had acute loss of an equivalent amount of blood within 90 days prior to study drug administration.

19. Criterion modified per Amendment 2.

    19.1. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, or is a family member of a site employee or the investigator.

20. Criterion modified per Amendment 1.

    20.1. Criterion deleted per Amendment 2.

21. Subject is a male who is sexually active with a pregnant female, or plans to be sexually active with a pregnant female while enrolled in this study.

22. Subject is pregnant or breast-feeding, or planning to become pregnant or breastfeed while enrolled in this study or within 3 months after the last dose of study drug.

23. Subject is judged by the investigator to be unable to perform or comply with all study-specific requirements.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2, Screening Phase, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Criterion modified per Amendment 2.

    1.1. Subjects must agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements; prohibitions on donation of blood, sperm, and eggs [ova, oocytes]).

2. Criterion modified per Amendment 1.

    2.1. Subjects must abstain from using illegal drugs or recreational or medically prescribed cannabis from screening through the end of the posttreatment phase.

3. Criterion modified per Amendment 2.

    3.1. On study visit days, alcohol must be avoided prior to the time of the visit. At all other times after enrollment, subjects at or above the legal drinking age will be instructed to limit their alcohol consumption to that consistent with moderate drinking (ie., up to 1 drink/day for women and 2 drinks/day for men).

4. Criterion modified per Amendment 2.

    4.1. Moderate and strong inducers or inhibitors of CYP3A4 are prohibited from Day 1 through the end of the posttreatment phase.

5. Subjects are prohibited from taking/consuming grapefruit, grapefruit juice, Seville oranges or poppy seeds from screening through the end of the posttreatment phase.

6. Criterion modified per Amendment 1.

   6.1. Subjects must not take any sedating medications on the day of the Task Battery (other than any preexisting daily medications) and must not consume caffeine within 2 hours prior to the battery.

7. Criterion modified per Amendment 2.

   7.1. On days when biomarker blood samples are drawn, subjects should be advised to follow a low-fat diet for at least 8 hours prior to their scheduled visit. Subjects should be advised to refrain from strenuous exercise and use of nonsteroidal anti-inflammatory drug (NSAID) medications for 24 hours before their scheduled visit. Information regarding compliance with these restrictions should be recorded on the CRF or lab requisition form.

8. Criterion modified per Amendment 2.

   8.1. Refer to Section 8, Prestudy and Concomitant Therapy, for details regarding prohibited and restricted therapy during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

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 kits 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 (aged 13-17 years) will be randomized until at least 8 subjects are on the active drug, following which screening of subjects of that age range will be temporarily paused while an interim PK analysis is conducted. The analysis will be performed when all 8 adolescent subjects have participated in the PK sampling at Week 2. Adolescent subjects already in screening may be randomized, and screening and randomization of subjects 18-35 years will continue as

normal. Any adolescent subjects already randomized will continue per protocol. If PK samples are not able to be obtained from 1 of the adolescent subjects, it may be necessary to screen and/or randomize additional adolescent subjects. If PK results are consistent with prespecified parameters (see Section 11.5) screening and randomization of adolescent subjects will resume. If not, unless agreement is obtained from FDA to continue enrolling adolescent subjects it may be necessary to complete enrollment with only adult subjects.

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 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.

6. DOSAGE AND ADMINISTRATION

Following Protocol Amendment 5, subjects will self-administer double-blind study medication twice daily for 12 weeks. Study medication will be provided as JNJ-42165279 25 mg tablets, or matching placebo, packaged in bottles. All tablets (JNJ-42165279 /placebo) are identical in appearance.

On all visits in the treatment phase, study medication will be taken at the clinic. Treatment Phase visits should be scheduled to occur in the morning, and the dose administered in the clinic should be the first dose of the day for each subject. Dosing should occur after all subject-related procedures, except as noted for blood draws, when feasible. Dosing must occur after confirmation of eligibility and subjects' baseline safety assessments on Day 1 and after administration of the JAKE Task Battery at all applicable visits. On all other days between visits, subjects will be instructed to take their study medication at home once in the morning and once in the evening, with as close as possible to a 12-hour interval between dosings. No more than 2 pills should be taken in one day (defined here as midnight to midnight). There should be at least 6 hours between doses; if this is not possible, a dose should be skipped. Subjects should be informed of the importance of taking the evening dose on the day prior to the Week 2 and 12 visits as close as possible to their routine evening dose time.

Diaries will be provided to subjects/caregivers to record dates of non-compliance (missed doses or >2 pills taken), as well as the time of morning and evening dosings on the day prior to the Week 2 and 12 visits.

A study-site investigational product manual including instructions for dispensing, storage (on site and at home) and intake of the study medication will be supplied to the study site.

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

In case of any change in dose levels prior to study start or during the study the responsible Ethical Committee(s) and Health Authorities, if applicable, will be notified.

7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Study drug will be self-administered by subjects. As such the number of study drug tablets dispensed will be recorded and compared with the number returned.

At study visits on which the dose is to be held, study drug will be self-administered on site, which will be witnessed by designated study-site personnel at the study sites.

Subjects will receive instructions on compliance with study drug administration upon study medication (bottle) dispensing. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any subject who is not compliant with taking the study drug.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies administered up to 3 months before screening must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with signing of the initial informed consent until the end-of-study visit (Follow up). Concomitant therapies should also be recorded beyond this time only in conjunction with new or worsening adverse events until resolution of the event.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from the study drug must be recorded in the CRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

Any pharmacologic, diet, or behavioral intervention for the core or associated symptoms of ASD such as but not limited to an ABA program, PRT, TEACCH, Floor Time and DIR, RDI, Early Start Denver Model, Discrete Trial Training or a social skills program whether school-based or not must:

A) Have begun at least 1 month prior to the baseline visit and continue unchanged through the double-blind period, or

B) Have ended at least 1 month prior to the baseline visit

If such therapy is started, discontinued or changed substantially during the course of the double-blind study the subject should be discontinued.

Subject should not take any sedating medications on the day of the Test Battery (other than preexisting daily medications) and should not consume caffeine within 2 hours prior to the battery.

Moderate and strong inducers or inhibitors of CYP3A4 are prohibited through the end of the posttreatment phase. Attachment 2 provides examples of moderate and strong inducers or inhibitors of CYP3A4. The investigator should evaluate all prestudy and concomitant medications to assess whether they are moderate or strong inducers or inhibitors of CYP3A4 and consult with the Sponsor if unsure.

On biomarker blood collection days, subjects should be informed to refrain from use of NSAID medications for 24 hours before their scheduled visit. This is because the use of NSAIDs may impact biomarker measurements, specifically via altering circulating and inducible cytokine levels. In addition, NSAIDs also have been reported to inhibit FAAH directly so there is a particular need in FAAH studies to restrict their use. Any use of NSAIDs within 24 hours prior to the visit should be recorded on the CRF or lab requisition form.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedule summarizes the visits as well as the frequency and timing of assessments applicable to this study. A visit window of ±3 calendar days will be allowed for all visits after Day 1, unless otherwise indicated in the Time and Events Schedule. All visits are in principle single day visits; however, they may be performed over multiple days within the allowed visit window in case of logistical issues or subject's preference. Visits during the treatment period should be scheduled on the same type of day (weekday vs weekend).

Information regarding collection, handling, shipment, and labeling of biological samples (including safety labs) will be provided in a separate lab manual. Any changes to the lab manual will not result in a protocol amendment.

In the event of abnormal safety findings during the conduct of the study, additional measurements may be made immediately and subsequently at a frequency considered appropriate by the attending physician.

The person that will serve as the designated caregiver for the trial will be determined at screening. This person will perform all caregiver responsibilities described in this protocol, including attending all study visits and completing all caregiver assessments.

The time points for individual measures may be changed by the sponsor (with or without affecting the overall frequency of these investigations) prior to and during the study based on newly obtained data (eg, interim analysis, DMC) to allow for optimal fit to the actual safety or PK/PD profile of the study drug. This modification may result in a change in the overall frequency of the individual measures (eg, safety measures, blood samplings) provided the maximal total blood volume collected per subject defined will not be exceeded. Such modifications, where performed only to allow optimal fit to the actual safety, PK/PD profile of the study drug, will not be considered to be an (substantial) amendment to the protocol.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

The following describes the order of procedures at study visits:

- The order of blood draws versus dosing, when both occur at a visit, is as follows (see the Time and Events Schedule for further information):
  - On Day 1, blood samples will be collected postdose.
  - At the Week 2 and 12 visits, blood samples will be collected both prior to and after dosing.
  - At the Week 4 and 8 visits, blood samples may be collected before or after dosing.

- The order of procedures, other than the order of blood draws relative to dosing, is as follows:
  - On Day 1, all procedures required for determination of eligibility and all safety assessments must be completed prior to randomization and dosing.
  - For all visits, including screening, all subject-related procedures should be completed prior to blood sample collection.
  - It is recommended that dosing at study visits occur after all subject-related procedures.
  - For each subject, the JAKE Task Battery should be conducted at approximately the same time of day, when feasible, and must be completed prior to blood draws and dosing.

Venous blood will be collected for all blood-based analysis. Actual dates and times of assessments will be recorded in the source documentation and CRF or lab requisition form. The exact times for each blood draw will be recorded in the lab requisition form. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should preferably be performed in the following order: ECG(s), vital signs, blood draw. The order of multiple assessments within 1 protocol time point should also be the same throughout the study. Blood may be drawn by using a cannula or by venipuncture. The volume of blood to be collected from each subject is summarized in Table 1. For each subject, the maximum amount of blood drawn in this study will not exceed 200 mL.

Table 1: Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Total Volume of Blood (mL)[a]
Safety (including screening and posttreatment assessments)			
Serum chemistry	2.5	5	12.5
TSH (with reflex to T3/T4 if needed)	3.5	1	3.5
Hematology	2.0	5	10.0
PT (INR) and aPTT	1.8	5	9.0
Serology			
Hepatitis B virus surface antigen and Hepatitis C virus antibody	2.5	1	2.5
HIV ½ antibody diff. and HIV-1/HIV-2 antibodies	2.5	1	2.5
- Serum β-hCG pregnancy test (females)[b]	0	1	0
PK sample	2	5	10
CCI biomarker sample	6	5	30
Cytokines and miRNA sample	10	2	20
Pharmacogenomics sample (DNA)	2	1	2
Approximate Total[b]	NA		102.0

[a] Calculated as number of samples multiplied by amount of blood per sample.
[b] Volume for serum chemistry sufficient for pregnancy testing as well.
[c] Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
Note: Blood may be drawn by using a cannula or by venipuncture.
Abbreviations: aPTT= activated partial thromboplastin time; DNA= deoxyribonucleic acid; CCI [redacted]; HIV= human immunodeficiency virus; INR= international normalized ratio; PK= pharmacokinetics; PT= prothrombin time; TSH= thyroid-stimulating hormone.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

See Attachment 16 for guidance on study conduct during the COVID-19 pandemic.

9.1.2. Screening Phase

Before any study specific procedures are conducted and following an explanation of the purpose and risks of the study, written consent, and if applicable, assent, will be obtained (see Section 16.2.3, Informed Consent and Assent Form, for further information).

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.

Recording of adverse events/concomitant medication will start following consent and will continue until completion of the study.

During screening, assessments/procedures will be performed as described in the Time and Events Schedule.

If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant.

Retesting of abnormal laboratory values that may lead to exclusion will be allowed one time. Retesting will take place during an unscheduled visit in the screening phase or at the second screening visit.

Urine drug screens to determine eligibility may be repeated once, at the discretion of the investigator.

Eye calibration may be repeated during the screening period if "good" calibration is not achieved at the first screening visit.

If a subject is not able to complete all screening procedures within the screening window, or does not meet all inclusion and exclusion criteria (ie, is a screen failure), but at some time in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on 1 occasion only. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

9.1.3. Double-Blind Treatment Phase

Throughout the treatment phase, study medication will be dispensed at study visits and subjects will self-administer the medication as outlined in Section 6, Dosage and Administration. Clinic visits should be scheduled for the morning, as the in-clinic dosing should be a subject's first dose of the day.

On Day 1, subjects who successfully complete the screening phase will visit the clinical site/unit to be randomized on Day 1 of the double-blind phase. Prior to dosing, eligibility will be confirmed and the baseline safety assessments and the JAKE Task Battery will be performed as described in the Time and Events Schedule.

During the double-blind treatment period, following Day 1, subjects will return to the investigational site at Week 2 (Day 15), Week 4 (Day 29), Week 8 (Day 57), and Week 12 (Day 85). Assessments will be performed as specified in the Time and Events Schedule.

9.1.4. Posttreatment Phase (Follow up)

At 14 days (±1 week) following last dosing (Week 12), subjects will return to the clinical site for a safety follow up visit. The procedures to be completed during the follow up visit are listed in the Time and Events Schedule.

Investigators may re-contact the subject to obtain long-term follow up information to determine the subject's safety or survival status (refer to Section 16.2.3, Informed Consent).

9.2. Efficacy

9.2.1. Endpoints

Primary

The primary endpoints will be measured as follows:

- Change from baseline to Day 85 in the ABI Core Domain Score (Social Communication and RRB).
- Change from baseline to Day 85 in the ABI Social Communication Domain Score.
- Change from baseline to Day 85 in the ABI RRB Domain Score.

Secondary

The secondary endpoints are as follows:

- The change from baseline to Day 85 in the ABI Mood & Anxiety, Challenging Behavior, and Self-Regulation domains.
- The change from baseline to Day 85 in the ABC, ABI-S, ABI-C, CGI-S, RBS-R, ZBI, CASI-Anx, SRS-2, Caregiver GI-S scales.
- Caregiver Assessment of Treatment, Self GI-I, and CGI-I at Day 85.

9.2.2. Evaluations

Evaluations throughout the study will encompass several categories:

- My JAKE/My JAKE MMApp, including the ABI, ABI-S, and Daily Tracker, as well as system components available only in My JAKE (Journal and Event Tracker, Therapy Tracker, and Medical/Development History), to be completed periodically as instructed.

- The ABI-C, to be completed periodically by the PI or delegate as instructed.
- The JAKE Sense Continuous Biosensor, with training and manuals to guide appropriate use.
- The JAKE Task Battery with the JAKE Sense Periodic Biosensors.
- Standard assessment instruments and rating scales for evaluating ASD core and related symptoms, functioning, clinicians' global impressions of disease severity and improvement, and caregiver stress.
- Caregivers' and subjects' global impressions (Caregiver GI-S, Caregiver Assessment of Treatment, Self GI-I).

9.2.2.1. Caregiver Reporting Tool: Modules and Components

My JAKE and My JAKE MMApp are two applications containing the caregiver reporting tool that can be used by the caregiver during the study to enter information about the behavior and mood of the subjects. Caregivers will register and use either the first application of the reporting tool, My JAKE, or the second application of the tool, My JAKE MMApp, dependent upon the application which is operational at the time. If neither version is available, caregivers will record information on paper forms as described below.

My JAKE encompasses various modules for use by clinicians, caregivers, and the sponsor. My JAKE MMApp is for use by caregivers and the sponsor. Both applications are accessible through most modern web browsers ("My JAKE Web"), as well as mobile devices ("My JAKE Mobile"). My JAKE or My JAKE MMApp is used throughout the study. Specific instructions for certain modules are below.

Not all modules described are available for both My JAKE Web and My JAKE Mobile interfaces.

Some modules in My JAKE are not available in My JAKE MMApp nor on paper forms. Table 2 provides further information on available modules and features.

Table 2: Caregiver Reporting Tool: Available Modules and Features

	My JAKE (1st application)	My JAKE MMApp (2nd application)	Paper Forms
Secondary caregiver reporting [a]	X		
ABI & ABI-S	X	X	X
Daily Tracker	X	X	X
Journal [a] & Events Tracker	X		
Therapy Tracker [a]	X		
Medical/Developmental History	X		

Abbreviations: ABI=Autism Behavior Inventory; ABI-S: Autism Behavior Inventory-Short Form
[a.] Completion is optional in My JAKE

The same primary caregiver should complete all components of the caregiver reporting tool and standard scales throughout the study. Additional caregivers can complete My JAKE components as secondary users.

It is understood that caregivers of independent, adult subjects may not be able to enter the same amount into the caregiver reporting tool as caregivers of subjects who live with them.

Site and institution personnel will not modify, adjust, troubleshoot, change or alter the hardware or software of the JAKE System unless instructed to do so by or under the supervision of the sponsor.

Caregivers using My JAKE should be instructed not to revoke site or sponsor's access to My JAKE and Microsoft HealthVault without investigator approval to do so.

9.2.2.1.1. ABI

The ABI is a series of approximately 65 questions related to the core and associated symptoms of ASD. 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 ABI was developed by review of existing instruments in consultation with experts in the field and testing in the target population. The current versions of the ABI, ABI-S, and Autism Behavior Inventory-Clinician interview (ABI-C) are a result of a statistical and clinical review process, and qualitative review and feedback from users, including cognitive interviewing.

The development of the ABI adhered to the following FDA guidelines, (1) Precise definition of the target construct, (2) The need for the new measure and how it will enhance the substantive knowledge base, (3) Initial pool of items was submitted to expert review,[143] (4) Identification and justification for sampling strategy, (5) Used Exploratory Factor Analysis (EFA) to assess the underlying factor structure to refine item pool,[30] (6) Description of covariance and correlation matrix, (7) Use of psychometric techniques during scale refinement that included Item Discrimination, Item Difficulty, Correlation if items were deleted, Differential Item Functioning (DIF): a Rasch Analysis approach.

Validation of the ABI began in ASD-001, where in a small sample of around 25 parents and 20 clinician ratings, good test-retest reliability was found. Correlation between the ABI and validated instruments measuring similar domains was also good, and there was divergence between scales which were not expected to correlate. Validation, including an assessment of sensitivity to change, continued in the ASD-002 study.

The full ABI will be completed by the primary caregiver at screening, Day 1 (predose), Week 4, Week 8, and Week 12. It should be completed at the site and on the same day as it is begun.

The ABI-S is a shorter version of the ABI with approximately 20 items. The caregiver will complete the ABI-S on Week 2 (site), Week 6 (home), and Week 10 (home) as outlined in the Time and Events Schedule.

Following a caregiver interview, the PI or delegate will complete the ABI-C on visits listed in the Time and Events Schedule.

For each subject, the ABI and ABI-S should be completed by the same caregiver, and the ABI-C should be completed by the same site personnel, at all administrations.

ABI-C

The ABI-C covers the domains and subdomains of the ABI-S 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 severe difficulties with an area of functioning. There are 14 items across each of the 5 domains. The ABI-C is completed on paper. See Attachment 3 for a representative example of this instrument.

9.2.2.1.2. Daily Tracker

The caregivers are required to select 3 items to track on a daily basis. Following completion of the ABI at the screening visit, a clinician at the site will discuss possible items to track with the caregivers and help them with their selection. Caregivers will have the 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, as well as report on subjects' overall type of day, using an 8-point scale, ranging from 'troubling' to 'encouraging'.

A Mood Report is completed after 6 pm each day. The report allows the caregiver an opportunity to report the subject's state, in terms of valence and arousal levels. It is presented twice, requiring caregivers to: 1) report subject's overall mood for that day and 2) report the subject's most extreme mood for that day.

In addition, each morning the caregiver will be asked to report on how well the subject slept the previous night using the same 8-point scale used for behavior ratings.

9.2.2.1.3. Journal and Event Trackers

This module will:

- Allow ad hoc free-text entry by caregivers.
- Provide an interface for tracking both events and journal entries (tantrum, stereotypy, social interaction, etc.) as they occur. Caregivers will also be able to track progress towards a particular target behavior that they have entered.
- Keep track of items of interest, including sleep problems, seizures and diet on a daily basis.

Events can be reported on a daily basis throughout the study, either as they occur or at a later stage. The clinician at the site will discuss 1 or 2 specific behaviors which the caregiver will aim to track using the event trackers. The caregiver will be encouraged to record 3 instances of these behaviors, as they happen, each week. Use of the journal will be encouraged but is considered optional.

In My JAKE, the Mood Report can be completed at any time through the Events Tracker, in addition to reporting within the Daily Tracker.

9.2.2.1.4. Therapy Tracker

This module will track the subject's various medical appointments, treatments, and other therapies. It can also be used to set up and schedule study visits with the parent or caregiver. Use of the therapy tracker will be encouraged but is considered optional.

9.2.2.1.5. Medical/Developmental History

This module is to be filled out by caregivers (with assistance, if needed) during the screening/on-boarding phase of the study. Certain sections, such as the developmental milestones may continue to be edited throughout the study.

If the Medical/Development History section is not completed by the caregiver, the site is responsible for ensuring completion of required fields in My JAKE.

9.2.2.2. JAKE Sense

Biosensors will be evaluated and used as per the Time and Events Schedules and descriptions below.

9.2.2.2.1. Continuous Biosensor

Continuous Biosensors can be worn over extended periods of time such as throughout the day or during sleep. The Continuous Biosensor will also be worn and assessed during study visits as with the Periodic Biosensors below. Description of the Continuous Biosensor and its use in this study is provided below.

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.

The subject will be required to wear the Continuous Biosensor during every site visit so that data can be collected afterwards by study site personnel.

ActiGraph Link is a recognized medical device in the United States - 510(k) number K040554 Code: GWQ. While this device is being used in compliance with its intended use, it is not being used in such a way as to diagnose, treat, or prevent any disease, nor is its output being used in (or in support of) any regulatory filing (now or in the future).

9.2.2.2.2. 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;

see more complete description below). Periodic Biosensors and their description and use in the study are described below.

9.2.2.2.2.1. Electroencephalogram (Brain Products ActiCHamp 32)

- 24-bit battery-supplied, active channel amplifier using the actiCAP active electrodes
- available with 32, 64, 96, 128 and 160 EEG channels
  - Intended 19 channels for measurement: Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T7, T8, P3, P4, P7, P8, Pz, O1, O2; reference electrode position on left mastoid bone
- 8 integrated AUX inputs can be used with a full range of biosignal sensors (eg, electrooculogram [EOG], electromyogram [EMG], ECG, respiration, acceleration, temperature, blood pulse, photo sensor, microphone, etc.)
  - A photo sensor will be connected to the first AUX input to detect visual stimuli changes (onset and duration)
- high sampling rate (up to 100 KHz) and wide hardware bandwidth
- simple plug and play concept to easily increase the number of channels (by adding modules of 32 channels)

9.2.2.2.2.2. Actiwave Cardio Single-Channel ECG

Heart rate data will be collected using the Actiwave Cardio Single-Channel Electrocardiogram (patch); (http://www.camntech.com/products/actiwave-cardio/actiwave-cardio-overview). The Actiwave Cardio is a water-resistant ultra-miniature single channel ECG waveform recorder. It consists of 2 electrodes connected by a short lead which simply clip onto 2 standard ECG pads worn on the chest. It also contains a tri-axial accelerometer, the signal from which allows the user to determine resting body position. Adhesive, disposable electrodes are applied to the subject's chest – the device is then clipped to the electrodes.

The Actiwave Cardio is a recognized medical device in the United States - 510(k) number K100266 Code: MWJ. While this device is being used in compliance with its intended use, it is not being used in such a way as to diagnose, treat, or prevent any disease, nor is its output being used in (or in support of) any regulatory filing (now or in the future).

NOTE: The Actiwave Cardio is used only for JAKE Sense Periodic Biosensor evaluation and is different from the 12-lead ECG used for drug safety assessments.

9.2.2.2.2.3. Eye Tracker (Tobii X2-30)

The Tobii X2-30 features include the following (http://www.tobii.com/de/eye-tracking-research/global/products/hardware/tobii-x2-30-eye-tracker/):

CCI

9.2.2.2.2.4. iMotions Biometric Research Platform: Emotient FACET Module

iMotions® Biometric Research Platform: Emotient™ FACET Module (https://imotions.com/blog/facial-expression-analysis/) will be used for affect detection via computer recognition of subject affect. Facial recognition will take place throughout the administration of the JAKE Task Battery using a standard computer web camera.

In addition, 5 minutes of video intended to elicit facial expressions (e.g., 'funny animals') will be shown during the Task Battery. Subjects will also be asked to make faces to reflect core emotions: Happy, Sad, Surprise, Scared, Angry, Yucky (disgust).

9.2.2.3. JAKE Task Battery: Tasks and Stimuli for use With Periodic Biosensors

Tasks and stimuli (the JAKE Task Battery) for use with Periodic Biosensors will comprise a battery of tests approximately 30 minutes in duration. All stimuli are presented using the software application platform iMotions® Biometric Research Platform (formerly known as Attention Tool). Subjects will use all Periodic Biosensors throughout all components of the Task Battery, though certain components are focused on specific sensors as indicated by the section headers. A subset of these sensors will interface directly with iMotions® Biometric Research Platform, while others will use their own proprietary software to operate.

Additionally, subjects will continue wearing the Continuous Biosensor during administration of the Task Battery. Tasks and stimuli will be presented on a computer monitor and may require interaction as described below. The tasks are presented in 2 sets of approximately 13 minutes. Breaks are permitted between sets and as necessary within a set (though this is discouraged). Devices should continue to be worn during all breaks.

Images/video within a task will be counterbalanced for order between subjects.

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CCI

[redacted]

CCI

9.2.2.4. Caregiver Reporting Tool: Data Processing

The JAKE Data Pipeline is an internal set of tools designed specifically to handle data that is entered through My JAKE. While My JAKE will have access to all data contained within a subject's Microsoft HealthVault account, only a subset of this information is collected and archived by the sponsor through the My JAKE Data Pipeline.

My JAKE MMApp Data Processing incorporates an integrated set of tools designed specifically to handle data that is entered through My JAKE MMApp. The sponsor will have full access to all information entered through My JAKE MMApp.

The sponsor will use the information collected through the My JAKE Data Pipeline and My JAKE MMApp to track study progress and outcomes and perform related study analysis. This information may contain limited personal "identifiers." The information collected and archived may be shared with other members of the Johnson & Johnson family of companies, its contractors and consultants, and regulatory authorities such as FDA.

To ensure that access to protected health information (PHI) stored in Microsoft HealthVault is limited, high risk fields are filtered out during the My JAKE Data Pipeline data collection procedure. These fields include (but are not limited to) names, phone-numbers, street and email

addresses, dates (related to appointments or medical care), and descriptive free-text fields (journal entries, event descriptions).

High-risk personally-identifiable fields required by My JAKE MMApp (such email address, dependent's first name, etc.) are excluded from final study datasets.

9.2.2.5. JAKE Sense Data Pipeline

The JAKE Sense Data Pipeline is an internal set of tools designed specifically to handle data collected by JAKE Sense. First, packages are archived to ensure traceability of derived analyses. Second, a series of utilities scans the packages to produce a series of extracted features in the form of flat .CSV-formatted files. Finally, the files are stored in a secured server file share (and combined with outputs from the My JAKE Data Pipeline) for the purpose of exploratory, POC data mining.

The information collected and archived via the JAKE Sense Data Pipeline is subject to the same treatment and sharing policies as data collected and archived via the My JAKE Data Pipeline.

9.2.2.6. Standard Instruments and Scales

The diagnosis of ASD will also be established or confirmed via standard instruments and scales. Subjects will be required to have a formal DSM-5 diagnosis of ASD using the ADOS-2. An ADOS-2 completed within 24 months prior to the screening visit is acceptable but the item responses must be available for entry into the study eCRF. Assessments will follow the Time and Events Schedule. All caregiver rating scales should be completed by the primary caregiver. Preferably the same person should complete the scales throughout the study.

9.2.2.6.1. Autism Diagnostic Observation Schedule™, Second Edition

The ADOS-2 is a validated scale that allows a reliable diagnosis of ASD across age, developmental level, and language skills. One of the 4 ADOS-2 modules should be selected according to the publisher's manual. Module 4 should be scored according to the algorithm published in Hus et al, 2014.[53]

See Attachment 4 for a representative example of this instrument.

9.2.2.6.2. Kaufman Brief Intelligence Test, Second Edition

The KBIT-2 is a 10-item questionnaire used to obtain a quick estimate of intelligence at screening in order both to help select subjects capable of performing the required tasks and for analysis of data. Three composite standard scores are calculated from the questionnaire.

See Attachment 5 for a representative example of this instrument.

9.2.2.6.3. Zarit Burden Interview

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 0-4 (never to nearly always).

See Attachment 6 for a representative example of this instrument.

9.2.2.6.4. Social Responsiveness Scale 2™

The SRS-2 distinguishes autism spectrum conditions from other child psychiatric conditions by identifying the presence and extent of autistic social impairment. There are 5 subscales, 65 items. The SRS-2 comes in 3 versions- for preschool, school age, and adult. The PI will choose whether the school age or adult version is most appropriate for each subject using the instructions in the SRS-2 manuals.

See Attachment 7 for a representative example of this instrument.

9.2.2.6.5. Child Adolescent Symptom Inventory Anxiety

The CASI-Anx 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. One or 2 key symptoms of each of the following disorders are also included: obsessive-compulsive disorder, posttraumatic stress disorder, specific phobia, panic attack, motor tics, vocal tics, and substance use.

The Total Scale includes 173 items for parent version (teacher: 125).

This study will use only the 21-point anxiety scale (CASI-Anx) which was recommended as a possible outcome measure for autism.[64] Responses will range from 0 (never) to 3 (very often).

See Attachment 8 for a representative example of this instrument.

9.2.2.6.6. Repetitive Behavior Scale-Revised (parent)

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).

See Attachment 9 for a representative example of this instrument.

9.2.2.6.7. Aberrant Behavior Checklist-Community

The ABC is a 58-item behavior rating scale used to measure behavior problems across 5 subscales Irritability, Lethargy (Social Withdrawal), Stereotypy, Hyperactivity, 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.

See Attachment 10 for a representative example of this instrument.

9.2.2.6.8. Clinical Global Impression-Severity and Improvement

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 at baseline and other visits. The CGI-I is a

single-item instrument that requires the clinician to assess the degree of improvement in the subject from the initiation of treatment using a 7-point scale. The time points for these assessments are included in the Time and Events Schedule.

See Attachment 11 for a representative example of each of these instruments.

9.2.2.6.9. Caregiver Global Impression of Severity

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 at baseline and per the Time and Events Schedule.

9.2.2.6.10. Caregiver Assessment of Treatment

The Caregiver Assessment of Treatment is a 3-item questionnaire completed at the end of the treatment period. Caregivers rate their global impression of improvement in their child's autism, whether there was improvement in specific symptoms, and their interest in having their child continue the study medication.

See Attachment 14 for a representative example of this questionnaire.

9.2.2.6.11. Self-Assessment of Improvement

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.

9.2.2.6.12. Evaluation of JAKE

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.

9.2.2.7. JAKE Help/Manuals

JAKE will include robust help for sites and caregivers for all components of the system. My JAKE will display only the appropriate content to the logged in account (ie, help sections intended for site personnel are not accessible to subjects or caregivers). The help system will contain (but is not limited to) general information, troubleshooting steps, and instructional guides in the form of quick reference guides, training videos, or checklists for each JAKE System component. My JAKE MMApp will contain a reduced set of checklists appropriate for the caregiver. Study sites are expected to be proficient in using the help system and following all of the steps outlined in the instructional guides prior to enrolling subjects. Training will be conducted on the use of the help system, instructional guides, and their related components.

A hardcopy of the JAKE manual will be provided to clinical sites, and will be available online in My JAKE. Caregivers will be given a hardcopy of a Caregiver Guide, which will also be available online in both My JAKE and My JAKE MMApp. These documents and / or applicable

help sections may be updated during the trial. Any updates will be proactively communicated to sites. An interactive, site-only, on-line version of the full help manual will be available.

There will also be a toll-free helpline available for sites and caregivers. Callers will be instructed not to provide their name, call-back numbers, or any other identifiable information to protect subject and caregiver identity. The toll-free helpline is operated by employees and contractors of the sponsor.

9.2.2.8. National Database for Autism Research/Global Unique ID

Subjects will participate in NDAR data sharing. Prior to their first subject each PI must apply to NDAR (to obtain access to the GUID creation tool). During screening, the site will generate a GUID for each subject using PHI such as name, place of birth and date of birth. PHI is 18 classes of information defined by US law and regulation that can be used to identify an individual. The storage and transmittal of PHI is restricted by US regulation. This PHI does not leave the site and is not transmitted to the sponsor or to National Institutes of Health (NIH). The GUID cannot be used to recreate the PHI. The site will enter the GUID into the sponsor's eCRF system.

There are 2 components to NDAR.

1. The sponsor may use the GUID to access data held by NDAR on individual subjects that has been shared with NDAR from other research projects and studies. Such data will be de-identified and will only be held in NDAR if the subject or legally appointed representative had granted consent in an Institutional Review Board (IRB) approved study for it to be sent to NDAR and shared with other researchers
2. Data from this study may be submitted to the NDAR using the GUID. NDAR is a computer system run by the National Institutes of Health that allows researchers studying autism to collect and share information with each other. With an easier way to share, researchers hope to learn new and important things about autism more quickly than before.

Data obtained from and shared with NDAR will be that of subjects in this study. The sponsor will be able to obtain additional data on subjects in this study from NDAR and potentially use that data to learn more about autism and improve the JAKE System.

During and after the study, the sponsor may send information about subject's health and behavior and any other data gathered in this study to NDAR. All data sent to NDAR will be provided through the JAKE Sense Data Pipeline and first de-identified in compliance with 45 CFR 164.514(b)(1). Only the NDAR GUID will link data from different sources to unique subjects. Researchers nationwide can then file an application with the NIH to obtain access to study data for research purposes. Experts at the NIH with expertise in the protection of health and science information will review every request carefully to minimize risks to subjects' privacy.

9.3. Biomarker Evaluations

During the study, the following PD evaluations will be performed at the time points indicated in the Time and Events schedule: plasma concentrations of CCI [redacted].

Additionally, blood biomarkers related to autism (including but not limited to cytokines and miRNAs) will be investigated to allow for exploratory immunophenotyping and for an exploratory PD evaluation. Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

The biomarker data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between ASD and phenotypes and biomarkers.

For visits that include biomarker sample collection, subjects should be advised to follow a low-fat diet for at least 8 hours prior to their scheduled visit. Subjects should be advised to refrain from strenuous exercise and use of NSAID medications for 24 hours before their scheduled visit. This is because the use of NSAIDs may impact biomarker measurements, specifically via altering circulating and inducible cytokine levels. In addition, NSAIDs also have been reported to inhibit FAAH directly so there is a particular need in FAAH studies to restrict their use. Information regarding compliance with these restrictions should be recorded on the CRF or lab requisition form.

9.4. Pharmacokinetics

9.4.1. Evaluations

Venous blood samples for analysis of JNJ-42165279 in plasma will be collected at the time points indicated in the Time and Events Schedule.

Blood samples will be used to evaluate the plasma PK of JNJ-42165279. Samples collected for analyses of JNJ-42165279 plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

The date and time of study drug administration in the clinic on Day 1, Week 2 and Week 12 visits, and the day prior to the Week 2 and 12 visits (both morning and evening doses) must be accurately recorded. Subjects will be instructed to take the dose of study drug at the Week 2 and 12 visits at the clinical site after collection of the first PK blood sample on those days.

9.4.2. Analytical Procedures

Plasma will be analyzed to determine concentrations of JNJ-42165279 using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry method by or under the supervision of the sponsor.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method. In addition, plasma samples may be stored for future analysis of protein binding and the metabolite profile.

9.4.3. Pharmacokinetic Parameters

The oral clearance and apparent distribution volume of JNJ-42165279 are assumed to be logarithmically distributed. The intersubject variabilities (expressed as percent coefficient of variation) of these parameters are 35.9% and 18.1%, respectively, based on previously conducted population analyses that used pooled PK data from studies with JNJ-42165279 in adults. Assuming a similar PK variability (ie, 35.9%) for subjects who are 13 to < 18 years of age and a sample size of 15 subjects, the probability that the 95% confidence interval for the geometric mean of each PK parameter will fall within 71% to 140% of the true geometric mean is 80%.

The plasma concentration-time data of JNJ-42165279 will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, apparent clearance, apparent distribution volume) will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of JNJ-42165279 will be explored. The results of the population PK analyses may be reported separately.

9.5. Pharmacogenomic (DNA) Evaluations

A pharmacogenomic blood sample will be collected from all eligible subjects. Deoxyribonucleic acid (DNA) samples will be analyzed for *FAAH* gene variants. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data. DNA samples may also be used for the identification of genetic and/or epigenetic factors that may influence the PK, PD, efficacy, safety and/or tolerability of JNJ-42165279, and for exploratory genetic and/or epigenetic analyses, including of autism.

DNA samples will be used for research related to JNJ-42165279 or ASD. They may also be used to develop tests/assays related to JNJ-42165279 or ASD. Pharmacogenomic research may consist of the analysis of 1 or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to JNJ-42165279 or ASD clinical endpoints.

The pharmacogenomics data obtained from this study may also be included in an ongoing cross-study analysis to investigate the relationship between ASD and phenotypes and biomarkers.

9.6. Safety Evaluations

During the study, regular safety assessments will be performed as listed in the Time and Events Schedule. These safety assessments include but are not limited to: vital signs, electrocardiogram (ECG), physical examination, adverse events, Columbia Suicide Severity Rating Scale (C-SSRS), Aberrant Behavior Checklist-Irritability Subscale (ABC-I), and clinical laboratory tests.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the case report form (CRF).

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

9.6.1. Adverse Events

Adverse events will be reported by the subject (or when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) from the time informed consent is signed until completion of the subject's last study-related procedure. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

9.6.2. Suicidality Evaluation

The C-SSRS and/or the ABC-I will be used in the evaluation of suicidality, as indicated below:

- At screening, the investigator will determine if evaluation of suicidality using the C-SSRS is feasible for each subject.
- If feasible, both the C-SSRS and ABC-I should be performed at screening.
- If the investigator determines that the C-SSRS is not feasible at screening, only the ABC-I will be used at screening and throughout the study.
- If both were used at screening, then both should continue to be used throughout the study unless the investigator determines that it is no longer feasible to use the C-SSRS; in this case, the ABC-I should be used alone for the remainder of the trial.
- The irritability subscale of the ABC (ie, ABC-I) will be collected at every visit except the second screening visit, either as part of the full ABC or alone. This is irrespective of whether the C-SSRS is performed.
  - Note: The full ABC includes the ABC-I subscale. Thus, administration of the ABC-I subscale alone is only needed when the full ABC is not performed.

The results of the C-SSRS and ABC-I should be reviewed by the investigator at each visit collected prior to the subject's departure. If a suicide-related thought or behavior is identified at any time or if there are any other concerning findings or changes, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

9.6.2.1. Columbia Suicide Severity Rating Scale

Consistent with regulatory guidance, any occurrence of suicide-related thoughts and behaviors will be assessed. An interview to assess the risk of suicidal ideation and behavior will be conducted at the time points listed in the Time and Events Schedule.

The C-SSRS is a measure of the spectrum of suicidal ideation and behavior that was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[97] The C-SSRS is a clinical interview providing a summary of both ideation and behavior that can be administered during any evaluation or risk assessment to identify the occurrence and intensity of suicidal thoughts and suicidal behaviors. It can also be used during treatment to monitor for clinical worsening.

Both pediatric and adult versions of the C-SSRS are available and the investigator should use the appropriate version per C-SSRS instructions and training.

The Baseline/Screening version of the C-SSRS will be used at screening and the Since the Last Visit version will be used at all other visits.

See Attachment 12 and Attachment 13 for representative examples of the C-SSRS (Baseline/Screening) and C-SSRS (Since Last Visit), respectively.

9.6.2.2. Aberrant Behavior Checklist - Irritability Subscale

The ABC-I is a subscale of the ABC (described in Section 9.2.2.6.7) focusing on irritability, aggression and self-injurious behavior. As the C-SSRS may not be appropriate for all subjects in this study, the ABC-I may be used as a substitute as per instructions in Section 9.6.2, Suicidality Evaluation.

9.6.3. Vital Signs

Sitting vital signs (body temperature, pulse/HR, blood pressure) will be collected at the time points indicated in the Time and Events Schedule.

9.6.4. Electrocardiogram

Twelve-lead ECGs will be collected at the time points listed in the Time and Events Schedule.[12]

At all time points, triplicate ECGs are required. The individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. It should be noted that the single-lead ECG used during the JAKE Task Battery is not used as a substitute for the 12-lead recorder.

During the study, the clinical investigator will review the ECG for immediate management and to mark abnormalities. A description of the overall assessment (ie, normal or abnormal plus reason) will be made and a copy of the trace will be placed with the source data.

9.6.5. Physical and Neurological Examination

The study investigator or other authorized and appropriately qualified designee will perform the physical examination at screening, Week 12, and at final follow up.

Height will be measured at screening only. Body weight will be measured at screening, Day 1, and at other times as specified in the Time and Events schedule.

The neurological examination can be adapted as necessary but at screening should include mental status (orientation and memory); oculomotor motion and vision for cranial nerve testing; limb strength and abnormal movements for motor function; and tests of cerebellar function: gait, finger-to-nose, heel-to-shin, and rapid alternating movements. Tests of sensation (eg, pain, vibration, etc) should be included only if indicated by clinical history/symptoms. Neurological examinations subsequent to screening may be more abbreviated and directed for follow up of abnormalities.

9.6.6. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents. The following tests will be performed at a central laboratory appointed by the sponsor:

- Hematology Panel

  -hemoglobin
  -hematocrit
  - red blood cell (RBC) count
  - white blood cell (WBC) count with differential
  - platelet count
  - mean corpuscular volume
  - mean corpuscular hemoglobin
  - mean corpuscular hemoglobin concentration

- Coagulation

  -prothrombin time
  -activated partial thromboplastin time (aPPT)
  - International normalized ratio (INR)

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -glucose
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)
  -gamma-glutamyltransferase (GGT)
  -total and direct bilirubin
  -magnesium
  -alkaline phosphatase
  -creatine phosphokinase (CPK)
  -lactic acid dehydrogenase (LDH)
  -uric acid
  -calcium
  - phosphate
  -albumin
  -total protein

- Urinalysis

  Dipstick
  -specific gravity
  -pH
  -glucose
  -protein
  -blood
  -ketones
  -bilirubin
  -urobilinogen
  -nitrite
  -leukocyte esterase

  Flow Cytometry
  -RBC
  -WBC
  -epithelial cells

  Sediment
  -crystals
  -casts
  -bacteria

Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. RBC, WBC, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically.

- Urine Drug Screen: opiates (including methadone), cocaine, amphetamines, cannabinoids, barbiturates, benzodiazepines, phencyclidine, and MDMA.
- Serology (HBsAg, anti-HCV, HIV, and thyroid-stimulating hormone [TSH]).
- Pregnancy tests:
  - In all women, a serum β-hCG will be performed at screening.
  - In WOCBP; a urine pregnancy test will be performed at all other timepoints beginning on Day 1.
  - If the urine pregnancy test is positive, a serum β-hCG test will be performed.

The use of local laboratories is allowed in cases where initiation of treatment or safety follow up is time-critical and the central laboratory results are not expected to be available before the need to begin dosing or if actions need to be taken for safety reasons (samples will be taken in parallel for the central laboratory).

10. SUBJECT COMPLETION / WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed the ABI at Week 12 (Day 85) of the double-blind phase. Subjects who prematurely discontinue study treatment for any reason before completion of the double-blind phase will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment and Withdrawal from Study

A subject's study treatment should be discontinued and the subject withdrawn from the study if:

- The blind is broken at the site
- The investigator believes that for safety reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- A subject experiences a severe adverse event or SAE while receiving treatment, that is considered at least possibly related to study drug, after discussion with and agreement of the medical monitor
- Liver function test criteria (any of following):
  - ALT or AST >5xULN
  - ALT or AST >3xULN **and** (Total Bilirubin Level [TBL] >2xULN **or** INR >1.5)
  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- Noncompliance with study drug (ie, less than 80% compliance) during the blinded treatment phase
- Serious violation of protocol procedures after discussion with and agreement of the medical monitor
- A subject becomes pregnant
- Lost to follow up
- Withdrawal of consent

If a subject is lost to follow up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the double-blind treatment phase, ET/EW and posttreatment follow up assessments should be obtained.

If the decision to discontinue treatment or withdraw from the study is made at a study visit, that visit may be converted into the EW visit. The follow up visit should take place afterwards as per the Time and Events Schedule.

If the decision to discontinue treatment or withdraw from the study is made in-between study visits, the subject should return to the site as soon as possible for an EW visit. The follow up visit should take place afterwards as per the Time and Events Schedule.

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

Statistical analyses will be conducted by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy, safety, tolerability, PD and PK data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

11.1. Subject Information

The primary efficacy and safety analysis sets are defined below.

- Intent-to-treat (ITT-BID): all subjects enrolled under BID dosing who receive at least 1 dose of study medication and have both a baseline and a postdose efficacy evaluation.

- Safety: all randomized subjects who receive at least 1 dose of study medication

11.2. Sample Size Determination

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 (under BID dosing) 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 analytic intervention leads to medium-to-large effects on a variety of scales for children with autism.[136] Additionally, previous studies of selective serotonin reuptake inhibitors (SSRIs), antipsychotics and antiepileptic drugs (AEDs) 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 RRB domains and 0.90 between each of the domains and the ABI Core Domain Score.

11.3. Efficacy Analysis

11.3.1. Primary Efficacy Endpoints

The primary efficacy analysis will be based on the ITT-BID analysis set. 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 RRB Domain Score during the double-blind treatment phase. Each will be analyzed using a mixed effects model for repeated measures (MMRM). The model will include time, treatment, time-by-treatment interaction, age group (13-17 years and 18-35 years, inclusive), and gender (male and female) as factors, and baseline score as a continuous covariate. An unstructured variance-covariance matrix will be used. In case of convergence problems, simpler variance-covariance structures such as Toeplitz or autoregressive order 1 (AR[1]) will be considered.

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.

Additional sensitivity analyses for the primary efficacy endpoints may be specified in the SAP.

Descriptive statistics for values and changes from baseline will be provided by treatment group at each time point during the double-blind phase. Descriptive statistics of the primary efficacy endpoints may be provided by subgroups; this will be specified in the SAP.

11.3.2. Secondary Efficacy Endpoints

Descriptive statistics for values and changes from baseline (where applicable) will be provided for all secondary efficacy measures by treatment group at each time point during the double-blind phase.

For the secondary efficacy endpoints, comparisons between JNJ-42165279 and placebo will be performed by means of an MMRM model as described for the primary efficacy endpoints.

Relationships between select biosensors and scales will be measured with the appropriate correlation analyses. These relationships will be further defined in the SAP.

Descriptive statistics of actual values and changes from baseline (where applicable) by treatment group at each time point during the double-blind phase will be provided for key biosensor measures and standard scales.

11.4. Biomarker and Pharmacogenomic Analysis

Baseline biomarker values (collected during screening) and changes from baseline to the time points specified in the Time and Events Schedule will be assessed. Biomarker values will be tabulated by treatment group over time points and summary statistics will be calculated. Associations between biomarkers and clinical endpoints will be explored. Correlations between CCI values with efficacy and other clinical evaluations will be assessed.

Pharmacogenomic analyses may include candidate gene analyses or genome-wide association analyses in relation to treatment response.

Results from biomarker and/or pharmacogenomic analyses may be presented in a separate report.

11.5. Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis

An interim analysis will be conducted to evaluate the concentrations of JNJ-42165279 in plasma of adolescent subjects. The analysis would be performed after approximately 16 adolescent subjects (ie, 8 adolescent subjects randomized to active drug) have been randomized and participated in the PK sampling at the Week 2 visit. A procedure will be developed that maintains the double-blind. The interim analysis is intended to confirm that the observed JNJ-42165279 mean concentrations in adolescent subjects fall below the upper limit of the 95% prediction intervals of mean JNJ-42165279 concentrations at corresponding time points predicted using allometric scaling.

The individual plasma JNJ-42165279 concentration-time values will be listed and summarized descriptively.

A population PK modeling of plasma concentrations of JNJ-42165279 will be undertaken, if warranted at the time of the interim analysis and after completion of the study.

Where appropriate, the relationship between plasma concentrations of JNJ-42165279 and corresponding plasma concentrations of CCI will be plotted to evaluate the relationships graphically.

Population PK/PD analysis of biomarkers and/or efficacy markers may also be performed, and a suitable dose- and/or exposure-response model may be developed. If necessary or relevant for the analysis, Phase 1 data may be integrated to inform the model structure or key parameter values.

Details of the PK/PD analyses, if conducted, will be described in an analysis plan and results may be provided in a separate report.

11.6. Safety Analysis

All randomized subjects who receive at least 1 dose of study medication will be included in the safety analysis set.

Adverse Events

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events with onset during the double-blind treatment phase (ie, treatment-emergent adverse events [TEAEs], and adverse events that have worsened since baseline) will be included in the analysis. For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group and dose level. Serious adverse events will be summarized separately.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who withdraw due to an adverse event, or who experience a severe adverse event or a SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline, and for observed values and changes from baseline at each scheduled time point.

The number and percentage of subjects experiencing a laboratory result below or above markedly abnormal ranges will be provided for each laboratory analyte by treatment group and dose level.

Listings of subjects with any laboratory result outside the markedly abnormal ranges will be provided.

12-Lead ECG

Heart rate and ECG intervals (RR, PR, QRS and QT) as well as corrected QT intervals according to Fridericia's formula (QTcF) from the 12-lead ECG will be summarized at baseline and at each

scheduled time point and for changes from baseline using descriptive statistics. Subjects with abnormal findings in ECG will be listed.

The number and percentage of subjects with QTcF value >450 msec (males only), >470 msec (females only), >480 msec (all subjects), or >500 msec (all subjects) will be summarized by treatment group, as will the number and percentage of subjects with a change from baseline in QTcF >30 or >60 msec.

Data listings of subjects with any potentially clinically important values (QTcF value >450 [males only], >470 [females only], >480, or >500 msec), or with a change from baseline in QTcF >30 or >60 msec, will be provided.

Vital Signs

Descriptive statistics of pulse, blood pressure (systolic and diastolic), temperature, and body weight values and changes from baseline will be summarized at each scheduled time point.

The percentage of subjects with values beyond clinically important limits will be provided.

Columbia Suicide Severity Rating Scale

Suicide-related thoughts and behaviors based on the C-SSRS will be summarized by treatment group in incidence tables.

Aberrant Behavior Checklist-Irritability Subscale

Irritability, aggression, and self-injurious behavior based on the ABC-I will be summarized descriptively at each scheduled visit by treatment group.

11.7. Data Monitoring Committee

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.

The DMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures (SOPs) in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Participants should be aware that the comments, journal entries, and other information they may enter through My JAKE/My JAKE MMApp, or Microsoft HealthVault are not being actively reviewed for clinical purposes. Participants must inform the site immediately of any medical or psychiatric issues.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Unanticipated Study Device Effects (USDE) – UNITED STATES

A USDE is defined as "A serious study effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or study brochure (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients" (21 CFR 812.3[s]).

Unanticipated study device effects are considered a subset of SAEs in this study.

All study device effects will be collected per the same procedures as AEs.

Serious Adverse Event

A SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

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

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For JNJ-42165279, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- For this study, safety events of interest/adverse events of special interest include diplopia, vision impairment, gait disturbance, and severe headache. These events will trigger a neurological examination and a narrative by the investigator.

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow up of safety). Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the SAE Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All other events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 15.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). For anticipated events reported as individual serious adverse events the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the intervention caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The sponsor assumes responsibility for appropriate reporting of anticipated events to the regulatory authorities according to requirements of the countries in which the studies are conducted. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee (IEC)/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number

- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the SAE Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow up reports of a SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the subject for (part of) the duration of the treatment period.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study intervention.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The JNJ-42165279 solid dosage formulation will be supplied as 25-mg tablets.

The JNJ-42165279 placebo will be supplied as tablets, matching visually to the active tablets. JNJ-42165279/placebo will be manufactured and provided under the responsibility of the sponsor.

Refer to the Investigator's Brochure for a list of excipients.

Packaging

The study drug will be packaged in individual subject kits. Each kit will consist of 1 bottle containing 33 tablets.

All JNJ-42165279/placebo solid formulation study drug will be dispensed in child-resistant packaging.

14.2. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.3. Preparation, Handling, and Storage

All study medication at the clinical site will be stored in a secure area with restricted access.

The JNJ-42165279 and placebo solid dosage formulation must be stored at controlled temperatures, as indicated on the product specific labeling.

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.4. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives, where applicable, must be instructed to return all original containers, whether empty or containing study drug.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with, but not limited to, the following supplies:

- Investigator's Brochure for JNJ-42165279
- Pharmacy manual/study site investigational product manual
- Laboratory kits and manual
- IVRS/IWRS Manual
- Electronic data capture (eDC) Manual
- Sample ICFs
- JAKE System quick start guides
- Biosensors
  - EEG (and associated peripherals)
  - Eye Tracker
  - Wristbands
    - Actigraph GT9X Link (and associated peripherals)
  - Actiwave Cardio Single-Channel ECG (and associated peripherals)
- Caregiver, clinician, and subject scales
  - ADOS-2
  - CASI-Anx
  - ZBI
  - RBS-R
  - SRS-2
  - KBIT-2
  - ABC
  - CGI-S and CGI-I

  - C-SSRS
  - ABI-C
  - Caregiver GI-S
  - Caregiver Assessment of Treatment
  - Evaluation of JAKE
  - Self GI-I
  - Paper versions of ABI, ABI-S, and Daily Tracker
- Computer equipment
  - JAKE Sense Workbench PC
  - External monitor (for use with JAKE Sense Workbench PC and Task Battery)
  - Laptop docking station / port replicator (for use with JAKE Sense Workbench PC and Task Battery)
  - USB mouse (for use with JAKE Sense Workbench PC and Task Battery)
  - High definition web camera (for use with JSW PC and Task Battery)
  - Secured Apple iPad(s) to be used for the caregiver reporting tool registration and task completion during site visits
  - Verizon Jetpack (or similar 4G mobile hotspot) to permit Internet connectivity for the JSW PC and iPad(s)
  - Cart (if needed by investigator, for use with JAKE Sense Workbench PC and Task Battery)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically

subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parent(s) still want them to participate.

The majority of subjects with ASD have normal intelligence and are expected to be able to give consent (adults) or assent (children). Those participants who are not competent to give consent should have their legally authorized representative give consent as per local regulations.

The treatment duration in this study of subjects with ASD is supported by the available toxicology and clinical data (see Investigator's Brochure). A safety signal of reversible mild elevation of liver transaminases was identified in the Phase 1 multiple dose study, occurring in subjects exposed to more than 4 days dosing with 100 mg. To mitigate the risk to subjects participating in this trial, a dose of 25 mg BID (total daily dose of 50 mg) was selected that should allow for testing of the pharmacology of the compound. All subjects will be screened and those with evidence of pre-existing liver dysfunction will not be enrolled, clinical safety labs will be collected as per the Time and Events Schedule and available for ongoing monitoring by the investigator and sponsor, and 'stopping rules' have been developed for stopping treatment in the event that subjects have elevated liver function analytes.

A placebo arm is warranted and necessary to allow for an accurate assessment of the safety and tolerability of the study drug. Treatment with placebo dosing is not equivalent to non-treatment. All medication treatment will occur within the context of carefully supervised and supportive care. Only investigators experienced in the treatment of ASD will participate in the trial and can provide expert guidance on the alternatives for treatment if subjects elect to discontinue the study prior to the last visit or after the completion of the study.

Only experienced and medically-qualified study site personnel are allowed to perform safety assessments.

The total blood volume to be collected will not exceed 200 mL, which is considered to be safe and acceptable even for the youngest participants in this study in comparison to a Red Cross blood donation.

No treatments for ASD are required to be discontinued for this study. The inability to change or add new treatments during the study will not cause potential harm as there are no approved treatments for the core symptoms of ASD.

Females will be enrolled in this study only if they are of non-childbearing potential or agree to use highly effective contraception. Pregnancy testing will be performed at screening and throughout the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects

- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC about the study completion [(if applicable, the notification will be submitted through the head of investigational institution)].

16.2.3. Informed Consent and Assent Form

Each subject (or a legally acceptable representative) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is

voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject (or legally acceptable representative), is authorizing such access, includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject (or legally acceptable representative) will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's (or his or her legally acceptable representative's) personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Where local regulations require, a separate ICF may be used for the required DNA component of the study.

If the subject (or legally acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or if applicable legally acceptable representative.

The person who will be performing the caregiver study responsibilities (parent, legally acceptable representative, or other) must sign a caregiver consent form indicating that he or she understands and is willing and able to adhere to the caregiver’s responsibilities in the study.

When prior consent of the subject is not possible (and the subject's legally acceptable representative is not available), enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The

subject (or legally acceptable representative) must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative, if applicable) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker, DNA, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand JNJ-42165279, to understand ASD or other psychiatric disorders, to understand differential drug responders, and to develop tests/assays related to JNJ-42165279 and ASD. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.2, Discontinuation of Study Treatment and Withdrawal from Study [Withdrawal from the Use of Samples in Future Research]).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the PI
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.

- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the PI, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and, if needed, month and year of birth.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the

protocol; record of all adverse events and follow up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Instruments and scales described in Section 9.2.2.6, Standard Instruments and Scales, will be recorded on paper forms and will be considered source data. If paper forms are used for the Daily Tracker, ABI, or ABI-S, the paper forms will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. Data must be entered

into CRFs in English. Study site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory and ECG data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding JNJ-42165279 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of JNJ-42165279, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the

information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENTS

Attachment 1: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **Infertile due to medical condition**
  No menses for 12 months and permanently infertile due to an underlying medical condition. Documentation of a workup conclusively diagnostic of permanent infertility due to primary ovarian insufficiency will be required.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectables
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Attachment 2: Examples of Prohibited Cytochrome P450 (CYP) 3A4 Inhibitors and Inducers

Note: This is not a comprehensive list of all moderate and strong CYP3A4 inhibitors and inducers.

Inducers	**Inhibitors**
Carbamazepine	Amiodarone
Dexamethasone	Clarithromycin
Nevirapine	Clotrimazole
Phenobarbital	Conivaptan
Phenytoin	Delavirdine
Primidone	Diltiazem
Rifabutin/rifampicin	Erythromycin
St. John's Wort	Fluconazole
	Fluvoxamine
	Grapefruit
	Indinavir
	Isoniazid
	Itraconazole
	Ketoconazole
	Miconazole
	Nefazodone
	Nelfinavir
	Nifedipine
	Norfloxacin
	Omeprazole
	Propoxyphene
	Quinine
	Ritonavir
	Saquinavir
	Seville oranges
	Telaprevir
	Troleandomycin
	Verapamil
	Zafirlukast

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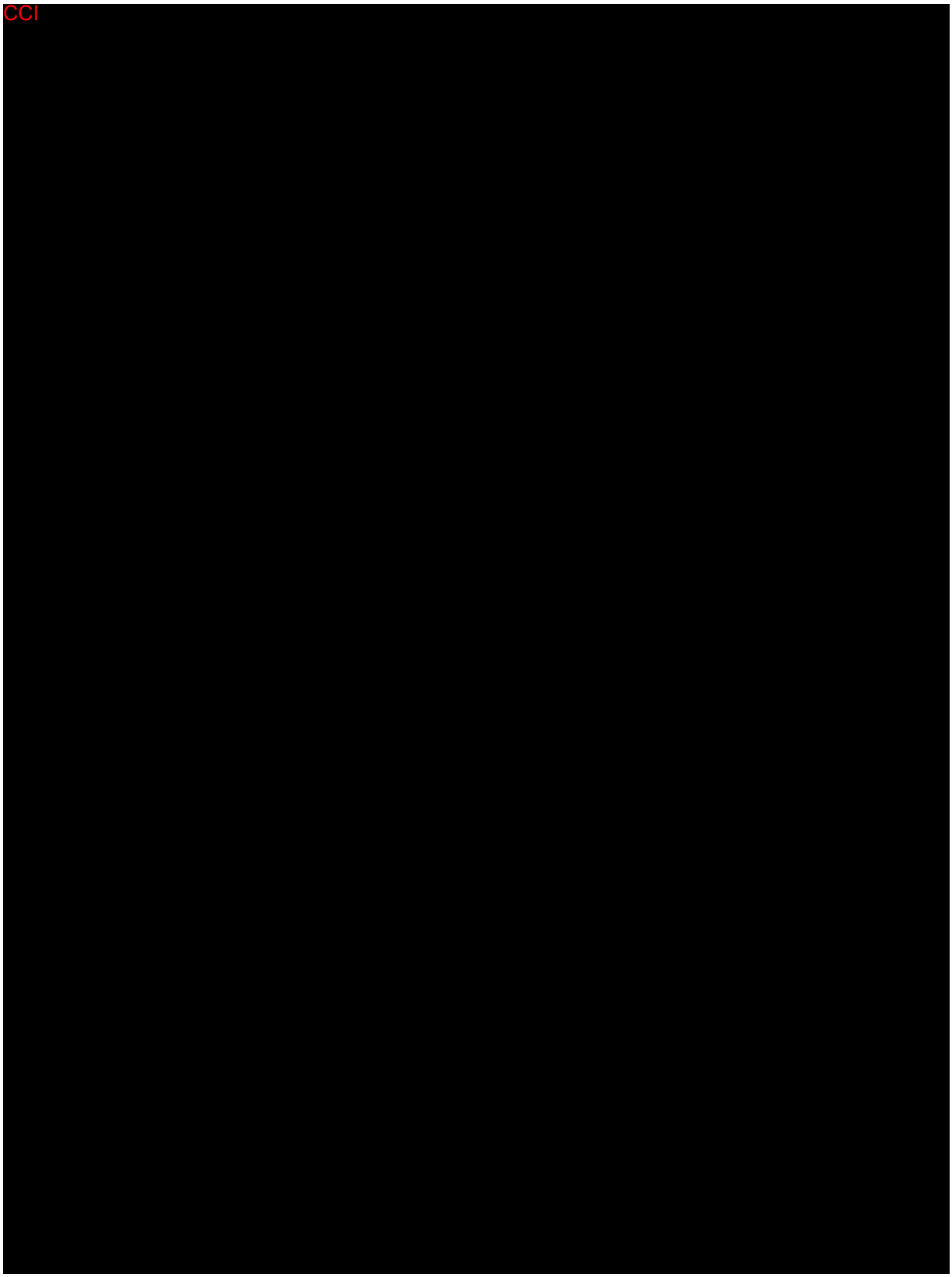

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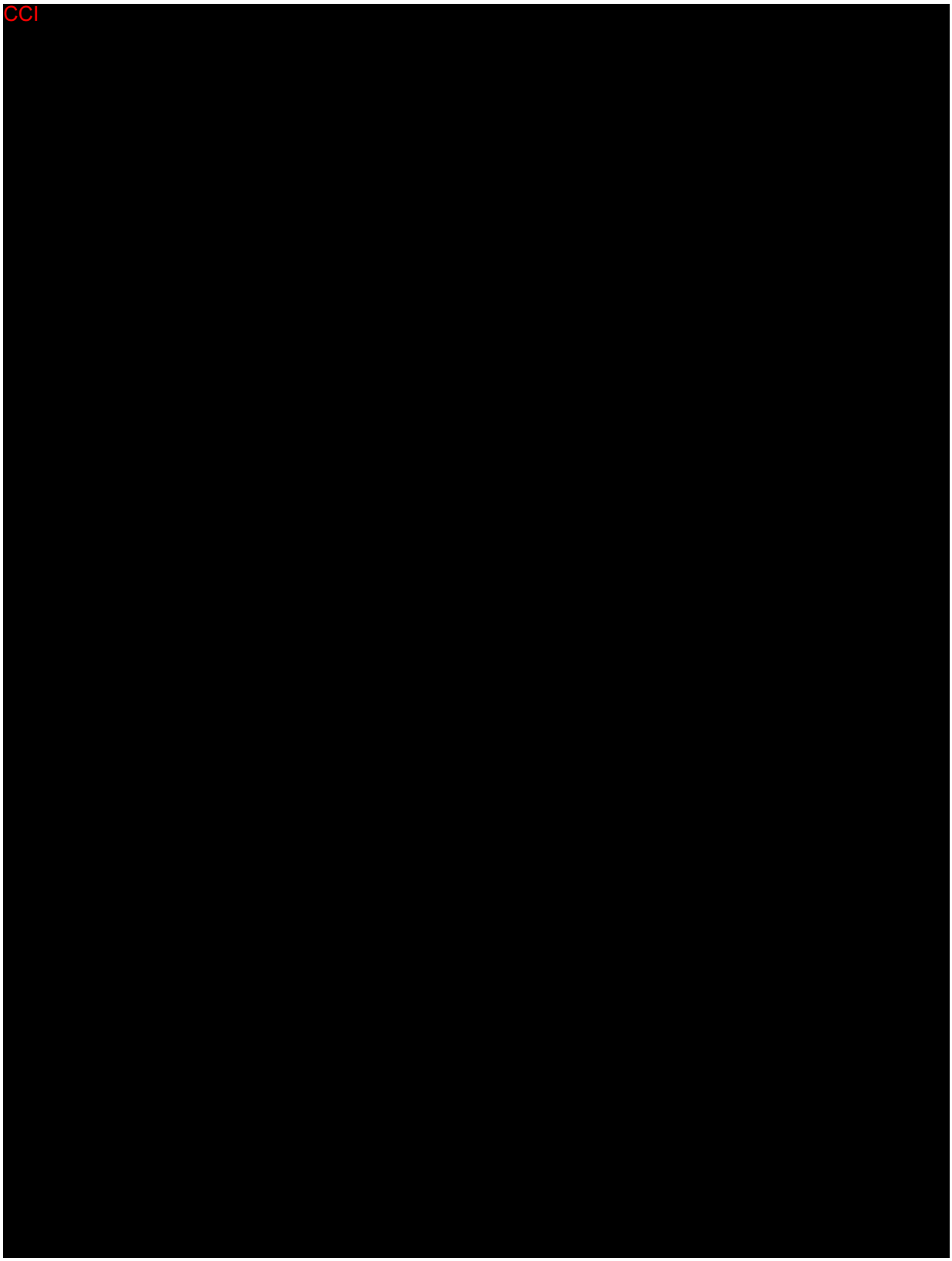
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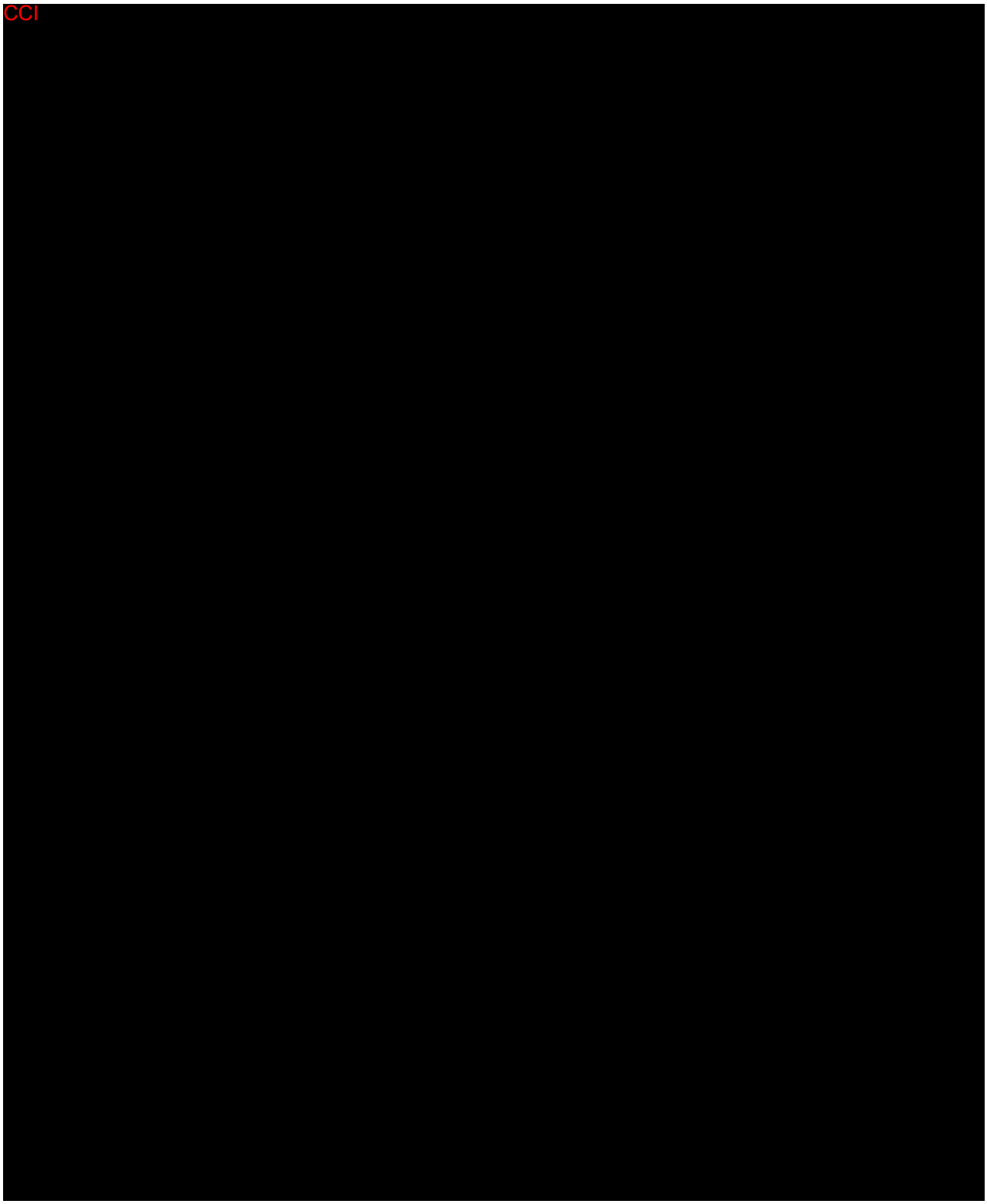

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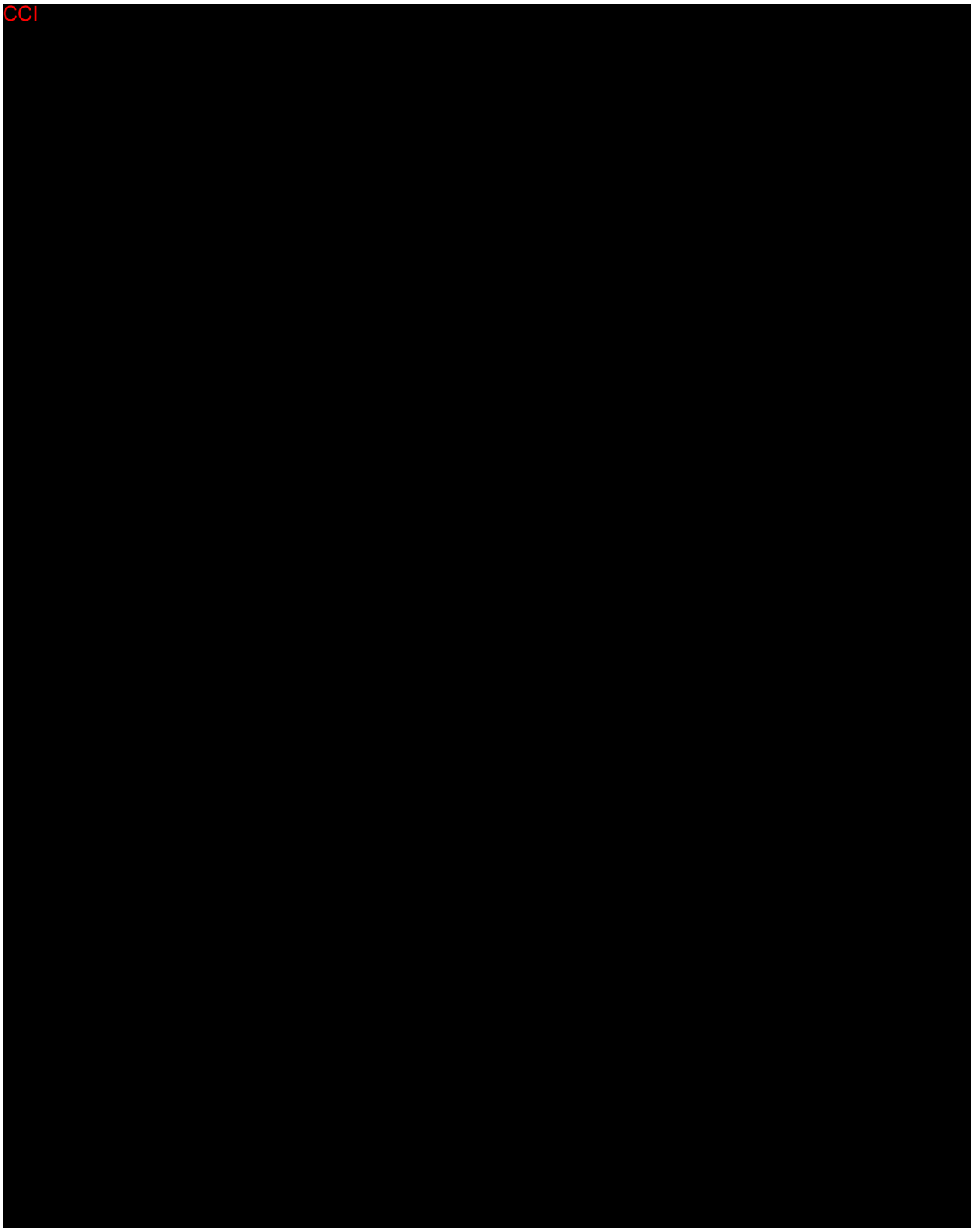

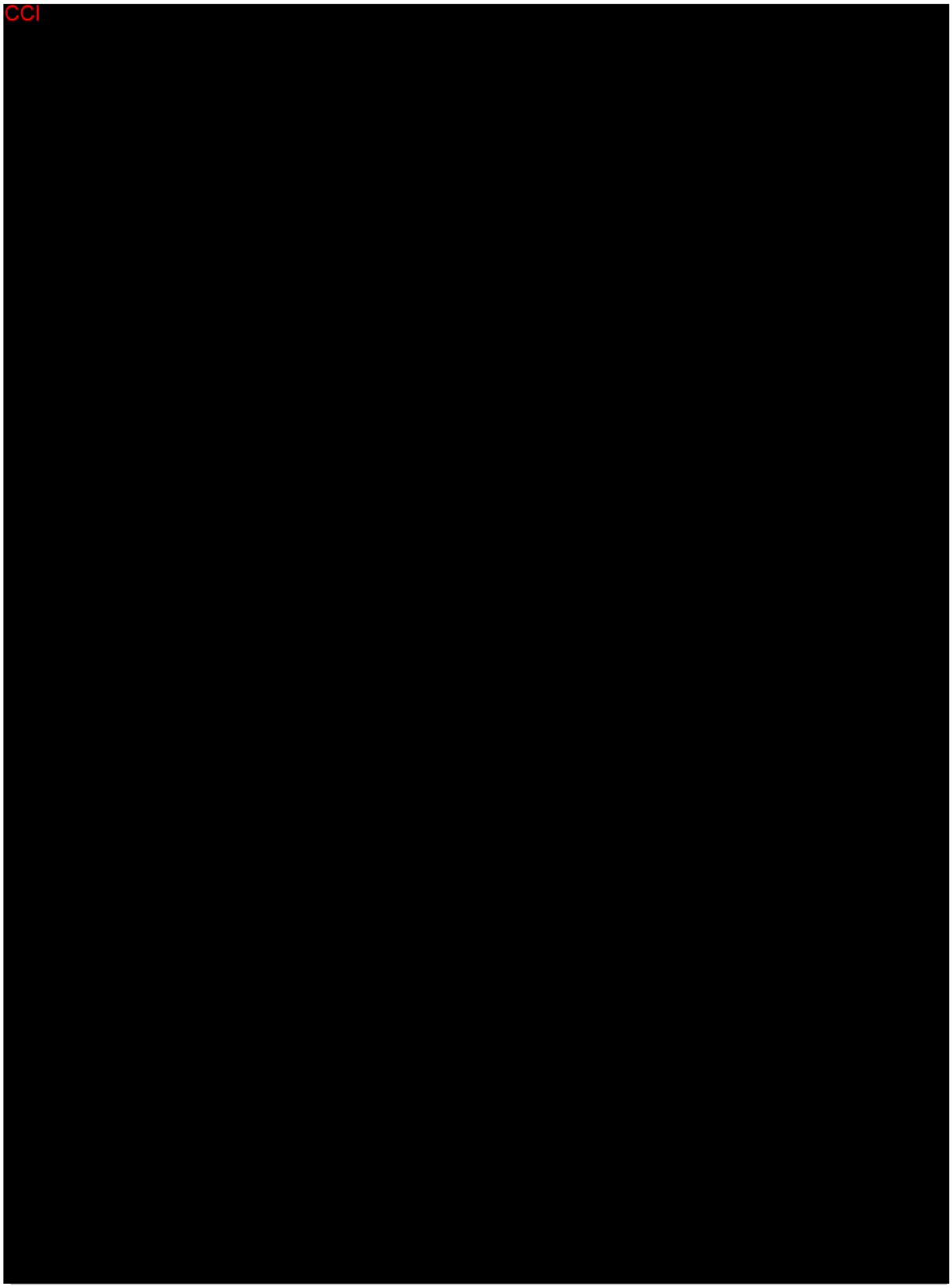
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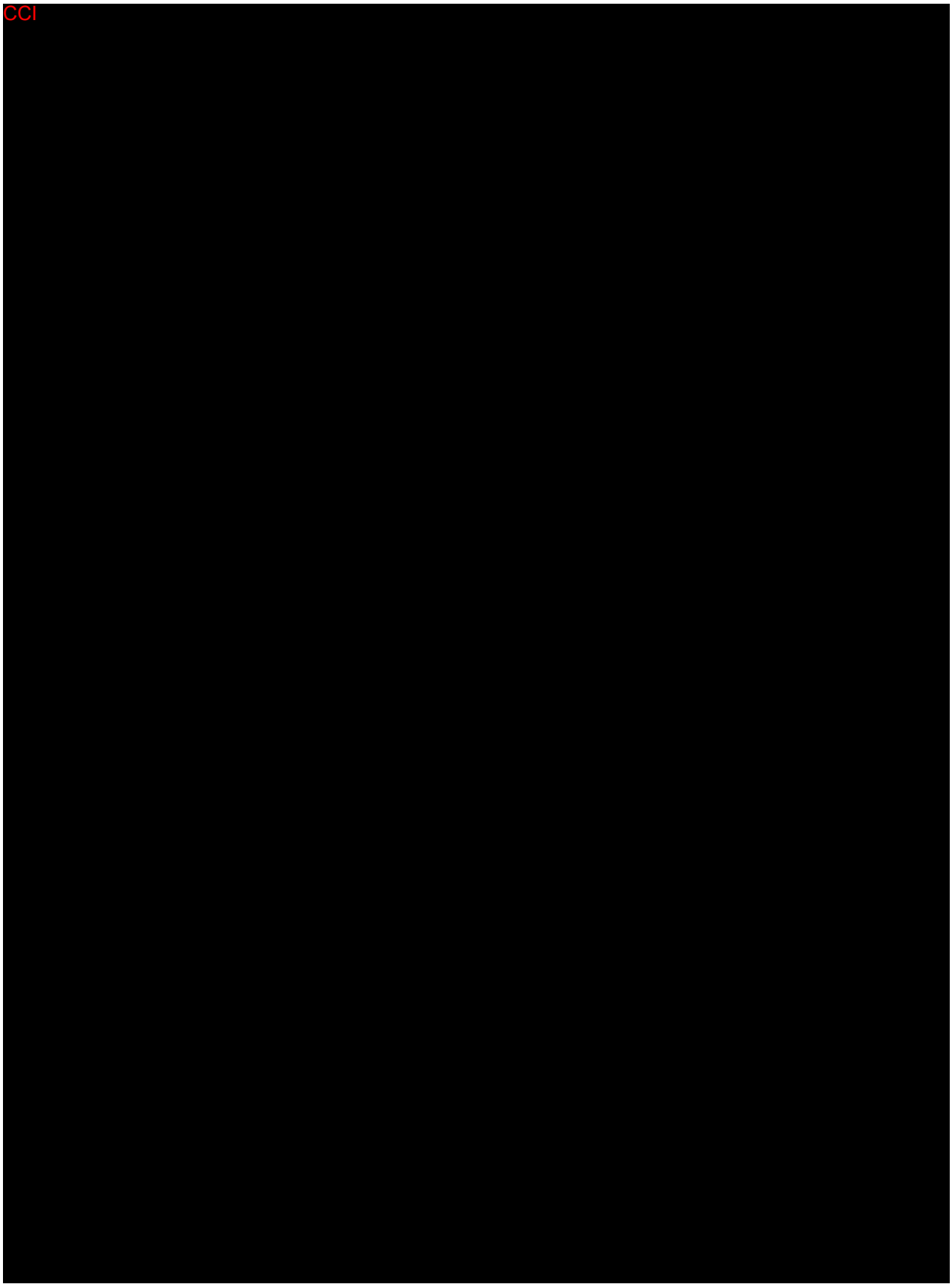

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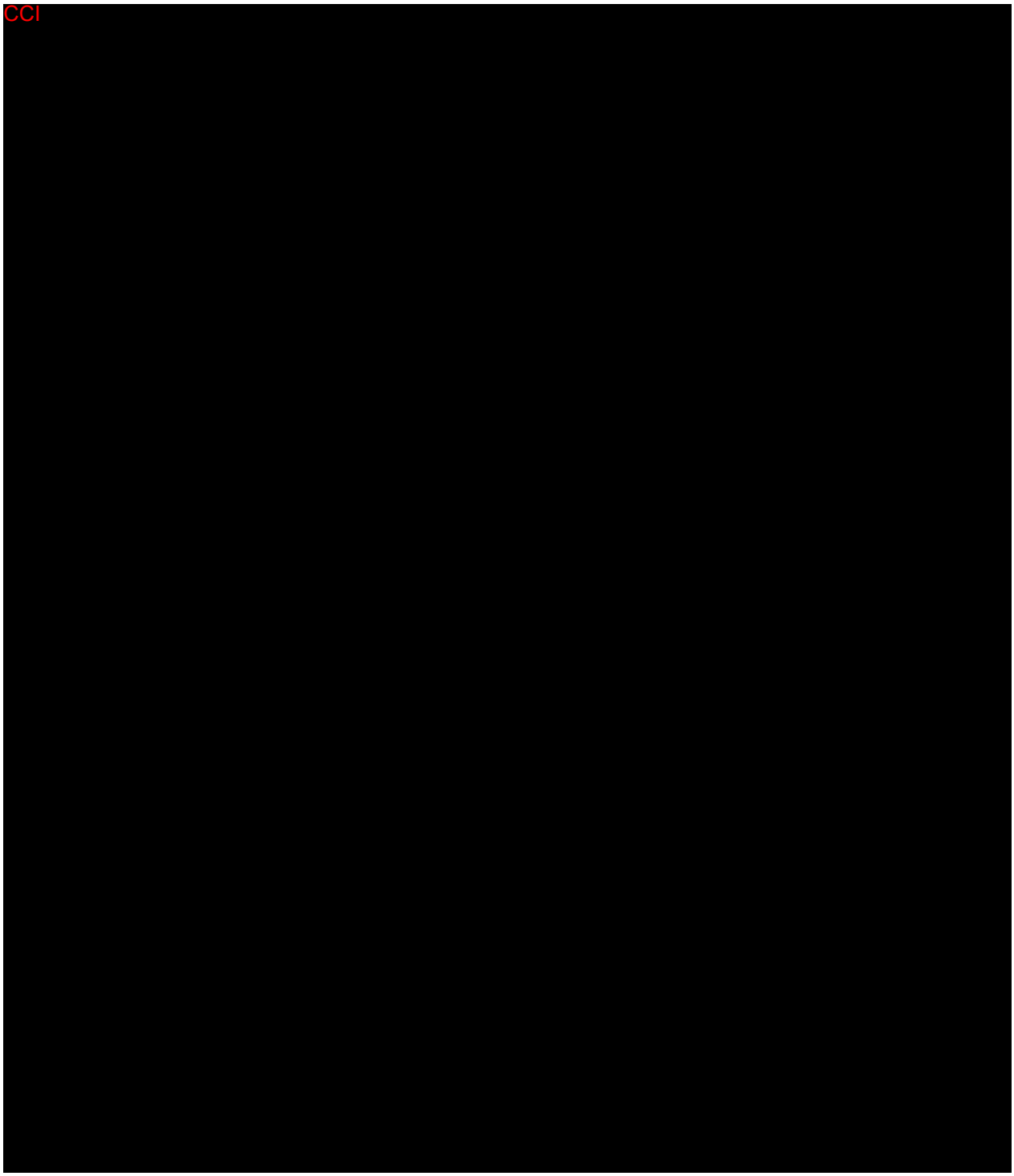
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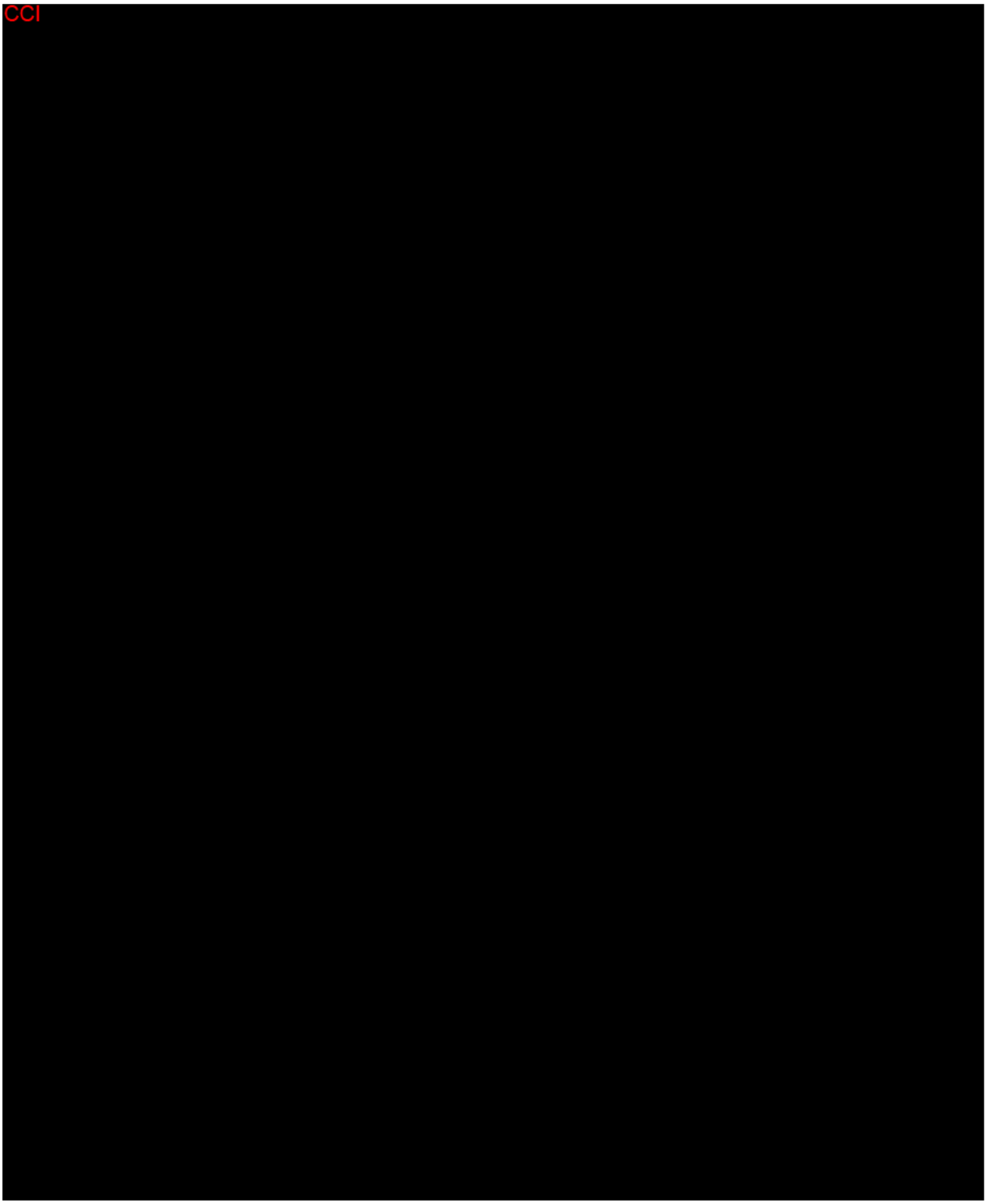
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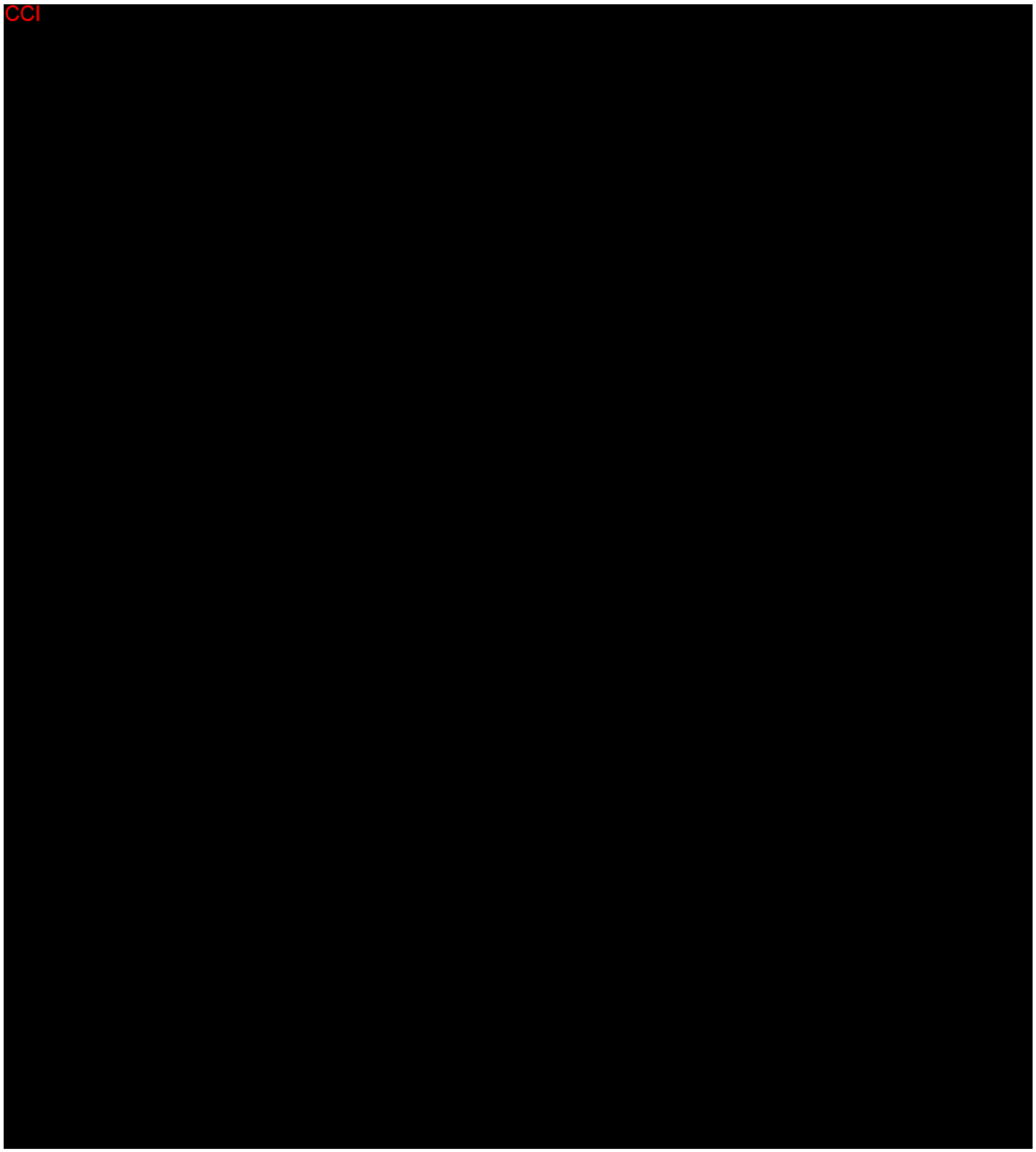
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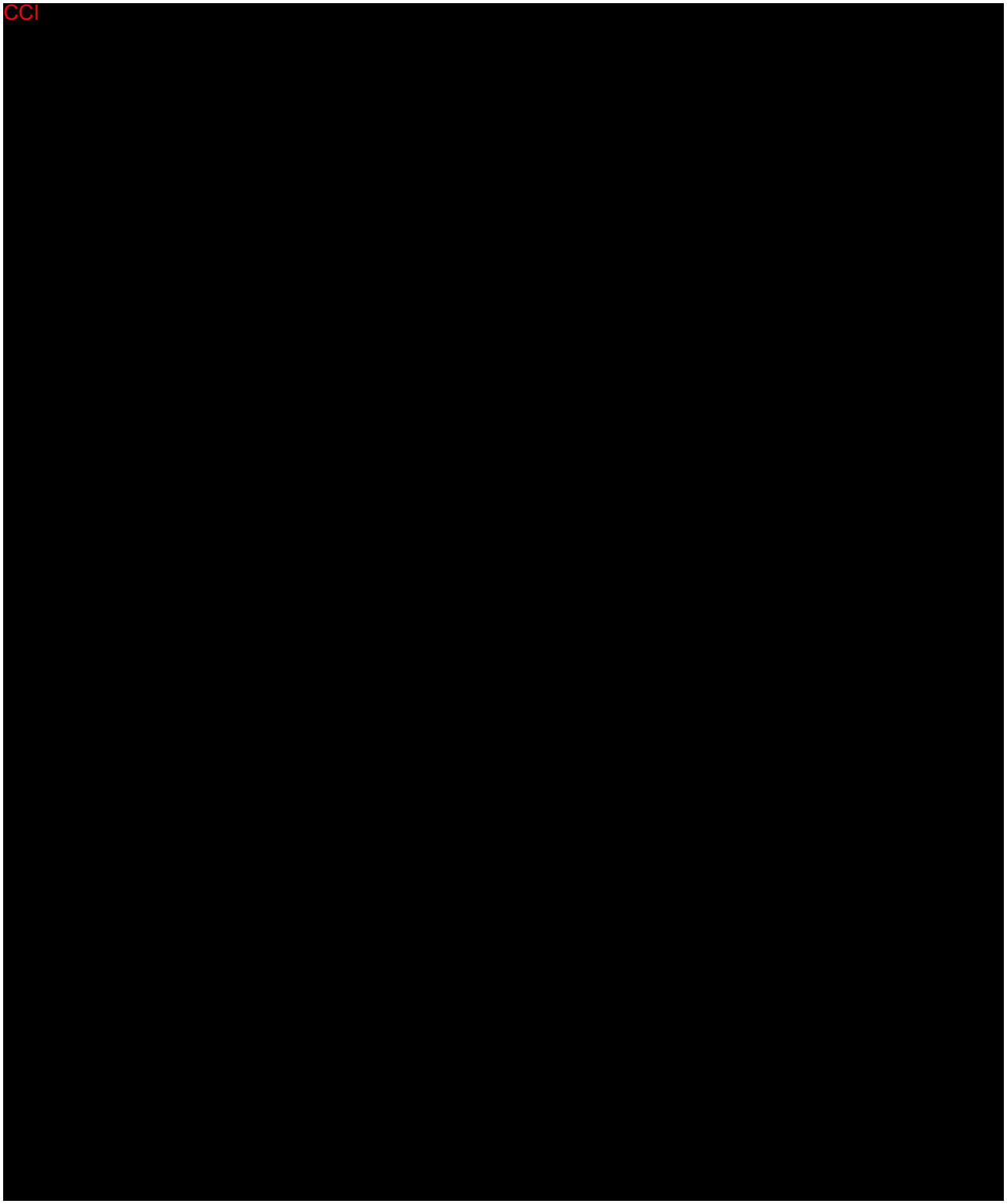
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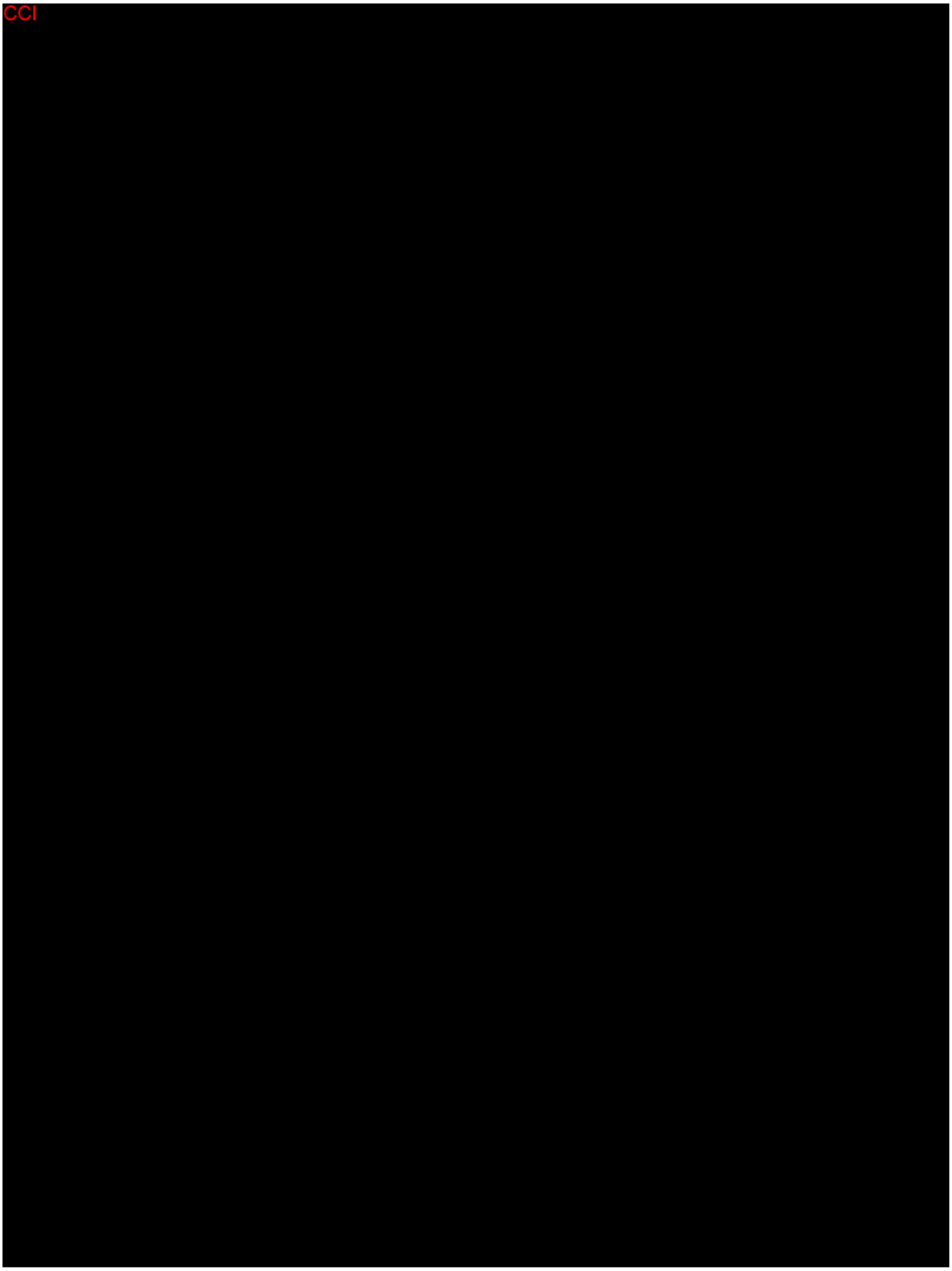
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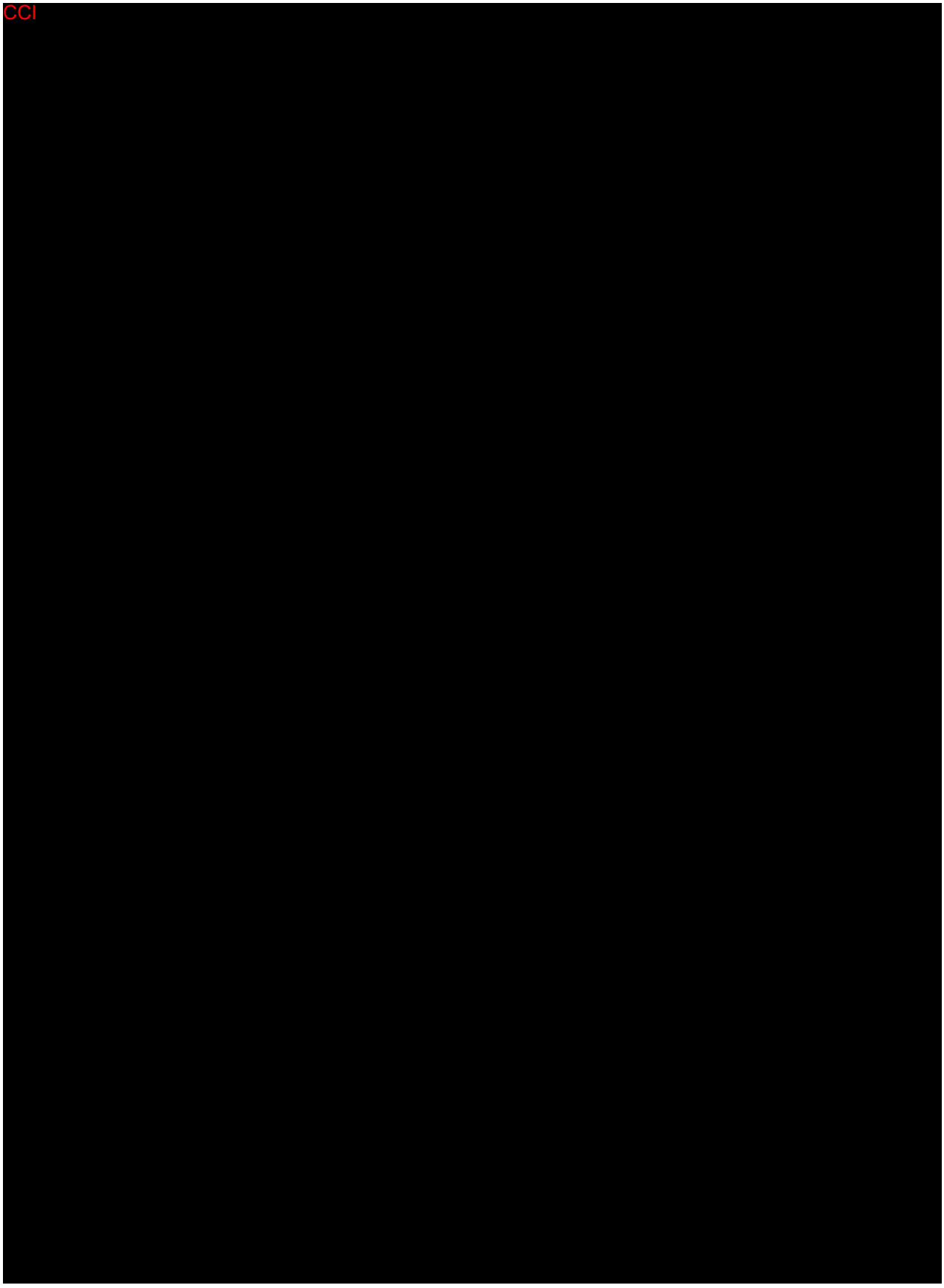
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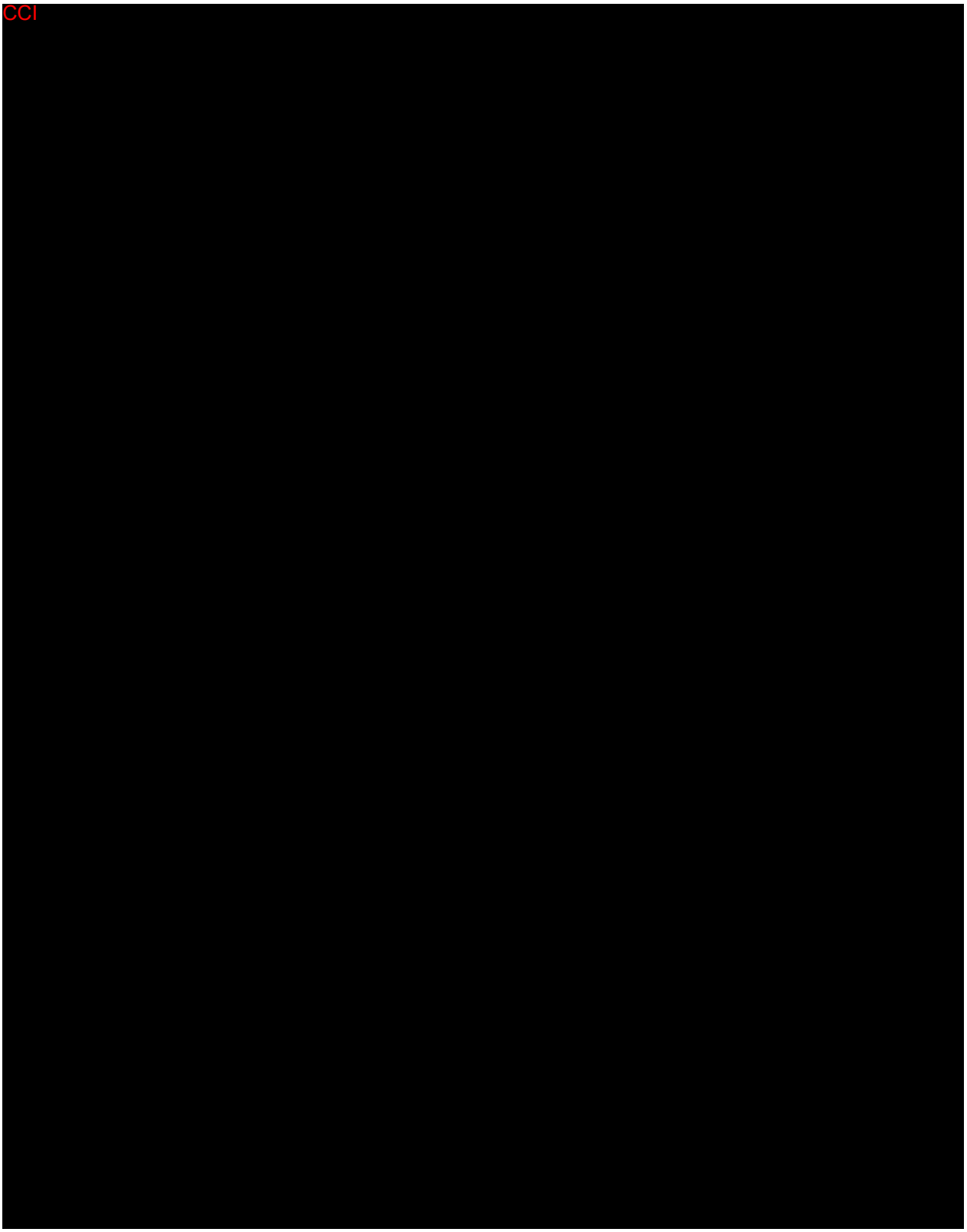
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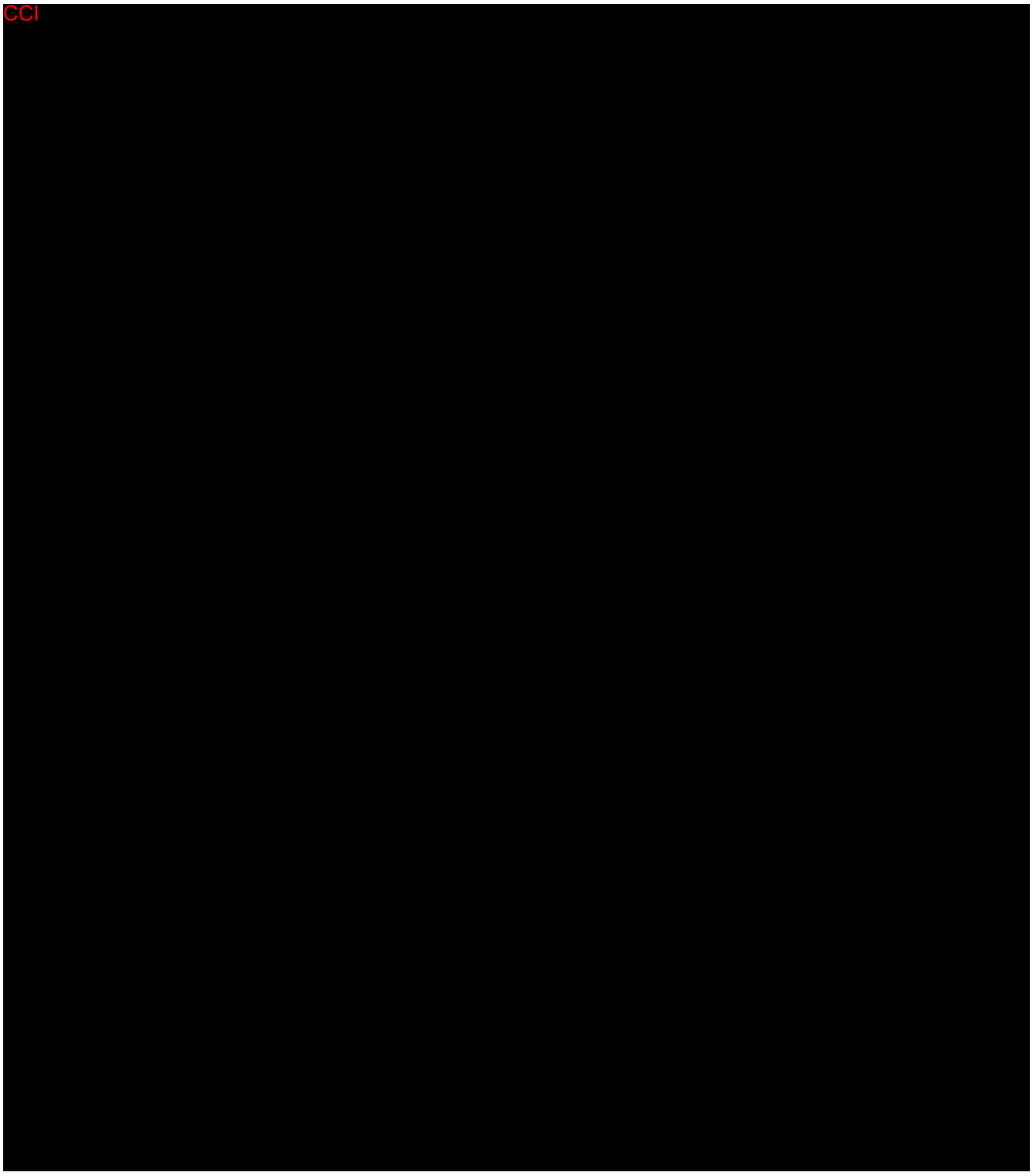


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Attachment 15: Anticipated Events

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- anxiety
- depression
- self-injurious behavior
- disruptive/challenging behavior

Reporting of Anticipated Events

These events will be captured on the eCRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events.

Any event that meets SAE criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Attachment 16: COVID-19 Appendix

Guidance on Study Conduct during the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

Continuation of Study Intervention

- Any issue with continuation and/or provision of study intervention should be discussed with the sponsor and should be well documented.

Study Visits:

- Whenever possible, subjects and caregivers should come to the clinic for their study visits in order to conduct assessments which can only be performed in-person (eg, select safety assessments, ADOS-2, KBIT-2, JAKE Task Battery, sample collection). Every study visit except Screening Visit 2 includes some assessments that can only be performed in-person.
- Screening Visit 2 can be conducted 1) completely in-clinic, 2) completely remotely using telemedicine, or 3) a combination of in-clinic and remote collection via telemedicine.

Telemedicine:

- Telemedicine (via phone or video conversation) conducted by qualified site personnel may be used for procedures that do not require in-person interaction, if needed, to reduce the duration of exposure between clinical staff and subjects/caregivers or if an in-clinic visit is not possible. Assessments that are collected by interview/questioning of subjects or caregivers, as well as patient- and caregiver-reported outcomes, may be collected by telemedicine. This can be done by using telemedicine at the clinical site (eg, in separate rooms) or at home. Telemedicine used within the clinic will not be considered remote data collection.

Laboratory Assessments:

- Samples should be collected at the clinical site and shipped to a central laboratory whenever possible. The use of an authorized/certified local laboratory is allowed if this is not possible. A copy of the local laboratory report should be reviewed by the investigator and filed with the source documents, along with reference ranges.

Informed Consent:

- Consenting and re-consenting of participants for the measures taken (including also remote consenting by phone or video consultation) will be performed as applicable and according to local guidance for informed consent applicable during the COVID-19 pandemic. The process is to be documented in the source documents.

Monitoring:

- In case on-site monitoring visits are not possible, monitoring visits and activities may be conducted remotely (in accordance with site and local requirements). Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

Site Audits:

- During the COVID-19 pandemic and at the impacted sites, study site GCP audits with direct impact/engagement from the investigator and study site personnel may be waived in order to comply with national, local, and/or organizational social distancing restrictions. Additional quality assurance activities such as remote audits or focused review of study related documents may take place with limited impact/engagement if possible.

COVID-19-Related Documentation:

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF). Other relevant study data elements impacted by the pandemic should also be documented/ labeled as "COVID-19-related" in CRFs and/or other study systems, as directed by sponsor guidance.

Data Analyses:

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and any additional data analyses will be outlined in study SAP(s).

Known or suspected COVID-19-positive patients:

Screening:

- Patients should be excluded from study participation if they or their study-designated caregiver 1) are known or reported to have a positive test for COVID-19, or 2) are suspected to have COVID-19 by the investigator based on symptoms, or 3) have had recent exposure to someone who is known to be COVID-19 positive, and have not yet successfully completed a period of self-isolation per local and federal guidelines.
  - Subjects may be eligible to rescreen at Investigator discretion provided that local and federal guidelines are followed for self-isolation and symptom resolution (if applicable) prior to the rescreening and if the subject has not already met the rescreening limit (only one rescreen permitted by protocol).

During Study Conduct:

- If a subject has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss whether the subject can continue in the study and plans for study intervention and follow-up. It may be possible to continue study participation if the subject is asymptomatic or mildly symptomatic provided that:
  - current local and federal guidelines can be followed without significant impact to scheduled visits or procedures (including guidelines pertaining to the recommended self-isolation period).
  - the subject/caregiver can obtain the study drug from the clinic and can remain adherent to the restrictions outlined in Section 8.1 Prestudy and Concomitant Therapy.
  - the subject is believed to be able to resume in-clinic visits without significant visit delay to complete assessments that are not easily replicated by telemedicine.
  - the subject's COVID-19 symptoms, if present, are judged to be unlikely to impact data integrity.
- If the study-designated caregiver has tested positive for COVID-19, the decision whether to continue subject participation in the study should be discussed with the sponsor's responsible medical officer.

INVESTIGATOR AGREEMENT

JNJ-42165279

Clinical Protocol 42165279AUT2001 Amendment 6

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Digitally signed by Julie Willard PPD Reason: I attest to the accuracy and integrity of this document. Date: 2020.09.29 18:36:41 -07'00' Adobe Reader version: 11.0.20 Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 29 September 2020