STATISTICALANALYSISPLAN

STUDYPRODUCT

ARRY-371797

PROTOCOL

ARRAY-797-001 V1.0

Protocol Date: 01DEC2014

SPONSOR

Array BioPharma, Inc.

3200 Walnut St.

Boulder, CO 80301

STUDYTITLE

AnOpen-labelRolloverStudy ofARRY-371797inPatients withSymptomaticGenetic DilatedCardiomyopathyDuetoaLaminA/CGeneMutation

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Signature Page

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TABLEOFCONTENTS

1. LISTOFABBREVIATIONSANDDEFINITIONS

Abbreviation orspecial term	**Explanation**
6MWT	6-minute walk test
AE	Adverse event
ATC	Anatomical therapeutic chemical classification codes
AUC	Area under the curve
BID	Twice daily
BLQ	Below the limit of quantitation
BP	Blood pressure
bpm	beats per minute
$C_{postdose,SS}$	Post dose concentration at steady state
C_{max}	Maximum concentration
CV	Coefficient of variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ICD	Implantable cardioverter defibrillator
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire

Abbreviation orspecial term	**Explanation**
LMNA	Gene encoding the Lamin A/C protein
LV	Left ventricular
MR	Metabolite-to-parent concentration ratio
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
N_{BLQ}	Number of BLQ observations
NC	Not calculated
N_{valid}	Number of valid observations
PK	Pharmacokinetic(s)
PR	Pulse rate
R	Drug accumulation
QOL	Quality of life
QT	QT interval: a measurement of the time between the start of the Q wave and the end of the T wave in an ECG
QTcF	QT interval corrected for heart rate using Fridericia's formula
RV	Right ventricular
RVEDD	Right ventricular end-diastolic diameter
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure

Abbreviation orspecial term	**Explanation**
SD	Standard Deviation
SF-36	Medical Outcomes Study 36-item Short-Form Health Survey
SOC	System Organ Class
SpO_2	Oxygen saturation
TEAE	Treatment Emergent Adverse Event
VT	Vitality
WHODDE	WHO Drug Dictionary enhanced

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to ensure the validity of the findings of Array BioPharma Study ARRAY-797-001 by specifying a priori the statistical approaches to the analyses. It was developed based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines, and information provided in Protocol ARRAY-797-001, Version 1.0, dated 01 December 2014 [1].

3. STUDYOBJECTIVESANDENDPOINTS

3.1. PrimaryObjective

- To evaluate the safety of ARRY-371797 administered after completion of the parent study.

3.2. SecondaryObjectives

- To evaluate measures of efficacy of ARRY-371797
- To determine the exposure of ARRY-371797 and metabolites

3.3. Endpoints

3.3.1. PrimaryEndpoint

- Incidence and severity of adverse events (AEs), clinical laboratory tests (hematology, chemistry), physical examination, vital signs (blood pressure [BP] and pulse rate [PR]) and 12-lead electrocardiogram (ECG) values.

3.3.2. SecondaryEndpoints

Assessed at 24, 48, 72 and 96 weeks and termination visit (if applicable):

- 6-minute walk test (6MWT)
- Left ventricular (LV) end systolic volume index (LVESVI)
- Left ventricular end diastolic volume index (LVEDVI)
- LV mass
- LV ejection fraction
- LV mass-to-volume ratio
- Right ventricular (RV) end-diastolic diameter (RVEDD) and RV fractional area
- Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) and Quality of Life (QOL) by Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Plasma concentrations of ARRY-371797 and metabolites pre-dose and at a single time point 1 to 2 hours post-dose at the Screening Visit and at 12 and 24 weeks

4. STUDYDESIGN

4.1. GeneralDesignCharacteristicsandStudyTreatment

This rollover study is designed to investigate the safety and efficacy of ARRY-371797 administration in patients who previously received ARRY-371797 in a LMNA mutation study sponsored by Array BioPharma and may, in the investigator's opinion, derive benefit from continued treatment.

Patients will be screened for eligibility at the last visit in the treatment period of the parent study. Eligible patients will be enrolled into the study immediately upon confirmation of eligibility so that ARRY-371797 administration is not interrupted.

Clinic visits for safety assessments and study drug dispensing will be performed every 12 weeks (± 14 days) through 48 weeks, then every 24 weeks (± 14 days) until treatment discontinuation criteria are met. Efficacy assessments (6MWT, echocardiogram, SF-36 and QOL KCCQ) will be performed at 24, 48, 72 and 96 weeks and termination visit (if applicable). Patients will undergo a termination visit as soon as possible after study drug discontinuation and a safety follow-up visit 30 days (± 14 days) after the last dose of study drug.

4.2. DosesandScheduleofAdministration

Patients will receive ARRY-371797 at the same dose and schedule they were administered at the conclusion of the parent study.

If a patient has tolerability concerns at 400 mg BID, they may be down-titrated to 200 mg BID (400 mg total daily dose). If a patient has tolerability concerns at 200 mg BID, they may be down-titrated to 100 mg BID (200 mg total daily dose).

If a patient's machine-read post-Baseline visit triplicate ECG includes 2 or more individual ECGs with a QTcF value > 500 msec, or QTcF mean value increases by ≥ 60 msec from Baseline, administration of study drug should be held until over-read mean triplicate values are available. The over-read should be conducted by the Investigator or designated cardiologist reviewer. The Medical Monitor will be advised of any QTcF alterations and will assess the clinical significance of QTcF values with the Investigator and determine actions to be taken with dosing (e.g., if the patient has cardiac resynchronization therapy/ICD/pacemaker, the Investigator and Medical Monitor may determine that the patient can continue if findings are not clinically significant and/or unchanged from Baseline). Whenever possible, the over-read should be completed promptly in order to avoid or minimize treatment interruption.

If the over-read by the Investigator or designated cardiologist reviewer indicates that the mean triplicate value of either parameter is > 500 msec, action may be taken with study drug dosing if deemed necessary by the Investigator and Medical Monitor. Dosing should be held until QTcF returns to ≤ 480 msec.

- If the patient is currently receiving 400 mg BID, the patient can be re-challenged at 200 mg BID after QTcF returns to ≤ 480 msec.
- If the patient is currently receiving 200 mg BID, the patient can be re-challenged at 100 mg BID after QTcF returns to ≤ 480 msec.
- If the patient is currently receiving 100 mg BID, the patient can be re-challenged at 100 mg BID after QTcF returns to ≤ 480 msec. If upon re-challenge at 100 mg BID the QTcF remains > 500 msec on over-read, study drug treatment should be discontinued.

4.3. TreatmentCompliance

Compliance with protocol-specified study drug treatment will be evaluated by an accounting of supplied and returned drug product and patient interviews at each clinic visit and may be further evaluated by plasma concentration analysis.

4.4. TreatmentArmAssignment

Patients will receive ARRY-371797 at the same dose and schedule they received at the conclusion of the parent study. Pending availability, all patients will receive the tablet formulation.

4.5. Blinding

Not applicable.

4.6. StudyProceduresandEvaluations

The anticipated overall length of the study for each patient is that patients may continue receiving ARRY-371797 as long as no treatment discontinuation criteria are met.

The primary endpoint will be Safety assessments assessed throughout the study. Secondary endpoints will be assessed at Weeks 24, 48, 72 and 96 and, if applicable, till termination visit. Efficacy assessments include the 6MWT, LVESVI, LVEDVI, LV Mass, LV mass-to-volume ratio, RVEDD and RV fractional area, SF-36, and KCCQ. Safety assessments include adverse events, physical examination, vital signs and 12-lead ECG] and clinical laboratory tests (Hematology and Chemistry). PK assessments on blood samples will also be performed in this study.

The study schedule of events is shown in Appendix I.

4.7. TreatmentDi scontinuation

4.7.1. TreatmentDiscontinuationforIndividualPatients

ARRY-371797 administration must be discontinued for patients meeting any of the following criteria:

- Withdrawal of consent
- Unacceptable AE(s) or failure to tolerate ARRY-371797
- Pregnancy or initiation of breastfeeding
- Lost to follow-up

In addition, the Investigator may remove a patient from the study if, in the opinion of the Investigator, it is not in the best medical interest of the patient to continue the study. Wherever possible, procedures and evaluations scheduled to occur at the Follow-up/Termination Visit should be conducted for all patients who discontinue prior to study completion. The Sponsor should be notified of all study withdrawals in a timely manner. The Sponsor may also request that a patient be removed based on assessment of AEs, lack of compliance, protocol violation or the current medical status of the patient.

Patients may withdraw their consent to participate in the study at any time for any reason. If a patient withdraws consent, the date and stated reason for withdrawal of consent should be documented in the patient source documents and the eCRF. Patient data collected up to the date of consent withdrawal will be included in analyses.

In addition, a patient may decide to stop participating in the study at any time for any reason without prejudice to future medical care by the physician or at the institution. If a patient's participation in the study is ended prematurely (whether due to patient request or Investigator or Sponsor decision), study drug will be discontinued and study staff must confirm if the patient wishes to also withdraw his/her consent to participate in the study.

If a patient does withdraw consent to participate in the study, previously collected samples and data will be processed for analysis and assessment for study purposes.

If a patient does not withdraw consent to participate in the study, a Follow-up Visit should be performed as soon as possible after treatment cessation, ideally no later than 7 days after the last dose of study drug. The date and stated reason for study discontinuation should be documented.

If a patient does not respond to three consecutive follow-up attempts (i.e., telephone calls), a certified letter will be sent to the patient. The patient will be considered lost to follow-up if they do not respond to the certified letter within 2 weeks or the patient cannot otherwise be contacted or located.

4.7.2. SponsorDiscontinuationCriteria

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons or at the discretion of the Sponsor. Should the study be terminated prematurely, the Sponsor will provide written notification to all Investigators and regulatory authorities and will specify the reason(s) for early termination. The Investigator must

inform the Institutional Review Board (IRB) promptly and provide the reason(s) for the termination.

5. STATISTICALCONSIDERATIONS

5.1. DefinitionsandConventions

Assessments of change from baseline to post-baseline will include only those patients with both baseline and post-baseline measurements. The handling of missing or dropout data is described in Section 5.3. The Baseline value for a parameter is defined as the last non-missing value before the initial administration of study treatment in parent study, unless otherwise specified.

For laboratory, vital signs, ECGs and echocardiograms, a last observation on treatment value will be defined as the last non-missing post-baseline value on or prior to the last dosing date before the patient is withdrawn from study treatment. This value will be set to missing if no such observation exists. The last observation on treatment may be a repeated or unscheduled test.

Electronic Case Report Form (eCRF) data will be captured and then converted to SAS datasets. All statistical analyses will be conducted using SAS® Version 9.3 or higher or SAS Enterprise Guide® version 4.3.

Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus, version 16.1. All prior and concomitant medications will be coded according to the WHO Drug Dictionary enhanced (WHODDE), version March 1, 2012. Adverse events and laboratory data will be graded for toxicity according to the *Guidancefor IndustryToxicityGradingScaleforHealthy AdultandAdolescentVolunteersEnrolledin PreventiveVaccineClinicalTrials* [2].

For laboratory parameters where the Guidance does not provide cutoffs, shift tables will not be provided.

The following modifications will be made to the vaccine toxicity grading scale in this analysis:

- The criteria to map hemoglobin laboratory values to severity grades are 2-fold. The first criterion is based only on actual hemoglobin value; the second is based on change from Baseline hemoglobin. For this study, only observed hemoglobin values will be used to determine severity grade; change from Baseline will not be used to determine severity grade.

- Presentation of these laboratory shift data will depend upon the actual laboratory value as reported, and will not reference any action taken or any other clinical activity.

    - Example 1: By the vaccine toxicity grading scale, a Grade 4 creatinine is defined as creatinine > 2.5 mg/dL or requiring dialysis. In this study the severity will be determined from the creatinine value alone.

- Example 2: By the vaccine toxicity grading scale, Grade 4 urine protein requires that the patient was hospitalized or received dialysis. Because hospitalization and dialysis are clinical actions, not urine protein values, the highest grade that would be reported for urine protein (2+) using the vaccine toxicity grading scale would be Severe (Grade 3). However, clinical laboratory results for urinary protein may be reported in different way. E.g. if the reported lab data is using 4 levels of severity ("negative," "trace," "30," "100" and "≥ 300"), the urine protein results will be graded and reported as follows:

AssignedGrade	LaboratoryResult	VaccineToxicityGrading Scale
Mild (1)	Trace	Trace
Moderate (2)	30	1+
Severe (3)	100	2+
Very Severe (4)	≥ 300	Hospitalization or dialysis

Through a querying process, an attempt will be made to reconcile the reported grade for the laboratory abnormality and the grade of an associated AE. Reporting of an AE will sometimes incorporate information beyond the laboratory value, so some differences in reporting may remain.

When using this toxicity grading scale, lab data will be kept to one more significant digit than the scale and then rounded and graded according to the scale. E.g. for Sodium-Hyponatremia, Grade 1 is 132-134mEq/L, Grade 2 is 130-131mEq/L. If the sodium level is 131.3mEq/L, it will be graded to Grade 2 toxicity.

5.2. AdjustmentforCovariates

Not applicable.

5.3. HandlingDropoutsorMissingData

Missing item responses for the SF-36 and QOL by KCCQ scales are assumed to be the same as the response to the scale's answered item(s). KCCQ scale scores will be computed when ≥50% of the items are non-missing. If fewer than 50% of the items are non-missing the scale score will be set to missing.

No other imputation will be performed in this study.

5.4. InterimAnalysisandDataMonitoring

No interim analysis is planned for this study.

This study will not have a data monitoring committee (DMC). However, data from this study may be made available to a DMC associated with another study evaluating ARRY-371797.

5.5. MulticenterStudies

The sample size in this study is too small to permit incorporation of study center into the analyses. Centers will be pooled for all tabular summaries.

5.6. MultipleCompar isons/Multiplicity

Not applicable.

5.7. ExaminationsofSubgroups

Not applicable.

5.8. SampleSizeEstimation

The parent study enrolled 12 patients. Eligible patients from parent study may rollover to this study.

6. ANALYSISPOPULATIONS

6.1. SafetyAnalysisSet

The safety analysis set will include all enrolled patients who received at least one dose of study drug. The safety analysis set will be used for the analysis of all safety endpoints.

6.2. Efficacy AnalysisSet

The Efficacy Analysis Set will include patients who had at least one post-Baseline efficacy evaluation. Patients who have no post-Baseline efficacy assessments will not be included in the efficacy analyses.

6.3. PharmacokineticAnalysisSet

The PK analysis set will include all patients who had at least one plasma sample with associated PK concentration results.

7. ASSESSMENTS,ANALYSES,ANDPRESENTATIONS

Unless otherwise indicated, continuous variables will be summarized using the following descriptive statistics: the number of patients (n), mean, standard deviation, median, minimum, and maximum. Means and medians will be reported to one decimal place more than what is reported on the eCRF or by the laboratory. Standard deviations (SD) will be reported to two decimal places more than what is reported in the data. Minimum and maximum values will be reported to the same number of decimal places displayed on the eCRF or by the laboratory. Percentages will be reported to one decimal point only.

The frequency and percentage of observed levels will be reported for categorical measures. Percentages will be based on the number of patients in the relevant analysis set. In general, all data will be listed and sorted by dose group at baseline, and then patient number. When appropriate, data will further sorted by study day and study hour within patient. Dates will be displayed as DDMMMYYYY in the listings. For displays that include the relative study day, the day of the first dose of the follow up study drug administration is defined as Study Day 1.

Tabular summaries will present results for overall. Demographic and baseline data and safety summaries will be based on the safety analysis set. Efficacy summaries will utilize the efficacy analysis set for all relevant visits. No p-values will be presented.

Relative study day will be flagged in the listings to indicate dose down titrations. Flags will be as follows: * = 1st down titration, ** = 2nd down titration. Flags will be displayed for all study days beginning with the study day on which the dose change occurred.

Unless otherwise specified, listings will be based on the safety analysis set. The listing of disposition data will be based on all screened patients.

Summary tables and supportive individual patient data listings will be numbered in accordance with ICH guidelines for the structure and content of clinical study reports. Complete lists of the proposed tables, graphs and patient data listings are provided in Appendix III.

7.1. Theformatofthefinaltablesandlisting sisexpectedtore semblepre-specified templatesascloselyaspossibleregarding thechoiceofvariables,labelingof categories,formattingofheaders,etc.Alldatalistingswillpresentdataindose group, patient anddate/timeorder.Patient Disposition

Frequency counts and percentages of all patients who enrolled, completed this follow up study, and discontinued early will be presented. In addition, reason for termination will be summarized by frequency counts and percentages in the table. The number of screened patients will be included.

A by-patient listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented for all screened patients with the reasons for screen failure listed.

7.2. DemographicandOther BaselineCharacteristics

Descriptive statistics will be used to summarize continuous demographic and baseline variables including age, height, weight and 6MWT distance at baseline for overall for the safety analysis set. Categorical demographic and baseline characteristics variables will be summarized using the number and percentage of patients in each level of such variables (including sex, ethnicity and race) for overall for the safety analysis set. A listing of demographic and baseline characteristics will be provided.

7.3. MedicalHistory

Significant (at the Investigator's discretion) past and present medical history will be recorded at the Screening visits only. Any ongoing condition observed prior to the initiation of study drug will be recorded as medical history. Any new condition, or worsening of a pre-existing condition, during study conduct after the start of follow up study or at any time after consent, if thought to be related to a study procedure, will be recorded as an adverse event.

Medical history data will be coded using MedDRA 16.1 and summarized by system organ class (SOC) and preferred term (PT) with the number and percentage presented for overall for the Safety Analysis Set. A by-patient listing of medical history information will be provided.

7.4. PriorandConcomitantMedications

Prior and concomitant medications will be coded using WHODDE and summarized for overall for the safety analysis set using anatomical therapeutic chemical classification codes (ATC) class level 2 and preferred term. Patients will be counted only once within a medication class, and once for each medication. Prior and concomitant medications will also be provided as a listing.

7.5. EfficacyAnalyses

7.5.1. Secondary EfficacyEndpointandAnalysis

Secondary efficacy endpoints include:

- Change from Baseline in 6MWT at Day 1(parent study Week 48),Weeks 24, 48, 72 and 96 and, if applicable, termination visit
- Measures of cardiac function as described below
- Quality of life assessments (SF-36 and KCCQ) at Day 1, Weeks 24, 48, 72 and 96 and, if applicable, termination visit

As the SAP section 5.1 noted, the Baseline value for a parameter is defined as the last non-missing value before the initial administration of study treatment in parent study, unless otherwise specified. The study Day 1 for this follow-up study is the final visit from patent study (e.g. the Week 48 visit of the parent study). Both the pre-dose baseline values and the study Day 1 values will be included in tables.

7.5.1.1 6MWTat Weeks24,48,72and96and,ifapplicable,terminationvisit

A summary of actual values, change from Baseline, and percent change from Baseline in 6MWT distance and the associated 80% CIs for overall will be provided for the following timepoints: Baseline, Day 1, Weeks 24, 48, 72 and 96 and, if applicable, termination visit. The number and percentage of patients who had at least 10% improvement in 6MWT will be summarized for overall. The predicted distance and percent predicted distance will also be summarized.

Plots for the mean of actual values, the mean percent change and the mean change from Baseline including 80% CIs of 6MWT distance at each timepoint for overall will be provided. 6MWT data will be listed for the Safety Analysis Set.

Heart rate, Borg scales for dyspnea and fatigue, SpO_2, whether oxygen was given during the test, whether the patient paused before 6 minutes, and other symptoms at end of exercise (angina, dizziness, and calf pain) will be summarized by timepoint.

7.5.1.2EchocardiogramCompletewithContrast

A 2 dimensional (2D) echocardiogram complete with contrast will be performed at the following timepoints: Baseline, Day 1, Weeks 24, 48, 72 and 96 and, if applicable, termination visit. Descriptive statistics will be used to summarize actual values and the change from Baseline (post-Baseline) for overall. The following cardiac function parameters will be summarized:

- LVESVI and LVEDVI

- LV mass
- LV ejection fraction
- LV mass-to-volume ratio
- RV end-diastolic diameter
- RV fractional area

Echocardiogram data will be listed for the Safety Analysis Set.

7.5.1.3SF-36

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale where it is assumed that each question carries equal weight. The eight sections are:

- Vitality (VT)
- Physical functioning (PF)
- Bodily pain (BP)
- General health (GH)
- Role Physical (RP)
- Role Emotional (RE)
- Social functioning (SF)
- Mental health (MH)

Detailed information on SF-36 scoring is described in the *User'sManualfortheSF-36v2Health Survey* (3rd ed.)[3]. The SF-36 will be scored using QualityMetric Health Outcomes Scoring Software 4.5. A brief description of the scoring process will be given here.

Scoring the SF-36 raw score is a two-step process. First, precoded numeric values are recoded so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores. The table below shows the items averaged together to create each scale.

Table1: SF-36ScaleComponents

Scale	Numberofitems	Items
Physical functioning	10	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
Role physical	4	4a,4b,4c,4d

Role emotional	3	5a,5b,5c
Vitality	4	9a, 9e, 9g, 9i
Mental health	5	9b, 9c, 9d, 9f, 9h
Social functioning	2	6,10
Bodily Pain	2	7,8
General health	5	1, 11a, 11b, 11c, 11d

After the scale scores are obtained, a norm-based transformation is applied so that component-specific scales can be meaningfully compared with one another. First, a *z* score is computed by subtracting each health domain scale's 2009 U.S. general population mean from the 0–100 score for that scale, and then dividing the difference by the given scale's standard deviation. The z-scores are then transformed to T scores (mean = 50, *SD* = 10). This is done by multiplying each *z* score by 10 and adding 50 to the resulting product.

The mental and physical summary scores (MCS, PCS) are computed by aggregating the norm-based component scores using factor score coefficients from the 1998 general U.S. population. The aggregated summary scores are standardized to have a mean of 50 with a standard deviation of 10, again in the general 2009 U.S. population.

Descriptive summaries for the eight SF-36 scales, MCS and PCS will be provided. Actual values and the change from Baseline for overall will be provided at Baseline, Day1, Weeks 24, 48, 72 and 96 and, if applicable, termination visit. SF-36 scale scores and summary scores will be listed for the Safety Analysis Set.

7.5.1.4QOLbyKCCQ

The Quality of Life (QOL) Kansas City Cardiomyopathy Questionnaire (KCCQ) measures the effects of symptoms, functional limitations and psychological distress on an individual's QOL. In completing the QOL KCCQ, patients indicate how each of 23 facets prevented them from living as they desired using a 5- to 7-point Likert scale.

Ten scores are generated from the KCCQ-12, representing seven scales and three summary scores: Physical Limitation Score (KCCQ12-PL), Symptom Stability Score, Symptom Frequency Score (KCCQ12-SF), Symptom Burden Score, Total Symptom Score, Self-Efficacy Score, Quality of Life Score (KCCQ12-QL), Social Limitation Score (KCCQ12-SL), Clinical Summary Score, and Overall Summary Score (KCCQ12). Instructions for scoring the QOL

KCCQ are provided in the Kansas City Cardiomyopathy Questionnaire Scoring Instructions (Spertus J, revised 3/27/01) Appendix II.

A descriptive summary of actual values and the change from Baseline for the four scales and summary score will be provided for overall at Baseline, Day 1, Weeks 24, 48, 72, 96 and Early Termination (if applicable). QOL KCCQ scale scores and summary scores will be listed for the Safety Analysis Set.

7.6. Safety Analyses

Safety is determined by the incidence and severity of AEs, clinical laboratory tests (hematology, chemistry, urinalysis), physical examination, vital signs (blood pressure and pulse rate) and 12-lead ECGs at all visits and, if applicable, termination visit. All safety analyses are based on the safety analysis set. Listings of all safety data sorted by dose group, patient and assessment date will be provided.

7.6.1. ExtentofExposure

Total cumulative dose and compliance will be summarized for the safety analysis set. The total cumulative dose for a patient is the dose in mg that the patient took during the treatment period. Compliance will be calculated based on the following study drug administration eCRF fields and summed over all visits:

$$\frac{\text{Total number of capsules taken}}{\text{Total number of capsules expected to be taken}} \times 100\%$$

The number and percentage of patients with ≥80% and <80% compliance will be summarized for overall.

A summary table of dose modifications will be presented based on the safety analysis set. The number of patients at each dose will be tabulated by timepoint. A by-patient listing of study drug exposure information will be provided.

7.6.2. Adverse EventsandSeriousAdverseEvents

An adverse event (AE) is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product regardless of causality. An overdose of study drug (whether symptomatic or asymptomatic) will be reported as an AE. An overdose will be only based on patient reporting; it will not be based on pill counting. Any new condition, or worsening of pre-existing condition, during study conduct after the start of study drug or at any time after consent, if thought to be related to a study procedure, will be recorded as an AE.

A treatment emergent AE (TEAE) is defined as an AE that: occurs during treatment, having been absent at pre-treatment; or one that re-occurs during treatment, having been present during screening but stopped prior to treatment; or one that worsens in severity since treatment relative to the pre-treatment state, when the AE is continuous.

A serious adverse event (SAE**)** is any untoward medical occurrence that meets any of the following criteria.

- Results in death.
- Is immediately life-threatening (refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Based upon appropriate medical judgment, represents an important medical event that may jeopardize the patient or may require intervention to prevent one of the outcomes described above.

The severity rating of an AE refers to its intensity. The severity of each AE will be categorized using the *ToxicityGradingScaleforHealthyAdu ltandAdolescentVolunteersEnrolledin PreventiveVaccineClinicalTrials* . Intensity should be assigned a grade of 1 through 4, as outlined by the guidelines in protocol Appendix 1.

Causality is determined for the cause of the AE, considering all relevant factors such as (but not limited to) the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication and de-challenge or re-challenge.

- Yes (possibly, probably or definitely related): there is a reasonable possibility that the study drug caused the event.

- No (unlikely, probably not related or definitely not related): there is no reasonable possibility that the study drug caused the event.

Adverse events and serious adverse events will be summarized by system organ class, preferred term within each system organ class. Adverse events and serious adverse events also will be summarized by relationship to study medication and by toxicity grade.

The MedDRA (version 16.1) will be used to map the AE verbatim to preferred term, and system organ class for summary purposes. All AEs, including the AE verbatim term and the associated AE preferred term, will be provided in the patient data listings.

The following summaries will be presented for the safety analysis set by system organ class (SOC) and preferred term for overall:

- Overall Incidence of Treatment-Emergent Adverse Events
- Number and Percentage of Patients with Treatment-Emergent Adverse Events Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term
- Number and Percentage of Patients with Treatment-Emergent Serious Adverse Events Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term
- Number and Percentage of Patients with Treatment-Emergent Adverse Events Related to Study Medication Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term
- Number and Percentage of Patients with Treatment-Emergent Adverse Events Leading to Treatment Discontinuation Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term

The incidence of AEs will be calculated by dividing the number of patients who have experienced the event by the number of patients. If a patient has repeated episodes of a particular AE, only the worst toxicity episode, or the episode with the strongest causal relationship to study medication, will be counted. A patient with more than one type of AE in a particular SOC will be counted only once in the total of patients experiencing AEs in that particular SOC. Since a patient may have more than one type of AE within a particular SOC, the sum of patients experiencing different AEs within the SOC may appear larger than the total number of patients experiencing AEs in that SOC. Similarly, a patient who has experienced an AE in more than one SOC will be counted only once in the total number of patients experiencing AEs in all SOCs.

All occurrences of all AEs will be listed for each patient, grouped by dose group. In the listing of individual patients who have adverse events, the following information on each episode will be provided: MedDRA SOC/preferred term, toxicity grade, relationship to study medication, day of onset, duration, treatment given for the adverse event, and the outcome. A listing for SAEs and a listing with all AEs that resulted in study treatment discontinuation will also be presented.

Adverse events ongoing at the time of informed consent are to be followed under the parent protocol. Any AE that occurs from the signing of the informed consent form through the final study visit (e.g., Follow-Up Visit) must be recorded on the AE eCRF. After the final study visit, only SAEs assessed as related to study drug need to be captured on the AE eCRF and reported to the Sponsor.

7.6.3. Death

Detailed listings of each death will be provided based on the safety analysis set.

7.6.4. Laboratorydata

Descriptive statistics for chemistry and hematology will be presented at Baseline, Day 1, Weeks 12, 24, 36, 48, 72, 96 and, if applicable, Termination and Follow-Up. Actual values and the change from baseline will be summarized. A categorical summary for urinalysis lab data will be provided showing the number and percentage of patients in each category.

Shift tables of baseline to the worst post baseline toxicity grade in chemistry and hematology tests will be provided. Repeated or unscheduled tests will be included. For a given patient, if the toxicity grade is missing for all post baseline assessments for one laboratory test, the patient will be counted only once for that laboratory test under the "Missing" toxicity grade category. If a patient has both missing and non-missing toxicity grades for one laboratory test, the missing toxicity grade of that laboratory test will be treated as the lowest grade. For each test condition, percentages are calculated based on the number of patients in the safety analysis set who have a baseline and at least one post-baseline assessment.

Laboratory tables and listings will be based on the safety analysis set.

7.6.5. VitalSigns

Vital sign measurements including temperature (°C), pulse rate (bpm), diastolic blood pressure (DBP) and systolic blood pressure (SBP) (mm Hg) will be collected according to institutional standards at Baseline, Day 1, Weeks 12, 24, 36, 48, 72, 96 and, if applicable, Termination and Follow-Up. Actual values and the change from baseline will be summarized using descriptive statistics and listed based on the safety analysis set.

7.6.6. ECG

Triplicate 12-lead ECGs will be performed at the timepoints specified in the schedule of assessments. The mean of the triplicate ECG measurements performed at each timepoint will be used for this summary. The following ECG parameters will be summarized: heart rate, PR, QRS, RR, QT and QTcF. Parameters will be summarized for actual results and the change from baseline for the safety analysis set for overall at Day 1, Weeks 12, 24, 36, 48, 72, 96 and, if applicable, Termination and Follow-Up.

A frequency table with values divided into classes of interest for individual patients' maximum baseline and post-baseline QT interval values and QTcF values will be provided for overall. The classes of interest will be QT interval > 500 msec, QTcF > 450 msec, QTcF >480 msec, QTcF >500 msec, and change from baseline in QTcF >30 msec and >60 msec.

Each individual QT/QTcF value within a triplicate ECG will be considered when deriving the frequency classes QT > 500 msec, QTcF > 450 msec, QTcF >480 msec, and QTcF >500 msec,. For the change from baseline in QTcF >30 msec and >60 msec, the mean of the triplicate QTcF will be used. Percentages will be calculated based on the number of patients in the Safety Analysis Set who had a baseline and at least one post-baseline ECG assessment.

ECG data will be presented in a listing. Values with QT interval > 500 msec, QTcF > 450 msec, > 480 msec, and >500 msec, and change from baseline in QTcF >30 msec and >60 msec will be flagged. Both the individual and the mean of the triplicate QT and QTcF records at each timepoint will be listed.

7.6.7. PhysicalExamination

A complete physical examination will assess general physical well-being and it will be performed at screening. A brief physical examination will be performed at all other timepoints, but may include further evaluation if any areas of concerns are identified. Abnormal results will be recorded as adverse events. The number and percent of patients with physical examination abnormalities at Screening will be summarized based on the safety analysis set for overall. Physical examination findings will be presented as the patient listing.

7.7 PharmacokineticAnalyses

For the presentation of concentration related descriptive statistics where BLQ observations may be observed are to be handled as follows. If the BLQ ratio (N_{BLQ}/N_{valid}) is equal to 0, all values in a designated group are numeric (i.e no BLQ values were observed), the descriptive statistics to be reported include minimum, maximum, median, mean, geometric mean, SD, CV, geometric CV and geometric SD. If the BLQ ratio is ≤ 1/3, a number of ½ the LLOQ for a given analyte will be used and all descriptive statistics listed above will be presented and the value for the minimum will be reported as BLQ. If the BLQ ratio is <0.5 and >1/3, only the median, minimum and maximum will be reported, and the minimum will be reported as BLQ. The SD, CV, geometric SD, geometric CV will be reported as not calculated (NC). If the BLQ ratio for a given group is equal to 0.5, only the maximum will be reported and the minimum will be listed as BLQ. The mean, geometric mean, median, SD, CV, geometric SD, geometric CV will be listed as NC. If the BLQ ratio is <1 and >0.5 only the maximum will be reported, and the minimum and median will be reported as BLQ. Mean, geometric mean, SD, CV, geometric SD, geometric CV, will be reported as NC. If all observations in a given group are listed as BLQ (BLQ ratio of 1), the minimum, maximum, median, mean and geometric mean will be reported as BLQ. The SD, CV, geometric SD, geometric CV and listed as NC.

Blood collection for the measurement of plasma concentrations of ARRY-371797 and the metabolites AR00420643, AR00428028 and AR00486705 will be drawn at the timepoints specified in the protocol. Plasma concentrations of ARRY-371797 and AR00420643, AR00428028 and AR00486705 will be summarized by timepoint and analyte using descriptive statistics and will be contained in a listing and will be accompanied by a figure of individual concentration-time profiles grouped by actual dose. Geometric mean concentration versus time profiles, with geometric SD error bars, grouped by dose, will be presented on a linear and logarithmic scale for the screening, Week 12, and Week 24 visits.

For the calculation of secondary PK parameters, metabolite-to-parent concentration ratio (MR) based on pre- ($MR_{predose}$) and postdose ($MR_{postdose}$) measurements will be calculated and listed by determining the ratio of each metabolite concentration to the corresponding parent concentration for each given sample timepoint and analyte and listed as $MR_{predose}$ and $MR_{postdose}$ for each

patient, timepoint and analyte. $MR_{predose}$ and $MR_{postdose}$ will be grouped by actual dose and summarized using descriptive statistics by timepoint and analyte. Drug and metabolite accumulation (R) will be calculated and listed ($R_{predose}$ and $R_{postdose}$) for each patient by timepoint and actual dose. R will be calculated by dividing the concentration of parent drug or metabolite for week N and postdose or predose timepoint by the respective parent or metabolite concentration at the screening visit and corresponding predose or postdose timepoint. R will be grouped by actual dose and summarized using descriptive statistics by timepoint and analyte.

8. PROTOCOLDEVIATIONSANDMAJOR PROTOCOL VIOLATIONS

Protocol deviations/violations will be listed by category. Criteria to identify protocol deviations/violations will be determined prior to database lock.

9. REFERENCES

1. *AnOpen-labelRolloverStudyofARRY-371797in PatientswithSymptomaticGenetic DilatedCardiomyopathyDueto aLaminA/CGeneMutation.* Array BioPharma, Inc. Protocol No. ARRAY-797-001, Version 1, dated 01 December 2014.
2. *GuidanceforIndustryToxicityGradingScaleforHealthyAdultandAdolescent VolunteersEnrolledinPreventiveVaccineClinicalTrials.* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, September 2007.
3. Maruish, M. E. (Ed.). *User'sManualfortheSF-36v2HealthSurvey* (3rd ed.). Lincoln, RI: QualityMetric Incorporated.

APPENDIXI.SCHEDULEOFEVENTS

Procedure or Assessment	Screening Period	Treatment Period			Follow-up Period	
	Screening (Final Visit in Parent Study)	Weeks 12, 36	Weeks 24, 48, 72, 96	Every 24 Weeks After Week 96	Termination Visit	Follow-up Visit 30 Days After Last Dose
Informed Consent	X					
Confirm Eligibility Criteria	X					
Medical History	X					
Concomitant Medications[a]	X[b]	X	X	X	X	X
Physical Exam/Weight/ Vital Signs[c]	X[b]	X	X	X	X	X
Triplicate ECGs	X[b]	X	X	X	X	X
Hematology/Chemistry Blood Sample[d]	X[b]	X	X	X	X	X
6-Minute Walk Test	X[b]		X		X[e]	
Echocardiogram	X[b]		X		X[e]	
SF-36 and QOL KCCQ	X[b]		X		X[e]	
Urine Pregnancy Test[f]	X[b]	X	X	X	X	X
Urinalysis	X[b]					
Dispense Study Drug	X	X	X	X		
PK Blood Sample[d,g]	X	X[h]	X[i]			
Assess AEs	X[b]	X	X	X	X	X

All activities are performed predose with the exception of post-dose PK blood samples. Visit windows are ± 14 days.

[a] Include all prescription and nonprescription drugs, vitamins and dietary or herbal supplements.

[b] These assessments are performed as part of the final visit of the parent study.

[c] Blood pressure measurements to be performed in accordance with institutional standards. Height will be measured at the Screening Visit only.

[d] Sample collection to be performed in accordance with the methods described in the Laboratory Manual.

[e] To be performed at Termination Visit only if not performed within the prior 30 days.

[f] Required for females of childbearing potential only.

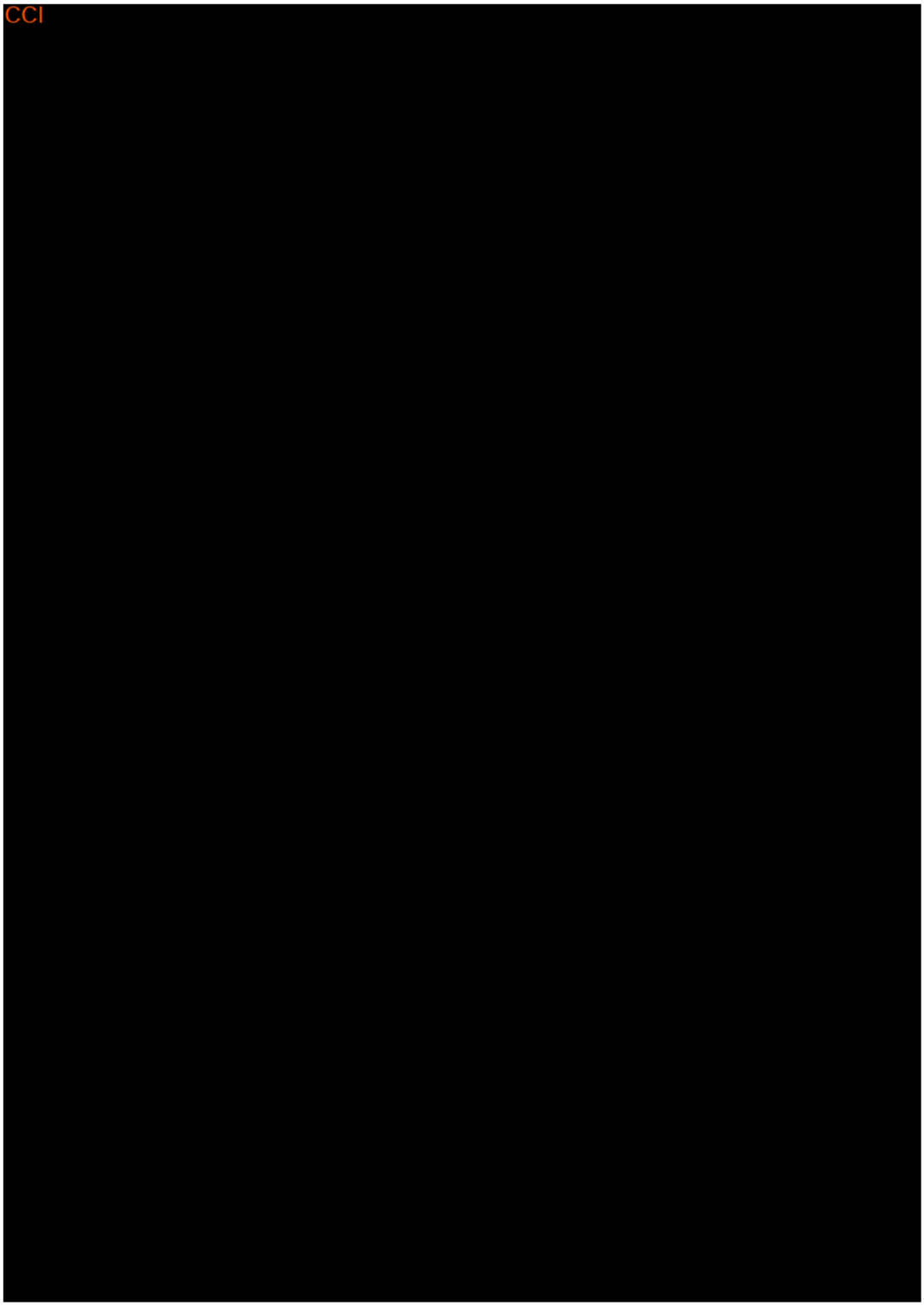
[g] In patients who previously participated in Clinical Study ARRAY-797-231, samples are to be collected pre-dose and 1 to 2 hours post-dose (exact post-dose time of blood draw must be documented).

[h] Week 12 only.

[i] Week 24 only.

CCI

[redacted]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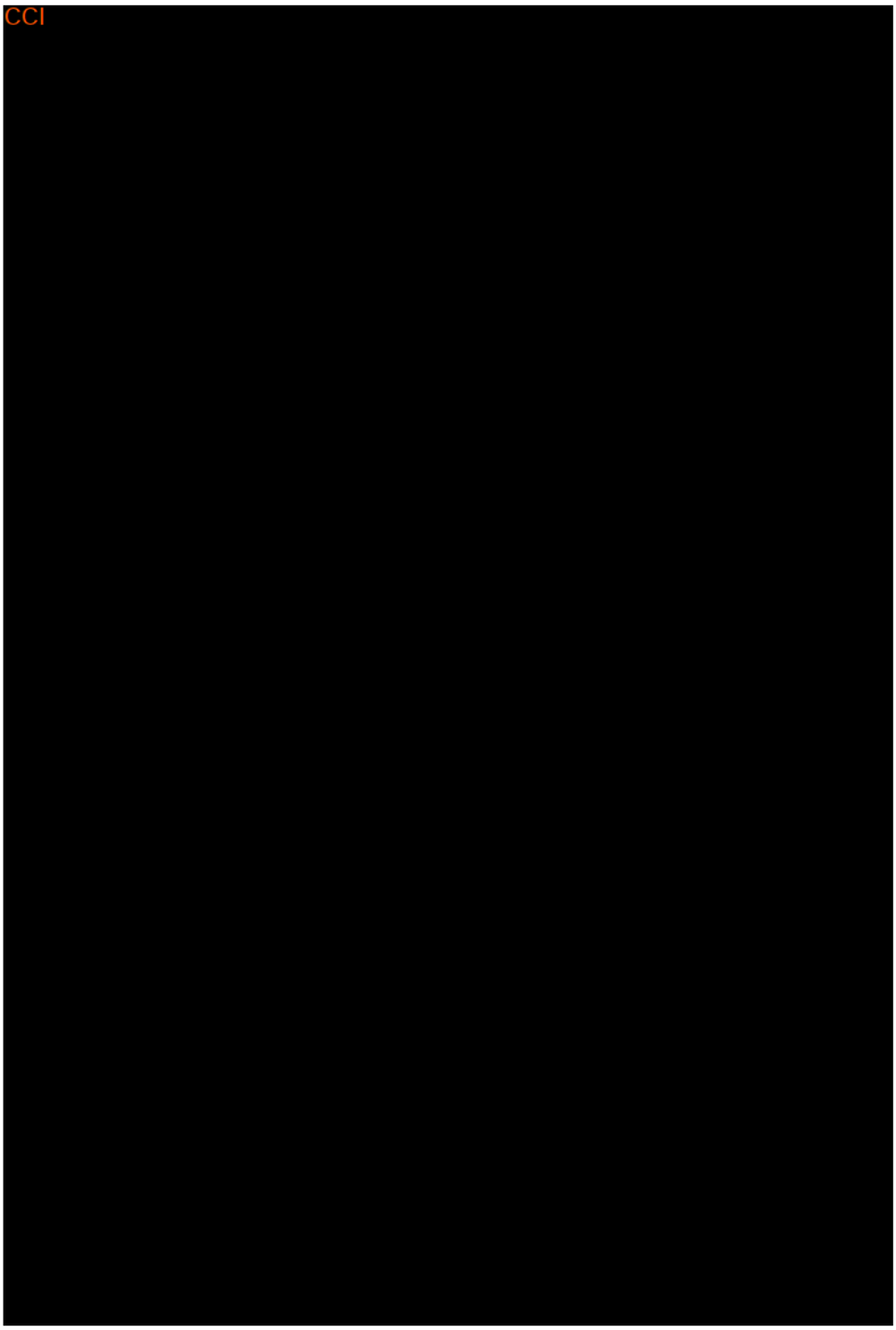

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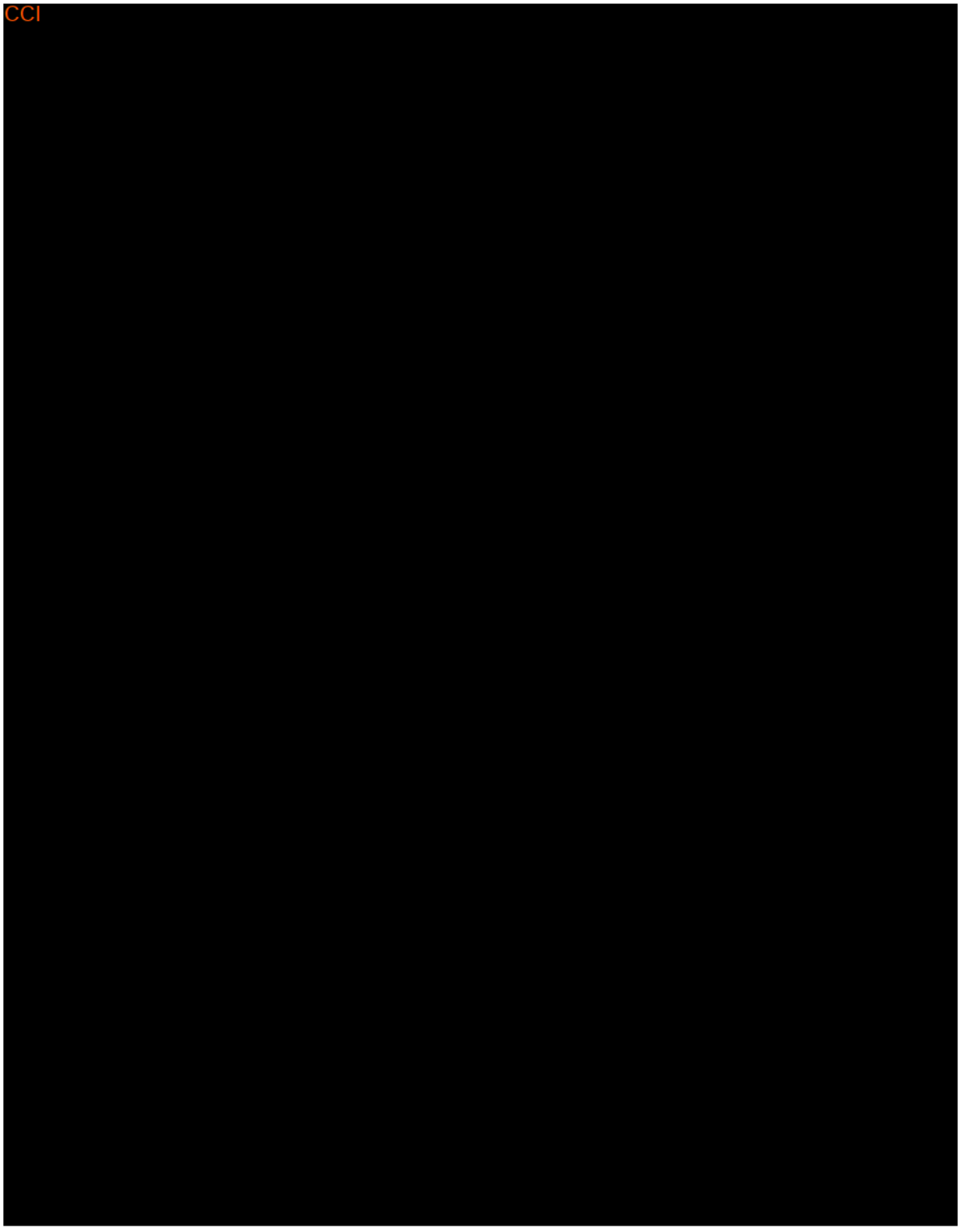

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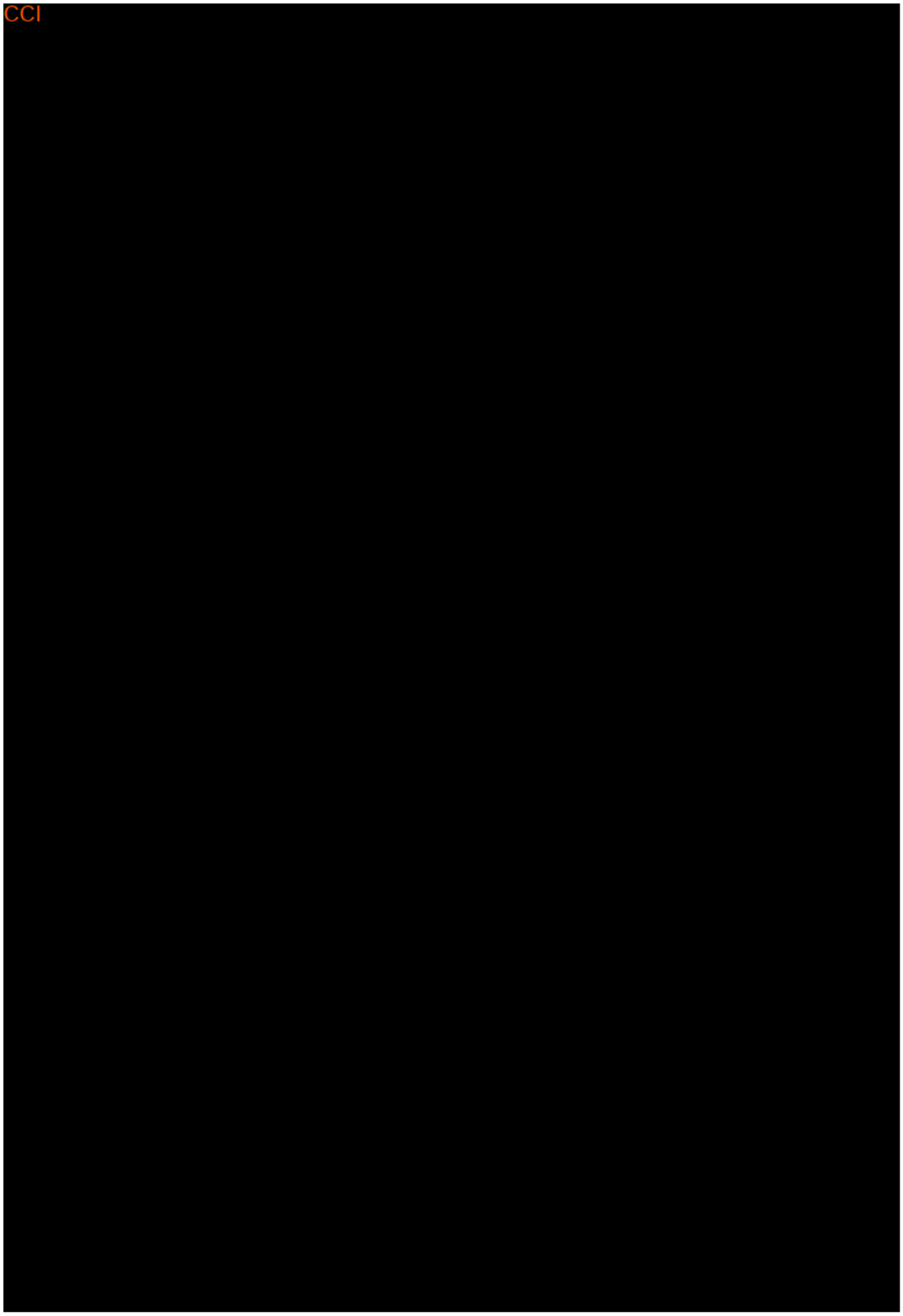

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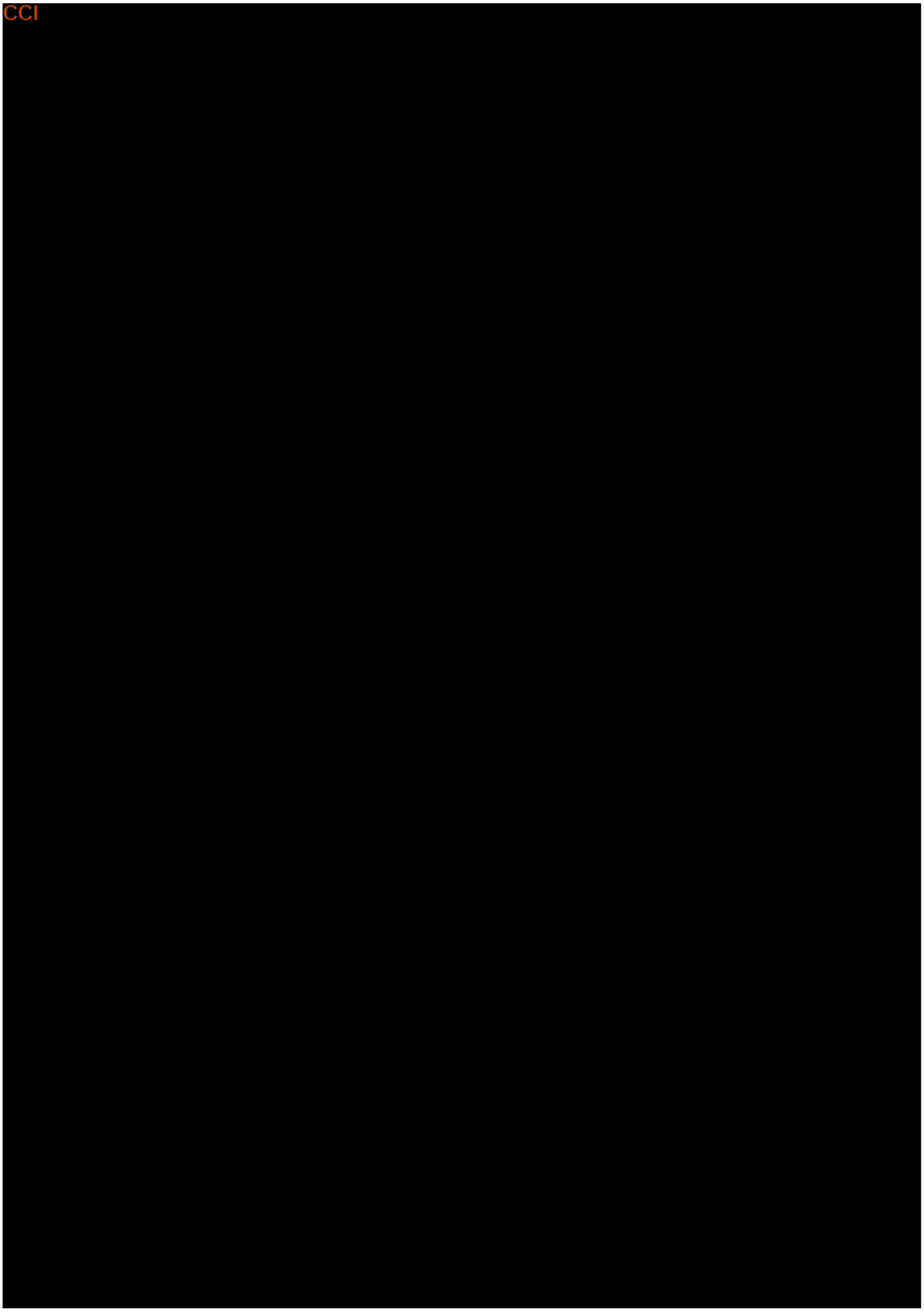

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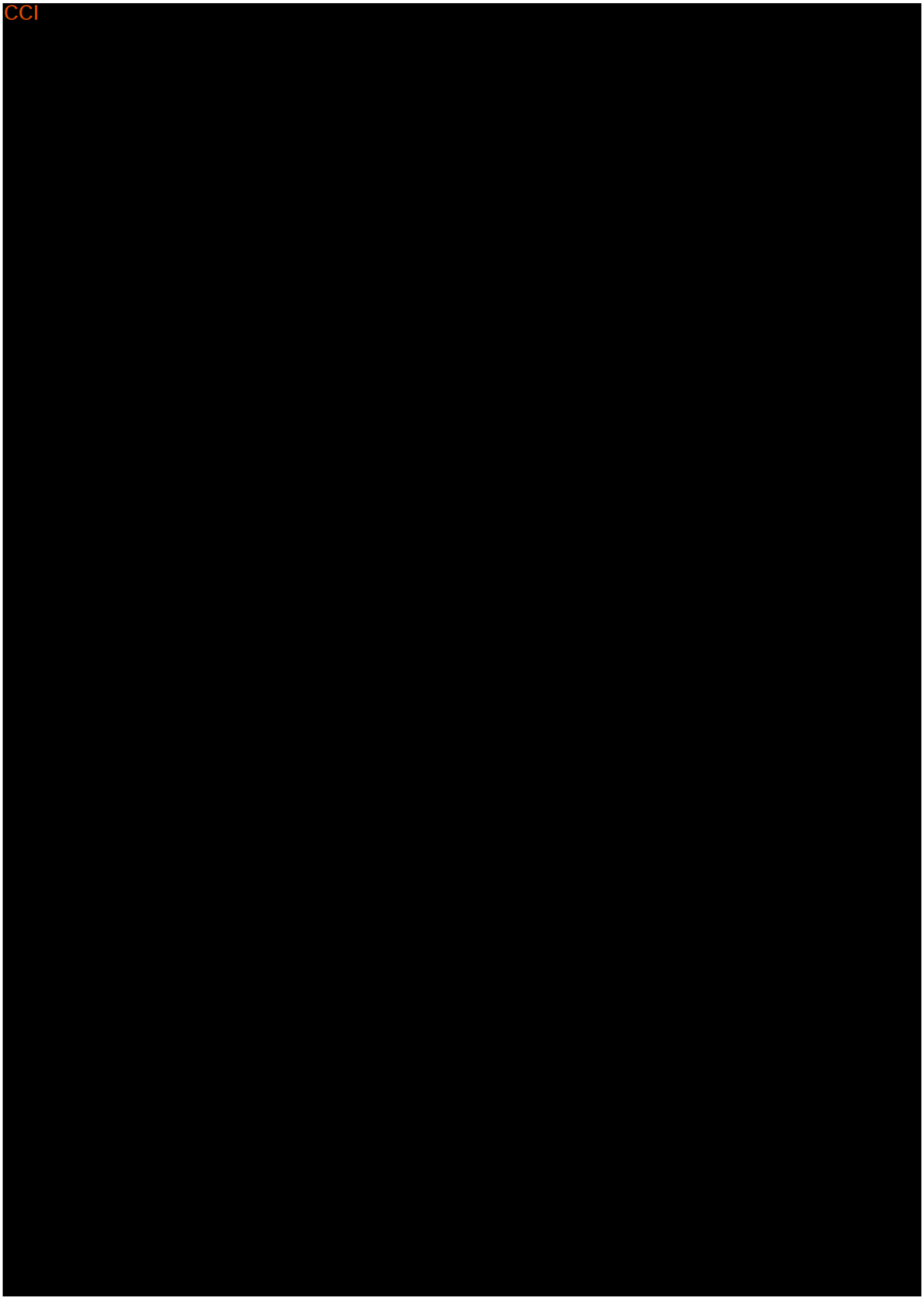

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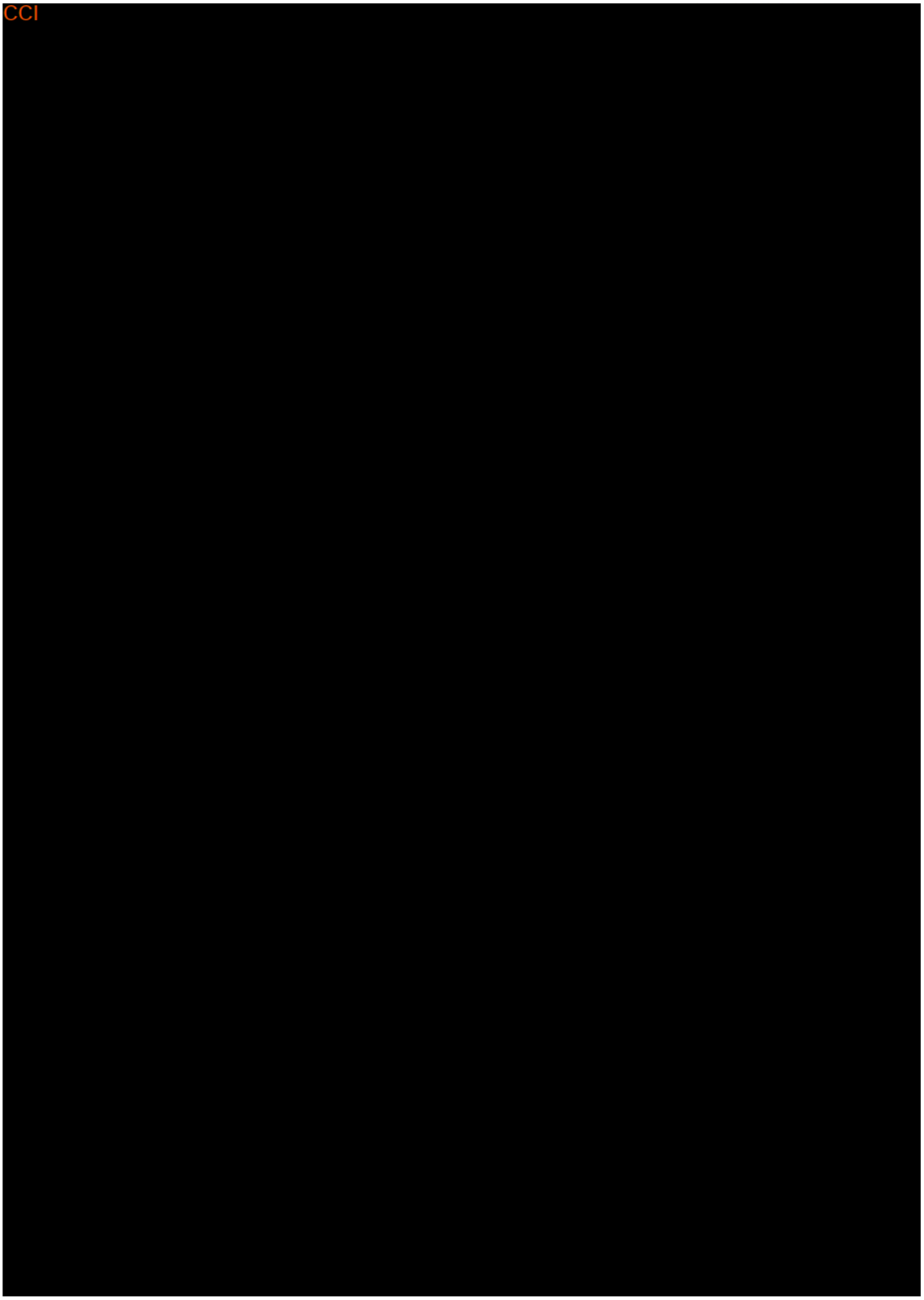

APPENDIXIII. LISTOFPLANNEDTABLES,LISITNGSANDFIGURES

Type	Number	Title
TABLES		
Table	14.1.1	Summary of Patient Disposition (All Screened Patients)
Table	14.1.4	Summary of Demographics and Baseline Characteristics (Safety Analysis Set)
Table	14.1.5.1	Summary of Study Drug Exposure (Safety Analysis Set)
Table	14.1.5.2	Summary of Dose Modifications (Safety Analysis Set)
Table	14.1.6	Summary of Medical History by System Organ Class and Preferred Term (Safety Analysis Set)
Table	14.1.7	Summary of Concomitant Medications by Medication Class and Preferred Term (Safety Analysis Set)
Table	14.1.7.1	Summary of Prior Medications by Medication Class and Preferred Term (Safety Analysis Set)
Table	14.1.8	Summary of Physical Examination Screening Results (Safety Analysis Set)
Table	14.2.1.1	Summary of Six Minute Walk Results, Change and Percent Change from Baseline (Efficacy Analysis Set)
Table	14.2.1.2	Summary of Six Minute Walk Responders (Efficacy Analysis Set)
Table	14.2.2	Summary of Echocardiographic Results and Change from Baseline (Efficacy Analysis Set)
Table	14.2.3	Summary of SF-36 Results and Change from Baseline (Efficacy Analysis Set)
Table	14.2.4	Summary of KCCQ-12 Results and Change from Baseline (Efficacy Analysis Set)
Table	14.3.1.1	Overall Incidence of Treatment-Emergent AEs(Safety Analysis Set)
Table	14.3.1.2	Number and Percentage of Patients with Treatment-Emergent Adverse Events Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term (Safety Analysis Set)
Table	14.3.1.3	Number and Percentage of Patients with Treatment-Emergent Serious Adverse Events Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term (Safety Analysis Set)
Table	14.3.1.4	Number and Percentage of Patients with Treatment-Emergent Adverse Events Related to Study Medication Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term (Safety Analysis Set)
Table	14.3.1.5	Number and Percentage of Patients with Treatment-Emergent Adverse Events Leading to Treatment Discontinuation Summarized by Worst Toxicity Grade, System Organ Class, and Preferred Term (Safety Analysis Set)
Table	14.3.1.6	Number and Percentage of Patients with Treatment-Emergent Adverse Events Summarized by Preferred Term in Descending Order of Frequency (Safety Analysis Set)
Table	14.3.4.1	Summary of Results and Change from Baseline in Laboratory Tests – Hematology (Safety Analysis Set)
Table	14.3.4.2	Summary of Results and Change from Baseline in Laboratory Tests – Chemistry (Safety Analysis Set)
Table	14.3.4.3	Summary of Results in Laboratory Tests – Urinalysis Safety Analysis Set)
Table	14.3.4.4	Shift Table from Baseline to the Worst Post Baseline Toxicity Grade in Laboratory Tests – Hematology (Safety Analysis Set)
Table	14.3.4.5	Shift Table from Baseline to the Worst Post Baseline Toxicity Grade in Laboratory Tests – Chemistry (Safety Analysis Set)
Table	14.3.5	Summary of Vital Signs Results and Change from Baseline (Safety Analysis Set)
Table	14.3.6.1	Summary of 12-Lead Electrocardiogram (ECG) Results and Change from Baseline (Safety Analysis Set)
Table	14.3.6.2	Summary of Patients Meeting Pre-Specified QT/QTcF Criteria (Safety Analysis Set)
Table	14.3.8.1	Summary of Plasma ARRY-371797 and AR00420643, AR00428028, AR00486705

		Concentrations by Actual Dose Level (PK Analysis Set)
Table	14.3.8.2	Summary of PK Parameters (PK Analysis Set)
LISTINGS		
Listing	16.2.1.1	Listing of Patient Disposition (All Screened Patients)
Listing	16.2.1.2	Listing of Deaths (Safety Analysis Set)
Listing	16.2.2.1	Listing of Protocol Deviations and Violations
Listing	16.2.2.2	Listing of Patients Not Meeting Inclusion/Exclusion Criteria
Listing	16.2.4.1	Listing of Demographic and Baseline Characteristics (Safety Analysis Set)
Listing	16.2.4.2	Listing of Medical History (Safety Analysis Set)
Listing	16.2.4.3	Listing of Prior and Concomitant Medications (Safety Analysis Set)
Listing	16.2.5.1	Listing of Study Drug Administration (Safety Analysis Set)
Listing	16.2.5.2	Listing of Study Drug Exposure (Safety Analysis Set)
Listing	16.2.6.1	Listing of Six Minute Walk Assessment (Safety Analysis Set)
Listing	16.2.6.2	Listing of Echocardiographic Assessment (Safety Analysis Set)
Listing	16.2.6.3	Listing of SF-36 Scores (Safety Analysis Set)
Listing	16.2.6.4	Listing of KCCQ-12 Assessment (Safety Analysis Set)
Listing	16.2.7.1	Listing of Treatment-Emergent Adverse Events (Safety Analysis Set)
Listing	16.2.7.2	Listing of Treatment-Emergent Serious Adverse Events (Safety Analysis Set)
Listing	16.2.7.3	Listing of Treatment-Emergent Adverse Events Related to Study Medication (Safety Analysis Set)
Listing	16.2.7.4	Listing of Treatment-Emergent Serious Adverse Events Related to Study Medication (Safety Analysis Set)
Listing	16.2.7.5	Listing of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation (Safety Analysis Set)
Listing	16.2.7.6	Listing of Treatment-Emergent Adverse Events Related to Study Drug Leading to Treatment Discontinuation (Safety Analysis Set)
Listing	16.2.8.1	Listing of Laboratory Tests – Hematology (Safety Analysis Set)
Listing	16.2.8.2	Listing of Laboratory Tests – Chemistry (Safety Analysis Set)
Listing	16.2.8.3	Listing of Laboratory Tests – Urinalysis (Safety Analysis Set)
Listing	16.2.9	Listing of Vital Signs Data (Safety Analysis Set)
Listing	16.2.10	Listing of 12-Lead Electrocardiogram (ECG) Data (Safety Analysis Set)
Listing	16.2.11	Listing of Physical Examination (Safety Analysis Set)
Listing	16.2.13.1	Listing of Plasma ARRY-371797 and AR00420643, AR00428028, AR00486705 Concentrations (PK Analysis Set)
Listing	16.2.14.1	Listing of PK Parameter Data (PK Analysis Set)
FIGURES		
Figure	14.2.1.1	Plot of Six Minute Walk Distance by Visit (Efficacy Analysis Set)
Figure	14.2.1.2	Plot of Mean Change from Baseline in Six Minute Walk Distance by Visit (Efficacy Analysis Set)
Figure	14.2.1.3	Plot of Percent Change from Baseline in Six Minute Walk Distance by Visit (Efficacy Analysis Set)
Figure	14.3.8.1	Geometric Mean Plasma ARRY-371797 and AR00420643, AR00428028, AR00486705 Concentrations Versus Time (Linear Scale) by Actual Dose Level (PK Analysis Set)

Figure	14.3.8.1.1	Geometric Mean Plasma ARRY-371797 and AR00420643, AR00428028, AR00486705 Concentrations Versus Time (Logarithmic Scale) by Actual Dose Level (PK Analysis Set)
Figure	14.3.8.5	Individual Plasma ARRY-371797 and AR00420643, AR00428028, AR00486705 Concentrations Versus Time (Linear Scale) by Actual Dose Level (PK Analysis Set)
Figure	14.3.8.5.1	Individual Plasma ARRY-371797 and AR00420643, AR00428028, AR00486705 Concentrations Versus Time (Logarithmic Scale) by Actual Dose Level (PK Analysis Set)