Clinical Study ARRAY-797-001

An Open-label Rollover Study of ARRY-371797 in Patients with Symptomatic Genetic Dilated Cardiomyopathy Due to a Lamin A/C Gene Mutation

Protocol Version 1: 01 December 2014

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SIGNATURE PAGE (SPONSOR)

I have read and understand the contents of the clinical protocol for Clinical Study ARRAY-797-001 dated 01 December 2014 and agree to meet all obligations of Array BioPharma Inc. as detailed in all applicable regulations and guidelines. In addition, I will ensure that the Principal Investigators are informed of all relevant information that becomes available during the conduct of this study.

PPD

PPD MD

PPD

12/2/2017
Date

PRINCIPAL INVESTIGATOR AGREEMENT

I have read and understand the contents of the clinical protocol for Clinical Study ARRAY-797-001 dated 01 December 2014 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the study in accordance with the requirements of this protocol and also protect the rights, safety, privacy and well-being of study patients in accordance with the following:

- International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonized Tripartite Guideline for Good Clinical Practice E6(R1)
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations
- Requirements for reporting serious adverse events (SAEs) defined in Section 10.9 of this protocol
- Terms outlined in the Clinical Study Site Agreement

My signature also acknowledges that:

- Neither my subinvestigators nor I are members of the Institutional Review Board (IRB) reviewing this protocol, or
- I and/or my subinvestigators are members of the IRB, but I/we will not participate in the initial review or continuing review of this study

Name of Principal Investigator	Signature of Principal Investigator

Date

PROTOCOL SYNOPSIS

Title	**An Open-label Rollover Study of ARRY-371797 in Patients with Symptomatic Genetic Dilated Cardiomyopathy Due to a Lamin A/C Gene Mutation**
Protocol Number	ARRAY-797-001
Study Center(s)	All applicable study centers worldwide
Objectives	**Primary:** • Evaluate the safety of ARRY-371797 administered after completion of the parent study **Secondary:** • Evaluate measures of efficacy of ARRY-371797 • Determine the exposure of ARRY-371797 and metabolites
Endpoints	**Primary:** • 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 **Secondary:** Assessed at 24, 48, 72 and 96 weeks and termination visit (if applicable): • 6-minute walk test (6MWT) • Left ventricular end systolic volume index (LVESVI) • Left ventricular (LV) end diastolic volume index • 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) In patients who previously participated in Clinical Study ARRAY-797-231: • 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

Design	This rollover study is designed to investigate the safety and efficacy of ARRY-371797 administration in patients who previously received ARRY-371797 in a lamin A/C gene (*LMNA*) mutation study sponsored by Array BioPharma (the "parent study") 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.
Treatment Regimens	Patients will receive ARRY-371797 at the same dose and schedule they were administered at the conclusion of the parent study.
Study Population	Patients with genetic dilated cardiomyopathy secondary to *LMNA* mutations who received ARRY-371797 in a *LMNA* mutation study sponsored by Array BioPharma, and may, in the investigator's opinion, derive benefit from continued treatment.
Duration of Study Participation	Patients may continue receiving ARRY-371797 as long as no treatment discontinuation criteria are met.
Treatment Discontinuation Criteria	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 discontinue study treatment if, in the opinion of the Investigator, it is not in the best medical interest of the patient to continue treatment.

Eligibility Criteria	Patients must meet all of the following criteria to be eligible for enrollment in the study. 1. Provide a personally signed and dated informed consent document prior to initiation of any study-related procedures that are not considered standard of care. 2. Received ARRY-371797 as treatment for genetic dilated cardiomyopathy secondary to *LMNA* mutations in a clinical study sponsored by Array BioPharma. 3. May, in the opinion of the Investigator, benefit from continued ARRY-371797 treatment. 4. Male patients and female patients of childbearing potential must agree to use a highly effective method of contraception. 5. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures. Patients meeting any of the following criteria are ineligible for enrollment in the study. 1. Discontinued treatment in the parent study for any reason other than study completion or Sponsor termination of the study. 2. Pregnant or breastfeeding women. 3. Local access to commercially available ARRY-371797.
Statistical Considerations	Safety, efficacy and plasma concentration data will be summarized using descriptive statistics. Formal statistical comparisons will not be performed.
Sponsor	Array BioPharma Inc.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
2D	2 dimensional
6MWT	6-minute walk test
AE	Adverse event
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
C	Celsius
CK	Creatine kinase
C_{max}	Maximum concentration
COMP	Cartilage oligomeric matrix protein
CPK	Creatine phosphokinase
CRA	Clinical research associate
CRO	Contract research organization
CSD	Conduction system disease
CTX-I	C-terminal cross-linking telopeptide of type I collagen
CV	Curriculum vitae
CYP	Cytochrome P450
DCM	Dilated cardiomyopathy
dL	Deciliter(s)
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or special term	Explanation
EDC	Electronic data capture
EDMD	Emery-Dreifuss muscular dystrophy
ERK	Extracellular signal-regulated kinase
F	Fahrenheit
FDA	U.S. Food and Drug Administration
FMO	Flavin-containing monoooxygenase
FSH	Follicle-stimulating hormone
g	Gram(s)
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
HEENT	Head, eyes, ears, nose, throat
HSP27	Heat shock protein 27
IC_{50}	Half-maximal inhibitory concentration
ICD	Implantable cardioverter defibrillator
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
JNK	c-Jun N-terminal kinase
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	Kilogram(s)
L	Liter(s)
LMNA	Gene encoding the Lamin A/C protein
LPS	Lipopolysaccharide

Abbreviation or special term	Explanation
LS	Least squares
LV	Left ventricular
LVEDD	Left ventricular end diastolic diameter
LVEDVI	Left ventricular end diastolic volume index
LVEF	Left ventricular ejection fraction
LVESD	Left ventricular end systolic diameter
LVESVI	Left ventricular end systolic volume index
µg	Microgram(s)
µL	Microliter(s)
m	Meter(s)
MAO	Monoamine oxidase
MAP3K	Mitogen-activated protein kinase kinase kinase
MAPK	Mitogen-activated protein kinase
MAPKK	Mitogen-activated protein kinase kinase
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
mRNA	Messenger ribonucleic acid
MTX	Methotrexate
nM	Nanomolar
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OA	Osteoarthritis
PD	Pharmacodynamic
PDF	Portable document format
PGE_2	Prostaglandin E_2
PK	Pharmacokinetic(s)
PR	Pulse rate

Abbreviation or special term	Explanation
QD	Once daily
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
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid arthritis
RBC	Red blood cell(s)
RV	Right ventricular
RV-FS	Right ventricular fractional shortening
RVEDD	Right ventricular end-diastolic diameter
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard Deviation
SF-36	Medical Outcomes Study 36-item Short-Form Health Survey
SOP	Standard operating procedure
$t_{1/2}$	Terminal half-life
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor-alpha
ULN	Upper limit of normal
US	United States (of America)
WBC	White blood cell(s)
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

1.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Principal Investigator is the person responsible for the conduct of the study at the investigational site. A subinvestigator is any member of the clinical study team designated and supervised by the Principal Investigator to perform critical study-related procedures and/or to make important study-related decisions.

Prior to study initiation, the Principal Investigator at each site must provide to Array BioPharma Inc. (Array BioPharma/Sponsor) a signed protocol signature page, a fully executed and signed United States (US) Food and Drug Administration (FDA) Form 1572, a current curriculum vitae (CV), medical license and a financial disclosure form. Financial disclosure forms, current CVs and medical licenses must also be provided for all subinvestigators listed on Form 1572 who will be directly involved in the treatment or evaluation of patients in this study.

The study will be administered and monitored by employees or representatives of Array BioPharma and/or a contract research organization (CRO) in accordance with all applicable regulations. Clinical research associates (CRAs) will monitor each site on a periodic basis and perform verification of source documentation for each patient. The Array BioPharma Drug Safety Department (and/or the CRO, if applicable) will be responsible for ensuring timely reporting of expedited serious adverse event (SAE) reports to regulatory authorities and Investigators.

2.0 INTRODUCTION

2.1 Background Therapeutic Information

LMNA-RELATED DILATED CARDIOMYOPATHY

Lamins are critical components of the nuclear lamina, which lie between the inner nuclear membrane and the chromatin, and provide structural support for the cell nucleus, participate in many different nuclear processes, including chromatin organization, connecting the nucleus to the cytoplasm, gene transcription, and mitosis. Mutations in *LMNA* (gene encoding the lamin A/C protein) cause a variety of human diseases, known collectively as laminopathies. Dilated cardiomyopathy (DCM) is one of the more common phenotypes associated with *LMNA* mutations, and *LMNA*-related DCM appears to be one of the more common causes of familial dilated cardiomyopathy, accounting for up to 8% of all cases.[1,2,3] *LMNA*-related DCM is typically autosomal dominant in inheritance, and is usually accompanied by atrial arrhythmias and/or conduction system disease (CSD). To date, ~100 *LMNA* mutations have been reported that were associated with cardiac disease (DCM and/or CSD).[4] Differential response to treatment based on the specific mutation identified has not been observed. The prevalence of familial DCM is approximately 1 in 2,500 persons in the US.[4,5] Of these individuals, it has been estimated that 5% to 8% carry disease-causing *LMNA* mutations.[5,6] Thus, the population of patients in the US (based on a US population estimate of ~316 million in September 2013)[7] with *LMNA*-related DCM is in the range of 6,000 to 10,000 patients.

The majority of patients with *LMNA*-related DCM follow a clinical course starting with CSD and/or arrhythmias in early to mid-adulthood, with some early mortality due to sudden cardiac arrest from a fatal arrhythmia or embolus. Over time, most patients progress to DCM, which can lead to rapidly progressive heart failure. Although the age of presentation in *LMNA*-related DCM varies, the age of onset typically appears to be in the third and fourth decades.[6,8] Furthermore, *LMNA*-related DCM patients have a more malignant clinical course than other familial DCM types, due to high rates of progressive heart failure and sudden cardiac death from ventricular tachyarrhythmia, despite conventional heart failure therapies, unless prevented by an implantable cardioverter defibrillator (ICD).[9,10,11] Spontaneous improvement is not seen in *LMNA*-related DCM, and while the response to conventional heart failure therapies has not been fully characterized in this specific form of DCM, the relentless progression of disease despite conventional medical therapies suggests that it is poor.

Currently, there is no effective, disease-specific treatment available or known to be in clinical development for *LMNA*-related DCM. To date, treatment is limited to conventional therapies for DCM (angiotensin-converting-enzyme inhibitors or angiotensin 2 receptor blockers, beta blockers, aldosterone receptor antagonists and diuretics) which are largely symptomatic and supportive. Progressive deterioration in left ventricular (LV) function and refractory heart failure symptoms are often treated with resynchronization therapy (bi-ventricular pacing/ICD). In

patients whose disease continues to progress in spite of aggressive cardiovascular management, cardiac transplantation may be considered.

2.2 Investigational Medicinal Product

ARRY-371797 is a selective oral inhibitor of the α-isoform of p38 mitogen-activated protein kinase (MAPK), a key enzyme of the MAPK family that regulates the production of the enzymes that are responsible for prostaglandin synthesis and for the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNFα), interleukin (IL)-1β and IL-6. ARRY-371797 has demonstrated potent activity against p38 MAPK, possesses broad anti-inflammatory activity ex vivo and in vivo, and has undergone investigation for a number of indications including inflammatory conditions and the treatment of cardiac dysfunction in patients with *LMNA*-related DCM.

2.2.1 Nonclinical Studies with ARRY-371797

Detailed information regarding nonclinical studies of ARRY-371797 is presented in the Investigator's Brochure.

2.2.1.1 Nonclinical Pharmacology

Numerous in vitro and in vivo studies were performed to evaluate and confirm the ability of ARRY-371797 to interact with its intended target, p38 MAPK. In enzyme studies, ARRY-371797 inhibits the α-isoform of p38 with an IC_{50} of 8.2 nM. In cellular studies, ARRY-371797 is a potent inhibitor of p38-mediated downstream phosphorylation of heat shock protein 27 (HSP27) in HeLa cells with an IC_{50} of 17 nM. Also, in the well-accepted ex vivo assay of p38 activity, lipopolysaccharide (LPS)-induced TNFα in human whole blood, ARRY-371797 demonstrated extraordinary potency with an IC_{50} of 0.3 nM. This compound has demonstrated little to no activity against over 210 enzymes, receptors, channels and transporters.

In vivo studies have been conducted to evaluate the activity of ARRY-371797 with respect to inhibiting cytokine production and inflammation in vivo. ARRY-371797 has been evaluated in inflammatory disease models and has proven to be a potent anti-TNF/anti-inflammatory compound in vivo with bone protective effects in animal models of arthritis. Several murine models of *LMNA*-related DCM have allowed exploration of pathophysiologic mechanisms of disease progression and novel therapies for these conditions. In vivo studies have demonstrated that the p38 MAPK is activated in murine models of *LMNA*-related DCM and that this activation of p38 MAPK precedes the development of cardiac dysfunction. ARRY-371797 has been tested in the homozygous *LMNA* H222P model of Emery-Dreifuss muscular dystrophy (EDMD) with cardiomyopathy (EDMD2, MIM:181350) and in the homozygous *LMNA* N195K model of *LMNA*-related DCM, one of the original *LMNA* mutations linked to familial DCM with conduction defects (CMD1A, OMIM:150330.0006). These two nonclinical models bracket the spectrum of phenotypes (EDMD2: cardiac and skeletal muscle disease and DCM: cardiac disease

only). Results from these studies confirm that treatment with ARRY-371797 improves cardiac structure and function and reduces myocardial apoptosis. In these mouse studies, the LV functional measures of left ventricular end diastolic diameter (LVEDD)/body weight and left ventricular end systolic diameter (LVESD)/body weight are indices that correlate with the human clinical study endpoints of left ventricular end diastolic volume index (LVEDVI) and left ventricular end systolic volume index (LVESVI), respectively. The measure of left ventricular ejection fraction (LVEF) is common to both mouse and human echocardiography. In addition, ARRY-371797 improves survival in the murine *LMNA*-related DCM model (LMNA N195K).

2.2.1.2 Nonclinical Pharmacokinetics and Absorption, Distribution, Metabolism and Excretion

Pharmacokinetic (PK) studies were conducted with single doses of ARRY-371797 in mice, rats and monkeys. The mean observed systemic plasma clearance values were high (range, 67.1 to 135 mL/min/kg) where monkey > mouse > rat, and mean plasma terminal half-life ($t_{1/2}$) values were on the order of monkey ≈ mouse < rat (range, ~0.6-5.9 hours). The mean steady-state volume of distribution values ranged from 0.609 L/kg (mouse) to 10.2 L/kg (rat). The area under the plasma concentration-time curve (AUC) and maximum concentration (C_{max}) values increased in a greater than dose-proportional manner in mice, rats and monkeys following intravenous (IV) or oral administration. The mean absolute oral bioavailability was similar in mice, rats and monkeys, generally increasing with increases in dose (range, 1.3% to 32%); AR00333953 was the principal metabolite in mice, rats and monkeys. In monkeys, the metabolite (AR00333953) exposure was greater than that of the parent (3.1-fold greater exposure), whereas, in mice and rats, the ARRY-371797 exposure was greater than that of the metabolite (1.4- to 2-fold greater exposure). ARRY-371797 is approximately 27 times more potent than AR00333953 at inhibiting LPS-induced tumor necrosis factor (TNF) in an ex vivo human whole blood assay. Formation of the major in vivo circulating metabolite, AR00333953, was not mediated by cytochrome P450 (CYP)s. Multiple Phase I enzymes (CYPs, flavin-containing monoooxygenases [FMOs], amidases and esterases) are involved in the metabolism of ARRY-371797.

In vitro experiments indicated that ARRY-371797 has moderate membrane permeability and may be a substrate for active efflux. ARRY-371797 was moderately, but reversibly, bound to plasma proteins in vitro across mouse, monkey and human plasma, as was AR00333953. ARRY-371797 was predicted to have moderate-to-good stability in humans with respect to hepatic metabolism and was metabolized in vitro primarily by CYP3A4 and CYP2D6. Other Phase I enzymes (FMOs, amidases, and esterases) were involved in the metabolism of ARRY-371797. ARRY-371797 was a weak inhibitor of 5 major CYP isoforms in vitro. ARRY-371797 was not a time-dependent inhibitor of CYP3A4, nor did it induce in vitro enzymatic activity or messenger ribonucleic acid (mRNA) expression of CYP3A4 or CYP1A2 in hepatocytes. ARRY-371797 was not a substrate or inhibitor of recombinant monoamine oxidase (MAO)-A or MAO-B. AR00333953 was a principal metabolite from in vitro incubations with liver microsomes, hepatocytes, plasma or blood and was also a principal metabolite in vivo.

Other, less abundant, metabolites that were found in vitro or in vivo were a result of oxidative metabolism. No glucuronide conjugates were detected in hepatocyte incubations.

2.2.1.3 Nonclinical Toxicity and Safety

Preclinical toxicological studies have indicated that ARRY-371797 was well tolerated at multiple doses of up to 100 mg/kg twice daily (BID) in rats and monkeys, with gastrointestinal (GI) side effects and minimal clinical pathology changes. Associated histopathology changes were reversible in monkeys treated with doses of up to 100 mg/kg BID for 28 days. Histopathology findings in rats receiving ARRY-371797 for 28 days were partially reversible with respect to severity and incidence at the 100 mg/kg BID (200 mg/kg/day) dose level. In the chronic dosing studies for up to 6 months in the rat and 9 months in the monkey at doses up to 30 mg/kg BID, there were no significant adverse histopathology findings. In general, administration of ARRY-371797 at doses of up to 30 mg/kg BID was tolerated in-life in rats and monkeys in chronic safety studies.

Administration of ARRY-371797 to rats was associated with microscopic findings of skeletal muscle fiber changes, with no effects on clinical chemistry. Evidence of gastric irritation and increased gastric fluid secretion was observed in rats after a single oral dose of 100 mg/kg of ARRY-371797. After treatment with ARRY-371797 for multiple days, evidence of changes in stool consistency, ranging from loose stools to diarrhea was observed in monkeys. The GI disturbances were mild to moderate in the lower dose groups. In most dose groups, these GI effects resolved within 28 days after discontinuation of treatment with ARRY-371797.

In all of the studies that were conducted, ARRY-371797 had no significant effect on vital signs, ophthalmologic examinations, coagulation parameters, troponins or urinalysis parameters after administration of doses of up to 100 mg/kg BID in rats and monkeys for 28 consecutive days and up to 30 mg/kg BID for chronic dosing in rats and monkeys. Occasional increases in liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), total bilirubin, blood urea nitrogen (BUN), glucose levels and decreases in potassium levels were observed in rats after BID administration of ARRY-371797 at doses of up to 100 mg/kg. Mild increases in liver enzymes (ALT and AST) were observed in monkeys. Mild increases in lymphocytes and neutrophils were observed in both rats and monkeys, but these changes did not appear to have any functional or pathological consequences. No electrocardiogram (ECG) abnormalities related to ARRY-371797 administration were observed in monkeys.

There was no evidence of genotoxicity from the 2 in vitro assays (bacterial reverse mutation or mouse lymphoma), nor from the 1 in vivo assay (mouse micronucleus). The genotoxicity tests were conducted at concentrations of the standard limits for these test systems. The embryo-fetal developmental toxicity studies support the exclusion of pregnant women from clinical studies of ARRY-371797 and the continued requirement that women of childbearing potential use appropriate contraception.

2.2.2 Clinical Experience with ARRY-371797

ARRY-371797 has been investigated in 10 completed placebo-controlled clinical studies, including 5 Phase 1 studies in healthy subjects and 5 five studies (one Phase 1b and four Phase 2) in patients with inflammatory disorders. ARRY-371797 is currently undergoing evaluation in a Phase 2 study in stable patients with genetic DCM secondary to *LMNA* mutations, and is also being studied in a single-patient study under a named-patient Investigational New Drug Application (IND) for the treatment of progressive DCM and congestive heart failure.

Detailed information regarding clinical studies of ARRY-371797 is presented in the Investigator's Brochure.

2.2.2.1 Clinical Pharmacokinetics

The clinical PK of ARRY-371797 and AR00333953 have been evaluated in healthy subjects following single- and repeat-dose administration. Following single doses of ARRY-371797, exposure of ARRY-371797 increased in a dose-proportional manner up to the highest dose evaluated (2000 mg total daily dose). After repeat-dose administration, exposure increased in a nearly dose-proportional manner. The maximal plasma concentrations were generally observed ~1 to 2 hours following dose administration with consistent plasma concentration-time profile shapes at all doses evaluated. The $t_{1/2}$ was ~1.5 to 5 hours and was dose-dependent, with longer half-lives at higher doses. Less than 2-fold accumulation was observed (1.3 to 1.8). The metabolite (AR00333953)-to-parent ratio ranged from ~9 to 22. In general, low-to-moderate inter-subject variability was observed for exposure-related PK parameters.

Exposure was also assessed in the rheumatoid arthritis (RA), ankylosing spondylitis (AS), osteoarthritis (OA) and post-surgical pain patient populations. Analysis in the RA population could neither detect nor rule out a significant drug-drug interaction of ARRY-371797 with methotrexate (MTX). In addition, greater exposure of ARRY-371797 and AR00333953 was observed following administration of ARRY-371797 under fasted conditions as compared to fed conditions; however, the clinical significance of this difference is unclear due to the study design and limited data. In patients with OA, AS and postsurgical pain, exposure was evaluated with sparse sampling. Although formal PK analyses were not performed, evaluation of plasma concentration data indicated that exposure to ARRY-371797 was comparable to that in healthy subjects.

2.2.2.2 Clinical Pharmacodynamics

After both single-day and 14-day repeat-dose administration of ARRY-371797 in healthy subjects, inhibition of ex vivo, LPS-induced IL-1β, TNF and prostaglandin E_2 (PGE_2) production was observed, with the greatest degree of inhibition generally observed following the highest doses. IL-6 was also inhibited by ARRY-371797 but to a much lesser extent than IL-1β and TNF.

The observed inhibitory effects of ARRY-371797 on ex vivo LPS-induced cytokine production and prostaglandin levels were generally sustained for at least 4 to 6 hours after single- or repeat-dose oral administration. ARRY-371797 did not appear to have an effect on PGE_2 metabolite or creatinine levels in urine.

2.2.2.3 Clinical Efficacy

In a 29-day Phase 1 study of ARRY-371797 in RA (Clinical Study ARRAY-797-103), an analysis of patient's assessment of arthritis pain suggested that perceived pain was lower in the ARRY-371797 groups than in the placebo group. Decreases from Baseline in the patient assessment of arthritis pain were observed at Day 29 in the 100 mg group (decreases of 30% to 35%) and the 200 mg group (decreases of 29% to 41%). In comparison, decreases of ~5% were observed in the placebo group, although that group had substantially higher Baseline values than either active treatment group.

In two Phase 2 studies (Clinical Study ARRAY-797-221 and Clinical Study ARRAY-797-222) evaluating ARRY-371797 in the treatment of moderate to severe postsurgical dental pain, results demonstrated that ARRY-371797 administered at single doses of 200, 400 and 600 mg was an effective anti-inflammatory agent, clearly superior to placebo in a variety of measures of analgesic efficacy for the treatment of patients with moderate to severe acute postsurgical dental pain. Non-inferiority to celecoxib was not established (Clinical Study ARRAY-797-222).

A Phase 2, randomized, double-blind, double-dummy, active- and placebo-controlled parallel-group study evaluated 4 weeks of treatment with ARRY-371797 in patients with moderate to severe pain due to OA of the knee, despite chronic use of a single nonsteroidal anti-inflammatory drug (NSAIDs). ARRY-371797 demonstrated a statistically significant treatment effect on the primary endpoint, with a least squares (LS)-mean decrease in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score from Baseline to Week 4 of -2.65 for the ARRY-371797 group compared with -1.84 for the placebo group (LS-mean difference = -0.80; p = 0.049 [90% CI: -1.47 to -0.13]). A statistically significant and clinically meaningful reduction in WOMAC pain subscale scores was observed after 1 week of treatment, and the reduction in pain continued to improve numerically through 4 weeks of treatment as compared to placebo. Nearly all secondary endpoints favored the ARRY-371797 treatment group; however, none reached statistical significance. Treatment with ARRY-371797 was also associated with significant reductions in C-terminal cross-linking telopeptide of type I collagen (CTX-I) and cartilage oligomeric matrix protein (COMP), markers of bone resorption and cartilage degradation, suggesting a possibility for disease-modifying activity, which warrants further investigation.

The efficacy and safety of ARRY-371797 is being investigated in a single named-patient IND. A male patient with progressive DCM and congestive heart failure is being treated with 400 mg BID for an indefinite duration. After 6 months the patient had an improvement in his clinical

symptoms from New York Heart Association (NYHA) class II to class I and an improved LVEF and right ventricular fractional shortening (RV-FS) from Baseline.

To further evaluate the activity of ARRY-371797, a Phase 2 study in stable patients with genetic DCM secondary to *LMNA* mutations has been initiated.

2.2.2.4 Clinical Safety

Five Phase 1 safety, PK and pharmacodynamics (PD) studies of ARRY-371797 in healthy subjects have been completed (Clinical Study ARRAY-797-101, Clinical Study ARRAY-797-102, Clinical Study ARRAY-797-104, Clinical Study ARRAY-797-107 and Clinical Study ARRAY-797-108). ARRY-371797 demonstrated an acceptable safety profile when administered at single doses up to 900 mg once daily (QD), up to 400 mg/day for 14 days and up to 2000 mg/day for 7 days. In these studies, the most commonly reported adverse events (AEs) in subjects receiving ARRY-371797 were dizziness, headache, diarrhea, nausea and acne; the incidence of these AEs was not clearly related to the ARRY-371797 dose nor to the duration of exposure.

In patients with RA receiving stable doses of MTX who received doses of 100 or 200 mg BID of ARRY-371797 or placebo for 29 days, the primary AEs reported by patients receiving ARRY-371797 were diarrhea and nausea (Clinical Study ARRAY-797-103). In a 12-week study of patients with AS (Clinical Study ARRAY-797-201), events reported most commonly by patients receiving doses of 100 or 200 mg BID or 400 mg QD of ARRY-371797 were stomach discomfort, pharyngeal erythema, peripheral edema and dizziness. In studies of postsurgical dental pain (Clinical Study ARRAY-797-221 and Clinical Study ARRAY-797-222), events reported most commonly by patients receiving doses of 200, 400 or 600 mg ARRY-371797 were nausea, vomiting, dizziness and headache. In patients with knee pain due to OA despite chronic use of an NSAID who received 400 mg BID of ARRY-371797 for 4 weeks (ARRAY-797-223), the most common AEs were dizziness, diarrhea, nausea, somnolence, constipation, headache, insomnia and stomatitis.

No clinically meaningful association has been observed between treatment with ARRY-371797 and abnormalities in hematology or urinalysis parameters. Mild elevations in creatine phosphokinase (CPK) and AST have been noted in 1 study (ARRAY-797-223). In the same study, mild reduction in mean arterial pressure was also noted. No other association between treatment with ARRY-371797 and changes in vital signs in any of the clinical studies has been observed. While there is no nonclinical evidence for corrected QT interval (QTc) prolongation, in a pooled analysis across clinical studies, there is some evidence for dose-related prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF), compared with placebo in patients receiving ARRY-371797. The magnitude of mean placebo-adjusted QTcF prolongation at the projected therapeutic dose of 400 mg BID or lower is about 8 ms or less while at supra-therapeutic doses of up to 500 mg q6h, the magnitude is about 20 to 25 ms.

2.3 Rationale for the Study

The p38 MAPK family is involved in the regulation of a number of diverse cellular functions in a variety of cell types in all eukaryotes from yeast to humans. Classical MAPK signaling occurs in cascades, involving MAPKs that are activated by MAPK kinases (MAPKK), which are in turn activated by MAPK kinase kinases (MAP3K). These latter kinases are activated by multiple extracellular stimuli, particularly cell stressors such as bacterial endotoxins, osmotic shock, cytotoxic agents and pro inflammatory cytokines. Subsequent downstream activation of p38 MAPK leads to a multiplicity of responses such as the activation of transcription factors and other kinases, resulting in prostaglandin and cytokine production, cell cycle arrest, cell differentiation and/or apoptosis.[12,13] Since p38 MAPK and p38α, in particular, appear to play a central role in the cellular response to stress, inhibitors of this pathway have been evaluated predominantly in the context of treating inflammatory diseases.[14,6]

In addition to its role in inflammation, activation of the p38 MAPK pathway has been linked to aberrant cardiovascular function in patients with DCM due to *LMNA* gene mutations. Nonclinical studies using genetically modified mouse models have identified important molecular mechanisms of disease in *LMNA*-related DCM. For example, homozygote knock-in mice expressing a human *LMNA* mutation associated with cardiomyopathy, (*LMNA*H222P/H222P mice) develop LV dilatation and depressed contractile function starting at 8 to 10 weeks of age. This phenotype is associated with abnormal activation of the extracellular signal-regulated kinase (ERK), the c-Jun N-terminal kinase (JNK), and the p38α branches of the MAPK signaling cascade in cardiomyocytes.[8,15,16] When mice with *LMNA*-related DCM were treated with p38 MAPK inhibitors, such as ARRY-371797, they demonstrated improved cardiac function and survival.[17] Upregulation of p38 MAPK has also been reported in the hearts from human patients with *LMNA*-related DCM.[15]

Progress reports that include echocardiographic findings are being obtained in an ongoing single-patient IND (Sponsor: Meriter Medical Group; IND 117,699) in which a male patient with DCM and CSD due to *LMNA* mutation (*LMNA*-related DCM with CSD) is receiving the p38α MAPK inhibitor, ARRY-371797. After 3 months of BID oral treatment, this patient has demonstrated improvements that appear similar to the cardiac functional improvements observed in the mutant mouse model studies.

Based on these nonclinical and single-patient data, Array BioPharma considers that inhibition of p38 MAPK with the selective p38 α inhibitor ARRY-371797 may provide a novel therapeutic approach and has the potential to fill an unmet medical need for the treatment of cardiovascular dysfunction in patients with progressive *LMNA*-related DCM.

The current open-label rollover study (Clinical Study ARRAY-797-001) 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 (the “parent

study") and may, in the investigator's opinion, derive benefit from continued treatment.
In addition, to allow evaluation of plasma concentrations associated with the original capsule formulation as well as a new tablet formulation, patients enrolling in the current study from Clinical Study ARRAY-797-231 will undergo plasma concentration measurements at the Screening Visit (i.e., following an extended treatment period with the capsule formulation) and at 12 and 24 weeks (i.e., after transition to the tablet formulation).

2.4 Dose Selection

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

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- Evaluate the safety of ARRY-371797 administered after completion of the parent study

3.1.2 Secondary Objectives

- Evaluate measures of efficacy of ARRY-371797
- Determine the exposure of ARRY-371797 and metabolites

3.2 Study Endpoints

3.2.1 Primary Endpoint

- 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

3.2.2 Secondary Endpoints

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

- 6-minute walk test (6MWT)
- Left ventricular end systolic volume index (LVESVI)
- Left ventricular (LV) end diastolic volume index
- 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)

In patients previously receiving ARRY-371797 capsules in Clinical Study ARRAY-797-231:

- 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

4.0 STUDY DESIGN

4.1 Study Design Overview

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 Doses and Schedule of Administration

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).

4.3 Blinding

Not applicable.

4.4 Estimated Study Duration

Patients may continue receiving ARRY-371797 as long as no treatment discontinuation criteria are met.

4.5 Data Monitoring Committee

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(ies) evaluating ARRY-371797.

5.0 PATIENT POPULATION

The eligibility criteria described in this study protocol are designed to identify patients for whom treatment is considered appropriate. All relevant medical and nonmedical conditions should be considered when deciding whether a patient is suitable for enrollment in the study.

Questions regarding patient eligibility should be addressed to the Sponsor prior to enrollment. Patients must fulfill all of the following inclusion criteria and none of the exclusion criteria to be eligible for admission to the study.

5.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for enrollment in the study.

1. Provide a personally signed and dated informed consent document prior to initiation of any study-related procedures that are not considered standard of care.

2. Received ARRY-371797 as treatment for genetic dilated cardiomyopathy secondary to *LMNA* mutations in a clinical study sponsored by Array BioPharma.

3. May, in the opinion of the Investigator, benefit from continued ARRY-371797 treatment.

4. Male patients and female patients of childbearing potential must agree to use a highly effective method of contraception.

5. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

5.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible for enrollment in the study.

1. Discontinued treatment in the parent study for any reason other than study completion or Sponsor termination of the study.

2. Pregnant or breastfeeding women.

3. Local access to commercially available ARRY-371797.

5.3 Lifestyle Guidelines

5.3.1 Requirements for Contraception

5.3.1.1 Contraception Requirements for Female Patients

Female patients of non-childbearing potential are not required to use contraception. To be considered of non-childbearing potential, a female patient must meet at least one of the following criteria:

- Postmenopausal AND at least 55 years old.
- Postmenopausal AND a follicle-stimulating hormone (FSH) value > 30 IU/L at the Screening Visit of the parent study.
- Hysterectomy OR bilateral oophorectomy.
- Tubal ligation at least 5 years prior to the Screening Visit with no subsequent pregnancies.

Female patients of childbearing potential are required to use one of the following methods of contraception:

- Hormonal contraceptive (e.g., oral, injected, intrauterine, extrauterine [e.g., vaginal ring], transdermal or implanted) for at least 2 full cycles prior to first dose of study drug until 30 days after the last dose of study drug.
- Any of the following mechanical contraceptive methods for at least 14 days prior to first dose of study drug until 30 days after the last dose of study drug:
    - Copper-containing intrauterine device (IUD).
    - Diaphragm with spermicidal foam/gel/film/cream/suppository.
    - Vaginal condom with spermicidal foam/gel/film/cream/suppository.
    - Cervical cap with spermicidal foam/gel/film/cream/suppository.

In addition, female patients of childbearing potential must instruct male partners, even those who have undergone vasectomy, to use a condom.

5.3.1.2 Contraception Requirements for Male Patients

Male patients, even those who have undergone vasectomy, are required to use a condom as contraception with female partners of childbearing potential from the first dose of study drug through 90 days after the last dose of study drug.

In addition to using a condom, male patients must ensure that female partners of childbearing potential use another form of contraception as described in Section 5.3.1.1.

5.3.2 Restrictions on Physical Activity and Other Activities

Patients should abstain from strenuous exercise (e.g., heavy lifting, weight training and aerobic activity) for 48 hours prior to each blood collection for clinical laboratory tests.

Male patients are restricted from sperm donation until 90 days after last dose of study drug.

5.4 Prior and Concomitant Medications

Ancillary treatments will be administered according to labeled instructions as medically indicated for patients. All concomitant medications will be recorded in the electronic case report form (eCRF) using generic drug names when possible.

Concomitant medications can be administered at the Investigator's discretion to conform to standard practice during the treatment period. Caution should be used when initiating treatment with a drug known to prolong QT intervals.

As with any novel therapeutic for which limited clinical experience exists, Investigators should exercise caution when prescribing concomitant medications.

6.0 STUDY TREATMENT

6.1 Study Drug Supply

6.1.1 Manufacturing and Formulation

ARRY-371797 is supplied as 2 different manufactured drug products:

- Formulated granules in Size "0" Swedish Orange opaque, hard gelatin capsules in 100 mg and 200 mg dose strengths.
- Brown capsule-shaped film-coated tablets in 100 mg dose strength.

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.

All treatments must be processed by a pharmacist or by appropriately trained and designated study personnel. Instructions for dose calculations will be provided to the pharmacist or designee before study initiation.

6.1.2 Packaging and Labeling

ARRY-371797 will be packaged in bottles with a pre-counted number of capsules or tablets required for the appropriate dosage and treatment duration between visits. Detailed instructions for storage, handling and accountability of study drug will be provided in the Pharmacy Manual.

6.1.3 Shipping, Storage and Handling

ARRY-371797 capsules and tablets should be stored at room temperature (15 to 30°C).

Labeled, packaged study drug will be shipped to each site by the Sponsor or designee following receipt of the necessary regulatory documents. The Investigator or an approved representative (e.g., registered pharmacist, trained and delegated study coordinator) will ensure that all study drugs are stored as outlined in the Pharmacy Manual and in accordance with applicable regulatory requirements. The drug storage area at the site must be secure, with access limited to authorized personnel.

Stability studies to support drug storage conditions have been conducted by the Sponsor or an affiliate. The Sponsor will continue to monitor the stability of the study drug and will alert the site if a lot is nearing the end of its anticipated shelf life.

Detailed instructions for storage and handling of study drug will be provided in the Pharmacy Manual.

6.1.4 Accountability and Return of Study Drug Supply

The Investigator or an approved representative (e.g., pharmacist) must maintain accurate records of dates and quantities of study drug received, to whom study drug is dispensed (patient-by-patient accounting), and accounts of any study drug accidentally or deliberately destroyed. The Investigator must retain all unused or expired study drug supplies until the study monitor has confirmed the accountability data. If a site's policy prohibits holding study drug supplies for monitor review, then a copy of the standard operating procedure (SOP) for processing drug returns must be provided to the Sponsor.

Study drug will be returned to the Sponsor for destruction, as outlined in the Pharmacy Manual. If a site's policy prohibits returning study drug for destruction by the Sponsor (e.g., it is destroyed locally), then a copy of the SOP for drug destruction must be provided to the Sponsor.

To ensure adequate records, all study drug will be accounted for on a drug accountability inventory form as instructed by the Sponsor. Refer to the Pharmacy Manual for details on how to process all unused or expired study supplies.

6.2 Study Drug Dispensing and Administration

Dosing should occur at roughly the same time each day and occur every 12 hours ± 2 hours. When administered at clinic visits, study drug should be given after all questionnaires have been completed and blood samples for clinical laboratory assessments have been collected.

Study drug is to be taken orally with or without food. Patients will swallow the study drug whole, and will not chew the capsule(s) or tablet(s) prior to swallowing.

Complete dosing instructions, including the timing of study drug administration, dosing in relation to meals and instructions for missed doses, will be provided in the Pharmacy Manual.

6.3 Dose Modification

If a patient's machine-read triplicate ECG includes 2 or more individual ECGs with a QTcF value > 500 msec, or QTcF 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. 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).

If the over-read mean triplicate value of both parameters is ≤ 500 msec, study drug administration may resume. Whenever possible, the over-read should be completed promptly in order to avoid or minimize treatment interruption.

If the over-read value 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.

6.4 Treatment Compliance

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.

7.0 STUDY PROCEDURES AND ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section in narrative form, described by study visit in Section 8.0 and summarized in Table 2. Detailed instructions regarding all laboratory procedures, including collection and handling of samples, will be included in the Laboratory Manual.

Written informed consent must be granted by each patient prior to the initiation of any study procedure or assessment (other than those considered standard of care).

7.1 Screening Assessments

Screening assessments for determination of patient eligibility will be performed at the last visit in the treatment period of the parent study (e.g., the Week 48 visit of Clinical Study ARRAY-797-231). Assessments performed at that visit will represent the patient's Baseline values for the current study.

7.2 Safety Assessments

7.2.1 Adverse Events

Adverse events will be assessed by direct observation and patient interviews. Patients should be questioned using non-leading questions. Assessment and reporting of AEs is described in detail in Section 10.0.

7.2.2 Medical History

The patient's medical history documented in the parent study will be transferred to the eCRF of the current study.

7.2.3 Physical Examination

Physical examinations will be performed by trained medical personnel at the time points specified in Table 2. General physical well-being will be assessed by brief evaluation of the head, eyes, ears, nose, throat (HEENT), skin, cardiovascular (including assessment of peripheral pulses, heart, bruits, edema), lungs, abdomen, extremities and other conditions of note. Weight will be measured at every assessment. Height will be measured at the Screening Visit only.

7.2.4 Vital Signs

Vital sign measurements (BP, PR and temperature as appropriate) will be collected according to institutional standards at the time points specified in Table 2. When vital signs are to be collected at the same time point as a blood collection, vital signs should be collected first.

At each visit, sitting systolic and diastolic BP and PR will be measured and recorded on the eCRF. Sitting BP will be measured with the patient's arm supported at the level of the heart, and recorded to the nearest mm Hg after 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. The same size BP cuff and method (automated or manual), which has been properly sized and calibrated, will be used to measure BP throughout the study. The use of automated devices for measuring BP and PR is preferred; when done manually, PR will be measured in the brachial or radial artery for at least 30 seconds. Baseline BP is defined as the systolic and diastolic BP measures performed at the Screening Visit (i.e., the last assessment in the parent study) and will serve as the comparator for values obtained at later visits.

7.2.5 Electrocardiogram

Triplicate 12-lead ECGs will be performed at the time points specified in Table 2. At each measurement, three serial ECGs will be obtained over a period of 5 to 10 minutes. All ECGs will be over-read by the Investigator. The mean of the over-read triplicate ECG measurements performed at the Screening Visit (i.e., the last assessment in the parent study) will serve as each patient's Baseline value for all post-dose comparisons.

When ECGs are to be performed at the same visits as study drug administration, blood collection and/or vital sign measurements, ECGs should be performed first. Abnormal ECGs may be repeated at the Investigator's discretion.

In some cases, it may be appropriate to repeat abnormal ECGs. If a machine-read corrected QT value (QTc) is prolonged, repeat measurements may not be necessary if the Investigator's interpretation determines that the QTc values is in the acceptable range. Interpretation will be documented on the ECG source and signed and dated by the reader.

7.2.6 Pregnancy Test

All females of childbearing potential are required to undergo urine pregnancy assessment at the Screening Visit and during the study at the time points specified in Table 2. Any positive test will result in immediate study drug discontinuation. Women of non-childbearing potential (see Section 5.3.1.1) do not require pregnancy tests.

Urine collections and testing for pregnancy occurring on dosing days must be performed prior to study drug administration.

7.2.7 Clinical Laboratory Tests

7.2.7.1 Hematology and Chemistry

Blood and urine samples for the laboratory tests listed in Table 1 will be collected as outlined in Section 8.0 and at the time points specified in Table 2. Additional clinical laboratory tests for safety can be obtained at any time during the study at the Investigator's discretion. Clinically significant findings at the final assessment should be followed to resolution or stabilization.

All blood and urine collections occurring on dosing days must be performed prior to study drug administration.

Table 1: Summary of Clinical Laboratory Tests

Hematology	Chemistry	Others
Hemoglobin	Albumin	If applicable:
Hematocrit	Alkaline phosphatase	• Urine pregnancy test
RBC	AST	
Platelets	GGT	
WBC	ALT	
Neutrophils	Bicarbonate (CO_2)	
Lymphocytes	Total bilirubin	
Monocytes	BUN	
Eosinophils	Calcium	
Basophils	Chloride	
	CK	
	Creatinine	
	Glucose	
	Magnesium	
	Inorganic Phosphate	
	Potassium	
	Total protein	
	Sodium	
	Uric acid	
	Direct bilirubin (if total bilirubin values are abnormal)	
	NT-proBNP	
	Troponins	

7.2.7.2 Urinalysis

Urinalysis will not be performed during this study. However, urinalysis results from the last visit in the treatment period of the parent study will be captured on the eCRF as the patient's Baseline urinalysis values.

7.3 Efficacy Assessments

7.3.1 6-Minute Walk Test

The 6MWT will be performed at the time points specified in Table 2.

The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes, evaluating the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility. The test should be performed at approximately the same time of day when assessed and by the same evaluator whenever possible.

7.3.2 Echocardiogram Complete with Contrast

The 2-dimensional (2D) echocardiogram complete with contrast will be performed by trained personnel at the time points specified in Table 2.

These assessments will be standard transthoracic 2D echocardiograms (with contrast to optimize accuracy and precision of intracardiac measurements) and will include:

1. Left ventricular: systolic and diastolic function; size, mass and geometry.
2. Right ventricular size and function; pulmonary artery size.
3. Left atrial dimensions, volumes and pressures.
4. Valvular (aortic, mitral, tricuspid and pulmonary) stenosis and regurgitation (severity).

7.3.3 SF-36

The SF-36 questionnaire will be completed at the time points specified in Table 2.

Patients complete 36 questions to measure functional health and well-being from the patient's point of view. The SF-36 provides scores for each of 8 health domains and psychometrically based physical and mental component summary scores. The questionnaire takes approximately 5 to 10 minutes to complete.

7.3.4 QOL KCCQ

The QOL KCCQ questionnaire will be completed at the time points specified in Table 2.

The QOL 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.

7.4 Pharmacokinetic Assessments

For patients who previously participated in Clinical Study ARRAY-797-231, blood collection for measurement of plasma concentrations of ARRY-371797 and metabolites will be drawn at the time points specified in Table 2. Complete instructions for sample processing, handling and shipment will be provided in the Laboratory Manual.

8.0 SCHEDULE OF PROCEDURES AND ASSESSMENTS

The procedures and assessments that will be conducted during this study are described in this section by study visit, described in narrative form in Section 7.0 and summarized in Table 2. Detailed instructions regarding all laboratory procedures, including collection and handling of samples, will be included in the Laboratory Manual.

During screening, a unique 14-digit number (based on the study number and patient number from the parent study) will be assigned to each patient who provides written informed consent. The unique 14-digit number will be the parent study number (e.g., 797-231) followed by the parent study patient number (e.g., 1020-0002), with a hyphen as a connector (e.g., 797-231-1020-0002). The patient will be identified by that number for the duration of the study.

At the site, the Investigator will maintain a log for all screened patients (including patients who fail screening after providing written informed consent) and all enrolled patients.

8.1 Screening Visit (Final Visit in Parent Study)

At the final visit in the parent study, the Investigator (or an appropriate delegate at the study site) will obtain written informed consent from each patient, after which confirmation of eligibility criteria will be performed. The following assessments, performed as part of the final visit in the parent study, will be documented on the eCRF for the current study to serve as the patient's Baseline values.

- Medical history (information documented in the parent study will be transferred to the eCRF of the current study)
- Recording of prior/concomitant medications, including all prescription and nonprescription drugs, vitamins, and dietary or herbal supplements
- Physical examination including height and body weight
- Vital sign measurement
- Triplicate 12-lead ECG
- Collection of hematology/chemistry blood sample
- 6MWT
- Echocardiogram
- SF-36 and QOL KCCQ

- Urine pregnancy test prior to dosing (females of childbearing potential only)
- Urinalysis
- Assessment of AEs
- Patients who previously participated in Clinical Study ARRAY-797-231 only: Collection of PK blood sample pre-dose (after vital sign measurement) and 1 to 2 hours post-dose

Following confirmation of eligibility and enrollment into the current study, study drug will be dispensed (initial dose in clinic).

8.2 Study Period

8.2.1 Weeks 12 and 36

- Recording of concomitant medications
- Physical examination including body weight
- Vital sign measurement
- Triplicate 12-lead ECG
- Collection of hematology/chemistry blood sample
- Urine pregnancy test prior to dosing (females of childbearing potential only)
- Dispense study drug (initial dose in clinic)
- Assessment of AEs
- Patients who previously participated in Clinical Study ARRAY-797-231 only: Collection of PK blood sample pre-dose (after vital sign measurement) and 1 to 2 hours post-dose (Week 12 only)

8.2.2 Weeks 24, 48, 72, 96

- Recording of concomitant medications
- Physical examination including body weight
- Vital sign measurement

- Triplicate 12-lead ECG
- Collection of hematology/chemistry blood sample
- 6MWT
- Echocardiogram
- SF-36 and QOL KCCQ
- Urine pregnancy test prior to dosing (females of childbearing potential only)
- Dispense study drug (initial dose in clinic)
- Assessment of AEs
- Patients who previously participated in Clinical Study ARRAY-797-231 only: Collection of PK blood sample pre-dose (after vital sign measurement) and 1 to 2 hours post-dose (Week 24 only)

8.2.3 Every 24 Weeks After Week 96

- Recording of concomitant medications
- Physical examination including body weight
- Vital sign measurement
- Triplicate 12-lead ECG
- Collection of hematology/chemistry blood sample
- Urine pregnancy test prior to dosing (females of childbearing potential only)
- Dispense study drug (initial dose in clinic)
- Assessment of AEs

8.3 Termination Visit

A Termination Visit should be completed as soon as possible after study drug discontinuation and every effort should be made to perform the following procedures:

- Recording of concomitant medications

- Physical examination including body weight
- Vital sign measurement
- Triplicate 12-lead ECG
- Collection of hematology/chemistry blood sample
- 6MWT (if not performed for another visit within 30 days prior to the Termination Visit)
- Echocardiogram (if not performed for another visit within 30 days prior to the Termination Visit)
- SF-36 and QOL KCCQ (if not performed for another visit within 30 days prior to the Termination Visit)
- Urine pregnancy test (females of childbearing potential only)
- Assessment of AEs

8.4 Follow-Up Visit 30 Days After Last Dose

- Recording of concomitant medications
- Physical examination including body weight
- Vital sign measurement
- Triplicate 12-lead ECG
- Collection of hematology/chemistry blood sample
- Urine pregnancy test (females of childbearing potential only)
- Assessment of AEs

Table 2: Schedule of Events

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.

9.0 TREATMENT DISCONTINUATION

9.1 Treatment Discontinuation for Individual Patients

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 discontinue study treatment if, in the opinion of the Investigator, it is not in the best medical interest of the patient to continue treatment. Wherever possible, procedures and evaluations scheduled to occur at the Termination and Follow-up visits should be conducted. The Sponsor should be notified of all study treatment withdrawals in a timely manner. The Sponsor may also request that a patient be removed from study treatment 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. The study staff must determine whether the patient will allow further study-related contact (e.g., scheduling of a Follow-up Visit). These decisions along with the date and stated reason for withdrawal of consent must be documented.

If a patient does not withdraw consent to participate in the study, a Termination 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 3 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.

9.2 Sponsor Discontinuation Criteria

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.

10.0 ADVERSE EVENTS

10.1 Adverse Event

An AE is any untoward medical occurrence, including the exacerbation of a pre-existing condition, in a patient administered a pharmaceutical product regardless of causality.

10.2 Serious Adverse Event

An 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.

10.3 Clarifications to Serious Adverse Event Reporting

- Death is an outcome of an SAE and not an SAE in itself. When death is an outcome, report the event(s) resulting in death as the SAE term (e.g., “pulmonary embolism”). If the cause of death is unknown, report “Death, unknown cause” as the SAE term.
- Pre-planned or elective hospitalizations are excluded from SAE reporting. In addition, emergency room visits and admissions under 23-hour observation are excluded from SAE reporting; however, such events should still be reported on the appropriate AE eCRF page.

10.4 Assessment of Severity

The severity rating of an AE refers to its intensity. The severity of each AE will be categorized using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Intensity should be assigned a grade of 1 through 4, as outlined by the guidelines in Appendix 1.

10.5 Assessment of Causality

Medical judgment should be used to determine 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; one or more of the following criteria apply:

- The event follows a reasonable temporal sequence from administration of study drug.
- The event could not be reasonably attributed to the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- The event follows a known pattern of response to study drug.
- The event disappears or decreases on cessation or reduction in dose of the study drug. (It should be noted that in some situations an AE will not disappear or decrease in intensity upon discontinuation of study drug despite other clear indications of relatedness).
- The event reappears or worsens when the study drug is re-administered.

No (unlikely, probably not related or definitely not related): there is no reasonable possibility that the study drug caused the event; one or more of the following criteria apply:

- The event does not follow a reasonable temporal sequence from administration of study drug.
- The event could be reasonably attributed to the known characteristics of the patient's clinical state, concurrent illness, environment or toxic factors or other modes of therapy administered to the patient.
- The event does not follow a known pattern of response to study drug.
- The event does not disappear or decrease on cessation or reduction in dose of the study drug, and it does not reappear or worsen when the study drug is re-administered.

10.6 Overdose

An overdose of study drug (whether symptomatic or asymptomatic) will be reported as an AE.

10.7 Pregnancy or Drug Exposure During Pregnancy

If a patient becomes pregnant during the study, administration of study drug is to be discontinued immediately.

Pregnancies (both those of female patients and female partners of male patients) must be reported to the Sponsor within 24 hours of the Investigator's knowledge using the Clinical Pregnancy Report form. All pregnancies will be followed through to outcome and the outcome must be reported to the Sponsor using the Clinical Pregnancy Outcome Report.

Pregnancies themselves are not considered AEs or SAEs. However, any AEs or SAEs occurring during pregnancy are to be reported using the appropriate AE or SAE form.

10.8 Clinical Laboratory Abnormalities

Clinical laboratory abnormalities will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (Appendix 1) and appropriate reference range(s). All abnormal values assessed to be of clinical concern and at least possibly related to study drug or of uncertain causality must be repeated. Persistent abnormal values and changes of possible clinical concern that remain within the normal range should be followed at the discretion of the Investigator.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if an action on the study drug is made as a result of the abnormality, if intervention for management of the abnormality is required, or at the discretion of the Investigator.

10.9 Reporting of Serious and Nonserious Adverse Events

All AEs, serious and nonserious, will be fully documented on the appropriate eCRF. For each AE, the Investigator must provide its duration (start and end dates or ongoing), intensity, assessment of causality and whether specific action or therapy was required.

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.

All SAEs, regardless of relationship to study drug, must be reported to the Sponsor within 24 hours of the Investigator's knowledge. This should be done by faxing the completed SAE Form to the Sponsor at the number provided on the SAE report fax cover sheet.

Investigators must follow patients with AEs/SAEs until the event has resolved, the condition has stabilized, withdrawal of consent, the patient is lost to follow-up, or completion of the Follow-up Visit. Nonserious AEs do not need to be followed beyond the Follow-up Visit.

If the patient dies, this should be captured as the outcome of the associated SAE. If the cause of death is unknown, death will be reported as a separate event. If a patient is lost to follow-up, this should be captured accordingly within the AE eCRF and on a follow-up SAE report.

10.10 Review of Safety Data

The Medical Monitor and the Sponsor's Drug Safety Department will be responsible for the ongoing review and evaluation of safety data, including AEs, laboratory data, and any other safety evaluations, throughout the duration of the study.

11.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

11.1.1 General Considerations

A detailed statistical analysis plan (SAP) will be finalized prior to database lock.

11.1.2 Safety Analysis

The Safety Population will consist of all patients who receive at least 1 dose of study drug.

Safety data will be presented in tabular and/or graphical format and summarized descriptively by study day, where appropriate.

Adverse events, including deaths due to any cause, ECG, vital signs and laboratory data will be summarized. All AE, ECG and safety laboratory abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively where appropriate. Absolute value data and change from Baseline data will be summarized as appropriate.

Severity of AEs and laboratory abnormalities will be graded using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, as appropriate. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Incidence tables of patients with AEs will be presented for all AEs by maximum severity, serious AEs, AEs assessed as related to study drug and AEs resulting in discontinuation of study drug. Changes in ECG and laboratory measurements will be summarized.

Listings of all safety data sorted by patient and assessment date will be provided.

11.1.3 Efficacy Analysis

All efficacy endpoints are considered secondary endpoints (Section 3.2.2). Descriptive statistics for efficacy endpoints will be reported at 24, 48, 72 and 96 weeks and termination visit (if applicable).

11.1.4 Pharmacokinetic Analysis

Plasma concentrations of ARRY-371797 and its metabolites will be summarized using descriptive statistics. Metabolite-to-parent ratio and drug accumulation will be assessed as appropriate. Results may also be used for separate cross-study analyses. Any additional cross-study analyses will be outlined in a separate analysis plan.

12.0 DATA RECORDING, RETENTION AND MONITORING

12.1 Case Report Forms

Data will be collected using an electronic data capture system (EDC) at the clinical site. The Investigator or designee will record data specified in the protocol using eCRFs. Changes or corrections to eCRFs will be made by the Investigator or an authorized member of the study staff according to the policies and procedures at the site.

It is the Investigator's responsibility to ensure eCRFs are complete and accurate. Following review and approval, the Investigator will electronically sign and date the pages. This signature certifies that the Investigator has thoroughly reviewed and confirmed all data on the eCRF. The Investigator is personally responsible for the accuracy and completeness of all data included in the eCRF.

A portable document format (PDF) file of the eCRFs will be provided to the site after all data have been monitored and reconciled. An electronic copy will be archived at the site.

12.2 Data Monitoring

This study will be closely monitored by representatives of the Sponsor throughout its duration. Monitoring will include personal visits with the Investigator and study staff as well as appropriate communications by telephone, fax, mail, email or use of the EDC system, if applicable. It is the monitor's responsibility to inspect eCRFs at regular intervals throughout the study to verify the completeness, accuracy and consistency of the data and to confirm adherence to the study protocol and to Good Clinical Practice (GCP) guidelines. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of this study are resolved promptly. The Investigator and site will permit study-related monitoring, audits, IRB review and regulatory inspection, including direct access to source documents.

It is understood that study monitors and any other personnel authorized by the Sponsor may contact and visit the Investigator and will be permitted to inspect all study records (including eCRFs and other pertinent data) on request, provided that patient confidentiality is maintained and that the inspection is conducted in accordance with local regulations.

Every effort will be made to maintain the anonymity and confidentiality of patients during this study. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor as well as authorized representatives of regulatory authorities to inspect the facilities used in the conduct of this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled in the study.

12.3 Quality Control and Quality Assurance

Quality control procedures will be conducted according to the Sponsor's internal procedures. The study site may be audited by a quality assurance representative of the Sponsor. All necessary data and documents will be made available for inspection.

13.0 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

13.1 Good Clinical Practice

The study will be performed in accordance with the protocol, guidelines for GCP established by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and applicable local regulatory requirements and laws.

13.2 Institutional Review Board Approval

The Investigator must inform and obtain approval from the IRB for the conduct of the study at named sites, the protocol, informed consent documents and any other written information that will be provided to the patients and any advertisements that will be used. Written approval must be obtained prior to recruitment of patients into the study and shipment of study drug.

Proposed amendments to the protocol and aforementioned documents must be submitted to the Sponsor for review and approval, then to the IRB. Amendments may be implemented only after a copy of the approval letter from the IRB has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented prior to receiving Sponsor or IRB approval. However, in this case, approval must be obtained as soon as possible after implementation.

Per GCP guidelines, the Investigator will be responsible for ensuring that an annual update is provided to the IRB to facilitate continuing review of the study and that the IRB is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor.

13.3 Regulatory Authority Approval

The study will be performed in compliance with the requirements of IRBs and each country's regulatory authorities and will also meet all of the requirements of ICH GCP guidance. Amendments to the protocol will be submitted to the relevant regulatory authorities prior to implementation in accordance with applicable regulations.

13.4 Other Required Approvals

In addition to IRB and regulatory authority approval, all other required approvals (e.g., approval from the local research and development board or scientific committee) will be obtained prior to recruitment of patients into the study and shipment of study drug.

13.5 Informed Consent

Informed consent is a process that is initiated prior to the patient's agreeing to participate in the study and continues throughout the patient's study participation. It is the Investigator's responsibility (or designee) to obtain written informed consent from each patient after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any study procedures are initiated. Each patient should be given a copy of the informed consent document and associated materials. The original copy of the signed and dated informed consent document must be retained at the site and is subject to inspection by representatives of the Sponsor or regulatory authorities. If any amendments occur throughout the course of the study that affect the informed consent form (i.e., when new study procedures or assessments have been added), all active patients should be re-consented using the same process for the initial consent.

13.6 Patient Confidentiality

The Investigator must ensure that the patient's privacy is maintained. On the eCRF or other documents submitted to the Sponsor, patients will be identified by a patient number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent documents) should be kept in a confidential file by the Principal Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory authorities and ethics committees to review the portion of the patient's medical record that is directly related to the study. As part of the required content of informed consent documents, the patient must be informed that his/her records will be reviewed in this manner.

13.7 Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Principal Investigator may use this information for the purposes of the study only.

It is understood by the Principal Investigator that the Sponsor will use information obtained in this clinical study in connection with the clinical development program, and therefore may disclose it as required to other clinical investigators and to regulatory authorities. In order to allow the use of the information derived from this clinical study, the Principal Investigator understands that he/she has an obligation to provide complete test results and all data obtained during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

13.8 Publication of Study Data

The conditions regulating dissemination of the information derived from this study are described in the Clinical Trial Agreement.

14.0 ADHERENCE TO THE PROTOCOL

Investigators must apply due diligence to avoid protocol deviations, and the Sponsor (and designee[s]) will not pre-authorize deviations. If the Investigator believes a change to the protocol would improve the conduct of the study, this must be considered for implementation in a protocol amendment. Protocol deviations will be recorded.

14.1 Amendments to the Protocol

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Investigator. The only exception is when the Investigator considers that a patient's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the Investigator should inform the Sponsor and the full IRB within 5 working days after the emergency occurred. All amendments that have an impact on patient risk or the study objectives or require revision of the informed consent document must receive approval from the IRB prior to implementation.

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APPENDIX 1: TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007 Contains Nonbinding Recommendations

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Guidance for Industry
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate
2 Contains Nonbinding Recommendations to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	**Mild (Grade 1)**	**(Moderate(Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

A. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate. **Serum ***	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	100 – 110 110 – 125	111 – 125 126 – 200	>125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1– 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN

Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from Baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from Baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11– 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

APPENDIX 2: NYHA CLASSIFICATIONS

Doctors usually classify patients' heart failure according to the severity of their symptoms. The table below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

NOTE: Class IIIa: No Dyspnea at rest; **Class IIIb**: Recent Dyspnea at rest

SOURCE:

American Heart Association: Classes of Heart Failure

Internet address:
http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX 3: 6-MINUTE WALKING TEST

ARRAY-797-001

Instructions for the Six-Minute Walk Test

SOURCE:

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS MARCH 2002

Am J Respir Crit Care Med Vol 166. pp 111–117, 2002

DOI: 10.1164/rccm.166/1/111

Internet address: www.atsjournals.org

BACKGROUND:

The Six-Minute Walk Test (6MWT) is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

Contraindications and Patient Evaluation Preceding Test

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The

results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Safety Considerations and Precautions for Six-Minute Walk Testing

The following measures should be in place prior to starting the 6MWT at a site:

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following:

(1) chest pain,
(2) intolerable dyspnea,
(3) leg cramps,
(4) staggering,
(5) diaphoresis, and
(6) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TEST PROCEDURES:

LOCATION

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (*See* the Worksheet in Attachment1).

4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

   The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk.
5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* the Borg scale and instructions here).

THE BORG SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation.

   Now I'm going to show you. Please watch the way I turn without hesitation." Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

   "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

   Start now, or whenever you are ready."

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

   After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

   When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

   When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you." When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted.

Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
    (*see* Borg Scale and instructions above in step 5)
11. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

Notes for Sites:

- Whenever possible, the same technician should administer the 6MWT for a given patient, in order to minimize variability on coaching and patient performance
- The technician must use only the standardized phrases for encouragement during the test (as specified previously here).
- If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow.

Attachment 1

6MWT worksheet and report:

Lap counter: __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

Medications taken before the test): _____ Dose:_____ Time:____ : ____

_____ Dose:_____ Time:____ : ____

_____ Dose:_____ Time:____ : ____

_____ Dose:_____ Time:____ : ____

Supplemental oxygen during the test: (circle) No Yes, flow _____ L/min, type _____

	Baseline	End of Test	
Time	___:___	___:___	
Heart Rate	_____	_____	
Dyspnea	____	____	(Borg scale)
Fatigue	____	____	(Borg scale)
SpO2	____ %	____%	

Stopped or paused before 6 minutes? (circle) No Yes, reason: _____

Other symptoms at end of exercise: (circle all that apply) Angina / Dizziness / Hip, leg, calf pain

Number of laps: ____ (_60 meters) Final partial lap: _____ meters

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____%

Tech comments:
Interpretation (including comparison with a pre-intervention 6MWD):

APPENDIX 4: SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activites	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activites (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. **During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much <u>bodily</u> pain have you had during the <u>past week</u>?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

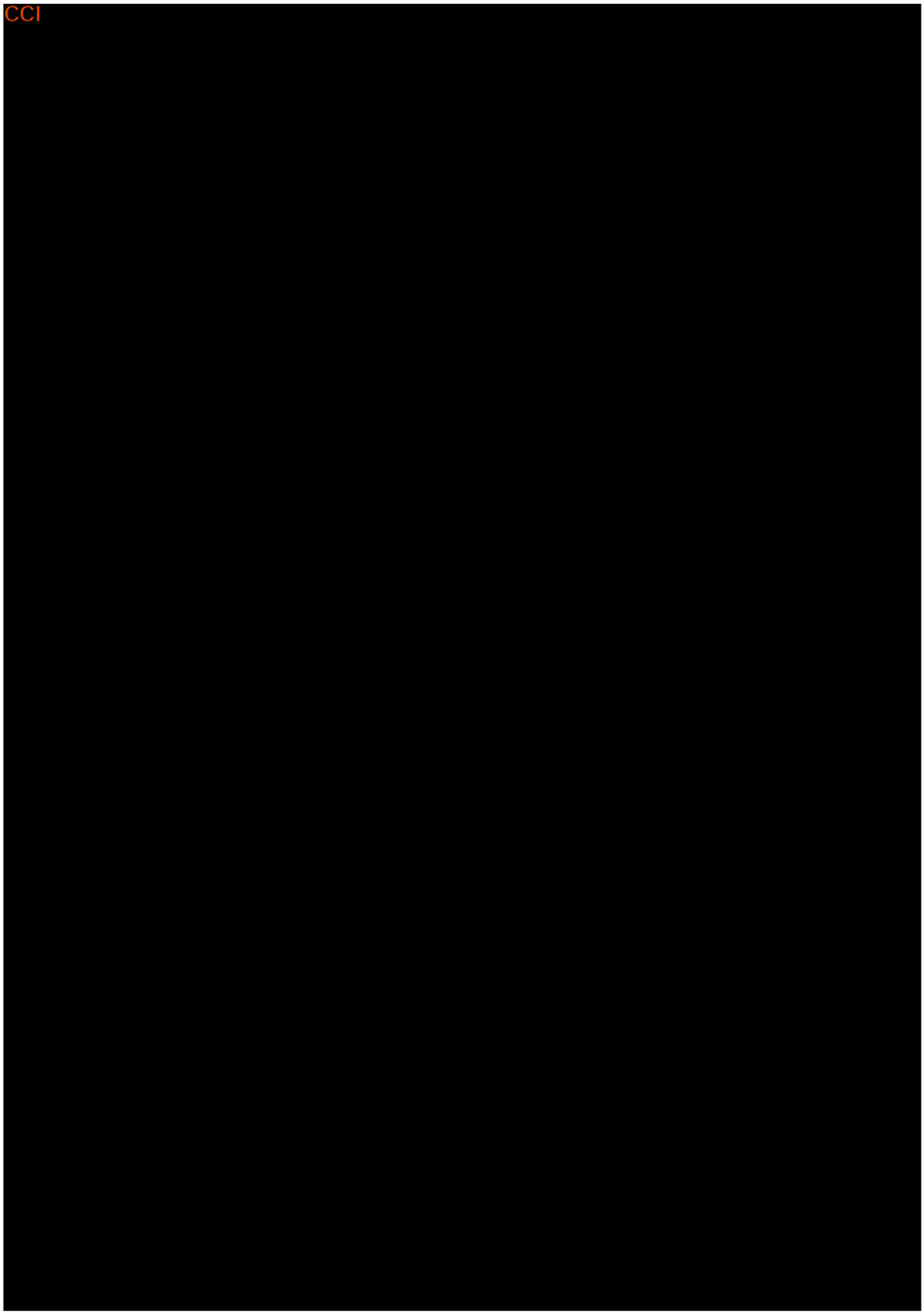
10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!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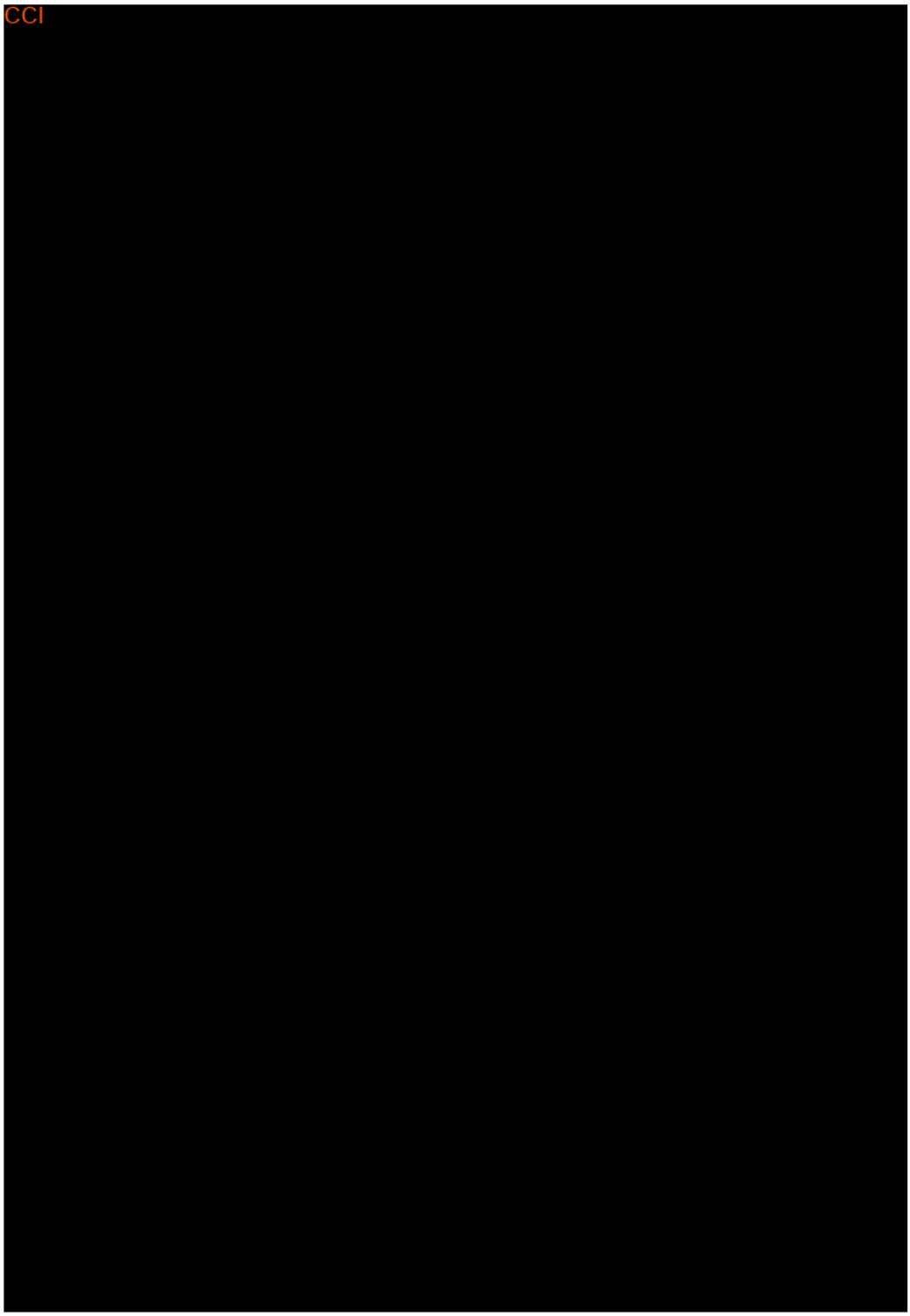
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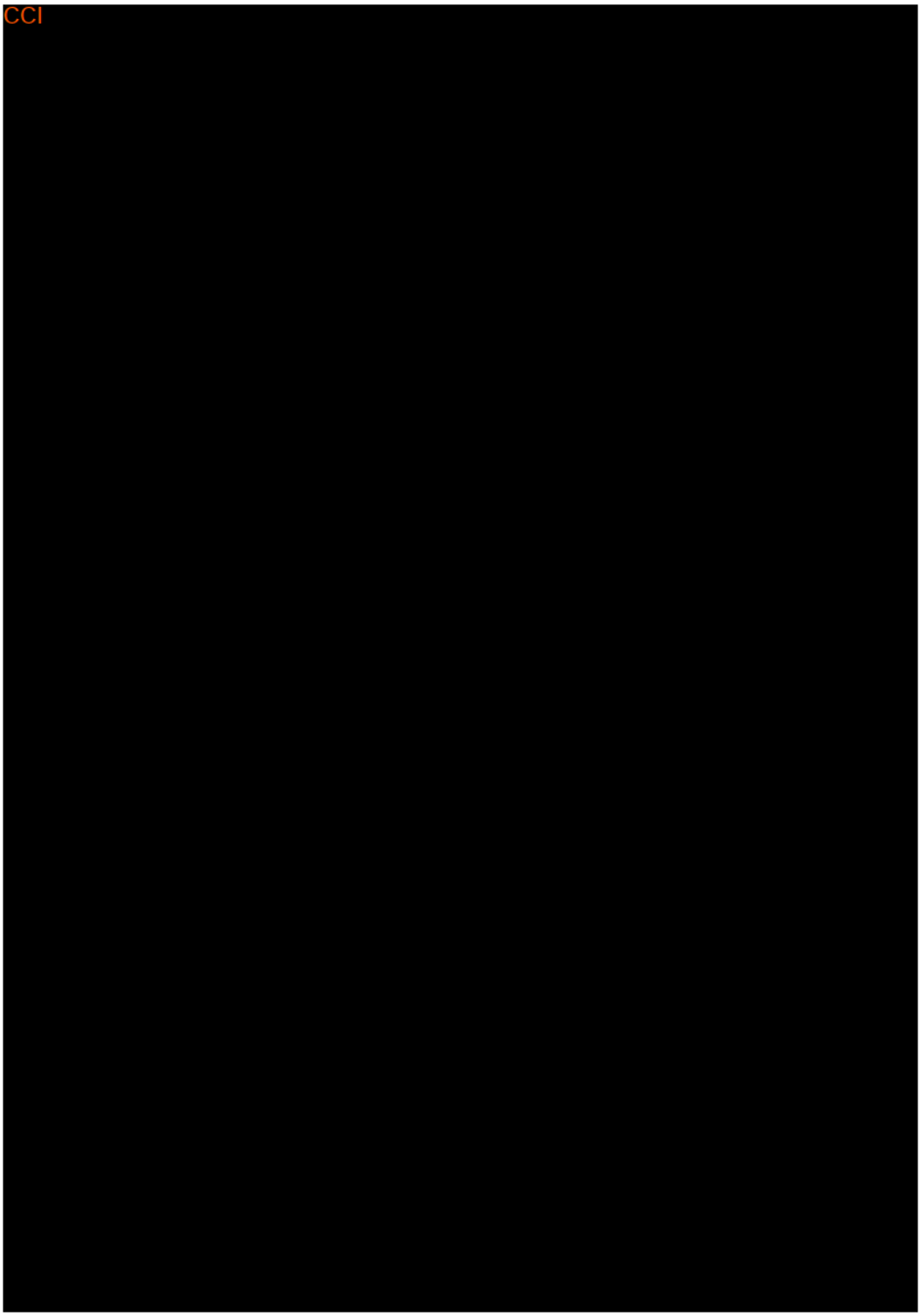
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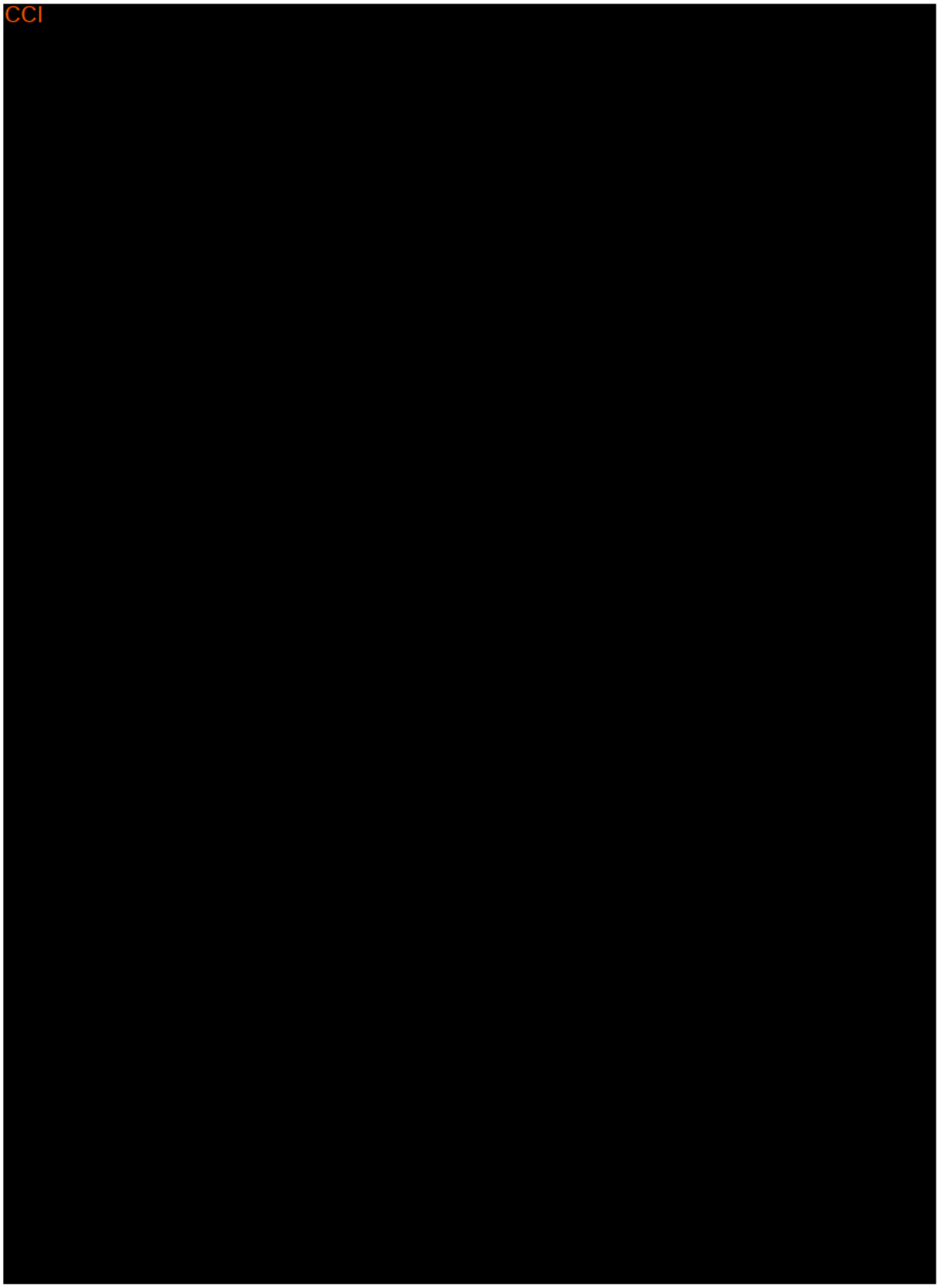
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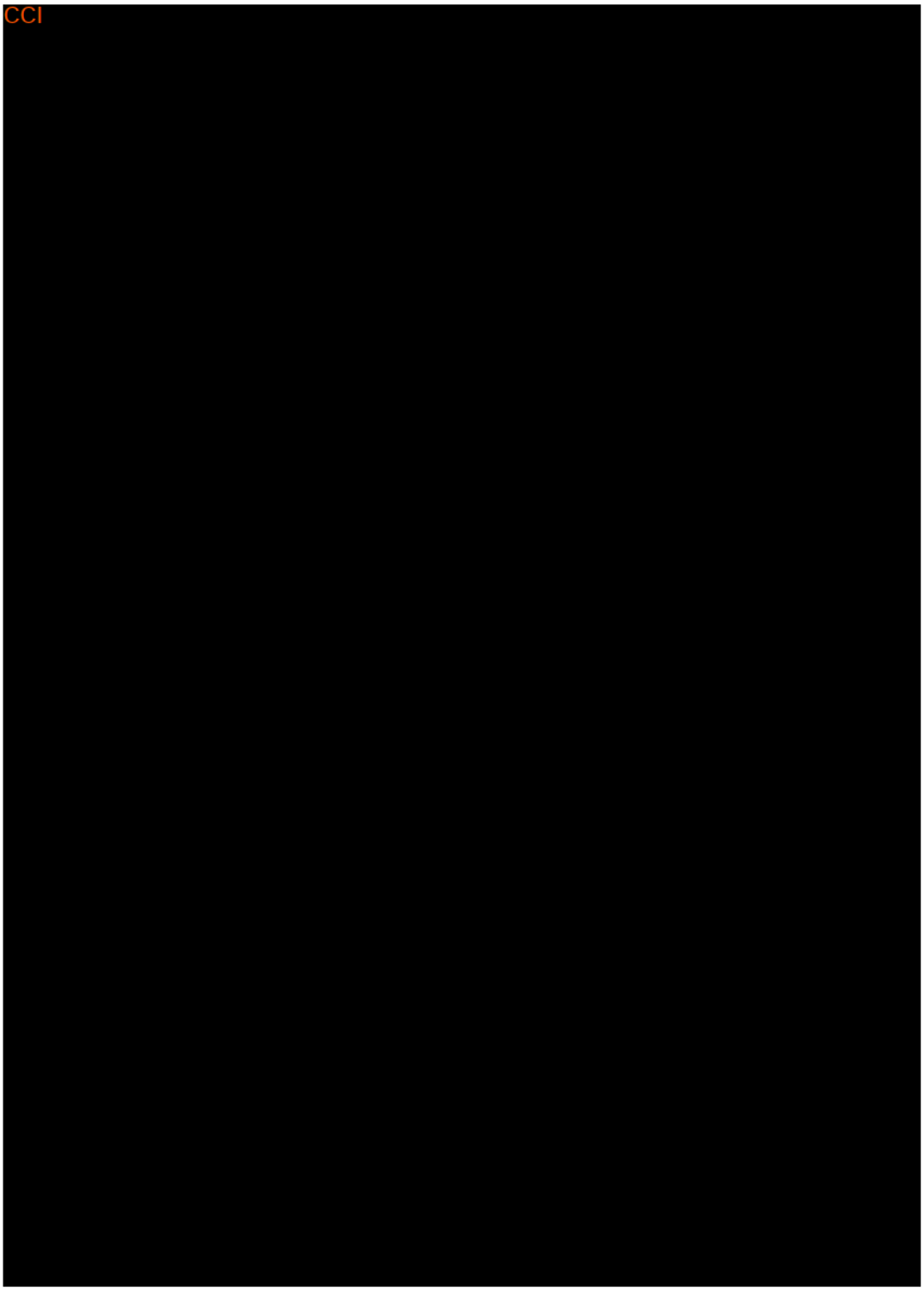

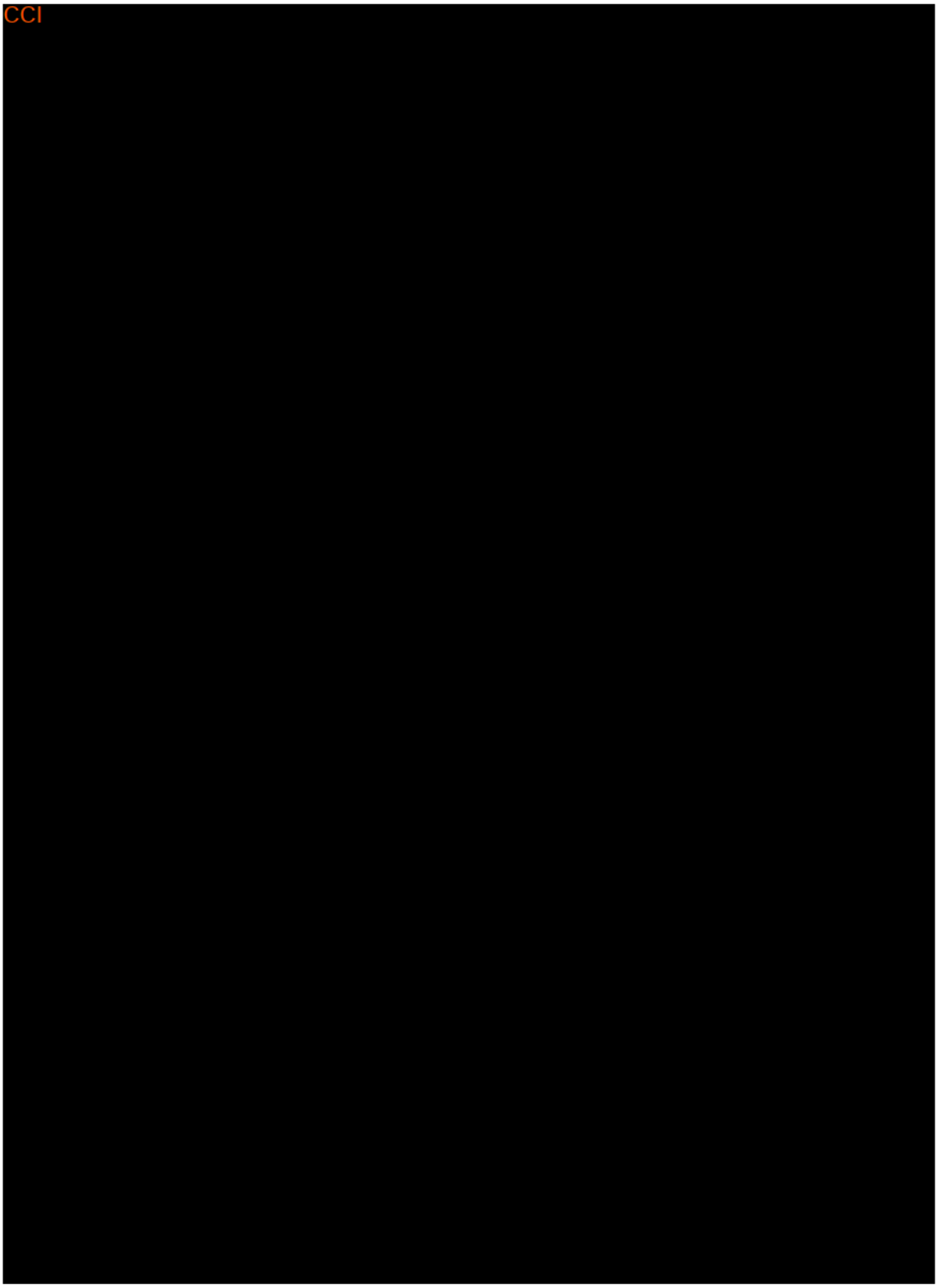
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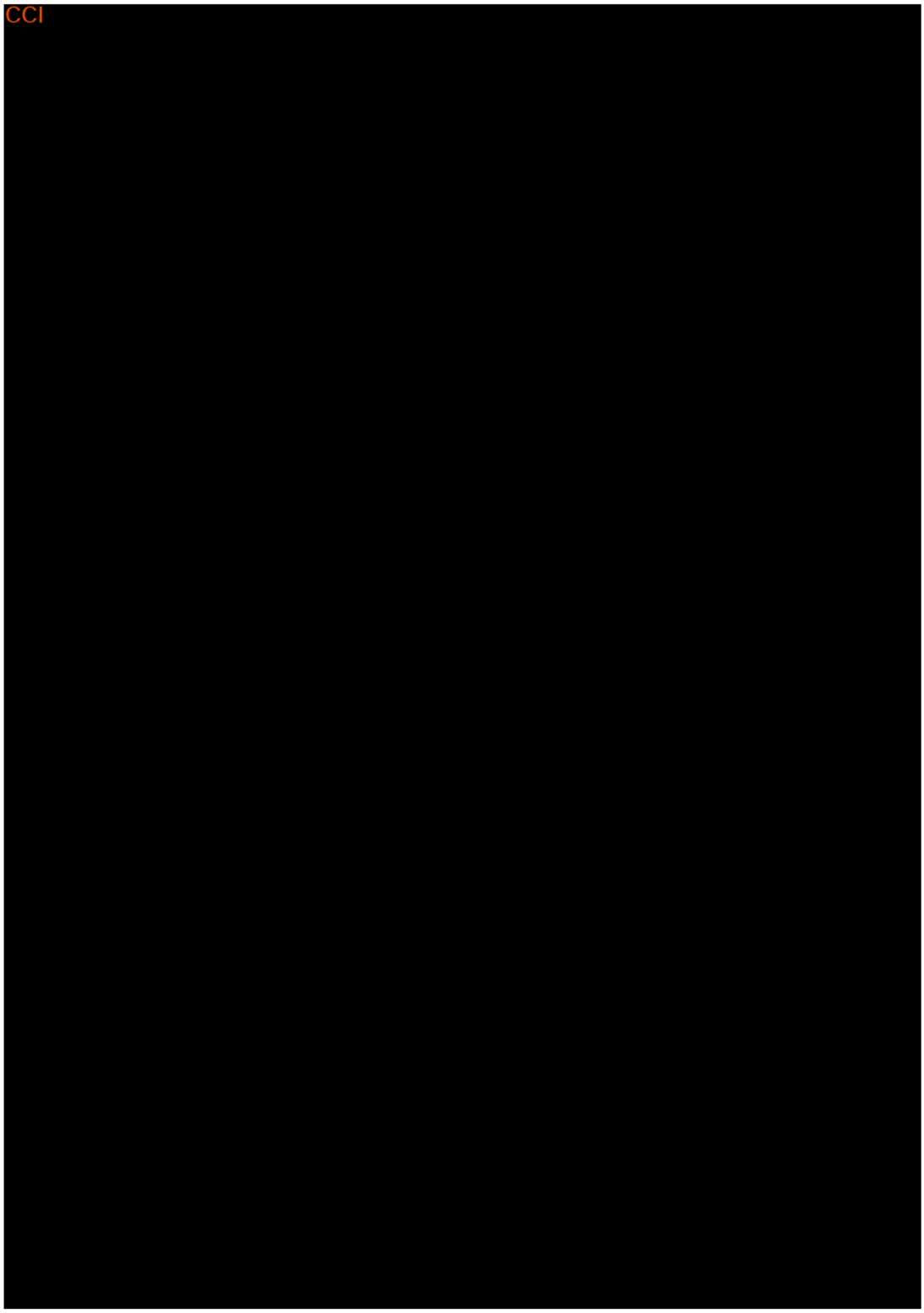
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