Official Title: A Phase 2/3, Randomized, Double-Blind, Vehicle-Controlled Study to Determine the Efficacy and Safety of AP0302 in the Treatment of Delayed Onset Muscle Soreness (DOMS)

NCT Number: NCT03852459

Applicant/IND: Aponia Laboratories, Inc.

Version Date: 02-Jul-2018

1 TITLE PAGE

STUDY PROTOCOL

Title of Study: A Phase 2/3, Randomized, Double-Blind, Vehicle-Controlled Study to Determine the Efficacy and Safety of AP0302 in the Treatment of Delayed Onset Muscle Soreness (DOMS)

Protocol Number: AP-007

Phase of Study: 2/3

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Date of Protocol:
Original – 26-Sep-2017
Amendment 1 – 23-Oct-2017
Amendment 2 – 31-Oct-2017
Amendment 3 – 02-Jul-2018

PROTOCOL SIGNATURE PAGE

Title of Study: A Phase 2/3, Randomized, Double-Blind, Vehicle-Controlled Study to Determine the Efficacy and Safety of AP0302 in the Treatment of Delayed Onset Muscle Soreness (DOMS)

Protocol Number: AP-007

Signatures:

The undersigned acknowledge that they have received and read Protocol Amendment 3 dated 02-Jul-2018.

Investigator	Signature	Date
PI , MD	PI	PI
Sponsor Representative	**Signature**	**Date**
PI	PI	PI

By signing this protocol, the investigator has agreed to conduct this study in accordance with the requirements of this clinical protocol and also in accordance with established principles of current Good Clinical Practice (cGCP), Title 21 of the Code of Federal Regulations sections 50, 56 and 312, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6, and the ethical principles that have their origin in the Declaration of Helsinki.

2 STUDY SYNOPSIS

TITLE	A Phase 2/3, Randomized, Double-Blind, Vehicle-Controlled Study to Determine the Efficacy and Safety of AP0302 in the Treatment of Delayed Onset Muscle Soreness (DOMS)
PROTOCOL NUMBER	AP-007
INVESTIGATOR AND STUDY SITE	PI , MD PI
OBJECTIVE(S)	Primary objective: • To evaluate the efficacy of AP0302 5% (CBI CBI in DOMS of the elbow flexors in generally healthy subjects Secondary objective: • To evaluate the safety of AP0302 CB in DOMS of the elbow flexors in generally healthy subjects
STUDY DESIGN	This is a Phase 2/3, randomized, single-center, double-blind, vehicle-controlled, parallel-group study designed to determine the efficacy and safety of AP0302 (CBI for the treatment of muscle pain/soreness associated with DOMS. Enough subjects will be screened to randomize 250 subjects. Subjects will be screened up to 28 days prior to Day 1. After completing the informed consent and screening processes, the following procedures will be completed: physical examination, medical history and concomitant medications collections, inclusion/exclusion criteria review, baseline laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing (females of child-bearing potential), drug and alcohol testing, and vital sign measurements. Subjects who meet initial inclusion/exclusion criteria will be scheduled to return to the research center to undergo an exercise regimen CBI . Between CBI following the end of the exercise regimen, subjects will return to the clinic to be evaluated for eligibility into the active treatment phase of the study. To qualify for randomization, subjects must report a CBI CBI

	CBI [redacted] Qualified subjects will be randomized to receive either AP0302 or vehicle control. CBI [redacted] CBI [redacted] CBI [redacted] a potential placebo effect from the vehicle application alone. CBI [redacted]. All doses and efficacy assessments will be completed while the subject is an inpatient at the study site. Subjects will be awakened for IP dosing and efficacy assessments as necessary. Subjects will complete the following assessments at baseline: • PI-NRS with movement • Categorical Pain Rating Scale with movement (baseline only) • Muscle Stiffness Numerical Rating Scale (NRS) with movement The following assessments will be completed at CBI [redacted] hours post-initial dose of IP and immediately prior to the subsequent doses of IP: • PI-NRS with movement • Muscle Stiffness NRS with movement The following assessment will be completed at CBI [redacted], and CBI [redacted] post-initial dose of IP and immediately prior to a subsequent dose of IP if one occurs CBI [redacted] • Relief from starting pain with movement on the Categorical Relief Rating Scale At C [redacted] hours post-initial dose of IP (or prior to early termination, if applicable), the subject will also complete a Subject Global Assessment to give their overall assessment of the IP. Safety evaluations will include adverse event (AE) reports, physical examination, vital signs, ECG, application site assessments, and laboratory testing. The final safety assessments will be done at approximately CBI [redacted] and subjects will be discharged from the site at that time. There will be a safety Follow-up Telephone Call on Day 7 (±1 day).

	CBI [redacted]
STUDY POPULATION	A sufficient number of generally healthy subjects of either gender will be enrolled to obtain 250 randomized subjects.
DURATION OF TREATMENT AND STUDY PARTICIPATION	CBI [redacted]
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION	
REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION	
ELIGIBILITY CRITERIA	**Inclusion criteria** 1. Generally healthy subjects of either gender aged 18 to 55 years (inclusive) at the time of signing the study informed consent form (ICF). The subject is in good health, with no clinically significant medical conditions, as determined by the investigator based on medical and exercise history, physical examination, ECG, and screening laboratory results. 2. Female subjects of childbearing potential (women who have experienced menarche and are not postmenopausal or permanently sterilized [by tubal ligation, hysterectomy, or bilateral salpingectomy]) will agree to use medically acceptable methods of contraception including but not limited to abstinence, birth control pills or patches, vaginal rings, diaphragm with vaginal spermicide, condom with vaginal spermicide, intrauterine device, and progestin implant or injection (used consistently for 3 months prior to study dosing) throughout the study and for 30 days following the last dose of IP. Male subjects will agree to use abstinence or condom throughout the study and for 30 days following the last dose of IP. Male subjects will agree to refrain from sperm donation and female subjects from egg donation throughout the

	study and for 30 days following the last dose. 3. Subject has a history of experiencing muscle pain/soreness after moderately strenuous exercise. 4. Subject has a body mass index between 18 and 30, inclusive. 5. The subject has signed the ICF approved by the Institutional Review Board (IRB). 6. Subject is willing and able to complete the standardized exercise regimen. **Post-Exercise:** 7 CBI [redacted] **<u>Exclusion criteria</u>** 1. Subjects who have regularly worked out or exercised the upper extremities with weights or gym equipment during the past 3 months. 2. Subjects who have a job or hobby that involves regular lifting or involvement of the upper extremities (eg, rock climbers, movers, construction workers). 3. Subjects with a history of surgery, significant trauma, significant musculoskeletal pathology, or significant nervous system pathology in the neck or in the non-dominant arm or shoulder that is likely to be exacerbated by the exercise regimen, in the opinion of the investigator. 4. Subjects with any condition, in the investigator's judgment, that may interfere with local tolerability assessments in the area of study drug application, including recently applied tattoos. 5. History of any muscle disorder (eg, statin myopathy or any muscular dystrophy), neuropathy, fibromyalgia, rhabdomyolysis, or chronic fatigue syndrome. 6. Presence of another painful physical condition that, in the opinion of the investigator, may confound study assessments. 7. Any contraindication to the use of ibuprofen, or any nonsteroidal anti-inflammatory drug (NSAID) or cyclooxygenase-2 inhibitor, or aspirin, including any history of asthma or recent history of gastritis or gastrointestinal bleeding. 8. Presence of an allergy or intolerance to any NSAID or aspirin or any of the components of the study drug. 9. Presence of a latex allergy (customized armband components contain latex). 10. Any skin condition that could potentially interfere with absorption of drug (eg, keloid, rash, dermatitis). 11. Have received chronic opioid therapy defined as greater than

	15 morphine equivalents units per day for greater than 3 out of 7 days per week in any 1-month period within 12 months prior to Day 1. 12. Have received an opioid within 30 days prior to Day 1. 13. Routine use (defined as 3 out of 7 days per week) of any analgesic drug (over-the-counter [OTC] or prescription). 14. Consumption of any medication (prescription or OTC medications, vitamins, minerals, and dietary supplements) within 2 weeks prior to Day 1. Exception: continuing hormonal contraception and hormone replacement therapy is allowed. 15. Any history of drug or alcohol abuse (according to the investigator's judgment) in the prior 5 years. 16. The subject has received an investigational drug or device within 3 months prior to screening. 17. The subject has participated previously in this trial or the subject has participated in another clinical trial involving exercise of the upper extremities within the last 6 months. 18. The subject is an employee or relative of an employee of the study site directly involved with the study. 19. Any medical or other condition that, in the opinion of the investigator, might affect the subject's ability to safely complete all study procedures (including the exercise regimen) or might interfere with the efficacy results of the study.
EFFICACY VARIABLES	**Primary Endpoint:** Sum of the time-weighted pain intensity differences from baseline with movement ($SPID_{MOVE}$) over 0-24 hours post-T_0 ($SPID_{MOVE}$ 0-24 hr). **Key Secondary Endpoints:** 1. $SPID_{MOVE}$ over the following intervals: 0-6, 6-12, 0-12, 12-24, 24-36, 0-36, 24-48, 36-48, and 0-48 hours post-T_0. **Other Secondary Endpoints:** 1. Sum of time-weighted differences from baseline in muscle stiffness with movement ($SSID_{MOVE}$) over the following intervals: 0-6, 6-12, 0-12, 12-24, 0-24, 0-36, 24-48, and 0-48 hours post-T_0. 2. Total relief with movement ($TOTPAR_{MOVE}$) 0-6 hours post-T_0. 3. Subject's global assessment of study medication assessed at approximately 48 hours post-T_0 (or upon early termination, if applicable).
SAFETY VARIABLES	• AEs • Local tolerability assessments • Clinical laboratory assessments • Physical examination, including neuromuscular and strength assessment of upper extremities • Vital signs (blood pressure, heart rate, temperature, and respiratory rate) • ECGs

ANALYSIS POPULATIONS	Three analysis populations will be used: **Safety Population:** all subjects who receive at least 1 dose of study drug. **Full Analysis Set (FAS):** all subjects who are randomized, receive at least 1 dose of study drug, and have at least 1 post-baseline efficacy assessment. **Per Protocol Set (PPS):** all subjects in the FAS without a major protocol deviation. The sponsor will identify which protocol deviations are considered major before unblinding the study.
PRIMARY ENDPOINT ANALYSIS	The primary efficacy endpoint will be the $SPID_{MOVE}$ for 0-24 hours post-T_0. The muscle pain/soreness intensity differences will be calculated by subtracting each post-T_0 muscle pain/soreness intensity score from the baseline muscle pain/soreness intensity score. The weight given to each pain intensity difference (PID) will be equal to the elapsed time since the previous evaluation. The mean $SPID_{MOVE}$ for 0-24 hours post-T_0 will be compared between treatments using an analysis of covariance model with baseline muscle pain/soreness score as a covariate.

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5 LIST OF ACRONYMS AND ABBREVIATIONS

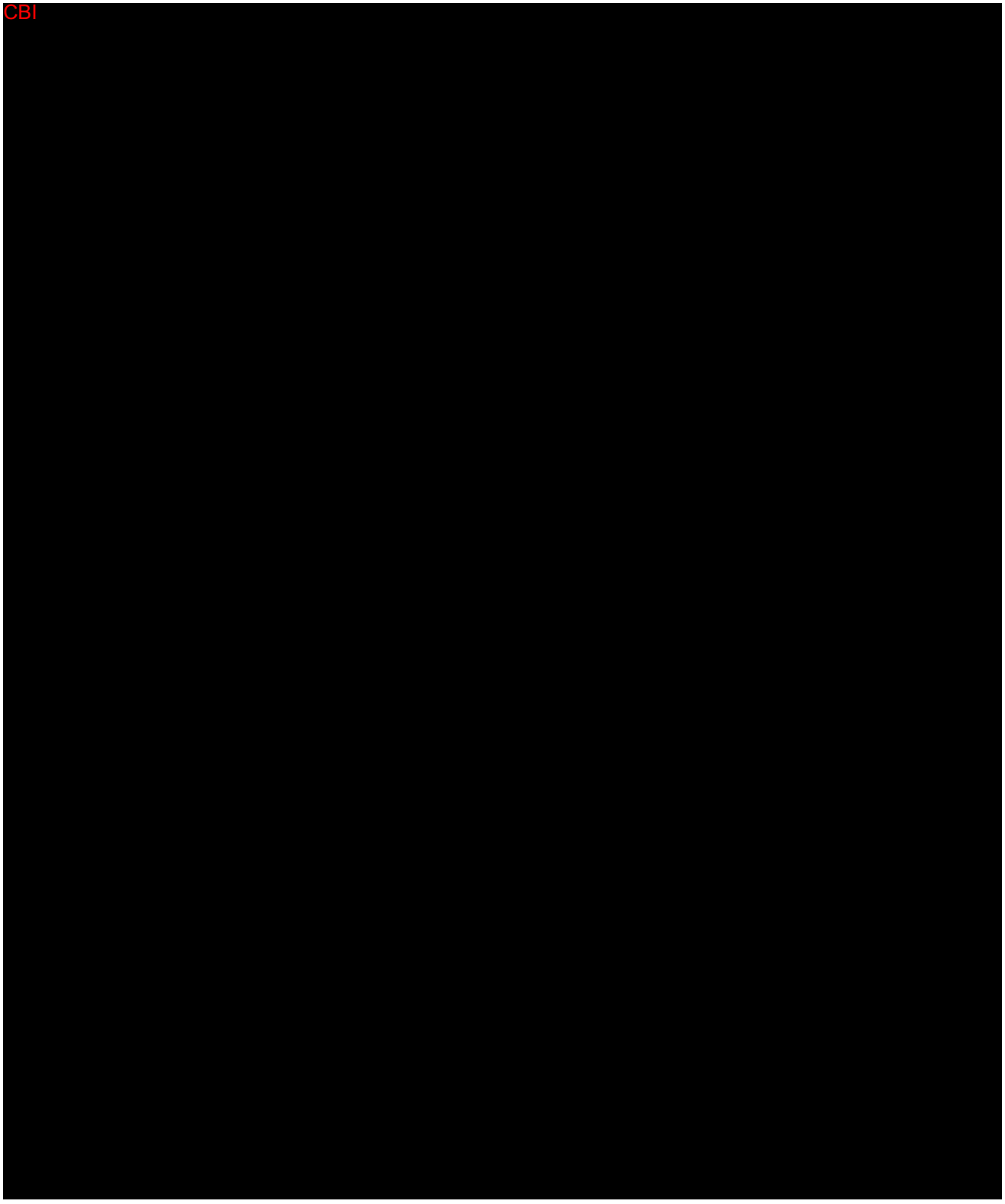
1RM	1 repetition maximum
AE	adverse events
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CK	creatine kinase
CRF	case report form
DOMS	delayed onset muscle soreness
ECG	electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, and throat
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
OTC	over-the-counter
PI-NRS	Pain Intensity Numerical Rating Scale
PID	pain intensity difference
PPS	Per Protocol Set
SAE	serious adverse event
SOC	system organ class
$SPID_{MOVE}$	sum of the time-weighted pain intensity differences from baseline with movement

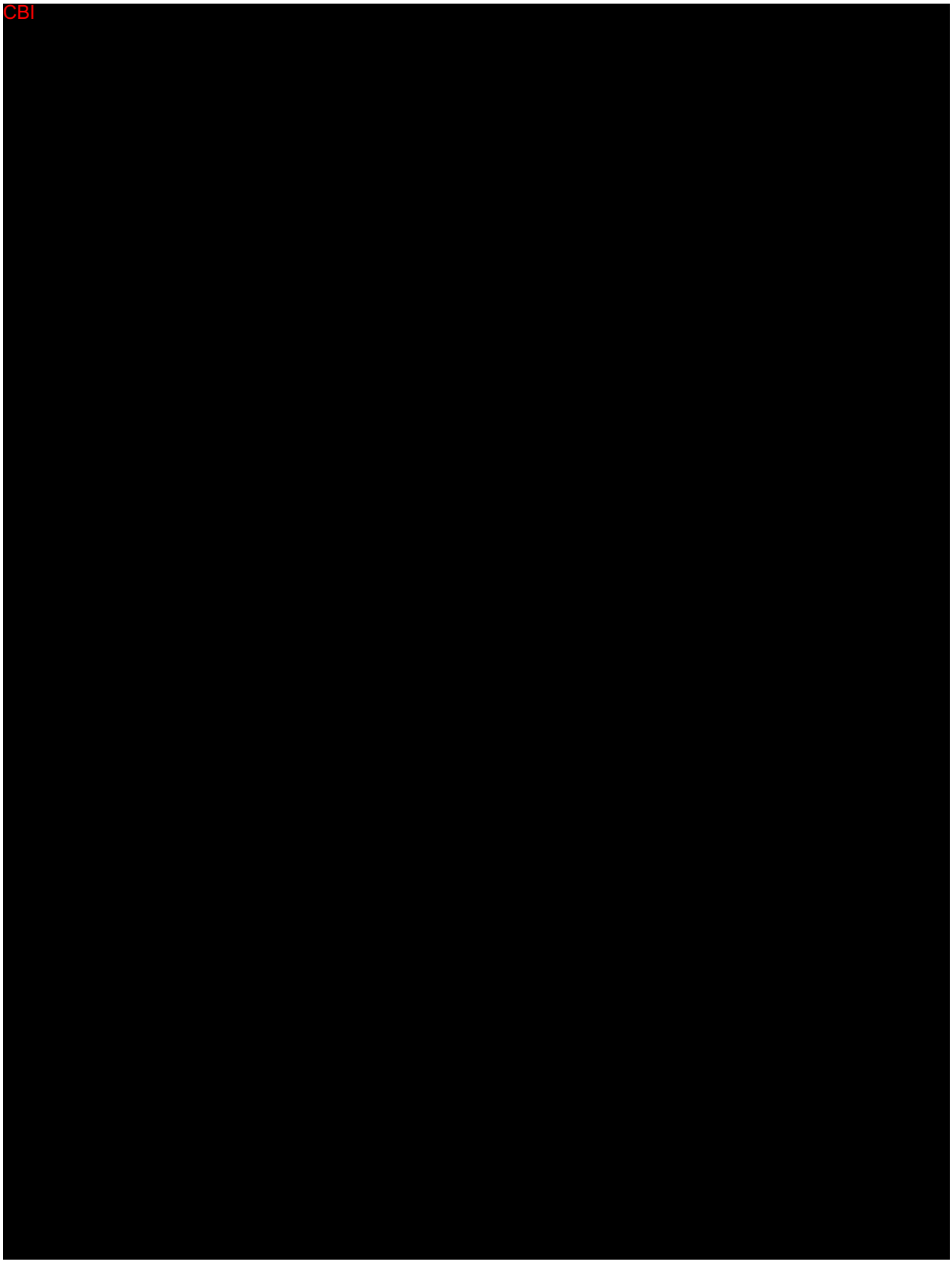
$SSID_{MOVE}$	sum of the time-weighted differences from baseline in muscle stiffness with movement
T_0	time zero, time of completion of first application of study drug
TEAE	treatment-emergent adverse event
$TOTPAR_{MOVE}$	total relief with movement
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential

6 INTRODUCTION

CBI [redacted]

CBI




CBI

CBI

6.4 Indication

The proposed indication for AP0302 CB is for CBI

CBI

CBI [redacted]

7 STUDY OBJECTIVE

7.1 Objectives

The primary objective of this study is to evaluate the efficacy of AP302 CBI topical gel) CBI in DOMS of the elbow flexors in generally healthy subjects.

The secondary objective is to evaluate the safety of AP0302 CBI in DOMS of the elbow flexors in generally healthy subjects.

8 OVERVIEW OF STUDY DESIGN

This is a Phase 2/3, randomized, single-center, double-blind, vehicle-controlled, parallel-group study designed to determine the efficacy and safety of AP0302 (CBI CBI) for the treatment of muscle pain/soreness associated with DOMS. Enough subjects will be screened to randomize 250 subjects.

Subjects will be screened up to 28 days prior to the Day 1. After completing the informed consent process, the following procedures will be completed: physical examination, medical history and concomitant medications collection, inclusion/exclusion criteria review, baseline laboratory testing, 12-lead electrocardiogram (ECG), pregnancy testing (females of child-bearing potential), drug and alcohol testing, and vital sign measurements.

Subjects who meet initial inclusion/exclusion criteria will be scheduled to return to the research center to undergo an exercise regimen CBI

Between CBI hours following the end of the exercise regimen, subjects will return to the clinic to be evaluated for eligibility into the active treatment phase of the study.

To qualify for randomization, subjects must report a CBI

CBI [redacted]

CBI [redacted]

Qualified subjects will be randomized to receive either AP0302 or vehicle control. CBI [redacted]

CBI [redacted] All doses and efficacy assessments will be completed while the subject is an inpatient at the study site. Subjects will be awakened for IP dosing and efficacy assessments as necessary.

Subjects will complete the following assessments at baseline:

- PI-NRS with movement
- Categorical Pain Rating score with movement (baseline only)
- Muscle Stiffness Numerical Rating Scale (NRS) with movement

The following assessments will be completed at CBI [redacted], CBI [redacted] hours post-initial IP dose and immediately prior to the subsequent doses of IP:

- PI-NRS with movement
- Muscle Stiffness NRS with movement

The following assessment will be completed at CBI [redacted] post-initial IP dose and immediately prior to a subsequent dose of IP if one occurs prior to CBI [redacted]:

- Relief from starting pain with movement on the Categorical Relief Rating Scale.

At CBI [redacted] post-initial dose (or prior to early termination, if applicable), the subject will complete a Subject Global Assessment to give their overall assessment of the IP.

Safety evaluations will include AE reports, physical examination, vital signs, ECG, application site assessments and laboratory testing. The final safety assessments will be done approximately 6 hours after the last dose, and subjects will be discharged from the site at that time. There will be a safety Follow-up Telephone Call on Day 7 (±1 day).

CBI [redacted]

8.1 SUBJECT SELECTION

8.1.1 Inclusion Criteria

1. Generally healthy subjects aged 18 to 55 years (inclusive) at the time of signing the study informed consent form (ICF). The subject is in good health, with no clinically significant medical conditions, as determined by the investigator based on medical and exercise history, physical examination, ECG, and screening laboratory results.
2. Female subjects of childbearing potential (women who have experienced menarche and are not postmenopausal or permanently sterilized [by tubal ligation, hysterectomy, or bilateral salpingectomy]) will agree to use medically acceptable methods of contraception including but not limited to abstinence, birth control pills or patches, vaginal rings, diaphragm with vaginal spermicide, condom with vaginal spermicide, intrauterine device, and progestin implant or injection (used consistently for 3 months prior to study dosing) throughout the study and for 30 days following the last dose of IP. Male subjects will agree to use abstinence or condom throughout the study and for 30 days following the last dose of IP. Male subjects will agree to refrain from sperm donation and female subjects from egg donation throughout the study and for 30 days following the last dose.
3. Subject has a history of experiencing muscle pain/soreness after moderately strenuous exercise.
4. Subject has a body mass index between 18 and 30, inclusive.
5. The subject has signed the ICF approved by the Institutional Review Board (IRB).
6. Subject is willing and able to complete the standardized exercise regimen.

Post-Exercise:

7. CBI [redacted]

"moderate" on a Categorical Pain Rating Scale using the words "none" "mild," "moderate," or "severe."

8.1.2 Exclusion Criteria

1. Subjects who have regularly worked out or exercised the upper extremities with weights or gym equipment during the past 3 months.
2. Subjects who have a job or hobby that involves regular lifting or involvement of the upper extremities (eg, rock climbers, movers, construction workers).
3. Subjects with a history of surgery, significant trauma, significant musculoskeletal pathology, or significant nervous system pathology in the neck or in the non-dominant arm or shoulder that is likely to be exacerbated by the exercise regimen, in the opinion of the investigator.
4. Subjects with any condition, in the investigator's judgment, that may interfere with local tolerability assessments in the area of study drug application, including recently applied tattoos.
5. History of any muscle disorder (eg, statin myopathy or any muscular dystrophy), neuropathy, fibromyalgia, rhabdomyolysis, or chronic fatigue syndrome.
6. Presence of another painful physical condition that, in the opinion of the investigator, may confound study assessments.
7. Any contraindication to the use of ibuprofen, or any nonsteroidal anti-inflammatory drug (NSAID) or cyclooxygenase-2 inhibitor, or aspirin, including any history of asthma or recent history of gastritis or gastrointestinal bleeding.
8. Presence of an allergy or intolerance to any NSAID or aspirin or any of the components of the study drug.
9. Presence of a latex allergy (customized armband components contain latex).
10. Any skin condition that could potentially interfere with absorption of drug (eg, keloid, rash, dermatitis).
11. Have received chronic opioid therapy defined as greater than 15 morphine equivalents units per day for greater than 3 out of 7 days per week in any 1-month period within 12 months prior to Day 1.
12. Have received an opioid within 30 days prior to Day 1.
13. Routine use (defined as 3 out of 7 days per week) of any analgesic drug (OTC or prescription).

14. Consumption of any medication (prescription or OTC medications, vitamins, minerals, and dietary supplements) within 2 weeks prior to Day 1. Exception: continuing hormonal contraception and hormone replacement therapy is allowed.
15. Any history of drug or alcohol abuse (according to the investigator's judgment) in the prior 5 years.
16. The subject has received an investigational drug or device within 3 months prior to screening.
17. The subject has participated previously in this trial or the subject has participated in another clinical trial involving exercise of the upper extremities within the last 6 months.
18. The subject is an employee or relative of an employee of the study site directly involved with the study.
19. Any medical or other condition that, in the opinion of the investigator, might affect the subject's ability to safely complete all study procedures (including the exercise regimen) or might interfere with the efficacy results of the study.

8.2 Subject Identification

Subjects will be identified by an assigned screening number and randomization number to maintain confidentiality.

8.3 Replacement of Subjects

Subjects who discontinue prior to completion of the study may be replaced at the sponsor's discretion.

9 STUDY TREATMENTS

9.1 Identification and Description of Investigational Product

9.1.1 Study Drug

CBI

CBI

[redacted]

9.2 Storage and Accountability

CBI

[redacted]

9.3 Study Drug Administration

CBI

[redacted]

9.4 Blinding

This is a double-blind, randomized study. The sponsor, site staff and subjects will be blinded as to whether each tube of IP contains active treatment or vehicle. The study blind may be broken for a specific subject only in the event of a medical emergency and when a decision regarding the subject's condition requires knowledge of the treatment assignment. Any such cases will be clearly justified and explained in a note to file. The investigator will notify the Aponia medical monitor immediately in the event of the situation.

9.5 Study Drug Randomization

Subjects will be required to meet the eligibility for study drug application on Day 1 (see Section 11.3), prior to assignment of the study drug box. Study drug boxes will be assigned by predetermined randomization and distributed sequentially starting with the lowest box number.

9.6 Compliance

Study staff will observe and document each dose of study medication application. The tubes will be weighed prior to the first dose and after the last dose.

9.7 Study Restrictions

9.7.1 Prior/Concomitant Medications

The following restrictions on prior/concomitant medications will apply:

- May not have received chronic opioid therapy defined as greater than 15 morphine equivalents units per day for greater than 3 out of 7 days per week in any 1-month period within 12 months prior to Day 1.
- May not have received an opioid within 30 days prior to Day 1.
- Must not routinely use (defined as 3 out of 7 days per week) any analgesic drug (OTC or prescription).
- Must not have consumed of any medication (prescription or OTC medications, vitamins, minerals, and dietary supplements) within 2 weeks prior to randomization. Exception: continuing hormonal contraception and hormone replacement therapy is allowed.

Any medication, including supplements, vitamins, and non-medicinal therapies taken by the subject from 30 days prior to the Screening Visit through the Follow-up Telephone Call will be recorded in the case report form (CRF).

9.7.2 Non-medicinal Therapies

Between the end of the exercise regimen and throughout the inpatient treatment phase, the application of heat, ice or other non-medicinal therapies involving the non-dominant arm are prohibited.

9.7.3 Activity Restriction

CBI

[redacted]

10 STUDY ASSESSMENTS

10.1 Subject Rating Scales

Subjects will receive training on how to use rating scales to report muscle pain/soreness, muscle stiffness and relief from starting pain (see separate study reference document and subject rating scales presented in Appendix 2).CBI

CBI

10.1.1 Pain Intensity NRS

Subjects will rate muscle pain/soreness with movement CBI

CBI

10.1.2 Categorical Pain Rating Scale for Eligibility

At baseline only, subjects will also report muscle pain/soreness with movement on the Categorical Pain Rating Scale: “none,” “mild,” “moderate” or “severe.” CBI

CBI .

10.1.3 Muscle Stiffness NRS

Subjects will rate muscle stiffness with movement using an 11-point Muscle Stiffness NRS anchored at zero (0) for no stiffness and 10 for the worst possible stiffness.

10.1.4 Categorical Relief Rating Scale

Subjects will rate relief from starting pain with movement using a 5-point categorical relief scale: “no relief,” “a little relief,” “some relief,” “a lot of relief,” or “complete relief.”

10.1.5 Subject Global Assessment

Subjects will rate their global assessment by answering the following question:

Overall, how would you rate the investigational product you received?

☐ Poor (0)
☐ Fair (1)
☐ Good (2)
☐ Very Good (3)
☐ Excellent (4)

10.2 Efficacy Assessments/Endpoints

10.2.1 Primary Endpoint

The primary endpoint is the sum of the time-weighted pain intensity differences (PIDs) from baseline with movement ($SPID_{MOVE}$) over 0-24 hours post-T_0 ($SPID_{MOVE}$ 0-24 hours). Muscle pain/soreness with movement will be scored using the PI-NRS described in Section 10.1.1 at the time points described in Section 11. The PIDs from 0-24 hours after T_0 will be calculated by subtracting each post-T_0 pain score from the baseline (prior to T_0) pain score. The weight given to each PID will be equal to the elapsed time since the previous evaluation.

10.2.2 Key Secondary Endpoints:

- $SPID_{MOVE}$ over the following intervals: 0-6, 6-12, 0-12, 12-24, 24-36, 0-36, 24-48, 36-48, and 0-48 hours post-T_0.

10.2.3 Other Secondary Endpoints:

- Sum of time-weighted differences from baseline in muscle stiffness with movement ($SSID_{MOVE}$) over the following intervals: 0-6, 6-12, 0-12, 12-24, 0-24, 0-36, 24-48, and 0-48 hours post-T_0.
- Total relief with movement ($TOTPAR_{MOVE}$) over 0-6 hours post-T_0.
- Subject's global assessment of study medication assessed at approximately 48 hours post-T_0 (or upon early termination, if applicable).

10.3 Safety and Screening Assessments

10.3.1 Medical History and Exercise History

A complete medical history will be taken at the Screening Visit. The medical history will include significant past medical or surgical procedures as well as previous and current co-existent diseases. It should include relevant medical history for the following body systems: head, eyes, ears, nose, and throat (HEENT); respiratory; cardiovascular; gastrointestinal; endocrine; hematological; dermatological; genital-urinary (including reproductive history); neurological; musculoskeletal; psychological/psychiatric; and any other history of medical significance. Changes in health occurring between the Screening Visit and the Treatment Period Visit, prior to the first dose of study medication, will be captured as medical history.

At the Screening Visit and Exercise Visit, subjects will be questioned about their exercise history to verify continued eligibility. Subjects who have worked out or exercised the upper extremities with weights or gym equipment during the past 3 months will not be eligible for the study.

10.3.2 Adverse Events

Adverse events will be defined, described, recorded, and reported according to Section 12.

10.3.3 Local Tolerability Assessments

CBI

CBI

CBI [redacted]

10.3.4 Clinical Laboratory Tests

The subjects are not required to be in the fasted state for the clinical laboratory testing. Laboratory testing (multiphasic chemistry panel, hematology panel, coagulation, and urinalysis) will be performed at the Screening Visit and on Day 3 at 54 hours post T_0. Screening laboratory tests must be reviewed for clinical significance prior to exercise at the Exercise Visit on Day -1 or 2.

Urine drug screens and alcohol breath tests will be performed at the Screening Visit, at the Exercise Visit, and on Day 1 prior to the first dose. Urine dipsticks will be used for the urine drug screens.

In women of childbearing potential (WOCBP; women who have experienced menarche and are not postmenopausal or permanently sterilized [by tubal ligation, hysterectomy, or bilateral salpingectomy]), urine pregnancy tests will be performed at the Screening Visit, Exercise Visit and on Day 1 (pre-dose).

CBI [redacted]:

CBI

CBI **Physical Examination**

A complete physical examination will be conducted during the Screening Visit and on Day 3 at 54 hours and will include assessment of the following: HEENT; neck (including an examination of the thyroid); heart; lungs; abdomen (including an examination of the liver and spleen); lymph nodes; extremities; nervous system; and skin.

CBI

CBI [redacted]

An abbreviated, symptom-directed physical examination will be performed at the Exercise Visit on Day -1 or -2. The abbreviated, symptom-directed physical examination is to be performed at the Exercise Visit to re-assess any abnormal clinically significant findings identified at the screening exam and/or to assess any current symptoms at the time of the symptom-directed exam. If there are no abnormal clinically significant findings at the screening visit AND no current symptoms, a symptom-directed examination is not required.

10.3.6 Vital Signs

Vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be recorded at the Screening Visit, at the Exercise Visit (Day -1 or 2), on Day 1 pre-dose, and Day 3 at 54 hours (or at early termination, if applicable). Measurements are to be obtained after the subject has been seated and resting quietly for at least 5 minutes.

Height and weight will be recorded at the Screening Visit.

10.3.7 Electrocardiograms

A 12-lead ECG will be recorded at the Screening Visit and on Day 3 after the subject has been in the supine position resting quietly for 10 minutes. The results must be reviewed for clinically meaningful deviations from normal prior to exercise.

11 STUDY PROCEDURES

An overview of the study assessments and procedures is presented in the Schedule of Assessments, Appendix 1.

11.1 Screening Visit (Day -28 to Day -3)

The investigator or designated qualified study personnel will perform the following assessments at the Screening Visit:

- Obtain written informed consent.
- Verify eligibility via inclusion and exclusion criteria.
- Record demographics.

- Obtain medical history and exercise history. Subjects who have exercised the upper extremities with weights or gym equipment within the prior 3 months will not be eligible for the study.
- Height and weight will be recorded.
- Record prior/current medications and non-medicinal therapies.
- Perform a physical examination, CBI [redacted] CBI [redacted] (as described in Section 10.3.5).
- Record vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate) after subject has been in a seated position and resting quietly for at least 5 minutes.
- Perform 12-lead ECG with the subject in a supine position after subject has been resting quietly for 10 minutes. Results must be reviewed for clinically meaningful deviations from normal prior to exercise.
- Obtain screening laboratory tests as follows:
    - Obtain blood and urine for screening laboratory tests (multiphasic chemistry, hematology, coagulation, and urinalysis).
    - Obtain urine for urine drug screen.
    - Perform alcohol breath test.
    - Obtain sample for urine pregnancy test for WOCBP.

CBI [redacted]

All information and clinical findings will be recorded in the appropriate sections of the CRFs. The investigator will make the final determination of whether a subject is eligible for the study. All subjects screened will be documented on the Screening Log. Specific reasons for excluding any potential subject will be recorded.

11.2 Exercise Visit (Day -1 or -2)

Subjects will return to the research unit on the day of exercise. CBI [redacted] CBI [redacted]

The following assessments and procedures will be performed prior to the exercise:

- Eligibility will be re-assessed.

- Update medical history. Changes in health between the Screening Visit and the Exercise Visit will be captured as medical history.

CBI

- Record prior/current medications and non-medicinal therapies.
- An abbreviated, symptom-directed physical examination will be performed, if indicated.
- Vitals signs (blood pressure, heart rate, temperature, and respiratory rate) will be collected after the subject has been seated for at least 5 minutes.
- Obtain urine and perform urine drug screen. Results should be reviewed prior to exercise.
- Obtain urine sample and perform urine pregnancy test in WOCBP. Results should be reviewed prior to exercise.
- Perform the alcohol breath test. Results should be reviewed prior to exercise.

CBI

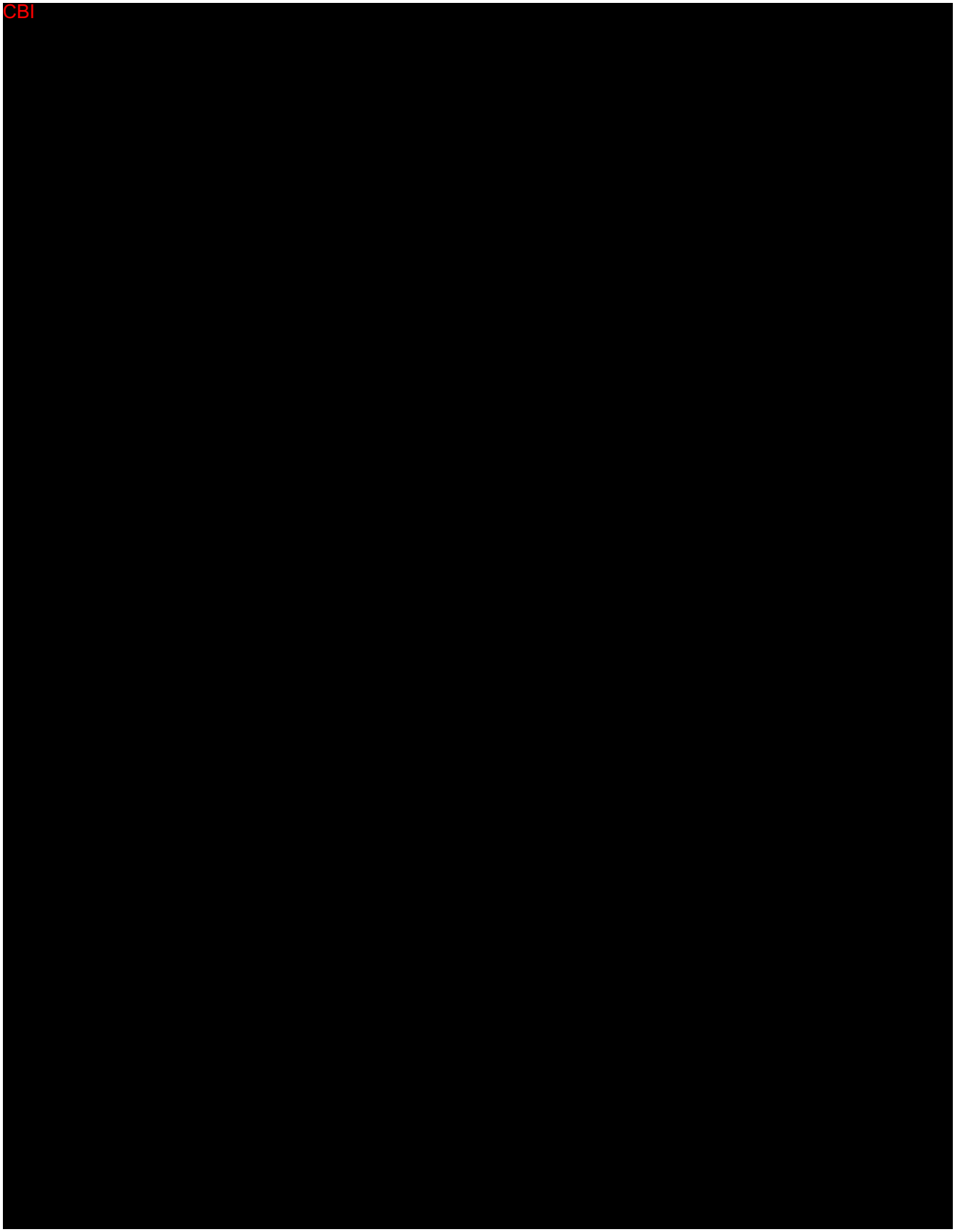
11.3 Treatment Period Visit (Days 1 to 3)

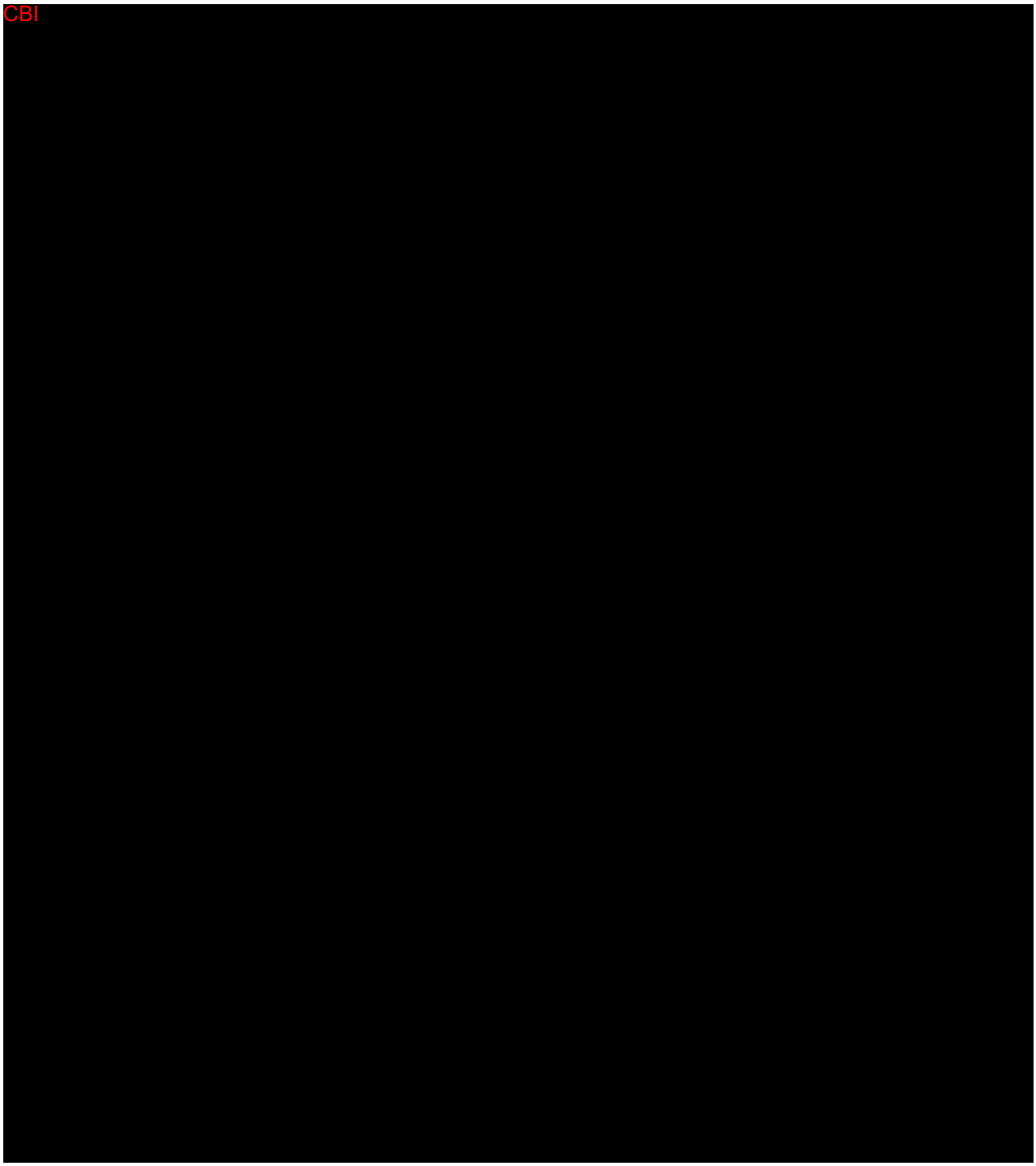
CBI [redacted]

CBI [redacted]. The following assessments and procedures will be performed to determine eligibility:

- Eligibility will be re-assessed.
- Update medical history. Changes in health between the Screening Visit until the Treatment Period Visit, prior to the first dose of study medication, will be captured as medical history.
- Review prior/current medications and non-medicinal therapies.
- Vitals signs (blood pressure, heart rate, temperature, and respiratory rate) will be collected after the subject has been seated for at least 5 minutes.
- Obtain urine for a urine drug screen. Results should be reviewed prior to treatment with IP.
- Perform the alcohol breath test. Results should be reviewed prior to treatment with IP.
- Obtain sample for urine pregnancy test in WOCBP. Results should be reviewed prior to treatment with IP.

CBI [redacted]


CBI



- The following assessments are to be completed at CBI, CBI post first dose of IP and immediately prior to the subsequent doses of IP:
    - Muscle pain/soreness with movement on the PI-NRS
    - Muscle Stiffness with movement on the Muscle Stiffness NRS

- The following assessment is to be completed at CBI post first dose of IP and immediately prior to a subsequent dose of IP, if one occurs prior to CBI
    - Relief from starting pain with movement on the Categorical Relief Rating Scale
- CBI .
- At approximately CBI post-T_0, the Subject Global Assessment of IP will be recorded in addition to the CBI NRS assessments.
- CBI
- Record any AEs and any concomitant medications or non-medicinal therapies throughout the visit.

On Day 3, at approximately CBI post-T_0, the following assessments and procedures will be performed:

- CBI
- Perform a physical examination, CBI).
- Record vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate) after subject has been in a seated position and resting quietly for at least 5 minutes.
- Perform 12-lead ECG with the subject in a supine position after subject has been resting quietly for 10 minutes.
- Obtain laboratory tests as follows:
    - Obtain blood and urine for laboratory tests (multiphasic chemistry, hematology, coagulation, and urinalysis).
- Any AEs and concomitant medications or non-drug therapies will be recorded.

After these final assessments have been performed, the subject can be discharged from the site.

CBI

11.4 Follow-up Telephone Call on Day 7 (±1 day)

Subjects will be called on Day 7 (±1 day) and the following assessments will be performed:

- Record prior/current medications and non-medicinal therapies.
- Record any AEs.

Each AE will be followed until it resolves, until the investigator assesses the subject's status to have returned to baseline, or until the investigator feels that the event is stable and chronic.

11.5 Order of Procedures

11.6 Allowable Windows

11.7 Early Termination Assessments

Subjects who discontinue early from the study after receiving IP, will undergo the following assessments and procedures:

- The subject's global assessment of IP will be recorded (if termination is prior to this 48-hour assessment).
- Perform a physical examination, including a neuromuscular and strength assessment of the upper extremities (as described in Section 10.3.5).
- Record vital sign measurements (blood pressure, heart rate, temperature, and respiratory rate) after subject has been in a seated position and resting quietly for at least 5 minutes.

- Perform 12-lead ECG with the subject in a supine position after subject has been resting quietly for 10 minutes.
- Obtain laboratory tests as follows:
  - Obtain blood and urine for laboratory tests (multiphasic chemistry, hematology, coagulation, and urinalysis).
- Any AEs and concomitant medications or non-drug therapies will be recorded.

CBI [redacted]

11.8 Subject Withdrawal

If a subject withdraws from the study after the receipt of IP, this will be considered an early withdrawal and the subject should undergo the assessments presented in Section 11.7.

The sponsor should be notified of any withdrawals, and the investigator should record the reason for discontinuation in the CRF. A subject may be removed from the study for medical or administrative reasons such as the following:

- AE
- Lack of efficacy
- Noncompliance with study drug
- Protocol deviation
- Subject withdrawal
- Lost to follow-up
- Physician decision
- Other reasons as determined by the investigator or the sponsor

11.9 Estimated Blood Loss

The amount of blood loss during this study per each subject is estimated to be as follows:

CBI [redacted]

12 ADVERSE EVENT REPORTING

12.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

A TEAE is defined as an AE that is new or worsened in severity after the first dose of study drug.

12.2 Recording of Adverse Events

The investigator should record any AEs that occur from time of first dose of study medication to 14 days after the last dose of study drug; the investigator should record any SAEs from the time of signing the ICF until 30 days after the last dose of study drug. Adverse events will not be considered treatment-emergent unless they are new or worsened in severity after the first dose of study drug.

At each contact with the subject, the investigator or designee must seek information on AEs by specific questioning and, as appropriate, by examination. All observed or volunteered AEs, regardless of suspected causal relationship to study drug, must be recorded on the AE page of the CRF.

Any events involving illnesses or injuries with onset during the study or any events involving exacerbations of pre-existing illnesses should be recorded. All clearly related signs and symptoms should be grouped together and recorded as a single diagnosis in the CRF. A pre-existing condition must not be reported as an AE unless the condition worsens during the trial. The condition, however, must be reported in the Medical History section of the CRF.

Scheduled or planned diagnostic and therapeutic procedures such as surgery must not be reported as AEs. The scheduled procedure and medical condition for which the procedure was performed must be reported in the CRF.

Each AE will be judged as to the relationship to study medication (as defined in Section 12.4), the severity (as defined in Section 12.5), and whether it meets the criteria for an SAE (as defined in Section 12.6).

Adverse events will be followed until resolution or until the investigator assesses the subject's status to have returned to normal, or until the investigator feels that the event is stable and chronic.

12.3 CBI

12.4 Causality Assessments

Each AE will be judged as to whether it is related, possibly related, or unrelated to the IP. The following definitions will be used for these causality assessments.

Related: This causal relationship is assigned when the AE:

- starts a reasonable time after study drug administration,
- stops/improves when study drug has been stopped,
- can reasonably be explained by known characteristics of the study drug, and
- cannot be reasonably explained by the subject's clinical state.

Possibly Related: This causal relationship is assigned when the AE:

- starts a reasonable time after study drug administration, but
- could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Unrelated: This causal relationship is assigned when the AE:

- is definitely not associated with the study drug administered and is readily explained by other events or diagnoses.

12.5 Severity Assessments

The severity of each AE will be graded according to the following definitions:

Mild: Does not interfere with subject's usual function.

Moderate: Interferes to some extent with subject's usual function.

Severe: Interferes significantly with subject's usual function.

12.6 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening,

Note: the term "life-threatening" in the definition of "serious" refers to an event in which the subject was 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 persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when based on appropriate medical judgment, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Local tolerability findings graded as a 4 using the scoring system in Section 10.3.3 will be considered medically important and reported to the sponsor as SAEs.

All SAEs, from the signing of the ICF until 30 days after the last dose of study drug, must be reported *immediately* (within 24 hours of knowledge of the event) to the Medical Monitor:

PI , MD
PI

E-mail: PI
Phone: PI

Reporting via e-mail must be followed up by a follow-up phone call to ensure receipt.

All SAEs must also be reported to the IRB/ Independent Ethics Committee (IEC) per their reporting guidelines. Information regarding the SAE must be completed on the provided SAE report form and recorded in the subject's CRF. The SAE report form and AE page from the subject's CRF should be scanned and emailed to the study personnel named above.

The SAE report forms and instructions will be provided prior to initiation of the study. The SAE report form must be completed with as much information available at the time of reporting. This should, in general, include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. New information regarding ongoing SAEs should be provided promptly to the medical monitor. In the case of a subject death, a summary of autopsy findings, if available, should be submitted. The SAE must be reported on the provided SAE report form and the investigator should ensure that the information reported immediately by telephone or other means and in the CRF is accurate and consistent.

The FDA and local regulatory authorities should be notified of AEs that are serious, unexpected, and associated with the use of study drug within 15 calendar days of the sponsor's initial receipt of such reports. The FDA and local regulatory authorities should also be notified of any fatal or life-threatening AEs that are unexpected and associated with use of study drug, within 7 calendar days of the sponsor's initial receipt of such reports. These reports should be submitted in a manner consistent with the applicable local regulatory requirements.

12.7 Pregnancy

If a female subject should become pregnant during the study, the medical monitor must be notified immediately and dosing stopped. Although pregnancy is not considered an SAE, an abnormal outcome of pregnancy may be an SAE. A pregnancy form should be used to report to the sponsor the pregnancy of a female subject. Pregnancies must be followed until birth, termination of the pregnancy, or loss of subject to follow-up.

13 DATA HANDLING

13.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to an electronic data record since the data collection method is an electronic data capture system, Medrio eClinical.

A CRF is required and should be completed for each screened subject. The completed original CRFs are the sole property of Aponia Laboratories, Inc. and should not be made available in any form to third parties, except for authorized representatives of Aponia Laboratories, Inc. or appropriate regulatory authorities, without written permission from Aponia Laboratories, Inc.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

13.2 Clinical Database

Creation and validation of the clinical database and entry and management of data will be conducted in accordance with Title 21 of the Code of Federal Regulations Part 11 and the guidance for industry on computerized systems used in clinical trials. Methods used to ensure the quality and integrity of the data will be documented in the data management plan.

14 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be signed off prior to the database lock.

14.1 Analysis Populations

The following populations will be utilized:

- **Safety Population:** all subjects who receive at least 1 dose of study drug. The demographic, baseline characteristics, and safety data summaries will be based on the Safety Population.
- **Full Analysis Set (FAS):** all subjects who are randomized, receive at least 1 dose of study drug, and have at least 1 post-baseline efficacy assessment.
- **Per Protocol Set (PPS):** all subjects in the FAS without a major protocol deviation. The sponsor will identify which protocol deviations are considered major before unblinding the study.

14.2 Randomization

Study drug will be assigned by predetermined randomization and distributed sequentially starting with the lowest available randomization number. Assignment to active and vehicle control will be in a 1:1 ratio.

14.3 Sample Size Determination

A sufficient number of generally healthy subjects of either gender will be enrolled to obtain 250 randomized subjects. The sample size of 250 subjects (125 for each of the treatment group) CBI [redacted]

14.4 Efficacy Analysis

All statistical testing will be performed with a 2-sided 0.05 level of significance. For each of the time intervals analyzed, completion of administration of the first dose of study drug is considered time 0, T_0. Efficacy parameters will be analyzed using both the FAS and the PPS.

14.4.1 Primary Efficacy Endpoint and Analysis

The primary efficacy outcome is the sum of the time-weighted differences from baseline in muscle pain/soreness with movement ($SPID_{MOVE}$) over 0-24 hours post-T_0 ($SPID_{MOVE\ 0\text{-}24h}$), that is the area under the differences from baseline pain/soreness intensity difference curve.

The PIDs with movement from time point A to time point B will be calculated using the trapezoid rule by subtracting each post-T_0 pain score with movement from the pain score with movement at time point T_i as follows:

- PID with movement at time point i ($PID_{MOVE\ i}$) = NRS score with movement at time point i – NRS score with movement at baseline.
- Mean of adjacent pain intensity differences $M_{MOVEi} = (PID_{MOVEi} + PID_{MOVE\ i+1}) / 2$
- The weight given to each $M_{MOVE\ i}$ score (W_i) = elapsed time to the next evaluation ($t_{i+1} – t_i$).
- $SPID_{MOVE\ A\text{-}B\ hr} = \sum_{i=A}^{B-1} W_i \ M_{MOVEi}$ where i refers to each NRS scheduled assessment time point between A and B (not including B).

Thus, $SPID_{MOVE\ 0\text{-}24h} = \sum_{i=0}^{18} W_i M_{MOVE_i}$, where i refers to each NRS scheduled assessment time point between baseline and 24 hours.

The general formula for computing SPID between any two time points a and b is as follows:

$$SPID_{a-b} = \sum_{i=a}^{b-1} \frac{(t_{i+1} - t_i)(PID_{I+1} + PID_i)}{2}$$

Where i refers to each scheduled assessment time point between a and b hours post baseline, t_i is the ith time point and PID_i is the pain intensity difference at time i

The mean $SPID_{MOVE}$ for 0-24 hours post-T_0 will be compared between the 2 treatment groups using an analysis of covariance (ANCOVA) model with baseline pain/soreness score as a covariate.

14.4.2 Key Secondary Efficacy Endpoints and Analyses

Following the similar formula mentioned in the previous section, the following $SPID_{MOVE}$ for the different time intervals will be estimated and compared for the 2 treatment groups using the same ANCOVA model.

- $SPID_{MOVE}$ over the following intervals: 0-6, 6-12, 0-12, 12-24, 24-36, 0-36, 24-28, 36-48, and 0-48 hours post-T_0. The mean $SPID_{MOVE}$ for 0-6, 6-12, 0-12, 12-24, 24-36, 0-36, 24-28, 36-48, and 0-48 hours post-T_0 will be compared between the 2 treatment groups (active versus vehicle) using an ANOCVA model with the baseline pain/soreness score as the covariate.

14.4.3 Other Secondary Analyses

The following other secondary endpoints for different time intervals will be compared between the 2 treatment groups using an ANCOVA model with the baseline pain/soreness score as the covariate.

- $SSID_{MOVE}$ over the following intervals: 0-6, 6-12, 0-12, 12-24, 0-24, 0-36, 24-48, and 0-48 hours post-T_0. The mean $SSID_{MOVE}$ for 0-6, 6-12, 0-12, 12-24, 0-24, 0-36, 24-28, and 0-48 hours post-T_0 will be compared between the 2 treatment groups (active versus vehicle) using an ANOCVA model with the baseline muscle stiffness score as the covariate.
- $TOTPAR_{MOVE}$ over 0-6 hours post-T_0. An ANOVA model will be used for these efficacy endpoints.

  $TOTPAR_{MOVE}$ A-B hr = $\sum_{i=A}^{B-1} \boldsymbol{PR_i}\ \boldsymbol{H}$ where i refers to each pain relief scheduled assessment time point between A and B (not including B).

The TOPAR endpoints will be compared between the 2 treatment groups using an ANOVA model.

The subject's global assessment of efficacy will be assessed at approximately 48 hours post-T_0 (or upon early termination if the subject withdraws prior to the 48-hour assessment). The distribution of 5 categories (poor, fair, good, very good, or excellent) will be compared between the 2 treatments (active versus vehicle) using the Chi-Squared test. In addition, the 5 categories will be dichotomized into 2 categories (good/very good/excellent versus poor/fair). The proportion of good, very good, and excellent ratings will be calculated for each treatment. This proportion will be compared between the 2 treatments (active versus vehicle) using the Fisher's Exact test.

14.5 Safety Analysis

For the safety analysis, descriptive statistics such as mean, median, minimum, maximum, and standard deviation will be summarized for continuous variables. Frequency distributions will be summarized for categorical variables. Since all subjects will receive vehicle on the dominant arm in addition to blinded study drug on the non-dominant arm, some subjects will receive both active and vehicle treatments. All safety-related data will be summarized as an overall group except AEs related to the area of application.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 (or higher). For summary tables, AEs coded to the same preferred term will be counted only once within a given subject. If an AE was recorded on multiple occasions in the same treatment period, only the highest severity and the highest degree of relationship to the study drug will be presented. If 2 or more clinical events are reported within a single AE entry, then the corresponding individual preferred terms will be coded separately.

All AEs, including those that are not treatment-emergent, will be listed. All summaries of AEs will be of TEAEs. A TEAE is defined as an AE that is new or worsened in severity after the first dose of study drug. Adverse events will be summarized by system organ class (SOC), and preferred term. Summaries will be prepared for all AEs, treatment-related AEs, and SAEs. The AE summary will also be presented with a breakdown by severity. Adverse events that are specific to the arm, such as application site reactions, will be summarized by treatment (active versus vehicle).

Changes from baseline in chemistry, hematology, coagulation, and urinalysis parameters will be summarized descriptively. Laboratory results will be classified as low, normal, or high according to the laboratory-supplied reference ranges. Shift tables describing out-of-range shifts from

baseline (in frequency counts) will be created and presented by treatment. All laboratory results will be listed.

The results of physical examinations will be summarized by body categories with frequency and percentages of normal versus abnormal, and if abnormal whether it is clinically significant or non-clinically significant. A listing of physical examination results will be presented by subject and assessment time point.

Results of the ECGs will be presented as normal, abnormal (clinically significant), and abnormal (not clinically significant). These results will be listed by subject and summarized descriptively.

Vital signs will be listed by subject and summarized descriptively by time point.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized descriptively. Prior medications are defined as any medications started prior to the day of the first dose of study drug. Concomitant medications are defined as any medications taken on the day of or after the first dose of study drug. Prior and concomitant medications will be coded using the WHO Drug Dictionary version of September 2014. A by-subject listing will be generated that contains both prior and concomitant treatments. Medications will be classified according to primary 4th level Anatomical Therapeutic Chemical codes and WHO Drug preferred terms in the listing. Subjects may have more than 1 concomitant treatment per drug class and per preferred term. Summary tables will be generated by treatment for both prior and concomitant treatments. In these summary tables, a subject will be counted only once for a given prior or concomitant treatment. Prior and concomitant non-medicinal therapies (non-drug treatments) will be coded using MedDRA and then summarized in a similar manner as prior and concomitant medications.

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14.6 Demographics and Baseline Characteristics

Demographic characteristics will be listed by subject and will be summarized descriptively. Medical history will be coded using MedDRA and summarized by SOC and preferred term.

15 REGULATORY AND ETHICAL ISSUES

15.1 Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Aponia Laboratories, Inc.

Any changes to the protocol will require approval of the sponsor, in writing, and the IRB/IEC prior to implementation. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Aponia Laboratories, Inc. in writing immediately after the implementation.

15.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the FDA, applicable local regulatory requirements and laws, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practices (GCPs) (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] 1996), and the Declaration of Helsinki (World Medical Association 2008). The rights, safety, and well-being of the study subjects are the most important consideration and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities.

15.3 Informed Consent

The investigator, or a person designated by the investigator, will obtain voluntary written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The subject will be given ample time to review the ICF and the opportunity to discuss any questions before making a decision about participation in this study. The process of informed consent will be documented in the subject’s source data. The investigator will retain the original of each subject's signed consent document and a signed copy will be provided to the subject.

The informed consent document must be in compliance with ICH guideline on GCPs, the FDA, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be approved by both the IRB/IEC and Aponia Laboratories, Inc. before use.

15.4 Confidentiality

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law.

Subject names, addresses, birth dates, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Aponia Laboratories, Inc. in order to de-identify the subjects. In case of data transfer, Aponia Laboratories, Inc. will maintain high standards of confidentiality and protection of subject personal data.

15.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCPs

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Aponia Laboratories, Inc. should be informed immediately.

In addition, the investigator will inform Aponia Laboratories, Inc. immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCPs that the investigator becomes aware of.

15.6 Access to Records

The investigator and study personnel will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

15.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or Aponia Laboratories, Inc., the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports).

The investigator must arrange for retention of study records at the site for 2 years after the AP0302 5% New Drug Application is approved or the Investigational New Drug application is withdrawn, as required by FDA regulations. If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Aponia Laboratories, Inc. should be immediately notified. The study records must be transferred to a designee acceptable to Aponia Laboratories, Inc., such as another investigator, another institution, or to an independent third party arranged by Aponia Laboratories, Inc.

The investigator must obtain Aponia's written permission before disposing of any records, even if retention requirements have been met.

15.8 Monitoring, Quality Control and Quality Assurance

During study conduct, Aponia Laboratories, Inc., or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitor will ensure there are no deviations to the informed consent process for all screened subjects. Source data will be reviewed to confirm that there are no deviations to the study protocol and data recorded on CRFs are accurate. The monitor will ensure the following: that essential documents are maintained and IRB approval current; that the study drug is stored appropriately; that drug accountability records are complete and accurate; and that the site's resources remain adequate for the conduct of the trial. The investigator and institution will allow Aponia Laboratories, Inc. monitors or its agents and appropriate regulatory authorities direct access to source documents and all study records to perform this verification.

The study site may be subject to review by the IRB/IEC, to quality assurance audits performed by Aponia Laboratories, Inc., or companies working with or on behalf of Aponia Laboratories, Inc., and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

15.9 Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Aponia Laboratories, Inc. In addition, Aponia Laboratories, Inc. retains the right to discontinue development of AP0302 5% at any time.

If a study is prematurely terminated or discontinued, Aponia Laboratories, Inc. will promptly notify the investigator. After notification, the investigator must contact all participating subjects

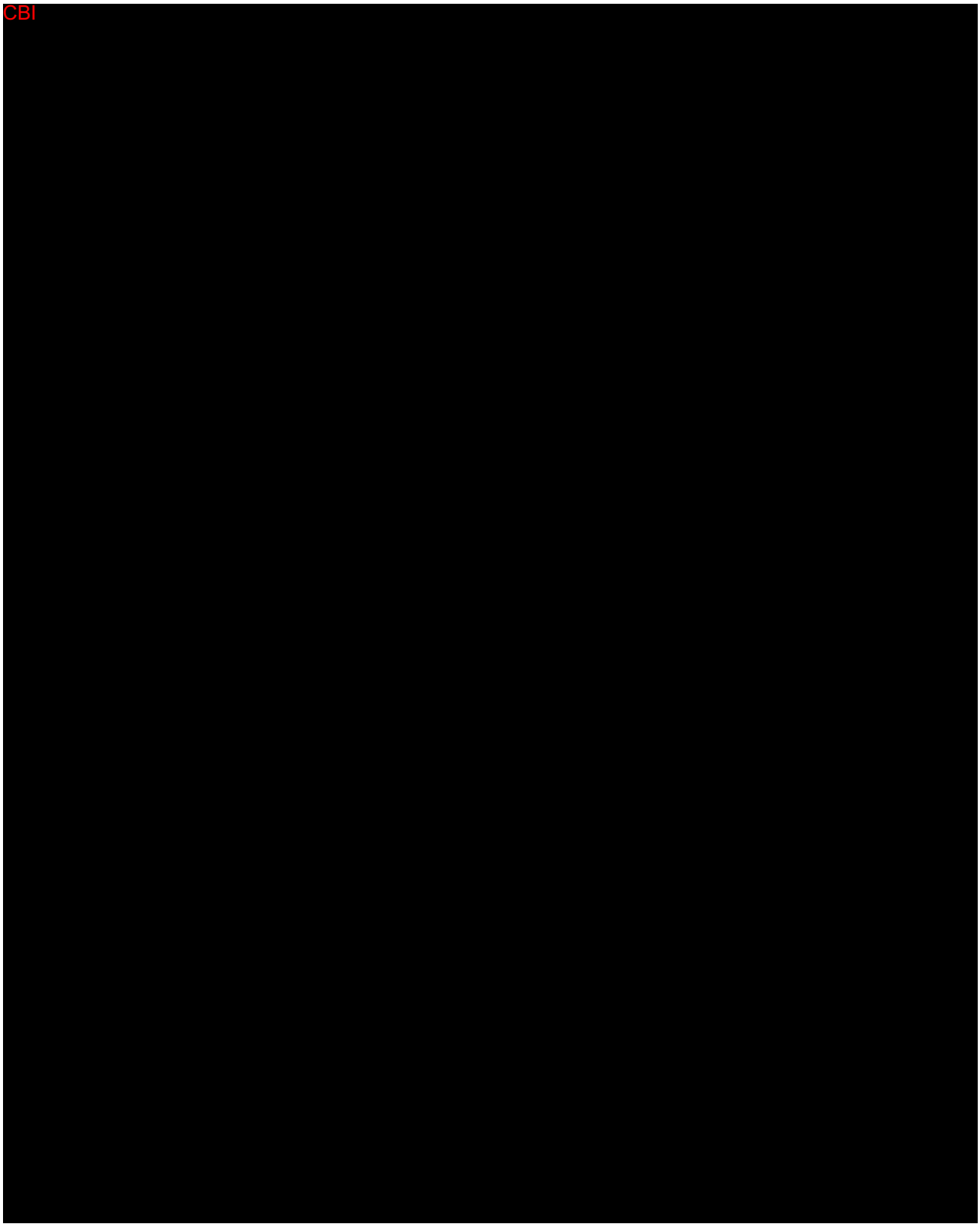
and the pharmacy (if applicable) within 14 days. As directed by Aponia Laboratories, Inc., all study materials must be collected and all CRFs completed to the greatest extent possible.

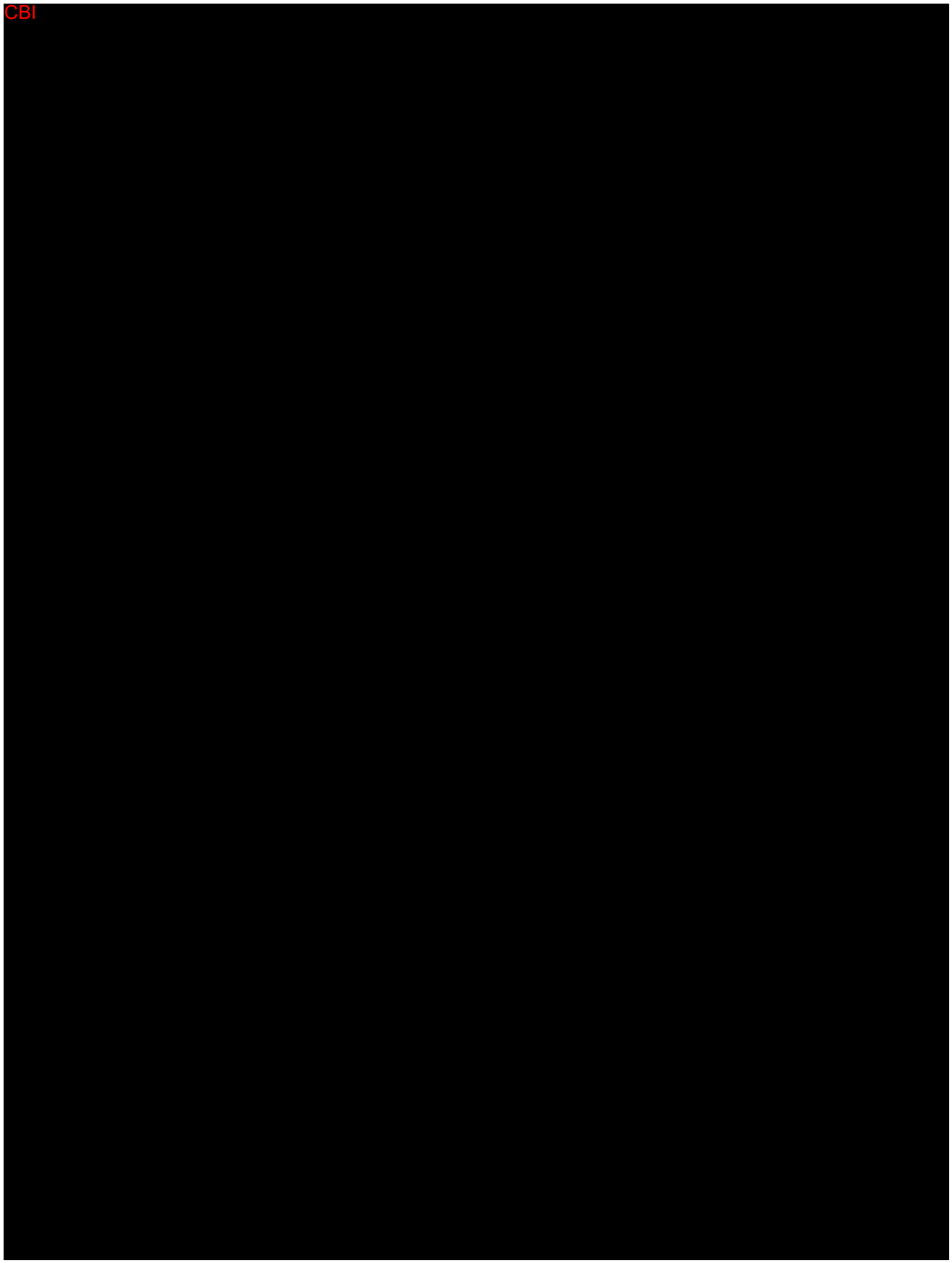
16 PUBLICATION OF STUDY RESULTS

Please refer to the Clinical Study Agreement for the details and requirements for investigators interested in publishing the results of this study.

17 REFERENCES

CBI

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Appendix 1 Schedule of Assessments

	Screening Visit	Exercise Visit	Treatment Period				Follow-up Phone Call
	Day-28 to Day -3	Day -2 or -1	CBI [redacted]				Day 7 ±1 day
Informed consent	X						
Verify/re-assess eligibility	X	X	X				
Demographics	X						
Medical history	X	X	X				
Exercise history	X	X					
Record height and weight	X						
Record prior/current medications and non-medicinal therapies	X	X	X	X	X	X	X
Physical examination	X					X	
Physical examination – abbreviated/symptom directed only based on Screening[1]		X					
Vital signs (BP, HR, temperature, and RR)	X	X	X			X	
12-lead ECG	X					X	
Clinical laboratory tests (chemistry, hematology, coagulation, and urinalysis)	X					X	
Urine drug screen/ Alcohol breath test	X	X	X				
Pregnancy test (WOCBP)	X	X	X				
CBI [redacted]	X						
Exercise regimen		X					
CBI [redacted]			CBI [redacted]				
Muscle pain/soreness with movement Categorical Pain Rating Scale[3]							
PI-NRS, Muscle stiffness with movement NRS[4]							
Relief from starting pain with movement Categorical Relief Rating Scale[5]				X			
Subject's global assessment of study medication[6]						X	
Adverse events				X	X	X	X

Abbreviations: BP = blood pressure; ECG = electrocardiogram; HR = heart rate; NRS = numerical rating scale; PI-NRS =Pain Intensity Numerical Rating Scale; RR = respiratory rate; T_0 = time of first application of study drug; WOCBP = women of childbearing potential.

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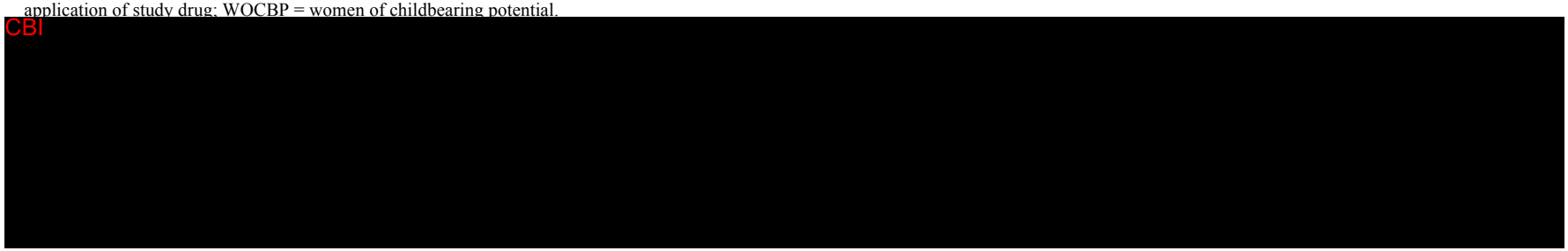

Appendix 2 NRS and Categorical Rating Scales

PAIN INTENSITY NUMERICAL RATING SCALE

What number represents your muscle pain/soreness with movement?

No Pain 0 1 2 3 4 5 6 7 8 9 10 Worst Possible Pain

CATEGORICAL PAIN RATING SCALE

What word best describes your muscle pain/soreness with movement?

☐ None (0)

☐ Slight (1)

☐ Moderate (2)

☐ Severe (3)

MUSCLE STIFFNESS NUMERICAL RATING SCALE

Stiffness refers to how hard it is to flex and extend your arm.

What number represents your muscle stiffness with movement?

No Stiffness 0 1 2 3 4 5 6 7 8 9 10 Worst Possible Stiffness

CATEGORICAL RELIEF RATING SCALE

What word best describes your relief from starting pain?

☐ No relief (0)

☐ A little relief (1)

☐ Some relief (2)

☐ A lot of relief (3)

☐ Complete relief (4)

SUBJECT GLOBAL ASSESSMENT

Overall, how would you rate the investigational product you received?

☐ Poor (0)

☐ Fair (1)

☐ Good (2)

☐ Very Good (3)

☐ Excellent (4)

CBI

[redacted]