A Placebo-controlled (Part 1) or Active-controlled (Part 2) trial of SABER®-Bupivacaine for the management of poStoperatIve pain following laparoScopic cholecysTectomy (PERSIST)

Unique Protocol ID:	C803-028
NCT Number:	NCT02574520
Date of Protocol:	08 March 2017

DURECT

PROTOCOL TITLE: A **P**lacebo-controlled (Part 1) or Active-controlled (Part 2) trial of SAB**ER**®-Bupivacaine for the management of po**S**toperat**I**ve pain following laparo**S**copic cholecys**T**ectomy (PERSIST)

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CLINICAL PROTOCOL

Protocol No.	C803-028
Title:	A **P**lacebo-controlled (Part 1) or Active-controlled (Part 2) trial of SAB**ER**®-Bupivacaine for the management of po**S**toperat**I**ve pain following laparo**S**copic cholecys**T**ectomy (PERSIST)
Phase	3
IND:	66086
Version:	**Original: 26 August 2015** **Amendment 01: 06 October 2015** **Amendment 02: 22 February 2016** **Amendment 03: 02 June 2016** **Amendment 04: 09 January 2017** **Amendment 05: 08 March 2017**

Sponsor: DURECT Corporation
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Cupertino, CA 95014, USA
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GCP Statement: The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) set forth in the International Conference on Harmonization (ICH) Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any local requirements.

Lead Principal Investigator: PPD
PPD
PPD

INVESTIGATOR AGREEMENT PAGE

DURECT Corporation

C803-028
Amendment 05: 08 March 2017

I have read and understood the information in this protocol and agree to conduct the trial according to the protocol (subject to any amendments), in accordance with the principles of Good Clinical Practice, the Investigator responsibilities stated in this protocol, and in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate IRB/IEC and any other institutional requirements. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of patients.

I agree to conduct in person or to supervise the trial. I will provide copies of the protocol, any subsequent protocol amendments, and access to all information provided by the Sponsor to the trial personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the test drug, the trial protocol, are aware of their obligations, are qualified to perform the tasks required, and are trained in any trial specific procedures

Principal Investigator:

Printed Name: **Date**
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Sponsor Approval:

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-MAR-2017
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1.0 TABLE OF CONTENTS

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2.0 Trial Synopsis

Title of Trial:	A **P**lacebo-controlled (Part 1) or Active-controlled (Part 2) trial of SAB**ER**®-Bupivacaine for the management of po**S**t-operat**I**ve pain following laparo**S**copic cholecys**T**ectomy (PERSIST)
Sponsor:	DURECT Corporation
Phase of Development:	Phase 3
Objective:	To evaluate the safety and efficacy of SABER®-Bupivacaine for alleviating postoperative pain on-movement compared with bupivacaine HCl in patients undergoing laparoscopic cholecystectomy.
Efficacy Endpoints:	Primary Efficacy Endpoint: • Pain intensity on movement measured at scheduled time points from 0-48 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM). Key Secondary Efficacy Endpoint: • Pain intensity on movement measured at scheduled time points from 0-72 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM). Additional Secondary Efficacy Endpoints: • Total IV morphine-equivalent dose of rescue opioids used during 0-72 hours following test drug administration • Composite endpoint of Silverman's Integrated Analgesic (SIA) assessment score over 0-72 hours following test drug administration • Proportion of patients taking no opioid rescue medication from PACU discharge until 72 hours after test drug administration • Time to first opioid rescue medication use after discharge from the PACU • Time to PACU discharge eligibility as assessed by modified Post-Anesthesia Discharge Scoring System (mPADSS)

CCI [redacted]

Safety Assessments:

- Adverse Events (both spontaneous and a solicited subset of AEs)
- Standard 12-lead ECG
- Safety Laboratory Tests
- Vital Signs and pulse oximetry
- Physical Examination
- Surgical site examination for bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and healing

Trial Design:

C803-028 is a randomized, parallel-group, double-blind, placebo-controlled (Part 1) and active-controlled (Part 2) multi-center trial evaluating the safety and efficacy of SABER®-Bupivacaine 5 mL in patients undergoing elective outpatient laparoscopic cholecystectomy. Randomization will be stratified by sex (See Sections 7.1, 11.3).

For Part 1 of the trial, the planned enrollment of approximately 320 eligible patients will be stopped early due to the transition to an active control in Part 2 of the trial. Approximately 90 patients will be enrolled in Part 1of the trial, before transition to Part 2. All data from these patients will remain blinded until completion of Part 2.

For Part 2 of the trial, 132 evaluable patients per treatment arm will provide at least 90% power (See Section 11.2) to meet the primary efficacy endpoint. Approximately 274 eligible patients will be randomized (See Section 5.3) in a 1:1 ratio to receive one of two treatments: 5 mL of SABER®-Bupivacaine instilled directly into the laparoscopic ports at the close of surgery or 15 mL of 0.5% bupivacaine HCl infiltrated into the port incisions at the close of surgery.

Five postoperative outpatient clinic visits will be scheduled for assessment of safety parameters including AEs and surgical site examinations and for collection of rescue medication usage data. All AEs, of whatever etiology and location, occurring after informed consent will be recorded on the eCRF. All AEs will be followed until resolution unless the patient is lost to follow up.

Pain intensity Measurements:	During the first 72 hours after test drug administration (i.e., through Study Day 4/Postoperative Day [POD] 3; See Table 1) pain intensity, CCI on movement (defined as sitting up, or attempting to do so, from a supine position), will be recorded by the patient. Patients will use an 11-point (0-10) numerical pain rating scale (NPRS) displayed by an electronic diary (LogPad®) to record their pain scores at specified times after administration of the test drug (see Table 2: Patient LogPad Schedule of Events). Pain intensity CCI on movement will also be recorded (1) prior to each IV fentanyl administration requested by the patient in the PACU, and (2) at home before the patient self-administers either one of two possible rescue medications (acetaminophen or oxycodone). CCI Patients should then record their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the patient is unable to sit up completely due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that pain score will be recorded.
Trial Population:	The trial population will consist of adult patients (males and females, 18 years of age and older) undergoing elective outpatient laparoscopic cholecystectomy under general anesthesia. For Part 1, approximately 90 patients will be randomized. For Part 2, approximately 274 eligible patients will be randomized in order to obtain 264 evaluable patients (i.e., patients who received any test drug). It has been estimated that 4% of randomized patients may not receive any test drug due to unforeseeable intra-operative exclusion (see Section 5.3).
Test drug, dosage and mode of administration:	SABER®-Bupivacaine 5 mL (660 mg bupivacaine base) will be instilled with a blunt-tipped applicator directly into the four laparoscopic ports just prior to closure. The 5 mL dose of test drug should be divided among the multiple ports to provide coverage of all surgical incisions. A sterile 5cc syringe with an attached 14G x 1¼ inch CCI IV catheter will be used to instill the test drug. Refer to Section 7.3.1 for detailed instructions.

Comparator, dosage and mode of administration:	For Part 1 of the study, 5 mL of 0.9% sterile normal saline will be instilled into the four laparoscopic ports in exactly the same way as SABER®-Bupivacaine. For Part 2 of the study, bupivacaine HCl, 15 mL of 0.5% solution (75 mg) without epinephrine, will be infiltrated into the four laparoscopic ports using a sterile 10 cc syringe and a 22 G x 1½ inch hypodermic needle. The dose should be divided between the four ports according to incision size in the same distribution proportion as for SABER®-Bupivacaine. Refer to Section 7.3.1 for detailed instructions. Each site will have a site specific Blinding Plan in place to describe the steps taken to ensure the blind is maintained as well as indicating which study staff will be blinded or un-blinded.
Power Calculations:	For Part 2 of the study, 132 subjects enrolled in each treatment group of the study will result in 90% power (assuming type 1 error rate of 5%) to detect a difference between 5 mL of SABER®-Bupivacaine and 15mL of bupivacaine HCl of[redacted] (the average pain on movement score during 48-hours post-dose). The sample-size estimate was based on an estimated effect size of[redacted] see Section 11.2).
Schedule of Events:	Refer to Table 1: Schedule of Events below.

Table 1: Schedule of Events

	Visit 1	Visit 2	Follow-up Call 1	Follow-up Call 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Trial Procedures	**Screening ≥ 5 days** (starts ≤ 30d and ≥ 5d pre-op)	**Day of Surgery** (Study Day 1)	**Study Day 2**	**Study Day 3**	**Study Day 4**	**Study Day 8 (±1 day)**	**Study Day 15 (±2 days)**	**Study Day 29 (± 3 days)**	**Study Day** 60 **(±3 days)**
			POD 1	POD 2	POD 3	POD 7 (±1 day)	POD 14 (±2 days)	POD 28 (± 3 days)	POD 59 (± 3 days)
Informed Consent (prior to any trial procedures)	√								
Demographics and Medical & Surgical History	√								
Physical Examination (including height and weight)	√							√[1]	√[1]
Inclusion / Exclusion Criteria	√	√[2]							
Safety Labs (Chemistry, Hematology, Urinalysis)	√[3]				√			√	√
Pregnancy Test	√[4]	√[5]							
12-lead ECG	√							√	√
Vital Signs[6] (BP, HR, RR, T) and SpO_2[7])	√	√[7]			√	√	√	√	√
Dispense LogPad and Train in Use	√								
CCI	√[9]	√							
Adverse Events[10,11]		←	—	—	—	—	—	—	→
Prior and Concomitant Medications		←	—	—	—	—	—	—	→
IWRS Randomization		√[12]							
CCI		√							
Surgery		√							
Dosing of Test Drug		√							
CCI		√							
mPADSS and PACU time of discharge[13]		√							
CCI	√	←	—	—	—	→			
Rescue Medication and Pain Scores[15]		←	—	—	—	→			
Surgical Site Exam and Assessment of Surgical Site AEs		√[16]			√	√	√	√	√
Discharge from hospital/surgcenter CCI		√							
Rescue Medication Reconciliation/Pill Count		√[17]			√	√	√	√	*
Surgical Complications Questionnaire			√	√					
Level of Activity (ambulation, sleeping, eating, and surgical wound pain[18])			√	√	√	√[18]	√[18]	√[18]	*
Medical Resource Utilization Assessment			√	√	√	√	√	√	*
Review LogPad data		√	√	√	√	√			

Footnotes for Schedule of Events Table:

1. Weight only
2. Review Inclusion/Exclusion Criteria to confirm patient is still eligible
3. In addition to safety labs, a urine drug screen for opiates, oxycodone, cannabinoids, amphetamines, cocaine, and methadone will be performed. Allow 3-7 days for central safety laboratory to process and provide results
4. Serum pregnancy test for females of childbearing potential
5. Urine pregnancy test for females of childbearing potential
6. Vital Signs measured after 5 minute rest (supine or sitting)
7. Vital signs and pulse oxygen saturation (SpO_2) will be measured on Visit 2 pre- and post-surgery. The vital signs (BP, HR, RR, temperature) and SpO_2 will be recorded on the eCRF at 15 minute intervals for a period of at least 2 hours after surgery.
8. CCI [redacted]
9. CCI [redacted]
10. AE collection starts from the time the patient signs the consent form and continues through final visit/early termination. All AEs will be followed until resolution. Resolution means no further changes in the event are expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.
11. Follow-up on both the pre-specified patient-reported AEs (including dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) solicited on the LogPad through POD 3, as well as spontaneous AEs.
12. If all Screening (i.e. pre-operative) Inclusion/Exclusion criteria are met randomization can be done up to CCI [redacted] day prior to surgery.
13. Eligibility for PACU discharge will be assessed by mPADSS. The mPADSS will be administered starting at 30 minutes after admission to the PACU and will be repeated at 15 minute intervals until a score of 9 or greater has been reached, indicating discharge eligibility.
14. CCI [redacted]
    Patients should then record their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded. Patients will complete assessments per the schedule detailed in Table 2: Patient LogPad Schedule of Events.
15. See Rescue Medication Regimen. Pre-rescue pain on movement score for oral rescue is recorded in the LogPad through Study Day 4. The site records IV rescue medication taken and corresponding pain score in the patient's chart and eCRF. The subject records oral opioid and acetaminophen rescue medication taken on the LogPad until Study Day 8. After Study Day 8 all rescue medication will be recorded in the investigative site source documents and Concomitant Medication (CM) eCRF. NSAIDs are not allowed until after Study Day 8.
16. On the day of surgery, Surgical Site Examination done at time of discharge to home (or hospital admission)
17. Record details of opioid prescription and acetaminophen dispensed for home use (identity, dose, amount dispensed, and dosing instructions) and if permitted, retain a copy of the opioid prescription in the source documents.
18. The site will ask the patient to rate their current surgical wound pain at Visit 4, 5 and 6.

* To be done only if completed as part of an Early Termination Visit.

Table 2: Patient LogPad Schedule of Events

Trial Procedures	**Screening**	**Day of Surgery** (Study Day 1)					**Study Day 2-4** (Postoperative Day 1 to 3)				**Study Day 5-8** (Postop Day 4 to 7)
	Target time	Hours post-dose					Target time (± 1 hour)				till Visit 4 (POD 7)
	20:00 (±1h)	1	4	6	8	10	08:00	12:00	16:00	20:00	
		+1 hour	(±30 minutes)								
Scheduled Pain Intensity CCI on Movement[1]	√[2] (5-7 days for training)	√[3]	√	√	√	√	√	√	√	√	
Solicited AE Checklist[4]				√		√				√	
Pain CCI on Movement Score prior to Oral Recue[1,5]		Oral med pain scores recorded on LogPad through POD 3 ◄——► IV med pain scores recorded on chart									
Oral Rescue Analgesia[5]		Subject records oral rescue medication on LogPad ◄——► Site records IV rescue medication on chart									

1 CCI [redacted] Patients should then record their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded.

2 CCI [redacted]

3 Investigative site personnel enter the time of test drug dosing into the LogPad prior to the subject awakening from anesthesia.

4 At each point of contact with the patient, investigative site personnel will follow-up with the patient regarding severity, frequency, duration and action taken of any AEs (including dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) reported on the LogPad.

5 Only oral rescue medication is recorded in the LogPad. IV rescue medication and corresponding pain CCI [redacted] on movement scores are recorded by the site in the patient's chart and eCRF.

3.0 List of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALT (SGPT)	Alanine amino transferase (Serum Glutamic Pyruvic Transaminase)
ANOVA	Analysis of variance
AR	Adverse reaction
AST (SGOT)	Aspartate amino transferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area under the curve
BA	Benzyl alcohol
BOCF	Baseline Observation Carried Forward
BP	Blood pressure
BSV	Between-subject-variability
BUN	Blood Urea Nitrogen
CDC/NHSN	Centers for Disease Control National Healthcare Safety Network
C_{max}	Maximum concentration
CFR	Code of Federal Regulations
CL/F	Apparent clearance
CM	Concomitant medication
CNS	Central nervous system
CRF	Case report form
CK	Creatine kinase
CRO	Contract research organization
CRU	Clinical Research Unit
CVS	Cardiovascular system
DEA	Drug Enforcement Administration
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ER	Extended Release
ES	Effect Size
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation or Term	Definition/Explanation
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive Web Response System
ITT	Intent to Treat
LC	Laparoscopic cholecystectomy
LDH	Lactate dehydrogenase
LogPad®	Electronic Diary
LS	Least square
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo method
mPADSS	Modified Post-Anesthesia Discharge Scoring System
MRI	Magnetic Resonance Imaging
nAUC	Normalized Area Under the Curve
NOTES	Natural Orifice Transluminal Endoscopic Surgery
NPRS	Numeric Pain Rating Scale
NRS	Numeric Rating Scale
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PACU	Post-Anesthesia Care Unit
PCA	Patient-Controlled Analgesia
PD	Pharmacodynamic
PK	Pharmacokinetic
POD	Postoperative Day
PONV	Postoperative Nausea and Vomiting
PR	Duration from onset of atrial depolarization until onset of ventricular depolarization, measured from the beginning of the P wave to the beginning of the QRS complex
QRS	Part of electrocardiographic wave representing ventricular depolarization

Abbreviation or Term	Definition/Explanation
QT	Duration of ventricular depolarization and subsequent repolarization, measured from the beginning of the QRS complex to the end of the T wave
QTc	Corrected QT interval
RBC	Red blood cell
ROA	Route of administration
RR	Respiratory rate
SABER®	Sucrose acetate isobutyrate extended release
SAE	Serious adverse event
SAIB	Sucrose acetate isobutyrate
SAP	Statistical analysis plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamate pyruvate transaminase
SIA	Silverman's Integrated Analgesic assessment score
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Half-life
WBC	White blood cell
WHO	World Health Organization
WOCF	Worst Observation Carried Forward

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[redacted]

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[redacted]

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[redacted]

5.0 Current trial

5.1 Trial Objective

To evaluate the safety and efficacy of SABER®-Bupivacaine for alleviating postoperative pain on-movement compared with bupivacaine HCl in patients undergoing laparoscopic cholecystectomy.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

5.3 Population

The trial population will consist of adult patients (males and females, 18 years of age and older) undergoing elective outpatient laparoscopic cholecystectomy under general anesthesia. In Part 1, approximately 90 patients will be randomized. In Part 2, approximately 274 eligible patients will be randomized in order to obtain 264 evaluable patients (i.e., patients who received test drug). It has been estimated that 4% of randomized patients may not receive any test drug due to unforeseeable intra-operative exclusion criteria such as need to convert to open laparotomy or need for a fifth port and trocar.

5.3.1 Inclusion Criteria

1. Patients scheduled for elective outpatient laparoscopic cholecystectomy using a conventional 4-port laparoscopic procedure.
2. Must be able and willing to provide written informed consent, complete trial-related procedures, and communicate with the trial staff.
3. Males and females 18 years of age or older.
4. ASA Class I, II, or III.
5. Patients of child-bearing potential must agree to use a medically acceptable method of contraception to prevent pregnancy for the duration of their participation in the trial. Medically acceptable methods of contraception that may be used by the patient and/or the partner include: oral contraception or patches (consistently for 3 months prior to trial dosing), NuvaRing (etonogestrel/ethinyl estradiol vaginal ring), diaphragm with vaginal spermicide, IUD (coil), condom and vaginal spermicide, surgical sterilization (6 months post-surgery), post-menopausal patient (not experienced a menstrual period for a minimum of two years), and progestin implant or injection (used consistently for 3 months prior to trial dosing).

6. Must be living close enough to the investigative site to attend the four scheduled follow-up clinic visits.

5.3.2 Screening Exclusion Criteria

1. Pregnant or nursing females.
2. Patients with absolute or relative contraindications to laparoscopic cholecystectomy. These include, but are not limited to: generalized peritonitis, septic shock from cholangitis, severe acute pancreatitis, untreated coagulopathy, previous abdominal operations which prevent safe abdominal access or progression of the procedure, advanced cirrhosis with failure of hepatic function, and suspected gallbladder cancer (SAGES Guidelines, 2010).
3. Patients with prior midline abdominal surgery who are at risk for adhesions that may complicate laparoscopic cholecystectomy and/or accurate pain assessments.
4. Patients requiring emergency surgery or urgent surgery (fewer than 5 days between screening and surgery). Patients that require the preoperative placement of a cholecystostomy tube for the management of acute cholecystitis are also excluded.
5. Patients with a pre-planned overnight stay or pre-planned hospital admission.
6. Patients scheduled for single incision, mini trocars, natural orifice transluminal endoscopic surgery (NOTES), robotic laparoscopic procedures, or any procedure (other than cholangiograms and minimal adhesiolysis) in addition to laparoscopic cholecystectomy.
7. Patients with known hypersensitivity to amide local anesthetics such as bupivacaine.
8. Patients with acute pain that is not due to cholecystitis.
9. Patients with a history of chronic pain unrelated to gallbladder disease.
10. Patients with ongoing depression or psychosis.
11. Patients undergoing long-term treatment with opioids or other analgesics, including acetaminophen, NSAIDs, anticonvulsants (gabapentin or pregabalin), and antidepressants (SSRIs, SNRIs, and tricyclics), but not including daily low-dose aspirin (see full list of excluded medications in Section 7.6.1).
12. Patients who are being treated chronically with systemic corticosteroids or who will require peri-operative corticosteroids because of adrenal insufficiency (inhalational or topical corticosteroids are permitted).
13. Patients who may be unsuitable for opioid administration (such as sensitivity [e.g., history of severe nausea and vomiting] hypersensitivity, known history of abuse or addiction, or unwillingness to take prescribed rescue opioids).
14. Use of long-acting anticoagulants and antiplatelet drugs (with the exception of low dose aspirin [81 mg]) in the 1-week prior to surgery. (Short-acting new oral anticoagulants should be discontinued prior to surgery according to the label instructions.)

15. Patients who are incapable of operating the electronic diary (LogPad) and/or miss more than 1 of the practice diary assessments (i.e., are less than 80% compliant) during screening should not be randomized. Compliance with the LogPad assessments is essential to the study.
16. Patients who self-report an alcohol dehydrogenase deficiency.
17. Patients participating in any other trial with an investigational drug or device concurrently or less than 30 days prior to surgery for this trial.
18. Patients who, in the Investigator's opinion, should not participate in the trial or may not be capable of following the trial procedures for any reason.

5.3.3 Post-randomization (i.e. Intra-operative) Exclusion Criteria

19. Patients who have been converted to an open cholecystectomy or who experience other serious, unexpected intra-operative complications should **not** be treated with test drug.
20. Patients who undergo unplanned additional surgical procedures (other than cholangiograms and minimal adhesiolysis) in addition to laparoscopic cholecystectomy should **not** be treated with test drug.
21. Patients who require intra-operative doses of fentanyl that are higher than permitted per protocol should **not** be treated with the test drug.
22. Patients who require the placement of a fifth laparoscopic port or percutaneous surgical drain should **not** be treated with test drug.

Patients excluded from test drug administration because of one of the above intra-operative exclusions (18-21) will be listed as "randomized, but not treated", and will be terminated from the trial.

5.4 Trial Design

C803-028 is a randomized, parallel-group, double-blind, placebo-controlled (Part 1) and active-controlled (Part 2), multi-center trial evaluating the safety and efficacy of SABER®-Bupivacaine 5 mL in patients undergoing elective outpatient laparoscopic cholecystectomy.

The randomization will be stratified by sex (See Section 11.3). For Part 1, it was planned to enroll approximately 320 eligible patients (See Section 5.3) in a 1:1 ratio to receive one of two treatments: SABER®-Bupivacaine 5 mL; or sterile normal saline 5 mL (placebo) instilled directly into the laparoscopic ports at the close of surgery. The 5 mL of test drug is divided between the multiple ports to provide coverage of all surgical incisions (see Section 7.3.1). CCI [redacted] The data from Part 1 patients will continue to be blinded until the completion of Part 2 of the trial.

For Part 2 of the trial, 132 evaluable patients per treatment arm will provide at least 90% power (See Section 11.2) to meet the primary efficacy endpoint. In order to obtain 264 evaluable

patients, approximately 274 eligible patients (assuming 4% of patients may not be dosed due to unforeseeable intra-operative exclusion) will be randomized in a 1:1 ratio to receive one of two treatments: 5 mL of SABER®-Bupivacaine instilled directly into the laparoscopic ports or 15 mL of 0.5% bupivacaine HCl infiltrated into the port incisions at the close of surgery.

Five postoperative outpatient clinic visits will be scheduled for assessment of safety parameters including AEs and surgical site examinations and for collection of rescue medication usage data. All AEs, of whatever etiology and location, occurring after informed consent will be recorded on the eCRF. All AEs will be followed until resolution unless the patient is lost to follow up. Resolution means no further changes in the event would be expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.

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5.4.1 Dose

Test drug for the trial consists of a single administration of one of two treatments based on a computer-generated randomization schedule prepared before the study:

Part 1

- Treatment Group 1: SABER®-Bupivacaine 5 mL (POSIMIR®)(132 mg/mL, 660 mg bupivacaine base)
- Treatment Group 2: Sterile normal saline 5 mL (0.9% sodium chloride injection, USP) (placebo)

Part 2

- Treatment Group 3: SABER®-Bupivacaine 5 mL (POSIMIR®)(132 mg/mL, 660 mg bupivacaine base)

- Treatment Group 4: Bupivacaine HCl without epinephrine, 15 mL of 0.5% solution (75 mg)

5.4.2 Primary and Secondary Endpoints

The primary efficacy endpoint is:

- Pain intensity on movement measured at scheduled time points from 0-48 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM).

  To account for the impact of rescue medication use on the scheduled pain scores, the half-life substitution method will be used. Specifically, if the scheduled pain score has been assessed within one plasma half-life after the use of rescue medication (IV or oral opioid or oral acetaminophen), and if the pre-rescue medication pain score is higher than the scheduled one, then the pain score recorded at the time of rescue medication administration will be substituted for the scheduled pain score (FDA, 2014). If a rescue medication pain score is missing, then the worst pain score up to that point will be substituted instead.

The key secondary efficacy endpoint is:

Pain intensity on movement measured at scheduled time points from 0-72 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM). Additional secondary endpoints are:

- Total IV morphine-equivalent dose of rescue opioids used during 0-72 hours following test drug administration (standard conversion factors are used to convert different opioids to IV morphine-equivalents; CCI [redacted]

- Composite endpoint of Silverman's Integrated Analgesic (SIA) assessment score (Dai et al, 2013 and Silverman et al, 1993) over 0-72 hours following test drug administration

- Proportion of patients taking no opioid rescue medication from PACU discharge until 72 hours after test drug administration

- Time to first opioid rescue medication use after discharge from PACU

- Time to PACU discharge eligibility as assessed by mPADSS (Chung, 1995; Awad and Chung, 2006)

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

5.5 Anesthesia Requirements

Operative anesthetic choices may have a significant bearing on postoperative pain. Investigators should therefore observe the following anesthesia requirements, the objectives of which are threefold: (1) to reduce variability in the baseline (pre-dose) state of the trial patients, (2) to limit the obscuring effect of excessive intra-operative opioid analgesia on the postoperative pain signal, and (3) to ensure that potential confounders, such as the use of local or regional anesthesia, can be avoided.

The anesthesia requirements are:

- General endotracheal anesthesia
- Midazolam, up to 2 mg, may be given pre-operatively
- Propofol induction
- Maintenance with inhalational anesthesia (sevoflurane or desflurane) and an oxygen/air mixture.
    - No isoflurane or nitrous oxide
    - No total intravenous anesthesia (TIVA)
- Intra-operative opioid analgesia will be limited to IV fentanyl, with a maximum dose of 2.5 mcg/kg (including the induction dose) during the first hour the patient is anesthetized. If necessary, additional fentanyl may be given starting in the second hour, with a maximum dose of 1.0 mcg/kg during each subsequent 30 minute interval.
    - Subjects requiring higher doses should not be treated with test drug, even if previously randomized.
    - Any fentanyl given per patient complaint of pain after emergence from anesthesia will be considered rescue medication and will be limited to doses of 12.5 mcg or 25 mcg at minimum 5 minute intervals, as described in Section 5.7.1.
- A single IV dose of a 5-HT_3 antagonist (ondansetron 4 mg, granisetron 1 mg, or dolasetron 12.5 mg) should be administered at the close of surgery to all patients for prophylaxis of post-operative nausea and vomiting (PONV).
    - No Aloxi® (palonosetron HCl) should be administered.

- No use of local anesthetics will be permitted for neuraxial analgesia, regional nerve block, intra-abdominal administration, and wound infiltration (other than test drug).
    - However, IV lidocaine may be used to ameliorate propofol injection pain; maximum dose of 40 mg.
- No peri-operative oral or IV acetaminophen or NSAIDs (including Toradol® [ketorolac] Injection, Caldolor® [ibuprofen] Injection, and Ofirmev® [acetaminophen] Injection), or any other agent with potential analgesic properties (e.g., ketamine, dexmedetomidine, other alpha-2 agonists) will be permitted.
- No dexamethasone or other corticosteroids will be permitted.

5.6 Surgical Requirements

- Patients must be scheduled for elective outpatient laparoscopic cholecystectomy. The surgery should be scheduled before noon to allow for completion of the 10 hour post-dose pain assessment at home.
    - Emergency or urgent cases will **not** be eligible.
    - Patients who require the pre-operative placement of a cholecystostomy tube for the management of acute cholecystitis are **not** eligible
    - Patients with a pre-planned overnight stay or pre-planned hospital admission are **not** eligible.
    - No combination procedures (other than cholangiograms and minimal adhesiolysis) should be contemplated pre-operatively. Patients who undergo additional surgical procedures intra-operatively should **not** be treated with test drug.
    - If during surgery, significant adhesions are encountered that, in the opinion of the investigator would complicate surgery and increase postoperative pain, that patient should **not** be treated with test drug.
    - Patients who require the placement of a fifth laparoscopic port or percutaneous surgical drain should **not** be treated with test drug.
- A conventional 4-port laparoscopic procedure using a combination of 5 mm and 10-12 mm port incisions to afford instrument access (Baron et al, 2015; SAGES Guidelines, 2010) will be required to allow standardization of test drug administration.
    - If more than 4 ports are required, the patient should **not** be treated with test drug.
    - **No** single incision, NOTES, or robotic laparoscopic cholecystectomy will be permitted.
    - **No** mini port incisions (i.e., less than 5 mm) will be permitted.
- Prophylactic antibiotics should be used as per institutional standards.

- For the larger 10-12 mm incisions, the fascia should be closed with interrupted absorbable sutures. The skin layer should be closed with absorbable subcuticular sutures, followed by application of Steri-Strips, Dermabond or equivalent skin adhesive.
    - If gauze or other opaque dressing is used, it must be lifted during the surgical site examination to permit visualization of the wound.
- Patients at high risk for conversion to open surgery are not suitable for randomization.
    - Patients who have been converted to an open cholecystectomy or who experience other serious, unexpected intra-operative complications that would increase postoperative pain or risks should **not** be treated with test drug.
- Thromboprophylaxis for DVT prevention should be provided, as needed, per institutional standards.
- Long-acting anticoagulants, such as warfarin, and long-acting antiplatelet drugs, such as clopidogrel, should be discontinued one week prior to surgery. Short-acting newer oral anticoagulants should be discontinued prior to surgery according to the labeled instructions. Low dose aspirin (81 mg) may be continued throughout surgery (Joseph, et al., 2015). The anticoagulants and antiplatelet agents may be restarted after surgery when hemostasis is assured and there are no bleeding complications from surgery

5.7 Rescue Analgesia for Postoperative Pain Management

PACU

- IV fentanyl 12.5 or 25 mcg bolus doses given at no less than 5-minute intervals

Home Use

- Oxycodone IR 5 mg tablets
- Acetaminophen 500 mg tablets

5.7.1 PACU Rescue Medication Regimen

In the PACU, pain may be treated with rescue analgesia (IV fentanyl in 12.5 or 25 mcg doses given at no less than 5-minute intervals). IV fentanyl should be given only as necessary to control pain, only at the patient's request, and not as a scheduled or prophylactic dose. The patient's pain score CCI on movement (defined as sitting up, or attempting to do so, from a supine position) should be assessed immediately before giving each rescue dose of IV fentanyl. If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that pain score will be recorded. The dose and time of administration of IV fentanyl and associated pain scores must be recorded on the patient's chart and on the eCRF. No IV acetaminophen, IV NSAIDs, or any analgesic drug (including Toradol® [ketorolac] Injection, Caldolor® [ibuprofen] Injection, and Ofirmev® [acetaminophen] Injection) other than IV fentanyl should be given during the PACU stay. However, the following exception will apply: at sites where patients are

transferred prior to discharge to a Phase 2 recovery unit (or step down unit), then oral oxycodone or oral acetaminophen may be given according to the instructions described in Section 5.7.2 for the use of oral rescue medication.

5.7.2 Oral Rescue Medication Regimen for Home Use

Patients will be provided written instructions regarding rescue medication usage prior to discharge. Prior to rescue dosing, the patient must record pain intensity CCI **on movement. Each dose of rescue medication will be recorded by the patient on the LogPad.**

From PACU discharge through Study Day 8 (POD 7), analgesic rescue medications are limited to oxycodone IR 5 mg tablets, prescribed by the surgeon (or surgeon's delegate), and acetaminophen 500 mg tablets, supplied by the Sponsor.

Patients must be instructed to not take both oxycodone and acetaminophen within 4 hours of each other. Generally, oxycodone should be taken for moderate to severe pain and acetaminophen should be taken for mild to moderate pain and the two drugs should not be taken together.

No Combination products (e.g., Percocet, Vicodin, Vicoprofen, Zydone, and Percodan) or extended release opioid products (e.g., Oxycontin, Opana ER, Kadian, and Ultram ER) will be permitted from screening to trial completion (Study Day 60).

Patients will be instructed that they must bring any unused rescue medication (oxycodone IR and acetaminophen) with them to the clinic visits (through Visit 6 or early termination) for reconciliation purposes. The number of tablets dispensed will be recorded and the number of remaining tablets will be counted at each clinic visit.

5.7.2.1 Rescue Oral Opioids

For the treatment of moderate to severe pain, patients will be prescribed oxycodone IR 5 mg tablets. Exactly 24 tablets should be prescribed. One or two tablets may be taken every 4 hours for moderate to severe pain. Each dose of oxycodone will be recorded by the patient on their LogPad.

5.7.2.2 Rescue Oral Acetaminophen

For the treatment of mild to moderate pain, patients will be supplied by the sponsor with acetaminophen 500 mg tablets (one bottle of 24 tablets). One or two tablets may be taken every 4 hours as required for pain. **No more than 8 tablets (4000 mg) may be taken in any 24 hour period.** Each dose of acetaminophen will be recorded by the patient on their LogPad. A screen will display an alert that they have reached the maximum allowed dose when a patient takes an 8^{th} tablet (4000 mg total) in any 24 hour period.

5.7.2.3 No Concomitant Use of Oxycodone and Acetaminophen

Oxycodone and acetaminophen may not be taken concomitantly within the same four hour interval.

6.0 Trial Conduct

6.1 Investigative Sites

The trial will be conducted at a minimum of 5 and up to 25 investigative sites in the United States.

Investigative sites will be selected based on experience in conducting analgesic studies and access to the selected patient population through either general surgery practices or hospitals where a general surgeon qualified by training or experience is available to perform or oversee procedures required by the protocol.

Each Investigator participating in this trial will meet the following criteria:

- Appropriate qualifications including current medical license, applicable certificates or personnel/sub-investigators with certificates (e.g. Drug Enforcement Administration [DEA] documentation regarding prescribing of Schedule II and higher drugs), and adequate GCP knowledge
- Availability of accessible, interested, and well organized support staff
- Availability of diagnostic facilities to support trial data requirements
- Adequate test drug storage facilities
- Availability of physician emergency response at all times

A full description of the Investigator responsibilities has been included in Appendix 6.

If a given investigative site approaches randomization of 20% of the total number of evaluable subjects (264) into Part 2 of the trial, the Sponsor will assess the appropriateness of allowing the center to continue randomizing additional subjects into the trial based upon factors such as monitored site performance including documentation and protocol compliance.

6.2 Sponsor Obligations of Trial Conduct

Sponsor responsibilities such as data management (including electronic case report forms), site management, site monitoring, and central safety laboratory services will be transferred to one or more contract research organizations (CRO).

The safety profile of bupivacaine is well established. SABER®-Bupivacaine treatment is not intended to prolong life or reduce risk of a major adverse health outcome or major morbidity. Therefore, a Data Safety Monitoring Board has not been planned for this trial, which involves a

single dose administration and short trial duration. However, periodic reviews of blinded safety data will be performed by the DURECT Medical Monitor according to the Safety Monitoring Plan (see Section 11.9). If pre-specified serious adverse events of interest (see Section 9.3.1) reach a specified threshold incidence, an independent Safety Assessment Committee will review unblinded safety data for the affected patients (see Section 9.3.4).

6.3 Duration

Patient participation will last for up to 93 days, consisting of:

- Up to 30 day screening period (minimum of 5 days, with at least 7 days recommended)
- Surgery (Study Day 1) and the administration of the single dose of test drug with discharge to home (or hospital admission, if necessary) on the day of surgery per local practice or ≥ 2 hours post-surgery, whichever is later.
- Follow-up phone calls on POD 1 and 2/Study Days 2 and 3
- Follow-up outpatient clinic visits on:
    - Study Day 4/POD 3,
    - Study Day 8/POD 7 ± 1 day,
    - Study Day 15/POD 14 ± 2 day,
    - Study Day 29/POD 28 ± 3 days,
    - A final clinic visit on Study Day 60/POD 59 ± 3 days.

Outpatient clinic visits will be done for assessment of AEs, surgical site examinations, and rescue medication usage.

All AEs, of whatever etiology and location, occurring after informed consent should be recorded on the eCRF as an AE. All AEs will be followed until resolution unless the patient is lost to follow up. Resolution means no further changes in the event are expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.

6.4 Discontinuation of Trial

DURECT Corporation reserves the right to terminate the trial at any time.

7.0 Trial Procedures

Surgery will be performed under general anesthesia as described in Section 5.5 at a hospital or ambulatory surgical center. Discharge will occur on the day of surgery per local practice. If conversion to open surgery is necessary, or more than 4 ports have been deemed necessary during the trial, then the patient is **not** to be dosed with test drug.

Operating room (OR) personnel will be un-blinded due to inherent differences between SABER®-Bupivacaine and Placebo saline or bupivacaine HCl in viscosity and color. Assessment of study endpoints, adverse events and surgical site examinations, must be done by blinded personnel. Patients must remain blinded throughout the study. Investigators will be asked to sign a form for each patient that appropriate personnel have remained blinded to patient group assignment.

During the first 72 hours after test drug administration (i.e., through CCI Day 4/Postoperative Day [POD] 3) pain intensity, both CCI on movement (defined as sitting up, or attempting to do so, from a supine position), will be recorded by the subject using a 11-point (0-10) numerical pain rating scale (NPRS) on an electronic diary (LogPad®) at specified times after recovery from anesthesia (see Table 2: Patient LogPad Schedule of Events).

Pain intensity CCI on movement will also be recorded (1) prior to each IV fentanyl administration requested by the patient in the PACU, and (2) at home before the patient self-administers either rescue medication. CCI Patients should then record their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded.

If a patient is admitted to the hospital following test drug administration, pain assessments and rescue medication should follow the same instructions as for home use, to the extent possible.

7.1 Patient Randomization

Part 1

It was planned that approximately 320 eligible patients would be randomized, in order to obtain 306 evaluable patients (i.e., patients who received any test drug and have at least one post-surgical pain intensity score). It had been estimated that 4% of randomized patients may not receive any test drug due to unforeseeable intra-operative exclusion. Patients would be randomized in a 1:1 ratio to receive one of two treatments based on a computer-generated randomization schedule prepared before the study:

- Treatment Group 1: SABER®-Bupivacaine 5 mL (POSIMIR®)(132 mg/mL, 660 mg bupivacaine base)
- Treatment Group 2: Sterile normal saline 5 mL (0.9% sodium chloride injection, USP) (placebo)

Due to the early administrative stopping, only approximately 90 subjects will be enrolled and randomized in Part 1.

Part 2

Approximately 274 eligible patients will be randomized, in order to obtain 264 evaluable patients (i.e., patients who received any test drug). It has been estimated that 4% of randomized patients may not receive any test drug due to unforeseeable intra-operative exclusion such as conversion to open cholecystectomy or need for a fifth port. Patients will be randomized in a 1:1 ratio to receive one of two treatments based on a computer-generated randomization schedule prepared before the study:

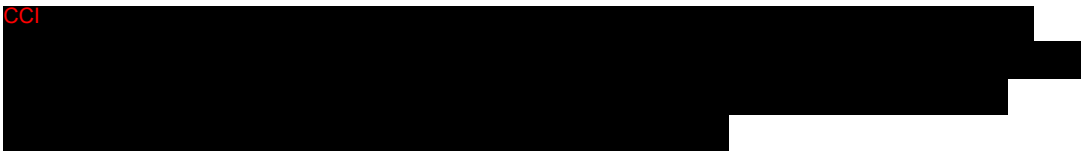
- Treatment Group 3: SABER®-Bupivacaine 5 mL (POSIMIR®)(132 mg/mL, 660 mg bupivacaine base)
- Treatment Group 4: Bupivacaine HCl without epinephrine, 15 mL of 0.5% solution (75 mg)

CCI

Following screening and confirmation of eligibility, an interactive web response system (IWRS) will be used to assign patients to a treatment group. The IWRS will confirm randomization via automatic notification to the investigative site.

If all Screening (i.e. pre-operative) Inclusion/Exclusion criteria have been met, randomization can be done up to 1 business day prior to surgery. In the event that a randomized patient does not have the surgical procedure for unforeseen circumstances (see Section 5.3.3) or does not receive any test drug, replacement of the patient has been planned. The IWRS system will be algorithmically instructed to issue the appropriate randomization replacement and to ensure the balance of treatment as planned. Precise details on the IWRS algorithm have been described in the IWRS specifications.

CCI



If a given study center approaches randomization of 20% of the total number of evaluable subjects (264) into Part 2 of the trial the Sponsor will assess the appropriateness of allowing the center to continue randomizing additional subjects into the trial based upon factors such as monitored site performance including documentation and protocol compliance.

7.2 Maintenance of the Blind

For the best chance of achieving a valid and reliable test of efficacy, the blind must be maintained despite the fact that several members of the site staff (pharmacist, operating room staff) will necessarily be un-blinded by the difference in color and viscosity between SABER®-Bupivacaine and comparator (saline placebo [Part 1] or bupivacaine HCl [Part 2]) test drugs.

Nonetheless, un-blinded trial staff must not disclose which test drug the patient received, or bias the patient or blinded staff by discussing the group assignments with them. Surgeons and other operating room personnel should take care not to include any potentially unblinding information (e.g., volume or method of test drug administration) in their operative notes or other routinely collected surgical records). Assessment of study endpoints, such as adverse events and surgical site examinations, must be done by blinded personnel. During any routine postoperative clinical examinations, the un-blinded surgeon must take care not to inadvertently un-blind the patient. Any clinical examinations done by the operating surgeon will be done for standard of care only and must not be used for any of the trial-related surgical site examinations. Each site will have a site specific Blinding Plan in place to describe the steps taken to ensure the blind is maintained as well as indicating which study staff will be blinded or un-blinded. Included in this Blinding Plan will be a form that must be signed by the principal investigator stipulating that un-blinded staff have not discussed group assignment with blinded staff, and that all protocol related evaluations have been performed only by the latter.

Vial cartons will carry identical labels and vials will be packaged in individual cartons to avoid any side-by-side comparisons of the vial carton contents. Each vial carton and the boxes containing multiple vial cartons will have tamper-evident seals.

If in a medical emergency knowledge as to whether SABER®-Bupivacaine or saline Placebo (Part 1) or bupivacaine HCl (Part 2) has been administered is critical for the supportive therapy of the patient or will influence further medical treatment of the patient, the Investigator or designee should obtain the patient's test drug treatment assignment from the IWRS system. If a patient is un-blinded by the investigative site, the IWRS system will send an alert to the Sponsor and their designee, and the site must contact the sponsor directly within 24 hours of the incident.

The date, time, reasons for breaking the blind and person doing so must be documented in the source record as it will be reviewed by Sponsor representatives. Unless medically indicated, the treatment should not be disseminated further or shared with the patient to prevent introduction of bias. Before a blind is broken, the Sponsor should be contacted if possible.

7.3 Trial Test Drug

7.3.1 Test Drug Administration Instructions for SABER®-Bupivacaine and Saline Placebo

Using sterile technique, the test drug (either SABER®-Bupivacaine 5 mL [Part 1 and Part 2] or sterile normal saline 5 mL [Part 1 only]) will be drawn up into a 5 mL Norm-Ject® syringe using

a 16 G hypodermic needle, both of which will be supplied by the Sponsor. A small excess of test drug (approximately 5.5 mL) should be drawn up into the syringe to allow for dead space in the catheter used for administration. The 16 G needle will be removed and replaced with a plastic 14G x 1¼ inch[CCI] IV catheter (supplied by Sponsor) to aid in the administration of the test drug into all of the port incisions. Once the catheter has been attached to the syringe, the excess contents will be expelled through the catheter (along with any air) to bring the total quantity in the syringe to 5 mL. The test drug may be drawn up into the syringe up to one hour before dosing.

After removal of the trocars, desufflation of the abdomen, and closure of the fascial layer associated with the larger ports, the test drug will be administered sequentially into each of the port incisions. Each incision will be closed with a running subcuticular suture. Prior to tying the final knot, the plastic syringe-tip applicator (IV catheter) will be inserted into the wound and directed down to the level of the fascia. While pulling mildly upward on the free ends of the suture to create a virtual intra-incisional space, the prescribed quantity of test drug will be instilled into the incision via the syringe-tip applicator. The applicator should be gradually withdrawn while instilling test drug to ensure even distribution throughout the wound, and mild upward tension on the suture ends should be maintained to ensure the test drug remains entirely within the wound. The final knot will then be tied to complete closure of the incision. The patient number, drug vial number, date and time of drug administration (defined as the time of completion of administration), and the volume of test drug administered into each laparoscopic port will be recorded.

The 5 mL dose of test drug should be divided among the multiple ports to provide coverage of all surgical incisions. In this clinical trial, a conventional 4-port laparoscopic procedure has been required to allow standardization of test drug administration. If more than 4 ports are required the patient should **not** be treated with the test drug. The test drug should be distributed according to the length of the port incisions and the function of the port. The 10-12 mm ports—and especially the port used for extraction of the gall bladder—should receive proportionally more of the test drug than the smaller 5 mm ports.

After subcuticular closure, any excess test drug remaining on the skin should be grossly removed with a sterile sponge or gauze pad. If a film of test drug remains on the skin, it should be wiped clean with one or more isopropyl alcohol wipes before application of Steri-Strips, Dermabond, or equivalent skin adhesive.

One of the two following test drug distribution patterns is recommended for typical laparoscopic ports:

Table 3: Test Drug Distribution in Laparoscopic Ports

Port size*	SABER®-Bupivacaine 5mL		Bupivacaine HCl 15mL	
4 ports	**Target Volume**	**Percentage of Total**	**Target Volume**	**Percentage of Total**
5 mm	0.5 mL	10%	1.5 mL	10%
5 mm	0.5 mL	10%	1.5 mL	10%
10-12 mm	2.0 mL	40%	6.0 mL	40%
10-12 mm	2.0 mL	40%	6.0 mL	40%
5 mm	0.8 mL	16%	2.4 mL	16%
5 mm	0.8 mL	16%	2.4 mL	16%
5 mm	0.8 mL	16%	2.4 mL	16%
10-12 mm	2.6 mL	52%	7.8 mL	52%

* This refers to the trocar diameter. The actual incision length will be longer and may vary depending on the method of abdominal entry.

NOTE: For Part 2, amount administered to each port must be recorded in the source and eCRF as a percentage rather than a millimeter amount to avoid inadvertent unblinding due to differences in the volume administered between the 2 treatment groups.

7.3.2 Test Drug Administration Instructions for Bupivacaine HCl (Part 2)

After completion of the laparoscopic cholecystectomy, desufflation of the abdomen, removal of the trocars, and closure of the fascial layer for the larger ports, bupivacaine HCl, 15 mL of 0.5% solution will be infiltrated into the margins of the incisions according to the distribution in Table 3. The infiltration should be done according to usual practice, using the supplied 10 cc syringes and the 22GA x 1½" hypodermic needles After infiltration of a total of 15 mL of bupivacaine HCl distributed among the four ports according to Table 3, the incisions are closed with subcuticular sutures and Steri-Strips, Dermabond, or equivalent skin adhesive.

7.3.3 Packaging and Labeling of Test Drug

Part 1

The Sponsor will provide SABER®-Bupivacaine (POSIMIR®) to the investigative site in single-use 10 mL glass vials with rubber stoppers (containing 6.2 ± 0.5 mL of SABER®-Bupivacaine) and vials containing 10 mL of commercial, sterile normal saline placebo (0.9% sodium chloride injection, USP).

The vial (i.e. kit) and/or carton label will contain a description of contents, trial identification, lot number, kit number, manufacture date (or retest date), relevant caution statements, storage conditions, and Sponsor information.

SABER®-Bupivacaine (POSIMIR®)132 mg/mL, 660 mg bupivacaine base) and commercial, sterile normal saline placebo (0.9% sodium chloride injection, USP) vial cartons will carry identical labels and will be packaged in individual cartons to avoid any side-by-side comparisons of the vial content. Each vial carton and the boxes containing multiple vial cartons will have tamper-evident seals. The vials containing SABER®-Bupivacaine (POSIMIR®) and commercial, sterile normal saline placebo will be labeled with their contents.

Part 2

The Sponsor will provide SABER®-Bupivacaine (POSIMIR®) to the investigative site in single-use 10 mL glass vials with rubber stoppers (containing 6.2 ± 0.5 mL of SABER®-Bupivacaine) and vials containing 30 mL of commercial, 0.5% bupivacaine HCl without epinephrine.

The vial (i.e. kit) and/or carton label will contain a description of contents, trial identification, lot number, kit number, manufacture date (or retest date), relevant caution statements, storage conditions, and Sponsor information.

SABER®-Bupivacaine (POSIMIR®)132 mg/mL, 660 mg bupivacaine base) and commercial, 0.5% bupivacaine HCl without epinephrine vial cartons will carry identical labels and will be packaged in individual cartons to avoid any side-by-side comparisons of the vial content. Each vial carton and the boxes containing multiple vial cartons will have tamper-evident seals. The vials containing SABER®-Bupivacaine (POSIMIR®) and commercial, 0.5% bupivacaine HCl without epinephrine will be labeled with their contents.

7.3.4 Storage of Test Drug

SABER®-Bupivacaine (POSIMIR®), commercial, sterile normal saline placebo and bupivacaine HCl will be stored at 20°C to 25°C (with temperature excursions allowed between 15 to 30° C) in a secure area with restricted access.

7.3.5 Preparation of Test Drug

The test drug requires no reconstitution or additional preparation prior to administration.

7.3.6 Drug Accountability

Test Drug

SABER®-Bupivacaine, saline placebo (Part 1) and bupivacaine HCl (Part 2) will be accounted for by the investigative site and recorded on the drug accountability log.

The test drug will be administered to the patient by the un-blinded surgeon; therefore no patient compliance measures with regard to the test drug are necessary. Additionally, specific test drug dosing information will be recorded on the appropriate source document and electronic case report form (eCRF).

All used syringes and needles will be disposed as per local health and safety standard operating procedures.

All used and unused test drug (SABER-Bupivacaine, saline placebo [Part 1], and bupivacaine HCl [Part 2]) vials will be kept at the investigative site until test drug reconciliation by the un-blinded monitor and must be available for verification during monitoring visits.

After monitoring, a final reconciliation of drug accountability records, and authorization by DURECT, all used and unused vials of test drug will be returned to DURECT or properly disposed of at the investigative site, if permitted per local SOPs and regulations. Documentation of disposition of all test drug will be provided to DURECT.

Sponsor Supplied Rescue Medication: Acetaminophen

Sponsor supplied acetaminophen will be accounted for by the investigative site and recorded on the drug accountability log. The number of tablets dispensed will be recorded and the number of remaining tablets will be counted at each clinic visit and recorded on the appropriate source document and eCRF.

After monitoring, a final reconciliation of drug accountability records, and authorization by DURECT, all used and unused Sponsor supplied acetaminophen will be returned to DURECT or properly disposed of at the investigative site, if permitted per local SOPs and regulations. Documentation of disposition of Sponsor supplied acetaminophen will be provided to DURECT.

Rescue Medication: Oxycodone

For the prescribed rescue opioid analgesia, the number of tablets dispensed will be recorded and the number of remaining tablets will be counted at each clinic visit (through Visit 6 or early termination) and recorded on the appropriate source document and eCRF. If a patient does not fill their prescription for rescue opioid analgesia, this fact will be written in the eCRF. Following this reconciliation the rescue opioid analgesia will be returned to the patient.

7.4 Trial Visits and Follow-Up Phone Calls

Refer to Table 1 for Schedule of Events by Visit and Table 2 for the LogPad Schedule of Events.

7.4.1 Visit 1 (Screening)

All screening procedures will be performed after obtaining informed consent no more than 30 days prior to day of surgery. A minimum screening duration of 5 days (with 7 days being recommended) will be required for completion of the screening procedures. After obtaining informed consent, patients will be assigned a patient number and screening procedures will be performed. For the patient number, patients will be numbered consecutively within each site in the order of their consent into the trial. Only their assigned patient number and date of birth will identify patients to the Sponsor in order to maintain anonymity.

Screening procedures include completion of:

- Demographic information including employment status.
- Medical and surgical history.
- Physical examination (including height and weight).
- Vital signs (BP, HR, respiratory rate, temperature).
- Review of inclusion / exclusion criteria.
- Safety laboratory tests (chemistry, hematology, urinalysis).
- Urine drug screen for opiates, oxycodone, cannabinoids, amphetamines, cocaine, and methadone
- Serum pregnancy test (females of childbearing potential). Childbearing potential is considered present until menopause has lasted for more than 2 years prior to screening or if surgical sterilization (e.g. hysterectomy, tubal ligation) has occurred at least 6 months prior to screening.
- 12-lead ECG.
- Record prior and concomitant medications (taken within 30 days of screening).
- Assign LogPad and train in use. Patient completes Log Pad evaluations. Remind patients that enrollment is dependent upon their compliance with preoperative LogPad training (must complete a minimum of 80% of preoperative practice assessments). Refer to Section 7.5.
- CCI [redacted]

Patients who meet inclusion / exclusion criteria (See Section 5.3.1 and 5.3.2, respectively) will return to the investigative site for the scheduled surgery. Surgery must occur within 30 days of the screening visit.

7.4.2 Visit 2 (Day of Surgery/Study Day 1)

Patients will arrive at the investigative site and will be prepared for their scheduled surgery as per the site's standard practice. The surgery should be scheduled before noon to allow for patient completion of the 10 hour post-dose pain assessment.

Pre-surgery trial procedures:

- Urine pregnancy test for female patients of childbearing potential
- Review and document adverse events reported and concomitant medications taken since the screening visit
- Review inclusion / exclusion criteria again to confirm patient remains eligible
- Re-review LogPad instructions (refer to Section 7.5)
- Patient re-watches the training video (refer to Section 8.2.1)

- Randomization to one of two treatment groups
    - Randomization may be done on the business day prior to surgery as long as the patient meets the Screening (i.e. pre-operative) inclusion/exclusion criteria at the time of randomization
- Vital Signs: Subjects will remain in rest (supine or sitting) for at least 5 minutes prior to vital signs (BP, HR, RR, T) and pulse oxygen saturation measurements

Surgery trial procedures:

The surgery will be performed under general endotracheal anesthesia. Epidural or spinal analgesia, regional nerve blocks, intra-abdominal application of local anesthetics, and peri-incisional injection of local anesthetics other than the test drug have been prohibited. If conversion to open surgery occurs, the patient should **not** be treated with the test drug. This surgery must occur within 30 days of the screening visit. See Sections 5.5 (Anesthesia Requirements) and 5.6 (Surgical Requirements) for additional detail.

- Record anesthesia and intra-operative medications
- Administer study drug as described in Section 7.3.1. Record the time of test drug administration which has been defined as completion of drug deposition into the surgical incisions.
- Record the length and anatomical placement of surgical incisions in the source and surgery eCRF.
- Record the time of arrival in PACU.

Post-surgery trial procedures:

- The test drug administration time will be entered by the clinical trial staff into the patient's LogPad within one hour post-dose.
    - The LogPad will be re-dispensed to the patient upon awakening.
- PACU discharge eligibility will be assessed by blinded personnel per the site specific Blinding Plan with the mPADSS, starting at 30 minutes after arrival in the PACU. The mPADSS will be repeated at 15 minute intervals (±5 minutes) until the patient is eligible for discharge (i.e. an mPADSS score of 9 or greater).

- Vital signs including pulse oximetry will be measured and recorded on the Vitals eCRF upon arrival in the PACU and continuing every 15 minutes (±5 minutes) for a period of at least two hours after surgery
    - All clinically significant abnormalities will also be documented in the appropriate source document and AE eCRF.
- All adverse events will be recorded as noted in Section 9.3.

- Postoperative pain will be treated according to the Rescue Analgesia instructions in Section 7.6.3.
    - In the PACU, the patient's pain score CCI on movement (defined as sitting up, or attempting to do so, from a supine position) should be assessed immediately before giving each rescue dose of IV fentanyl. If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that pain score will be recorded. The dose and time of administration of IV fentanyl and associated pain scores must be recorded on the patient's chart and on the eCRF.
- All other concomitant medications will be recorded as noted in Section 7.6.
- Prior to discharge to home, patients will be provided sponsor supplied acetaminophen, 500 mg and a prescription for oxycodone IR, 5 mg, including dosing instructions (see Section 7.6.3). If permitted, retain a copy of the opioid prescription in the source documents.
- Just prior to discharge, a blinded Investigator (e.g., not the operating surgeon or operating room personnel) will complete a baseline surgical site examination (see Section 9.2.6 for details).
- Discharge to home should occur ≥2 hours post-surgery.

Patient Instructions:

Patients will be given written discharge instructions, including routine post-surgical instructions, reminder of LogPad requirements, rescue medication instructions, and follow-up call and clinic visit schedule.

7.4.2.1 Patient Completed Postoperative Evaluations (Day of Surgery/Study Day 1)

Patients will evaluate their pain intensity CCI on movement (defined as sitting up, or attempting to do so, from supine position) using the LogPad. The scheduled pain intensity evaluations will be done at 1, 4, 6, 8, and 10 hours post-dose on the day of surgery (see Section 7.5) initially in the PACU, then later after the patient has been discharged to home.

Pain intensity evaluations prior to rescue medication (pain intensity CCI on movement) must also be completed (1) prior to each IV fentanyl administration requested by the patient in the PACU, and (2) at home before the patient self-administers either oral rescue medication. CCI
Patients should then record their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the sit up. If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded.

Postoperative pain will be treated according to the Rescue Analgesia instructions in Section 7.6.3. For all oral rescue medication, the pre-rescue pain scores [redacted] on movement, plus the time, name, and number of pills taken will be recorded in the LogPad.

Patients will also complete a solicited AE checklist (which includes dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) on the LogPad at 6 and 10 hours post-dose (see Sections 7.5).

7.4.3 Follow-up Calls (Study Day 2 and 3)

Postoperative Day 1 and 2

Blinded site personnel will complete the following evaluations during the follow-up calls:

- Review completeness of Log Pad assessments and reminder of importance of completion of all LogPad assessments in a timely manner.
- Review of Adverse Events (including details of any patient-reported AEs recorded on the LogPad) – All reported AEs will be documented as noted in Section 9.3
- Inquire about Surgical Site AEs – [redacted]
- Review of Rescue Analgesia and Concomitant Medications – All other reported concomitant medications must be documented as noted in Section 7.6
- Inquire about Level of Activity including ambulation, sleeping, and eating - [redacted]
- Medical Resource Utilization Assessment – including any hospital admissions, Emergency Department visits, or calls to their physician or surgeon with complaint of unmanageable pain, nausea/vomiting, or refills of rescue opioid prescription – [redacted]

7.4.4 Patient Completed Evaluations (Study Days 2, 3, and 4)

Postoperative Day 1 to 3

Patients will complete the following evaluations:

- Pain Intensity Evaluations- Pain assessments [redacted] on movement (defined as sitting up, or attempting to do so, from supine position) should be performed on the LogPad at the scheduled times noted in Table 2: Patient LogPad Schedule of Events.
- Rescue Medication – Postoperative pain will be treated according to the Rescue Analgesia instructions in Section 7.6.3. For all oral rescue medication, the pre-rescue pain scores [redacted] on movement, plus the time, name, and number of pills taken will be recorded in the LogPad.
- Solicited AE Checklist (which includes dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) – assessed on the LogPad each evening at 20:00 ± 1 hour (clock time).

- If the patient reports an AE on the LogPad, an email alert will be sent to the investigative site personnel.

7.4.5 Visit 3 (Study Day 4)

Postoperative Day 3

A clinic visit will be conducted for assessment of AEs, surgical site examination, and rescue medication usage. During the clinic visit, the following trial procedures will be completed:

- Surgical Site Examination and Assessment of Surgical Site AEs including bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and abnormal healing
- Review LogPad for compliance, rescue medication use, and solicited AEs
- Review of Adverse Events– All reported AEs will be documented as noted in Section 9.3
  - Follow-up on details of any AEs the patient reported on the LogPad
- Rescue Medication Reconciliation and Pill Count
  - Follow-up with the patient regarding any discrepancy between the pill count and the number of pills recorded in the LogPad and document in the rescue medication accountability log and eCRF.
- Review of Concomitant Medications – All other reported concomitant medications will be documented as noted in Section 7.6
- Vital Signs
- Safety Laboratory Tests (chemistry, hematology, urinalysis)
- Inquire about Level of Activity including ambulation, sleeping, and eating -CCI [redacted]
- Medical Resource Utilization Assessment –including any hospital admissions, Emergency Department visits, or calls to their physician or surgeon with complaint of surgical complications, unmanageable pain, nausea/vomiting, or refills of rescue opioid prescription -CCI [redacted]

7.4.6 Patient Completed Evaluations (Study Day 5 to 8)

Postoperative Day 4 to 7

Patients will complete the following evaluations:

- Rescue Medication – Postoperative pain relief will be prescribed according to the instructions in Section 7.6.3. The time, name, and number of pills for all oral rescue opioids or acetaminophen will be recorded in the LogPad.

7.4.7 Visit 4 (Study Day 8 ± 1 day)

Postoperative Day 7 ± 1day

A clinic visit will be conducted for assessment of AEs, surgical site examination, and rescue medication usage. During the clinic visit, the following trial procedures will be completed:

- Surgical Site Examination and Assessment of Surgical Site AEs including bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and abnormal healing
- Review LogPad for rescue medication use and any solicited AEs reported
    - Collect LogPad
- Adverse Events – All reported AEs will be documented as noted in Section 9.3
    - Follow-up on details of any AEs the patient reported on the LogPad
- Rescue Medication Reconciliation and Pill Count
    - Follow-up with the patient regarding any discrepancy between the pill count and the number of pills recorded in the LogPad and document in the rescue medication accountability log and eCRF.
- Review of Concomitant Medications – All other reported medications will be documented as noted in Section 7.6
- Vital Signs
- Inquire about Level of Activity including ambulation, sleeping, eating, and current surgical wound pain - CCI [redacted]
- Medical Resource Utilization Assessment –including any hospital admissions, Emergency Department visits, or calls to their physician or surgeon with complaint of surgical complications, unmanageable pain, nausea/vomiting, or refills of rescue opioid prescription - CCI [redacted]

7.4.8 Visit 5 (Study Day 15 ± 2 days)

Postoperative Day 14 ± 2 days

Approximately 14 days after surgery, a clinic visit will be conducted for assessment of AEs, surgical site examination, and rescue medication usage. During the clinic visit, the following trial procedures will be performed:

- Surgical Site Examination and Assessment of Surgical Site AEs including bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and abnormal healing
- Adverse Events – All reported AEs will be documented as noted in Section 9.3
- Rescue Medication Reconciliation and Pill Count

- Review of Concomitant Medications – As noted in Section 7.6, all medications (including rescue medications) taken since the last visit will be documented.
- Vital Signs
- Inquire about Level of Activity including ambulation, sleeping, eating, and current surgical wound pain - CCI [redacted]
- Medical Resource Utilization Assessment –including any hospital admissions, Emergency Department visits, or calls to their physician or surgeon with complaint of surgical complications, unmanageable pain, nausea/vomiting, or refills of rescue opioid prescription - CCI [redacted]

7.4.9 Visit 6 (Study Day 29 ± 3 days)

Postoperative Day 28 ± 3 days

Approximately 4 weeks after surgery, a clinic visit will be conducted for assessment of AEs, surgical site examination, and rescue medication usage. During the clinic visit, the following trial procedures will be performed:

- Surgical Site Examination and Assessment of Surgical Site AEs including bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and abnormal healing
- Adverse Events – All reported AEs will be documented as noted in Section 9.3
- Rescue Medication Reconciliation and Pill Count and collect Sponsor supplied acetaminophen
- Review of Concomitant Medications – As noted in Section 7.6, all medications (including rescue medications) taken since the last visit will be documented.
- Physical Exam (including weight)
- 12-lead ECG
- Vital Signs
- Safety Laboratory Tests (chemistry, hematology, urinalysis)
- Inquire about Level of Activity including ambulation, sleeping, eating, current surgical wound pain, and return to work status - CCI [redacted]
- Medical Resource Utilization Assessment –including any hospital admissions, Emergency Department visits, or calls to their physician or surgeon with complaint of surgical complications, unmanageable pain, nausea/vomiting, or refills of rescue opioid prescription - CCI [redacted]

7.4.10 Visit 7 (Study Day 60 ± 3 days)

Postoperative Day 59 ± 3 days

Approximately 2 months after surgery, a clinic visit will be conducted for assessment of AEs and surgical site examination. During the clinic visit, the following trial procedures will be performed:

- Surgical Site Examination and Assessment of Surgical Site AEs including bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and abnormal healing
- Adverse Events – All reported AEs will be documented as noted in Section 9.3
- Review of Concomitant Medications – As noted in Section 7.6, all medications (including pain medications) taken since the last visit will be documented.
- Physical Exam (including weight)
- 12-lead ECG
- Vital Signs
- Safety Laboratory Tests (chemistry, hematology, urinalysis)

All AEs, of whatever etiology and location, occurring after informed consent should be recorded on the eCRF as an AE. All AEs will be followed until resolution unless the patient is lost to follow up. Resolution means no further changes in the event are expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.

NOTE: Patients enrolled prior to IRB approval of Amendment 5 will not need to return for a Study Day 60 visit.

7.4.11 Early Termination Visit

If a patient terminates the study early the following study procedures should be performed unless the patient withdraws consent. If a patient withdraws consent they will be encouraged to complete an early termination visit and AE follow-up:

- Surgical Site Examination and Assessment of Surgical Site AEs including bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and abnormal healing
- Adverse Events – All reported AEs will be documented as noted in Section 9.3
- Rescue Medication Reconciliation and Pill Count and collect Sponsor supplied acetaminophen
- Review of Concomitant Medications – As noted in Section 7.6, all medications (including rescue medications) taken since the last visit will be documented.
- Physical Exam (including weight)

- 12-lead ECG
- Vital Signs
- Safety Laboratory Tests (chemistry, hematology, urinalysis)
- Inquire about Level of Activity including ambulation, sleeping, eating, current surgical wound pain, and return to work status - CCI [redacted]
- Medical Resource Utilization Assessment –including any hospital admissions, Emergency Department visits, or calls to their physician or surgeon with complaint of surgical complications, unmanageable pain, nausea/vomiting, or refills of rescue opioid prescription - CCI [redacted]

7.5 Electronic Diary (LogPad)

The LogPad is a handheld electronic device that records data entered by the patient and transfers it directly into a database maintained by the specific service provider. These devices will be provided to the patient by the investigative site at screening, the patient will bring the device with them on the day of surgery, the site will re-dispense the device to the patient in the PACU following surgery, and patients will return the device to the investigative site at Visit 4 (POD 7).

CCI [redacted]

The test drug administration time will be entered by the investigative site staff into the patient's LogPad via the Site Gateway within one hour post-dose.

The LogPad will be used to record pain intensity CCI [redacted] on movement (defined as sitting up, or attempting to do so, from a supine position) from Study Day 1 (day of surgery) through Study Day 4 (POD 3) (see Section 8.2.1 CCI [redacted] oral rescue medication (oxycodone IR or acetaminophen) till Study Day 8 (POD 7), the associated pre-rescue CCI [redacted] on movement scores through Study Day 4 (POD 3), and the solicited AE checklist (which includes dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) from Study Day 1 to Study Day 4 (see Table 2: Patient LogPad Schedule of Events). If the patient reports an AE on the LogPad, an email alert will be sent to the investigative site personnel.

Data collected in the LogPad device will automatically transmit following completion of each assessment. Trial staff will access the transmitted data via the CCI [redacted]

CCI [redacted]

7.6 Medication other than Test Drug

Any use of concomitant medications taken since 30 days prior screening will be recorded on the appropriate source document and concomitant medication (CM) eCRFs. This includes concomitant medications taken between screening and the surgery, medications taken during surgery, medications taken post-surgery (e.g. rescue medications, including titration and oral opioids, and acetaminophen), and for treatment of adverse events (AEs).

7.6.1 Prohibited Concomitant Medications

- Epidural or spinal analgesia, regional nerve blocks, intra-abdominal application of local anesthetics, and peri-incisional injection of local anesthetics other than the test drug have been **prohibited**.
- Use of systemic steroids, antidepressants, anticonvulsants or antiepileptics has been **prohibited** from screening until Visit 6 (Study Day 29).
    - Inhalational or topical corticosteroids are permitted
- Long-acting anticoagulants, such as warfarin, and long-acting antiplatelet drugs, such as clopidogrel, should be discontinued one week prior to surgery. Short-acting newer oral anticoagulants should be discontinued prior to surgery according to the labeled instructions. Low dose aspirin (81 mg) may be continued throughout surgery (Joseph et. al., 2015). The anticoagulants and antiplatelet agents may be restarted after surgery when hemostasis is assured and there are no bleeding complications from surgery.
- NSAIDs, both prescribed (including Toradol® [ketorolac] Injection and Caldolor® [ibuprofen] Injection) and over the counter (OTC), are **not** allowed for one week prior to surgery and for 1 week after surgery (Study Day 8). Restricted OTC medications include (but are not limited to):
    - Aleve® (naproxen sodium), Advil® (ibuprofen), Motrin® (ibuprofen), Aspirin (except low dose [81 mg] aspirin taken as an antithrombotic), Alka-Seltzer®, Excedrin®, Midol®
- Other OTC combination products containing acetaminophen are **not** allowed for one week prior to surgery and for 1 week after surgery (Study Day 8). Restricted OTC medications include (but are not limited to):
    - Products containing acetaminophen for the following brands: NyQuil®, DayQuil®, Robitussin®, Benadryl®, Sudafed®, Theraflu®, and generic equivalents

- The use of combination and extended/sustained release opioid analgesic medications are prohibited from screening until the final visit (Study Day 60). Prohibited medications include (but are not limited to):
    - Combination products: Norco®, Lortab®, Percocet®, Vicodin®, Xodol®, Vicoprofen®, Zydone®, Percodan®, promethazine/codeine syrup, and generic equivalents
    - Extended/Sustained Release/Long-acting products: Avinza®, Butrans®, Dolophine®, Duragesic®, Embeda®, EXALGO®, Hysingla™ ER, Kadian®, Methadose™, MS Contin®, Nucynta® ER, Opana® ER, OxyContin®, Zohydro® ER, and generic equivalents
- Participants are prohibited from using investigational, unapproved, or recreational drugs. "Medical" marijuana and opioids (other than immediate-release oxycodone and IV fentanyl) may **not** be used from screening until the final visit (Study Day 60).
- Naltrexone should not be taken after surgery.

7.6.2 Anesthesia

The surgery will be performed under general endotracheal anesthesia. Epidural or spinal analgesia, regional nerve blocks, intra-abdominal application of local anesthetics, and peri-incisional injection of local anesthetics other than the test drug have been prohibited. Intra-operative opioid analgesia will be limited to IV fentanyl with a maximum dose of 2.5 mcg/kg/hr, including the induction dose. The duration of the surgical procedure is anticipated to be approximately 1 hour. See Section 5.5 Anesthesia Requirements for additional details.

7.6.3 Rescue Analgesia for Postoperative Pain Management

PACU

- IV fentanyl 12.5 or 25 mcg bolus doses given at no less than 5-minute intervals

Home Use

- Oxycodone IR 5 mg tablets
- Acetaminophen 500 mg tablets

7.6.3.1 PACU Rescue Medication Regimen

In the PACU, pain may be treated with rescue analgesia (IV fentanyl in 12.5 or 25 mcg doses given at no less than 5-minute intervals). IV fentanyl should be given only as necessary to control pain, only at the patient's request, and **not** as a scheduled or prophylactic dose. The patient's pain score CCI on movement (defined as sitting up, or attempting to do so, from a supine position) should be assessed immediately before giving each rescue dose of IV fentanyl. If the patient is unable to sit up completely due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded. The dose and time of administration of IV fentanyl and associated pain scores

must be recorded on the patient's chart and on the eCRF. No IV acetaminophen, IV NSAIDs, or any analgesic drug (including Toradol® [ketorolac] Injection, Caldolor® [ibuprofen] Injection, and Ofirmev® [acetaminophen] Injection) other than IV fentanyl should be given during the PACU stay. However, the following exception will apply: at sites where patients are transferred prior to discharge to a Phase 2 recovery unit (or step down unit), then oral oxycodone or oral acetaminophen may be given according to the instructions described in Section 7.6.3.2 for the use of oral rescue medication.

7.6.3.2 Oral Rescue Medication Regimen for Home Use

Patients will be provided written instructions regarding rescue medication usage prior to discharge. Prior to rescue dosing, the patient must record pain intensity [redacted] **on movement. Each dose of rescue medication will be recorded by the patient on the LogPad.**

From PACU discharge through Study Day 8 (POD 7), analgesic rescue medications have been limited to oxycodone IR 5 mg tablets, prescribed by the surgeon (or surgeon's DEA licensed delegate), and acetaminophen 500 mg tablets, supplied by the Sponsor.

Patients must be instructed to not take both oxycodone and acetaminophen within 4 hours of each other. Generally, oxycodone should be taken for moderate to severe pain and acetaminophen should be taken for mild to moderate pain and the two drugs should not be taken together.

No Combination products (e.g., Percocet, Vicodin, Vicoprofen, Zydone, Percodan) or extended release opioid products (e.g., Oxycontin, Opana ER, Kadian, Ultram ER) will be permitted from screening to trial completion (Study Day 60).

Patients will be instructed that they must bring any unused rescue medication (oxycodone IR and acetaminophen) with them to the clinic visits (through Visit 6 or early termination) for reconciliation purposes. The number of tablets dispensed will be recorded and the number of remaining tablets will be counted at each clinic visit.

7.6.3.2.1 Rescue Oral Opioid

For the treatment of moderate to severe pain, patients will be prescribed oxycodone IR 5 mg tablets. Exactly 24 tablets should be prescribed. One or two tablets may be taken every 4 hours for moderate to severe pain. Each dose of oxycodone will be recorded by the patient on their LogPad.

7.6.3.2.2 Rescue Oral Acetaminophen

For the treatment of mild to moderate pain, patients will be supplied by the sponsor with acetaminophen 500 mg tablets (one bottle of 24 tablets). One or two tablets may be taken every 4 hours as required for pain. **No more than 8 tablets (4000 mg) may be taken in any 24 hour period.** Each dose of acetaminophen will be recorded by the patient on their LogPad. A screen

will display an alert that they have reached the maximum allowed dose when a patient takes an 8th tablet (4000 mg total) in any 24 hour period.

7.6.3.2.3 No Concomitant Use of Oxycodone and Acetaminophen

Oxycodone and acetaminophen may not be taken concomitantly within the same four hour interval.

7.6.3.3 Recording of Rescue Analgesia Data

Identity, dose and time of administration of rescue analgesia, will be recorded as follows:

- IV rescue medication and associated pre-rescue pain scores CCI on movement – On the appropriate source document and eCRF from patient awakening from anesthesia to discharge.
    - If the patient is unable to sit up all the way due to severe pain, weakness, or lack of recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded (e.g. if patient can only sit up partway, then the pain that the patient feels in that position will be recorded).
- Oral rescue medication (oxycodone or acetaminophen) in the LogPad till Study Day 8 (POD 7) and associated pre-rescue pain scores CCI on movement through Study Day 4 (POD 3).
- Rescue medication including NSAIDs taken for pain relief after Study Day 8 (POD 7) will be recorded on the appropriate source document and CM eCRF.
- The number of oxycodone and acetaminophen tablets prescribed/dispensed and the number of tablets remaining at each clinic visit will be recorded on the appropriate source document and eCRF.

The LogPad will be the primary data source for oral opioid rescue medication taken through Study Day 8 (POD 7) and the eCRF will be the primary data source for IV rescue medication taken throughout the trial and oral rescue medication taken after Study Day 8 (POD 7).

8.0 Assessment of Efficacy

8.1 Efficacy Assessments

Primary Efficacy Endpoint:

- Pain intensity on movement measured at scheduled time points from 0-48 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM).

To account for the impact of rescue medication use on the scheduled pain scores, the half-life substitution method will be used. Specifically, if the scheduled pain score has been assessed within one plasma half-life after the use of rescue medication (IV or oral opioid or oral acetaminophen), and if the pre-rescue medication pain score is higher than the scheduled one, then the pain score recorded at the time of rescue medication administration will be substituted for the scheduled pain score (FDA, 2014). If a rescue medication pain score is missing, then the worst pain score up to that point will be substituted instead

Key Secondary Efficacy Endpoint:

Pain intensity on movement measured at scheduled time points from 0-72 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM).Additional Secondary Efficacy Endpoints:

Total IV morphine-equivalent dose of rescue opioids used during 0-72 hours following test drug administration (standard conversion factors are used to convert different opioids to IV morphine-equivalents; CCI [redacted]

- Composite endpoint of Silverman's Integrated Analgesic (SIA) assessment score (Dai et al, 2013 and Silverman et al, 1993) over 0-72 hours following test drug administration
- Proportion of patients taking no opioid rescue medication from PACU discharge until 72 hours after test drug administration
- Time to first opioid rescue medication use after PACU discharge
- Time to PACU discharge eligibility as assessed by mPADSS (Chung, 1995; Awad and Chung, 2006)

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

8.2 Method and Rationale for Assessments

8.2.1 Pain Intensity Endpoints

Pain intensity evaluations will be completed [redacted] on movement (defined as sitting up, or attempting to do so, from a supine position). [redacted] Patients should then record their pain-on-movement score by sitting up, or attempting to do so, from a supine position and recording the worst pain experienced during the movement.

Patients will assess their pain intensity using an 11-point Numeric Pain Rating Scale (NPRS) (Breivik et al. 2008; Hjermstad et al 2011; Cook et al 2013), [redacted] with numerical rating scale (NRS) scores ranging from 0 (no pain) to 10 (worst pain imaginable). Each patient completes the NPRS by selecting the appropriate score on the scale and recording the score in the LogPad at the scheduled times noted in Table 2: Patient LogPad Schedule of Events and prior to taking an oral rescue medication through Study Day 4 (POD 3). Prior to receiving each dose of IV rescue medication in the PACU, the patient's pain scores [redacted] on movement (defined as sitting up, or attempting to do so, from a supine position) should be assessed and site personnel will record it on the appropriate source document and eCRF.

- If the patient is unable to sit up all the way due to severe pain, weakness, or incomplete recovery from anesthesia, the patient should be instructed to make his or her best attempt, and that score will be recorded (e.g. if patient can only sit up partway, then the pain score that the patient feels in that position will be recorded).
- Patients must **not** use motorized bed or recliner controls to sit up or receive assistance from a caregiver for the pain on movement assessments.
- All patients will watch the training video which is designed to inform the patient of the research goals of the trial, how to properly estimate their pain scores and how to appropriately use rescue medications.

Patient-reported pain is an established variable to capture postoperative analgesic effects (FDA, February 2014).

8.2.2 Rescue Opioid Endpoints

Rescue opioid medication (both IV and oral) may be taken for postoperative pain relief and will be recorded as noted in Section 7.6.3.

All opioid doses, whether administered IV or orally, will be converted into IV morphine milligram (mg) equivalents, a standard procedure to allow the calculation of analgesic effects even if opioids of different potency are used [redacted]

Reduction of opioid consumption after surgery is an important potential benefit of SABER®-Bupivacaine. Total opioid use over the first 72 hours following surgery will therefore

be evaluated as a secondary endpoint. The 72-hour assessment period corresponds with the expected duration of SABER®-Bupivacaine activity and the interval during which postoperative pain scores will be assessed. All opioid medications consumed during this period, including those administered intravenously in the PACU and those taken orally by the patient at home will be counted toward the total.

Two other measures of opioid use will also be assessed as secondary endpoints: (1) the time to first use of opioid rescue medication by the patient after discharge from the PACU (oral oxycodone in all cases except possibly those in which the subject has an unplanned admission to the hospital after surgery) and (2) the percentage of patients not requiring any opioid rescue medication after discharge from the PACU until 72 hours after test drug administration. In both these cases, only opioid analgesics administered after PACU discharge will be counted. The rationale for this arrangement is twofold. First, such opioid-sparing effects would likely be more meaningful if demonstrated in the uncontrolled environment of the patient's home than in the controlled and carefully monitored setting of the PACU, where use of postoperative opioids has been routine. Second, data from trial C803-025, Cohort 2 indicate that nearly all laparoscopic cholecystectomy patients receive at least 1 dose of opioid rescue medication in the PACU, which would render both these endpoints effectively moot.

In previous studies of SABER®-Bupivacaine in inguinal hernia repair (CLIN-803-006-0006) and sub-acromial decompression of the shoulder (BU-002-IM), outcomes related to reduced opioid consumption consistent with the three aforementioned endpoints were explored as primary, co-primary, or secondary endpoints. In both trials, SABER®-Bupivacaine 5 mL significantly reduced total postoperative opioid use and prolonged the time to first opioid use compared with SABER®-Placebo.

8.2.3 Modified Post-Anesthesia Discharge Scoring System (mPADSS)

PACU discharge eligibility will be assessed with the mPADSS, starting at 30 minutes after arrival in the PACU and repeated at 15 minute intervals (±5 minutes) until the patient is eligible for discharge (i.e. an mPADSS score of 9 or greater). The results will be recorded on the appropriate source document and eCRF. NOTE: patients must be monitored for vital signs for at least 2 hours after surgery as described in Section 9.2.4, even if their mPADSS score indicates that they may be discharged. Conversely, patients must continue to be monitored and may not be discharged until the mPADSS score has reached 9 or greater. The time of arrival CCI [redacted] from PACU will also be recorded on the appropriate source document and eCRF.

mPADSS is a widely recognized, published tool used to determine eligibility for discharge from the PACU after ambulatory surgery (Chung, 1995; Awad and Chung, 2006). The mPADSS includes an assessment of five parameters: vital signs, activity level, nausea/vomiting, pain, and surgical bleeding. For pharmacoeconomic purposes, this trial will evaluate eligibility for PACU discharge using a version of mPADSS that has been slightly modified for ease of administration and to suit the surgical model under study CCI [redacted] The mPADSS tool provides a standardized means of assessing eligibility for PACU discharge across multiple investigative

sites and also ensures that nonmedical complications, such as a missing ride home, do not interfere with evaluation of test drug effects.

9.0 Assessment of Safety

9.1 Safety Assessments: Patient Visits and Follow-Up Phone Calls

- Adverse events
  - Spontaneously reported AEs; either volunteered by the patient, prompted by non-directed questioning or reported by an investigator will be documented on the eCRF.
  - The following AEs will be solicited and recorded at specified time points (see Table 2) using the Log Pad: dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia
- Standard 12-lead ECG
- Safety Laboratory Tests (Serum chemistry, hematology, urinalysis)
- Vital Signs and Physical Examination
- Surgical site examination for CCI [redacted] bruising, bleeding or drainage from the incision(s), hematoma, dehiscence, infection and healing

9.2 Method and Timing of Assessments

9.2.1 Adverse Event Recording

Pain that has been evaluated as part of the efficacy endpoints will <u>not</u> be considered an adverse event.

Adverse events will be recorded from the time the patient signs the informed consent form through trial completion final visit/early termination (see Section 9.3).

9.2.1.1 Spontaneously Reported Adverse Events

At each contact between the investigative site and the patient (visit or phone call), after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. All AE details including severity and causality from screening through trial completion will be recorded by trial staff on the appropriate source document and AE eCRF.

9.2.1.2 Solicited Patient-Reported Adverse Events

The solicited patient-reported AEs that must be recorded at specified times on the LogPad (see Table 2) are: dizziness, somnolence (drowsiness), constipation, nausea, vomiting, pruritus

(itching), headache, Dysgeusia (metallic taste in mouth), paresthesia (tingling or pins and needles), and hypoesthesia (numbness) (see Section 7.5).

These ten adverse events were chosen for detailed study by solicitation on the LogPad for two reasons. First, many of these AEs are common symptoms associated with opioid administration (Zhao et al, 2004; Daniels et al, 2009; YaDeau et al, 2011). If treatment with SABER®-Bupivacaine results in a reduced consumption of rescue opioids compared to placebo or bupivacaine HCl, there may also be a concomitant reduction in the incidence of these adverse events. This reduction in opioid-related adverse events could then be regarded as an additional benefit of SABER®-Bupivacaine treatment.

CCI [redacted]

If the patient reports an AE on the LogPad investigative site personnel will receive an alert. At each point of contact, investigative site personnel will follow-up with the patient regarding severity, frequency, duration and action taken of any AEs reported on the LogPad and appropriately document this data and causality in the source and AE eCRF.

9.2.2 12-Lead ECGs

Standard resting 12-lead ECGs will be obtained at the Screening Visit, Visit 6, and Visit 7, or Early Termination Visit. Overall interpretation and machine read intervals (HR, PR, QRS, QT, and QTc) will be recorded on the ECG eCRF. Clinically significant ECG findings that emerge after treatment will be recorded on the AE eCRF.

9.2.3 Laboratory Tests

All routine laboratory analyses will be conducted by a central laboratory and have been listed below. Laboratory tests will be obtained as indicated on the Schedule of Events table. Instructions on sample collection, processing and shipment will be provided in a separate laboratory manual.

Female patients of childbearing potential will have a serum pregnancy test at Screening and a urine pregnancy test on the day of surgery. The urine pregnancy test will be performed locally at the investigative site.

Table 4: Safety Laboratory Tests

Blood Chemistry	
ALT (SGPT)	Creatine Kinase (CK)
Albumin	Glucose
Amylase (screening only)	Lactate dehydrogenase (LDH)
AST (SGOT)	Lipase (screening only)
Alkaline Phosphatase	Phosphorus
Bilirubin (direct and total)	Potassium
BUN	Protein (total)
Serum Creatinine	Sodium
Calcium	Triglycerides
Cholesterol (total)	Uric Acid
Chloride	Bicarbonate
Hematology	
Hematocrit	Red blood cell (RBC) count
Hemoglobin	Platelet count
White blood cell (WBC) count with differential (absolute count and percent of neutrophils, lymphocytes, monocytes, eosinophils, and basophils)	
Other	
Serum and Urine Pregnancy hCG	
Routine Urinalysis including Color, Appearance, Specific Gravity, pH, Protein, Glucose, Ketones, Bilirubin, Blood, Urobilinogen, Nitrite and Leukocyte Esterase	
Urine drug toxicology screen for opiates, oxycodone, cannabinoids, amphetamines, cocaine, and methadone (screening only)	

Laboratory values that are out of range for the Central lab will be identified and may be repeated at the Investigator's discretion and sent to the Central lab. The Investigator will classify laboratory values outside the normal range as either clinically significant or not clinically significant. Clinically significant laboratory values outside the normal range that emerge after treatment will be recorded on the AE eCRF. Clinically significant out of range laboratory values that emerge after treatment will be followed and treated (if appropriate) by the Investigator until they return to normal.

9.2.4 Vital Signs

Systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature will be measured. Blood pressure and heart rate will be measured after the patient has been resting (supine or sitting) for 5 minutes. Pulse oxygen saturation will be continuously measured on Visit 2 pre- and post-surgery, and recorded at 15 minute intervals for a period of at least 2 hours after surgery. Measurements will be taken at the times specified in the Schedule of Events table and will be recorded on the appropriate source document and Vital Sign eCRF.

9.2.5 Physical Examination

A physical examination including height and weight will be conducted at the Screening Visit to confirm if the patient meets trial criteria.

A physical examination (including weight) will be conducted at Visit 6 (Study Day 29) and Visit 7 (Study Day 60), or Early Termination Visit. Any changes from baseline outside the normal range that emerge after treatment will be recorded on the AE eCRF.

9.2.6 Surgical Site Examination and Assessment of Surgical Site AEs

At each clinic visit, the wound evaluator (an investigator or other medically qualified investigative site personnel who will remain blinded to treatment assignment) will assess the surgical sites for the presence or absence of bruising, bleeding or drainage from incision(s), hematoma, dehiscence, or infection. CCI

Surgical site healing will also be assessed with a questionnaire at the Study Day 2 and Study Day 3 Follow-up Phone Calls [redacted] This questionnaire may elicit clinically significant alterations in surgical site healing. During the next clinic visit (or earlier if medically necessary) investigative site personnel will follow-up on questionnaire responses suggesting clinically significant alterations in surgical site healing.

9.3 Adverse Events

9.3.1 Definitions

Adverse Event

An adverse event (AE) is 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 or symptom, including clinically significant laboratory values and test results, concomitant illness, accident, or worsening of an existing medical condition.

The following should not be recorded as an AE if noted at screening:

- A pre-planned procedure for an illness included in the patient's medical history, unless the condition for which the procedure was planned has worsened since baseline. Please observe that complications to pre-planned procedures should be recorded as AEs
- A pre-existing condition found as a result of screening procedures

Any worsening in severity or frequency of a baseline concomitant illness or any new illness diagnosed in the trial period must be regarded as an AE.

Pain that is evaluated as part of the efficacy endpoints will not be considered an adverse event.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event that, at any dose:

- Results in death
- Is life-threatening
    - Life-threatening refers to an event in which the patient is at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization – Inpatient hospitalization includes an overnight admission
- Results in persistent or significant disability/incapacity
    - Disability is defined as a substantial disruption of a person's ability to conduct normal life functions
- Results in the birth of a child with a congenital anomaly/birth defect
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE (when based upon appropriate medical judgment). These events may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Serious Adverse Events of Special Interest

Three serious adverse events are pre-specified as SAEs of special interest and were chosen for close monitoring by the sponsor medical monitor because of their clinical importance:

1) Wound dehiscence reported as an SAE
2) Wound hematoma reported as an SAE
3) Surgical site infection reported as an SAE

The detailed definitions for these surgical complications are in Section 9.2.6. Details of the monitoring procedures are in Section 9.3.4.

Adverse Reaction

An adverse reaction (AR) is any untoward and unintended response to a test drug that has been considered to have a causal relationship with the treatment.

Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is serious and where the nature or severity of which is not consistent with information in the current Investigator's Brochure.

Abnormal Laboratory Value as an AE

An abnormal laboratory value (i.e. any clinical laboratory abnormality or change that suggests a disease and/or organ toxicity and is of a severity that requires active management [i.e. change of test drug dose, discontinuation of test drug, medical treatment, more frequent follow-up or diagnostic investigation]), will be regarded as an AE. If clinical sequelae have been associated with a laboratory abnormality the diagnosis or medical condition should be reported (e.g. renal failure, hematuria) to replace the laboratory abnormality (e.g. elevated creatinine, urine RBC increased).

9.3.1.1 Classifications

Severity

A blinded Investigator will evaluate the severity of each adverse event using the following definitions:

Mild – Transient symptoms, no interference with the patient's daily activities

Moderate – Marked symptoms, moderate interference with the patient's daily activities

Severe – Considerable interference with the patient's daily activities

An AE that has been assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event should be described as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.3.1.

Causality

A blinded Investigator is obligated to assess the relationship between test drug and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine if there is a reasonable possibility that the pharmacological action of the test drug was responsible for the AE/SAE being reported. Alternative causes such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the test drug will be considered and investigated. The Investigator will also consult the Clinical Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

After careful medical consideration, the Investigator will evaluate the relationship of each adverse event to test drug applying the following definitions:

Probably Related – Good reasons and sufficient documentation to assume a causal relationship

Possibly related – A causal relationship is conceivable

Unlikely related – The event is most likely related to etiology other than the test drug

Not Related – Good reasons and sufficient documentation to exclude a causal relationship.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event prior to transmission of the SAE Report Form to the Sponsor (or designee).

9.3.2 Adverse Event Reporting

All events that meet the definition of an AE that occur in the period from when the patient has signed the informed consent form (ICF) through trial completion (final visit), or early termination, must be recorded on the adverse event eCRF. All SAEs will be recorded on the appropriate eCRF and on the Serious Adverse Event Report Form from the time written informed consent has been obtained through trial completion (final visit), or early termination.

At each contact between the investigative site and the patient (visit or phone), after the patient has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The following are examples of open-ended questions that may be used to obtain this information:

“How are you feeling?”

“Have you had any medical problems since your last visit/assessment?”

“Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?”

All AEs and SAEs will be documented in source records at each assessment time or when otherwise volunteered by the patient and recorded on the appropriate eCRF. Information to be collected includes the nature, date and time of onset, severity, duration, relationship to test drug, and outcome of the event. Even if the Investigator assesses the AE as not reasonably attributable to the test drug, its occurrence must be recorded in the source documents and reported on the eCRF along with the assessment of association.

The Investigator will treat the patient as medically required, and this may extend beyond the duration of the trial. The Investigator will record treatment and medications required to treat AEs on the appropriate eCRF(s). All AEs will be followed until resolution (no further changes in

the event are expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve) unless the patient is lost to follow up.

DURECT will evaluate all AEs with respect to seriousness, causality and expectedness in accordance with Directive 2001/20/EC (3) and FDA Guidelines. The expectedness of an AE will be determined according to the current version of the Investigators Brochure.

9.3.3 Reporting of Serious Adverse Events

Regardless of causality, the investigator must complete and submit an SAE form to CCI Safety Surveillance within 24 hours of knowledge of the event for all serious adverse events.

SAEs will be reported to: CCI Safety Surveillance

Fax: PPD (toll free)

The Investigator must indicate the SAE's relationship to test drug and sign the SAE form. When additional relevant information (final diagnosis, outcome, results of specific investigations, etc.) becomes available, the investigator must record that follow-up information in the eCRF. Follow-up information should be recorded according to the process used for reporting the initial event as described above. The investigator will follow all reportable events (i.e., SAEs) until resolution. Resolution means no further changes in the event would be expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering non-serious sequelae that may never resolve.

Safety Surveillance will follow all SAEs until resolution (no further changes in the event are expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve). Safety Surveillance will report all SAEs to DURECT within 1 business day of receipt.

All serious adverse events will also be reported on the AE CRF and concomitant medications administered in association with the serious AE will be documented on the CM CRF.

If a serious adverse event occurs and comes to the attention of the Investigator after trial completion/termination within 60 days of test drug dosing or within 30 days of the last trial visit (whichever occurs later), it must be reported immediately to Safety Surveillance in the same manner as the serious adverse events occurring during the trial. Investigators are not obligated to actively seek AEs from former study participants.

The Investigator must report SAEs to the IRB/IEC (per the IRB/IEC guidelines/SOPs), including all SAEs that have occurred at the investigative site and all trial related SAEs that have resulted in an expedited safety report to a regulatory agency. Concurrently, the Investigator must send DURECT documentation of such IRB/IEC notification or if reporting is not required

immediately per IRB/IEC guidelines, then a copy of the local SOP stating the reporting guidelines should be supplied by the site to DURECT and the CRO.

DURECT complies with applicable regulatory requirement(s) related to the reporting of SUSARs to the competent authorities and the IRBs/IECs. In addition, DURECT will prepare annual safety reports covering all SUSARs that have occurred in clinical studies with the concerned test drug during the reporting period.

9.3.4 Serious Adverse Events of Special Interest

Based on previous clinical experience, three serious adverse events are being pre-specified for close monitoring. The following pre-specified surgical wound complications, when reported as SAEs, are of special interest to DURECT [redacted] (see Section 9.2.6 for detailed definitions):

1) Wound dehiscence reported as an SAE
2) Wound hematoma reported as an SAE
3) Surgical site infection reported as an SAE

The sponsor medical monitor will carefully monitor the blinded safety data for any occurrence of these pre-specified SAEs. SAEs of special interest will be reported both to the Safety Assessment Committee (SAC), [redacted] and to the FDA in accordance with safety reporting regulations. The expected incidence rate of the individual SAEs of special interest will be less than 1% based on the previous clinical experience with SABER-Bupivacaine and the published literature (Richards et al, 2003; Fahrner et al, 2014; Keus et al, 2009; Shea et al, 1996). Non-serious instances of these surgical wound complications will be analyzed as AEs (as described in Section 9.2.6 and 9.3.2)

9.3.5 Cardiac or Neurological Serious Adverse Events

If a cardiac or neurological SAE occurs within 48 hours of dosing, a blood sample (approximately 8 mL) will be collected as soon as possible for measurement of plasma bupivacaine [redacted] The collection date and time should be documented. Refer to the sample processing, shipping and handling instructions provided within the laboratory manual.

9.3.6 Adverse Event Follow-up

During and after participation by a patient in a clinical trial, the Investigator will ensure that adequate medical care has been provided to the patient for any AEs including clinically significant laboratory values related to the trial. The Investigator will inform the patient when medical care will be needed for intercurrent illness(es) of which Investigator becomes aware.

All AEs must be followed by the Investigator until resolution (no further changes in the event are expected, i.e., the point at which a subject experiencing such an AE has been appropriately

treated and stabilized even though they may continue to experience lingering sequelae that may never resolve), until the subject is lost to follow-up, or died and until all queries related to the AEs have been resolved. Investigators will make at least 3 documented attempts to contact a subject before considering the subject lost to follow-up. The first two attempts may be by letter, email or documented phone call and the third and final attempt must be by Registered Mail, Return Receipt Requested. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor (or designee) must be notified immediately and then provided with a copy of any post-mortem findings, including histopathology.

9.4 Pregnancy

Female patients will be advised to notify the Investigator immediately if they become pregnant during the course of the trial.

The Investigator must complete the appropriate pregnancy reporting forms and send them to DURECT (or DURECT's designee) within 14 calendar days of obtaining information of the pregnancy. The Investigator will follow the pregnancy through its course and complete the appropriate documentation and forward immediately to DURECT (or DURECT's designee). The infant must be followed at least until one month of age. Consent of a parent must be obtained before registration of infant data.

Abortion, stillbirth and any malformation/disease must be reported as an SAE. A pregnancy outcome other than abortion, stillbirth and any malformation/disease as well as follow-up of the infant must be reported by the Investigator within 14 calendar days of obtaining the information using the appropriate pregnancy reporting forms.

10.0 Pharmacokinetics

No PK assessments have been planned for this trial.

11.0 Statistical Methods and Data Analysis

11.1 Trial Design Considerations

Part 1

This part will be a randomized, parallel-group, double-blind, placebo-controlled, multi-center trial evaluating the safety and efficacy of SABER®-Bupivacaine 5 mL in patients undergoing elective outpatient laparoscopic cholecystectomy.

CCI [redacted]

CCI [redacted]

Part 2

This part will be a randomized, parallel-group, double-blind, active-controlled, multi-center trial evaluating the safety and efficacy of SABER®-Bupivacaine 5 mL in patients undergoing elective outpatient laparoscopic cholecystectomy.

The primary efficacy objective will be to investigate whether SABER®-Bupivacaine will significantly reduce pain compared to bupivacaine HCl (75 mg) over 48 hours following test drug administration in patients undergoing laparoscopic cholecystectomy.

It has been planned that the data from centers that participate in this trial will be combined such that an adequate number of subjects will be available for analysis.

Unless otherwise specified, all statistical tests will be conducted employing a two-sided significance level of 0.05.

11.2 Sample Size Determination

Part 1

One hundred fifty three subjects enrolled in each treatment group of the study will result in 90% power (assuming type 1 error rate of 5%) to detect a difference between 5 mL of SABER®-Bupivacaine and 5 mL of saline placebo CCI [redacted]

[redacted] The size of the final enrollment will be approximately 90 subjects determined by the readiness of sites to enroll subjects under IRB-approved Part 2.

Part 2

One hundred thirty-two subjects enrolled in each treatment group of the study will result in 90% power (assuming type 1 error rate of 5%) to detect a difference between 5 mL of SABER®-Bupivacaine and 15 mL of 0.5% bupivacaine HCl CCI [redacted]

CCI [redacted]

11.3 Patient Randomization

Part 1

It was planned that approximately 320 eligible patients would be randomized, in order to obtain 306 evaluable patients (i.e., patients who received any test drug and have at least one post-surgical pain intensity score). It had been estimated that 5% of randomized patients may not receive any test drug due to unforeseeable intra-operative exclusion. Patients would be randomized in a 1:1 ratio to receive one of two treatments based on a computer-generated randomization schedule prepared before the study:

- Treatment Group 1: SABER®-Bupivacaine 5 mL (132 mg/mL, 660 mg bupivacaine base)
- Treatment Group 2: Sterile normal saline 5 mL (0.9% sodium chloride injection, USP) (placebo)

Due to the early administrative stopping, only approximately 90 subjects will be enrolled and randomized in Part 1.

Part 2

Approximately 274 eligible patients will be randomized, in order to obtain 264 evaluable patients (i.e., patients who are randomized and received any test drug). It has been estimated that 4% of randomized patients may not receive any test drug due to unforeseeable intra-operative exclusion. Patients will be randomized in a 1:1 ratio to receive one of two treatments based on a computer-generated randomization schedule prepared before the study:

- Treatment Group 3: SABER®-Bupivacaine 5 mL (132 mg/mL, 660 mg bupivacaine base)
- Treatment Group 4: Bupivacaine HCl without epinephrine, 15 mL of 0.5% solution (75 mg)

For both Part 1 and 2, the randomization will be balanced by using randomly permuted blocks (block size of 4) and will be stratified by sex. The rationale for stratification by sex was differences in pain response reported in the literature for both acute/chronic pain (Fillingim et al, 2009), postoperative pain studies in cholecystectomy (De Cosmo et al, 2008; Uchiyama et al, 2006) and a previous laparoscopic cholecystectomy trial (C803-025, Cohort 2) conducted by DURECT. De Cosmo et al found that females had a higher mean pain score (4.3 ± 2.1) than males (2.9 ± 1.6) during 24 hours postoperatively (p=0.003 from repeated measure ANOVA). A significant sex effect on 24-hour postoperative pain was also reported by Uchiyama et al.

If a given study center approaches randomization of 20% of the total number of evaluable subjects (264) into Part 2 of the trial, the Sponsor will assess the appropriateness of allowing the center to continue randomizing additional subjects into the trial based upon factors such as monitored site performance including documentation and protocol compliance. An IWRS system will be used to assign subjects to a treatment group.

If all Screening (i.e. pre-operative) Inclusion/Exclusion criteria are met, randomization can be done up to 1 business day prior to surgery. In the event that a randomized patient does not have the surgical procedure for unforeseen circumstances (such as conversion to open surgery, or the need to use more than 4 laparoscopic ports) or does not receive any test drug, replacement of the patient has been planned. IWRS system will be algorithmically instructed to issue the appropriate randomization replacement and to ensure the balance of treatment as planned. Precise details on the IWRS algorithm will be described in the IWRS specifications.

11.4 Definition of Analysis Population

ITT Population: The ITT population will consist of all randomized patients in both Part 1 and Part 2 independent of their exposure to test drug or completion of surgery. However, the primary efficacy analysis will include only Part 2 data.

Safety Population: The Safety population will consist of all subjects in both Part 1 and Part 2 who received any amount of test drug. The Safety population will be used for all safety analyses.

Modified Intention-to-Treat (mITT) Population: All randomized patients in both Part 1 and Part 2 who receive any test drug. However, the primary efficacy analysis will include only Part 2 data.

All efficacy endpoints will be analyzed using the mITT set.

11.5 General Statistical Analysis Considerations

The primary efficacy analysis will include only Part 2 data. Due to the early stopping of Part 1 enrollment, for secondary and exploratory efficacy endpoints, the efficacy data from the SABER®-Bupivacaine arm from Part 1 will be integrated with the same treatment arm from Part 2 and be compared to bupivacaine HCl (75 mg) over 72 hours. Inferential statistics will be derived from the comparison. Due to lack of full enrollment of subjects from Part 1, the efficacy will be descriptive, presented as either mean or ratio and its 95% confidence interval as appropriately applied.

Continuous variables will be generally summarized using descriptive statistics such as mean, median, standard deviation, standard error and ranges. Categorical variables will be summarized using frequencies and percentages. 95% confidence intervals will also be provided when appropriate. Inferential tests for the analysis of continuous variables will be primarily based on parametric general linear models and will be 2-sided and conducted at the overall 5% significance level unless otherwise stated.

The multiplicity of comparisons impact on the Type 1 error rate will be addressed below (Section 11.8.4). In the case where the general linear model assumptions appear to be significantly violated, nonparametric methods of analysis such as the Wilcoxon Rank-Sum test will be used. A data transformation will also be made in an attempt to achieve a successful normalization of non-normal data. Inferential tests for categorical variables will be based on logistic regression models and categorical data analysis models. In cases where the cell counts (i.e. percentages) are too small for asymptotic methods to be valid, exact tests such as Fisher's exact test will be used.

Unless otherwise specified, all statistical tests will be conducted employing a two-sided significance level of 0.05.

11.6 Methodology for Dropouts and/or Missing Data

Imputation for Missing Pain Score

For the primary efficacy endpoint (scheduled pain on movement, adjusted for prior rescue medication use) the repeated measures ANOVA will handle data missing at random. However, detailed tabulation of the amount, percentage of subjects, and pattern of missing data by treatment group over time will be presented. Two approaches will be used to impute a missing pain score. For any dropout prior to 72 hours due to adverse event or lack of efficacy, a single imputation of worst value carried forward (WOCF; FDA, 2014) will be used. For dropouts due to other reasons or intermittent missing values, a multiple imputation algorithm (Markov Chain Monte Carlo method [MCMC]) will be used (Yuan, 2010). The detailed implementation of these analyses will be described in a separate Statistical Analysis Plan (SAP).

Rescue Medication Use

If it is indicated on the LogPad that no rescue medication was used, a dose of zero milligrams will be imputed. The lack of rescue medication use will be verified using data from the site rescue medication reconciliation/pill count. If there is a discrepancy between the rescue medication entered in the LogPad and the pill count at the study visit, the LogPad results will be used for analysis.

Time-to-Event Variables

For any time to event variable (e.g., time to the first use of a rescue opioid after discharge from the PACU), the Kaplan-Meier method will be used to analyze it by using the event time when a subject has the first event or the entire follow-up time when a subject does not have the event. For the latter, the variable will be censored at the time of last follow-up. No imputation will be made.

11.7 Demographic and Baseline Characteristics

For Part 1 and 2, continuous variables will be summarized using descriptive statistics such as mean, median, standard deviation, standard error and ranges. Categorical variables will be

summarized using frequencies and percentages. 95% confidence intervals will also be provided when appropriate.

11.8 Statistical Analyses of Efficacy Endpoints

The principal analyses of the primary efficacy endpoint will be carried out based on the modified Intention-to-Treat (mITT) set comprising all randomized patients who receive trial drug in Part 2.

11.8.1 Primary Efficacy Endpoint

Part 2

The primary efficacy endpoint is:

- Pain intensity on movement measured at scheduled time points from 0-48 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM)

To account for the impact of rescue medication use on the scheduled pain scores, the following substitution method will be used. If the scheduled pain on movement score has been assessed within one plasma half-life after the use of rescue medication (IV or oral opioid, or acetaminophen), and if the pre-rescue medication pain score is higher than the scheduled one, the pain score will be censored and the rescue medication pain score will substitute for it (FDA, 2014). If any of the rescue pain scores are missing, then the worst pain score up to that point will be used instead.

Data derived from the assessment of pain intensity on movement will be used to test the hypotheses as described below:

Null hypothesis:

There is no difference in analgesic effect between subjects treated with SABER®-Bupivacaine and those treated with bupivacaine HCl, as measured by pain intensity on movement scores over 0-48 hours following test drug administration, with adjustment for sex effect and imputation for missing pain scores.

Alternate hypothesis:

There is a difference in analgesic effect between subjects treated with SABER®-Bupivacaine and those treated with bupivacaine HCl, as measured by pain intensity on movement scores over 0-48 hours following test drug administration, with adjustment for sex effect and imputation for missing pain scores.

The pain scores will be analyzed by a mixed effect ANOVA model of repeated measures (MMRM). The model includes the following fixed effects: sex stratum, treatment, sex by

treatment, time, interaction of treatment and time, study site and interaction of study site and treatment, with time as the repeating factor and subject as a random effect.

11.8.1.1 Sensitivity analysis of the primary endpoint

In addition to the primary analysis, several sensitivity analyses will also be employed as below:

- Pain intensity on movement measured at scheduled time points from 0-48 hours following test drug administration, adjusted for rescue medication use. The adjustment algorithm will be as such: If the scheduled pain on movement score has been assessed within one plasma half-life after the use of rescue medication (IV or oral opioid, or acetaminophen), the worst pain score from all observed ones prior to using rescue medication, if this score is higher than the pre-rescue pain score, will be used to substitute the scheduled pain score.

- Pain intensity on movement measured at scheduled time points from 0-48 hours following test drug administration will be analyzed by a mixed effect ANOVA model of repeated measures (MMRM) (i.e. no adjustments for rescue medication use)

- Analyze the observed cases without imputation for missing pain scores

- Analyze completers over 0-48 hours following test drug administration only

- Treat all missing pain as “failures” using WOCF imputation.

11.8.2 Secondary Efficacy Endpoints

For all secondary efficacy endpoints, data from SABER®-Bupivacaine arm in Part 1 will be combined with the same treatment arm in Part 2. The integrated data will be compared to Bupivacaine HCl.

<u>The key secondary efficacy endpoint:</u>

- Pain intensity on movement measured at scheduled time points from 0-72 hours following test drug administration, adjusted for prior rescue medication use and analyzed by a mixed effect ANOVA model of repeated measures (MMRM).

The adjustment algorithm for rescue medication use is the same as described for the primary endpoint in Section 11.8.1.

<u>Additional secondary efficacy endpoints:</u>

- Total IV morphine-equivalent dose of rescue opioids used during 0-72 hours following test drug administration (standard conversion factors will be used to convert different opioids to IV morphine-equivalents; CCI [redacted]

- Composite endpoint of Silverman's Integrated Analgesic (SIA) assessment score (Dai et al, 2013 and Silverman et al, 1993) over 0-72 hours following test drug administration
- Proportion of patients taking no opioid rescue medication from PACU discharge until 72 hours after test drug administration
- Time to first opioid rescue medication use after discharge from the PACU
- Time to PACU discharge eligibility as assessed by mPADSS (Chung, 1995; Awad and Chung, 2006).

The total IV morphine-equivalent dose of opioid rescue medication used during the first 72 hours post-dose will be analyzed by an ANOVA model adjusted for the stratification or by the van Elteren test (a stratified Wilcoxon Rank Sum test), depending on whether normality assumptions have been met.

A composite endpoint, Score of Integrated Analgesia (SIA) (Dai et al, 2013 and Silverman et al, 1993), that integrates pain assessment score with opioid use will be derived at 24, 48 and 72 hours post-surgery. The score derived for each subject represents a sum of the ranks (ranging from -200 to 200 with -200 being the best case and 200 the worst case). SIA will be analyzed by repeated measures ANOVA. The model will have treatment, sex, sex*treatment interaction and study site as the main effects, subject as the random effect and time as the repeating factor.

The categorical efficacy endpoint, proportion of patients taking no opioid rescue medication will be compared between the two treatment groups using the Cochran-Mantel-Haenszel (CMH) test stratified by sex.

Time to the first use of rescue opioid after discharge from PACU will be analyzed using the Kaplan-Meier method. Subjects who do not use any rescue opioids will be censored at 72 hours. The stratified Log rank test will be used to compare the treatment groups.

Time to PACU discharge eligibility by mPADSS will be analyzed by Kaplan-Meier method and compared between the treatment groups by stratified Log rank test.

CCI [redacted]

11.8.4 Adjustment for Multiple Hypotheses Testing

The serial gate-keeping approach (proposed by Westfall and Krishen, 2001) will be used to test the primary and secondary endpoints (order by its clinical relevance and importance) in the above specified sequence. It will be implemented in the following way: If (and only if) the null hypothesis associated with primary endpoint has been rejected at the 0.05 level, then the first secondary endpoint, movement pain adjusted for rescue medication use during the first 72 hours following administration of test drug will then be tested. If this second gate-keeping step has been passed, the next secondary endpoint will be tested until the p-value > 0.05, then no more formal hypothesis testing will be performed. Once this occurs, the additional endpoints will be analyzed in order to engender additional hypotheses concerning their effects.

11.8.5 Subgroup Analysis

Subgroup analyses will be conducted by age (< 45, 45-to-65, > 65), sex, and race for the primary and secondary efficacy endpoints. ANOVA analyses described for the analysis of the primary and secondary efficacy endpoints will be repeated at the subgroup level for the above-mentioned subgroups. In the subgroup analysis by sex, the sex stratum and the interaction of sex by treatment effects will not be included in the model.

Similar subgroup summaries will be also be provided for adverse events, where appropriate.

11.8.6 Analyses Strategy for Pooling Trial Centers

In order to have an adequate number of subjects represented from each trial site, data from any site that enrolls 3 or less subjects will be evaluated as a pooled site in the primary or secondary endpoints analysis.

11.9 Interim Analyses and Data Monitoring

There is no planned interim analysis. An interim analysis will only be implemented if the Safety Assessment Committee (SAC) stops the trial (see 11.9.1) for safety. Safety data will be monitored in a blinded manner throughout the study in accordance with the Safety Monitoring Plan. Unblinded review of SAEs will be conducted by the SAC at its discretion, in accordance with the SAC Charter and as described below in Section11.9.1. The Safety Assessment Committee comprises three members that are independent of the study (medical professionals and a statistician).

11.9.1 Study-Stopping Criteria

The following study stopping criteria, extracted from the SAC Charter CCI will be used for Part 2 of the trial.

11.9.1.1 General Provisions

- The Sponsor medical monitor will carefully and routinely monitor the blinded safety data for any occurrence of SAEs, will promptly provide all SAE data to the SAC and will convene an SAC meeting if any safety events require an immediate review by the committee.
- The period of observation will be based on safety data reported during the 60-day post-treatment period.
- The SAC will be responsible for determining whether SAEs provided to them meet the requirements for stopping the trial, as set forth in SAC Charter sections 4.2 and 4.3. To make this determination, the SAC at its discretion, may choose to un-blind the case for detailed examination.
- The bupivacaine control patients are receiving standard of care for this low-risk surgical procedure and will be at no greater risk than those undergoing laparoscopic cholecystectomy outside of the PERSIST clinical trial. For that reason, SAEs occurring in the control group will not constitute trial-stopping events, although they could prompt revision of the trial protocol if deemed appropriate.

11.9.1.2 Stopping due to Fatal Events

The SAC will convene in the event that any post-treatment fatality has been reported. The reported fatality will be un-blinded and all available clinical data will be investigated and

evaluated by the SAC. The SAC will recommend stopping the trial if, in its judgment, all of the following provisions (1), (2) and (3) have been met:

(1) SABER-Bupivacaine was administered to the patient.
(2) The fatal event had a temporal relationship to administration of SABER-Bupivacaine
(3) A clear alternate cause for the fatal SAE is not readily apparent

If the SAC recommends that the trial not be stopped because the fatality under review fails to meet the stopping criteria, it may instead recommend revisions to the study protocol to enhance patient safety and may also recommend a pause in enrollment until such revisions can be implemented.

11.9.1.3 Stopping due to Non-Fatal Serious Adverse Events

The SAC will review all SAEs reported during the PERSIST trial. The SAC may un-blind the patient data relating to any SAE it wishes to examine in detail for the purpose of determining whether stopping criteria have been met. The study will be stopped upon the occurrence of three non-fatal SAEs (including any wound hematoma, dehiscence, pruritus, and bruising), each of which, in the judgment of the SAC, meets all of the following provisions (1), (2), and (3):

(1) SABER-Bupivacaine was administered to the patient.
(2) The SAE had a temporal relationship to administration of SABER-Bupivacaine
(3) A clear alternate cause for the SAE is not readily apparent

If the SAC recommends that the trial not be stopped because the SAEs under review fail to meet the stopping criteria, it may instead recommend revisions to the study protocol to enhance patient safety and may also recommend a pause in enrollment until such revisions can be implemented.

11.10 Statistical Analysis of Safety Endpoints

11.10.1 Safety Variables and Summaries

Safety summaries will be based on the safety population. The safety population will include all subjects treated with SABER®-Bupivacaine 5 mL (660 mg bupivacaine base) or 0.9% sterile normal saline 5 mL (placebo) in Part 1; and all subjects treated with SABER®-Bupivacaine 5 mL or 15 mL of 0.5% bupivacaine HCl in Part 2. It will include summaries in the form of tables and patient listings by three treatment arms; SABER®-Bupivacaine 5 mL (660 mg bupivacaine base), 15 mL of 0.5% solution bupivacaine HCl (75 mg) or 0.9% sterile, normal saline 5 mL (placebo).

Safety variables include:

- Subject incidence rate of adverse events (both pre-specified patient-reported AEs solicited on LogPad through Study Day 4 [POD 3], as well as spontaneous AEs reported either by patient or investigator)

- Subject incidence rate of solicited AEs occurring in the first 6 hours after dosing of test drug.
- Time to the first occurrence of the solicited AEs
- Time to PACU discharge
- Change in standard 12-lead ECG at Screening, Visit 6 (Study Day 29), and Visit 7 (Study Day 60)
- Change in safety Laboratory Tests (serum chemistry, hematology, urinalysis) (Screening, Study Day 4, Study Day 29, Study Day 60)
- Change in vital Signs (heart rate, blood pressure, temperature, respiratory rate) (at each scheduled visit) and height, weight, BMI (Screening, Study Day 29, Study Day 60)
- CCI [redacted]

The subject incidence rate (number and percentage) of treatment emergent adverse events will be tabulated in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event and by relationship to test drug.

The individual rate of solicited patient-reported AEs (dizziness, somnolence, constipation, nausea, vomiting, pruritus, headache, dysgeusia, hypoesthesia, and paresthesia) will be derived. The risk ratio and 95% confidence interval (CI) for the individual AE rate will be presented with saline placebo and bupivacaine HCl as the control groups. For example, if the 95% CI for the risk ratio contains 1, the AE risk is considered comparable between the active and control groups.

Time to the first occurrence of the solicited AEs will be analyzed by the Kaplan Meier method. For subjects who do not have the AE, the observation will be censored in the analyses. Median time and 95% confidence interval (CI) will be determined.

The change in safety laboratory, ECG and vital signs parameters from baseline will be analyzed by shift tables. Descriptive statistics (means, medians, SD, minimum/maximum) for the safety variables and change from baseline will be summarized. Subjects found to have abnormal safety values considered clinically significant will be summarized.

The presence/absence of surgical site AEs (see definitions in Section 9.2.6) will be tabulated by treatment and study visit. The overall rate of each AE across study visits will be tabulated by treatment. The risk ratio and 95% CI will be derived for each AE. Known risk factors related to wound healing, such as being diabetic or having higher BMI, may be used for adjusted relative risk if they are not balanced by randomization alone. Time to the first occurrence of each AE

will be derived from the end of surgery. The data will be censored for subjects who do not have the AE. The median, 95% CI, 25th and 75th percentile for the time to each AE will be summarized by treatment. The time to resolution of each AE will also be derived and summarized.

CCI [redacted]

11.11 Changes and Deviations to the Statistical Analysis Plan

Prior to unbinding the trial, any deviations from the planned analyses methods and the rationale for such deviations will be carefully documented in the Statistical Analysis Plan (SAP) and as a protocol amendment, if applicable. CCI [redacted]

12.0 Access to Source Data/Documentation

The investigative site will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documentation (e.g. medical records, original laboratory records and original informed consent forms). The Investigator should immediately notify DURECT of any Health Authority inspection. Essential documents must be maintained at the investigative site throughout the trial.

12.1 Confidentiality

By consenting to participate in this trial, each patient will agree that Sponsor personnel, their representatives or the respective Health Authorities personnel may require direct access to the patient's data/personal records including photocopying source data in an anonymous form. The patient will also agree that his/her data will be processed and stored in an anonymous form for evaluation of this trial and any later overviews. Data may also be transferred in an anonymous form to third parties (e.g., other companies or authorities that may be located in other countries with potentially different regulations for data). Data will follow the development of the test drug and will be used for documentation of the product's efficacy and safety. Data will be transferred to involved parties only within the authority given by official agencies. The informed consent form will state that any data already obtained during trial participation will be kept if consent is withdrawn.

12.2 Data Identification

Pain intensity evaluations, solicited patient-reported AE checklists, and oral rescue analgesia completed by the patient on LogPads, electronic patient-reported data capture device, will be considered source data. Safety laboratory results from the central safety laboratory will be considered source data. All other data will be recorded on a source document prior to being entered into the eCRF.

13.0 Quality Control and Quality Assurance

13.1 Monitoring

DURECT or DURECT's designee will monitor the trial for regulatory and protocol adherence at all stages of trial conduct from inception to completion in accordance with ICH-GCP. This monitoring will be in the form of site visits and other communication and will include review of original source documents and eCRFs. DURECT's monitor or designee will notify the Investigator prior to conducting any site visit. These visits will include monitoring to assess facilities, required certifications, IRB/IEC records, equipment, patient recruiting ads, record-keeping, protocol adherence, data verification and transmission, adverse event reporting, e-diary email alerts and other factors. Final quality assurance visits by the Sponsor should be expected, and possibly by the FDA.

The completed eCRFs will be reviewed against source documents by the blinded monitor at each monitoring visit. If any data, signatures, or forms are missing or discrepant, the Investigator will be informed and appropriate written corrections will be made in a timely manner.

13.2 Protocol Deviations

All departures from the protocol will be referred to as protocol deviations and not protocol violations (ICH E3R1 Guidance, June 2012).

Definitions:

- A protocol deviation is "any change, divergence, or departure from the study design or procedures defined in the protocol."
- An important protocol deviation is "a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being"

The Investigator should not deviate from the protocol. Except for changes intended to eliminate any immediate hazard to patients, the trial should be conducted as described in the approved protocol. In medical emergencies, the Investigator will use medical judgment and will remove the trial participant from immediate hazard followed by notification to DURECT and the

IRB/IEC regarding the type of emergency and the course of action taken. All protocol deviations will be documented by the investigative site or monitor on the designated log.

13.3 Case Report Forms

Electronic case report forms will be used for this trial. Data entry will occur at the investigative site and will be performed by trained and qualified site personnel. The Investigator will ensure all eCRFs are completed after each patient visit in a timely manner. Specific instructions are provided in the eCRF completion guidelines.

The eCRF system and services for this study will be provided by BioClinica, Inc., with its principal place of business located at 800 Adams Avenue, Audubon, Pennsylvania 19403. The software version in place at study start is Express 5.4 (validation report dated June 2014).

13.4 Coding

MedDRA will be used to code adverse events. WHO-Drug will be used to code concomitant medications.

13.5 Data Safety Monitoring Committee

A Data Safety Monitoring Committee has not been planned for this trial, which involves using only a single dose administration and short trial duration. However, periodic reviews of blinded safety data will be performed by the Sponsor's medical monitor.

13.6 Safety Assessment Committee

If pre-specified serious adverse events of interest (see Section 9.3.1) reach a specified threshold incidence, an independent Safety Assessment Committee will review unblinded safety data for the affected patients (see Section 9.3.4).

14.0 Ethical Considerations

This trial will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and ICH guidance E6) for all studies.

All patients for this trial will be provided a consent form describing this trial and providing sufficient information for subjects to make an informed decision about their participation in this trial. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any trial procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. Each subject will be given a copy of the signed consent form.

All patients will have access to supplemental rescue analgesia as needed with IV, and/or oral opioids per common clinical practice to ensure ethical treatment and assess the magnitude of analgesic contribution by SABER®-Bupivacaine.

14.1 Institutional Review Board / Ethics Committee

The protocol, consent form, advertisements and any other information for patients will be reviewed and approved by DURECT Corporation (or DURECT's designee) and by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of the participating investigative site prior to the start of the trial at that site in accordance with the International Conference on Harmonization (ICH) and institutional IRB/IEC policies. All protocol amendments and changes to the consent form occurring during the trial must also be IRB/IEC approved.

14.2 Regulatory Compliance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) set forth in the International Conference on Harmonization (ICH) Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and any local requirements.

14.3 Regulatory Status

SABER®-Bupivacaine has not yet been approved by the US Food and Drug Administration or any other Health Authority.

14.4 Patient Information and Informed Consent

Prior to participation in the trial, the Investigator or designee will obtain written consent from each patient using the IRB/IEC-approved informed consent form that explains the nature, purpose, possible risks and benefits of the trial, and the duration of an individual's participation. The basic elements of the informed consent as specified by the FDA (21 CFR §50.25), and HIPAA will be followed.

Before consenting, the patient must be left with ample time to consider and to pose questions. The Investigator and/or the designated investigative site personnel who conduct the informed consent discussion must also sign and date the consent form. Each patient will be given a copy of the signed consent form. The original, signed consent forms will be maintained at the investigative site.

14.4.1 Patient Withdrawal

Patients will be informed during the informed consent process (in writing and verbally) that they are free to withdraw from the trial at any time. The Investigator may exercise his medical judgment to terminate a patient's participation in the trial due to clinically relevant changes in any clinical or laboratory parameter. DURECT Corporation also reserves the right to terminate

the trial at any time. All trial procedures normally performed at completion of the trial must be done at the time of the patient's early termination, before the scheduled final clinic visit, or on the scheduled final clinic visit as described in Section 7.4.11 unless the patient withdraws consent. If a patient withdraws consent they will be encouraged to complete an early termination visit and AE follow-up. All AEs will be followed until resolution. Resolution means no further changes in the event are expected, i.e., the point at which a subject experiencing such an AE is appropriately treated and stabilized even though they may continue to experience lingering sequelae that may never resolve.

Patients who withdraw prior to assignment of test drug will be considered as screen failures and will not be considered randomized (See Section 11.4).

15.0 Data Handling and Record Retention

15.1 Data Ownership

The eCRFs, associated documents and reports from the trial are the property of DURECT. DURECT has the right to use the results for registration purposes, internal presentation and promotion.

15.2 Retention of Trial Records

The Investigator will retain all trial documents (e.g., approved protocol, copies of completed eCRFs and electronic diaries, original informed consent forms, relevant source documents) in a secure place protected from fire and theft until:

- At least 2 years after the last approval of an NDA by the US FDA;
- At least 2 years after the last approval of a marketing application in an ICH region;
- There are no pending or contemplated marketing applications in an ICH region; or
- At least 2 years have elapsed since the formal discontinuation of the clinical development of the test drug

These documents should be retained for a longer period if required by the local/regional regulations or by an agreement with DURECT. It is the responsibility of the Sponsor to inform the Investigator/Institution when these documents no longer need to be archived.

The medical files of trial patients must be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

DURECT will maintain the documentation pertaining to the trial as long as the test drug is on the market.

Trial records must be made available by the Investigator for inspection upon reasonable request by authorized representatives of DURECT, the Food and Drug Administration (FDA), or the corresponding regulatory Health Authorities of the relevant countries.

DURECT will provide the Investigator with information concerning the current status of the test drug as it relates to the Investigator's responsibility for the retention of trial records. The Investigator should contact DURECT prior to disposing of any such records. DURECT will arrange for continued storage of all records, if necessary.

16.0 Finance and Insurance

Financing and insurance statements are addressed in the Clinical Trial Agreements and Indemnity Agreements.

17.0 Publication Plan

17.1 Confidentiality

Information concerning the test drug and patent applications, scientific data or other pertinent information is confidential and remains the property of DURECT.

Investigators are not allowed to disclose or publish any information concerning patent applications, manufacturing processes or formulation information about the test drug to others without permission from DURECT Corporation.

17.2 Clinical Trial Report

DURECT is responsible for finalizing a clinical trial report within 12 months of completion of the treatment and follow-up phase of this protocol. A publication has also been planned (see Section 17.3).

In this multi-center trial, the lead principal investigator will be designated to sign the final clinical trial report.

17.3 Publications

DURECT's publication policy of trial results will be included within the clinical trial agreement with each investigator. Results of this protocol will only be published if the Publication Committee of DURECT initiates such publication or provides written approval of a concept prepared by the investigative site. In case the investigator has no interest to publish, DURECT is free to use the data for publication. The investigator may be invited to be co-author. DURECT will submit the manuscript to the investigator, who will have the right to insist he/she is represented in such publications.

If an Investigator is invited to act as co-author for the publication, he/she can only be mentioned in the manuscript if giving permission. DURECT will provide the manuscript to the Investigator

for review and comments and the Investigator has the right to have his/her interpretation of the data properly represented in the publication. If the agreed upon timeline for submission of a draft publication to DURECT is not kept by the Investigator, DURECT holds the right to publish the data. After publication of the results of a multi-center trial or 24 months after the clinical trial report has been finalized, whichever comes first, DURECT acknowledges the Investigator's rights to publish results from this trial. Any such scientific paper, presentation, communication or other information concerning the trial described in this protocol must be submitted to DURECT for review prior to submission for publication/presentation. Review comments will be given approximately within a month from receipt of the manuscript.

In this multi-center trial, based on collaboration of all sites, any publication of results should reflect the entire trial and must acknowledge all sites enrolling patients into the trial. The Publication Committee will designate the principal author of the publication. Additional authors may include representatives of the Sponsor.

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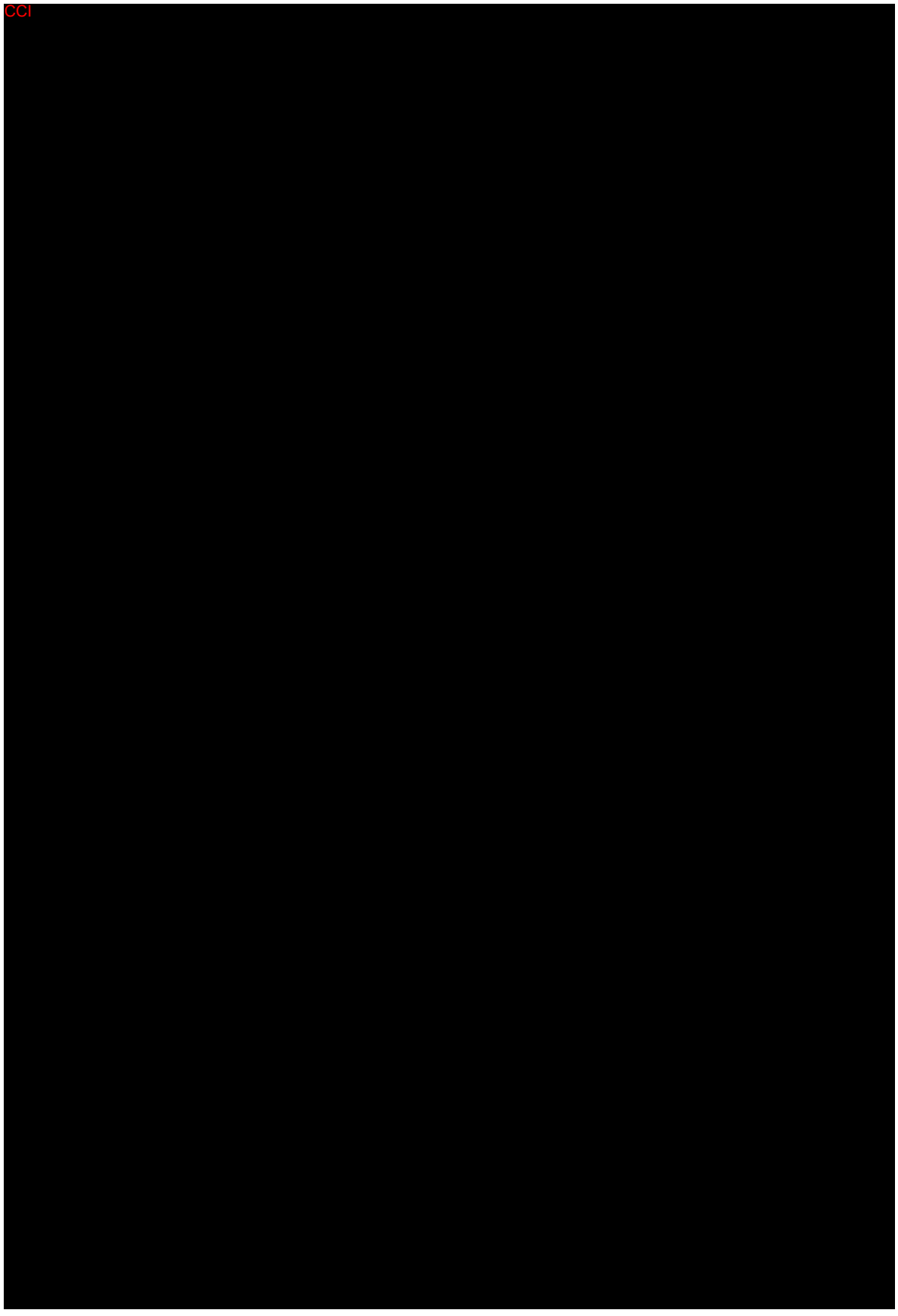
19.0 Appendices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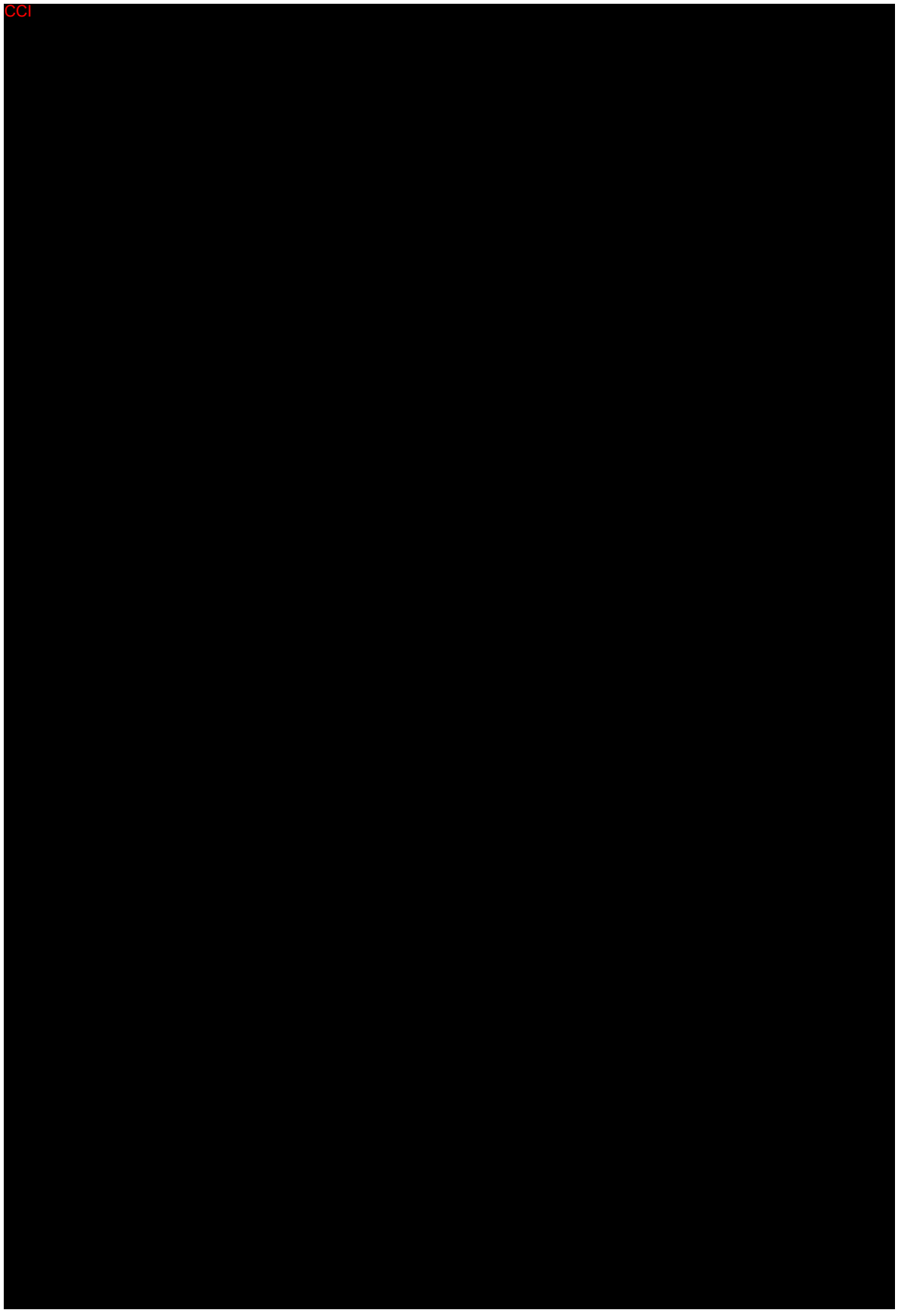
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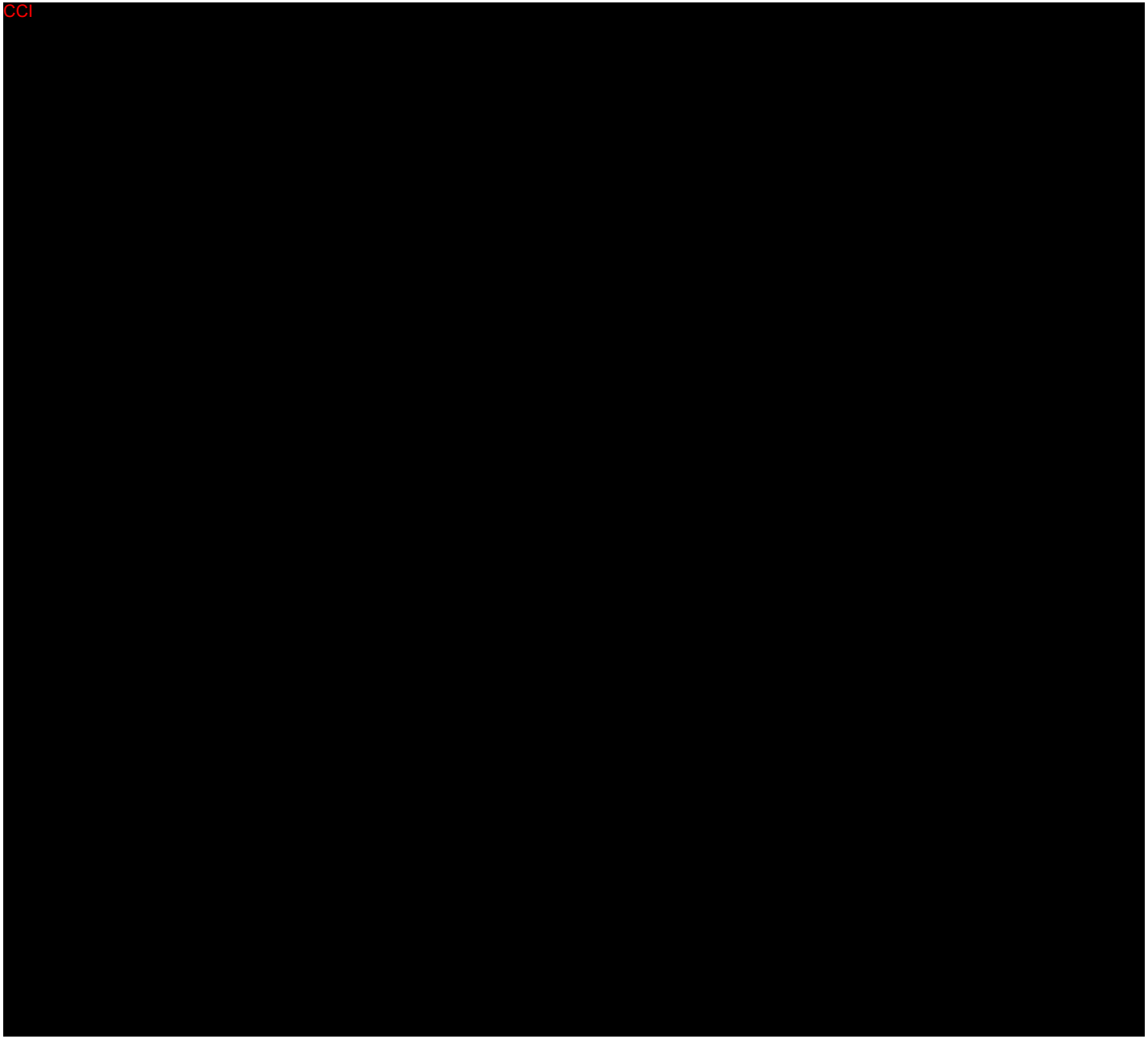
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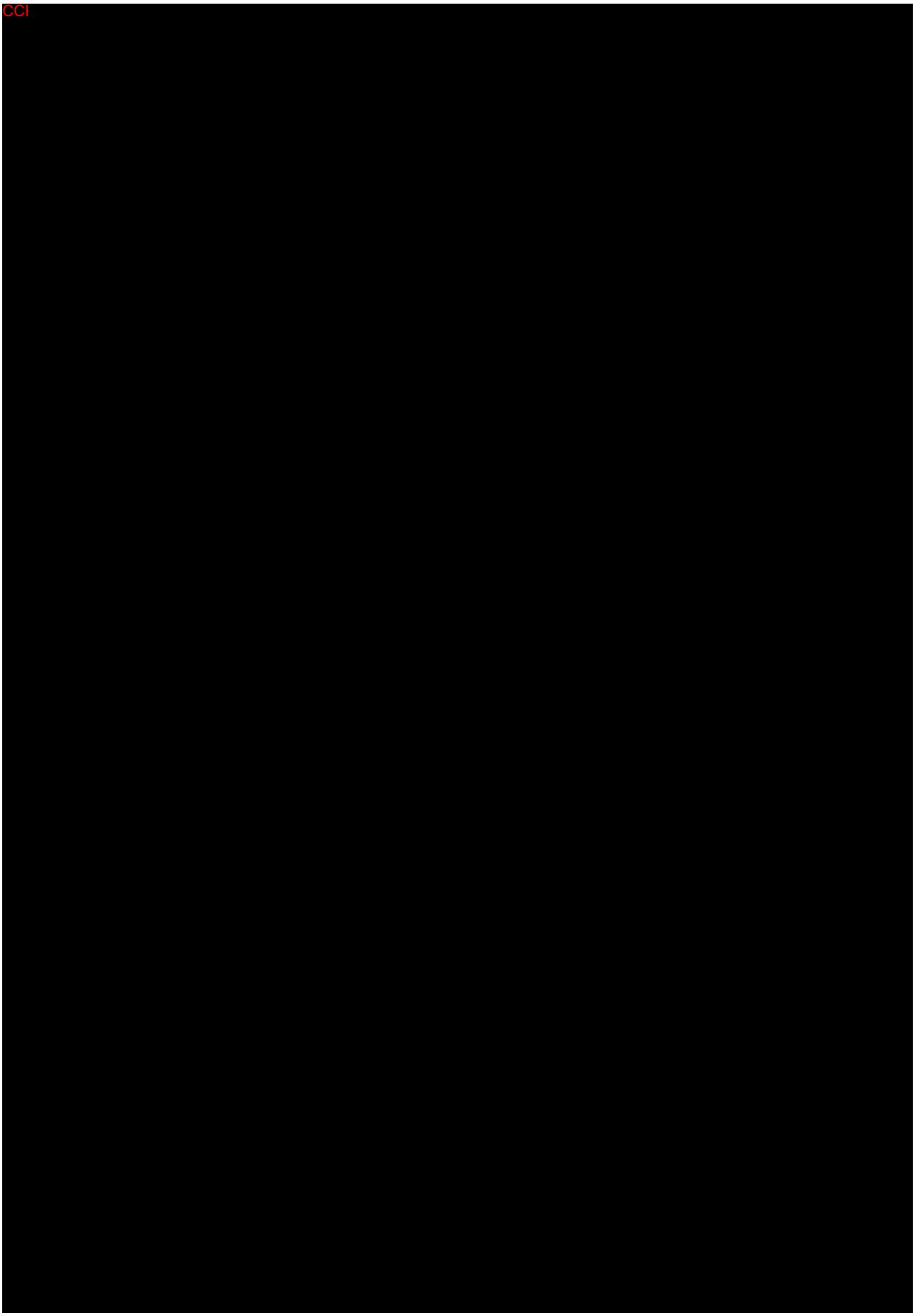
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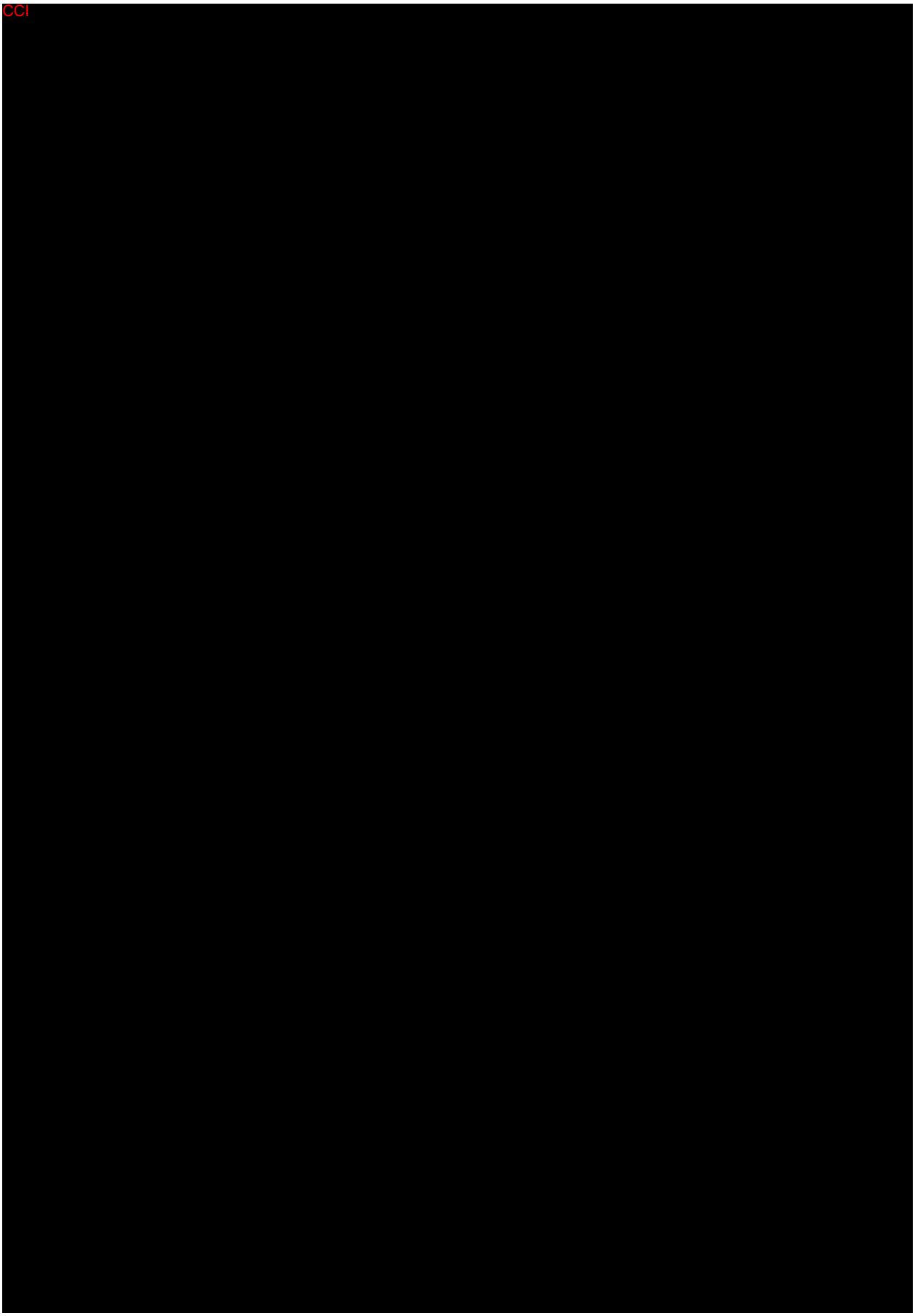
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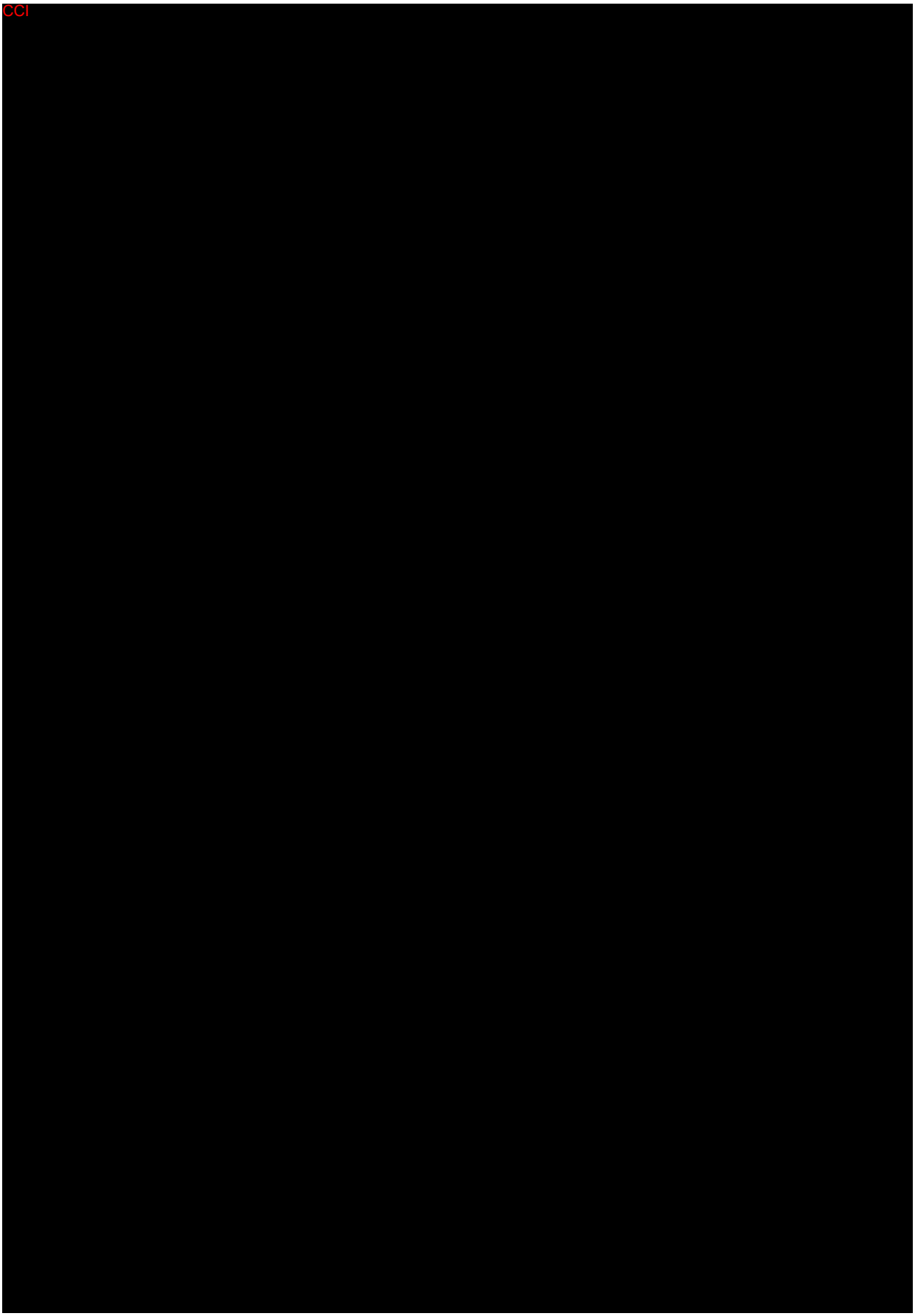
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Appendix 5: CDC/NHSN Surgical Site Infection Definitions and Diagnostic Criteria

CDC/NHSN Surgical Site Infection (SSI) definitions and diagnostic criteria (Table 2) are provided below. The full document may be accessed at the following website:

http://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf

Table 2. Surgical Site Infection Criteria

Criterion	Surgical Site Infection (SSI)
	Superficial incisional SSI Must meet the following criteria:
	Infection occurs within 30 days after any NHSN operative procedure (where day 1 = the procedure date), including those coded as 'OTH'* **AND** involves only skin and subcutaneous tissue of the incision **AND** patient has at least ***one*** of the following: a. purulent drainage from the superficial incision. b. organisms isolated from an aseptically-obtained culture from the superficial incision or subcutaneous tissue. c. superficial incision that is deliberately opened by a surgeon, attending physician** or other designee and is culture positive or not cultured **AND** patient has at least ***one*** of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. A culture negative finding does not meet this criterion. d. diagnosis of a superficial incisional SSI by the surgeon or attending physician** or other designee. *http://www.cdc.gov/nhsn/XLS/ICD-9-cmCODEScurrent.xlsx ** The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).
Comments	There are two specific types of superficial incisional SSIs: 1. Superficial Incisional Primary (SIP) – a superficial incisional SSI that is identified in the primary incision in a patient that has had an operation with one or more incisions (e.g., C-section incision or chest incision for CBGB) 2. Superficial Incisional Secondary (SIS) – a superficial incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site incision for CBGB)

Reporting Instructions for Superficial SSI	**The following do not qualify as criteria for meeting the NHSN definition of superficial SSI:** • Diagnosis/treatment of cellulitis (redness/warmth/swelling), by itself, does not meet criterion d for superficial incisional SSI. An incision that is draining or culture (+) is not considered a cellulitis. • A stitch abscess alone (minimal inflammation and discharge confined to the points of suture penetration) • A localized stab wound or pin site infection. While it would be considered either a skin (SKIN) or soft tissue (ST) infection, depending on its depth, it is not reportable under this module. **Note:** a laparoscopic trocar site for an NHSN operative procedure is not considered a stab wound. • Circumcision is not an NHSN operative procedure. An infected circumcision site in newborns is classified as CIRC and is not reportable under this module. • An infected burn wound is classified as BURN and is not reportable under this module.
	Deep incisional SSI Must meet the following criteria:
	Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table 3 **AND** involves deep soft tissues of the incision (e.g., fascial and muscle layers) **AND** patient has at least ***one*** of the following: a. purulent drainage from the deep incision. b. a deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, attending physician** or other designee and is culture positive or not cultured **AND** patient has at least ***one*** of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture negative finding does not meet this criterion. c. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test. ** The term attending physician for the purposes of application of the NHSN SSI criteria may be interpreted to mean the surgeon(s), infectious disease, other physician on the case, emergency physician or physician's designee (nurse practitioner or physician's assistant).

Comments	There are two specific types of deep incisional SSIs: 1. Deep Incisional Primary (DIP) – a deep incisional SSI that is identified in a primary incision in a patient that has had an operation with one or more incisions (e.g., C-section incision or chest incision for CBGB) 2. Deep Incisional Secondary (DIS) – a deep incisional SSI that is identified in the secondary incision in a patient that has had an operation with more than one incision (e.g., donor site incision for CBGB)
	Organ/Space SSI Must meet the following criteria:
	Infection occurs within 30 or 90 days after the NHSN operative procedure (where day 1 = the procedure date) according to the list in Table 3 **AND** infection involves any part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure **AND** patient has at least ***one*** of the following: a. purulent drainage from a drain that is placed into the organ/space (e.g., closed suction drainage system, open drain, T-tube drain, CT guided drainage) b. organisms isolated from an aseptically-obtained culture of fluid or tissue in the organ/space c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test **AND** meets at least ***one*** criterion for a specific organ/space infection site listed in Table 4. These criteria are in the Surveillance Definitions for Specific Types of Infections chapter.

Appendix 6: Investigator Responsibilities

The responsibilities of the Investigator conducting the trial are:

- Supervise the conduct of the trial and ensure that all trial personnel under their supervision are qualified and adequately trained to perform the tasks delegated to them.
- Obtain appropriate IRB/IEC approval to conduct the trial in a timely manner
- Provide DURECT with written documentation that the trial protocol, any protocol amendments, and the informed consent form have received IRB/IEC approval.
- Provide DURECT with a list of IRB/IEC members, including their affiliations and qualifications. As an alternative in the United States, a General Assurance number (as assigned by the Department of Health and Human Services) fulfils this requirement
- Report to the IRB/IEC as required. The IRB/IEC must assume continued responsibility for the trial and review the research on at least an annual basis, however some require more frequent periodic reviews.
- Maintain a file of all communications with the IRB/IEC on issues related to the trial.
- Complete sign and return to DURECT an original copy of the Statement of Investigator Form (Form FDA 1572).
- Provide DURECT current curriculum vitae of the Investigator and Sub-Investigator(s).
- Review the protocol and Investigator's Brochure. A copy of the protocol will be retained by the Investigator in the site's file. The Investigator's signature on the 1572, protocol signature page, and Sponsor contract are evidence of agreement with the conduct of the trial.
- All amendments to the protocol must be reviewed by the Investigator and submitted to the IRB/IEC in accordance with their requirements. A copy of protocol amendments will be retained by the Investigator in the site's file.
- Submit the Investigator's Brochure to the IRB/IEC for review. Provide DURECT with written documentation that the Investigator's Brochure was received and reviewed by the IRB/IEC.
- Conduct the trial in strict adherence to the protocol and ICH Good Clinical Practices.
- Supervise the use of the test drug as outlined in the protocol. Only staff working under the supervision of the Investigator for the purposes of this trial will be allowed to handle the test drug.
- Store the test drug in a secure and locked area. The storage custody and security of the test drug is the responsibility of the Investigator.

- The test drug should be administered to patients under the Investigator's direct supervision or that of his/her Sub-Investigators.
- Maintain adequate record of the receipt and disposition of all test drug, including dates and quantities dispensed to individual patients.
- Ensure that each patient is informed of the risks and benefits of participating in the trial, and a properly signed and witnessed informed consent forms for each patient has been obtained at the time of screening.
- Provide appropriate health care or referral for the patient throughout the trial.
- Document all adverse events on the Adverse Event CRF. Document all serious, life-threatening, or unexpected events on the appropriate CRF, and notify DURECT via telephone and facsimile report within 24 hours as required by the regulatory authorities.
- Report all serious, life-threatening, or unexpected adverse events to the IRB/IEC.
- Document and maintain adequate and accurate CRFs for all patients receiving test drug as required at the designated times. Review all CRFs affirming the completeness and accuracy of the data recorded. Storage, custody and security of all trial records are the responsibility of the Investigator.
- Provide the Trial Monitor with the original completed CRFs and all source documents for review at the investigative site during monitoring visits. Retain the CRFs, source documents, and informed consent forms at the investigative site.
- Maintain a file of all trial correspondence.
- Adhere to standard record retention policy as stated in the protocol.
- Cooperate with Sponsor auditor(s) and health authority inspector(s). Facilitate activities related to audits/inspections.

Appendix 7: Sponsor's Responsibilities

DURECT is responsible for ensuring that the trial is conducted in accordance with the principles of Good Clinical Practice (GCP) set forth in ICH Good Clinical Practice, the US Code of Federal Regulations (CFR Title 21), the HIPAA law and any additional local requirements.

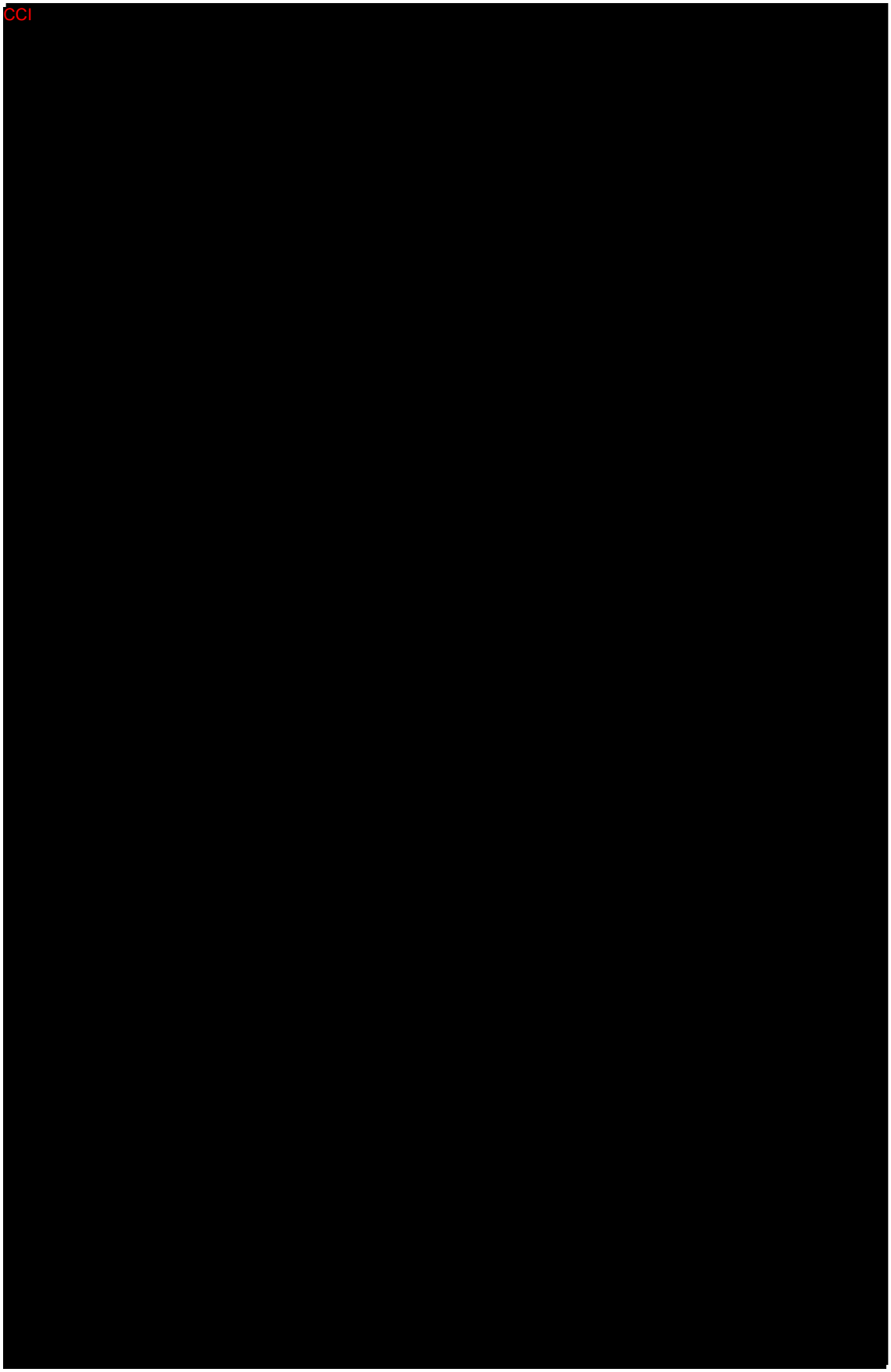
DURECT is responsible for selecting qualified investigators. DURECT will maintain a list of all investigators and important trial personnel and their current qualifications and curriculum vitae (CV).

DURECT will maintain a list and qualification records of all relevant sponsor trial personnel.

DURECT will provide investigators with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that the regulatory authorities and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the test drug.

DURECT or its designee (CRO) has the responsibility of ensuring the proper conduct of the trial in regard to protocol adherence. DURECT or its designee will assign Monitors for this trial. Their duties will be to aid the Investigator and DURECT in maintaining complete, legible, well-organized, and easily readable data. In addition, Trial Monitors will assure the Investigator's understanding of all applicable regulations concerning the clinical evaluation of a test drug, and assure an understanding of the protocol, reporting responsibilities, and the validity of the data.

The patients will be covered by DURECT Corporation's insurance according to applicable regulatory requirements.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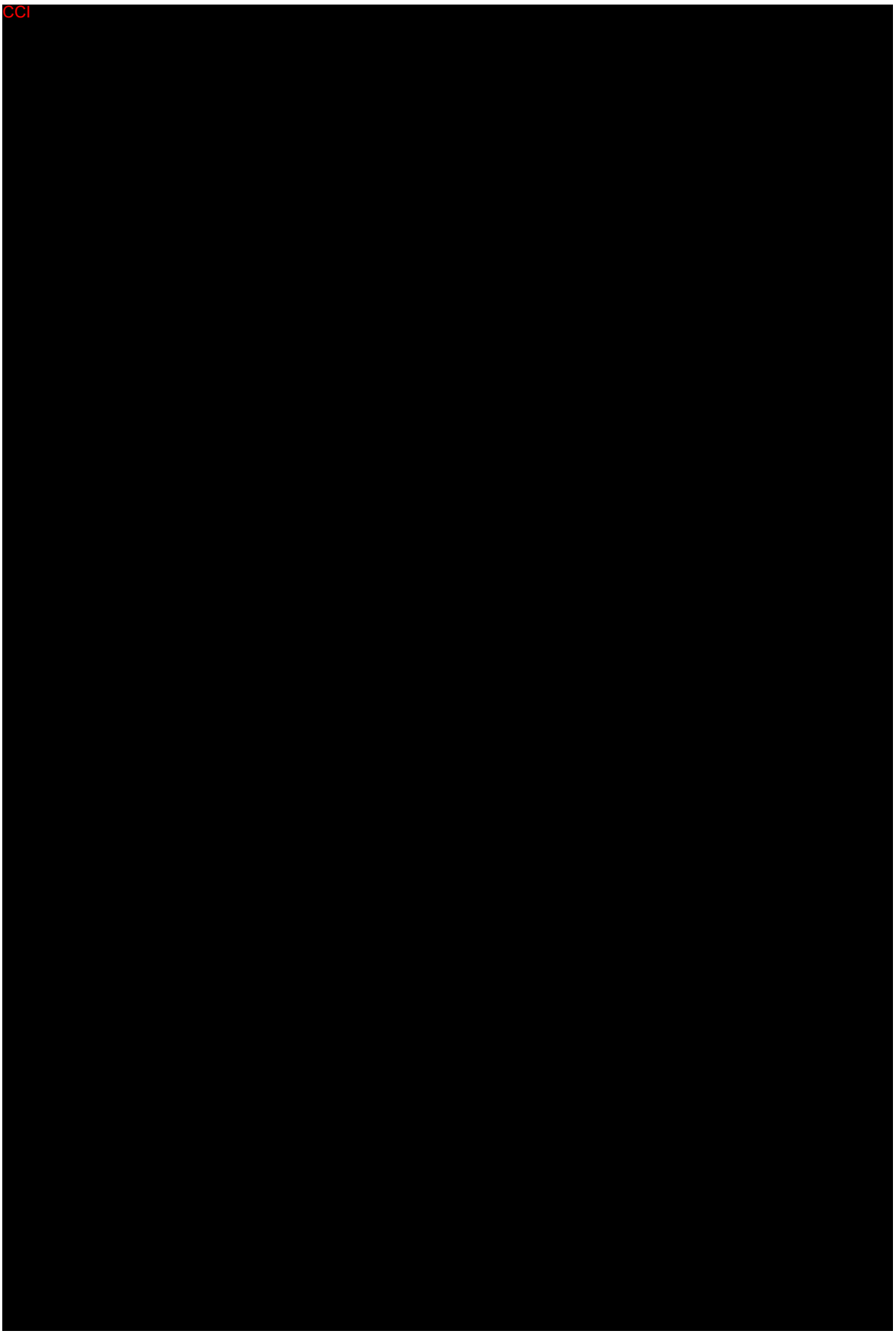
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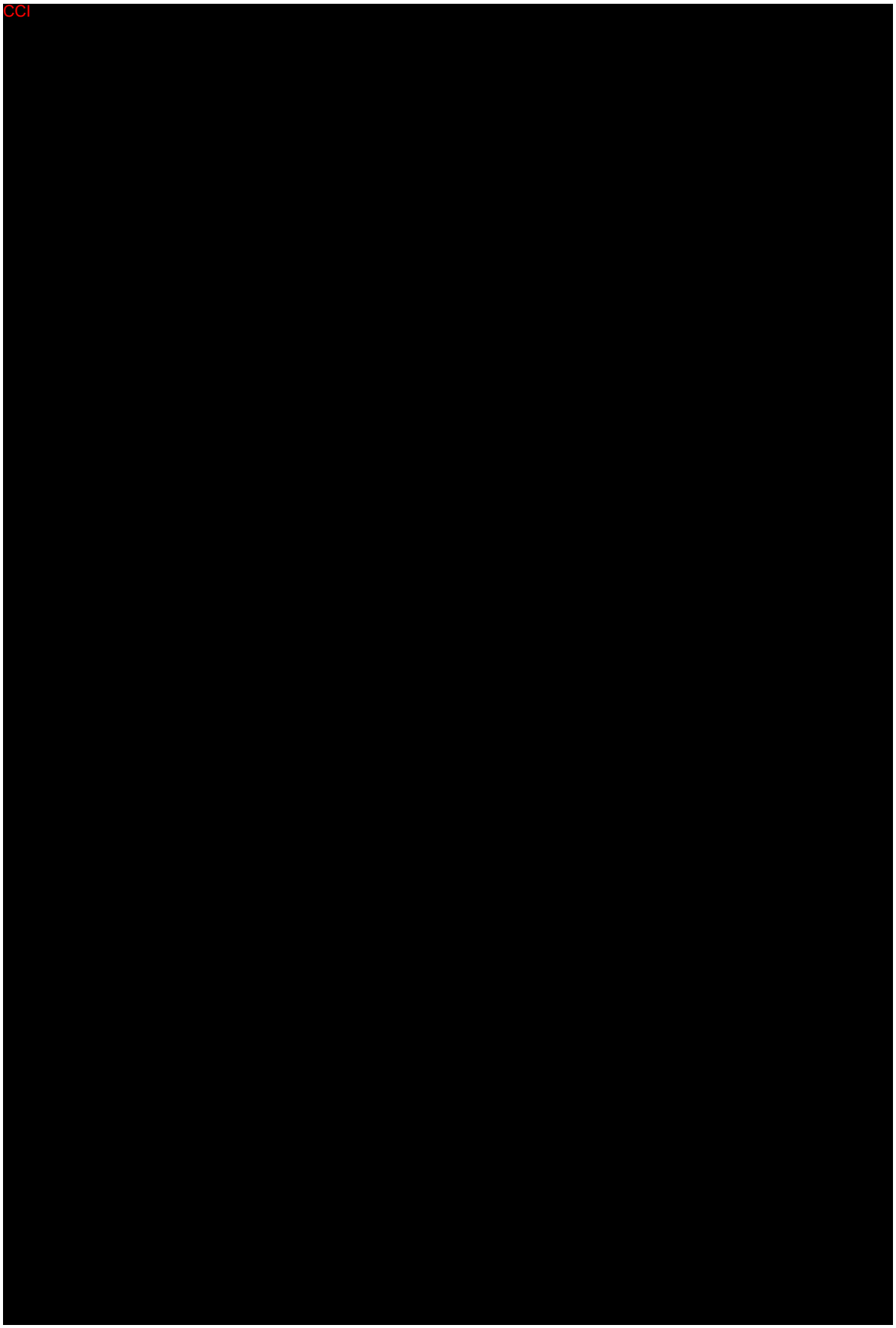
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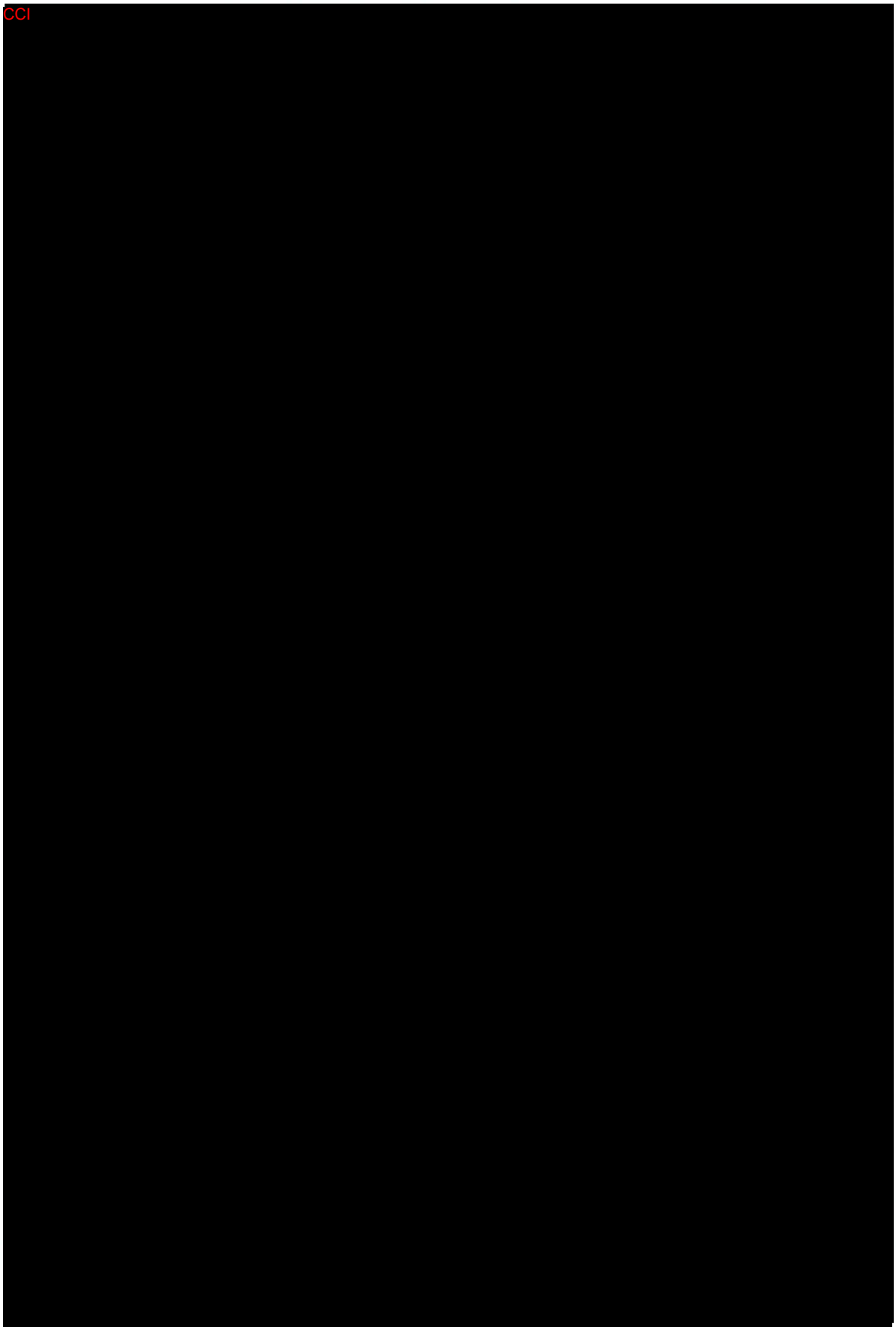
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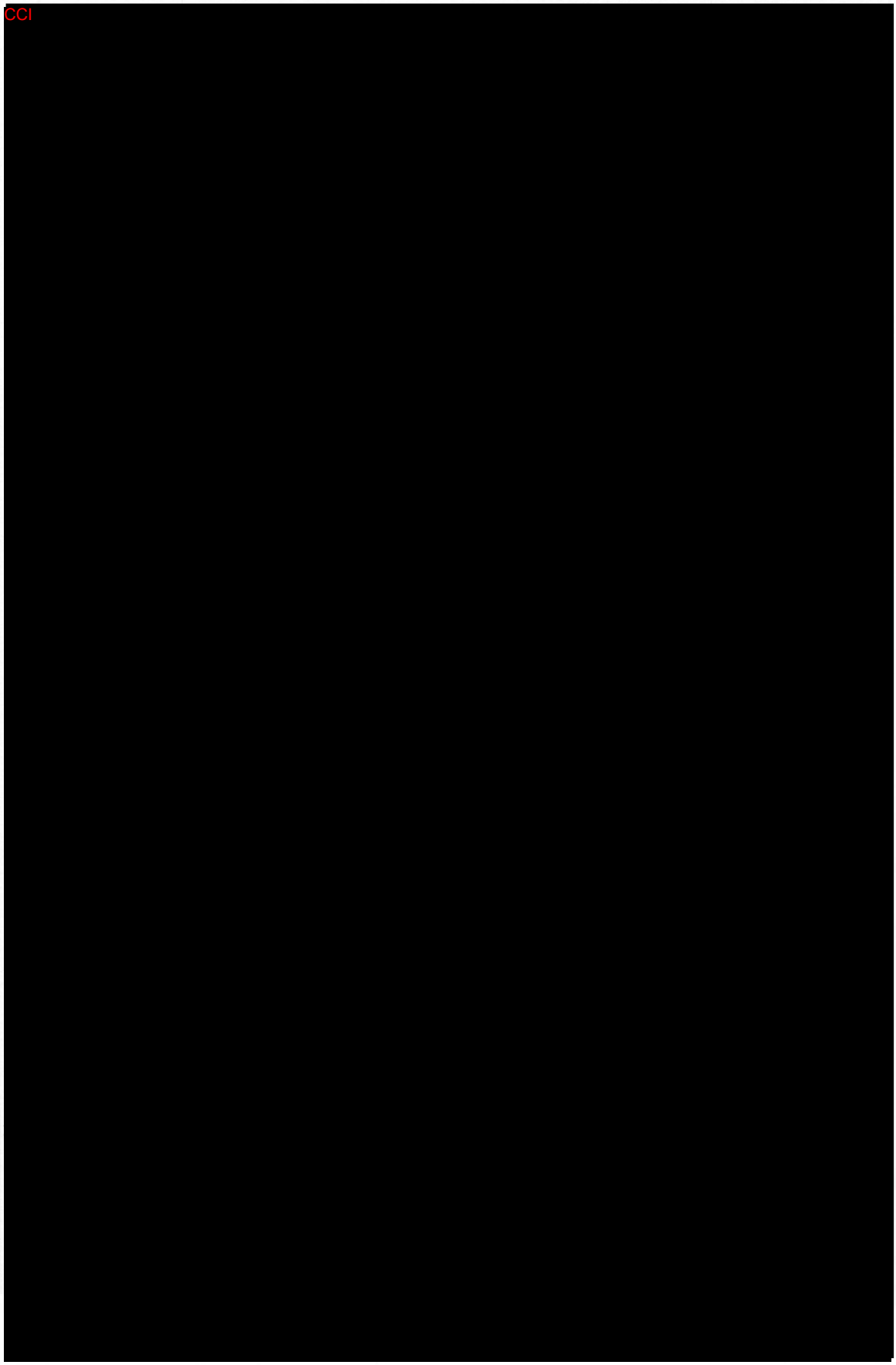
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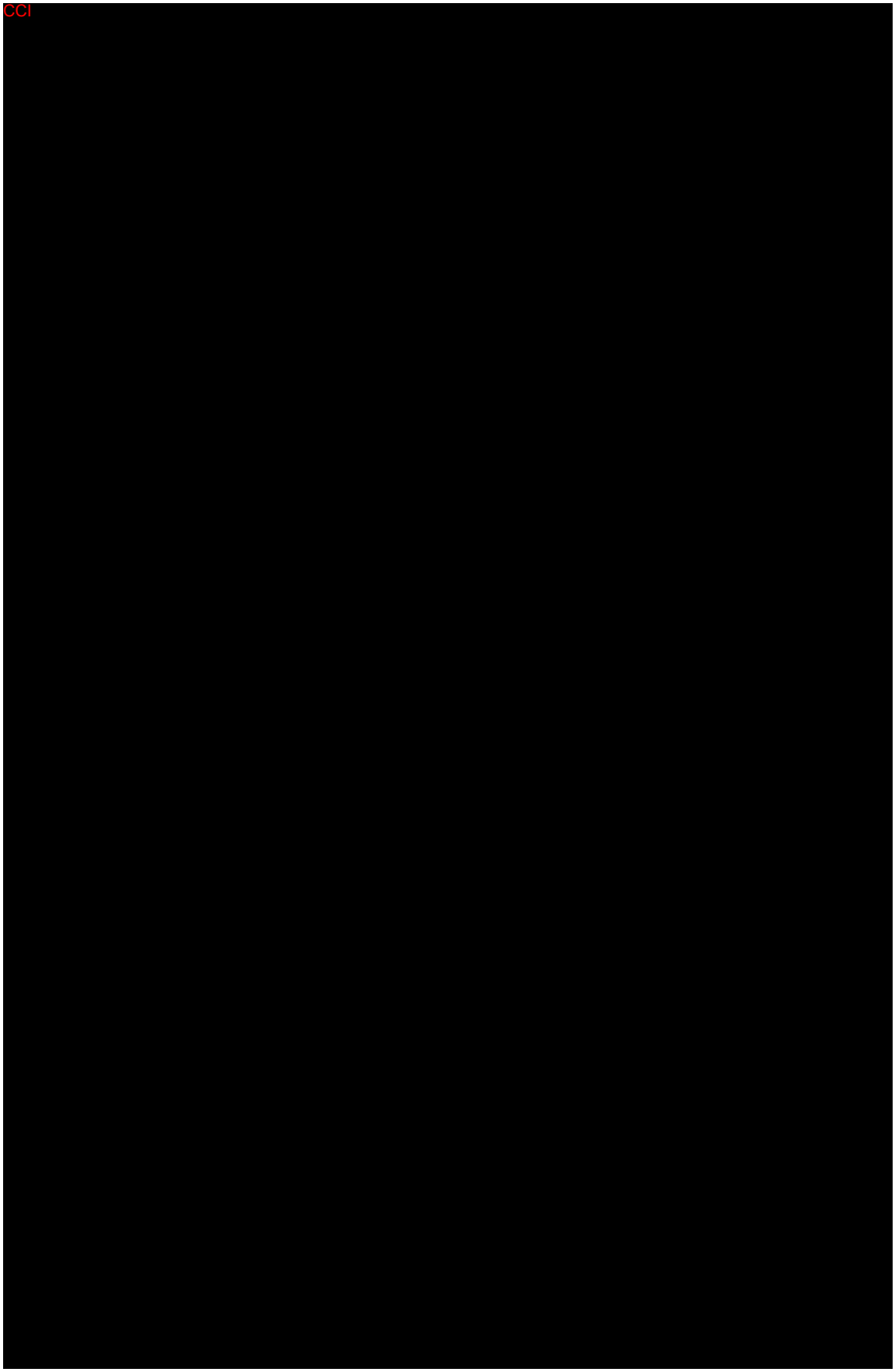
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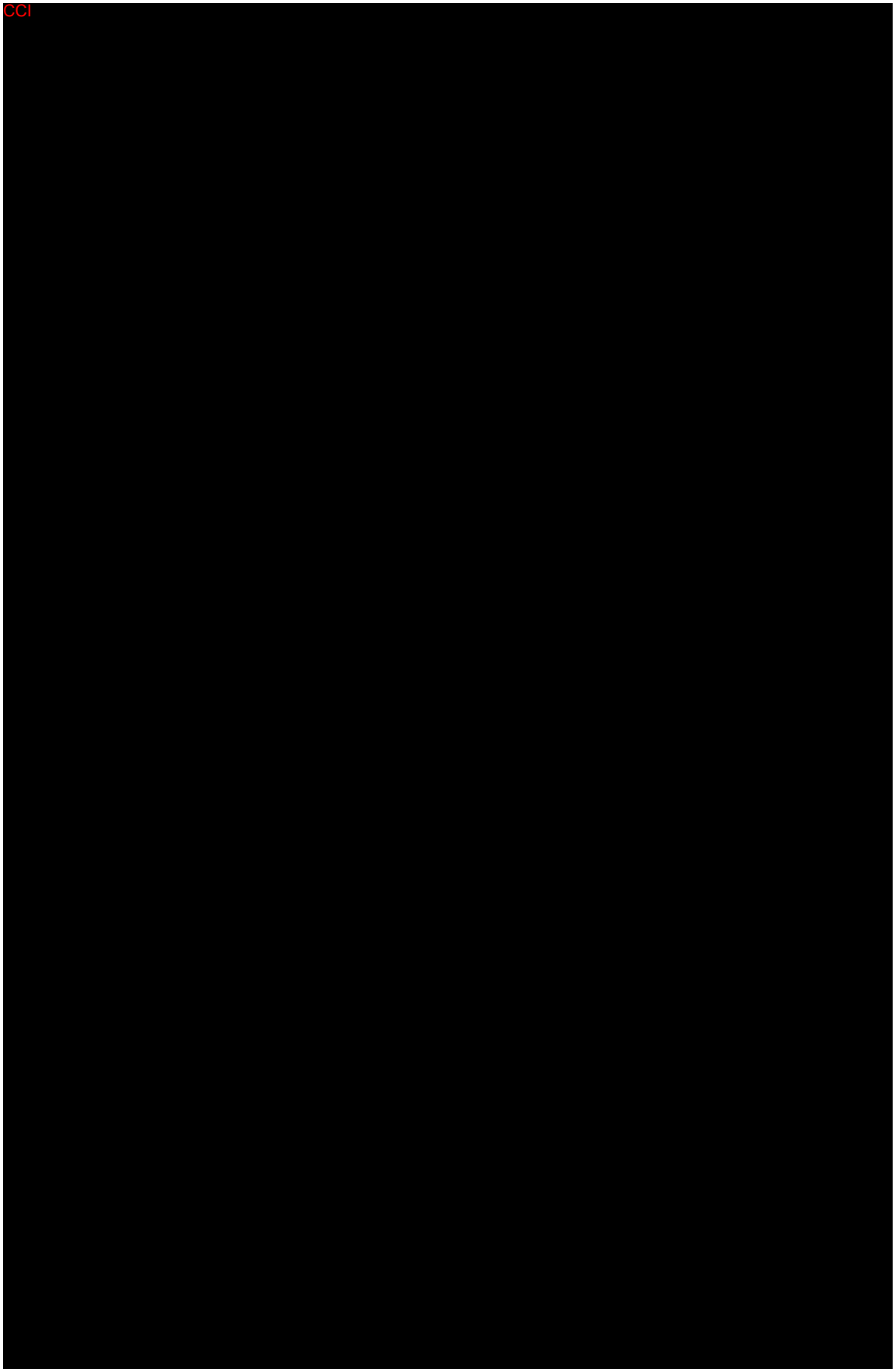
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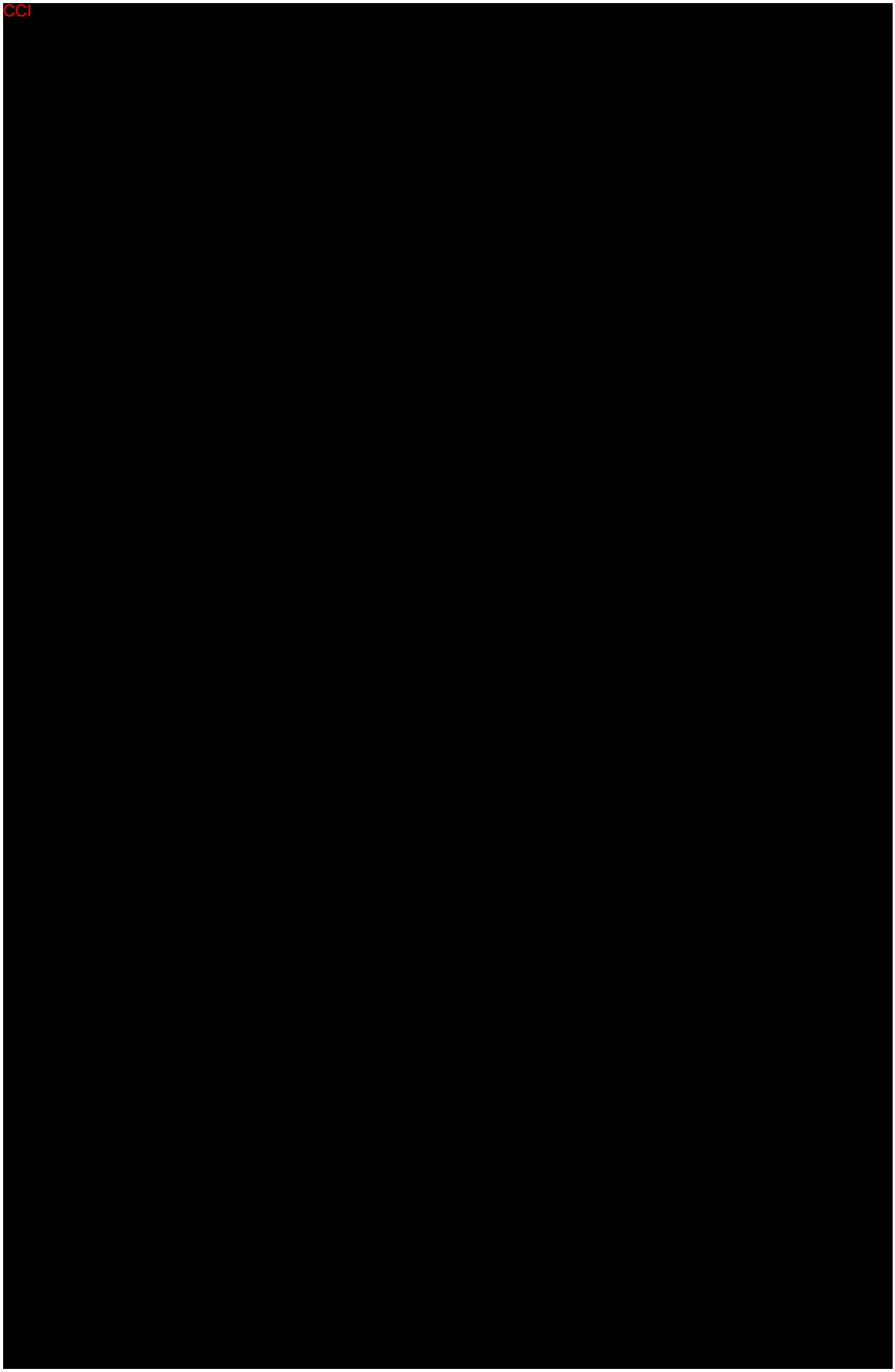
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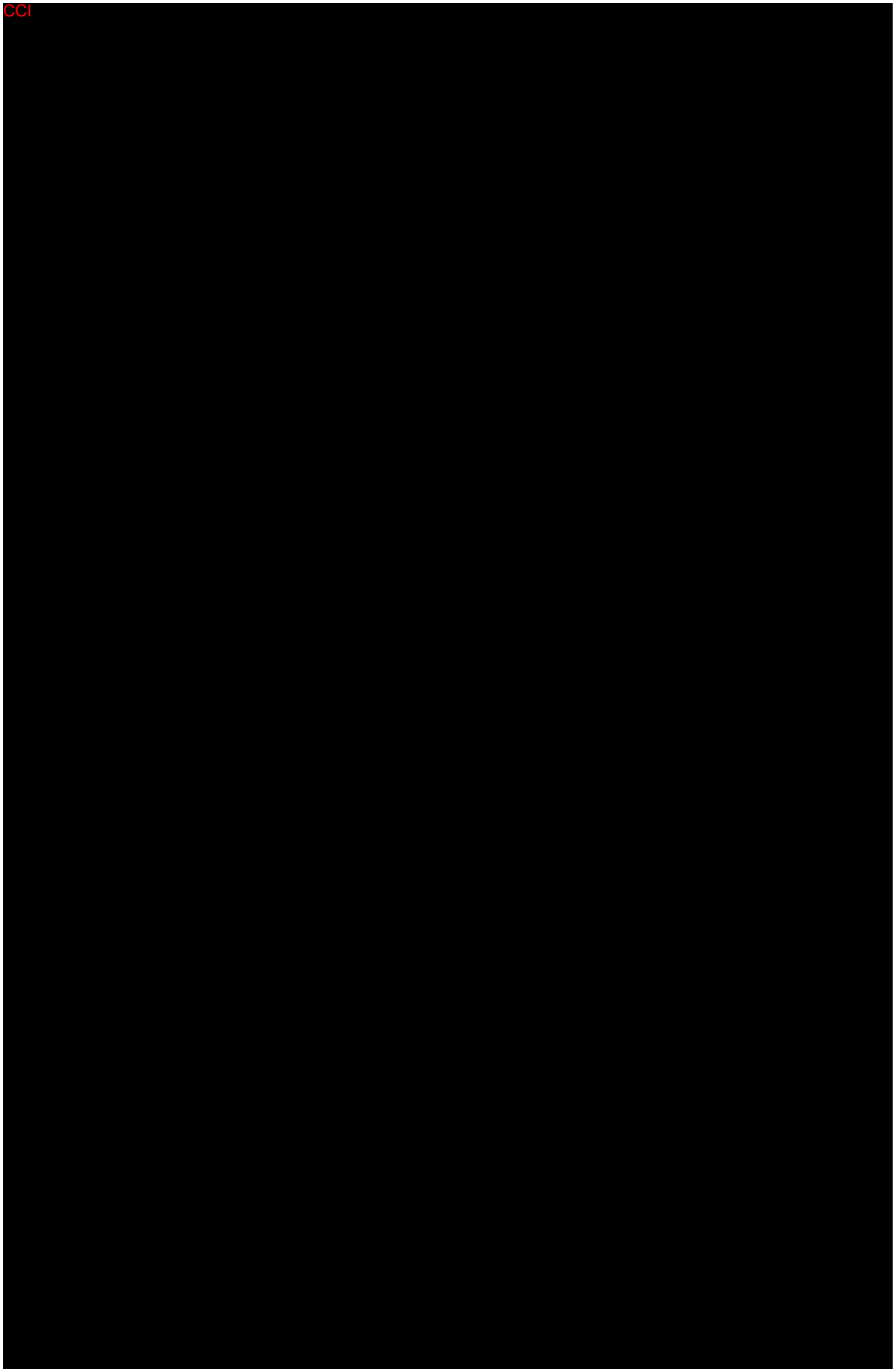
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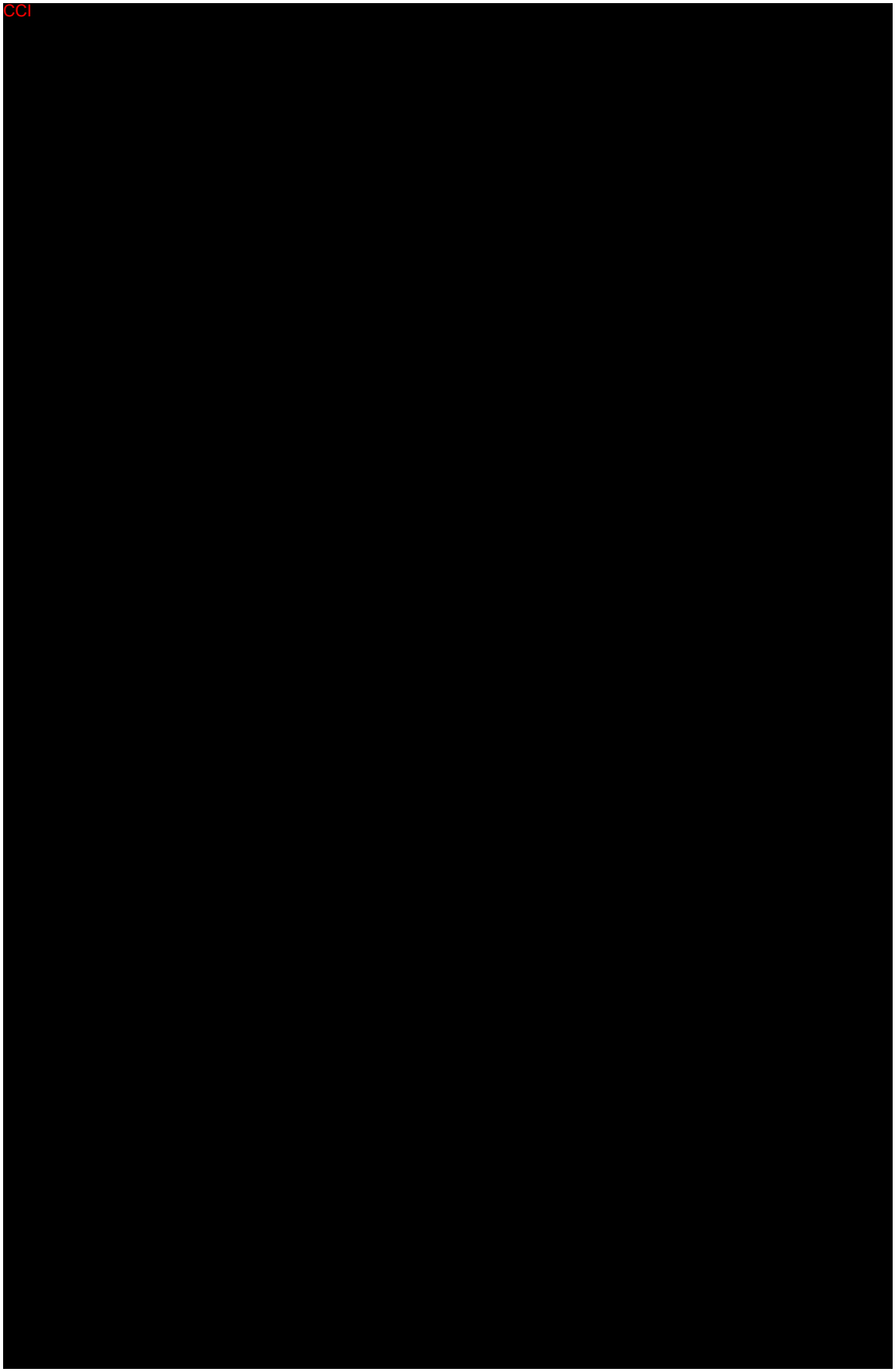
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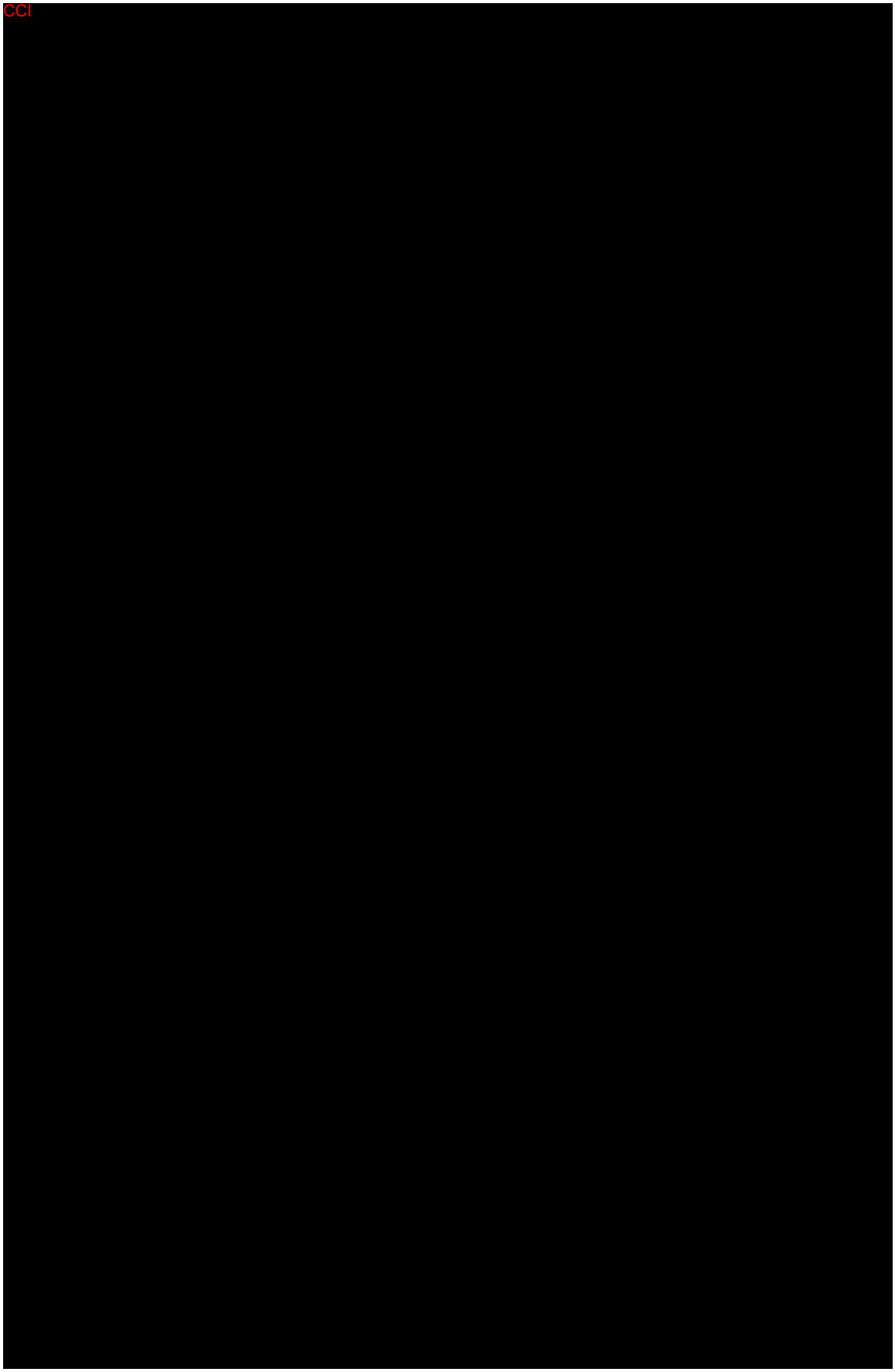
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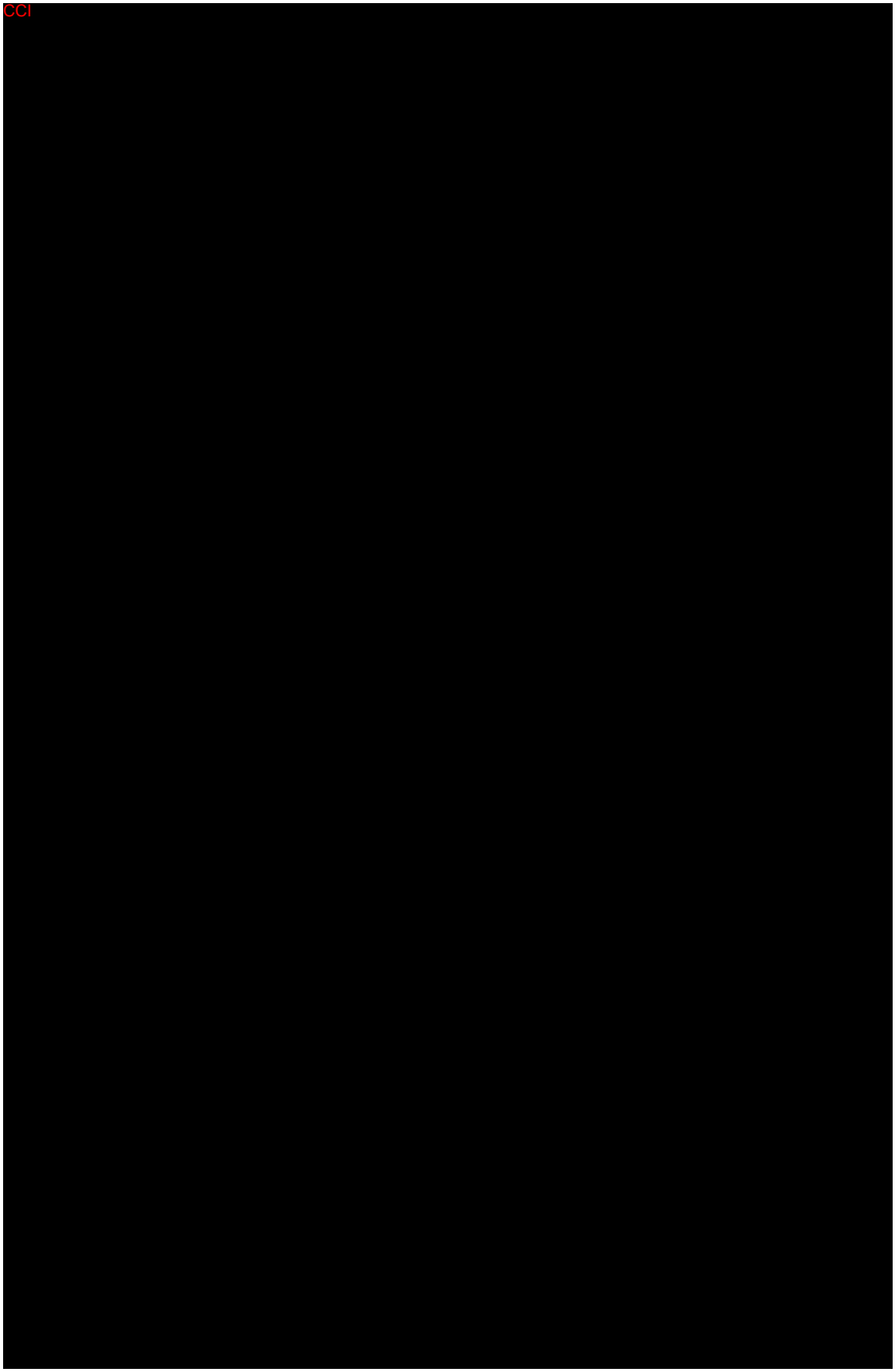
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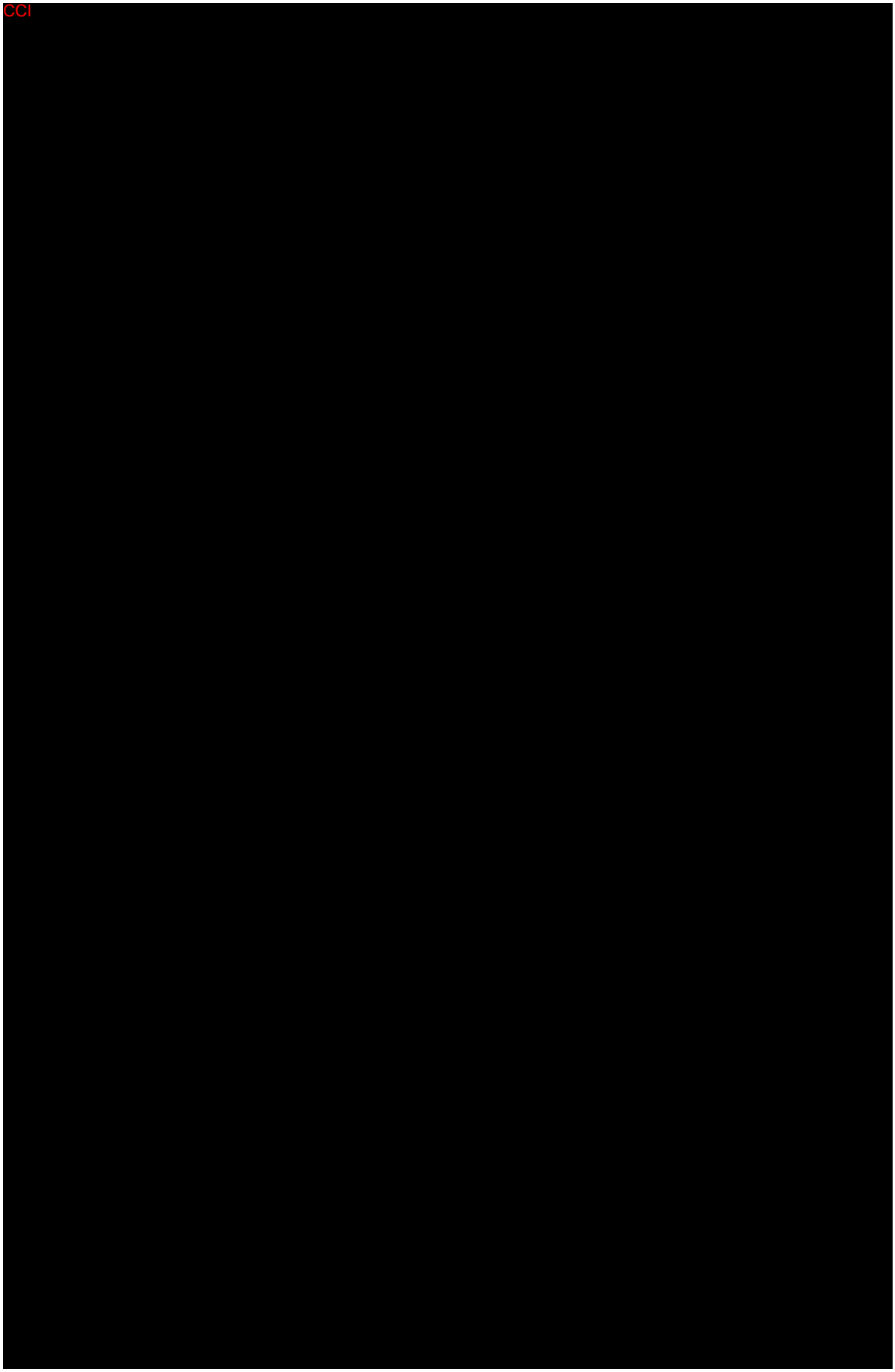
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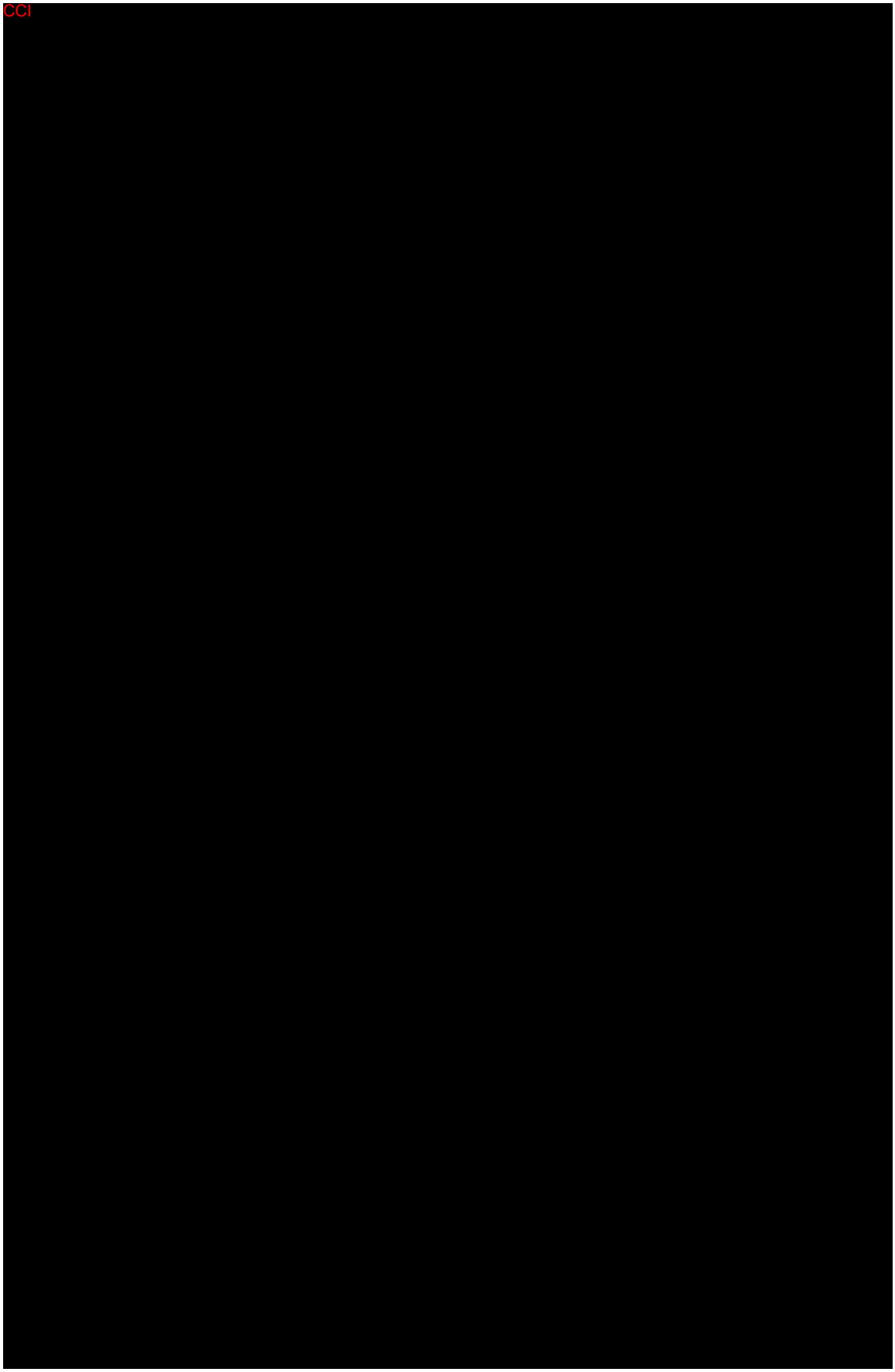
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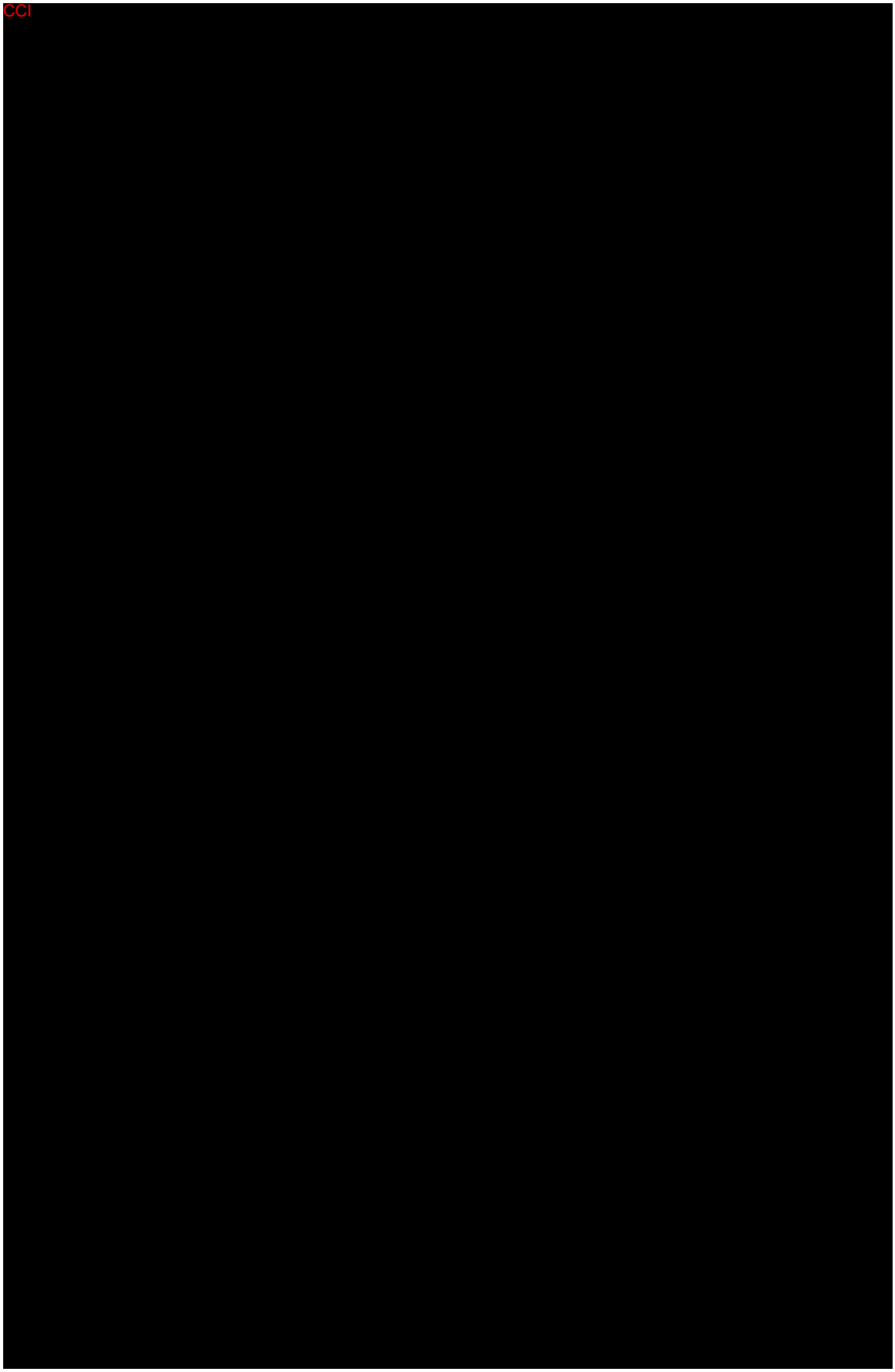
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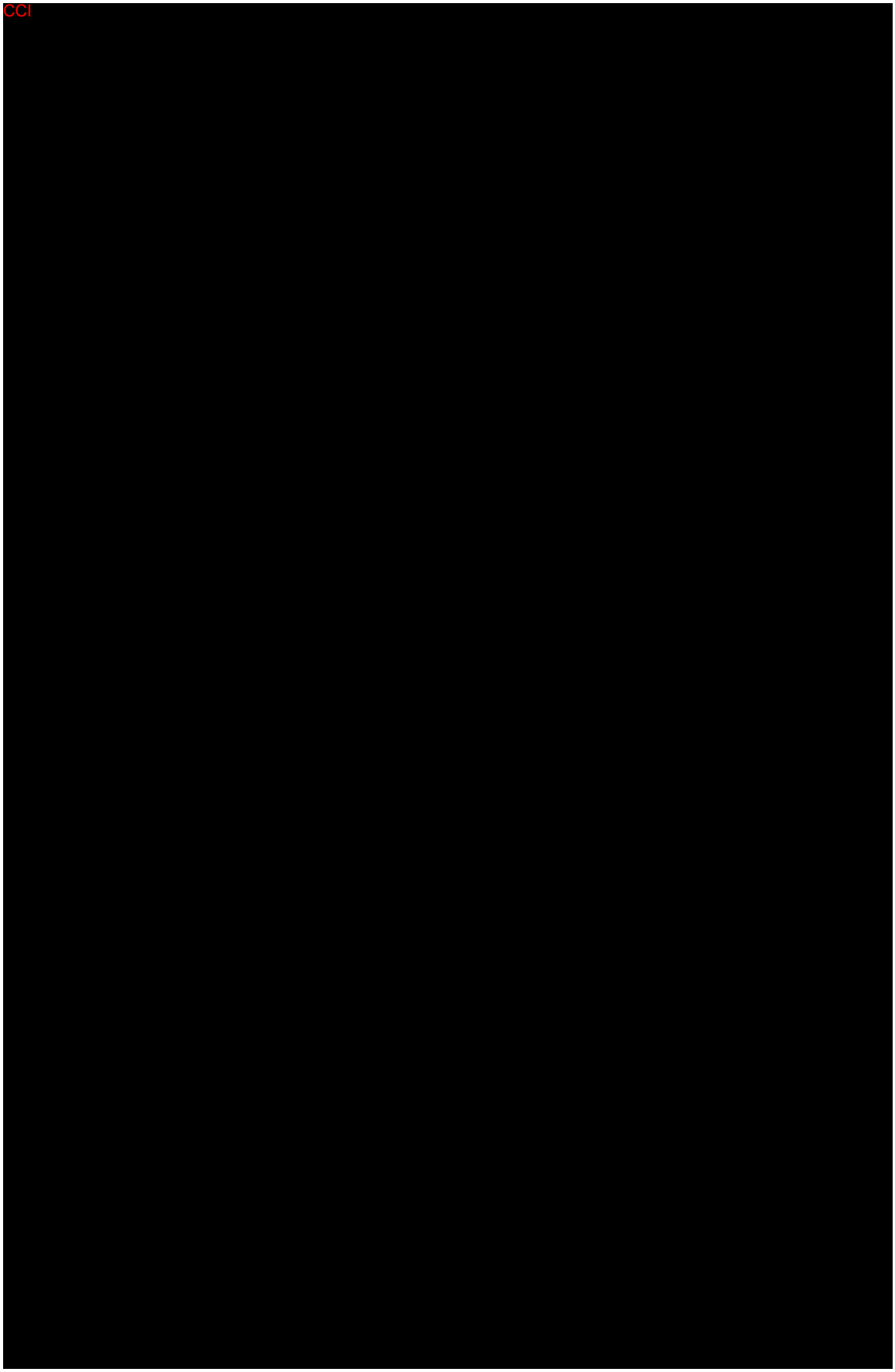
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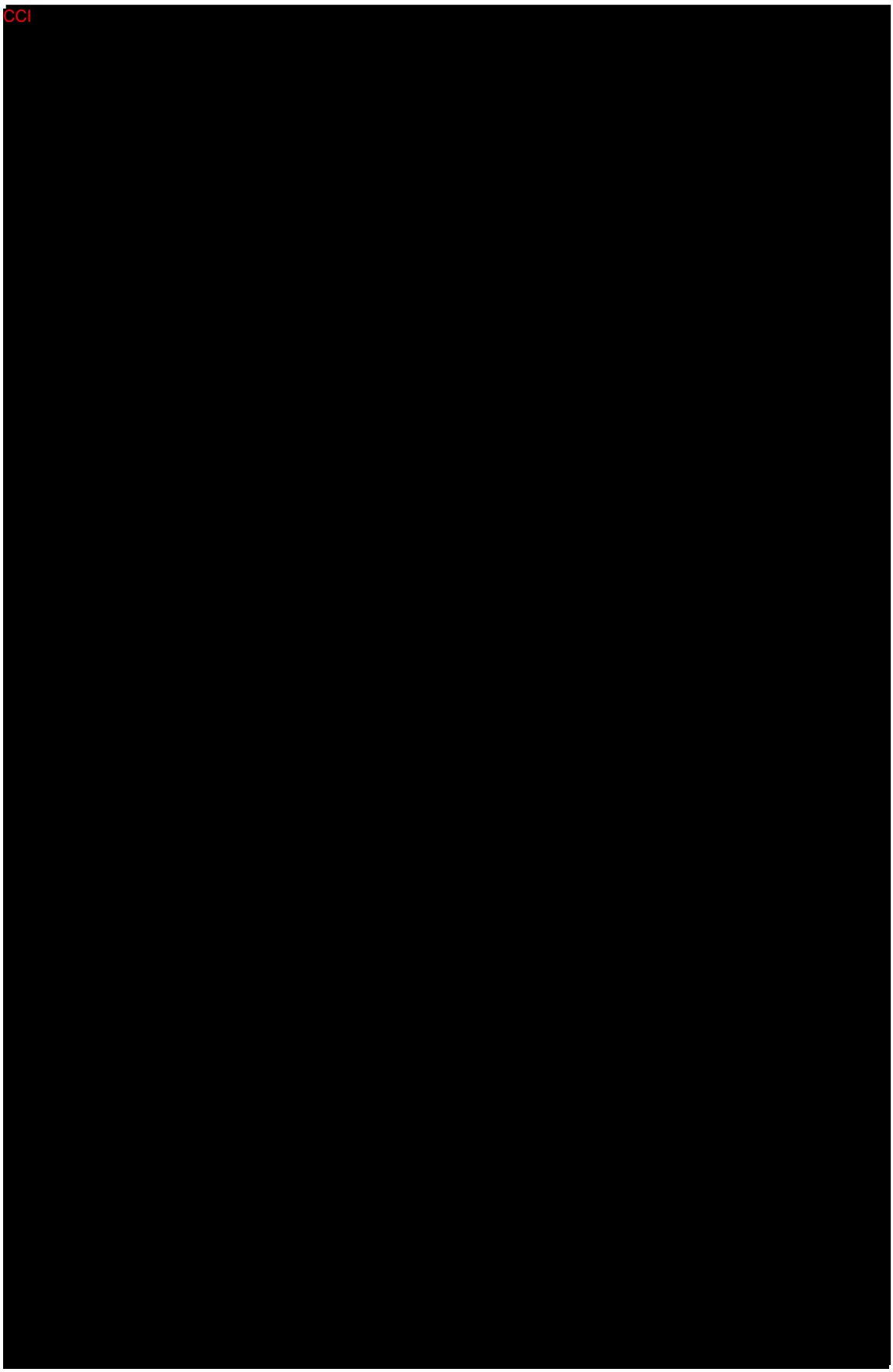
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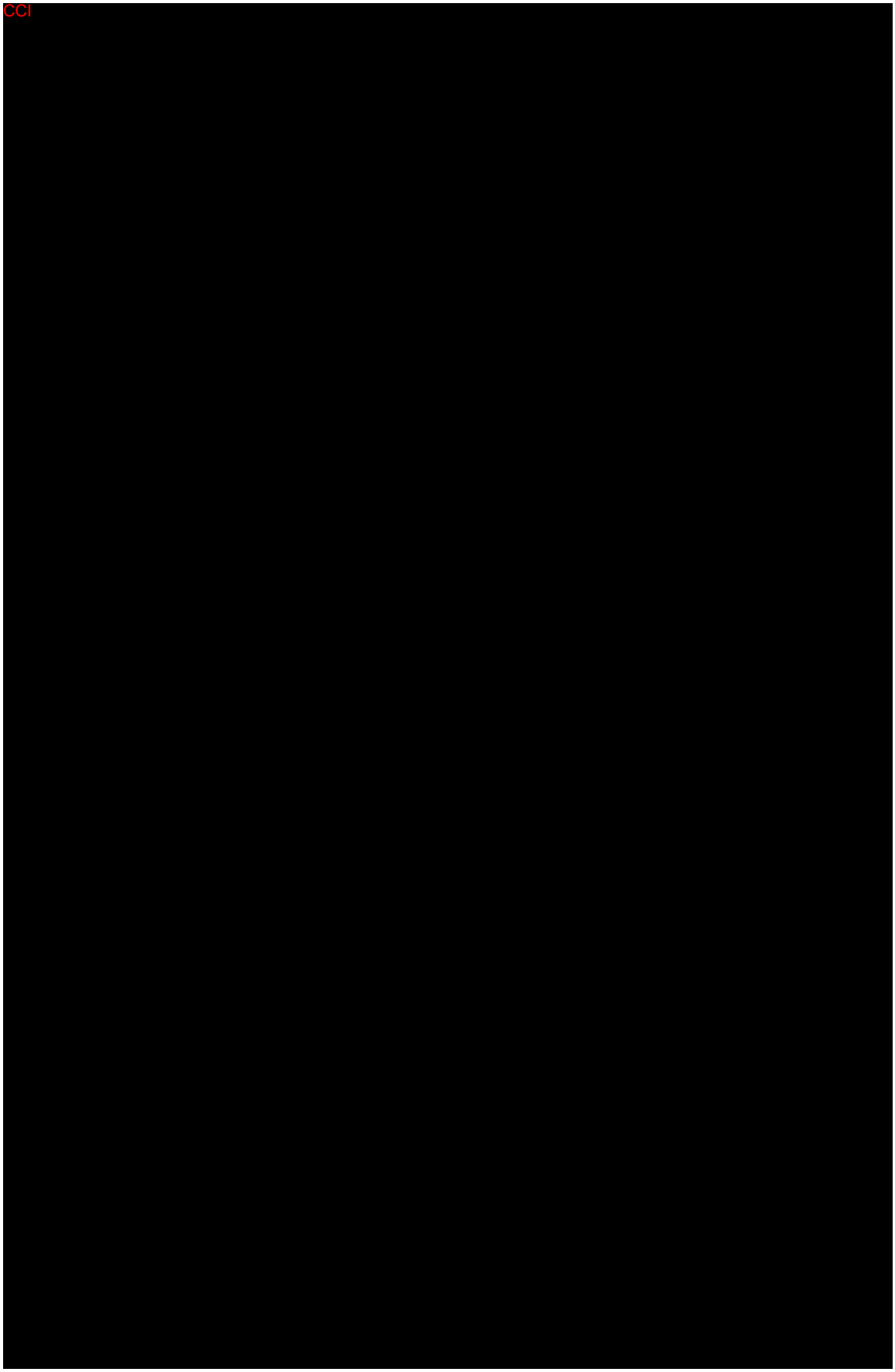
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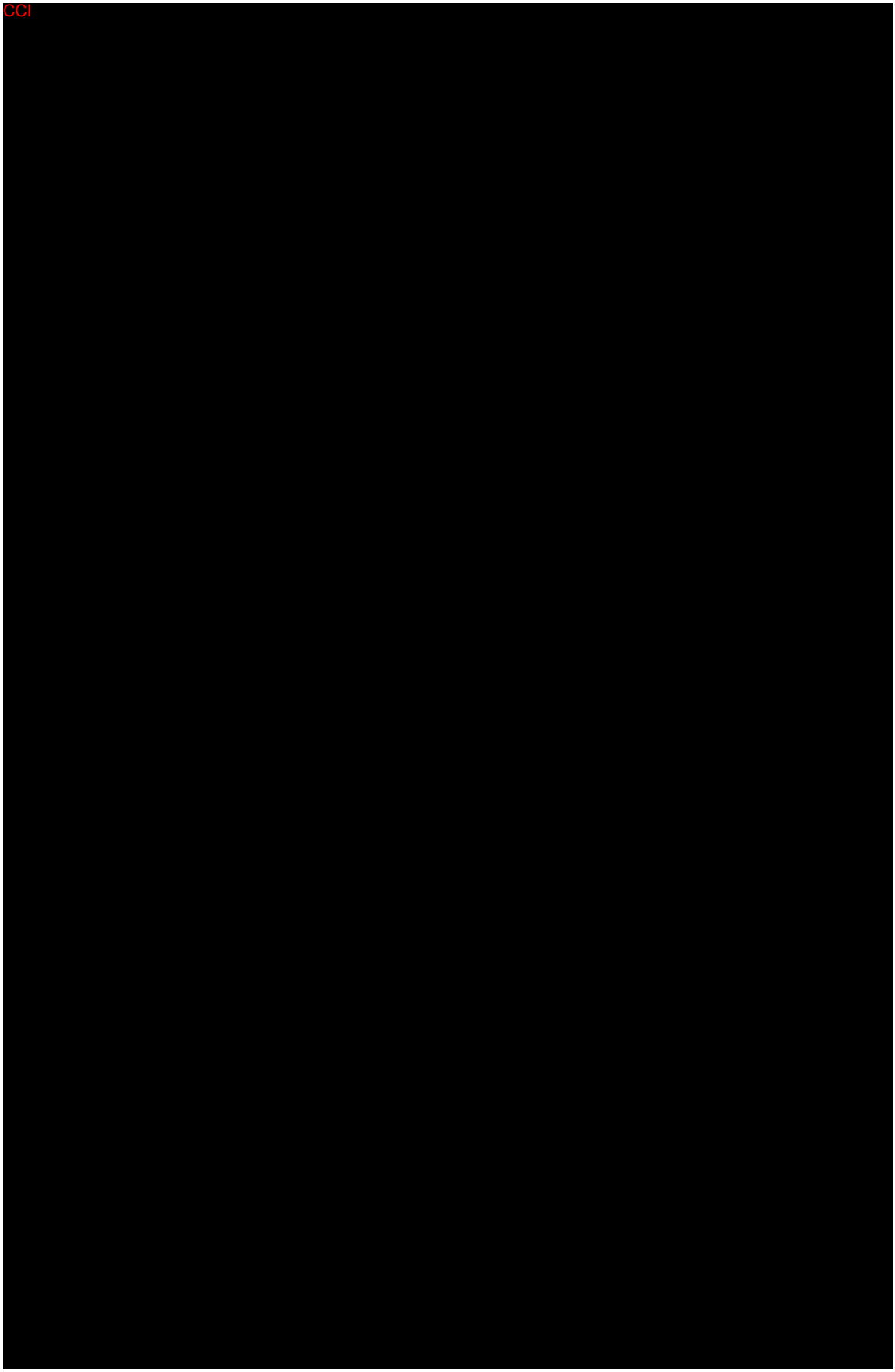
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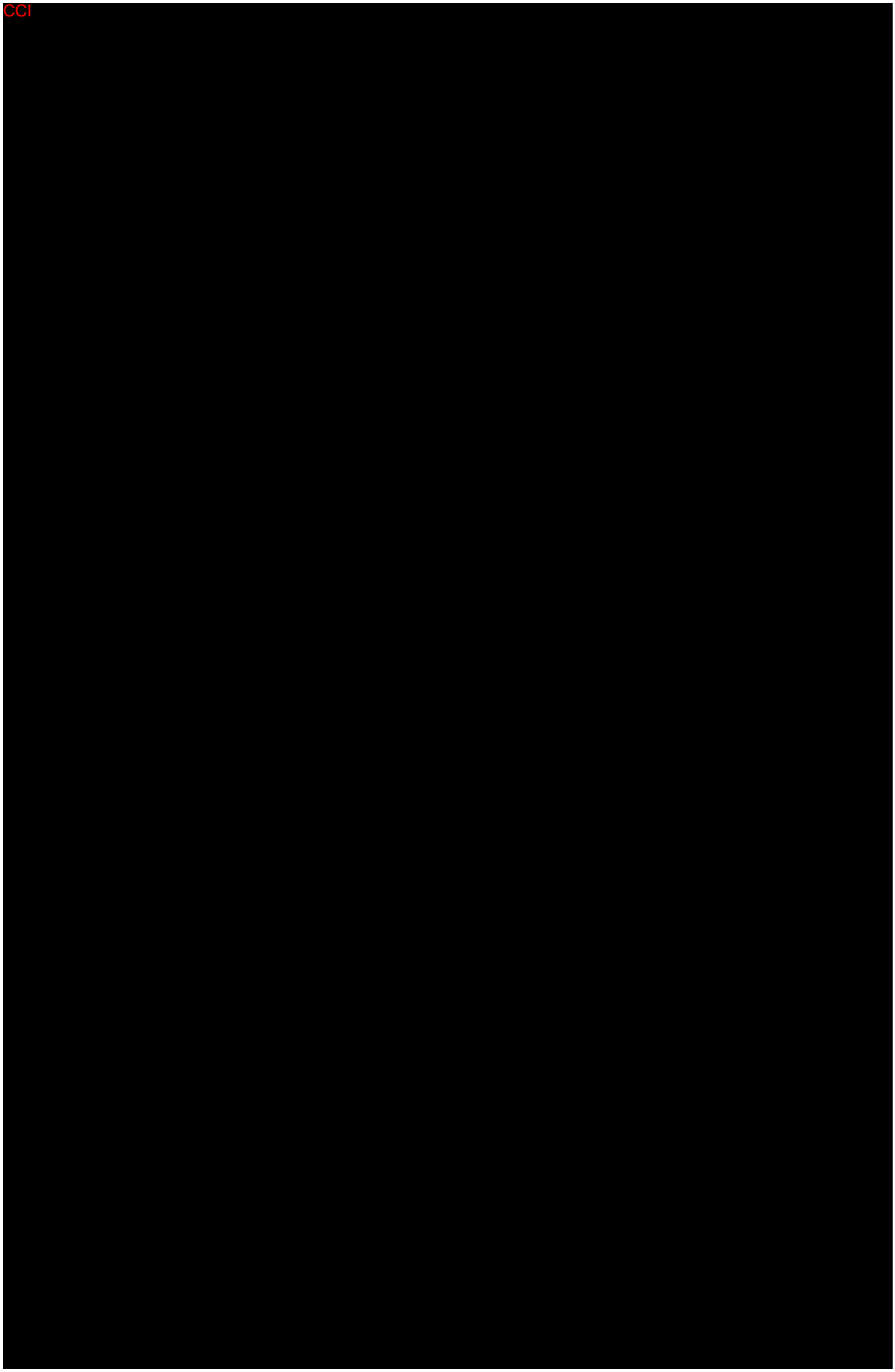
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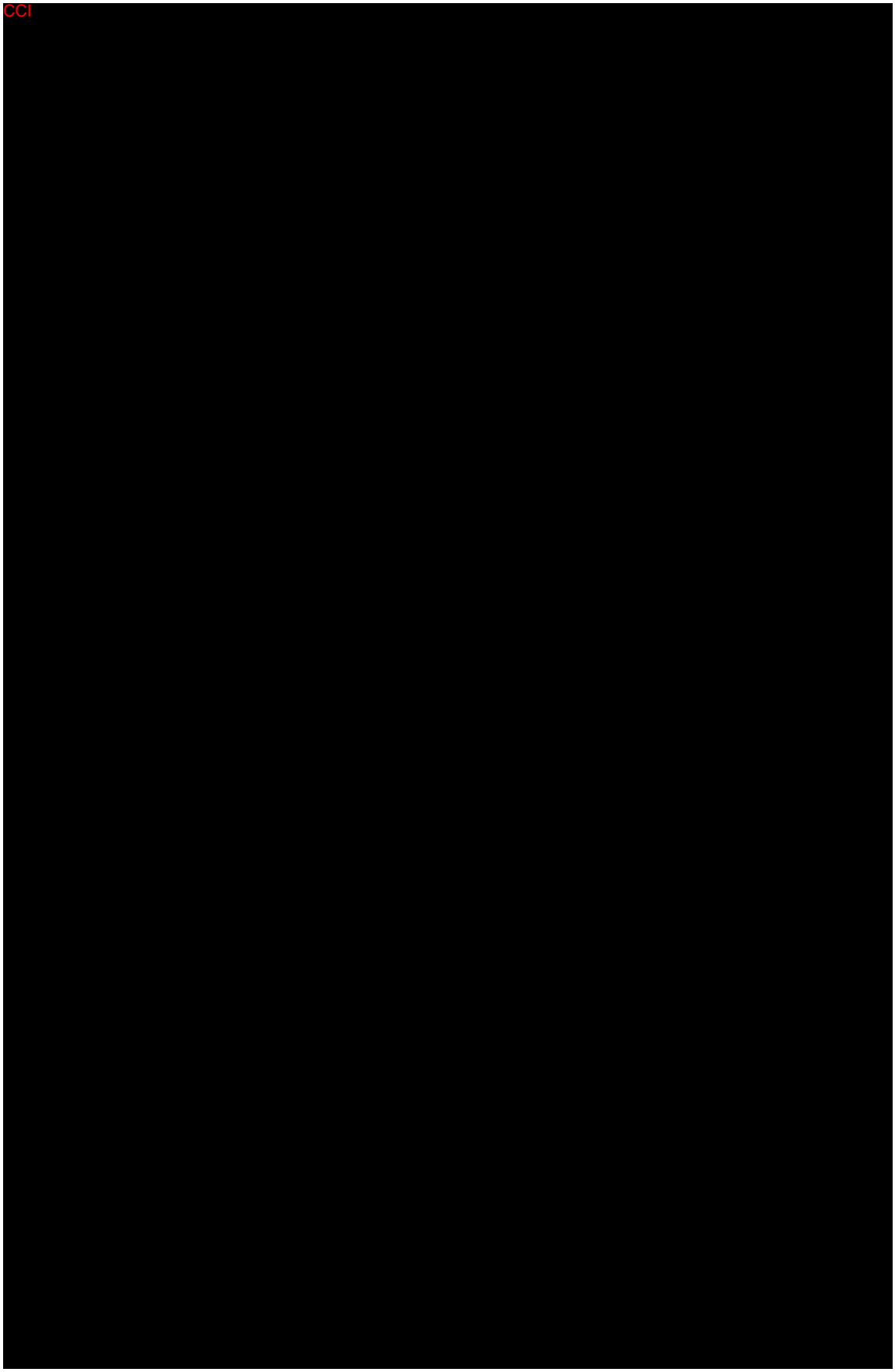
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