Clinical Study Protocol	
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A Randomised, Double-Blind, Parallel-Group, Multicentre, Phase III Study to Evaluate the Effect of Ticagrelor versus Placebo in Reducing the Rate of Vaso-Occlusive Crises in Paediatric Patients with Sickle Cell Disease (HESTIA3)

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VERSION HISTORY

Version 3.0, 20 April 2020
3.9.4 Procedures for discontinuation in relation to coronavirus disease 2019 (COVID-19): new subsection added for Investigational Product (IP) discontinuation procedures 6.3.10 Procedures in relation to COVID-19 infection: new subsection added for instructions to Investigators/study sites for recording of adverse events (AEs) and serious adverse events (SAEs) in relation to COVID-19 Minor changes to wording were implemented throughout to reflect the decision to allow for the use of local laboratory testing as needed due to the COVID-19 situation. Other minor changes have been made for consistency and clarity.

Version 2.0, 29 August 2018
Throughout: minor non-substantive edits made for consistency and clarity. Synopsis: Study Design and Duration of treatment: changes made to clarify that the design allows for either a completed 24 months treatment or a common study end with at least 12 months of treatment duration. Abbreviation list: added Common Study End Date (CSED) and Platelet Reactivity Index (PRI), revised CYP3A 1.2.2 Dose, control group and treatment duration: updated to read as “Treatment duration is at least 12 months for study participants but no longer than 24 months for any patients.” 1.4 Study Design: updated as above Figure 1, footnote b) updated for clarity 1.5.2 Data Monitoring Committee: amended text with details on formal interim pharmacodynamic (PD) assessment process and frequency. 3.2: Exclusion Criteria: clarified exclusion criterion #12 regarding excluded CYP3A inhibitors, substrates, or inducers.

4.2.3 End of Study Visit: clarified to occur at 24 months or as a common study end date. 5.1.2 Pain during a vaso-occlusive crisis (VOC): text added to highlight importance of providing training to caregivers not to influence the child when supporting in reporting of pain. 5.8 Revised blood volumes (Table 5 Volume of blood to be withdrawn from each patient) 7.7 Concomitant Medications: clarified text regarding CY3PA inhibitors, substrates, or inducers. Appendix D, Interview guide for VOC-triggered telephone calls: #3: specific questions added. Appendix E, Guide for scheduled telephone visits: clarifications related to use of contraceptives added. Appendix G: Drug Interactions: clarification regarding CYP3A inhibitors, substrates, or inducers.

Version 1, 23 January 2018
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

A Randomised, Double-Blind, Parallel-Group, Multicentre, Phase III Study to Evaluate the Effect of Ticagrelor versus Placebo in Reducing the Rate of Vaso-Occlusive Crises in Paediatric Patients with Sickle Cell Disease (HESTIA3)

International Co-ordinating Investigator

PPD

Study sites and number of subjects planned

The study will be conducted in approximately 18 countries worldwide. Approximately 80 centres will be initiated to randomise approximately 182 patients aged ≥2 years to <18 years. At least 50 evaluable patients should be recruited in each of the age groups, ≥2 years to <12 years and ≥12 years to <18 years.

Phase of development III

Study design

This is an international, multicentre, double-blind, randomised, parallel-group, placebo-controlled Phase III study to evaluate the effect of ticagrelor versus placebo in reducing the rate of vaso-occlusive crises (VOCs), which is the composite of painful crisis and/or acute chest syndrome (ACS), in paediatric patients with sickle cell disease (SCD). During the treatment period, patients will be monitored for occurrence of VOCs and other acute SCD complications.

Patients are to be followed until a common study end date is reached defined as 12 months after the last patient is randomised, or up to 24 months. In addition to the investigational product, standard of care such as background treatment with hydroxyurea will be allowed.

Definition of primary endpoint

The primary endpoint is the number of VOCs which is the composite of painful crisis and/or ACS. Each component is defined as:

- A painful crisis is an onset or worsening of pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral non-steroidal anti-inflammatory drugs (NSAIDs), or other analgesics prescribed by a health care provider in a medical setting (such as a hospital, clinic, or emergency room visit) or at home.

- An ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

Objectives

Primary Objective:	**Outcome Measure:**
To compare the effect of ticagrelor vs placebo for the reduction of VOCs, which is the composite of painful crisis and/or ACS, in paediatric patients with SCD	Number of VOCs

Secondary Objective:	**Outcome Measure:**
To compare the effect of ticagrelor vs placebo for the reduction of painful crises	Number of painful crises
To compare the effect on ticagrelor vs placebo for the reduction of ACS	Number of ACSs
To compare the effect of ticagrelor vs placebo for the reduction of duration of painful crises	Duration of painful crises
To compare the effect of ticagrelor vs placebo on the number of VOCs requiring hospitalisation or emergency department visits	Number of VOCs requiring hospitalisation or emergency department visits
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for VOC	Number of days hospitalised for VOC
To compare the effect of ticagrelor vs placebo on the number of acute SCD complications[a]	Number of acute SCD complications
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for acute SCD complications[a]	Number of days hospitalised for acute SCD complications
To compare the effect of ticagrelor vs placebo on the number of sickle cell-related red blood cell transfusions	Number of sickle cell-related red blood cell transfusions
To describe the health-related quality of life (HRQL) and fatigue	HRQL total score and by dimension using Paediatric Quality of Life Inventory (PedsQL) SCD Module and Fatigue total score and by dimension using the PedsQL Multidimensional Fatigue Scale (age appropriate versions: 2-4 years; 5-7 years; 8-12 years; 13-18 years)
To describe absence from school or work due to SCD	Proportion of days of absence from school or work (only if going to school or work at randomisation)

Secondary Objective:	Outcome Measure:
To describe the intensity of pain during VOC	Intensity of worst pain daily during VOC - For patients ≤4 years of age, observer reported using the Face, Legs, Activity, Cry, Consolability Scale (FLACC) - For patient ages ≥5 to 18 years of age, self-reported using the Faces Pain Scale - Revised (FPS-R)
To describe analgesics used during VOC	Type of analgesics (opioid and non-opioid) use
To describe patient acceptability of the formulation (palatability and swallowability)	- For patients ≤4 years of age taking the tablet dispersed or whole, an observer assessment of palatability and swallowability will be undertaken - For patients ≥5 years of age taking the tablet dispersed or whole, palatability will be assessed and categorized using the Facial Hedonic Scale

[a] The acute SCD complications will be defined in Section 5.1.5 in Clinical Study Protocol.

Safety Objective:	Outcome Measure:
To assess long-term safety and tolerability of therapy with ticagrelor vs placebo	Adverse Events/Serious Adverse Events, including bleeding Vital signs and laboratory safety variables

Target subject population

The target population is children aged ≥2 to <18 years of age and body weight of ≥12 kg diagnosed with homozygous sickle cell anaemia (HbSS) or sickle beta-zero-thalassaemia (HbS/β^0).

Patients that experienced at least 2 VOC events in the past 12 months prior to Visit 1 and fulfil eligibility criteria will be enrolled in this study.

Duration of treatment

Eligible patients will receive double-blind ticagrelor or placebo twice a day (bd) for at least 12 months but no longer than 24 months. The expected average follow-up is 18 months, assuming a uniformly distributed enrolment period of 12 months.

Investigational product, dosage and mode of administration

The double-blinded study drug dose will be weight dependent:

- ≥12 to ≤24kg: Ticagrelor 15 mg or matching placebo, twice a day
- >24 to ≤48 kg: Ticagrelor 30 mg or matching placebo, twice a day
- >48 kg: Ticagrelor 45 mg or matching placebo, twice a day.

Statistical methods

The primary analysis will be based on the intent-to-treat (ITT) principle. The number of VOCs will be analysed using negative binomial regression. The response variable is the number of VOCs experienced by a patient over the treatment period. Patient follow-up time (log-transformed) will be included as an offset in the linear predictor to adjust for patients having different exposure times. Additional covariates to be adjusted for in the linear predictor will be treatment group (placebo as reference group) and hydroxyurea therapy (Yes/No). The treatment effect will be tested at a 5% significance level. If the negative binomial distribution is not appropriate, a Wilcoxon rank sum test will be used. Ticagrelor data will be pooled and analysed irrespective of dose.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
ACS	Acute chest syndrome
ADP	Adenosine diphosphate
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
bd	bis in die (twice a day)
BP	Blood pressure
CRF	Case report form
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CSA	Clinical Study Agreement
CSED	Common Study End Date
CSR	Clinical Study Report
CV	Coefficient of variation
CYP3A	Cytochrome P450 3A
DMC	Data Monitoring Committee
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
eDevice	Electronic device
FLACC Scale	Face, Legs, Activity, Cry, Consolability Scale
FPS-R	Faces Pain Scale - Revised
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HbSC	sickle cell-haemoglobin C
HbSS	Homozygous sickle cell anaemia

Abbreviation or special term	Explanation
HbS/β^0	Sickle beta-zero-thalassaemia
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICI	International Co-ordinating Investigator: If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
ID	Identification
IP	Investigational product
IXRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NSAIDs	Non-steroidal anti-inflammatory drugs
$P2Y_{12}$	G protein-coupled platelet receptor for adenosine diphosphate (ADP)
PedsQL	Paediatric Quality of Life Inventory
P-gp	P-glycoprotein
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PRI	Platelet Reactivity Index
PRU	$P2Y_{12}$ reaction units
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SCD	Sickle cell disease
SD	Standard Deviation
TAMMV	Time averaged mean of the maximum velocity
TCD	Transcranial Doppler
TCDi	Transcranial Doppler imaging technique

Abbreviation or special term	Explanation
TIA	Transient Ischemic Attack
ULN	Upper limit of normal
VASP	Vasodilator-stimulated phosphoprotein
VOC	Vaso-occlusive crisis
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Sickle cell disease (SCD) is a genetic, autosomal, recessive blood disorder resulting an altered haemoglobin β-chain (HbS). When the altered haemoglobin is deoxygenated it aggregates into large polymers, distorting the shape of the red cells to sickle-shaped. A vaso-occlusive crisis (VOC) is a severe, acute painful episode that occurs when sickle-shaped red blood cells obstruct the microcirculation and restrict blood flow to an organ or tissue, resulting in ischaemia, necrosis and organ damage. The clinical presentation varies depending on the localisation of the obstruction and there are also specific SCD complications, such as acute chest syndrome (ACS) where the pulmonary vasculature is affected. Vaso-occlusion is initiated and sustained by complex interactions among sickle cells, endothelial cells and constituents of plasma. Activated platelets participate in the process by promoting the adhesion of sickle cells to the endothelium, and through the formation of platelet-leukocyte aggregates, which augment the inflammatory state and contribute to vaso-occlusion. In patients with SCD, platelets are activated during the non-crisis "steady state" and are further activated during painful episodes and markers of platelet inhibition have been shown to correlate with the frequency of pain crises (Ataga et al 2012).

There is a significant unmet need regarding treatment options to reduce VOCs in SCD. Curative treatment with bone marrow transplantation is only available to a very limited number of patients. Until recently, the only pharmacological treatment approved for reduction of VOCs was hydroxyurea (hydroxycarbamide). Hydroxyurea reduces the rate of painful crises, ACS and the need for blood transfusions in adults and children with SCD (Charache et al 1995, Wang et al 2011), but patients need to be closely monitored since hydroxyurea causes myelodepression and has other side effects. Moreover, hydroxyurea is not approved for use in children in all markets. In July 2017, the United States (US) FDA approved L-glutamine for the reduction of acute complications of SCD; however, with the limited experience with L-glutamine and current approval only in US, the role of this compound in the treatment paradigm remains to be established. Although the frequency of SCD complications are reduced with hydroxyurea and with L-glutamine, most patients continue to suffer from these complications despite treatment.

Inhibition of platelet activation has been proposed as a potential therapeutic option in the treatment of SCD. The antiplatelet drug ticlopidine, which has a similar mechanism of action as ticagrelor (prevention of adenosine diphosphate [ADP]-mediated platelet activation), significantly reduced the frequency of VOCs in patients with SCD (Cabannes et al 1984). Another G protein-coupled platelet receptor for ADP ($P2Y_{12}$) inhibitor, prasugrel, was recently investigated in children with SCD. The Phase III study in paediatric patients showed a numerical reduction in number of VOC events (component of painful crises and/or ACS), with fewer painful crises in prasugrel group than on placebo (66% versus 72%), but no difference in ACS (9% in each group); however, the differences versus placebo did not reach statistical significance (Heeney et al 2016). Of note is that the prasugrel doses used in this study only resulted in a mean platelet inhibition of approximately 20%

(Jakubowski et al 2017). Too low platelet inhibition may have contributed to the insufficient efficacy in this study (Heeney et al 2016).

Ticagrelor (BRILINTA™) is an oral, direct-acting, selective, reversibly-binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated platelet activation and aggregation. Ticagrelor, 90 mg twice a day (bd), was first approved in 2010 to reduce the rate of cardiovascular death, myocardial infarction, and stroke in adult patients with acute coronary syndromes, and is currently approved in >100 countries. An extended indication for ticagrelor 60 mg bd to include adult patients with a history of myocardial infarction was approved in 2015.

An additional mechanism of action with ticagrelor, increasing local endogenous adenosine levels (Nylander et al 2013), may contribute to a vasodilatory effect observed in healthy subjects and in patients with acute coronary syndromes as measured by coronary blood flow (Wittfeldt et al 2013, Alexopoulus et al 2013), which could help increase oxygen supply to ischaemic tissues during a VOC.

A programme is currently ongoing to assess the potential therapeutic benefits of ticagrelor in reduction of the occurrence of VOCs in children with SCD. The HESTIA1 study (D5136C00007) investigated pharmacokinetics/pharmacodynamics (PK/PD), safety and early signs of efficacy of ticagrelor in 45 patients aged 2 to 17 years. Ticagrelor exposure increased approximately proportionally to dose and the PK/PD relationship in children with SCD and appeared similar to what has been previously observed in adults with cardiovascular disease. Ticagrelor was well tolerated and no bleedings were reported during treatment. There were no apparent effects on symptoms related to SCD, but the number of patients and short study duration limit the conclusions on efficacy in this study. In addition, a ticagrelor study in 87 young adults (aged 18 to 30 years) with SCD compared effects from ticagrelor 10 mg, 45 mg or placebo given twice daily for 12 weeks (HESTIA2 study, D5136C00008). The proportion of days with pain as well as analgesic use decreased in all groups, including placebo, with no apparent differences between groups. Ticagrelor was well tolerated in young adults, bleeding events were few and reported with similar frequency as placebo and no major bleeding occurred. No safety concerns were raised in HESTIA1 or HESTIA2.

In summary, there is a high unmet need for treatment options in SCD and there is a scientific rationale, supported by clinical data, that platelet inhibition has the potential to reduce the risk for acute vaso-occlusions. This study will evaluate the efficacy, safety and tolerability of ticagrelor versus placebo in children with SCD during treatment for at least 12 months and up to approximately 24 months.

Detailed information on ticagrelor is found in the Investigator's Brochure (IB).

1.2 Rationale for study design, doses and control groups

1.2.1 Overall rationale and study population

Patients diagnosed with homozygous sickle cell (HbSS) or sickle beta-zero-thalassemia (HbS/β^0) will be eligible. Patients with clinically milder variants (eg, sickle cell-haemoglobin C [HbSC]) will not be eligible, since they usually have a lower frequency of painful crises (Ashley-Koch et al 2000). The different pattern of SCD manifestations in patients with HbSC (Gill et al 1995) could introduce heterogeneity into the study population. In addition, there are data to suggest that platelet activation in HbSS is elevated compared with HbSC (Blann et al 2007); thus, patients with HbSC may be less likely to benefit from $P2Y_{12}$ inhibition.

To be eligible for the study, patients must have experienced at least 2 VOCs (defined as painful crisis and/or ACS) events in the past 12 months prior to Visit 1, indicating that the severity of the patient's disease justifies preventive chronic long-term treatment. The intent is to enrol only children aged 2 years or above, since VOCs become more frequent with age. Above 2 years of age, children may have experienced more than 1 VOC, and established a pattern of frequency such that an intervention to reduce the rate of VOCs can be justified and meaningfully evaluated (Gill et al 1995, Platt et al 1991). Thus, the unmet need to prevent VOCs is most evident in children from 2 years of age and above.

Due to ticagrelor mechanism of action and the potential to reduce symptoms caused by ischaemia during a vaso-occlusion, a composite endpoint with painful crises and/or ACS has been selected for the primary endpoint, see Section 2.1. Painful crisis is the most common reason for emergency department visits for patients with SCD with a significant impact on young patients' lives, affecting them physically and emotionally. Acute chest syndrome is a potentially life-threatening condition involving vaso-occlusion, eg, when caused by pulmonary infarction or indirectly because of fat embolism secondary to bone marrow infarction, and/or a pulmonary infection (Vichinsky et al 2000). Both painful crises and/or ACS are identified by patients/parents as the acute SCD-related complications having the most impact on their lives (The Voice of the Patient 2014), and these endpoints are commonly used for evaluation of clinical outcome in trials in SCD. See Section 5.1.1 for the specific definition of the primary endpoint events in this study.

Secondary endpoints are included to broaden the understanding of effects in patients with SCD and to also assess potential benefits on symptomatic disease burden and health-related quality of life (HRQL).

1.2.2 Dose, control group and treatment duration

The ticagrelor PK/PD modelling and simulation work based on the results from HESTIA1 and HESTIA2 studies identifies 15, 30 and 45 mg bd, depending on body weight, as relevant doses in the HESTIA3 study. These doses are predicted to result in a platelet activity measured as $P2Y_{12}$ reaction units ([PRU] as measured by VerifyNow®) of less than 180, corresponding to >35% platelet inhibition in terms of reduction in PRU assuming a baseline

PRU of 280 (which was the baseline PRU observed in HESTIA1, and similar to prasugrel Phase III DOVE study [Heeney et al 2016]).

The predicted platelet inhibition in HESTIA3 is similar to what was observed in the 45 mg bd dose group in the HESTIA2 study in young adults, where after 1 week of treatment the mean percentage decrease from baseline PRU was 48% before morning dose and 81% at 2 hours after dose. The 45 mg bd dose group was well tolerated and events of bleeding were of the same number and similar compared to the placebo and the 10 mg bd dose groups. Given the reversible mechanism of action for ticagrelor, the level of $P2Y_{12}$ inhibition during ticagrelor treatment is expected to vary within a dosing interval and peak around 2 hours after dosing.

When developing the dosing strategy for this study, the target for platelet inhibition was guided by the results from the recent prasugrel Phase III study in paediatric patients with SCD aged 2 to 17 years, showing insufficient efficacy with a mean PRU of 207 (ie, approximately 20% reduction from baseline) (Jakubowski et al 2017). The lack of therapeutic benefit with prasugrel may have been related to a too low platelet inhibition (Heeney et al 2016), and consequently, doses for HESTIA3 were selected to achieve a greater level of platelet inhibition. Moreover, a study with ticlopidine in adolescents and adult patients with SCD showing significant reductions in VOC (Cabannes et al 1984) used doses that generally provide <60% inhibition of platelet aggregation, which provides further support for the platelet inhibition target and the selected doses for the HESTIA3 study.

There are no other drugs approved for reduction of VOCs in children with SCD with a similar mechanism of action as ticagrelor. Hydroxyurea is approved for use in children with SCD in some markets and more recently, L-glutamine was approved by the US FDA. Evaluation of ticagrelor when given in addition to standard of care including these medications, where available and when considered medically appropriate, is considered acceptable for studying the efficacy and safety of ticagrelor in this patient group as compared with placebo.

Treatment duration is at least 12 months for study participants, but no longer than 24 months for any patients. The expected average follow-up is 18 months, assuming a uniformly distributed enrolment period of 12 months. Considering inclusion of patients with at least 2 VOCs in the past year, this treatment duration is considered long enough to evaluate effects on VOC events as well as to capture safety and tolerability data supporting a potential future long-term use of ticagrelor.

1.3 Benefit/risk and ethical assessment

The aim with ticagrelor treatment in paediatric patients with SCD is to reduce the rate of VOCs, with an acceptable safety profile. Considering that the anticipated benefit would be mostly symptom reduction and that patients with SCD suffer from anaemia, the acceptance for bleedings will be low.

Episodes with VOCs are the most common cause for emergency room visits for children with SCD. The pain associated with VOC can be excruciating and have a significant impact on the child's life, and significantly disturbs routine activities such as food intake, sleep and school

activities during several days. The painful crises are repeatedly described as the most challenging symptom of their disease by patients with SCD. An ACS is a serious and potentially life-threatening condition that may lead to respiratory failure or multi organ failure, and is a common cause of death in SCD patients. Most cases of ACS require hospitalisation for >1 week (Vichinsky et al 2000). Besides the acute symptoms, the ischaemia during vaso-occlusion causes tissue damage that over time leads to impaired organ function (eg, renal failure) or complications such as bone necrosis, joint pain or cognitive impairment. Pharmacological treatments options to prevent VOC events in children are few and side effects can be dose-limiting (hydroxyurea). With previous studies of anti-platelet drugs suggesting potential to reduce VOCs (Cabannes et al 1984, Heeney et al 2016) and the high unmet need for new treatments, there is a clear value in continuing to investigate the role of anti-platelet therapies in the reduction of VOCs.

Inherent to their reduction in platelet reactivity, antiplatelet agents increase the risk of bleeding. Ticagrelor has been on the market since 2010 for use in adult patients with coronary artery disease to reduce the risk for cardiovascular events. The safety profile has been thoroughly evaluated in large trials. The PEGASUS study (D5132C00001) evaluated the combination of ticagrelor 60 or 90 mg bd with aspirin in adult patients with a history of myocardial infarction. This dual anti-platelet therapy resulted in more bleeding events overall compared to aspirin alone; however, the majority of these bleedings were of lesser severity (eg, epistaxis, bruising and hematomas). In the adult clinical programme for ticagrelor, including several large cardiovascular outcome studies, the number of reported events of fatal bleeding have been low and similar for ticagrelor and comparators (ie, clopidogrel, placebo, and aspirin). Doses in HESTIA3 have been selected to result in a less pronounced level of platelet inhibition (~35% to 80%) than doses used in adult patients with cardiovascular disease (>80%), and unlike in these patients, ticagrelor will not be combined with aspirin in HESTIA3. A lower bleeding risk is therefore anticipated in HESTIA3 than in previous adult cardiovascular outcome studies. Selected doses for HESTIA3 are within the range evaluated in children and young adults (HESTIA1 and HESTIA2). No safety concerns were raised from these studies, and there was no indication of an increased bleeding risk with ticagrelor.

Prasugrel and clopidogrel are other drugs in the $P2Y_{12}$ inhibitor class, but unlike ticagrelor, which reversibly inhibits the $P2Y_{12}$ receptors on platelets, these are irreversible $P2Y_{12}$ receptor inhibitors. The recent paediatric Phase III study with prasugrel in children with SCD (Heeney et al 2016) investigated doses resulting in around 20% platelet inhibition, with no significant difference in the safety endpoints, including the frequency of bleeding events requiring medical intervention, compared to placebo. Although not in children with SCD, the CLARINET study with clopidogrel randomised 906 infants aged ≤92 days with congenital heart disease to clopidogrel or placebo for a median of 5.8 months (Wessel et al 2013) using doses shown to give an average platelet inhibition of 45% to 50% (Wessel et al 2013, Li et al 2008). No increased bleeding risk was observed for clopidogrel compared to placebo in this study.

In HESTIA3, measures will be taken to minimise bleeding risk in participating patients. The eligibility criteria, restrictions and discontinuation criteria are tailored to exclude patients with increased risk for bleeding from participation, and other medications impacting platelet

activity or the coagulation system are restricted. Frequent monitoring of patients is included in the protocol. An independent Data Monitoring Committee (DMC) will review unblinded study results regularly during the trial and will have increased attention on bleeding events.

The procedures during study visits are not considered to increase risk above routine care. Topical anaesthesia will be offered prior to blood sampling, and sampling will be coordinated in time as much as possible to reduce discomfort to children.

This study will evaluate ticagrelor efficacy and safety when added to standard of care treatments in SCD. Hence, study participants are not withheld from any other treatments that may be used in SCD (eg, hydroxyurea) during the trial, which is important considering the use of a placebo control group.

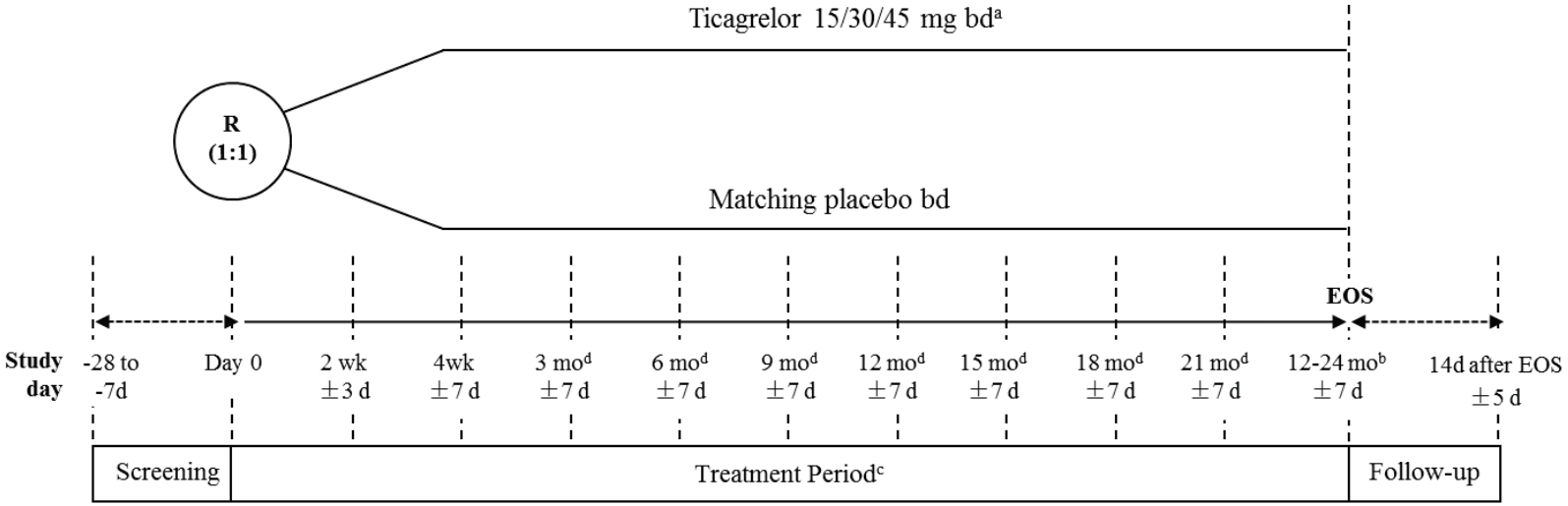
In summary, considering the high unmet need for treatments reducing the rate of such severe and serious conditions as VOCs in paediatric patients in SCD, previous trials in SCD populations with similar drugs suggesting potential for beneficial effects, and previous paediatric trials in patient with SCD or other diagnoses not raising safety concerns, and the specific measures taken in the HESTIA3 study to minimise the risk to study participants, the benefit-risk balance for participants in this study is considered favourable.

1.4 Study design

This is an international, multicentre, double-blind, randomised, parallel-group, placebo-controlled Phase III study to evaluate the effect of ticagrelor versus placebo in reducing the rate of VOCs in paediatric patients with SCD (Figure 1). During the treatment period, patients will be monitored for occurrence of VOCs and other acute SCD complications.

Study participants should receive standard of care for SCD, adjusted to the individual patient at the discretion of the Investigator, including routine health care screening examinations and immunisations according to local guidelines and health care programmes. Study drug will be given on the background of standard treatments for SCD. However, restrictions apply to some medications and interventions that may be necessary for the patient's health and well-being during the study. Temporary hold of study drug dosing could therefore be needed in case of short-term treatment with a medication not to be combined with study drug or in case of surgical interventions. Patients are to be followed for up to 24 months or until a common study end date (CSED) is reached defined as 12 months after the last patient is randomised. The target population are children aged ≥2 to <18 years of age and body weight of ≥12 kg diagnosed with HbSS or HbS/β^0. At least 50 evaluable patients should be recruited in each of the age groups, ≥2 years to <12 years and ≥12 years to <18 years.

Figure 1 Study Flow Chart



bd Twice a day; d Day; EOS End of study; mo Month; R Randomisation; wk Week

[a] Patients randomised to ticagrelor will receive doses based on weight band (at Screening): ≥12 to ≤24 kg=15 mg, >24 to ≤48 kg=30 mg, >48 kg=45 mg.

[b] EOS = Patients will be followed to common study end date defined as 12 months after the last patient is randomised, or up to 24 months.

[c] See Table 2 for assessments during site visits and Table 3 for telephone visits that will occur monthly after Week 4 between site visits.

[d] Interval must not be more than 100 days to ensure tablet supply for all days.

NB. Only on-site visits are shown.

1.5 Study governance and oversight

1.5.1 Steering Committee

A Steering Committee (SC) has been appointed for this study and has provided expert advice on, eg, the overall design, including the development of the protocol. The SC will continue to advice on any protocol amendments and will monitor study conduct, result interpretation and reporting of the study. The SC can propose to AstraZeneca their recommendations regarding study modifications or a potential early stop to the study based on the information received from the DMC. The SC is comprised of designated international academic leaders and non-voting members of the Sponsor, and will operate under a SC charter.

The Sponsor has the overall responsibility of the study.

1.5.2 Data Monitoring Committee

A DMC composed of independent SCD paediatric experts and including a platelet expert and statistician, will be appointed for this study and will report to the SC. The DMC will be responsible for safeguarding the interests of the patients in the study by assessing the safety of the intervention during the study, and for reviewing the overall conduct of the clinical study. The DMC will have access to unblinded individual data and be able to evaluate these while the study is ongoing. The DMC meeting schedule is shown in Table 1. Additional meetings could be initiated by the DMC chair or the Sponsor as needed.

The DMC will consider recommending study termination for any episode of bleeding deemed related to the ticagrelor treatment that is fatal, or is a spontaneous intracranial haemorrhage, or if the accumulating data suggest a strong likelihood of excessive haemorrhagic events possibly related to ticagrelor that require medical intervention as reported by the Investigator. Study termination will also be considered if the number of fatal or life-threatening serious adverse events (SAEs), including but not limited to bleedings, is greater in ticagrelor-treated patients compared to placebo.

The DMC will make recommendations on the progression of the study based on the totality of data (eg, AEs, safety laboratory variables, ticagrelor exposure and platelet inhibition) or other findings putting patients at undue risk. The Sponsor has the final decision on study progression including amendments, etc.

Additionally, the DMC will do a formal interim PD assessment when 60 patients have had their PK/PD sampling after 4 weeks in the study. In this interim PD assessment, the mean of pre-dose and 2 hours post dose PRI values at 4 weeks will be calculated for each individual and compared to their respective baseline values. The population mean of the platelet inhibition in the ticagrelor arm is expected to be above 35% during the study. If there is a risk of not achieving the targeted inhibition level of 35% to 80% in the study, the first task of the DMC would be to investigate if the PK values and the PK/PD relationship are as expected and in line with earlier documented PK/PD data of ticagrelor. If any finding is deemed by the DMC to not be in accordance with expected PK and PD data and all other reasons for the unexpected findings are ruled out, they will contact the Sponsor and ask for proof of treatment

compliance and potentially escalate the issue the Steering Committee regarding a potential amending of the study in order to evaluate the need for a dose change based on new modelling and simulations including the new data.

A DMC charter will be prepared to detail precise roles and responsibilities and procedures to ensure maintenance of the blinding and integrity of the study in the review of accumulating data and interactions with the SC.

Table 1 Data Monitoring Committee meeting schedule

Evaluation	Number of patients randomized	Completed visit (months)
1	40 patients completed Visit 4 or 10 patients completed Visit 6	4 (1) or 6 (3)
2	60 patients (formal interim PD assessment)	4 (1)
3	80 patients	6 (3)
4	80 patients	9 (6)
5	All patients	4 (1)
6	All patients	9 (6)
x	Patients remaining in study	As needed[a]

[a] As deemed necessary by the DMC chair and/or Sponsor.
PD pharmacodynamic.

2. STUDY OBJECTIVES

A VOC is the composite of a painful crisis and/or an ACS (Howard et al 2015, Yawn et al 2014). Each component is defined as:

A painful crisis is an onset or worsening of pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral non-steroidal anti-inflammatory drugs (NSAIDs), or other analgesics prescribed by a health care provider in a medical setting (such as a hospital, clinic, or emergency room visit) or at home.

An ACS is an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

2.1 Primary objective

Primary Objective:	Outcome Measure:
To compare the effect of ticagrelor vs placebo for the reduction of VOCs, which is the composite of painful crisis and/or ACS, in paediatric patients with SCD	Number of VOCs

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To compare the effect of ticagrelor vs placebo for the reduction of painful crises	Number of painful crises
To compare the effect on ticagrelor vs placebo for the reduction of ACS	Number of ACSs
To compare the effect of ticagrelor vs placebo for the reduction of duration of painful crises	Duration of painful crises
To compare the effect of ticagrelor vs placebo on the number of VOCs requiring hospitalisation or emergency department visits	Number of VOCs requiring hospitalisation or emergency department visits
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for VOC	Number of days hospitalised for VOC
To compare the effect of ticagrelor vs placebo on the number of acute SCD complications[a]	Number of acute SCD complications
To compare the effect of ticagrelor vs placebo on reduction of days hospitalised for acute SCD complications[a]	Number of days hospitalised for acute SCD complications
To compare the effect of ticagrelor vs placebo on the number of sickle cell-related red blood cell (RBC) transfusions	Number of sickle cell-related RBC transfusions
To describe the health-related quality of life (HRQL) and fatigue	HRQL total score and by dimension using Paediatric Quality of Life Inventory (PedsQL) SCD Module and Fatigue total score and by dimension using the PedsQL Multidimensional Fatigue Scale as presented in Appendix I (age appropriate versions)
To describe absence from school or work due to SCD	Proportion of days of absence from school or work (only if going to school or work at randomisation)
To describe intensity of pain during VOC	Intensity of worst pain daily during VOC - For patients ≤4 years of age, observer reported using the Face, Legs, Activity, Cry, Consolability Scale (FLACC) - For patient ages 5 to 18 years of age, self-reported using the Faces Pain Scale Revised (FPS-R)
To describe analgesics use during VOC	Type of analgesics (opioid and non-opioid) use

To describe patient acceptability of the formulation (palatability and swallowability)	- For patients ≤4 years of age taking the tablet dispersed or whole, an observer assessment of palatability and swallowability will be undertaken - For patients ≥5 years of age taking the tablet dispersed or whole, palatability will be assessed and categorised using the Facial Hedonic Scale

[a] The acute SCD complications are defined in Section 5.1.5.

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
To assess long-term safety and tolerability of therapy with ticagrelor vs placebo	AEs/SAEs, including bleeding Vital signs and laboratory safety variables

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
To compare the effect of ticagrelor vs placebo for the reduction of duration of ACS	Duration of ACS
To assess the pharmacokinetics (PK) of ticagrelor and AR-C124910XX in paediatric patients with SCD using a population PK model	Population PK parameters such as oral clearance (CL/F) and ticagrelor exposure (AUC)
	Observed plasma concentrations of ticagrelor and the active metabolite AR-C124910XX
To assess the effect of ticagrelor on platelet aggregation	PRI measured by vasodilator-stimulated phosphoprotein (VASP) assay

3. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, patients must fulfil the following criteria:

1. Provision of signed and dated informed consent prior to any study specific procedures not part of standard medical care (local regulations and international guidelines are to be followed in determining the assent/consent requirements for children).
2. Male or female paediatric patients aged ≥2 to <18 years and body weight of ≥12 kg (at Visit 1), diagnosed with HbSS or HbS/β^0 as confirmed by high-performance liquid

chromatography or haemoglobin electrophoresis.
Note: Diagnosis of SCD (if not confirmed prior to screening and records available on the medical file) should be confirmed for HbSS or HbS/β^0 by high-performance liquid chromatography or haemoglobin electrophoresis, performed at the site's local lab, in order to confirm the type of mutation.

3. Have experienced at least 2 VOCs (painful crisis and/or ACS) as judged by the Investigator in the past 12 months prior to Visit 1. These VOCs need to be documented in the patient's medical records or in other documents that can be reconciled.
4. If ≤16 years old, must have had transcranial Doppler (TCD) within the past year prior to Visit 1. If this is not the case, a TCD examination must be done before proceeding in the study.
5. If ≥10 years old, must have had an ophthalmological examination within the past year prior to Visit 1. If this is not the case, the patient must be examined by an ophthalmologist before proceeding in the study. If local guidelines dictate ophthalmological examination at younger ages, those local guidelines should be followed.
6. If treated with hydroxyurea, the weight-adjusted dose must be stable for 3 months before screening.
7. Suitable venous access for the study-related blood sampling
8. Prior to dosing on day of randomisation (Visit 2), a negative urine (dipstick) pregnancy test performed at Screening (Visit 1) and at Visit 2 must be available for female patients of childbearing potential.
9. Females of childbearing potential (after menarche) must not become pregnant during study. Sexually active females must use a highly effective method of contraception which results in a low failure rate (ie, less than 1% per year). If use of effective contraception cannot be secured in sexually active females, the patient cannot be included in this study. Refer to Section 3.8 for highly effective methods of contraception.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. History of transient ischaemic attack (TIA) or cerebrovascular accident (ischaemic or haemorrhagic), severe head trauma, intracranial haemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy.
2. Findings on TCD: Current or previous values for time averaged mean of the maximum velocity (TAMMV) that are Conditional or Abnormal. Patients with Conditional TAMMV values or higher (≥153 cm/sec using TCD imaging technique [TCDi] which is corresponding to ≥170 cm/sec by the non-imaging technique). Both the middle cerebral artery and the internal carotid artery should be considered. Any other criteria that would locally be considered as TCD indications for chronic transfusion would also exclude the patient.
3. Active pathological bleeding or increased risk of bleeding complications according to Investigator
4. Haemoglobin <6 g/dL from test performed at Screening (Visit 1)
5. Platelets <100 x 10^9/L from test performed at Screening (Visit 1)
6. Undergoing treatment with chronic red blood cell transfusion therapy

7. Chronic use of NSAIDs defined as continuous intake >3 days per week that cannot be discontinued
8. Receiving chronic treatment with anticoagulants or antiplatelet drugs that cannot be discontinued
9. Moderate or severe hepatic impairment defined as laboratory values of alanine aminotransferase (ALT) >2 × upper limits of normal (ULN), total bilirubin >2 × ULN (unless judged by the Investigator to be caused by haemolysis), albumin <35 g/L (3.5 g/dL) and International normalised ratio (INR) >1.4, or symptoms of liver disease (eg, ascites) from test performed at Screening (Visit 1).
10. Renal failure requiring dialysis
11. Patient considered to be at risk of bradycardic events (eg, known sick sinus syndrome or second or third-degree atrioventricular block) unless already treated with a permanent pacemaker.
12. Concomitant oral or intravenous therapy with strong cytochrome P450 3A (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers (see full list in Appendix G), which cannot be stopped at least 5 half-lives before randomisation.
13. Active untreated malaria. Patients with suspected malaria at Screening (Visit 1) will be tested.
14. Known hypersensitivity or contraindication to ticagrelor
15. Patients who are currently pregnant or breastfeeding, or planning to become pregnant during the study or have given birth less than 3 months prior to Screening (Visit 1)
16. Any condition which, in the opinion of the Investigator, would make it unsafe or unsuitable for the patient to participate in this study
17. Concern for the inability of the patient or caregiver (defined as legally authorised representative) to comply with study procedures and/or follow-up
18. Previous randomisation in the present study
19. Participation in another clinical study with an IP or device during the last 30 days preceding screening.
20. Involvement of member of patient's family, or patient self, in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

Procedures for withdrawal of incorrectly enrolled patients see Section 3.3.

3.3 Subject enrolment and randomisation

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening. Enrolment can occur 7-28 days before randomisation.

The Investigator(s) will:

1. Obtain signed informed consent/assent (per local requirements) from caregiver of the potential patient and from the patient (if applicable) before any study specific procedures are performed.
2. Assign (using the Interactive Voice/Web Response System [IXRS]) potential patient a unique enrolment number, beginning with 'E + 4-digit site number + 3-digit patient

number starting with 501. For example, the first patient at site 9999 would be assigned the patient number: E9999001. This number will be used for identification (ID) throughout the study and will not be used for any other participant.
3. Determine patient eligibility. See Sections 3.1 and 3.2.
4. Assign eligible patient unique randomisation code (patient number), by accessing IXRS.

Patients who have not been randomised can be re-enrolled in the study if they meet eligibility criteria at a later date; however, no patient can be re-randomised. Any re-enrolment of patients must be done in consultation of the Sponsor's Study Physician and any decision must be captured in the patient's medical notes. If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomised subjects

Patients who fail to meet the eligibility criteria must not, under any circumstances, be enrolled or receive IP. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician or representative immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca Study Physician or representative must ensure all decisions are appropriately documented.

In those cases where continuation of study therapy is judged not to present a concern related to safety and disease management, the rationale for continuing study therapy must be clearly documented. The patient should continue follow-up in accordance with defined study procedures.

3.5 Methods for assigning treatment groups

The randomisation codes will be computer generated by AstraZeneca R&D and loaded into the IXRS database. Randomisation codes will be generated in blocks to ensure approximate balance (1:1) between the 2 treatment arms (ticagrelor or placebo bd). Stratification for baseline hydroxyurea use by country will be applied.

For each patient randomised the IXRS will provide the Investigator with a unique kit ID number matching the treatment arm assigned to the patient. Following randomisation, the first dose of study drug will be administered to the patient as soon as possible. At randomisation and subsequent dispensing visits, the patient should always be provided medication with the kit ID(s) allocated by the IXRS. If a patient receives the incorrect randomised treatment at any time during the study, this must be corrected as soon as discovered after discussing with the Study Physician.

3.6 Methods for ensuring blinding

This is a double-blind study. Ticagrelor and matching ticagrelor placebo tablets will be identical in appearance and packaging. The bottles with IPs will be labelled with unique ID numbers allocated from the IXRS, but it will not indicate treatment allocation.

No member of the study team at AstraZeneca or representative, personnel at study centres or any contract research organisation (CRO) handling data will have access to the randomisation scheme during the conduct of the study, with the exception of the AstraZeneca personnel generating the randomisation scheme and the bioanalysis personnel analysing the pharmacokinetic (PK) samples as well as AstraZeneca Supply Chain, the Patient safety data entry site and the CRO companies providing the IXRS and carrying out the packaging and labelling of IPs. This documentation will be kept in a secure location until the end of the study.

There will be an independent, unblinded statistical team that will support the DMC with data during the study. Personnel involved in the clinical study at AstraZeneca or representative will remain blinded to these analyses and will have no knowledge of the results presented to the DMC.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists from the IXRS. Routines for this will be described in the IXRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca or representative staff. The number of individuals at the study site who become aware of the treatment status should be kept to an absolute minimum including keeping the patient blinded if possible. Treatment with study drug should be continued if considered appropriate.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

3.8 Restrictions

The following restrictions will be applied for patients participating in the study:

1. Patients may not participate in another clinical study that involves an IP (active or placebo) or device during this study.

2. Females of childbearing potential (after menarche) must not become pregnant. Sexually active females of childbearing potential must use a highly effective method of contraception, which results in a low failure rate (ie, <1% per year) from enrolment to the follow-up visit. If this cannot be secured, the patient cannot continue in this study. Examples of highly effective methods include implants, injectables, combined oral contraceptives, some intrauterine devices, or vasectomized partner. For male study participants, there are no restrictions against fathering a child when treated with ticagrelor.
3. For concomitant medications which are restricted during the study, see Appendix G.
4. If the patient is receiving digoxin, levels should be monitored closely following initiation of IP and with any change in IP, see Appendix G.
5. Intake of grapefruit juice is not allowed.
6. Patients should participate in annual ophthalmological and TCD examinations in age groups according to guidelines.
7. On visits with PK or vasodilator stimulated phosphoprotein (VASP) sampling, the morning dose of IP should not be taken at home. The dose will be administered at the site. See Table 2 for study assessment schedule, and Sections 5.4.1 (PK) and 5.5.2 (VASP).

3.9 Permanent discontinuation or temporary stop of investigational product

3.9.1 Permanent discontinuation

Patients may be permanently discontinued from IP in the following situations:

1. The patient (or caregiver) is at any time free to discontinue treatment or advise the patient to discontinue treatment, without prejudice to further treatment
2. AE, as judged by Investigator, that with continued treatment would put the patient at undue risk
3. Severe non-compliance with the study protocol, as judged by Investigator and/or AstraZeneca
4. Severe illness or risk to the patient as judged by the Investigator
5. Any major bleeding, for bleeding definitions see Section 6.3.8.
6. Repeated minor bleedings not needing medical intervention unless clearly not related to study drug (eg, minor trauma during playing), as judged by the Investigator
7. For females of childbearing potential, who are sexually active and where effective contraception cannot be secured, the study treatment must be discontinued
8. In the event of pregnancy, study drug should be immediately permanently discontinued. The patient is encouraged to continue to be followed in the study according to the study plan.
9. Conditional or Abnormal TCD findings, ie, TAMMV values are ≥153 cm/sec using TCDi technique (corresponding to ≥170 cm/sec by the non-imaging technique), indicating an increased risk of stroke.
10. Pathological findings on any imaging technique indicating increased risk of ischaemic or haemorrhagic stroke
11. TIA or stroke (ischaemic or haemorrhagic)
12. Need for chronic transfusion therapy
13. Findings indicating impaired liver function and/or coagulopathy:

- ALT or aspartate aminotransferase (AST) >5 × ULN, ALT or AST >3 × ULN and total bilirubin level >2 × ULN (unless bilirubin increase clearly explained by haemolysis), INR >1.5. For potential Hy's Law laboratory criteria: the elevation in transaminases must precede or coincide with (ie, on the same day as) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

14. Renal failure requiring dialysis
15. Patients with clinical symptoms of bradyarrhythmia as judged by the Investigator and/or ECG findings of significant sinus pauses or high degree atrioventricular block
16. Development of proliferative retinopathy.
17. Need for chronic use of NSAIDs defined as continuous intake >3 days per week

3.9.2 Temporary discontinuation

Patients may be temporarily discontinued from IP in the following situations:

1. Clinically significant thrombocytopenia (platelet count <80 x 10^9/L) which mandates an interruption of IP due to patient safety in the assessment of the Investigator. Repeat laboratory studies and standard of care should be followed until resolution of laboratory abnormality and if deemed appropriate, the IP can be restarted when platelet counts are >100 x 10^9/L.
2. Major or minor surgery or invasive procedures, for example, intramuscular injections. The IP should be temporary stopped 5 days prior to the procedure and can be restarted when bleeding risk is considered low, as judged by the Investigator.
3. Temporary need of treatment with prohibited concomitant medications, see Appendix G. The IP may be interrupted temporarily at the discretion of the Investigator; however, such cases are recommended to be discussed with the IQVIA Study Physician and the Sponsor Physician as soon as the Investigator is aware.
4. Novel coronavirus (COVID-19) pandemic, see Section 3.9.4.

Discontinuation of IP does not mean discontinuation of follow-up or termination of study participation. Study assessments should continue in all cases if possible.

If patients are not willing to come back to study visits, the sites are encouraged to investigate patient barriers to study visit compliance and discuss with the Clinical Research Associate (CRA) if there is any alternative follow-up schedule which can meet patient expectations. Prior to implementing alternative follow-up schedules, AstraZeneca approval must be granted.

3.9.3 Procedures for permanent discontinuation of a subject from investigational product

At any time, patients are free to discontinue IP, without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AEs. Adverse events (AEs) will be followed up (see Section 6) and all IPs should be returned by the patient. Patients permanently discontinuing IP should always be asked to continue the regular visits. It is essential to collect as much data as possible for all patients throughout the study and especially all potential endpoint events. Complete

withdrawal from the study (withdrawal of consent) has a direct negative impact on the potential validity of all study data and should be avoided wherever possible.

If patients are not willing to come back to study visits, the sites are encouraged to investigate patient barriers to study visit compliance and discuss with the CRA if there is any alternative follow-up schedule which can meet patient expectations. Prior to implementing alternative follow-up schedules, AstraZeneca approval must be granted.

If a patient is withdrawn from study, see Section 3.10.

3.9.4 Procedures and guidance for temporary IP discontinuation in relation to coronavirus disease 2019 (COVID-19)

If a patient is diagnosed with COVID-19 or is suspected to have COVID-19 and an AE/SAE is reported (see Section 6.3.10), the Investigator should determine whether the patient's IP administration should continue or be temporarily discontinued**.** Patients who are discontinued from IP due to COVID-19 are to remain in the study whenever possible for safety follow-up.

In case a patient is unable to attend on-site visits for undergoing safety-related assessments as detailed in the Schedule of Assessments (Table 2), due to local public health rules, patient inability or patient/caregiver decision, the patient must be temporarily discontinued from IP, unless the safety-related assessments (including vital signs, physical examination, blood samples for safety laboratory assessments, urine for urinalysis, eDevice review, ECGs, VOCs, and recording of concomitant medications and AEs) can be performed at the patient's home and/or local laboratories or other local facilities by delegated site staff.

Such temporary discontinuation of IP does not mean discontinuation of follow-up. In case it is not possible to perform on-site visits, the site staff should keep in close contact with the patient to maintain awareness of their status and on-site visits should be replaced by telephone contacts following the same procedures as detailed in the Schedule of Assessments for telephone visits (Table 3).

Deviations from the study schedule of assessments due to COVID-19 will be identified as COVID-19 related protocol deviations and recorded appropriately.

In the event a patient is temporarily discontinued from IP, every effort should be made to have the patient/caregiver return all unused IP and empty bottles to the study site and study site staff should perform accountability as detailed in Section 7.6.

If this is not possible:

- patients should be clearly instructed that, in case of any tablets leftover in bottles already dispensed to them, they are not allowed to take the IP if they are not visiting the site
- remaining IP should be returned during the first possible on-site visit
- reasons for not returning the IP and instructions given to the patient should be thoroughly documented.

According to the local public health rules and recommendations, as soon as the patient is able to undergo safety-related assessments as detailed in the Schedule of Assessments (Table 2), then IP can be dispensed and treatment restarted.

In the event a study site is impacted by COVID-19 in a way that results in an inability to perform study activities, the study monitor should be informed as soon as possible.

If a patient is to be withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Failure to meet randomisation criteria' (ie, patient does not meet the required inclusion criteria or meet any of the exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (ie, permanent discontinue of IP and study schedule assessments), without prejudice to further treatment.

Withdrawal of consent from the study must be documented by the Investigator in the patient medical records and recorded in the electronic case report form (eCRF) as well as in the Informed Consent Form (ICF). The reason for permanent discontinuation of IP, the date of the last dose of the IP, reason for withdrawal and the presence of any AEs must be documented in the eCRF. The Investigator will follow-up AEs outside of the clinical study. The patient will return the electronic device (eDevice).

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn patients will not be replaced after randomisation.

3.11 Discontinuation of the study

The study may be terminated at individual centres per agreement between the Principal Investigator (PI) and AstraZeneca, eg, if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. Enrolment in a country may be terminated in order to ensure a reasonable international distribution of patients.

AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study (see Section 1.5.2 for DMC) or in any other study with ticagrelor.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The Schedule of Assessments is presented in Table 2. The Schedule of Assessments for telephone visits is presented in Table 3.

Table 2 Schedule of Assessments - Physical visits at study sites

	Screening period	Treatment period[a]										Follow-up period	For details see CSP Section
	Enrol-ment	Random-isation											
Visit Number	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**End of Study (EOS)**	**Safety Follow-up**	
Day/Week/Month	**-7 d**	**0 d**	**2 wk**	**4 wk**	**3 mo[b]**	**6 mo[b]**	**9 mo[b]**	**12 mo[b]**	**15 mo[b]**	**18 mo[b]**	**21 mo[b]**	**{12 to 24 mo}**	**14d after EOS**	
Visit Window	**-28 to -7 d**	**N/A**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±14 d**	**±5 d**	
Signed and dated informed consent/assent	X													10.4
Inclusion/exclusion criteria	X	X[a]												3.1 and 3.2
Assign E-code via IXRS	X													3.3
Relevant SCD, medical and surgical history	X													4.1
SCD diagnosis (if needed)	X													4.1
Demographics[c]	X													4.1
Transcranial Doppler[d]	X													4.1
Ophthalmology examination (if not performed within previous 12 months)[d]	X													4.1
Randomisation via IXRS		X												3.3 and 3.5
BP and pulse rate	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
Weight and height	X	X[e]				X		X		X		X		5.2.4
Physical examination (complete/brief)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.2
12-Lead ECG	X					X						X	X	5.2.3
Malaria testing for symptomatic patients[g]	X													4.1
Virology screen (HIV, HBsAg, and HCV)	X													5.2.1

Table 2 Schedule of Assessments - Physical visits at study sites

	Screening period	Treatment period[a]										Follow-up period	For details see CSP Section
	Enrol-ment	Random-isation											
Visit Number	**1**	**2**	**3**	**4**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**End of Study (EOS)**	**Safety Follow-up**	
Day/Week/Month	**-7 d**	**0 d**	**2 wk**	**4 wk**	**3 mo[b]**	**6 mo[b]**	**9 mo[b]**	**12 mo[b]**	**15 mo[b]**	**18 mo[b]**	**21 mo[b]**	**{12 to 24 mo}**	**14d after EOS**	
Visit Window	**-28 to -7 d**	**N/A**	**±3 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±14 d**	**±5 d**	
Blood samples for haematology and clinical chemistry	X	X[h]	X	X		X		X		X		X	X	5.2.1
Blood samples for coagulation (INR, PT and APTT)	X													5.2.1
Urine pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Urine for urinalysis (dipstick)	X	X[h]		X		X		X		X		X	X	5.2.1
Training and handout/collection of eDevice		X										X		
Review of eDevice device entries and reminder of use[j]			X	X	X	X	X	X	X	X	X	X		5.3.1
HRQL (PedsQL) assessment[k]		X				X		X		X		X		5.1.3
Palatability/swallowability[l]		X				X								5.3.1
Blood sampling for pharmacokinetics[m]		X		X		X		X		X		X		5.4
Blood sampling for pharmacodynamics (VASP)[m]		X		X		X		X		X		X		5.5
Dispense IP		X			X	X	X	X	X	X	X			7
Return IP and IP accountability			X	X	X	X	X	X	X	X	X	X		7.5 and 7.6
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Adverse event collection (AEs and SAEs)	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	6

AE Adverse event; APTT Activated partial thromboplastin time; BP Blood pressure; D Day; ECG Electrocardiogram; EOS End of study; eDevice Electronic device; FLACC Face, Legs, Activity, Cry, Consolability Scale; FPS-R Faces Pain Scale-revised; HBsAg Hepatitis B surface antigen; HCV Hepatitis C

virus; HIV Human immunodeficiency virus; HRQL Health-related quality of life; INR International normalised ratio; IP Investigational product; IXRS Interactive Voice/Web Response System; mo Month; PedsQL Paediatric Quality of Life Inventory; PD Pharmacodynamics; PK Pharmacokinetics; PT Prothrombin time; SAE Serious adverse event; SCD Sickle cell disease; TCD Transcranial Doppler; VASP Vasodilator-stimulated phosphoprotein; VOC Vaso-occlusive crisis; wk Week.

[a] Confirm patient still meets inclusion and exclusion criteria prior to randomising the patient in IXRS; SCD diagnostic testing not necessary if documented in medical records.

[b] Interval must not be more than 100 days to ensure tablet supply for all days.

[c] Age is required, but partial birthdate (year/month) is allowed if full data is not allowed or known.

[d] See inclusion criteria #4 for TCD and #5 for ophthalmology exam. Results must be available prior to randomisation and these examinations should thereafter be done annually during the study period.

[e] Only weight will be measured at Visit 2.

[f] A complete physical examination will be performed at Visit 1, EOS and Follow-up Visit and a brief examination at all other visits (see Section 5.2.2).

[g] Local/standard tests to be used for diagnosis of malaria for patients who are symptomatic at Screening.

[h] If the patient has had any serious illness after Visit 1 but before Visit 2, the need for repeated eligibility laboratory sampling must be evaluated before randomisation. If the Visit 1 laboratory results are less than 10 days old at randomisation, they can replace randomisation safety laboratory sampling to minimise the blood volume drawn.

[i] For females of childbearing potential.

[j] Electronic recording of worst pain according to FPS-R/FLACC and localisation of pain after experiencing a VOC, analgesic use and absence from school/work due to SCD.

[k] The HRQL (PedsQL) instruments are patient-reported if 5-7 years, 8-12 years, or 13-18 years and reported by a caregiver if the patient is ≤4 years.

[l] Morning dose of IP to be taken at the site. The palatability/swallowability questionnaire assessed by an observer in children ≤4 years, and by Facial Hedonic Scale (FHS) for children ≥5 years.

[m] Samples for PK and PD analysis will be taken 0 hour (predose) and 2 hours postdose at specified visits and in case of changed dose due to weight increase. No predose PK sample at Visit 2.

[n] SAEs should be collected from when the ICF is signed. AEs should be collected from time of randomisation.

Note: In case of modified follow-up when IP is discontinued, the study site visits can be replaced with telephone contact visits as per Table 3.

Table 3 Schedule of Assessments - Telephone visits during treatment period

	Treatment period[a]								For details see Protocol Section
Visit Number	**5**	**7, 8**	**10, 11**	**13, 14**	**16, 17**	**19, 20**	**22, 23**	**25, 26**	
Month	**2**	**4, 5**	**7, 8**	**10, 11**	**13, 14**	**16, 17**	**19, 20**	**22, 23**	
Visit Window	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	
Reminder of eDevice use and ensure data collection of potential VOC events[b]	X	X	X	X	X	X	X	X	5.1.1
Concomitant medications	X	X	X	X	X	X	X	X	7.7
Adverse event collection (AEs and SAEs)	X	X	X	X	X	X	X	X	6

AE Adverse event; d Day; eDevice Electronic device; FLACC Face, Legs, Activity, Cry, Consolability Scale; FPS-R Faces Pain Scale-revised SAE Serious adverse event; VOC Vaso-occlusive crisis.

[a] See Appendix E, a Guide for Scheduled Telephone Visits.

[b] Electronic recording of pain according to FPS-R/FLACC when experiencing a VOC, analgesic use and absence from school/work due to SCD.

4.1 Screening period

Procedures will be performed according to the Schedule of Assessments (Table 2).

Before any study-related assessments are performed, the informed consent/assent should be provided by the caregiver/patient, see Section 10.4.

At Screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

If the patient has had any serious illness after Visit 1 but before Visit 2, the need for repeated eligibility laboratory sampling must be evaluated before randomisation.

If the Visit 1 laboratory results are less than 10 days old at randomisation, they can replace randomisation safety laboratory sampling to minimise the blood volume drawn.

Unless done within previous 12 months, the Investigator must ensure TCD and ophthalmology examination are performed before proceeding in the study, see Section 3.2 for exclusion criteria related to these examinations. These examinations should thereafter be done annually during the study period.

4.2 Treatment period

4.2.1 Physical visits at study sites during the treatment period

Descriptions of the procedures for this period are included in the Schedule of Assessments for physical visits at study sites (Table 2).

At Visit 2, ensure the eligibility of the patient before continuing study-related assessments. The Paediatric Quality of Life Inventory (PedsQL) should be the first study assessment, ie, before blood sampling, electrocardiogram (ECG), etc. The patient will be administered his/her first dose of the double-blind treatment at the site. The collection of study assessments should be ensured before dispensing of the first dose. After the first dose is taken, assess palatability/swallowability.

For all on-site visits, remind the patient:

- To bring the IP bottles and the electronic Device (eDevice; including unscheduled visits) to the study site
- Not to take their dose at home in the morning of the visits with PK/PD sampling scheduled at the visit. The patient should be reminded on how to use the eDevice including during a potential VOC event, regardless of primary setting of treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated), see Section 5.1.1.

Contraceptive method should be reviewed and monitored in females of childbearing potential.

On visits with PedsQL, the instrument should be completed before any other study assessments.

Ensure that there are not more than 100 days between two planned visits containing dispensing of IP to ensure tablet supply for all days.

If feasible, study visits may take place at the patient's home or other setting if travel to the site is not possible due to the COVID-19 situation.

4.2.2 Telephone visits during treatment period

Descriptions of the procedures for this period are included in the Schedule of Assessments for telephone visits during the treatment period (Table 3).

Telephone visits should occur between the Investigator at the study site, and the caregiver for the patient. The Investigator may decide to speak directly with a patient in the late teenage period, if judged appropriate based on the Investigator's thorough knowledge of the patient.

Similar to on-site visits, the telephone visit should be documented in the patient's medical records. Notes are to include:

- Any AEs,
- Whether an AE fulfils criteria for VOC endpoint or not,
- Any changes of medications,
- Any use of contraceptives (applicable to females of childbearing potential).

See Appendix E, a Guide for Scheduled Telephone Visits for further details on conduct of the telephone visits.

4.2.3 End of study visit

Patients are to be followed up to 24 months or until a common study end date is reached defined as 12 months after the last patient is randomised. After the CSED have been communicated by AstraZeneca or representative, all patients still in the treatment period should be scheduled for the End of Study Visit (see Table 2). The End of Study Visit should be done within 30 days after CSED. The patients should return the eDevice and the IP bottles.

The Safety Follow-up Visit should be scheduled.

4.2.4 Safety follow-up visit

Descriptions of the procedures for this visit are included in the Schedule of Assessments (Table 2).

4.2.5 Unscheduled visits

For any safety or tolerability reasons, the patients may return to the clinic for an unscheduled visit.

The Investigator's evaluation should be documented in the source documents in the same manner as a regular planned visit. Procedures performed are at the discretion of the Investigator. Unscheduled visits should not affect the regular visit schedule and assessments.

5. STUDY ASSESSMENTS

The Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

An eDevice will be used by the patient/caregiver for electronic recording of pain according to FPS-R/FLACC when experiencing a VOC, analgesic use and absence from school/work due to SCD.

5.1 Efficacy assessments

5.1.1 Vaso-occlusive crisis

A VOC is the composite of a painful crisis and/or an ACS (Howard et al 2015, Yawn et al 2014). Each component is defined as:

A painful crisis is an onset or worsening of pain that lasts at least 2 hours, for which there is no explanation other than vaso-occlusion and which requires therapy with oral or parenteral opioids, parenteral NSAIDs, or other analgesics prescribed by a health care provider in a medical setting (such as a hospital, clinic or emergency room visit) or at home.

An ACS is an acute illness characterised by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest X-ray.

5.1.1.1 Collection of VOC

A VOC occurring during the study should be recorded by the Investigator both as a primary endpoint event, and also as an AE. A potential VOC judged by the Investigator not to fulfil the definition of the primary endpoint should be also recorded as an AE according to standard AE reporting procedures (see Section 6).

Collection of some information related to the potential VOC should be done by the patient/caregiver in real-time in the eDevice, and not based on recollection at the next planned visit. When information related to a potential VOC is entered in the eDevice, the Investigator will be alerted and should, unless a contact already occurred, call the caregiver within 72 hours from the onset of the potential event to enable a medical consultation and event data collection (see Appendix D, Interview Guide for VOC-triggered Telephone Calls). Families

will be instructed to call the site in case of a VOC, unless already contacted by the site within 72 hours.

Regardless of primary setting of treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated), some VOC-related information outlined below must be documented by the caregiver in the patient's eDevice. The Investigator only, will judge if the potential VOC fulfil the definition of VOC (see Section 5.1.1 for definition). If needed, the Investigator should request medical records and/or other documents from other medical facility than the study site. It will be the Investigators' responsibility to document the VOC in medical records and ensure that the VOC data in the eCRF is correct.

Following information will be captured in the eDevice to be reviewed by the Investigator:

- Start and stop date/time of the VOC event
- Assessment of worst pain intensity will be done once daily throughout the duration the VOC event (Patient/Observer Reported), see Section 5.1.2.
- Report of anatomical location(s) of pain will be done once daily throughout the duration of the VOC event (Patient/Observer Reported).
- If analgesics are taken during the VOC (Yes/No) and the Investigator will enter details of the analgesics (ie, name, type, dose, routes of administration, frequency) into the eCRF.

The following data should be collected in the eCRF, based on review of eDevice entries, information from the medical consultation and copies from other medical facilities:

- Confirmation if the event fulfils the VOC definition
- Date of any telephone contact
- Start and stop date/time of the event
- Primary setting for VOC treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated)
- Start and stop date/time of any in-patient hospitalisation
- Treatments administered of the event
- Complete AE/SAE form.

5.1.1.2 Training in the collection of VOC events

Patients will be supplied with a handheld eDevice for the treatment period. Caregivers must be willing to learn and use the eDevice and/or supervise the use of the eDevice. At Visit 2, all patients and their caregiver will be carefully instructed and trained on how to handle and complete the eDevice. Written information will be supplied to each patient and caregiver in an age-adapted way in their local language. Instructions for use of the eDevice will also be described in writing in the ICF for the caregiver, in age-adapted language in the paediatric assent form (if used in certain age groups), and in the ICF for any participants turning 18 years of age during the study period.

The patient and the caregiver will be instructed on how and where to request help if problems occur. The Investigator is responsible to ensure that this training is performed at Visit 2 and any subsequent visits as needed.

The patient/caregiver should be reminded to use the eDevice during a potential VOC event, regardless of primary setting of treatment (eg, in-patient hospitalisation, short-stay outpatient unit, emergency department or self-treated). The patients and caregiver must bring the eDevice to each visit for the Investigator to review of eDevice entries.

The patients and their caregiver should also be informed that pain during a VOC, location of pain and use of analgesic should be entered daily to the eDevice. The daily questions on pain intensity, pain localisation and analgesic use must be responded to on the actual day; these data cannot be entered for other dates. In case an already resolved VOC event was not registered in the eDevice, start and stop date are still possible to record retrospectively. Pain intensity, pain localisation and analgesic use cannot be recorded for these events in the eDevice. However, analgesic use during resolved events need to be recorded by the Investigator in the eCRF together with any other event details as for all VOC events.

When information related to a potential VOC is entered in the eDevice, the Investigator will be alerted and should, unless a contact already occurred, call the caregiver within 72 hours from the onset of the potential event to enable a medical consultation and event data collection. Families will be instructed to call the site in case of a VOC, unless already contacted by the site.

Expectations on Investigator's documentation of endpoint events will be discussed at the Investigators meetings. Before the first patient is enrolled into the study at a study site, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents again with the study staff in the Start-up Meeting, and train them in any study-specific procedures, including collection of data for the primary efficacy endpoint. Study monitoring will include review of data entered for the primary efficacy endpoint to ensure the data are complete. Re-training of study staff will take place as needed.

5.1.2 Pain during a VOC

Pain is commonly reported in clinical trials by having patients provide a rating of their own pain. In this study, pain rating will be done in the eDevice. Different measures of numerical rating scales have demonstrated good psychometric properties, but are not fit for purpose for the youngest age groups due to their limited understanding of number concepts. Therefore, pain-rating scales with a series of faces depicting different levels of pain have been developed.

For young children (2 to ≤4 years of age), subjective observation of pain-related behaviours is recommended. The Face, Legs, Activity, Cry, Consolability (FLACC) assessment tool is a measurement developed for and used to assess pain for children between the ages of 2 months and 7 years. The FLACC behavioural pain tool has shown good reliability and validity in assessing pain in critically ill adults and children (Voepel-Lewis et al 2010). The FLACC will be caregiver-reported for patients ≤4 years of age daily during the VOC event. Each of the

5 behaviours observed are assigned a score of 0, 1 or 2. The total FLACC score will then range between 0 and 10, with 0 representing no pain.

The Faces Pain Scale - Revised (FPS-R) will be administered to all patients aged ≥5 years. When needed the caregiver can help the child with the assessment. It is important to train caregivers not to attempt to influence child's response in any way. The scale consists of 6 faces and scoring ranges between 0 and 10 (with an increase in numeric value by 2 [ie, 0, 2, 4, 6, 8, 10]), where 0 is no pain and 10 is very much pain. The FPS-R was validated by Hicks et al 2001 in 3 studies and has been judged as a well-established pain assessment tool in patients >4 years of age (Cohen et al 2008).

A body outline diagram will also be presented and the patient/caregiver will be asked to indicate the location(s) of the pain. See Appendix H for details of these pain assessments. Worst pain ratings will be collected once daily throughout the duration of the VOC event using an eDevice.

All instruments will be based on patients' age at baseline, and the same version should be used throughout the study.

5.1.3 Health-related quality of life (HRQL)

The HRQL will be assessed using the PedsQL SCD Module and Multidimensional Fatigue Scale. The SCD module consists of 43 items and measures problems with the patients' pain (severity, impact, management/control), worry, emotions, treatment and communication. The SCD module measures 9 sub-scales and a total score. The Multidimensional Fatigue Scale consists of 18 items measuring problems with general, sleep/rest and cognitive fatigue. The Multidimensional Fatigue Scale measure 3 sub-scales and a total score. The SCD module and the Fatigue Scale when used in SCD have shown acceptable to excellent measurement properties in both the patient-reported versions for ages 5 to 18 years and the parent-reported version for ages 2 to 4 years (Panepinto et al 2013, Panepinto et al 2014).

Both instruments have been developed in age-specific versions. In this study, the patient-reported versions are for patients ages 5 to 7, 8 to 12, and 13 to 18 years, respectively. For patients 2 to 4 years of age, the parent-reported version will be reported by a caregiver. See Appendix I for details of HRQL. Data will be collected using pen and paper at the site and will be administered at randomisation and every 6 months thereafter.

Appropriate procedures for minimising bias and enhancing compliance will be followed throughout the study. To ensure this, all study personnel will be trained to instruct the patient in a standardised way and further be responsible for providing all relevant instructions and training to the patients. A standardised procedure for the administration of the HRQL questionnaires should be applied.

Each centre must allocate responsibility for completion of the PedsQL questionnaires to a specific individual (eg, a Research Nurse). It is also important that the significance and relevance of the data are explained carefully to participating patients/caregivers so that they

are motivated to comply with data collection. The following applies to completing the PedsQL questionnaires:

- The patient/caregiver must complete it in private in their own time.
- PedsQL should preferably be completed before any investigations or discussions about the disease with the clinic staff and prior to any other study-related procedures.
- The patient/caregiver should be reassured that there are no right or wrong answers and that the answers are strictly confidential.
- Help should not be given from caregivers or clinical staff with the exception that the patient can receive help from a study nurse in understanding the instructions. However, under no circumstances should help in interpreting the questions or in selecting responses be provided.
- A form will be completed by the clinic staff to indicate if a questionnaire has been completed at each visit, and if not, the reason will be recorded.
- On completion of the questionnaires they should be handed back to the person responsible for questionnaires who should check for completeness.
- Only 1 answer should be recorded for each question.

5.1.4 Absence from school/work due to SCD

For patients attending school or work at randomisation, absences from school/work due to SCD will be recorded weekly by the patient in the eDevice with the help of the caregiver, if needed. The patients will be asked the question 'Have you been at home from school/work the last 7 days because of your disease'. If the reply is 'Yes', the patient will be prompted to answer how many days he/she has been absent. Days off from school due to study visits will not be recorded.

5.1.5 Acute SCD complications

The acute SCD complications will be defined as the composite of individual complications and be evaluated as secondary endpoint: TIA/ischaemic stroke, hepatic sequestration and splenic sequestration, priapism and dactylitis. If the frequency allows, the individual components can be assessed as exploratory endpoints.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, virology, coagulation and urinalysis will be taken at the times indicated in the Schedule of Assessments (Table 2). Local clinical routine procedures to reduce pain and discomfort from blood sampling in children will be followed, eg offering topical anaesthesia, coordinated sampling to avoid repeated punctures and use of in-dwelling catheters as appropriate in accordance with ethical and instruction guidelines for paediatric blood sampling. Additional safety samples for laboratory assessment may be collected during unscheduled visits if clinically indicated at the discretion of the Investigator. The date and time of collection will be recorded in the eCRF.

The clinical chemistry, haematology, virology and coagulation analyses will be performed at a central laboratory when possible or at an authorised/certified local laboratory as needed. All sampling, handling and transporting of samples will be in accordance with IATA Guidance Document (Appendix B).

Urinalysis is to be performed at the investigational site by dipstick. Urine pregnancy test will be taken at all visits for females of childbearing potential. If female patients achieve menarche during the study, a urine pregnancy test should be performed before any study procedures at the next visits.

The laboratory variables in Table 4 will be measured.

Table 4 Laboratory variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum)**
B-Haemoglobin (Hb)	S-Creatinine
B-Haematocrit	S-Bilirubin, total
B-Leukocyte count	S-Bilirubin, direct
B-Leukocyte differential count (absolute count)	S-Alkaline phosphatase (ALP)
B-Platelet count	S-Aspartate transaminase (AST)
	S-Alanine transaminase (ALT)
Urinalysis (dipstick)	S-Lactate dehydrogenase (LDH)
U-Hb/Erythrocytes/Blood	S-Uric Acid
U-Protein/Albumin	S-Blood Urea Nitrogen (BUN)
U-Glucose	S-Albumin
U-beta-human chorionic gonadotropin (β-hCG)	S-Potassium
	S-Chloride
Virology Screen[a]	S-Sodium
Hepatitis B surface antigen (HBsAg)	S-Glucose
Hepatitis C virus (HCV)	S-Haptoglobin
HIV	
Malaria Screen (not mandatory)	**Coagulation**[a]
Microscopy (blood smear evaluation)	International normalised ratio (INR)
Rapid diagnostic tests	Prothrombin time (PT)
	Activated Partial Thromboplastin Time (APTT)

B blood; S serum; U urine.

[a] Virology screen and coagulation will be conducted at the Screening Visit only.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed, dated and retained at centre

as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3 × ULN **and** total bilirubin ≥2 × ULN, refer to Section 6.3.7 for further instructions.

5.2.2 Physical examination

A complete physical examination will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal and neurological systems.

A brief examination of physical examination will include the following: general appearance, respiratory, cardiovascular and abdomen systems.

Physical examination will be performed at timelines as specified in the Schedule of Assessment in Table 2. Investigators should pay special attention to new or worsening abnormalities as they may qualify as AEs, see Section 6.3.6 for details.

5.2.3 ECG

5.2.3.1 Resting 12-lead ECG

A 12-lead ECG (standard ECG with a paper speed of 25 or 50 mm/second covering at least 6 sequential beats) will be recorded after the patient has been lying down to rest for up to 5 minutes. After ECG has been recorded, the Investigator or designated physician will review each of the ECGs and enter as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the Investigator should document the specific abnormality as clinically significant or not.

A standardised ECG machine should be used and a paper copy of ECG tracing should be filed in the patient's medical records.

5.2.4 Vital signs

5.2.4.1 Weight and height

Weight and height assessments will be performed at the visits as shown in Table 2. Results available in medical records, as taken on the visit day, will be recorded in the eCRF.

The study site staff should use a digital precision scale if possible, and record the weight in kilograms or pounds to the first decimal point (eg, 95.3 kg). The same scale should be used and the patient should wear a standard hospital-type gown or equivalent light clothing and no shoes for the body weight measurement at each visit.

5.2.4.2 Pulse rate and blood pressure

Pulse rate, systolic and diastolic blood pressure will be assessed using non-invasive equipment after the patient has been sitting at rest for 5 minutes. Results will be recorded in the eCRF.

5.3 Other assessments

5.3.1 Palatability and swallowability

Palatability will be assessed by age groups. The Facial Hedonic Scale (FHS) is a well-established method for assessing paediatric patients' responses to drug palatability for patients down to 3 years of age (Davies and Luleu 2008). The FHS consists of 5 faces with descriptions ranging from 'Dislike very much' to 'Like very much'. Patients ≥5 years of age will be asked to evaluate palatability immediately after dosing using the FHS at baseline and at 6 months. For patients <5 years of age an observer's assessment of the patient's behaviour, including willingness to swallow, will be performed directly after the patient has received the IP at baseline and at 6 months. See Appendix F for details.

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of ticagrelor and its active metabolite (AR-C124910XX) in plasma will be taken at the times presented in Table 2. Collection of PK samples should be time matched with PD samples. The PK results will not be available to site. The actual date and time for each sample will be collected in the eCRF.

A PK sample will be collected 0 hours (predose) and 2 hours postdose (no predose sample at randomisation visit). On visits with PK and/or VASP sampling, patients should not take IP (morning dose) at home prior to the visit, as this will be administered at the site. If morning dose accidently was taken prior to visit, no new dose will be administered at the site and no predose sample will be taken. The actual time for dosing should be noted and a postdose sample aiming for 2 hours should be taken. Regardless of time in relation to actual dose intake the time for this postdose sample should be recorded.

The time of last dose intake prior to any PK visits (ie, the evening dose the day before the visit) needs also to be precisely recorded in the eCRF to be able to relate the predose PK sample concentrations to time after ticagrelor dose intake.

The predose PK sample also contains important information on the relationship of ticagrelor dose to exposure and platelet inhibition response and therefore, the correct time recording of the evening dose is equally important as the sample itself.

In case of increased dose due to increased weight, PK sample will be collected at the next following visit. The PK sample will be collected 0 hours (predose) and 2 hours postdose.

Samples will be collected, labelled stored and shipped as detailed in the Laboratory Manual. A central laboratory will be used for the logistic arrangements.

5.4.2 Determination of drug concentration

Samples for determination of ticagrelor and its active metabolite (AR-C124910XX) in plasma will be analysed by Covance on behalf of the Sponsor, using an appropriate bioanalytical

method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

All samples still within the known stability of the analytes of interest (ie, ticagrelor and its active metabolite), at the time of receipt by the bioanalytical laboratory, will be analysed.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the Clinical Study Report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

For each placebo patient, samples will only be analysed on a 'for cause' basis, eg, if no quantifiable concentrations were observed in a patient's samples when the drug was expected to be present.

5.5 Pharmacodynamics

5.5.1 Vasodilator-stimulated phosphoprotein

Vasodilator-stimulated phosphoprotein is a critical protein that is expressed in platelets at high levels and plays a major role in negatively regulating secretory and adhesive events that are involved in platelet aggregation. The effect of ticagrelor on inhibition of platelet aggregation will be assessed by the VASP assay during treatment period (Voepel-Lewis et al 2010; Laine et al 2013).

5.5.2 Collection of samples

Blood samples for determination of platelet aggregation in whole blood will be taken at the time presented in Table 2. Except for the important PD sample taken prior to first dose of study drug at Visit 2 randomisation where no PK sample is taken, the collection of PD samples are thereafter matched with PK samples. To maintain the blinding of treatment allocation, the PD results will not be available to the site, and individual PD results will not be available to the Sponsor.

The time of last dose intake prior to any VASP visits (ie, the evening dose the day before the visit) needs also to be precisely recorded in the eCRF to be able to relate the predose VASP inhibition to time after ticagrelor dose intake.

The predose VASP sample also contains important information on the relationship of ticagrelor dose to exposure and platelet inhibition response and therefore, the correct time recording of the last dose the evening before the visit is equally important as the sample itself.

In case of increased dose due to increased weight, the PD sample will be collected at the following visit. The PD sample will be collected 0 hours (predose) and 2 hours postdose.

Samples will be collected and labelled as detailed in the Laboratory Manual.

5.5.3 Storage and destruction of pharmacodynamics samples

Pharmacodynamic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacodynamic samples to further evaluate and validate the analytical method before finalisation of the CSR. Any results from such analyses may be reported separately from the CSR.

Samples will be stored until the study is finalised, after which they will be destroyed. Detailed information about samples storage can be found in the Laboratory Manual. The results of any investigation will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

5.6 Genetics (Not applicable)

5.7 Biomarker analysis (Not applicable)

5.8 Volume of blood

The total maximum volume of blood that will be drawn from each patient at each study visit is listed in Table 5 below.

Table 5 Volume of blood to be withdrawn from each patient

	Total maximum volume (mL)	
	12 to 24 kg body weight	**>24kg body weight**
Visit 1 (Enrolment)	9,9	13,8
Visit 2 (Randomisation)	6,6	7,7
Visit 3 (2 weeks)	3,4	4,5
Visit 4 (4 weeks)	7,8	8,9
Visit 6 (3 months)	0	0
Visit 9 (6 months)	7,8	8,9
Visit 12 (9 months)	0	0
Visit 15 (12 months)	7,8	8,9
Visit 18 (15 months)	0	0
Visit 21 (18 months)	7,8	8,9
Visit 24 (21 months)	0	0

Table 5 Volume of blood to be withdrawn from each patient

	Total maximum volume (mL)	
	12 to 24 kg body weight	**>24kg body weight**
End of Study (EOS)	7,8	8,9
Follow Up Visit	3,4	4,5
Total (mL)	62,3	75

Note: Visits 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25 and 26 are telephone visits.
Note: blood volumes are applicable to central laboratory only; local laboratory practices may vary, however the maximum volume should not exceed those recommended in the appropriate local guideline.
*Maximum volume during 30 days: 19,9 mL ** Maximum volume during 30 days: 26 mL

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from the time of randomisation, and throughout the study, including the follow-up period. Any SAEs should be collected from when the ICF is signed.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the electronic case report form (eCRF). AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of

disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

The definitions for intensity rating are:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

6.3.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: *'Have you/the child had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.7 Liver biochemistry and evaluation of Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN need to be reported as SAEs, except if the elevation is caused by the underlying sickle cell disease, ie, haemolysis, as judged by the Investigator. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Assessment of bleeding events

Bleeding events will be recorded as AEs. The Investigator will do the classification of bleeding events. Bleeding events will be recorded in the eCRF.

For patients experiencing a bleeding event that fulfils criteria in more than 1 category, the bleed will be assigned to the most severe category. The bleeding definitions (Mitchell et al 2011) are:

- **Major bleeding:** defined as any fatal bleeding, clinically overt bleeding associated with a decrease in Hb of at least 20 g/L (2 g/dL), bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system or bleeding that requires surgical intervention in an operating suite.
- **Clinically relevant non-major bleeding:** defined as overt bleeding for which a blood product is administered and which is not directly attributable to the patient's underlying medical condition, and bleeding that requires medical or surgical intervention to restore haemostasis, other than in an operating suite.
- **Minor bleeding:** defined as any overt or macroscopic evidence of bleeding that does not fulfil the above criteria for either major bleeding or clinically relevant, non-major bleeding. Menstrual bleeding resulting in a medical consultation and/or intervention will be classified as a minor bleeding event.

6.3.9 Vaso-occlusive crisis (VOCs) and acute SCD complications

A VOC and acute SCD complications (TIA/ischaemic stroke, hepatic sequestration and splenic sequestration, priapism and dactylitis) occurring during the study should be recorded by the Investigator as AEs. For a definition and collection of VOCs, see Section 5.1.1 and for acute SCD complication, see Section 5.1.5.

- A VOC fulfilling the criteria should also be recorded as an adverse event with the diagnosis Sickle cell anaemia with crisis.
- If the VOC event includes symptoms of other acute SCD complications, these should also be recorded, but separately from the VOC event in the eCRF.

6.3.10 Procedures in relation to COVID-19 infection

If a patient presents with clinical signs and symptoms consistent with COVID-19 infection, the Investigator should request a test where possible and this should be recorded in the AE field of the eCRF as follows:

- If test is positive, record as "COVID-19 confirmed".
- If test is negative, record the AE/SAE signs and symptoms and/or other diagnosis.
- If test is not available and signs and symptoms, as judged by the Investigator, are highly suspicious of COVID-19 infection, record as "COVID-19 suspected".

If other concurrent diagnoses exist, eg, pneumonia, the Investigator should record as separate AEs.

If an AE/SAE is associated with COVID-19, the Investigator should determine whether the patient's IP should be continued, temporarily interrupted or permanently stopped. Refer to Section 3.9.4 for guidance on procedures in relation to COVID-19.

All AE reporting instructions in this section and SAE reporting in Section 6.4 also apply to any AE/SAE associated with COVID-19.

6.4 Reporting of serious adverse events

All SAEs have to be reported to the appropriate AstraZeneca representative, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, other than mentioned in Section 6.3.9, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it (see also Section 6.4.1).

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug.

6.4.1 Reporting of SAEs that are also endpoints in the study

Efficacy endpoints in the study (VOCs and acute SCD complications [TIA/ischaemic stroke, hepatic sequestration and splenic sequestration, priapism and dactylitis]) fulfilling the criteria for SAE will not be reported by AstraZeneca to health authorities to avoid unnecessary unblinding of efficacy endpoints that are also SAEs.

6.5 Overdose

An overdose is considered any dose greater than that specified in the protocol.

There is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not expected to be dialysable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive ticagrelor dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

In healthy adults, ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity (nausea, vomiting, diarrhoea) was dose-limiting in healthy adults following ascending single doses. Other clinically meaningful adverse effects, which may occur with overdose, include dyspnoea and ventricular pauses. In the event of overdose, observe for these potential adverse effects, and consider ECG monitoring. Measure platelet inhibition to determine the extent and duration of excessive platelet inhibition.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For overdoses not fulfilling SAE criteria, AstraZenceca will ensure that the overdose is reported to the AstraZeneca data entry site within 30 calendar days of awareness.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca representatives.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The eCRF is used to report the pregnancy. The outcome of the pregnancy is reported on a separate form outside the eCRF.

6.6.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study. Pregnancies in partners are not to be reported.

6.7 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the patient

- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IXRS errors)
- Wrong drug administered to patient (excluding IXRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IXRS - including those which lead to 1 of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.8 Management of IP-related toxicities

See Section 3.9.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor 15 mg tablet	Oral, plain, round, biconvex, white/off-white, uncoated, 15 mg	AstraZeneca
Placebo for ticagrelor 15 mg tablet	Oral, plain, round, biconvex, white/off-white, uncoated, containing no active ingredient	AstraZeneca

Ticagrelor tablets of 15 mg and its matching placebo (approximately 6 mm in diameter) will be packed in high-density polyethylene bottles containing 100 tablets. Subsequent intervals between dispensing visits should not be more than 100 days.

7.2 Dose and treatment regimens

Allocation of IP bottles will be managed via the IXRS and at Visit 2, first dose of the IP will be administered at the clinic by site staff. Subsequent doses should be taken morning and evening, at approximately 12-hour intervals. The IP can be taken with or without food.

7.2.1 Treatment during double-blind randomisation period

Randomisation to twice daily double-blind treatment with ticagrelor or placebo will occur at Visit 2 via the IXRS. Eligible patients will be randomly assigned to 1 of 2 treatment regimens, based on body weight at Visit 2:

- ≥12 to ≤24 kg body weight: 15 mg - 1 tablet of ticagrelor 15mg or 1 tablet of placebo to match ticagrelor 15 mg twice daily
- >24 to ≤48 kg body weight: 30 mg - 2 tablets of ticagrelor 15mg or 2 tablets of placebo to match ticagrelor 15mg twice daily
- >48 kg body weight: 45 mg - 3 tablets of ticagrelor 15mg or 3 tablets of placebo to match ticagrelor 15mg twice daily

At Visit 2, the first dose of IP will be administered at the clinic by site staff as soon as possible after randomisation and after all baseline assessments have been completed. Subsequent doses should be taken morning and evening, at approximately 12-hour intervals. Missed doses of ticagrelor or placebo blinded IP should not be compensated (ie, if a dose is missed the next regularly scheduled dose should be taken and should not be doubled).

The study drug will be administered orally either swallowed whole or dispersed in water, other suitable liquids or vehicles based on age and/or ability to swallow study drugs. Refer to handling instructions for further details.

7.2.2 Dose increase during study

For any patient having a weight gain during the study period clearly exceeding the upper weight limit of the band (≥27 kg and ≥54 kg, respectively), the dose will need to be increased according to the next weight band.

In case of a dose increase:

- IXRS will generate correct dose based on body weight range entered
- Stop date for the old dose and start date for the new dose should be recorded in the eCRF
- The patient should return all unused IP and empty bottles and new IP bottles should be dispensed
- PK and PD samples should be taken at the following visit after the adjusted dose has been dispensed, see Sections 5.4 and 5.5.

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of IP (ticagrelor or placebo) should be recorded in the appropriate sections of the eCRF.

Each time IP is dispensed, compliance will be reinforced. The caregiver will be asked to bring all unused IP and empty bottles to the study site at each on-site visit. When IP is returned, compliance will be assessed based upon an interview with the caregiver and a count of the tablets returned.

7.6 Accountability

The IP provided for this study will be used only as directed in the Clinical Study Protocol.

The study site staff will account for all IPs dispensed to and returned from the patient.

The caregiver will be asked to bring all unused IP and empty bottles to the study site at each on-site visit. The Investigator or delegate will enter the amount of returned tablets in the eCRF.

Study site personnel or the AstraZeneca delegated monitor will account for all IPs received at the site, empty bottles, unused study drugs and for appropriate destruction, according to local procedures at an authorised site. Certificates of delivery, destruction and return must be signed by an AstraZeneca representative.

7.7 Concomitant medication and other treatments

See Appendix G for a complete list of restricted medications. All concomitant medications and any changes during the study should be recorded by the Investigator in the eCRF.

Use of anti-platelet aggregation drugs like ADP receptor blockers (eg, cangrelor, clopidogrel, prasugrel, ticlopidine) or aspirin, or phosphodiesterase inhibitors (eg, dipyridamole and cilostazol) is not allowed in the study.

Treatment with oral or parenteral anticoagulants (except for heparins for flushing of catheters) is not allowed in the study. Chronic non-steroidal anti-inflammatory agents (requiring treatment >3 days/week) is not allowed in the study (see exclusion criteria in Section 3.2).

CYP3A inhibitors

Concomitant use of strong inhibitors of CYP3A (eg, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) is not allowed. When macrolide antibiotics is indicated azithromycin is allowed.

CYP3A substrates or inducers

Co-administration of CYP3A substrates with a narrow therapeutic index is not allowed. Co-administration of strong inducers of CYP3A (eg, rifampin/rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, avasimibe, St. John's wort) is not allowed.

P-glycoprotein interactions

Ticagrelor is a weak inhibitor of P-glycoprotein (P-gp), a drug efflux transporter. Digoxin is a substrate of P-gp and concurrent treatment with ticagrelor modestly increases digoxin levels. If the patient is receiving digoxin, levels should be monitored closely following initiation of IP and with any change in IP.

7.7.1 Blood transfusions

If a patient requires any blood transfusion during the study, this information will be captured in the eCRF.

7.7.2 Other concomitant treatment

If a patient is treated with hydroxyurea, the weight-adjusted dose must be stable for 3 months before enrolment.

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, like L-glutamine may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF. The entry must include the dose, regimen, route, indication and dates of use.

Patients may not participate in any other interventional drug study for at least 30 days prior to starting this study and may not participate in any other interventional drug study throughout the study period.

7.8 Post study access to study treatment (Not applicable)

8. STATISTICAL ANALYSES BY ASTRAZENECA OR DELEGATE

Statistical analyses are summarised below. Further details will be provided in the Statistical Analysis Plan (SAP).

8.1 Statistical considerations

Statistical analyses will be performed by IQVIA under the direction of Biometrics & Information Sciences, AstraZeneca using SAS® version 9.2 or higher and, where appropriate, additional validated software.

IQVIA will finalise the SAP according to any required regulatory timelines but before review of any potential treatment revealing data is undertaken (this includes Blind Deliverable Reviews and Data Monitoring Committee reviews).

8.2 Sample size estimate

The number of VOCs is assumed to have a negative binomial distribution with shape parameter 0.8. The mean number of crises per year is assumed to be 2.0 in the placebo group with reduction of 50% in the ticagrelor group. Patients will be randomised to 1:1 ratio and with minimum follow-up of 12 months and average follow-up of 18 months, 154 patients provide about 90% power for a 2-sided test of the mean number of crises for ticagrelor versus placebo, at significance level 5%. Allowing for dropouts, the sample size is increased to 182. The calculations were based on simulation with 5,000 repetitions.

Scenarios and simulations were evaluated to assess the risk with shorter and longer mean follow-up time. To ensure that the study is adequately powered the recruitment rate will be monitored and the sample size may be adjusted to a maximum of 200 patients. With a mean follow-up time of 13 month, 200 patients will provide 90% power to detect a reduction of 50% in the ticagrelor group.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

All randomised patients, regardless of treatment received, will be included in the Full Analysis Set. The primary statistical analysis of the efficacy of ticagrelor will be carried out on the Full Analysis Set. Patients will be analysed according to their randomised IP.

8.3.2 Safety analysis set

All patients who receive at least 1 single dose of randomised IP, ticagrelor or placebo, and for whom any postdose data are available, will be included in the safety analysis set. Erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group, where actual treatment is defined as: ticagrelor if a patient receives at least 1 dose of ticagrelor, otherwise actual treatment is placebo.

8.3.3 PK analysis set

All patients who receive at least 1 dose of IP and provide at least 1 post dose analysable plasma sample for PK analysis will be included in the PK analysis set.

Patients with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PK may be excluded from the PK analysis set.

8.3.4 PD analysis set

All patients who have receive at least 1 dose of IP and provide at least 1 postdose analysable sample for PD analysis will be included in the PD analysis set.

Patients with major protocol deviations including changes to the procedures that may impact the quality of the data, or any circumstances that can alter the evaluation of the PD may be excluded from the PD analysis set.

8.4 Outcome measure for analyses

See Section 2 for outcome measures.

8.5 Methods for statistical analyses

In general;

- Ticagrelor data will be pooled and analysed irrespective of dose.
- Safety, plasma concentrations of ticagrelor and active metabolite, HRQL variables will be presented using descriptive statistics and graphed as appropriate.
- Categorical variables will be summarised in frequency tables (number of patients and percentage), by treatment group.
- Continuous variables will be presented with descriptive statistics (n, arithmetic mean, standard deviation [SD], median, min, max), within treatment group. If appropriate, geometric mean and coefficient of variation (CV) will be used instead of arithmetic mean and SD, with CV (%) calculated as:
  $100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$ where s is the SD of the data on a log scale.
- Data will also be presented in individual patient listings.
- Baseline values will be the closest observation prior to and including the randomisation visit.

8.5.1 Analysis of the primary variable

The primary analysis will be based on the intent-to-treat principle. Ticagrelor data will be pooled and analysed irrespective of dose.

The number of VOCs will be analysed using negative binomial regression. Any VOC event with an onset date within 7 days from a prior event onset date will not be counted as a new

episode. The response variable is the number of VOCs experienced by a patient over the treatment period. Patient follow-up time (log-transformed) will be included as an offset in the linear predictor to adjust for patients having different exposure times. Additional covariates to be adjusted for in the linear predictor will be treatment group (placebo as reference group) and baseline hydroxyurea therapy (Yes/No). The treatment effect will be tested at a 5% significance level.

If the negative binomial distribution is not appropriate, a Wilcoxon rank sum test will be used. As the Wilcoxon rank sum test cannot be adjusted for the patients follow-up time, sensitivity analyses will be performed to ensure robustness of the results.

The primary analysis (under the treatment policy estimand) includes all data until patients withdraw from the study regardless of if they discontinue from randomised treatment. The primary analysis uses the negative binomial regression model with logarithm of the observation period as an offset term and assumes that missing data is missing at random. Hence, the model assumes that the frequency-of-events during an unobserved period is the same as the frequency estimated using observed data.

To examine the sensitivity of the results and the robustness of this assumption analyses will be performed using controlled multiple imputation method. For this method, an underlying negative binomial stochastic process for the number of VOCs is assumed and post study withdrawal counts will be imputed based on the observed number of events prior to the withdrawal.

The following, but not limited to, missing data analysis will be performed:

- Missing counts in each arm are imputed assuming the expected event rate within that arm. This method corresponds closely to the original model and the results are expected to correspond closely to the primary analysis. This analysis is included to allow for comparison with the partial-DRMI method.
- Multiple imputation based on dropout reason (partial-DRMI); Missing counts will be imputed differently depending on the reason for dropout; meaning that counts for patients in the ticagrelor arm who withdraw consent for a potential treatment related reason are imputed based on the expected event rate in the placebo arm, whereas the remaining patients who have withdrawn consent are imputed assuming missing at random. Potential treatment related reasons include but are not limited to AEs, deaths and development of study specified reasons.

8.5.2 Analysis of the secondary variables

If numbers allow, the following will be analysed using the same analysis method as the primary endpoint: number of painful crises, number of ACSs, duration of painful crises, number of VOCs requiring hospitalisation or emergency department visits, number of days hospitalised for VOC, number of acute SCD complications, number of days hospitalised for acute SCD complications, and number of sickle cell-related red cell transfusions.

Number (%) of patients per type of analgesic use will be summarised. Number (%) of patients per palatability and swallowability category will be summarised. Descriptive statistics will be presented for the intensity of VOC-related pain, proportion of day's absence from school or work due to SCD and HRQL score; no statistical testing will be performed for these endpoints. The descriptive statistics will include n, arithmetic mean, SD, median, minimum and maximum.

8.5.3 Analysis of the exploratory variables

For categorical variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Continuous variables will be summarised using descriptive statistics, including n, arithmetic mean, SD, median, minimum and maximum values. If appropriate, geometric mean and CV will be used instead of arithmetic mean and SD.

A population PK and PK/PD analysis may be performed and include an investigation of the impact of (or lack of) relevant demographic and disease-related covariates. This analysis will be reported separate from the CSR.

8.5.4 Analysis of the safety variables

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Number of patients with events and percentages will be tabulated by preferred term and system organ class. An event that occurred once or more times during the treatment period will contribute 1 observation to the numerator of the proportion. The denominator of the proportion will comprise all patients in the safety set. Adverse events will also be summarised by intensity/severity and separately, by causality/relatedness (as determined by the Investigator). Should a patient report the same preferred term/system organ class within multiple intensity/severity or causality/relatedness categories, the patient's worst occurrence (most severe/most related) will be tabulated. Serious AEs, AEs leading to discontinuation of IP, and commonly occurring AEs will be summarised in a generally similar manner. Adverse events, SAEs, AEs leading to death, and AEs leading to discontinuation of IP will be summarised for each treatment group as applicable.

Laboratory data will be summarised by presenting shift tables from baseline to end of study using normal ranges and by presenting summary statistics of observed and change from baseline values (means, medians, quartiles, ranges). The incidence of clinically notable laboratory abnormalities will be summarised.

Vital sign data will be summarised by presenting summary statistics of observed and change from baseline values. The incidence of clinically notable vital sign abnormalities will be summarised.

For summarising of bleeding event, the number and percent of patients who experience (1) at least 1 bleeding event; (2) at least 1 major bleeding event; (3) at least 1 major or clinically relevant non-major bleeding event; (4) at least 1 minor bleeding event, will be presented by treatment group. The total number of events will also be provided.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational site staff and also train them in any study specific procedures, such as the eDevice for reporting of some VOC-related information, the HRQL assessments and the WBDC system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all staff at the site involved in the study, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each centre should comply with all the terms, conditions and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the

conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2018 and to end by Q4 2020.

The Sponsor will notify the PI(s) when recruitment is complete.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by IQVIA.

Data will be entered into the WBDC (Inform) system at the study site. Trained site staff will be entering the data as specified in the protocol and according to the eCRF instructions. Data entered into the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed, queried and updated as needed.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the MedDRA. Medications will be classified according to the World Health Organisation Drug Dictionary. All coding will be performed by IQVIA.

The PI is responsible for signing the eCRF and this may be delegated to a trained Investigator.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.
A copy of the eCRF will be archived at the study site when the study is completed.

Serious adverse event (SAE) reconciliation

SAE reconciliation reports are produced and reconciled with the AstraZeneca Global safety database.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to the clinical database. External data reconciliation will be done with the clinical database as defined in the Data Management Plan.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee (EC)/Institutional Review Board (IRB) should approve the final Clinical Study Protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the Clinical Study Protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final Clinical Study Protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, EC/IRB and PI with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca or its representatives will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

This study consists of the main caregiver ICF that allows the patient to participate in the study and possibly multiple assent forms based on age group and country-specific requirements. Enrolment code must be obtained from IXRS.

If the patient turns 18 years of age during the study, the patient will sign a new ICF.

The PI(s) at each centre will ensure that:

- Each patient and caregiver is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Each patient and legal caregiver is notified that they are free to discontinue from the study at any time
- Each patient and legal caregiver is given the opportunity to ask questions and allowed time to consider the information provided
- Each patient and legal caregiver provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient and caregiver
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

10.5 Changes to the Clinical Study Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the SC and AstraZeneca or AstraZeneca delegate.

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before

implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca or AstraZeneca delegate will distribute any new versions of the Clinical Study Protocol to each PI. For distribution to EC/IRB see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's ICF, AstraZeneca and the centre's EC/IRB are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority or an EC may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca or AstraZeneca delegate immediately if contacted by a regulatory agency about an inspection at the centre.

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out subject treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between risk groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are, eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, hepatitis A, B, C, D and E viruses, human immunodeficiency viruses types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 - Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AEs) and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) **together with** total bilirubin ≥2 × ULN at any point during the study following the start of IP irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** total bilirubin level ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in total bilirubin level, but there is no specified timeframe within which the elevations in transaminases and total bilirubin level must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- AST ≥3 × ULN

- Total bilirubin level ≥2 × ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central or local laboratory
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section 2 Definitions within this appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF.

Follow-up

Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which tests available in the HL lab kit should be used.
- Complete the 3 Liver CRF Modules as information becomes available

If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and total bilirubin level elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the CRF accordingly and follow the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin level elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca Standard processes.

The 'Medically Important' serious criterion should be used if no other serious criteria apply.

As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

References

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D Interview Guide for VOC-triggered Telephone Calls

Instructions:

- *Establish* telephone contact with parent/caregiver when a potential VOC event is reported in the eDevice.
- *Check* the StudyWorks data reported from the eDevice either before or during the call.
- *Document* the call that is triggered by a potential VOC event in patient's medical records.
- *Note* the event details and whether or not event is considered to be fulfilling criteria for VOC endpoint or not.
- *Also note* any other AEs that come up during the conversation.
- *Also note* any change of medications that come up during the conversation.

When calling the parent/caregiver, the Investigator should introduce him/herself in an appropriate way and make sure he/she is speaking to the appropriate person.

> *In general, the parent/caregiver will be the appropriate person. The Investigator may decide to speak directly with a patient in late teenage age period, if judged more appropriate based on Investigator's thorough knowledge about the patient.*

Cover the discussion items below during the normal doctor-parent/caregiver conversation in the phone call. Depending on the situation and the responses, additional questions may be needed for the Investigator to complete the required information in the eCRF.

Discussion item	Specific question (as applicable)
1. Collection of any VOC endpoints **Purpose:** To ensure any VOC events not yet reported to Investigator are captured. Questions should be tailored to ensure all the relevant data are collected for events meeting criteria for a VOC endpoint (painful crisis or ACS) so the eCRF can be completed*, examples: • Judge if event meets VOC definitions for this study • Start/stop • Treatment setting • Pain localisation • Type of analgesics taken (opioid/non-opioid) • Any other treatments given *Note that depending on where the event was treated, copies of medical records from other clinic or hospital may be needed.	"Has <<patient name>> experienced any painful episodes or had any episodes with chest problems, fever, and often also breathing symptoms, since the last time we talked?"
2. AE collection **Purpose:** To collect any AEs other than the VOC event with onset since last contact and check status of ongoing AEs. Use follow-up questions as needed to cover start/stop, outcome, any treatments provided, seriousness, severity, relationship to study drug or study procedures, and any changes to study drug treatment as outlined in the corresponding eCRF modules.	"Has<<patient name>> had any new health issues since the last time we talked?" *If this patient has any ongoing AEs recorded in the eCRF, ask about the status of those events*: "What about the <<ongoing event (e.g. cold, ankle sprain, etc.) we talked about last time? What happened with that?"

Discussion item	Specific question (as applicable)
Update information as needed on any ongoing AEs in the eCRF.	
3. Concomitant medications **Purpose:** To ensure concomitant medications are correctly captured. Any changes to concomitant medications, both regularly taken and per needed, are to be further explored to ensure updated information is recorded in the eCRF. Depending on what information on medications that came out from Discussion item 1 on the VOC event, any changes to medications may need to be further explored.	"Please can you tell me about all the medications that <<patient name>> has taken since the last time we talked?" *Then continue to prompt with* "Anything else?" *until you have everything*
4. eDevice functionality and usage **Purpose:** To ensure eDevice is working OK and identify any need for re-training.	"Have you and <<patient name>> experienced any issues with using the eDevice?" *If any expected data in StudyWorks is missing:*

Discussion item	Specific question (as applicable)
Any issues reported for the eDevice should be identified, further explored and resolved. Remind parent/caregiver of the self-training availability in the eDevice. Extra visits to site should be offered for hands-on re-training as needed.	"Is there anything more relating to << pain intensity / absence from school/work>> that you haven't included?" "Is there anything else you haven't included? "Please can you tell me, if there is something we can do to help the eDevice recordings work better for you?"
5. Adherence to visit schedules and study procedures **Purpose:** To reinforce adherence to study visits and procedures. Provide reminder for the date and time for next visit to site or telephone visit. Remind to not administer study drug at home in the morning of visits with PK/PD sampling. Remind to bring all study drug bottles (including empty ones) to study visits.	

Appendix E Guide for Scheduled Telephone Visits

Instructions:

- *Schedule* Telephone Visits monthly between On-site Visits.
- *Have the appropriate information* on the patient before the call. Check the StudyWorks entries made by the parent/caregiver/patient from their eDevice before the call.

Similar to On-site Visits, document the Telephone Visits in patient's medical records. Notes are to include:

- Any adverse events,
- Whether the event fulfils criteria for VOC endpoint or not,
- Any changes of medications,
- And any use of contraceptives (applicable to females of childbearing potential and
- Consider if appropriate to discuss in telephone visits*).*

When calling the parent/caregiver, the Investigator should introduce him/herself in an appropriate way and make sure he/she is speaking to the appropriate person.

> *In general, the parent/caregiver will be the appropriate person. The Investigator may decide to speak directly with a patient in late teenage period, if judged more appropriate based on Investigator's thorough knowledge about the patient.*

Cover the discussion items below during the normal doctor-parent/caregiver conversation in the phone call. Depending on the situation and the responses, additional questions may be needed for the Investigator to complete the required information in the eCRF.

Discussion item	Specific question (as applicable)
6. AE collection **Purpose:** To ensure AEs are captured during study.	"Has <<patient name>> had any new health issues since the last time we talked?" *If this patient has any ongoing AEs recorded in the eCRF, ask about the status of those events*:

Discussion item	Specific question (as applicable)
Collect any AEs with onset since last contact, and check status of ongoing AEs. As outlined in the corresponding eCRF modules, use follow-up questions as needed to cover: • Start/stop, • Outcome, • Any treatments provided, • Seriousness, • Severity, • Relationship to study drug or study procedures, • And any changes to study drug treatment	"What about the <<ongoing event (eg, cold, ankle sprain, etc.) >> we talked about last time? What happened with that?"
7. Collection of any VOC endpoints **Purpose:** To ensure any VOC events not yet reported to Investigator are captured. Questions should be tailored to ensure all the relevant data are collected for events meeting criteria for a VOC endpoint (painful crisis or ACS) so the eCRF can be completed*, examples: • Judge if event meets VOC definitions for this study • Start/stop • Treatment setting • Pain localisation • Type of analgesics taken (opioid/non-opioid) • Any other treatments given	*Unless already sorted out during the AE Discussion Item above, ask specifically about VOC events:* "Has <<patient name>> experienced any painful episodes or had any episodes with chest problems, fever, and often also breathing symptoms, since the last time we talked?"

Discussion item	Specific question (as applicable)
*Note that depending on where the event was treated, copies of medical records from other clinic or hospital may be needed.	
8. eDevice functionality and usage **Purpose:** To ensure that the eDevice is working OK and identify any need for re-training. Questions should be tailored based on entries made in StudyWorks, eg, if perfect compliance to weekly assessments of school/work absence but no VOC events, question could focus on ensuring no potential VOC events have been missed. Potential problems with using the eDevice should be further explored and resolved. Remind parent/caregiver of the self-training availability in the eDevice. Offer extra visits to site for hands-on re-training as needed.	"Have you and <<patient name>> experienced any issues with using the eDevice?" *If any expected data in StudyWorks is missing:* "I can see that you have not recorded much about <<pain intensity / absence from school/work>> in your eDevice." "Is there anything more relating to << pain intensity / absence from school/work>> that you haven't included?" "Is there anything else you haven't included?" "Please can you tell me if there is something we can do to help the eDevice recordings work better for you?"

Discussion item	Specific question (as applicable)
9. Some VOC event details need to be recorded in the eDevice **Purpose:** To ensure the VOC details to be reported by the parent/caregiver/patient for any VOC events are captured in the eDevice. Provide reminder to record any painful crises and ACS events, and to do a daily VOC pain rating while the event is ongoing, regardless of where such events are treated. Also provide reminder to bring the eDevice with them in case they seek medical care.	
10. Parents/caregivers to contact the study site in case a suspected VOC **Purpose:** To ensure a timely collection of event-related information to have high-quality VOC endpoint data. Provide reminder to call site within 72 hours in the event of any painful crises and/or ACS. Also check that parent/caregiver knows contact details to the site.	

Discussion item	Specific question (as applicable)
11. Concomitant medications **Purpose:** To ensure concomitant medications are captured during study. Any change to concomitant medications is to be further explored to ensure updated information is recorded in the eCRF.	"Please can you tell me about all the medications that <<patient name>> has taken since the last time we talked?" *Then continue to prompt with* "Anything else?" *until you have everything.*
12. Use of contraceptive methods (when applicable) **Purpose:** To reduce risk for pregnancies during study in fertile female participants. Remind parent/caregiver/patients that female, fertile participants should not get pregnant during study. An individually appropriate contraceptive method should be discussed (See study protocol section 3.8) and the importance of use re-enforced. *Consider if appropriate to discuss contraceptives in Telephone Visits or only at On-site Visits.*	"You know that young girls should not get pregnant while in this study. Is there a need for <<patient name>> to use any contraceptive method to not get pregnant? What is she using?"
13. Adherence to visit schedules and study procedures **Purpose:** To reinforce adherence to study visits and procedures. Remind patient about the date and time for next visit to site or telephone visit.	

Discussion item	Specific question (as applicable)
Remind to not administer study drug at home in the morning of visits with PK/PD sampling. Remind to bring all study drug bottles (including empty ones) to study visits.	

Appendix F Palatability and Swallowability Assessment

Study Medication Palatability Assessment for patients 5 years of age or older

Facial Hedonic Scale (FHS)

Instructions to Study Staff

Immediately after administration of investigational product (IP) on Visit 2 and Visit 9, capture the patients' assessment of the taste of the medication. Use this question for all patients taking the study drug who are 5 years of age or older.

Read to patient:

I have a question about the medication you have just taken. I would like you to tell me how you feel about the taste of the medicine you have just swallowed. You can give your answer by making a mark ("X") on the box below the faces to show how much you like or dislike the taste of the medicine. You can choose from 'Dislike very much' to Like very much' [**If child cannot read, point at 1 face at a time and read the descriptive text below**].

☐	☐	☐	☐	☐
Dislike very much	Dislike a little	Not sure	Like a little	Like very much

Patient ID:_____

Assessment Date: _____

Assessment Time:_____

Initials of person administering the assessment: _____

Study Medication Palatability Assessment

Observer Assessment for Patients 2 - 4 Years of Age

Instructions to Study Staff

Immediately after administration of Brilinta at Visit 2 and Visit 9, capture the patient's reaction of the taste of the medication. Use this case report form (CRF) for all patients taking the study drug who are 2 to 4 years of age.

1. Choose the response that best matches a description of what you observe of the patient's willingness to swallow the study drug.

Willingness to swallow

- ☐ Swallowed without problem
- ☐ Some resistance but did swallow
- ☐ Spit out some / all of medication
- ☐ Vomited up medication

2. Was any behaviour observed when the study medication was given to this patient that would be indicative of a negative response to the palatability of the study medication?

☐ NO ☐ YES

If answered YES, please answer the following questions:

2a. Did the patient turn his/her head to reject intake of the medication?

☐ NO ☐ YES

2b. Did the patient twist his/her face or mouth in an expression of displeasure?

☐ NO ☐ YES

2c. Did the patient display any other negative behaviour?

☐ NO ☐ YES

If YES, please describe: _____

Patient ID:_____

Assessment Date: _____

Assessment Time:_____

Initials of person administering the assessment: _____

Appendix G Drug Interactions

1. Platelet aggregation inhibitors: NOT ALLOWED

- Other adenosine diphosphate (ADP) receptor blockers - cangrelor, clopidogrel, prasugrel, ticlopidine
- Dipyridamole
- Cilostazol
- Aspirin.

2. Anticoagulants: NOT ALLOWED

- Coumarins - warfarin
- Heparins (except for flushing venous catheters prior to sampling)
- Factor Xa inhibitors - fondaparinux, apixaban, rivaroxaban, edoxaban
- Thrombin inhibitors - bivalirudin, dabigatran, argatroban, desirudin, lepirudin.

3. Non-steroidal anti-inflammatory agents: NOT ALLOWED if chronically used, requiring treatment >3 days/week.

- Propionic acid derivates - ibuprofen, dexibuprofen, naproxen, ketoprofen
- Acetic acid derivates - indomethacin, ketorolac, tolmetin, sulindac, diclofenac
- Enolic acid derivates - piroxicam, meloxicam, tenoxicam
- Selective COX-2 inhibitors - celecoxib, parecoxib, etoricoxib
- Others - clonixin.

4. CYP3A inhibitors: NOT ALLOWED as they substantially increase ticagrelor exposure.

- Strong inhibitors - boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole
- Intake of grapefruit juice.

5. CYP3A substrates or inducers: NOT ALLOWED as they reduce ticagrelor exposure and may result in reduced efficacy.

- Rifampin/rifampicin
- Rifabutin
- Rifapentine
- Phenytoin
- Carbamazepine
- Phenobarbital
- Avasimibe
- St. John’s wort
- Simvastatin/lovastatin (metabolised by CYP3A- increases their concentration - avoid doses greater than 40 mg)

6. P-glycoprotein interactions

- Digoxin - If the patient is receiving digoxin, levels should be monitored closely following initiation of investigational product (IP) and with any change in IP.
- Cyclosporine - NOT ALLOWED as it increases ticagrelor exposure.

Appendix H Pain Assessment

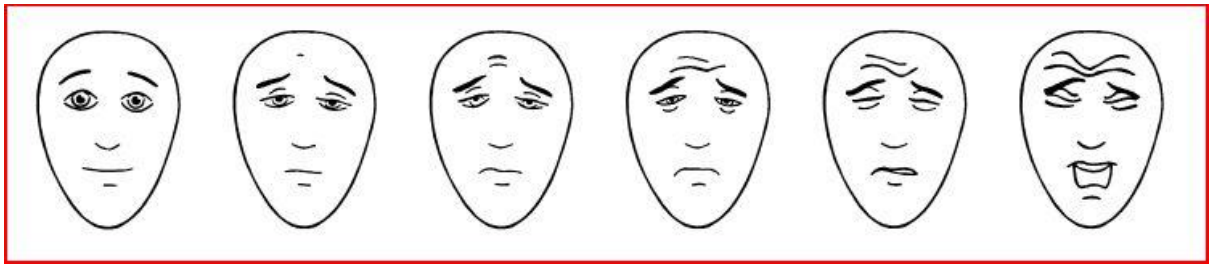
Faces Pain Scale - Revised (FPS-R)

For patients aged ≥5 years

NB - this will be administered via an electronic device

Instructions

These faces show how much something can hurt. The face to the left shows no pain. The faces show more and more pain up to the right face - it shows very much pain. Please choose the face that shows the worst pain you had.



0 2 4 6 8 10

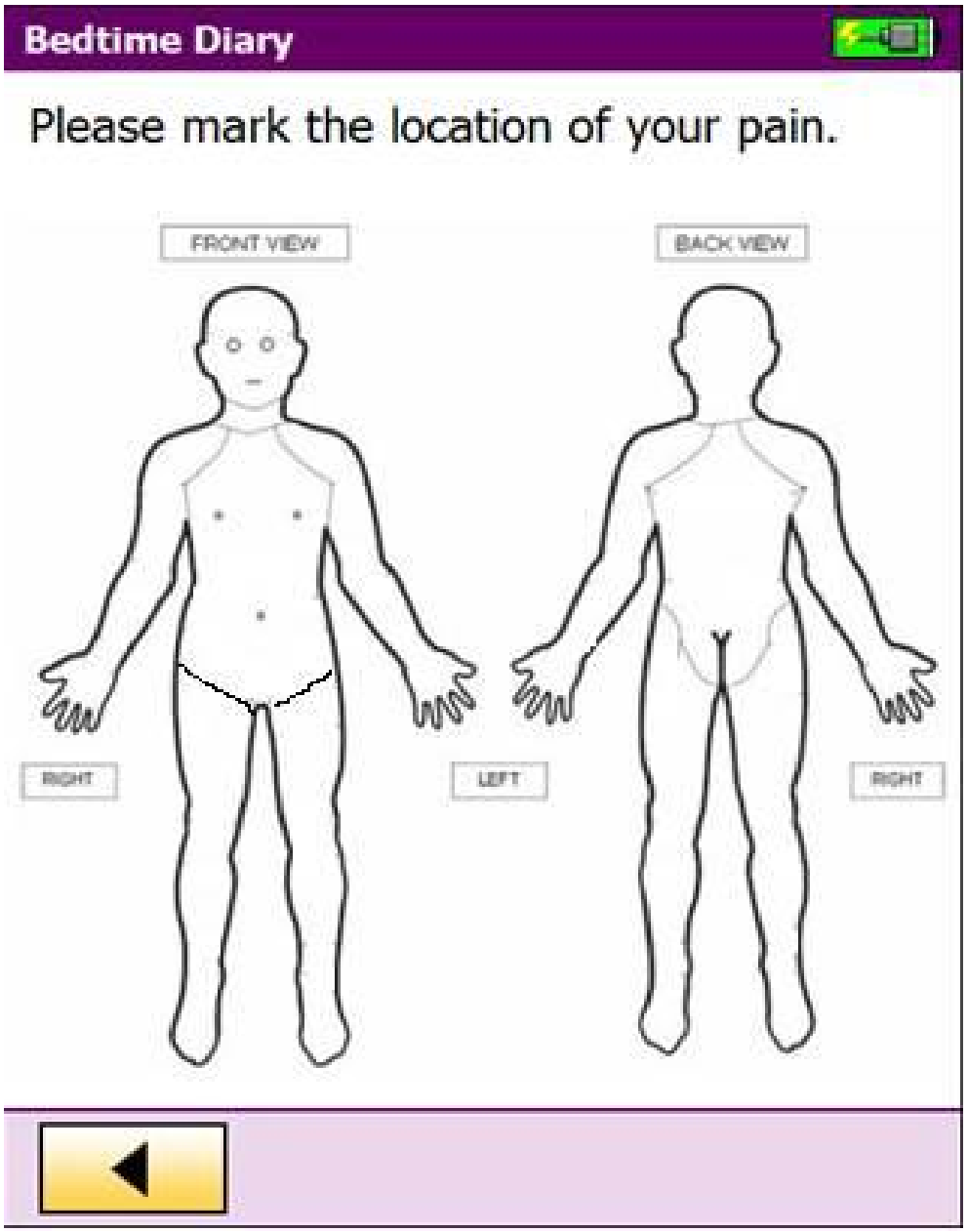
Patient ID:_____

Assessment Date: _____

Assessment Time:_____

Initials of person administering the assessment: _____

Marking of localisation of pain



The Face, Legs, Activity, Cry, Consolability (FLACC)

For patients ages 2-4 years

NB - this will be administered via an electronic device

Patient ID/E-code : _____ Assessment Date : _____

Please describe how your child behaved because of the pain.

FACE	No particular expression or smile ☐ 0	Occasional grimace or frown, withdrawn, disinterested ☐ 1	Frequent to constant frown, clenched jaw, quivering chin ☐ 2
LEGS	Normal position or relaxed ☐ 0	Uneasy, restless, tense ☐ 1	Kicking, or legs drawn up ☐ 2
ACTIVITY	Lying quietly, normal position, moves easily ☐ 0	Squirming, shifting back and forth, tense ☐ 1	Arched, rigid, or jerking ☐ 2
CRY	No cry (awake or asleep) ☐ 0	Moans or whimpers, occasional complaint ☐ 1	Crying steadily, screams or sobs, frequent complaints ☐ 2
CONSOLABILITY	Content, relaxed ☐ 0	Reassured by occasional touching, hugging, or being talked to, distractable ☐ 1	Difficult to console or comfort ☐ 2

References:

English for USA

Merkel, S., Voepel-Lewis, T., Shayevitz, J., & Malviya, S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatric Nursing 1997 23(3),293-297.

Appendix I HRQL Assessment

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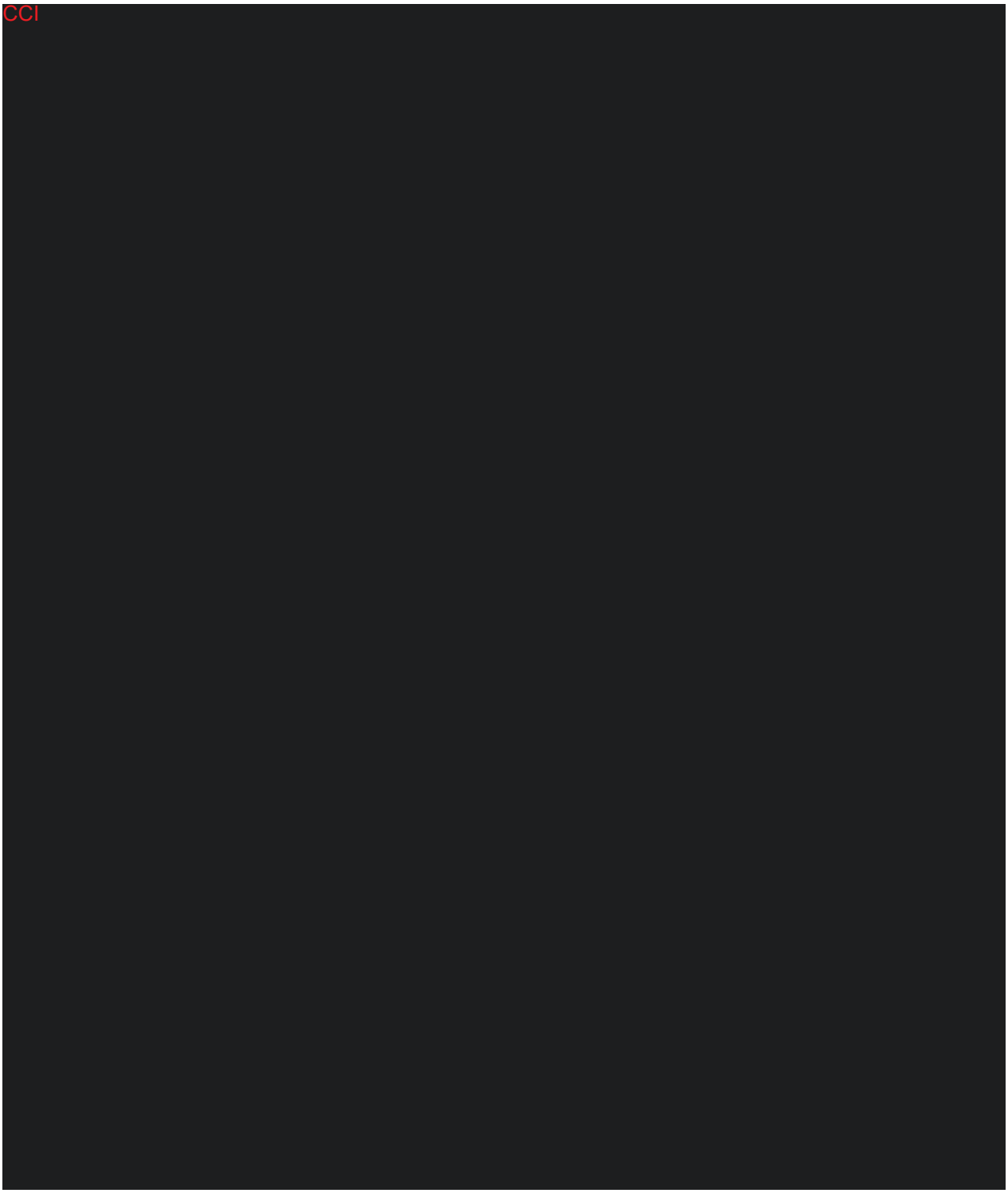

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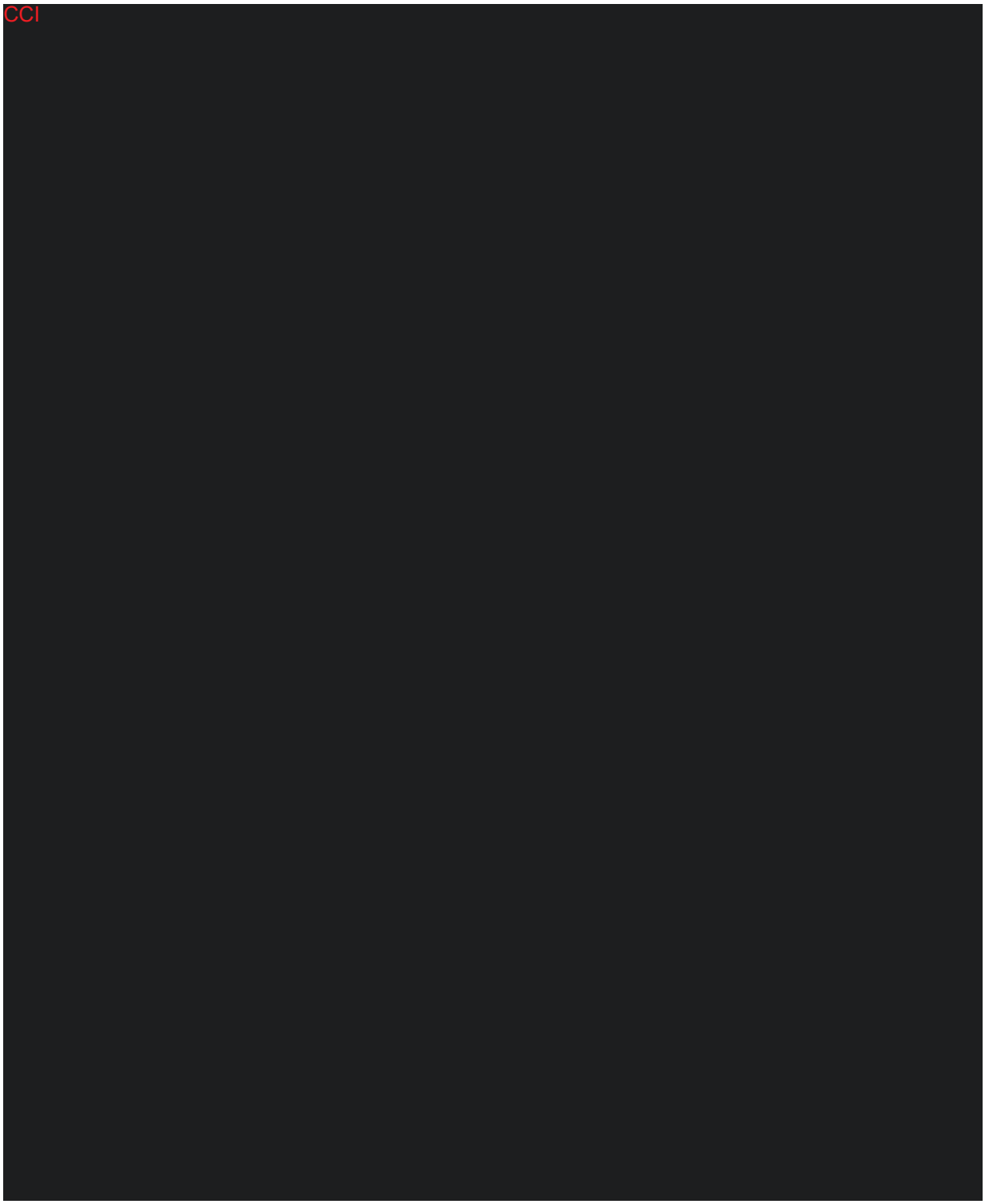

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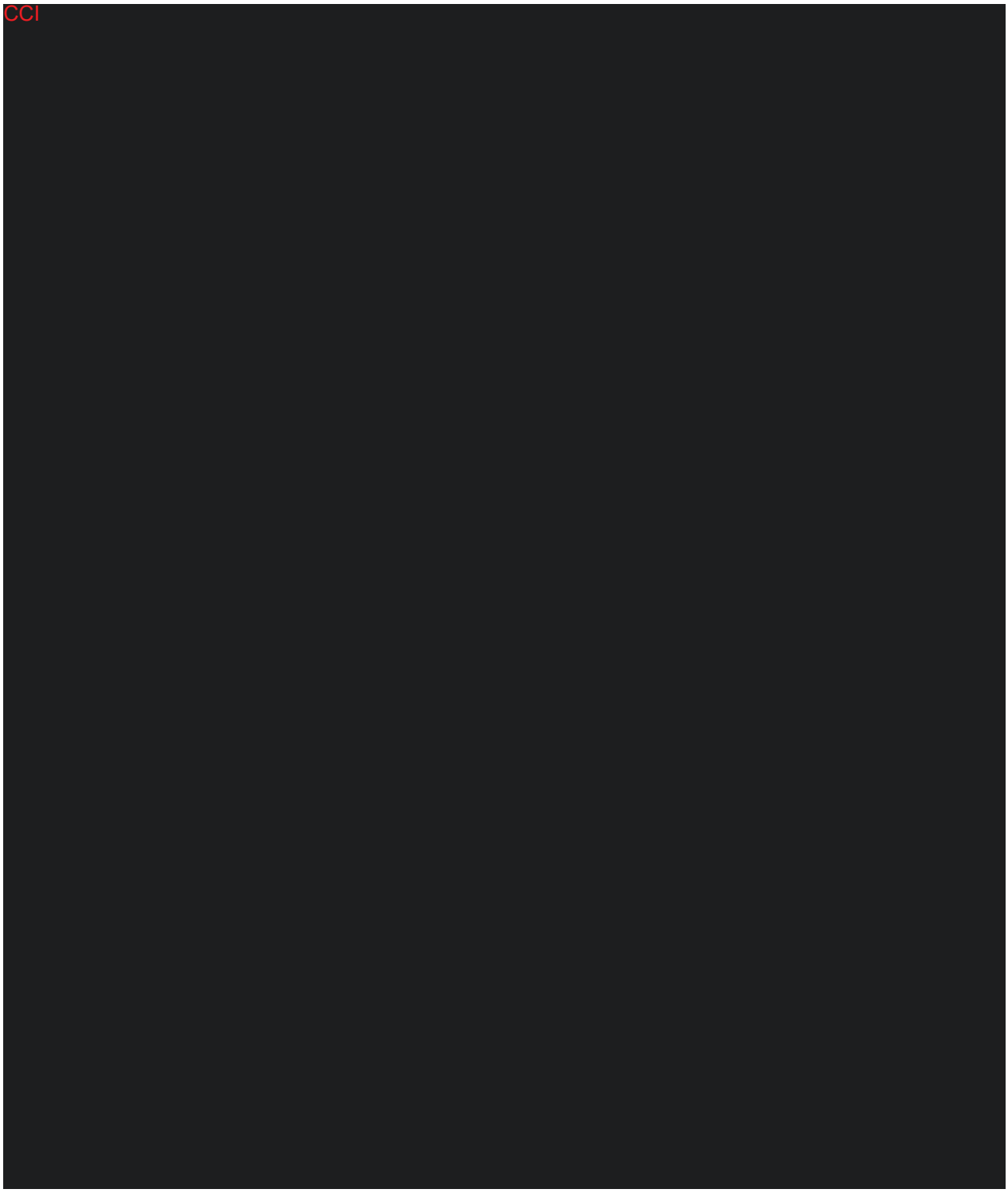

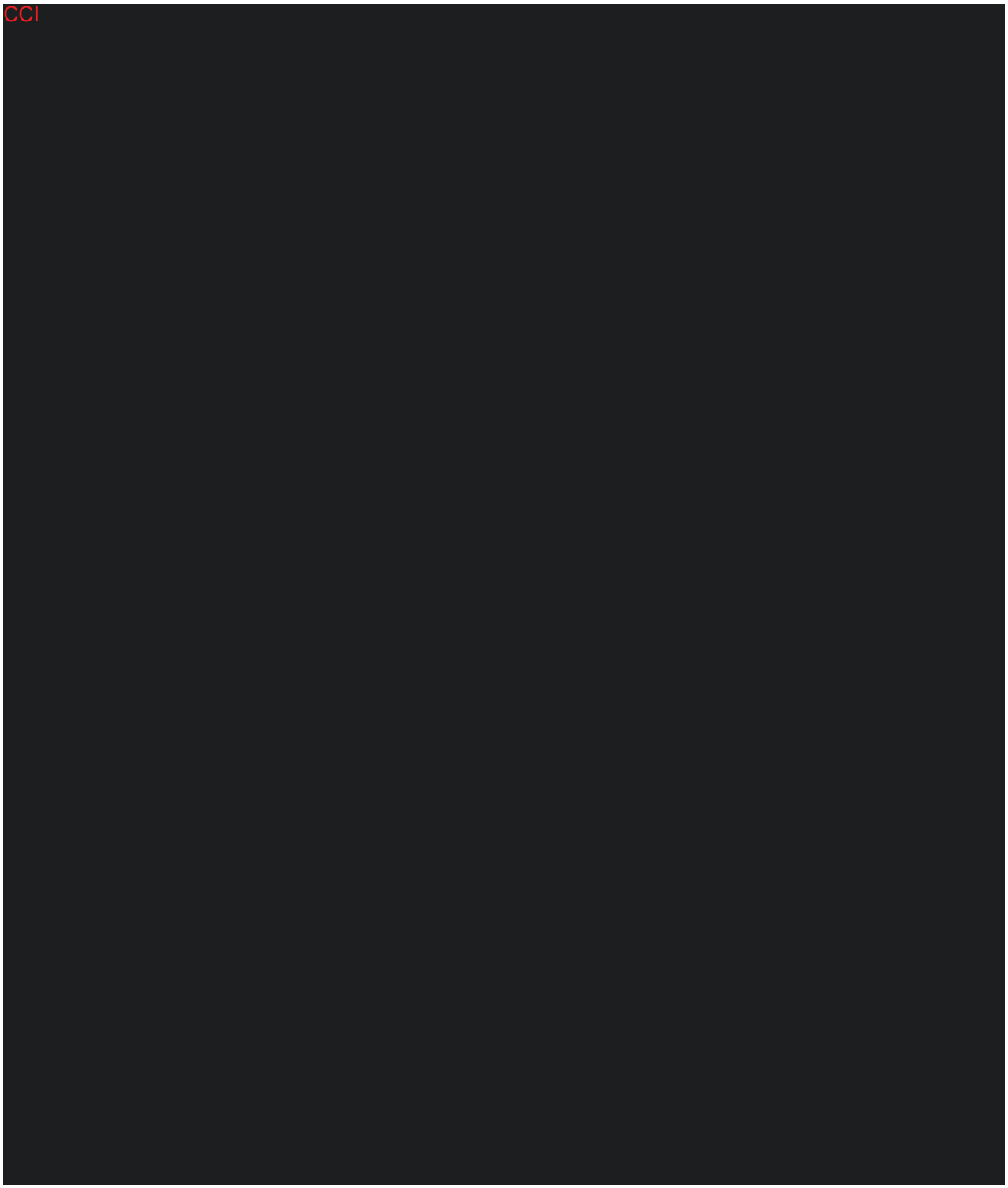
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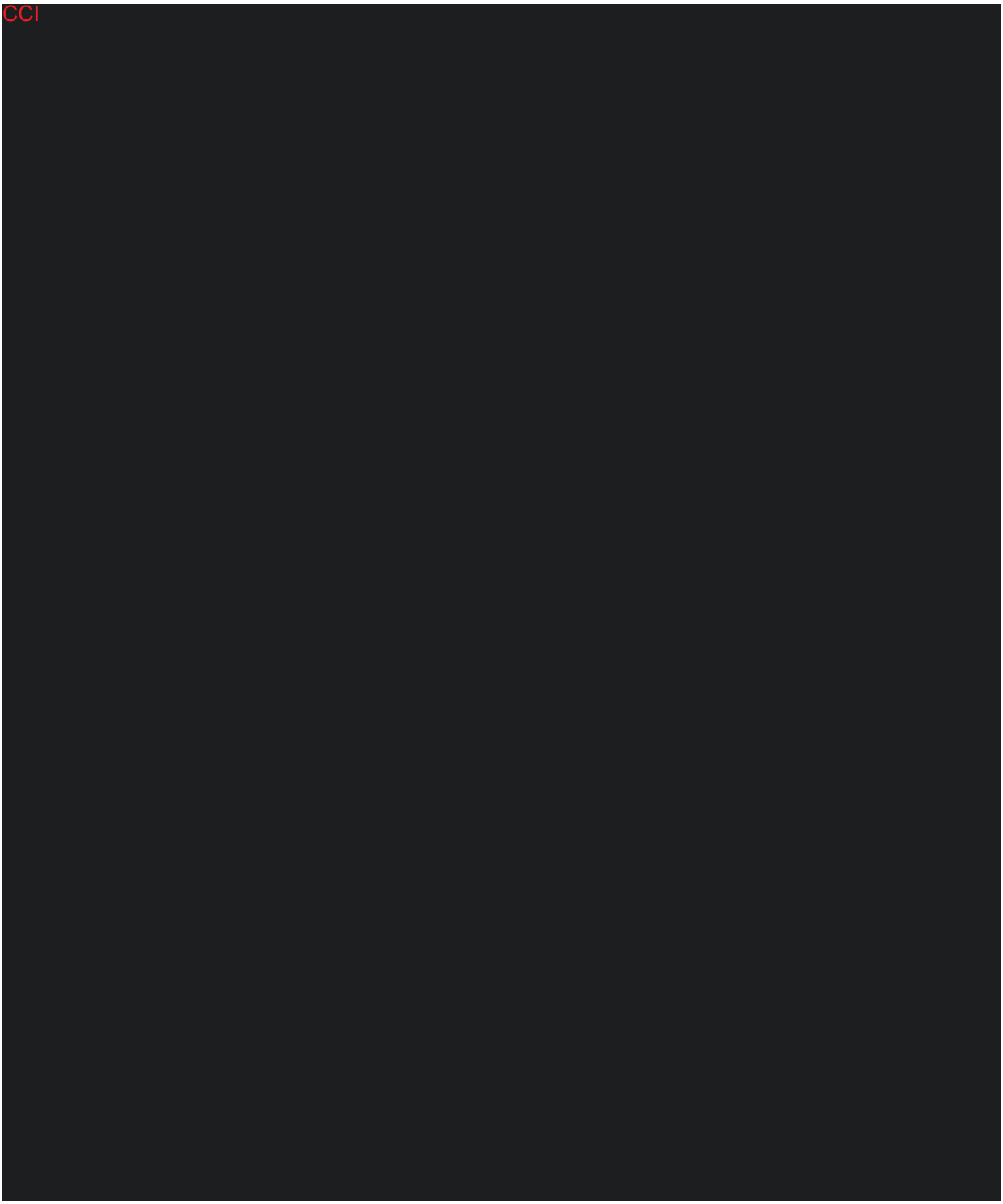

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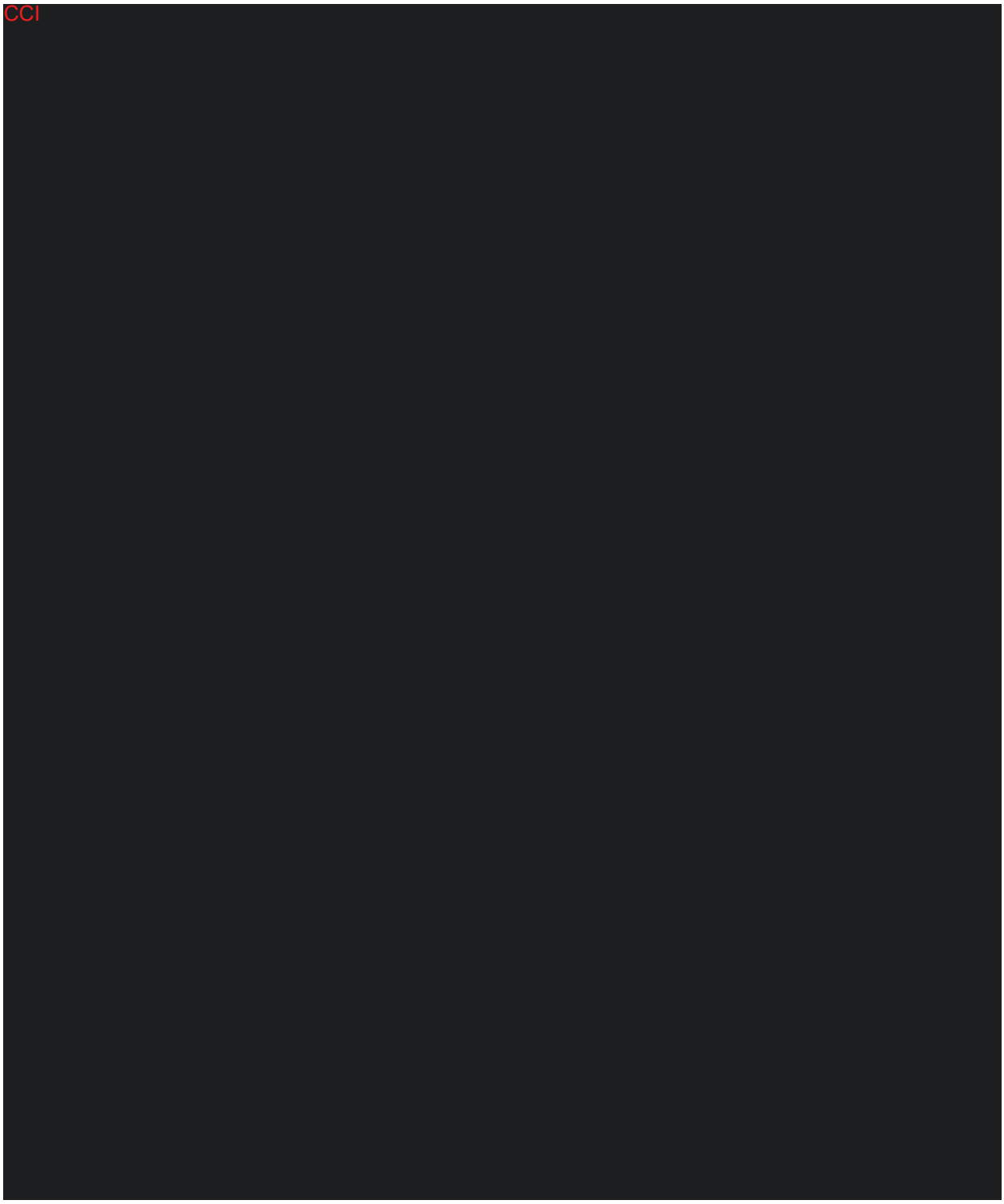

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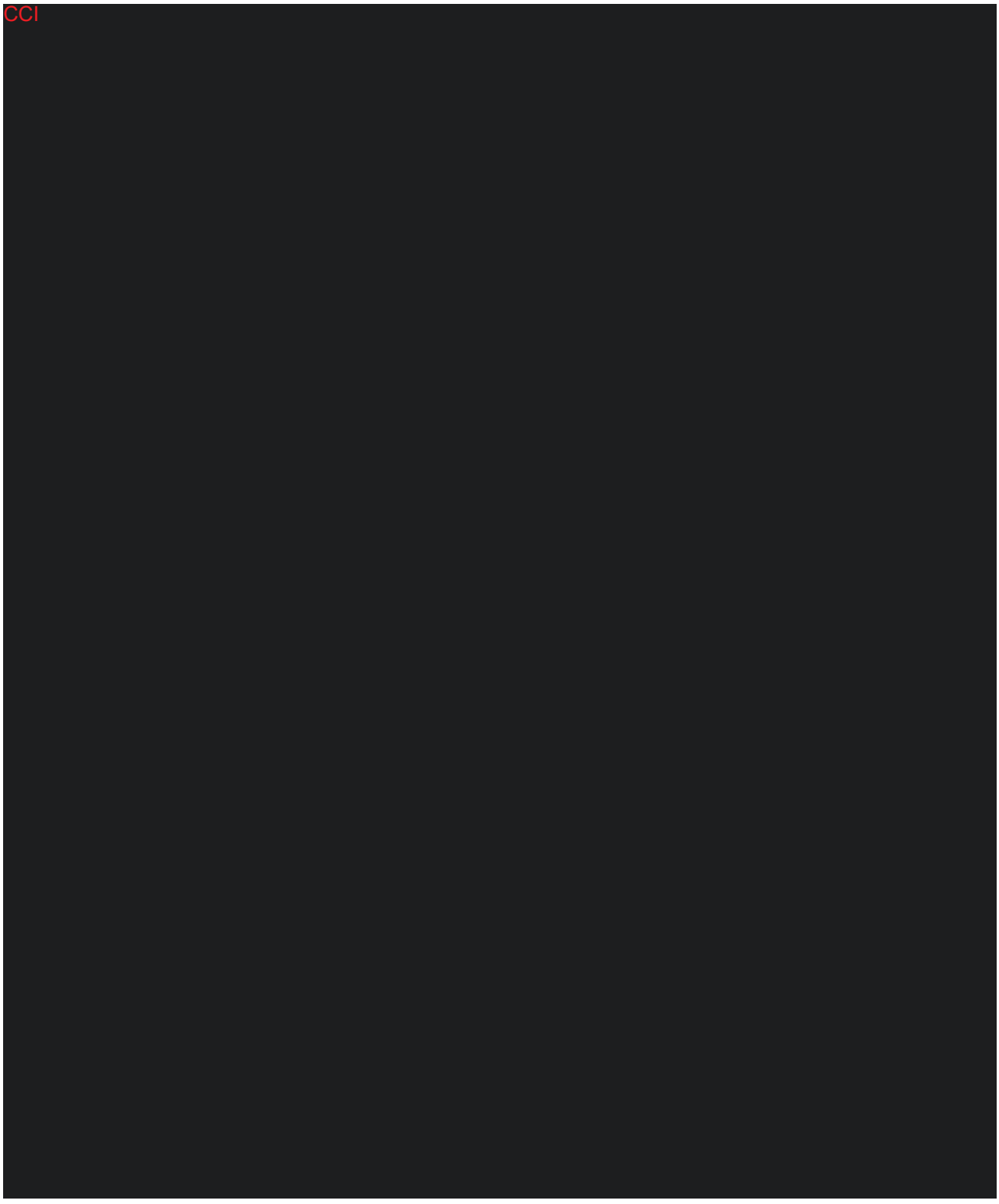

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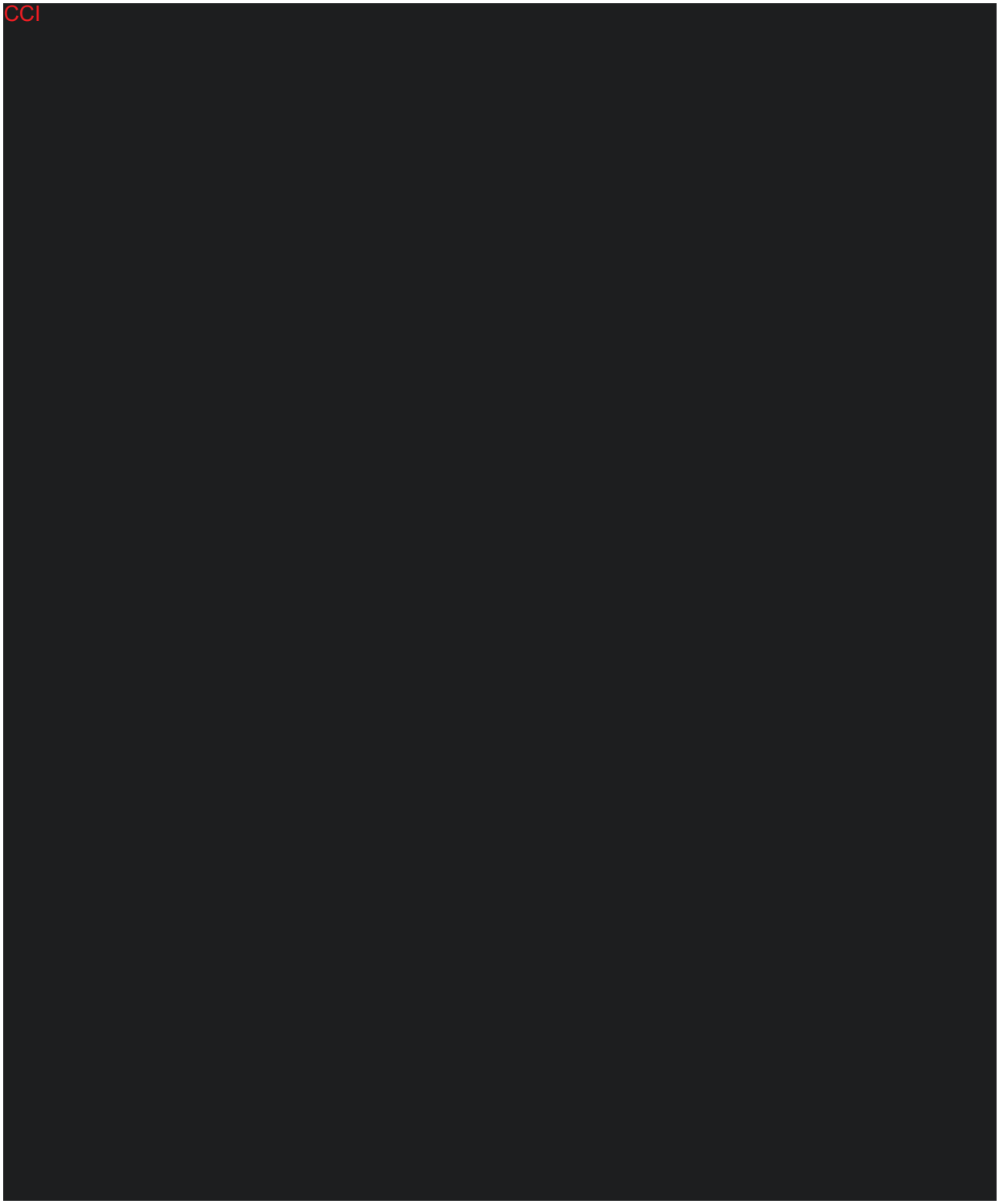

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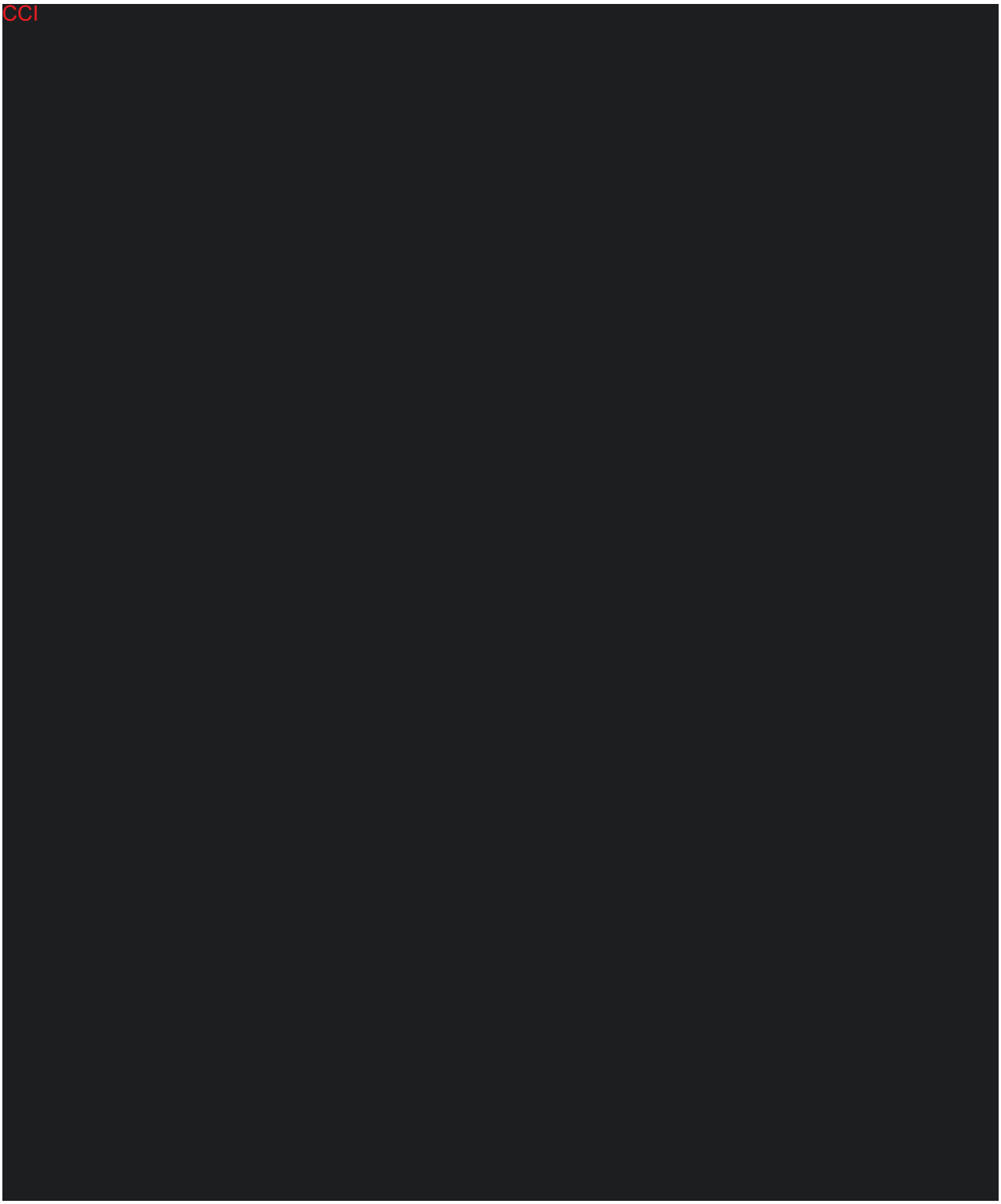

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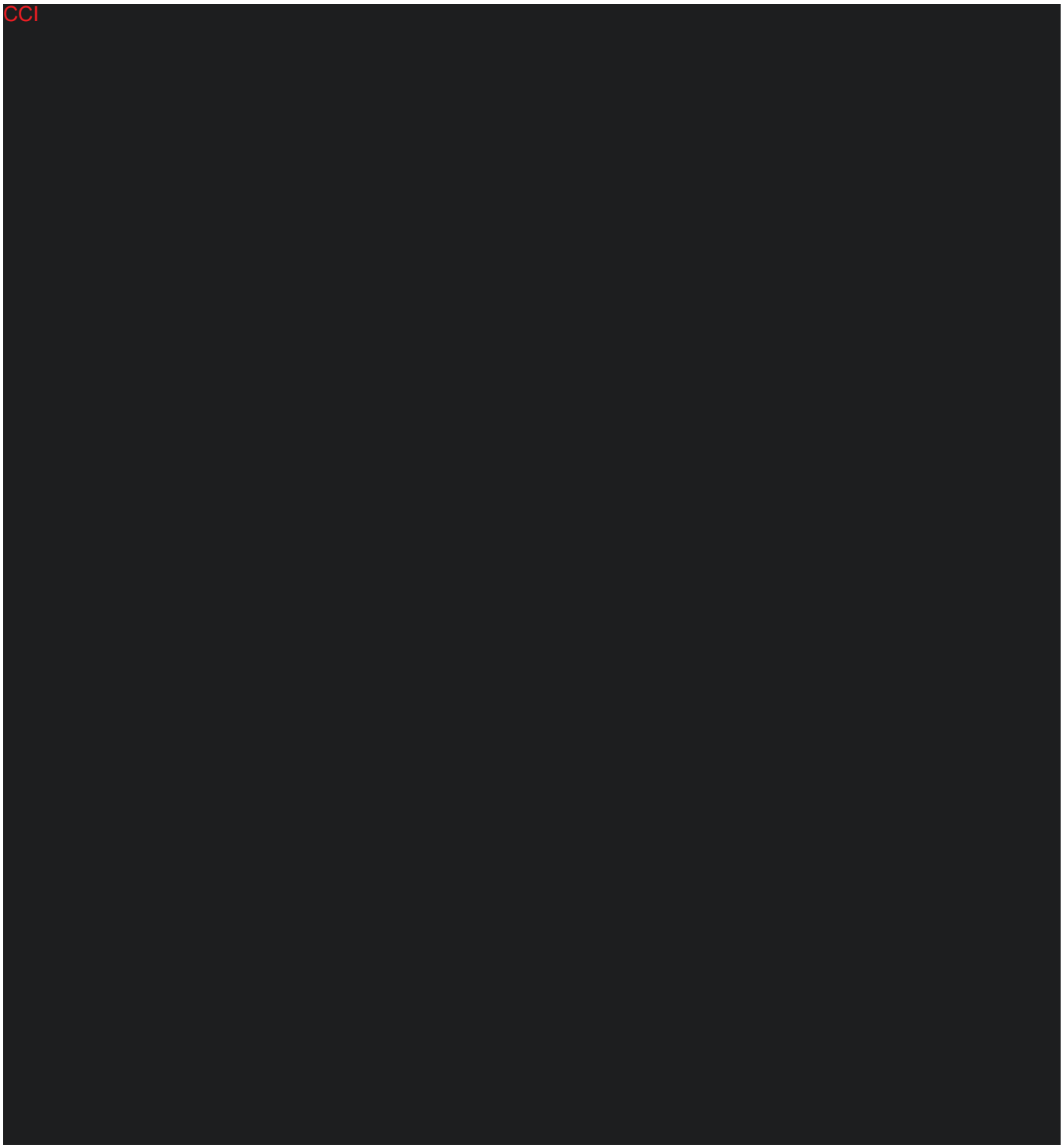

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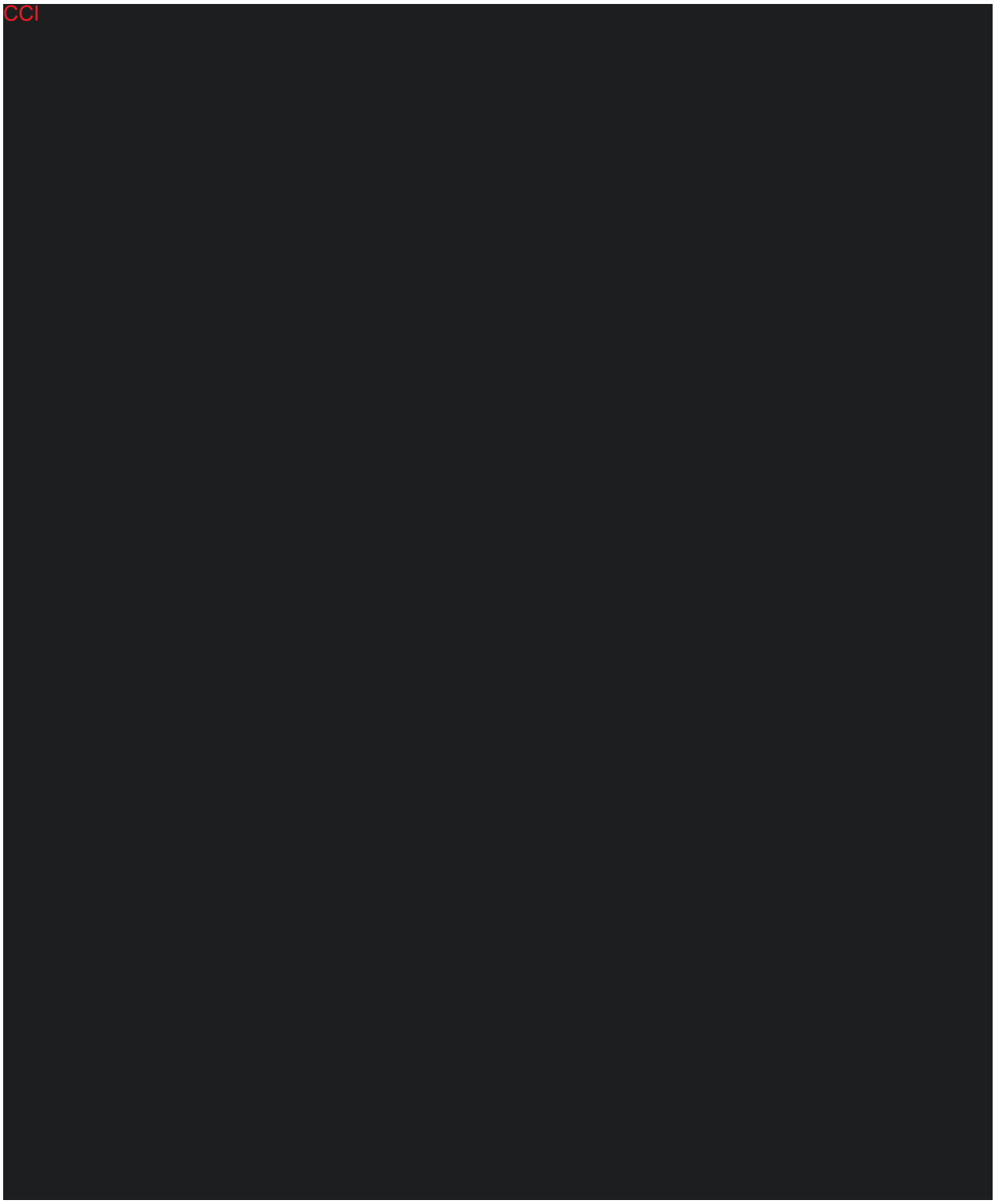

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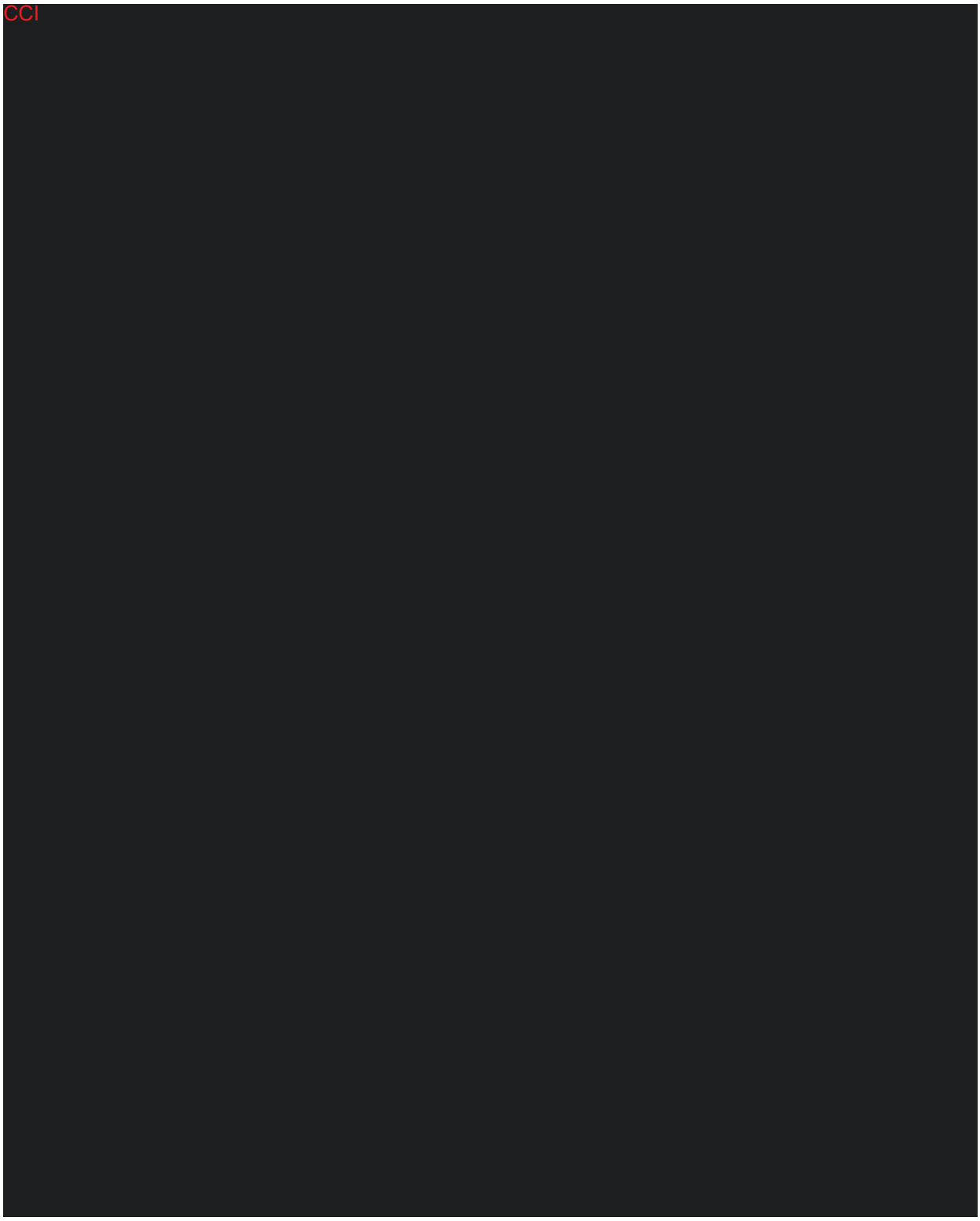

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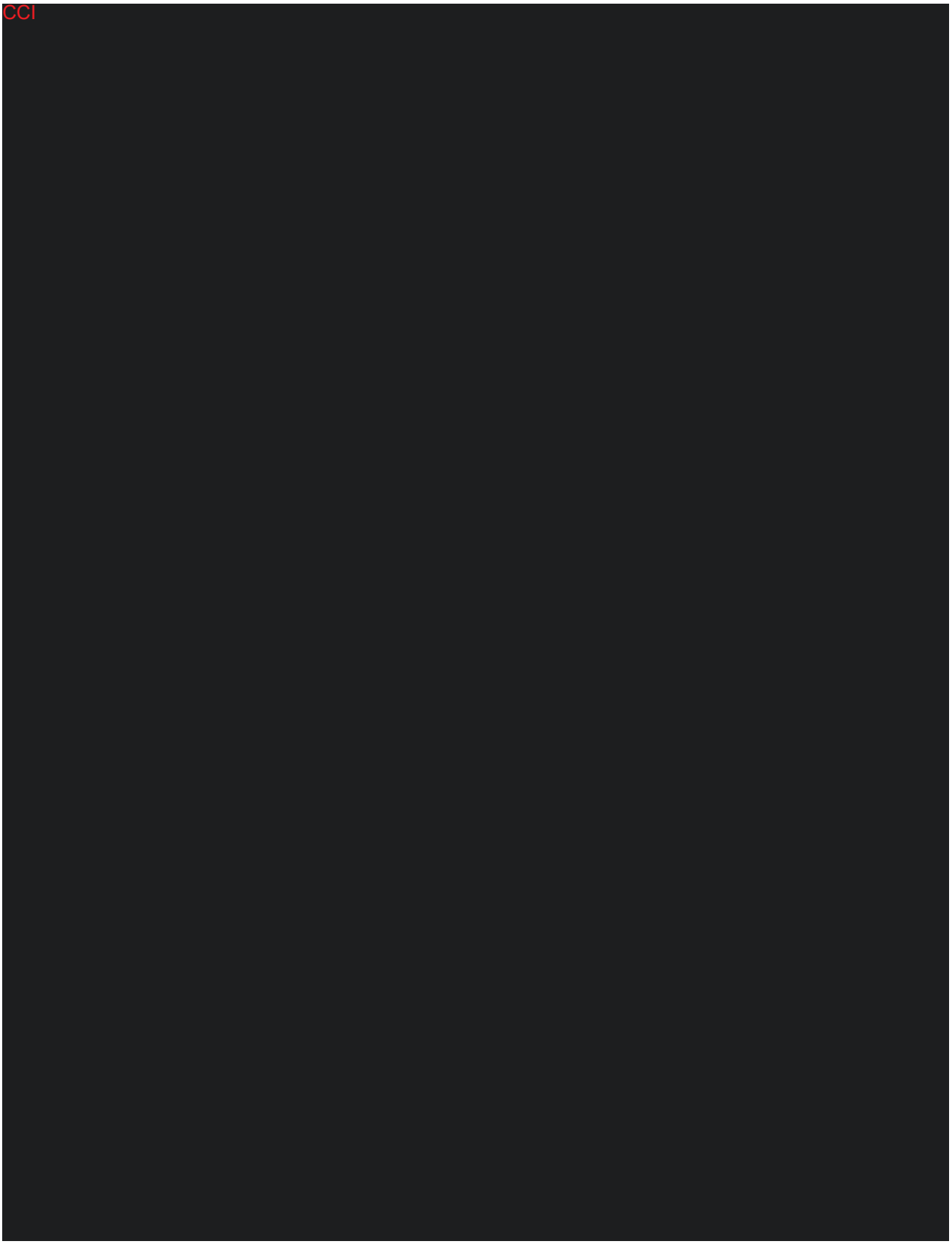

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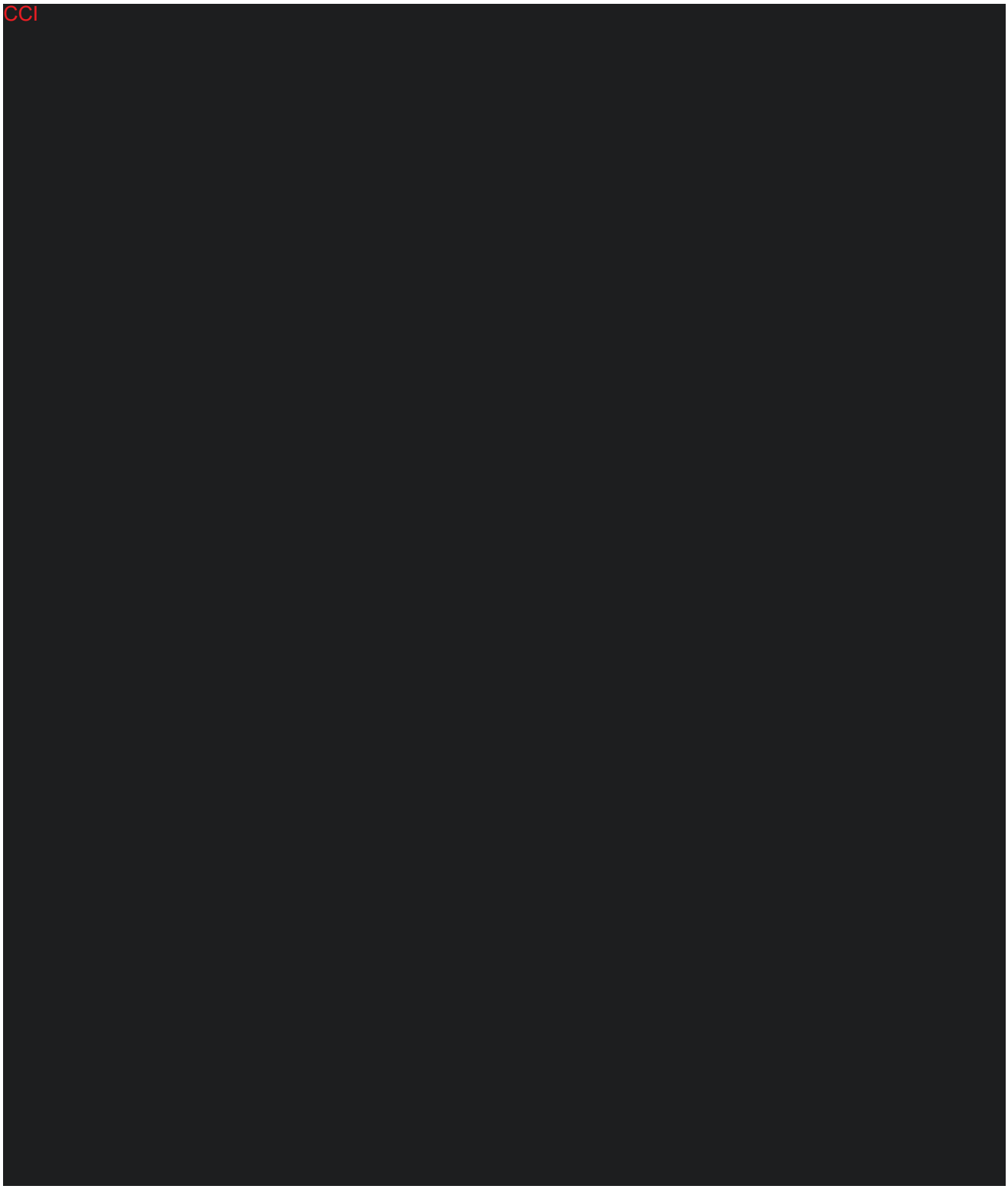


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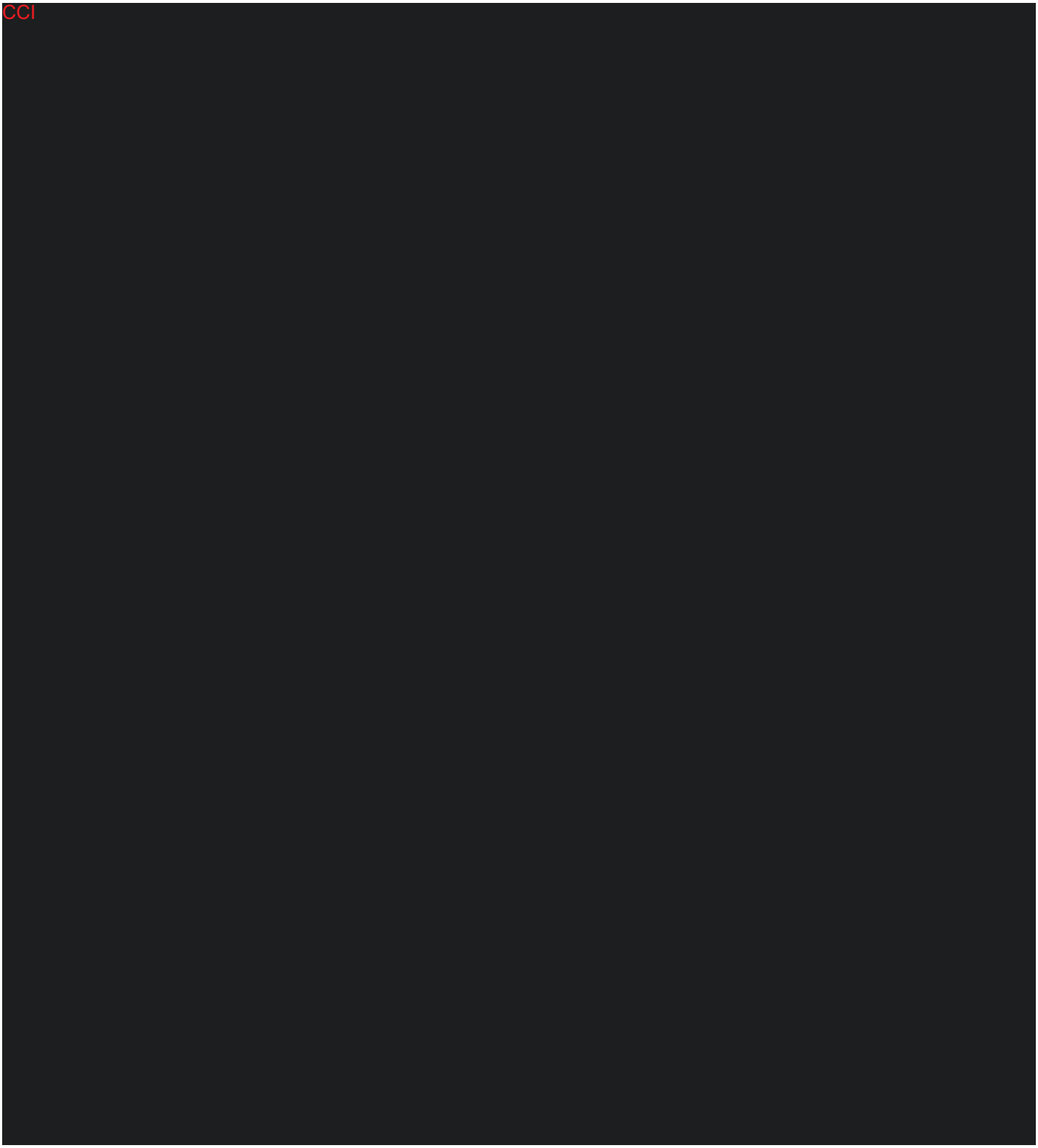

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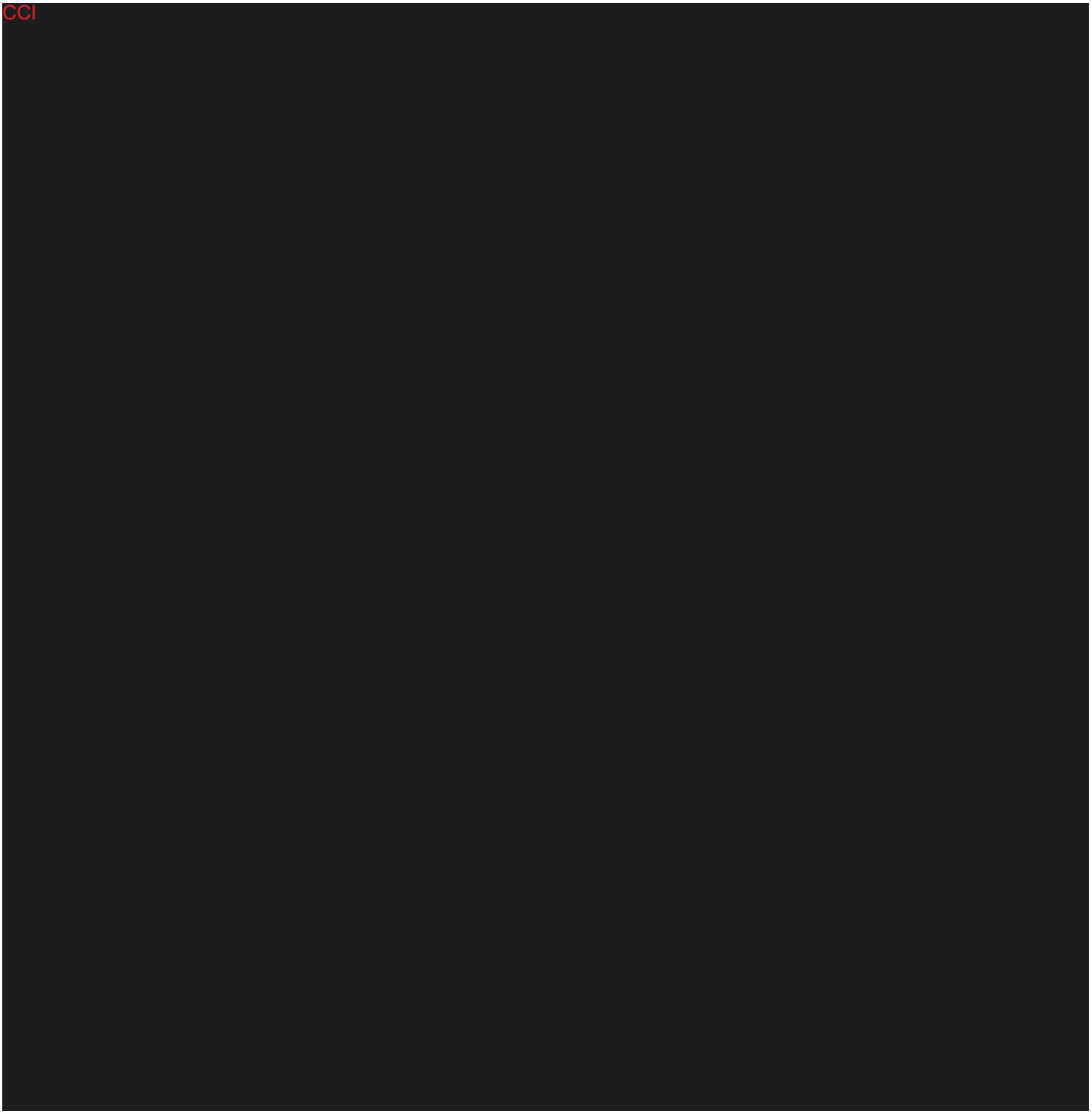

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