Title: Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain

NCT Number: NCT02899884

Protocol Approve Date: 19 Feb 2016

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-Interventional Study Protocol

Short title: Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain

Title: Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain

Study ID: CARPE-DIO

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Study phase: Medical Affairs, Non-registration Company Sponsored (Observational)

Date of final version of protocol: 19 Feb 2016

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1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	Spain Contact
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

Summary

Short Title of Study

Characterisation and Epidemiology of Breakthrough Cancer Pain in Spain

Study sites

66 planned sites from Spain

Objectives

To determine the prevalence of breakthrough cancer pain in an unselected, representative cohort of oncology outpatients with pain that is controlled with opioids.

Methodology

Non Interventional, non post-authorization, cross-sectional, epidemiological study

Number of subjects

We estimate that more than 10 patients per day attend consultations for cancer in Medical Oncology, Radiotherapeutic Oncology, Hematology and Palliative Care Departments and around 5 patients in Pain Units. Breakthrough cancer Pain (BCP) is a common and incapacitating subtype of pain that affects a percentage of patients with cancer that varies between 40% and 90% according to different publications. Conservatively, we hope to detect the prevalence in 50% of patients, and we estimate that at each site a total of approximately 200 patients, or around 13,200 across the 66 planned sites, will be interviewed on the prevalence of breakthrough cancer pain. This sample will enable us to detect the prevalence of breakthrough pain with a 95% confidence interval and precision of ±1%.

For the assessment of the secondary objective, i.e., characterising the breakthrough pain based on aetiology, underlying pathology and other clinical characteristics, if we consider the detection of common characteristics in at least 10% of patients in our population to be representative, it will be necessary to recruit 529 patients in order to detect said characteristics with a 95% confidence interval and precision of ± 2.5%.

Diagnosis/Disease/Condition and main selection criteria

Inclusion criteria

- Patient ≥ 18 years old
- Patients with baseline cancer pain that is adequately controlled with opioids

- Presence of episodes of breakthrough pain associated with the cancer pain
- Meeting the diagnostic criteria for breakthrough cancer pain (patient history and Portenoy's criteria) and the Davies algorithm
- Patients who are not receiving treatment for breakthrough pain. It is not permitted the inclusion of patients receiving treatment for breakthrough cancer pain in order to avoid bias that may involve the treatment for the characterisation of breakthrough pain
- Signing of the informed consent

Exclusion criteria

- No severe mental illness
- Any medical condition or situation complicating the collection of study data as determined by the investigator is not permitted

Time (if cross-sectional) or Duration of data collection per subject

Investigator will collect the study data in a single visit.

Criteria for evaluation

Population descriptors

The primary assessment variable is the prevalence of breakthrough pain in patients with cancer pain controlled with opioids.

Demographic data and information relating to the characteristics of the cancer will be collected from all patients.

The characterisation of breakthrough pain will be carried out using the information collected in the tools used for the clinical assessment of the breakthrough pain:

- Alberta Breakthrough Pain Tool
- BPI questionnaire and
- Numerical Rating Scale for the assessment of pain intensity

To assess the quality of life of patients, we will use: SF-12 Questionnaire and Karnofsky performance status.

Main outcome variables

The primary assessment variable is the prevalence of breakthrough pain in patients with cancer pain controlled with opioids. All patients who attend pain consultations with cancer pain during 1 month will be used to determine the prevalence of breakthrough pain.

Health economics

None.

Statistical methods

The incidence/prevalence of breakthrough cancer pain and corresponding 95% confidence interval will be calculated as the percentage of subjects presenting breakthrough pain among patients with cancer pain controlled with opioids, collected by each investigator over one month.

The incidence/prevalence of breakthrough cancer pain and corresponding 95% confidence interval will also be calculated relative to the number or cancer patients collected.

The statistical methodology used will be based primarily on an exploratory analysis of the data through the calculation of descriptive parameters.

A descriptive analysis of the study variables will be carried out and the values of the continuous variables will be summarised in a table showing the mean, median, standard deviation and maximum-minimum range for each. The categorical variables will be presented as absolute frequencies and percentages.

The assessment of breakthrough pain intensity will be performed using the scores obtained on the numerical rating scale. A description of the scores will be given using the mean, median, standard deviation, maximum and minimum.

Each of the items on the BPI questionnaire and Alberta scale will be described, using the mean, median, standard deviation and range to describe the continuous variables and frequency distributions and percentages to describe the categorical variables.

The SF-12 quality of life scale scores will be given using the mean, median, standard deviation and range.

Breakthrough pain in patients with cancer pain will be characterised based on aetiology and pathogenesis, as well as other clinical characteristics. Continuous variables will be summarised showing the mean, median, standard deviation and maximum-minimum range for each and categorical variables will be presented as absolute frequencies and percentages.

The quality of life of patients with breakthrough cancer pain will be analysed based on its possible relationship with demographic characteristics and other clinically significant variables related to the cancer or to the breakthrough pain such as aetiology, frequency of episodes, pain intensity, time until peak of pain, crisis duration, cause, etc.

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APPENDICES

List of Abbreviations and Definition of Terms

AE:	Adverse Event
ADR:	Adverse Drug Reaction
AEMPS	Spanish Agency of Medicines and Medical Devices
CA:	Competent Authority
BCP	Breakthrough cancer pain
BPI	Brief Pain Inventory (BPI)
CCSI:	Core Company Safety Information
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Curriculum Vitae
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
NRS	Numerical Rating Scale
PAS	Post-authorisation study
PSUR:	Periodic Safety Update Report
PSUR:	Periodic Safety Update Report
QA	Quality Assurance
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SPC:	Summary of Product Characteristics

2 Introduction

Oncology consultations are generally short in duration (20-30 minutes). The primary consideration for most oncologists during this time is treatment of the tumour: the choice of treatment to be administered to the patient (chemotherapy, radiotherapy, etc.), the administration of recommended treatment, and the monitoring and control of the efficacy and safety of these treatments, principally in relation to tumour response and survival [4].

Symptoms, such as pain, are often given less attention during diagnosis and treatment. Pain is one of the most common symptoms of cancer [5-7]. However, published estimates of the prevalence of pain in outpatients are inconsistent and vary between 18% and 62%, probably due to differences between the various selection criteria, the use of dissimilar assessment tools and/or different tumour stages [5-7].

Breakthrough pain is understood as the temporary exacerbation of pain occurring either spontaneously or in relation to a specific, predictable or unpredictable trigger in spite of relatively stable and adequately controlled baseline pain.

Breakthrough cancer pain is a common and distressing subtype of pain that affects a percentage of patients with cancer that varies between 40% and 90% according to different publications [1, 2]. The type of breakthrough pain seen in cancer is described as “a temporary increase in pain with an intensity above that considered moderate, overlying baseline pain of moderate or low intensity” in cancer patients treated with opioids [8].

Breakthrough cancer pain is a high intensity, short duration pain that manifests in several daily episodes and does not respond to normal treatment. The clinical approach to breakthrough cancer pain is changeable. The data show that daily exacerbations of pain need to be monitored closely, differentiating where possible between fluctuations in baseline pain and the end-of-dose effect [9].

The causes of cancer breakthrough pain are the same as those of cancer pain, and they can be related to the neoplasm, with diagnostic tests, treatment or other concomitant problems concurrent with cancer [10]. In terms of physiology, breakthrough pain may be nociceptive, neuropathic or mixed [10].

Even today, clinical focus in breakthrough pain varies considerably between clinics, from complete denial of its existence to overestimation [9].

Recently it carried out a study with the participation of specialists from Medical Oncology services, Radiation Oncology services, pain units and palliative care units. The survey showed a high level of agreement among the experts consulted, but there were some areas where no agreement was reached, indicating that there are some areas for improvement related to clinical practice in the management of breakthrough pain that are worth investigating [11]. In patient evaluation a correct diagnosis and proper classification of breakthrough pain are the essential steps to achieve optimal pain treatment [12].

The management of breakthrough pain requires an interdisciplinary approach that includes all stakeholders involved in the treatment of patients with cancer. Since the breakthrough pain affects the patient during the course of the disease, all the specialists who treat cancer should be familiar with its detection and management. Moreover, treatment of breakthrough pain should be multimodal. An integrated strategy that includes the availability of specific cancer treatment, the use of appropriate analgesics, basal proper pain control, and adequate pain management procedures is required [13].Patients with breakthrough cancer pain report a reduction in quality of life, a high level of anxiety and depression, more dissatisfaction with treatment, and are more prone to using healthcare resources [14]. Data on breakthrough cancer pain in patients attending outpatient oncology consultations are insufficient; however, recent studies report a prevalence of breakthrough cancer pain of 33-37% in these patients [15, 16]. The studies are usually conducted by a specialty and lack of the approach of the other specialties. This justifies the disparate prevalence between studies, the lack of real characterization of breakthrough pain and also the need for multidisciplinary and rigorous studies to assess the breakthrough cancer pain in a transversal manner.

With the aim of identifying those patients with clinically significant pain, questions can be formulated regarding the intensity of the pain. Once patients have been identified, the next essential step is the diagnosis/appropriate classification of the pain. In addition to pain intensity, it is important to identify the characteristics of this pain.

Before the routine assessment of symptoms such as pain can be incorporated into normal clinical practice, it is important to accurately estimate the prevalence of these symptoms. A

suitable methodology that will allow the symptoms to be correctly classified will then need to be developed.

Breakthrough pain is classified based on its relationship with specific events: 1) spontaneous pain (also known as idiopathic pain), that occurs unexpectedly and 2) incident pain (also known as precipitated pain or, where appropriate, movement-related pain) that is triggered by specific events and may be sub-classified in three categories: volitional, non-volitional and procedural [17].

The objective of this study will be to characterise breakthrough pain in a diverse population of cancer patients in Spain, using the recommended diagnostic algorithm (Davies algorithm) and medical history to assess patients with regard to the presence of breakthrough pain [3], as well as the Alberta questionnaire, designed specifically for the assessment of breakthrough pain in cancer patients [18].

Although investigators have used various surveys or questionnaires to collect information on breakthrough pain in the context of clinical research, we preferred to use a standardised assessment tool for breakthrough pain, of demonstrated reliability and validity, that is used in patients with breakthrough cancer pain. The tool that will be used in this study was developed to support a research programme to assess novel interventions for breakthrough pain. The Alberta Breakthrough Pain Assessment Tool's design is well-researched and it is easy to understand for both patients and physicians [18].

We will also use the Spanish version of the BPI (Brief Pain Inventory), which has been validated in cancer patients, as a secondary assessment criterion [19]. The BPI questionnaire has two sections: pain intensity (4 items) and interference with activities of daily living (7 items). Each item is given a score on a numerical scale from 0 (no pain/interference with activities of daily living) to 10 (worst pain imaginable/maximum impact on activities of daily living). The results for these 11 items are then used to obtain two overall scores, one for each section: pain intensity and interference with activities of daily living.
It should be noted that the studies published previously on the characterisation of breakthrough cancer pain included a low number of patients and were often carried out at a single research site, with the exception of the study by Davies et al. (2013) [17]. However, in this study they included all specialties that see cancer pain.

Quality of life assessment is essential in these patients due to the impact that breakthrough cancer pain may have on patients' wellbeing and in particular because the patient may feel that it is a real threat to his/her life [20] having no previous studies with so many patients that assess the quality of life.

On the other hand, pain is a problem that is frequently accentuated in older patients in particular, whether caused by cancer or otherwise [21].

The incidence of cancer increases with age and approximately half of all cancer cases occur in patients over 65 years of age [22].

The treatment of cancer pain in elderly patients is challenging due to the increased risk of therapeutic complications resulting from the loss of performance status, associated comorbidities, geriatric syndromes and decreased cognitive function [22]. Moreover, despite the existence of effective treatments for pain, older patients are often undertreated [23].

Consequences include depression, anxiety, falls, malnutrition, decreased cognitive function, poor quality sleep, altered performance status, decreased social and leisure activities, increased healthcare costs and, overall, reduced quality of life [24].

The SF-12 health questionnaire is an abbreviated form of the SF-36 questionnaire, designed for use in situations in which the latter would be too long. The SF-12 questionnaire only takes around two minutes to complete. This questionnaire is a self-administered tool that measures health from the patient's perspective, through standardised responses to standardised questions [25].

Assessment of performance status in medicine (oncology and other fields) seeks to quantify the general wellbeing and activities of daily living of cancer patients. This measurement is used to determine whether patients can have chemotherapy, whether it is necessary to adjust the dose and as a means for establishing palliative care. It is also used as a measurement of quality of life in controlled and randomised oncological clinical cancer trials. There are various scoring systems, one of the most widely used being the Karnofsky performance status scale [26]. The Karnofsky performance status score includes 11

categories scored from 100 to 0, where 100 is “patient asymptomatic with no evidence of illness” and 0 is “death”, and a version is available in Spanish [27].

3 Study Objective(s)

Primary objective

- To estimate the prevalence of breakthrough cancer pain in an unselected representative cohort of cancer outpatients with or without pain who attend consultations at Medical Oncology, Hematology , Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units at participating sites.
  The estimated annual prevalence will be calculated relative to the population of cancer patients with or without pain seen in participating practices over one month.

Secondary objectives

- To estimate the annual incidence of patients with breakthrough cancer pain relative to the population of cancer patients with or without pain seen in participating practices over one month.
- To characterise breakthrough pain in patients with cancer pain based on medical history, aetiology and pathogenesis, tumour type, location, stage, comorbidities, etc., as well as other clinical characteristics (type of breakthrough pain, number of episodes per day, duration and intensity, and baseline pain management). This information will be collected with the tools used for the clinical assessment of breakthrough pain.
- To assess the prevalence of each of the different causes of pain.
- To determine the percentage of patients who present each of the different profiles/types of breakthrough cancer pain (characterisation/classification) and classify them based on the results obtained in the Alberta and BPI questionnaires.
- To determine the percentage of patients who present each of the profiles/types of breakthrough cancer pain and assess possible relationships with demographic characteristics and other clinically significant variables related to the cancer such as diagnosis, pain intensity, comorbidities, etc.
- To assess the quality of life of patients with breakthrough cancer pain and its possible relationship with demographic characteristics and other clinically significant variables related to the cancer or to the breakthrough pain such as aetiology, frequency of episodes, pain intensity, time until peak of pain, crisis duration, cause, etc.
- To assess the performance status of patients using the Karnofsky scale in order to know the degree of general wellbeing and ability to cope with activities of daily living presented by the patients studied.

4 Study Administrative Structure

National Co-ordinating Investigator

PPD

Sponsor

PPD

Pain Units Coordinating Investigator

PPD

Medical Oncology Coordinating Investigator

PPD

Radiotherapeutic Oncology Coordinating Investigator

PPD

PPD

Palliative Care Units Coordinating Investigator

PPD

Contract Research Organization

CCI

4.1 Study Sites

The study is planned to be conducted in 66 Sites in Spain (33 Hospitals), Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units. Global Research will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

4.2 Sponsor Personnel

Takeda LOC will keep a record of all relevant sponsor personnel.

4.3 Contract Research Organisation (CRO)

The CRO will keep a record of all involved CRO personnel.

CCI

CCI [redacted]

4.4 Essential Documents

The following essential documents must be received by Global Research before the study is initiated at a site:

- Written agreement between Takeda
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible
- Subject Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required)
- Written IEC / IRB approval / vote according to local regulations
- Authority approval according to local regulations

5 Ethics

This study is an observational study where the existence of the study has no impact on the subject except for collection of informed consent to use of the subject's data and the questionnaires that the patient should complete: Alberta Breakthrough Pain Assessment Tool, Brief Pain Inventory (BPI), Numerical Rating Scale (NRS) for the assessment of pain intensity and SF-12 Questionnaire.

5.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations.

The highest levels of professional conduct and confidentiality will be maintained at all times, following national data protection legislation. The subject's right to confidentiality is fundamental and will be guaranteed as established in Organic Law 15/1999 of 13 December on Personal Data Protection. The subject's identity in the study documents will be encoded and only authorised persons will have access to personal details that could identify the subject if so required by data verification procedures. Personal details that could identify the subject will be kept confidentia

The investigators are responsible for the accuracy of the data collected. The data obtained are completely confidential and only the sponsor, the coordinator and the investigators will have access to them.

With regard to the thoroughness of the study and the sponsor's obligations, when the personal data of the investigators and/or patients are held or handled, appropriate measures must be taken to protect these and avoid access to the same by unauthorised third parties.
In the interest of confidentiality, only the investigator, his/her staff and the technical staff participating in the collection of the study data will have access to patients' data.

The confidentiality of the information will be maintained to the extent permitted under the applicable legislation. If the results of this study are published, the identities of the participating subjects will remain confidential. The provisions of Spanish Organic Law 15/1999 of 13 December on Personal Data Protection will be complied with under all circumstances.

Takeda/the appointed CRO will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.
Takeda as the sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

This study will be financed by the Sponsor, Takeda Farmacéutica España S.A.

The sponsor shall finance the study in accordance with the directions given in this protocol. This funding includes the cost of submitting the study for approval to an accredited IEC, submitting the study for classification to the AEMPS, the design, maintenance and management of the database, as well as the statistical analysis and corresponding statistical report.

This study is observational, therefore it will not under any circumstances interfere in the physician's normal clinical practice, as it is limited to the collection of patient data and does not entail any diagnostic or therapeutic procedure outside of normal clinical practice.

For this reason, each physician will have to select those individuals eligible to participate in the study from among the population he/she treats. Whether the investigator decides to use a treatment or not will be independent of the study, and treatments may be altered based on normal clinical practice regardless of the patient's participation.

Before accepting and signing the investigator's commitment, the participating professionals must ensure that their participation in the study does not interfere with their prescribing habits or their healthcare duties.

No intervention outside of normal clinical practice will be performed; patients will receive the treatment considered most suitable by the investigator and this will not be provided by the sponsor.

The study does not entail any extraordinary expenses for the investigator or the site beyond the time spent by the investigator filling out the case report form with the required information.

All changes made to the protocol must be the subject of a written amendment that shall be signed by the investigator and the sponsor and filed together with the protocol. In some cases, the amendment may require that changes be made to the informed consent document. Any changes made to this protocol shall be reported to the IEC that performed its review. In the case of substantial amendments, those that affect the objectives, methods or ethical considerations shall be subject to a new evaluation by the IEC that gave a favourable opinion on the same, and administrative authorisation shall be sought for the amendment. For amendments that do not affect these aspects, the IEC will be notified, giving the reasons why the amendment is not considered substantial.

5.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/ IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Subject Information Sheet / Informed Consent Form

The appointed CRO or the Site Study Responsible will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results

Global Research will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

Authorities

Global Research or the appointed Contract Research Organisation (CRO) will send required documents to the competent authority (CA) and/or other national or regional authorities. Global Research will keep an updated list of submission and approval dates and a copy of all documents submitted.

Once the study has obtained classification from the AEMPS [Spanish Agency of Medicines and Medical Devices], approval by an IEC and the other administrative procedures have been completed, the study will commence at the participating sites.

5.3 Subject Information and Written Informed Consent

This study will follow standards of good clinical practice (GCP) as they apply to epidemiological studies, thereby ensuring that its design and conduct and the communication of the data are reliable and protect the rights and integrity of the participating subjects and the confidentiality of their data.

Before starting the study, the protocol, patient information sheet and informed consent form for the study will be submitted for approval to the Independent Ethics Committee (IEC) of one hospital and to any of the IECs of any participating sites that request it. The sponsor will keep the IEC's favourable opinion, together with the versions of the documents approved and the list of members of the committee having issued the opinion.

Patients who meet the inclusion criteria and give their informed consent will be recruited to the pain characterisation study until the indicated sample size is reached. Each subject invited to participate in the pain characterisation study will be given a written document called a "Patient Information Sheet" that will contain the relevant and necessary information to enable him/her to decide whether to participate in the study.

The investigator must inform the patient as fully as possible, using language and terms that the latter can understand, about the voluntary nature of participation and that this will not entail any change to his/her treatment or medical care with regard to what he/she would receive if not participating. The investigator will respond to the patient's doubts and questions and, in accordance with current legislation, obtain the subject's written informed consent which must be signed by the subject (in his/her own hand with name and date) or, if not possible, that of an impartial witness, in which case he/she shall sign the verbal informed consent form before witnesses, or of the patient's legal representative. The patient will receive a signed and dated hard copy of the informed consent form, signed also by the investigator.

Subjects participating in the study may at any time withdraw their consent to the use of their data in the analysis, without giving a reason and without incurring any liability or loss.

The Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (, parent or legal guardian) can understand, and obtain the subject's (and if applicable, the subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, parent or legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per see and is not consent to any interventional procedure or treatment.

The subject must agree that sponsor personnel, their representatives or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject and parent or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.

For details, see the Subject Information Sheet and Informed Consent Form.

5.4 Risk–benefit analysis for research subjects.

Due to its observational nature, there is no possibility of the study generating any risk whatsoever for the subjects studied as it does not entail any change in patient care with respect to normal clinical follow-up. The patient will not receive any benefit as a result of his/her participation in the study and will be treated in accordance with the participating physician's normal clinical practice. Nevertheless, this study may help to improve knowledge of the incidence and prevalence of patients with breakthrough cancer pain, as well as the characterisation of this type of pain, that can be incapacitating for the patient, which may enable improvements to be made in the care of such patients in normal clinical practice.

6 Study Design and Plan

This study is a 'non-interventional study' as defined in**:** G-STND-PV-006, Pending SOP, Directive 2001/20/EC (4) and will follow the guidelines for GPP (2).

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice
- No additional diagnostic or monitoring procedures shall be applied to the subjects
- Epidemiological methods shall be used for the analysis of collected data.

This is a cross-sectional, non-PAS, non-interventional, epidemiological study. Given the observational and cross-sectional nature of the study, the protocol does not include any interventions with regard to patient follow-up by the investigator.

The proposed design is considered sufficient to enable the collection of the data required to meet the study's objectives.

6.1 Study Schedule

Start of recruitment:	September 2016
End of recruitment:	June 2017
Data collection:	3 months
Data analysis:	December 2017
Total duration of study:	15 months

The Start of Study is defined as date of first Site Initiation.

Global Research will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB for each site, for each country and for the complete study, as locally required.

Global Research will ensure that results are posted on “clinicaltrials.gov” and as required by local authorities.

Based on upcoming knowledge, Takeda might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs and authorities will be informed promptly.

6.2 Discussion of Study Design

The study’s limitations derive from its design as a cross-sectional, non-PAS, non-interventional study in which the proportion of patients with breakthrough cancer pain attending consultations in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units may not be representative of the general population of cancer sufferers. However, it will allow us to obtain a valid estimate in the population attending said consultations.

A further limitation relates to the extrapolation of the results to the national population, as although 66 sites distributed throughout the country will participate in the study, it is possible that these may not be representative of Spain as a whole, due to the characteristics of the sites selected.

6.3 Selection of Study Population

Patients with cancer pain assessed in in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units at the hospitals participating in the study.

Inclusion criteria:

- Patient ≥ 18 years old
- Patients with baseline cancer pain that is adequately controlled with opioids
- Presence of episodes of breakthrough pain associated with the cancer pain
- Meeting the diagnostic criteria for breakthrough cancer pain (patient history and Portenoy's criteria) and the Davies algorithm
- Patients who are not receiving treatment for breakthrough cancer pain. It is not permitted the inclusion of patients receiving treatment for breakthrough cancer pain in order to avoid bias that may affect the characterisation or taxonomy of breakthrough cancer pain
- Signing of the informed consent

Exclusion criteria:

- Severe mental illness
- Any medical condition or situation complicating the collection of study data as determined by the investigator

The source of information will in all cases be the medical history, the patient and the questionnaires completed during the visit. In accordance with the study design, the investigator will collect the study variables and data in a single visit.

For a period of one month, each investigator must identify cancer patients who attend consultations in Medical Oncology, Hematology and Radiotherapeutic Oncology Departments or Pain and Palliative Care Units, using the Davies diagnostic algorithm [3] to confirm the presence of breakthrough pain. From those patients who report breakthrough pain, the first two patients each day who meet the inclusion criteria and give their informed consent for the characterisation of breakthrough pain will be recruited, until reaching 10 patients in Medical Oncology, Hematology, Radiotherapeutic Oncology and Palliative Care Departments and 5 patients in Pain Units. If an investigator has been unable to include the

expected number of patients planned for the characterization of breakthrough pain during the month that has collected prevalence data, the investigator will have two additional months to include them, and the investigator must confirm the presence of breakthrough pain by Davies algorithm before inclusion as detailed above.

Subjects should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available, will not be included in the final analysis and will be deleted from the database. All relevant actions will be taken according to GCP standarts and local legislation.

6.4 Treatments

The patients participating in this cross-sectional, non-PAS, non-interventional study will not receive treatment in relation to the study aside from the treatment already prescribed by their usual physician.

7 Conduct

Once the study has obtained classification from the AEMPS [Spanish Agency of Medicines and Medical Devices], approval by an IEC and the other administrative procedures have been completed, the study will commence at the participating sites.

Data will be collected from patients with cancer pain being treated with third-step opioids who attend consultation at the in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units of participating sites during a period of 1 month. Each of the participating investigators must identify the patients with cancer pain and confirm the presence of breakthrough pain using the Davies diagnostic algorithm [3]. The investigator will propose participation in the study on the characterisation of breakthrough pain to the first two patients each day who meet the selection criteria. If the patient agree to participate in the study they will be asked to sign the informed consent.If any of the patients refuses to participate the enrolment will continue the next day. It is expected that each investigator in the Medical Oncology, Hematology, Radiotherapeutic Oncology and Palliative Care Departments will recruit 10 patients to the study and investigators in the Pain Units will recruit 5 patients due to the lower number of cancer patients in Pain Units. In

accordance with the study design, the investigator will collect the necessary variables and data in a single visit.

The fieldwork will take 1 month to collect prevalence data and maximum 3 months for the collection of data for the characterization of breakthrough pain, if the investigator could not recruit all foreseen patients for this purpose in the first month. First month corresponds to the recruitment period required for the incidence/prevalence calculation, as due to the study's characteristics no follow-up period is planned. Data entry in the database, analysis and the drafting of the final report will be carried out once the recruitment period is concluded.

As this is an observational, cross-sectional, non-PAS and non-interventional study, it will not under any circumstances involve changes to normal clinical practice or the performance of tests not considered normal clinical practice. Throughout the study, each investigator must treat the patients diagnosed with breakthrough cancer pain and recruited to the study, whether treatment-naïve or currently untreated, after characterising their pain, in accordance with the criteria habitually used in clinical practice for patients of this type.

The study period is initially estimated at 12 months for data collection. This corresponds to the recruitment and data entry periods, as due to the study's characteristics no follow-up period is planned. Data entry in the database, analysis and the drafting of the final report will be carried out once the recruitment period is concluded. If, following the recruitment period planned in the protocol (maximum 3 months), the expected number of patients for the characterisation of breakthrough pain has not been reached, recruitment will be continued competitively within each specialty (120 patients included in each specialty except 60 patients in hematology), until 529 patients have been recruited.

The investigator will be responsible for ensuring the correct completion of all sections of the Case Report Form.

Description of the visit

A single visit per patient will be carried out for the purposes of this study, coinciding with the study recruitment visit.

For a period of one month, each investigator must identify patients with cancer pain being treated with opioids who attend consultations in in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units, using the patient's medical history and the Davies diagnostic algorithm [3] to confirm the presence of breakthrough pain.

Information relating to the prevalence of breakthrough pain will be collected in the corresponding section of the CRF, detailing for each patient whether he/she has pain, whether he/she has breakthrough pain, age, sex, Karnofsky PS, tumour type and stage.
From those patients who report breakthrough pain, the first two patients each day who meet the inclusion criteria and give their informed consent will be recruited, until reaching the indicated sample size of 10 patients in Medical Oncology, Hematology, Radiotherapeutic Oncology and Palliative Care Departments and 5 patients in Pain Units, until a total of 529 is reached.
If, following the recruitment period planned in the protocol (maximum 3 months), the expected number of patients for the characterisation of breakthrough pain has not been reached, recruitment will be continued competitively within each specialty (120 patients included in each specialty except 60 patients in hematology), until 529 patients have been recruited.

The information will be recorded on the Case Report Forms (CRFs) designed for this purpose. All the information will be filled in by the investigating physician using the data obtained during the study visit or by checking the patient's medical records when necessary.

The following information will be collected during the visit:

- Visit date
- Demographic data (age, sex, weight, height)
- Characteristics of the cancer (type, stage, treatments the patient has received for the underlying tumour: chemotherapy, radiotherapy, surgery, etc.) as well as whether he/she is currently receiving treatment for the tumour.
- Comorbidities
- Adverse events associated with the cancer treatment or sequelae of the tumour: (mucositis, xerostomia, nausea, vomiting, dysphagia, dyspnoea, peripheral neuropathy, tiredness/weakness, constipation, diarrhoea, sleep disorders, other)
- Clinical assessment of the breakthrough pain:
  - Alberta Breakthrough Pain Assessment Tool for the assessment of breakthrough pain in cancer patients
  - Brief Pain Inventory (BPI)

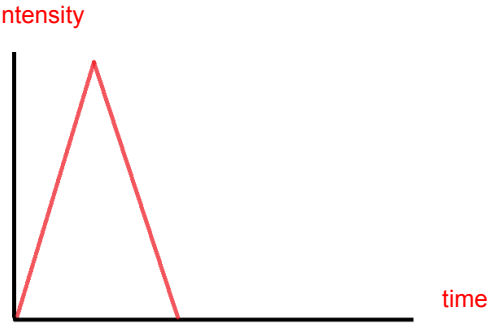
- Numerical Rating Scale (NRS) for the assessment of pain intensity
- Quality of life assessment:
  - SF-12 Questionnaire
  - Karnofsky performance status

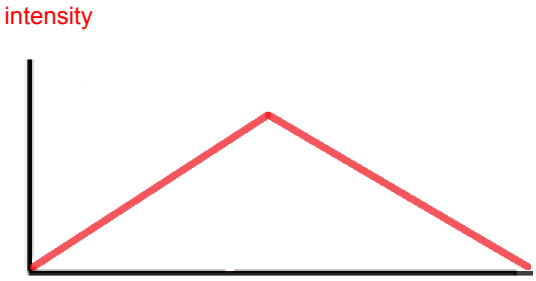
Using an anatomical drawing or doll, the exact location in which the patient presents the breakthrough cancer pain crisis will be identified, determining whether one or several breakthrough pains are involved.

A series of graphs illustrating various profiles for the behaviour of breakthrough pain will then be used, in order to determine which type(s) of breakthrough pain each patient recruited to the study presents.

The following graphs will be used:

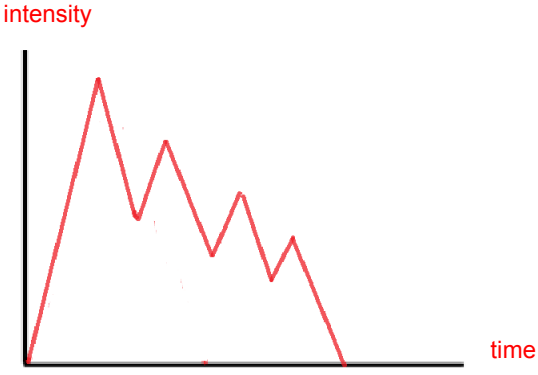
BCP type I graph:
This graph represents BCP of short duration and high intensity, that begins and ends suddenly.

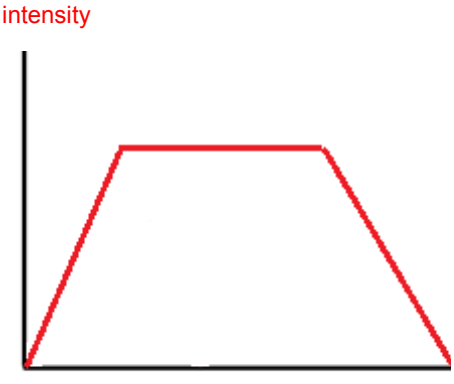




BCP type II graph:
This graph represents BCP of long duration and moderate-high intensity, that begins and ends gradually.

BCP type III graph:
This graph represents BCP with successive pain peaks of gradually decreasing intensity.





BCP type IV graph:
This graph represents BCP that starts gradually, reaches a maximum peak and is maintained for a period, before gradually decreasing.

The fundamental exposure factor in this study is patients with cancer who attend consultation at in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units with cancer pain controlled with opioids. Using patients' medical history and the Davies diagnostic algorithm [3], the investigator will confirm the presence of breakthrough pain. Those patients who agree to participate in the study to characterise breakthrough pain by signing the informed consent will be questioned on the other study variables and asked to complete the corresponding questionnaires.

All study data will be collected during the visit in which the patient signs the informed consent.

The data detailed below will be collected in relation to the study objectives:

- The primary assessment variable is the prevalence of breakthrough pain in patients with cancer pain controlled with opioids who attend consultations in Medical Oncology, Hematology and Radiotherapeutic Oncology Departments or Pain and Palliative Care Units for any reason.

  Breakthrough pain is understood as the temporary exacerbation of pain occurring either spontaneously or in relation to a specific, predictable or unpredictable trigger in spite of relatively stable and adequately controlled baseline pain.

For a period of one month, each investigator will identify patients with cancer pain being treated with opioids who attend consultations, using the patient's medical history and the Davies diagnostic algorithm [3] to confirm the presence of breakthrough pain.

The investigator will continue collecting information from patients to estimate the prevalence for a month, regardless of whether the investigator recruited the 10 assigned patients (5 in pain units) for the characterization of breakthrough pain before.

- The prevalence of breakthrough pain in patients with cancer who attend consultations in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units for any reason over one month will also be determined.
- In order to determine the incidence of breakthrough pain in patients with cancer pain controlled with opioids, the investigator will indicate on the prevalence data sheet whether the breakthrough pain has been diagnosed during the current visit or was diagnosed at an earlier date. Cases of breakthrough pain diagnosed during 1 month will be used to calculate its incidence.
- The incidence of breakthrough pain in patients with cancer who attend consultations in in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units for any reason over one month will also be determined.
- During the same visit, demographic data and information relating to the characteristics of the cancer will be collected from all patients with breakthrough cancer pain who agree to participate in the study.
- The characterisation of breakthrough pain in patients with cancer pain will be carried out using the information collected in the tools used for the clinical assessment of the breakthrough pain:
    - Alberta Breakthrough Pain Tool
    - BPI questionnaire and
    - Numerical Rating Scale for the assessment of pain intensity
- To assess the quality of life of patients with cancer pain, we will use:
    - SF-12 Questionnaire

- Karnofsky performance status

8 Safety Reporting

8.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction

An ADR is any response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of diseases or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

8.2 Classifications

Seriousness

A serious ADR or AE (SADR/SAE) is any ADR or AE which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Life-threatening in this context refers to a reaction/event in which the subject was at risk of death at the time of the reaction/event. It does not refer to a reaction/event that hypothetically might have caused death if more severe

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction.

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities.

Causality

- Related: A reasonable temporal relationsship between the medicinal product administration and the event where there is no other obvious explanation for the occurrence of the event
- Not related: There is evidence for (an) alternative explanation(s) for the event (e.g. the event is explained by one or more of the following: a) the subject's medical condition (medical history, disease progress, indication), b) a concomitant medication for which the event is labelled, or c) AE occurrence prior to the introduction of the medicinal product.

Outcome

- Fatal: The subject died due to the event. If the subject died due to other circumstances than the event the outcome should be stated as 'Not recovered' or 'Recovering'

- Recovered/Resolved: The subject has fully recovered from the event or the condition has returned to the level observed at baseline
- Recovering/Resolving: The event is improving but the subject is still not fully recovered
- Not Recovered/Not Resolved: The event is ongoing at the time of reporting and the subject has still not recovered
- Recovered with Sequelae/Resolved with Sequelae: As a result of the event, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed).
- Unknown: If Outcome is not known or not reported.

8.3 Reporting of Adverse Drug Reactions and Adverse Events

The present study makes no changes to normal practice and does not include investigational medicinal products. Being a cross-sectional, non-PAS, non-interventional study, it does not require expedited reporting of suspected adverse reactions.

Nevertheless, investigators are reminded of the requirement to comply with Order SAS/3470/2009 of 16 December, which publishes guidelines on post-authorisation observational studies of medicinal products for human use, which indicates that suspected serious adverse reactions that are detected must be reported to the contact point designated by the competent body for pharmacovigilance in the autonomous community where the healthcare professional reporting the case practices, within a maximum period of 15 calendar days from said person becoming aware of the suspected adverse reaction, citing the study code.

Investigators at participating sites must send Takeda initial and follow-up reports of serious or mild adverse reactions or any other relevant safety information relating to any product marketed by Takeda (about the use of the product, with or without an associated AR, related to breastfeeding, pregnancy, overdose, misuse/abuse, medication errors, lack of efficacy and off label use), using Takeda's adverse reactions reporting form (see appendix 5) within 24 hours of becoming aware of said reaction, and by email to PPD .

In the event that the CRO becomes aware of any adverse reaction or any other relevant safety information associated with a product marketed by Takeda, the CRO will be obliged to

report this to Takeda's pharmacovigilance department within 24 hours by email to PPD .

In the event that in order to evaluate an adverse reaction, the sponsor requires additional information and sends questions to the investigator at the site in question, the information provided by said investigator will be considered follow-up information on the adverse reaction and must therefore be reported to the contact point designated by the competent body for pharmacovigilance in the autonomous community where the investigator reporting the case practices, as well as to the sponsor having requested said information, with reference to the initial adverse reaction report. This report to the competent authorities and the sponsor shall be made as described in this section.

In summary, any ADRs and pregnancies observed during the study and follow-up information on these should be reported by the physician as soon as possible after having knowledge hereof directly to the authorities according to local regulations. In addition, a copy is sent to Takeda for ADRs related to a Takeda product.

No data on AEs or ADRs will be collected as part of the study database.

All safety-related data on study subjects collected in the study database or reported to Takeda according to the normal procedure for marketed drugs, e.g. serious and non-serious ADRs, must be summarised in the Non-Interventional Study Report.

9 Data Quality Control and Assurance

9.1 Quality Control

The application used for the collection of the data will have safety margins and internal coherence rules to avoid the entry of incorrect data or anomalous or incoherent values. A set of automatic data checks with data queries should be programmed for data cleaning. Patients will be reviewed individually, checking that all data have been collected or a reason provided where this is not the case. In the event that data are incorrect, incomplete or have not been collected in accordance with the protocol, the investigator will be asked to review and correct said data.

9.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

9.3 Inspection by IRB/IEC or Competent Authority

Representatives from IRB/IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Global Research and must make the records available as requested.

9.4 Data Management

Data Management will be carried out according to a Data Management Plan, which must be written and approved before the design of the study database is finalised. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

If a subject is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and adverse events/reactions (MedDRA) must be followed.

The subjects will be identified in the database only by Study ID, Site ID and subject number,

9.4.1 Data Collection Tools and Flow

The Study Site will receive access to electronic data capture from CCI. Whenever possible, complete data sets should be entered. Text field entries and any data collected should be legible and follow the requested language standard.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 7 and data on serious AE/ADR reactions collected according to section 6 should be signed off separately by a physician who may or may not be involved in the study.

9.5 Methods for obtaining data.

This study entails the cross-sectional collection of data over one month at each participating site. Given the observational nature of the study, the data will be obtained in a single visit from patients' medical history and/or from the patient using the tools detailed above and in accordance with the physician's normal clinical practice.

The presence of breakthrough pain and its characterisation will be assessed using the questionnaires detailed in section H4 of the protocol in those patients who agree to participate in the study by signing the informed consent.

9.6 Data handling.

In order to guarantee the confidentiality of the study data, only the following persons and entities will have access thereto: the investigator and his/her staff, the sponsor or a person designated by the sponsor, the IEC, the relevant healthcare authorities and the persons responsible for analysing the data.

The content of the CRFs, as well as the documents generated during the study, will be protected against non-permitted use by persons not involved in the investigation and will therefore be considered strictly confidential and will not be revealed to third parties.
The investigator must make sure to maintain patients' anonymity and protect their identity from unauthorised parties. Patients will not be identified by name on the CRFs, but by an identification code. The investigator must keep a record of patient recruitment, including the codes assigned for participation in the study.

The investigator will organise the safeguarding of the study documentation until the end of the study. He/she must also comply with the local standards/recommendations regarding the safeguarding of patients' records.

The processing of data of a personal nature required for this study is subject to Organic Law 15/1999 of 13 December on Personal Data Protection.

10 Statistical Methods and Determination of Sample Size

This section describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection.

10.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses.

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning.

For a period of one month, each investigator must identify patients with cancer pain being treated with opioids who attend consultations in in Medical Oncology, Hematology, Radiotherapeutic Oncology Departments, Pain Units and Palliative Care Units, using the Davies diagnostic algorithm [3] to confirm the presence of breakthrough pain. All patients who attend pain consultations with cancer pain during this period will be used to determine the incidence/prevalence of breakthrough pain.

All patients who meet the selection criteria and have given their informed consent will be included in the breakthrough pain characterisation and quality of life study.

Before beginning the statistical analysis of the data, a Statistical Analysis Plan will be prepared, detailing all the analyses to be performed.

The incidence/prevalence of breakthrough pain and corresponding 95% confidence interval will be calculated as the percentage of subjects presenting breakthrough pain among patients with cancer pain controlled with opioids, collected by each investigator on the corresponding page of the CRF over one month. This incidence/prevalence will also be

calculated by age group and sex. It will also be made an analysis by specialty to see the difference between the various participating specialties.

The incidence/prevalence of breakthrough pain and corresponding 95% confidence interval will also be calculated relative to the number or cancer patients, collected by each investigator on the corresponding page of the CRF over one month.

Given the descriptive nature of the study, the statistical methodology used will be based primarily on an exploratory analysis of the data through the calculation of descriptive parameters.

Initially, a descriptive analysis of the study variables will be carried out and the values of the continuous variables will be summarised in a table showing the mean, median, standard deviation and maximum-minimum range for each. The categorical variables will be presented as absolute frequencies and percentages.

The assessment of breakthrough pain intensity will be performed using the scores obtained on the numerical rating scale. A description of the scores will be given using the mean, median, standard deviation, maximum and minimum.

Each of the items on the BPI questionnaire and Alberta scale will be described, using the mean, median, standard deviation and range to describe the continuous variables and frequency distributions and percentages to describe the categorical variables.

The SF-12 quality of life scale consists of 12 items, from which total scores for the physical and psychological components are obtained. The correction methods indicated in the scale's validation manual will be used for the total score for each sub-scale, and the mean, median, standard deviation and range will be presented.

Breakthrough pain in patients with cancer pain will be characterised based on aetiology and pathogenesis, as well as other clinical characteristics (type of breakthrough pain, number of episodes per day, duration and intensity, and pain management). This information will be collected with the tools used for the clinical assessment of breakthrough pain.

Given the special characteristics of the elderly population and patients with multiple myeloma, a sub-analysis of pain characterisation will be performed in patients over 70 years of age and in those with multiple myeloma.

The percentage of patients who present the various profiles/types of breakthrough cancer pain (characterisation/classification) and the causes for the same will be determined.

The percentage of patients with the various profiles/types of breakthrough cancer pain will be given based on demographic characteristics and other clinically significant variables relating to the cancer diagnosis (tumour type, stage, etc.), pain intensity, comorbidities, etc.
The quality of life of patients with cancer breakthrough pain will be analysed based on its possible relationship with demographic characteristics and other clinically significant variables related to the cancer or to the breakthrough pain such as aetiology, frequency of episodes, pain intensity, time until peak of pain, crisis duration, cause, etc.

10.2 Interim Analyses

No interim analyses are planned for this study.

10.3 Determination of Sample Size

We estimate that more than 10 patients per day attend consultations for cancer in Medical Oncology, Radiotherapeutic Oncology, Hematology and Palliative Care Departments and around 5 patients in Pain Units, and each site shall have a recruitment period of 1 month. Cancer breakthrough pain is a common and incapacitating subtype of pain that affects a percentage of patients with cancer that varies between 40% and 90% according to different publications [1, 2]. Conservatively, we hope to detect the prevalence in 50% of patients, and we estimate that at each site a total of approximately 200 patients, or around 13,200 across the 66 planned sites, will be interviewed on the prevalence of breakthrough pain. This sample will enable us to detect the prevalence of breakthrough pain with a 95% confidence interval and precision of ±1%.

For the assessment of the secondary objective, i.e., characterising the breakthrough pain based on aetiology, underlying pathology and other clinical characteristics (type of breakthrough pain, number of episodes per day, duration and intensity, comorbidities and baseline pain management), if we consider the detection of common characteristics in at

least 10% of patients in our population to be representative, it will be necessary to recruit 529 patients in order to detect said characteristics with a 95% confidence interval and precision of ± 2.5%.

All patients recruited for characterisation of breakthrough cancer pain will be newly diagnosed and previously untreated for breakthrough cancer pain, although patients may be recruited who have been treated for breakthrough cancer pain in the past but are not currently being treated (at least 1 month wash-out) to avoid possible distortions in the classification of pain that may result from treatment.

Patients eligible to participate in the study must meet all the selection criteria, have a confirmed diagnosis of breakthrough cancer pain based on the Davies algorithm and must have given their informed consent in writing.

11 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

The definitive closure of this study will occur once all the data of the last patient included in the study has been completed. After closing the database, the statistical analysis shall be carried out and a report submitted, that will be reviewed and approved by the study sponsor and coordinating investigator.

In accordance with current legislation, a copy of the final report shall be submitted to the IECs that have authorised the study, the competent bodies in the autonomous communities where the study is conducted and the AEMPS.

12 Publications

Takeda aims to have the results of this study published.

Takeda has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

All information relating to the study is considered confidential and the property of the sponsor until its publication. It may not be revealed to others without the prior written consent of the sponsor and may not be used for any reason other than for the execution of this study.

Only the sponsor or its representatives may extend the information obtained in this study to physicians and regulatory bodies, unless this is demanded by means of an order.

The results of this study will be published in scientific journals and/or presented at conferences.

The final decision to publish any article/abstract/presentation shall be made by the sponsor.

13 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the essential documents (Section 3.5), the protocol, any amendments, the list of participating subjects, the written informed consents, the CRFs and the progress reports in the Study Site File. After final database lock the Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 5 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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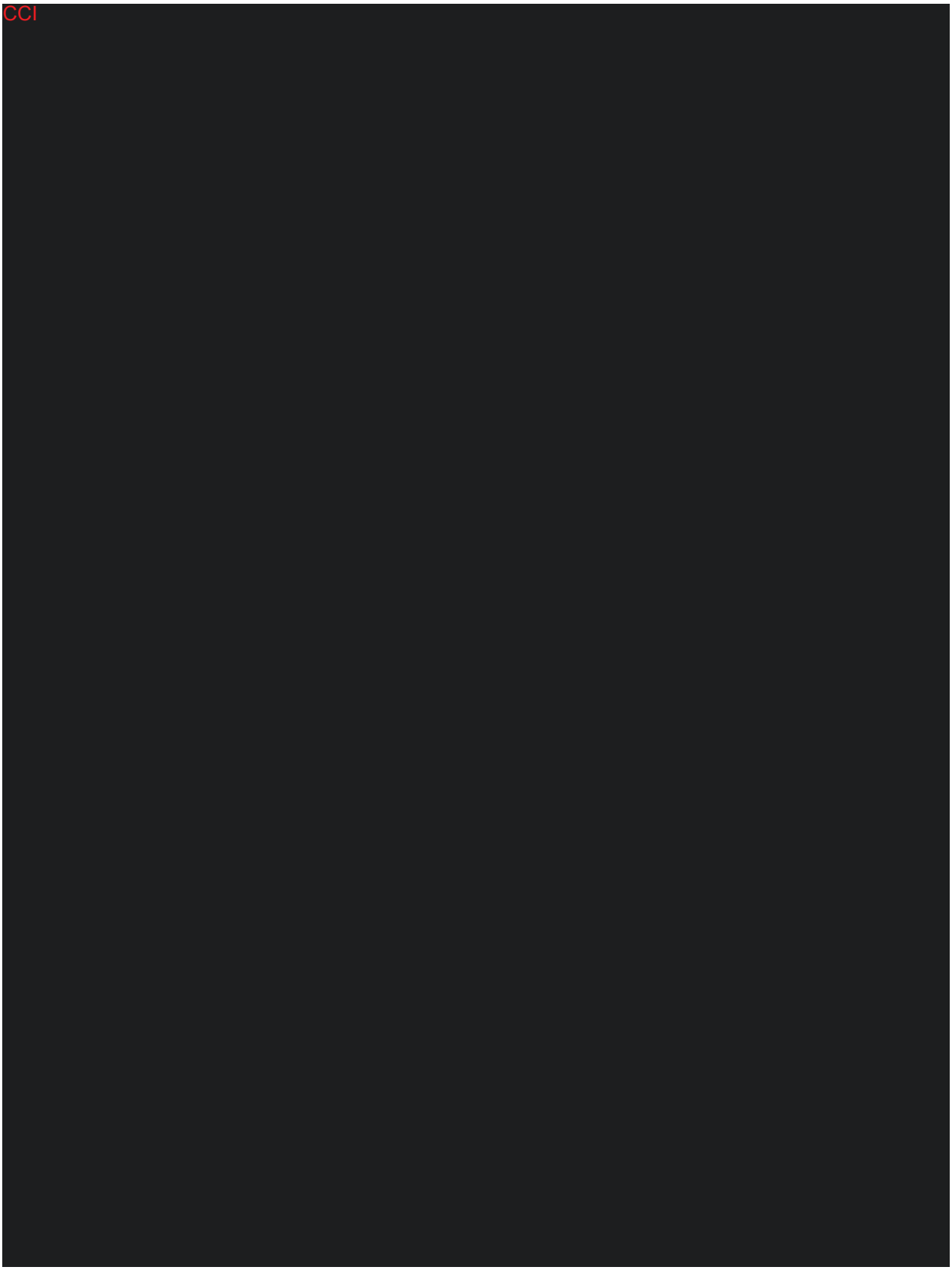
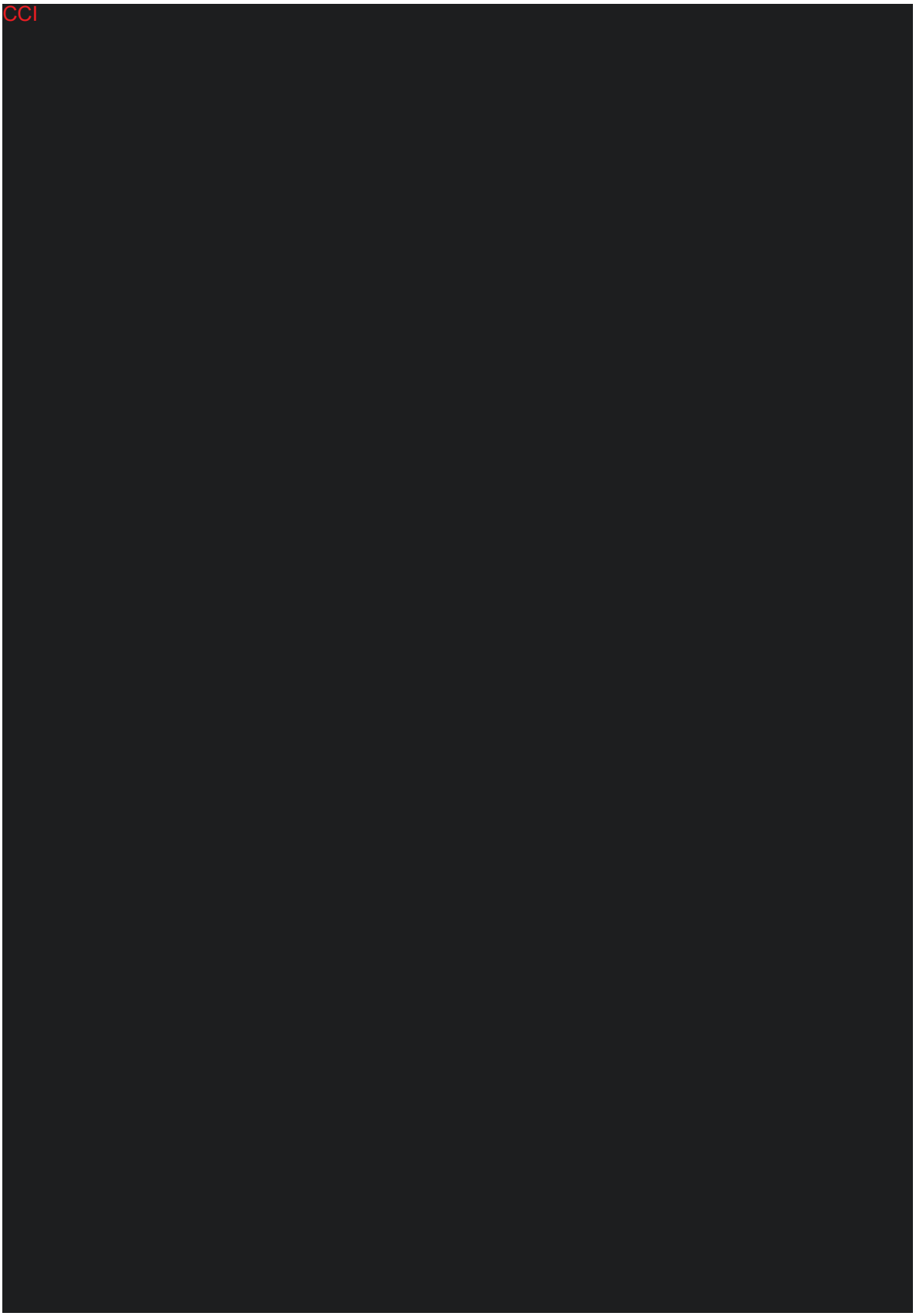
Appendix 1: Brief Pain Inventory (BPI).

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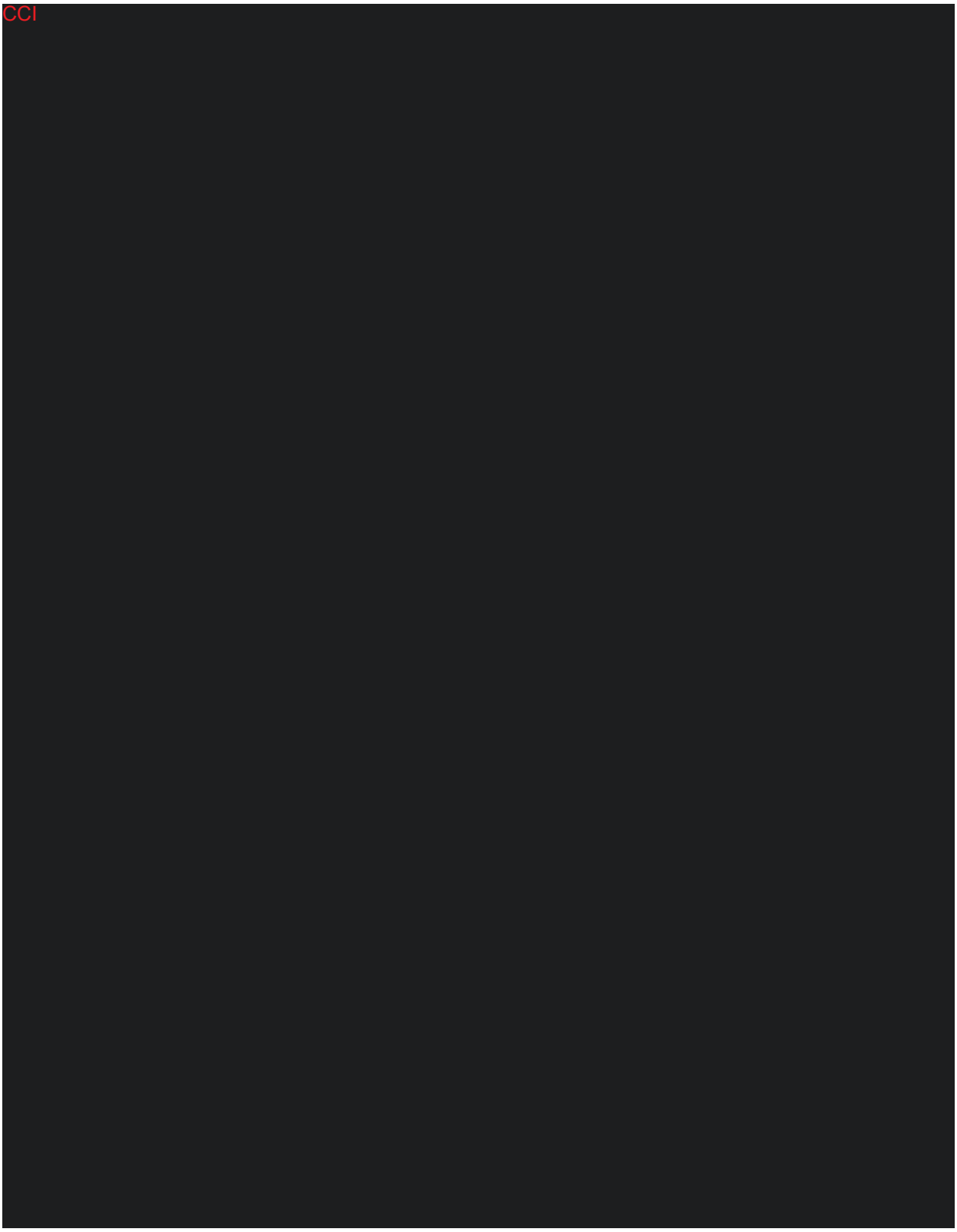
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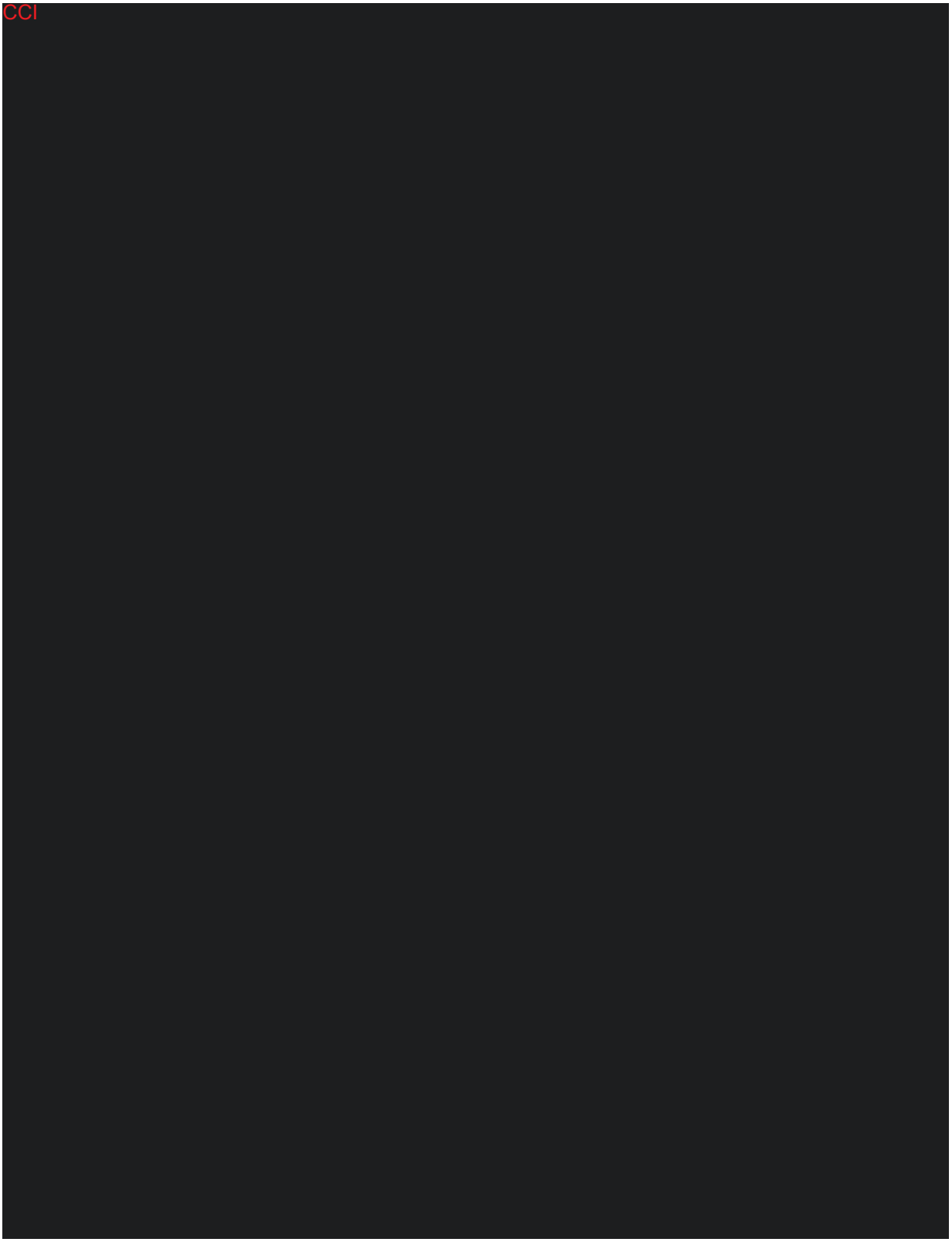
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Appendix 3: Karnofsky performance status.

Appendix 4: Alberta Breakthrough Pain Assessment Tool.

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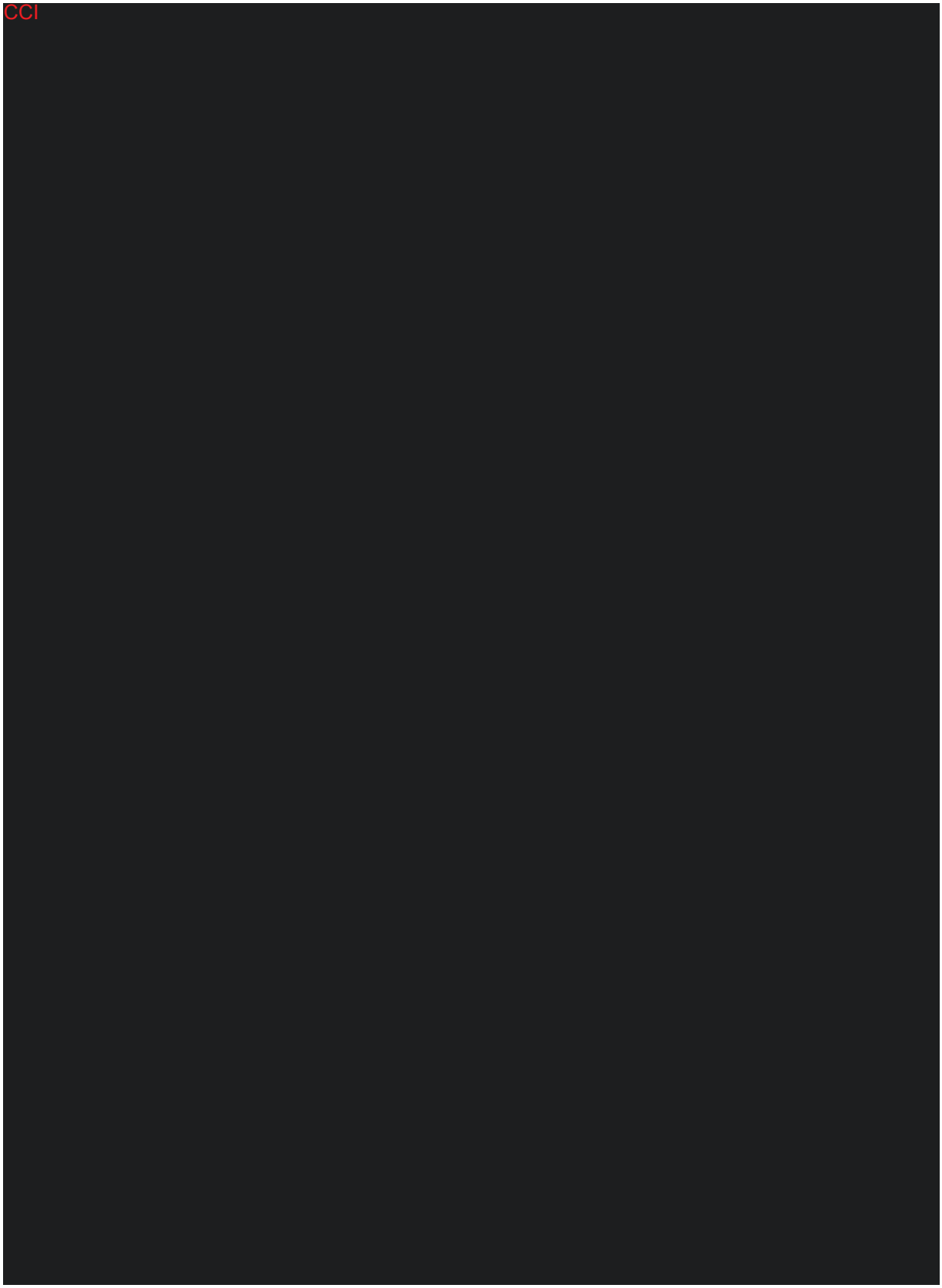

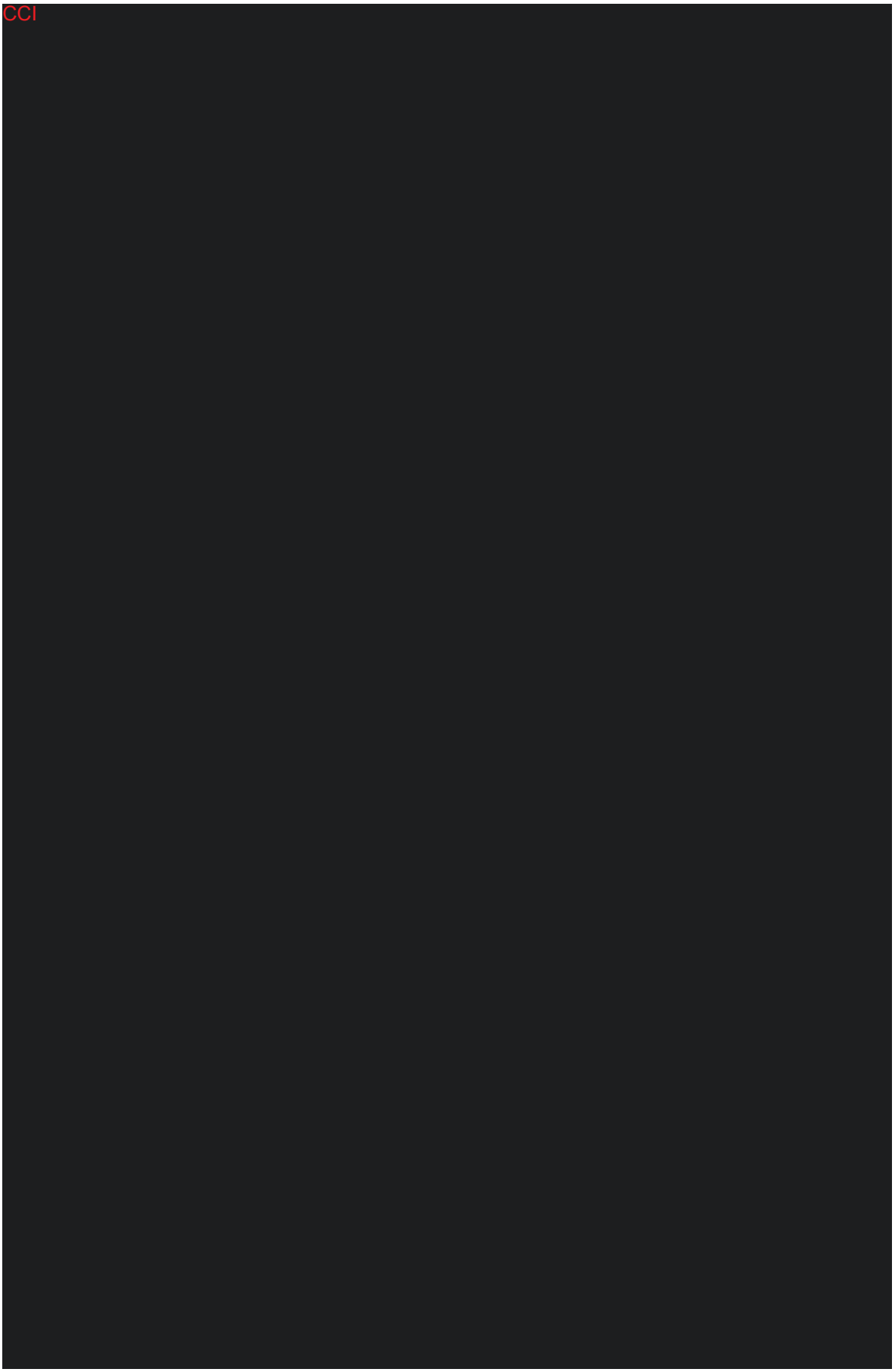
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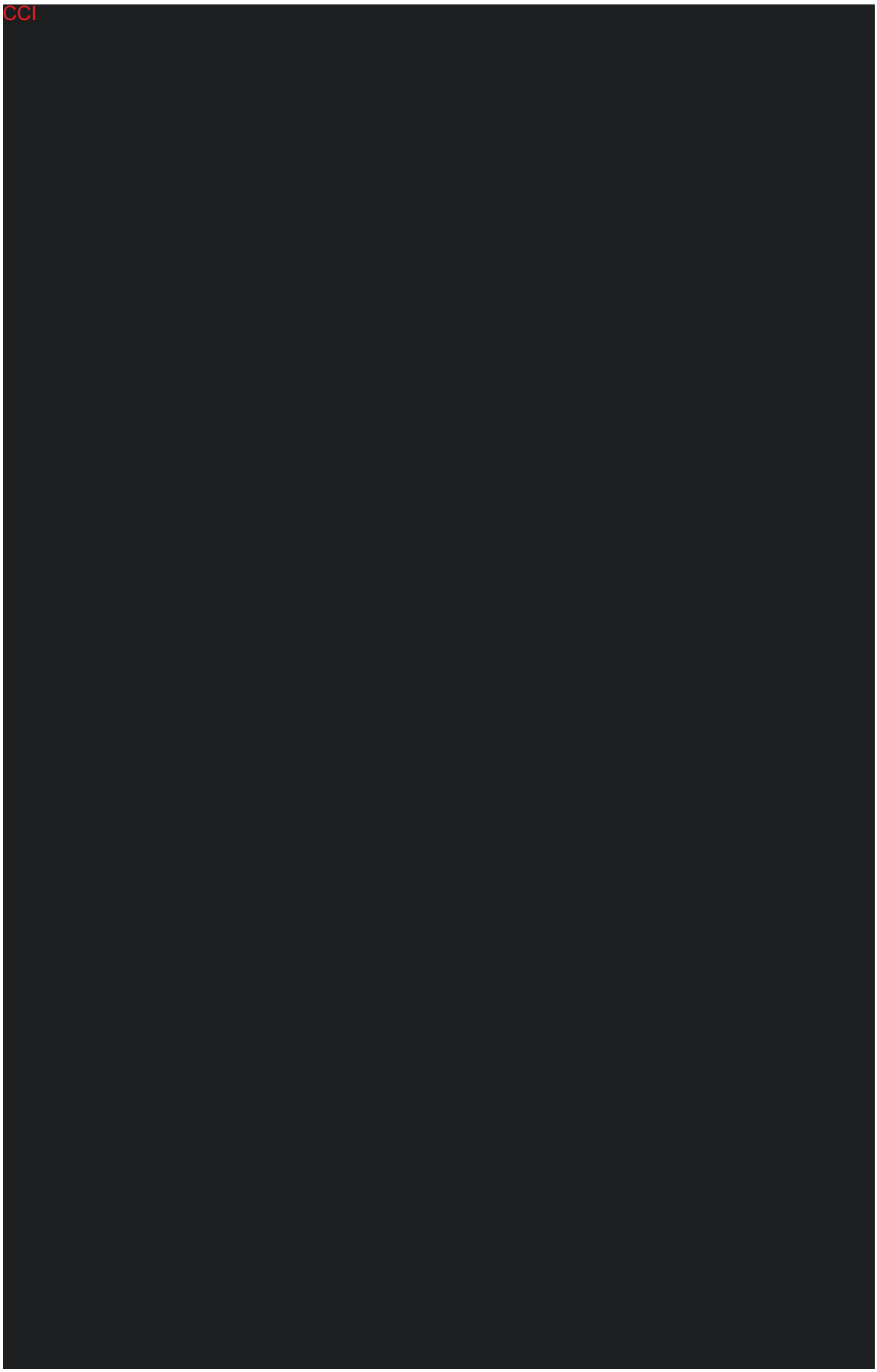

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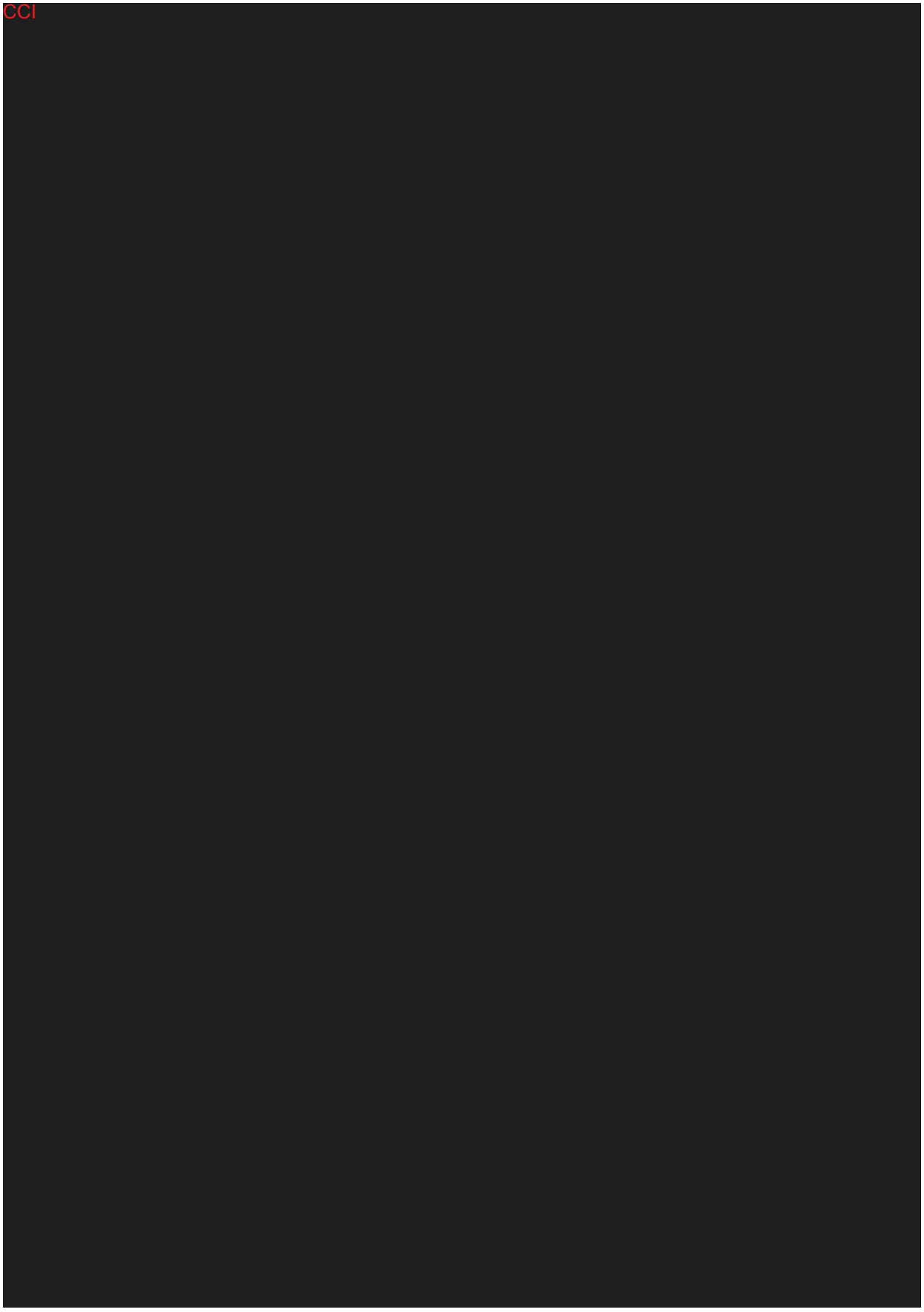

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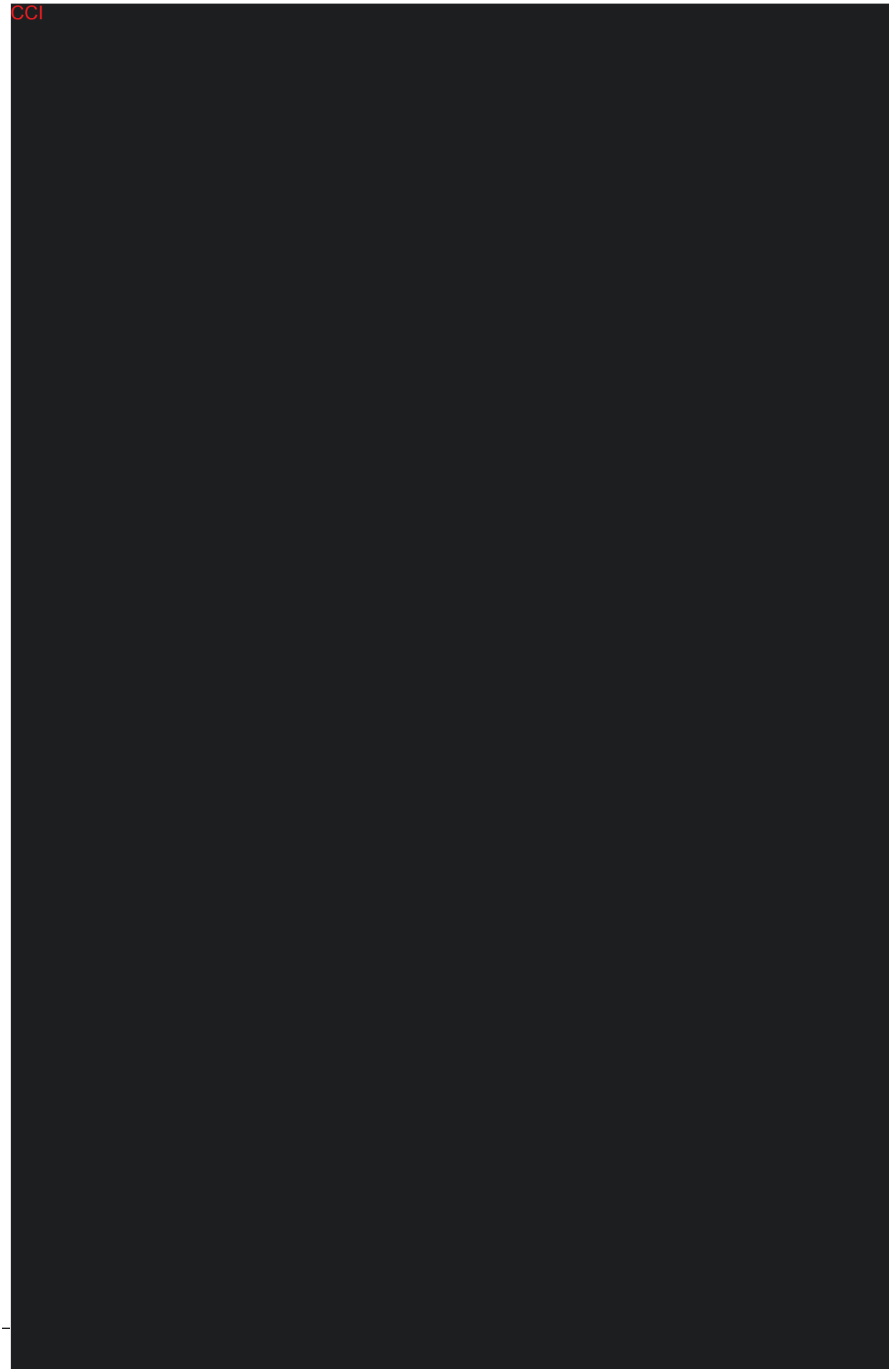

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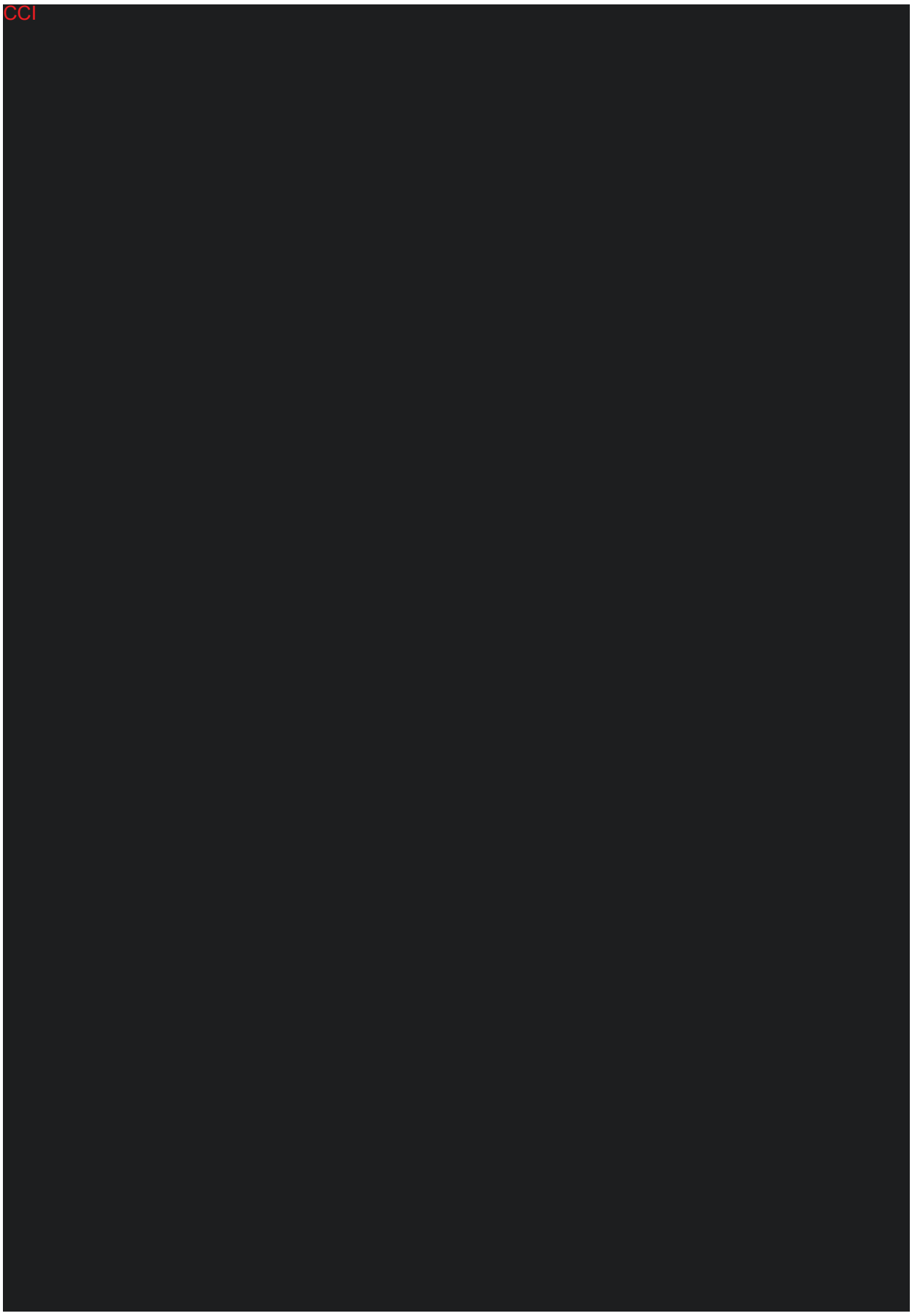

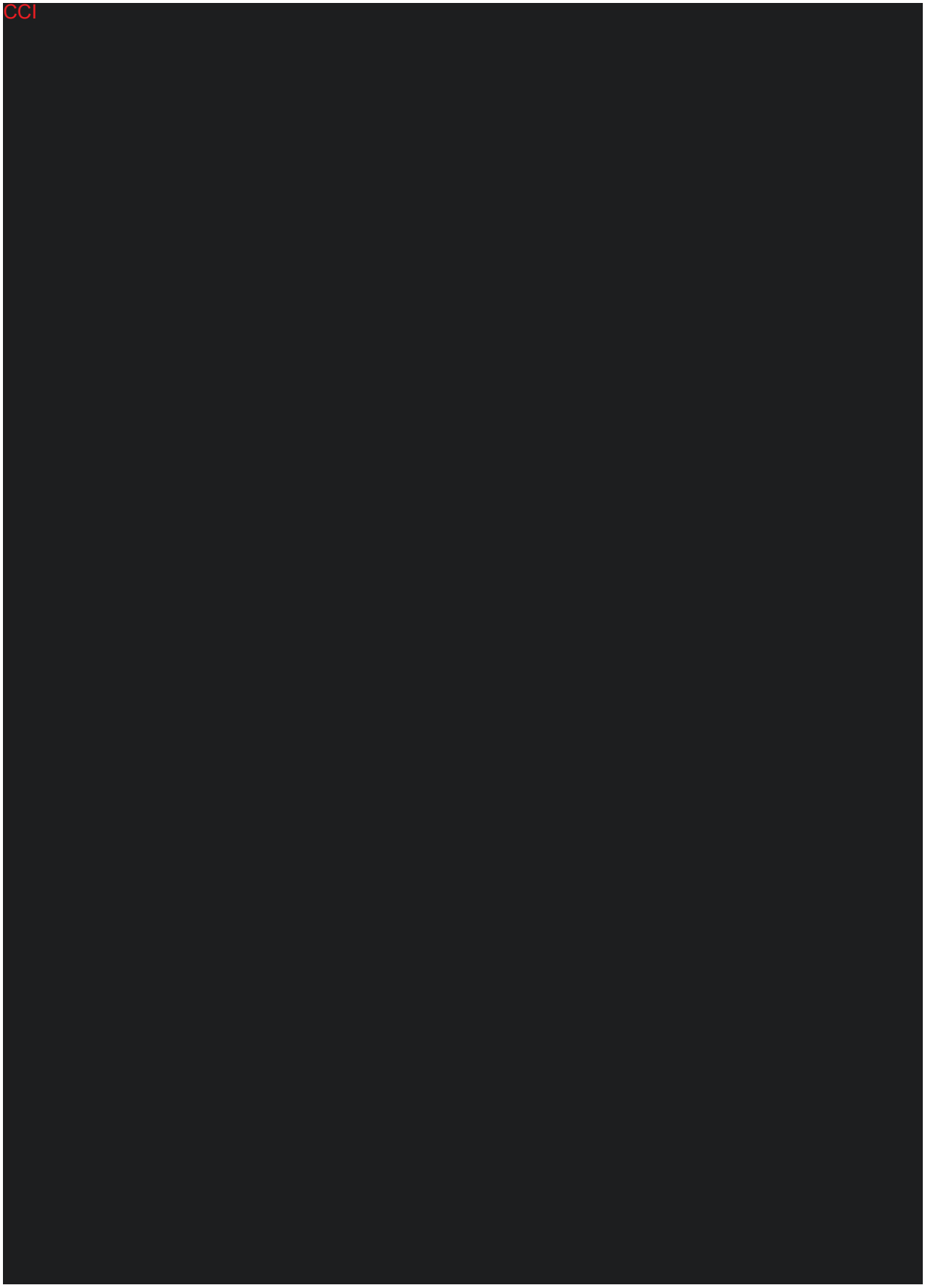
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