Title: A Multicenter, Open-Label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

NCT Number: NCT04654351

Protocol Approve Date: 21-DEC-2020

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 or company confidential information.

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

TAKEDA PHARMACEUTICALS

PROTOCOL

A Multicenter, Open-Label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

An Open-Label, Phase 3 Study of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-chome, Chuo-ku, Osaka, Japan		
Study Number:	TAK-667-3001		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-667		
Date:	21 December 2020	**Amendment Number:**	1

Amendment History:

Date	Amendment Number	Region
19 October 2020	Initial version	All sites
21 December 2020	Amendment No.1	All sites

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the annexes.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this 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.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD Date

PPD Date PPD Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects 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.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator. (Appendix B)

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

1.3 Protocol Amendment 1 Summary of Changes

This document describes the changes in reference to the Protocol Amendment No.1.

The primary purpose of this amendment is to provide an additional example for the basis of medical judgement on the diagnosis of hereditary angioedema (HAE), and also to add description so that the information planned to be obtained will be clear. Minor grammatical and editorial changes are included for clarification purposes only. Full details on changes of text are given in Appendix G, including detailed rationale. The following is a summary of the changes made in the amendment:

- "Information of genetic mutation" is added as an additional example for the basis of medical judgement on the diagnosis of HAE.
- "Presence of previous icatibant administration" and "any clinically significant conditions or diseases relevant to treatment" are added so that the information planned to be obtained will be clear.
- Clarification of representation in the original protocol.

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2.0 STUDY SUMMARY

Name of Sponsoren: Takeda Pharmaceutical Company Limited	**Compound:** TAK-667	
Title of Protocol: A Multicenter, Open-Label, Non-randomized, Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema	**IND No.:** Not Applicable	**EudraCT No.:** Not Applicable
Study Number: TAK-667-3001	**Phase:** 3	

Study Design:

This is a multicenter, open-label, phase 3 study to evaluate the safety, efficacy and pharmacokinetics (PK) of subcutaneous (SC) administration of icatibant in Japanese children and adolescents from 2 to less than 18 years of age with acute attacks of hereditary angioedema (HAE).

Once informed consent is obtained and subject eligibility is established at screening, subjects will begin to receive treatment with icatibant after they present with an acute attack of cutaneous, abdominal, or laryngeal edema. The region and severity of the attack is assessed by investigators.

Subjects eligible at pre-treatment physical examination and assessment will receive treatment with single-dose SC administration of icatibant per attack according to the subject's body weight within 12 hours after the onset of symptom. Up to 2 additional injections are permitted per attack with a time interval of at least 6 hours within 48 hours of the initial injection if there is insufficient relief or worsening of symptoms. If symptoms get worse or recur after more than 48 hours of the initial administration, it will be considered as a new attack. Icatibant will be administered by a healthcare professional, or be self-administered by the subject or the subject's caregiver, e.g. the subject's family, at the study site under the supervision of a healthcare professional. In the case that icatibant is administered by whom other than healthcare professionals, if the subject and his/her legal guardian agree and the investigator considers it appropriate after the subject receives education and training, the patient or his/her caregiver, e.g. the subject's family, will be allowed to self-administer icatibant under the supervision of a healthcare professional.

Subjects will be closely monitored in the hospital/study center for at least 8 hours after administration and receive physical examination and assessment to evaluate safety, efficacy and PK. Hospitalization may be prolonged until, in the opinion of the investigator, the subject is clinically stable and onset of HAE attack is completely resolved.

After discharge, follow-up to assess the subject's condition at >24-48 hours after the final administration (Day 2) will be conducted via a telephone call by investigators and follow-up of safety assessment will be conducted 7 days after initial administration of icatibant (Day 8) at the study site.

After having received initial treatment with icatibant, subjects who subsequently experience acute attacks may continue to receive treatment with icatibant for a total of 3 eligible icatibant-treated attacks if the subject and the subject's parent or the subject's legal guardian consent to further treatment. Further treatment with icatibant is contingent upon presentation of an acute cutaneous, abdominal, or laryngeal edema attack of HAE at least 7 days after first treatment for a prior attack. The new attack of within less than 7 days after first treatment for a prior attack should be treated in accordance with standard of care for HAE without being administrated icatibant. Except for PK assessment, all outcomes are to be measured after each attack as with the initial attack.

The period of active participation in the study may depend on the number of subsequent treatment and thus could be a maximum of approximately 25 days.

Objective:

To evaluate the safety, efficacy and PK of icatibant for the treatment of acute attacks in Japanese children and adolescents with type I or type II HAE.

Subject Population:

Japanese children and adolescents from 2 through <18 years of age who present with cutaneous, abdominal, or laryngeal attacks of acute HAE

Number of Subjects:

At least 3 subjects*

* The enrollment will be continued until the end of the enrollment period and the sample size may exceed 3 subjects.

Number of Sites:

4 sites

Dose Levels:

Regimen; A single, SC administration on the abdomen. If there is insufficient relief or worsening of symptoms, up to 2 additional injections are permitted per attack with a time interval of at least 6 hours within 48 hours of the initial injection.

Dosage; According to the table below, subjects will receive icatibant based on the subject's body weight. (Up to 30 mg)

Subsequent treatment with icatibant for up to 2 additional acute attacks of HAE, for a total of 3 acute attacks, will be offered to subjects who present with a new attack at least 7 days after first treatment for a prior attack if the subject and the subject's parent or the subject's legal guardian consent to further treatment. The dose selection and interval for treatment of subsequent attacks will be the same as that for treatment of the initial attack.

Weight Group	Dose (Injection Volume)
12 kg to 25 kg	10 mg (1.0 mL)
26 kg to 40 kg	15 mg (1.5 mL)
41 kg to 50kg	20 mg (2.0 mL)
51 kg to 65 kg	25 mg (2.5 mL)
>65 kg	30 mg (3.0 mL)

Route of Administration:

SC injection

Duration of Treatment:	**Period of Evaluation:**
Single administration Per attack, if necessary, up to 2 additional injections are permitted. Subjects may receive treatment with icatibant for a total of 3 attacks.	• For the initial attack 9 days: screening period (1 day), pre-treatment, treatment, and post-treatment (2 days), follow-up (7 days after first treatment) • For the subsequent attacks (second attack and third attack) 8 days: pre-treatment, treatment, and post-treatment (2 days), follow-up (7 days after first treatment) The period of evaluation in the study may vary depending on the number of subsequent treatment and could be a maximum of approximately 25 days.

Main Criteria for Inclusion:

1. In the opinion of the investigator or subinvestigator, the subject's parent or legal guardian is capable of understanding and complying with protocol requirements.
2. The subject's parent or the subject's legal guardian is capable of signing and dating a written informed consent form on behalf of the subject prior to the initiation of any study procedures. Written informed assent is also obtained from the subject as much as possible.
3. The subject is in Japan and is Japanese; defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
4. The subject is male or female and 2 to <18years of age (ie, from the second birthday through the day prior to the eighteenth birthday) at the time of informed consent.
5. The subject weighs ≥12 kg at the time of the current HAE attack.
6. The subject who has a documented and confirmed diagnosis of HAE type I or II. Diagnosis may be based on historical data using the following criteria:
   a. Family history of angioedema
   b. Characteristic attack manifestations, recurrent attacks
   c. Functional Complement 1esterase inhibitor (C1-INH) deficiency
   d. In the absence of a family history of angioedema, exclusion of other forms of angioedema (eg. angiotensin converting enzyme (ACE)-induced angioedema, allergic angioedema) based on medical judgement (eg, concomitant medication, response to antihistamines or glucocorticoids, information of genetic mutation).
7. If the subject does not have a documented and confirmed diagnosis of HAE type I or II based on historical data, including C1-INH deficiency, the subject's diagnosis must be determined prior to treatment by C1-INH test results which demonstrate a functional C1-INH deficiency.
   a. HAE type I: Low amount of C1-INH protein and low level of C1-INH activity; HAE type II: Normal or increased amount of C1-INH protein and low level of C1-INH activity
   b. In the absence of a family history of angioedema, exclusion of other forms of angioedema (eg. ACE-induced angioedema, allergic angioedema) based on medical judgement (eg, concomitant medication, response to antihistamines or glucocorticoids, information of genetic mutation).
8. The current HAE attack must be in the cutaneous, abdominal, and/or laryngeal (inclusive of laryngeal and pharyngeal) areas, but no prespecified attack severity criteria are required for treatment.
9. The subject commences treatment within 12 hours after the onset of current HAE attack.
10. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study, and proves negative in the pregnancy test at screening.

Criteria for Exclusion:

1. The subject will require an intervention to support the airway (eg, intubation, tracheotomy, cricothyrotomy) due to the current HAE attack.
2. The subject presents with an HAE attack with laryngeal/upper respiratory tract symptoms which are considered severe in the investigator's clinical judgment and which may necessitate urgent care and/or impede the conduct of study efficacy assessments.
3. The subject has a diagnosis of angioedema other than HAE
4. The subject has evidence of stroke or coronary artery disease based on medical history at the screening examination or at pretreatment; eg, acute ischemic heart disease, unstable angina pectoris, severe coronary heart disease or congestive heart failure, that in the investigator's judgment would be a contraindication for participation in the trial (New York Heart Association [NYHA] class 3 and 4)
5. The subject has received treatment with any pain medication since the onset of the current HAE attack.
6. The subject has received replacement therapy (C1-INH products, fresh frozen plasma [FFP]) within 5 days (120 hours) from the onset of the current HAE attack.
7. The subject has received treatment with ACE inhibitors within 7 days prior to treatment.
8. The subject has used hormonal contraceptive within 90 days prior to treatment.
9. The subject has received androgen or attenuated androgens (eg, danazol, testosterone) within 90 days prior to treatment.
10. The subject has participated in another clinical study within the past 30 days before screening.
11. The subject, the subject's parent, or legal guardian is unable to understand the nature, scope, and possible consequences of the protocol, or is unlikely to comply with the protocol assessments, unable to return for follow up visits, or unlikely to complete the study for any reason.
12. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study, during the study, and within 30 days after last dose of icatibant.
13. The subject has a history of hypersensitivity or allergies to icatibant.
14. The subject is judged by the investigator as being ineligible for any other reason; eg. a serious concomitant illness or condition.

Criteria for Evaluation and Analyses:

(1)Primary Endpoint

<Safety>

- Frequency and severity of treatment emergent adverse events (TEAEs), including injection site reactions

(2)Secondary Endpoints

<Safety>

- Resting 12-lead electrocardiogram parameters in comparison to baseline
- Vital sign measurements in comparison to baseline
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis) in comparison to baseline
- Reproductive hormone levels in comparison to baseline
- Immunogenicity (presence of anti-icatibant antibodies) in comparison to baseline

<Efficacy>

- Time to onset of symptom relief and time to minimal symptom, as measured by investigator- and subject-reported outcomes.
  - For all subjects (2 to <18 years of age): investigator assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score.
  - For subjects ≥4 to <18 years of age only: subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R).
  - For subjects 2 to <4 years of age only: investigator assessment of HAE-related pain using the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale.
- The incidence of rescue medication use.
- The proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC icatibant using investigator-rated symptom scores.
- Time to initial symptom improvement reported by investigator or subject.

<Pharmacokinetics>

Plasma concentrations of icatibant and its major metabolites (M-I and M-II) at 0.5, 1.0, 2.0, and 4.0 hours after the first SC injection for an initial attack.

Statistical Considerations:

(1)Safety

TEAE is defined as an AE that occurs on or after administration of icatibant for each attack and until the end of follow-up period (Day 8). TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and tabulated by the system organ class (SOC) and the Preferred Term (PT), and by icatibant-treated attacks and the total. Injection site reactions will be summarized by severity, and by icatibant-treated attacks and the total, and by severity.

For continuous values of laboratory parameters, vital signs and other safety parameters, summary statistics will be provided for observed values and change from baseline at each evaluation time point and icatibant-treated attack. Pre- and post-dose shift tables will be provided for categorical variables.

(2)Efficacy

All efficacy endpoints will be summarized by icatibant-treated attacks and listed. For the time-to-event endpoints, the survival function (e.g. proportion of subjects not achieving symptom relief) for each assessment time will be calculated by Kaplan-Meier method using the first icatibant-treated attacks within each subject. The second and third icatibant-treated attacks will be listed. Assuming independency in recurrent events within a subject, the survival function for each assessment time will be also calculated by Kaplan-Meier method. Due to the small sample size, no statistical inferences (statistical test nor confidence interval) will be performed.

(3)Pharmacokinetics

Plasma concentrations of icatibant and its metabolites (M-I and M-II) will be summarized at each time point.

Data collected in this study will be combined with those from global studies, and the population PK modeling and simulations will be performed.

Individual pharmacokinetic parameters (e.g. C_{max} and AUC) will be estimated by population PK analysis, if possible. Analysis plan and report of population pharmacokinetic analysis will be provided separately from the clinical study report.

Sample Size Justification:

The planned sample size chosen of 3 subjects administered icatibant in this study is based on the feasibility and is not statistically determined.

3.0 LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
AUC	area under the concentration-time curve
C_{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
C1-INH	complement 1 esterase inhibitor
ECG	12-Lead Electrocardiogram
eCRF	electronic case report form
FPS-R	Faces Pain Scale-Revised
FLACC	Faces, Legs, Activity, Cry, and Consolability
FFP	fresh frozen plasma
FSH	follicle stimulating hormone
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAE	hereditary angioedema
hCG	human chorionic gonadotropin
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IgG	immunoglobulin G
LDH	lactate dehydrogenase
LH	luteinizing hormone
M&S	Modeling & Simulation
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PT	prothrombin time
PT	preferred Term
QOL	quality of life
RMP	risk management plan
SAE	serious adverse event

SC	subcutaneous
SUSARs	suspected unexpected serious adverse reactions
SOC	system organ class
TEAE	treatment emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

4.0 INTRODUCTION

4.1 Background

Hereditary angioedema (HAE) is an autosomal dominant, rare, inherited disorder characterized by repeated episodes of edema in various parts of the body, including the skin, gastrointestinal tract, and larynx, resulting from a quantitative deficiency/dysfunction of complement 1 (C1) esterase inhibitor (C1-INH) caused by mutations of the C1 INH gene and thereby-induced increase of the bradykinin concentration. Skin edema is characterized primarily by disfiguring swelling, and gastrointestinal edema is characterized by acute colicky abdominal pain with vomiting and diarrhea. Laryngeal edema is particularly severe and can result in asphyxiation due to upper airway obstruction. Attacks of HAE usually begin in childhood, increase in frequency and severity around puberty, and recur throughout the patient's life. The attack is induced by various factors, and in many cases, it suddenly appears without recognizing the clear inducers. Therefore, the patients are always forced to live with anxiety and fear of the attack, and the quality of life (QOL) remarkably lowers, and the social participation may become difficult. This is also true for children, especially those who experience attacks, who are prone to anxiety, have difficulty in daily life and schooling, and may experience further attacks. Children also have a smaller airway diameter, which increases more risks of asphyxiation due to a laryngeal attack. Thus, HAE is a serious and life-threatening disease that begins in childhood.

The prevalence of HAE is estimated to be about 1 in 50,000, regardless of race [1]. Based on the estimated prevalence and the national population, the number of HAE patients in Japan is estimated to be about 2,500. However, the number of HAE patients actually reported is even smaller [2][3], and the number of patients diagnosed or treated is estimated to be around 400. The reason may be misdiagnosis due to the similar symptoms of HAE to other common angioedema, and the possibility that some patients may not be diagnosed due to insufficient recognition of the characteristics of the disease.

As for the number of pediatric HAE patients in Japan, there have been no accurate reports to date. The number is estimated to be approximately 30 to 50 patients based on the population estimate in 2020 (percentage of patients aged <15 years: 12.0%) and the percentage of children (aged 0 to 19 years) among 171 Japanese HAE patients confirmed in the latest Japanese HAE survey (8.2%, 14 patients) [3] and is extremely small compared to adults.

As for the treatment for pediatric patients, multiple therapies for acute attack have been developed to date. On the other hand, there is no therapeutic drug for children in Japan, and the development of a drug for pediatric use is an urgent issue.

Icatibant (Generic name: Icatibant Acetate), which is a synthetic decapeptide alleviates symptoms of acute attacks of HAE through a potent and specific competitive antagonism against bradykinin B2 receptor. In Japan, icatibant was approved in September 2018 as "Firazyr® Subcutaneous Injection 30 mg Syringe" for the indication of "acute attacks of hereditary angioedema" in adults. Overseas, it has been approved in approximately 40 countries as of July 2020, including the EU (approved in July 2008) and the US (approved in August 2011). In addition, development of

icatibant for pediatric use was initiated overseas and in October 2017, the indication related to "acute attacks of HAE in children aged 2 years and older" was approved in the EU, and icatibant has been approved in approximately 30 countries as of July 2020.

Global phase 3 study in 98 adult patients with HAE (HGT-FIR-054), Japanese phase 3 study in 8 adult patients with HAE (SHP-FIR-301), and global phase 3 study in 32 pediatric patients with HAE (HGT-FIR-086) were conducted as major clinical studies of icatibant in HAE patients.

In the placebo-controlled, double-blind study in adult patients with HAE (HGT-FIR-054), in the subjects with cutaneous and/or abdominal edema, subjects treated with icatibant consistently had an earlier onset of symptom relief than those who received placebo. The median time to symptom relief was 2.0 hours in the icatibant group and 19.8 hours in the placebo group, showing that icatibant is superior to placebo ($p < 0.001$). In the subjects with laryngeal edema, early symptom relief as seen in the non-laryngeal edema population was indicated. In Japanese open-label, uncontrolled study in 8 adult patients with HAE (SHP-FIR-301), the median time to symptom relief in all subjects was 1.75 hours, showing that the similar efficacy results as seen in the global study were obtained. In terms of safety, SC administration of icatibant was well tolerated in both studies. Although injection site reaction was observed as a common AE, it was mild or moderate in severity and generally transient.

In the open-label, non-randomized study in pediatric patients aged 2 to <18 years with HAE (HGT-FIR-086), the median time to symptom relief in the efficacy analysis set was 1.0 hours, with approximately 60% and 95% of patients showing symptom relief at 1 and 2 hours post-dose, respectively. Icatibant was generally well tolerated, the safety profile was similar to that of adult patients and no new safety concern was observed.

In the juvenile toxicity studies, the effects on hormone levels, reproductive organs, and sexual maturation in juvenile/immature rats and dogs repeatedly administered high doses of icatibant was observed. However, these findings were reversible and were less marked when icatibant was administered on an intermittent, clinically relevant dosing regimen. Furthermore, examination of effects on reproductive parameters in clinical studies demonstrated no effects of repeatedly administered icatibant on reproductive hormones, semen parameters, or menstrual cycle length.

As described above, HAE is a serious and life-threatening disease that begins in childhood, but there is still no medication for children in Japan. Therefore, in order to meet the unmet needs for pediatric HAE medication in Japan, pediatric development has been started with the aim of obtaining the pediatric dosage and administration of icatibant.

4.2 Rationale for the Proposed Study

As of now, there are no clinical study data of the safety, efficacy and PK of icatibant in pediatric patients in Japan. Therefore, this study was designed to assess the safety, efficacy and PK of icatibant in the planned dosage and administration in pediatric patients in Japan.

This protocol has been prepared in accordance with Good Clinical Practice (GCP).

For conducting this study, the sponsor had the end of phase 2 meeting with the Pharmaceuticals and Medical Devices Agency of Japan (PMDA) on [redacted]

4.3 Benefit/Risk Profile

The efficacy and safety of icatibant have been confirmed to be consistent in the global phase 3 study in adult patients with HAE (HGT-FIR-054), global phase 3 study in pediatric patients with HAE (HGT-FIR-086) and Japanese phase 3 study in adult patients with HAE (SHP-FIR-301).

The differences between the reference population, e.g. non-Japanese adult and pediatric patients and Japanese adult patients, and the target Japanese pediatric population are the ethnic factors and age (adults and children). Based on multiple researches, relevant guidelines in and outside of Japan and other pathological data, the disease pathophysiology, natural course, and disease course of HAE are considered to be similar between these ethnic groups and ages. An examination of the exposure-response relationships among the reference populations showed that ethnic and age differences had no substantial impact on the treatment response to icatibant, with similar treatment responses observed between non-Japanese and Japanese adult patients and between non-Japanese adult and pediatric patients. Therefore, favorable efficacy similar to that in non-Japanese adult and pediatric patients and Japanese adult patients is expected in Japanese pediatric patients. In addition, no specific safety risks to Japanese children are expected.

The risks of icatibant identified in Japanese and EU risk management plan (RMP) are as follows. This study defines these as adverse events of special interest and is carefully monitored.

- Injection site reaction – listed as important identified risk in Japan/EU RMP; Local injection site reactions were observed in almost all icatibant-treated subjects. Most injection site reactions were transient, mild to moderate in severity, and completely resolved within 4-8 hours of treatment. Injection site reactions will be evaluated by the investigator when the subject is at the hospital/study center, and the diameter of any erythema or swelling will be measured. After discharge, the subject (or the subject's parent/legal guardian on behalf of the subject as appropriate) will be interviewed about injection site reactions, either in person or by telephone contact.
- Immunogenicity (Hypersensitivity) – listed as important potential risk in Japan RMP; In clinical studies, icatibant was generally nonimmunogenic. In over repeated treatment, transient positivity in test results for the presence of anti-icatibant immunoglobulin G (IgG) antibodies was observed in rare cases. The immunogenicity of icatibant will be assessed. Serum samples for immunogenicity testing will be collected for determination of anti-icatibant antibodies.
- Reproductive hormone level in pubertal/ post-pubertal children – listed as important potential risk in EU RMP; Although in the juvenile toxicity studies, the effects on hormone levels, reproductive organs, and sexual maturation in juvenile/immature rats and dogs was observed, no clinically significant changes in reproductive hormones were observed during global clinical studies in pediatric HAE patients. Blood samples will be collected to assess follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone in females, and FSH, LH, and testosterone in males.
- Hypotension and cardiac dysfunction – listed as important potential risk in Japan RMP; In vitro studies have shown that icatibant activates human mast cells and decrease of blood pressure was observed in a high-volume bolus intravenous injection study of icatibant. In

addition, the bradykinin antagonism of icatibant may pose a potential risk to patients with cardiovascular disease. Although no clinically significant hypotensive action and safety concerns for cardiovascular system was observed in clinical studies, hypotension and cardiac dysfunction will be assessed by standard safety testing including vital signs and ECG.

The Investigator's Brochure should be referred for more detailed safety of icatibant.

Based on the benefits that can be conferred to pediatric HAE subjects, as well as the risks and the appropriate measures to mitigate them, a favorable benefit-risk profile is expected for this population.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objective

To evaluate the safety, efficacy and PK of icatibant for the treatment of acute attacks in Japanese children and adolescents with type I or type II HAE.

5.2 Endpoints

5.2.1 Primary Endpoint

Safety:

- Frequency and severity of treatment-emergent adverse events (TEAEs), including injection site reactions

5.2.2 Secondary Endpoints

Safety:

- Resting 12-lead electrocardiogram parameters in comparison to baseline
- Vital sign measurements in comparison to baseline
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis) in comparison to baseline
- Reproductive hormone levels in comparison to baseline
- Immunogenicity (presence of anti-icatibant antibodies) in comparison to baseline

Efficacy:

- Time to onset of symptom relief and time to minimal symptom, as measured by investigator- and subject-reported outcomes.
  - For all subjects (2 to <18 years of age): investigator assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score.
    - The time to onset of symptom relief, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which at least a 20% improvement is observed in the average post-treatment score with no worsening of any single component score.
    - The time to minimal symptoms, defined as the duration of time in hours from the time of icatibant administration to the earliest time post-treatment when all symptoms are either mild or absent based on the investigator-rated symptom score.
  - For subjects ≥4 to <18 years of age only: subject self-assessment of HAE-related pain using the Faces Pain Scale-Revised (FPS-R).

- ✧ The time to onset of symptom relief, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the post-treatment score improved by at least 1 level.
- ✧ The time to minimal symptoms, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the post-treatment score improved to 0.

➢ For subjects 2 to <4 years of age only: investigator assessment of HAE-related pain using the Faces, Legs, Activity, Cry, and Consolability (FLACC) scale.

- ✧ The time to onset of symptom relief, defined as the earliest time at which a 20% improvement is observed in the total post-treatment score.
- ✧ The time to minimal symptoms, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the total post-treatment score improved to 0.

- The incidence of rescue medication use.
- The proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC icatibant using investigator-rated symptom scores.
- Time to initial symptom improvement reported by investigator or subject
  - ✧ Time to initial symptom improvement reported by investigator, defined as the duration of time in hours from icatibant administration until the time when overall subject improvement was first noted by investigator.
  - ✧ Time to initial symptom improvement reported by subject, defined as the duration of time in hours from icatibant administration until the time when overall subject improvement was first noted by subject, subject's parent or subject's legal guardian.

Pharmacokinetics:

Plasma concentrations of icatibant and its major metabolites (M-I and M-II) at 0.5, 1.0, 2.0, and 4.0 hours after the first SC injection for an initial attack.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a multicenter, open-label, phase 3 study to evaluate the safety, efficacy and PK of SC administration of icatibant in Japanese children and adolescents from 2 to less than 18 years of age with acute attacks of HAE.

Once informed consent is obtained and subject eligibility is established at screening, subjects will begin to receive treatment with icatibant after they present with an acute attack of cutaneous, abdominal, or laryngeal edema. The region and severity of the attack is assessed by investigators.

Subjects eligible at pre-treatment physical examination and assessment will receive treatment with single-dose SC administration of icatibant per attack according to the subject's body weight within 12 hours after the onset of symptom. Up to 2 additional injections are permitted per attack with a time interval of at least 6 hours within 48 hours of the initial injection if there is insufficient relief or worsening of symptoms. If symptoms get worse or recur after more than 48 hours of the initial administration, it will be considered as a new attack. Icatibant will be administered by a healthcare professional, or be self-administered by the subject or the subject's caregiver, e.g. the subject's family, at the study site under the supervision of a healthcare professional. In the case that icatibant is administered by whom other than healthcare professionals, if the subject and his/her legal guardian agree and the investigator considers it appropriate after the subject receives education and training, the subject or his/her caregiver, e.g. the subject's family, will be allowed to self-administer icatibant under the supervision of a healthcare professional.

Subjects will be closely monitored in the hospital/study center for at least 8 hours after administration and receive physical examination and assessment to evaluate safety, efficacy and PK. Hospitalization may be prolonged until, in the opinion of the investigator, the subject is clinically stable and onset of HAE attack is completely resolved.

After discharge, follow-up to assess the subject's condition at >24-48 hours after the final administration (Day 2) will be conducted via a telephone call by investigators and follow-up of safety assessment will be conducted 7 days after initial administration of icatibant (Day 8) at the study site.

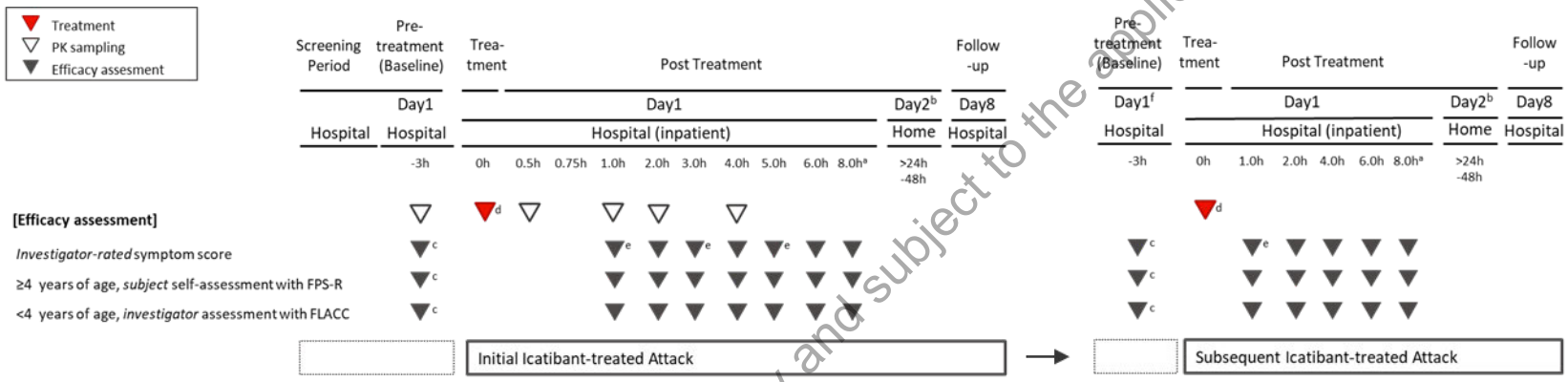
After having received initial treatment with icatibant, subjects who subsequently experience acute attacks may continue to receive treatment with icatibant for a total of 3 eligible icatibant-treated attacks if the subject and the subject's parent or the subject's legal guardian consent to further treatment. Further treatment with icatibant is contingent upon presentation of an acute cutaneous, abdominal, or laryngeal edema attack of HAE at least 7 days after first treatment for a prior attack. The new attack of within less than 7 days after first treatment for a prior attack should be treated in accordance with standard of care for HAE without being administrated icatibant. Except for PK assessment, all outcomes are to be measured after each attack as with the initial attack.

The period of active participation in the study may depend on the number of subsequent treatment and thus could be a maximum of approximately 25 days.

Sites will employ all efforts to see subjects in the hospital/study center for assessments. In unavoidable circumstances (eg, a widespread disease outbreak such as the coronavirus disease 2019 (COVID-19) pandemic or natural disaster), exceptions may be consulted for alternative visits or assessments for conducting subject visits with approval by the Medical Monitor and/or sponsor. Such instances will be documented in the study records as related to unavoidable circumstances (eg, COVID-19).

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



a) Hospitalization may be prolonged until the investigator determines that the clinical condition is stable and the subject's HAE symptoms are resolved. In this case, as a general rule, the efficacy evaluation (investigator-rated symptom score, FPS-R, FLACC scale) and injection site reaction evaluation are performed every 2 hours including 8 hours after administration, until discharge. Initial symptom improvement (investigator and subject), adverse events, and concomitant medications will be continuously evaluated until discharge. Physical examination, vital signs, ECG, clinical laboratory tests and reproductive hormone assessments are performed only at discharge.

b) A contact via telephone is scheduled at >24-48 hours after the final administration. If hospitalization continues 48 hours after the last dose, assessments are performed at the hospital.

c) Investigator-rated symptom score, FPS-R, FLACC scale will be performed within 1 hour prior to treatment. Other assessments are performed within the acceptable range up to 3 hours before administration.

d) Administration of icatibant will consist of 1 SC injection of icatibant. However, a maximum of 3 SC injections of icatibant with at least 6 hours intervals can be given for treatment of an attack if, within 48 hours of the initial injection, there is insufficient relief or worsening of symptoms.

e) The vomiting and diarrhea assessments will be performed every 2 hours and, therefore, are excluded from the investigator-rated symptom score at the time points indicated.

f) In the event that a subsequent attack occurs at least 7 days after first treatment for a prior attack, but within the window (+1 day) allowed for performance of follow-up (Day 8) assessments associated with a prior attack, the follow-up (Day 8) assessments may also serve as the pretreatment (baseline) assessments for the subsequent attack.

6.2 Justification for Study Design, Dose, and Endpoints

<Justification for Study Design>

The purpose of this study is to evaluate the safety, efficacy and PK of icatibant in the treatment of acute attacks in Japanese pediatric patients with HAE Type I or II. Considering the ethical point of view that this is a pediatric study and from feasibility point of view, it was determined to conduct the study as an open-label, single-arm study.

Studies HGT-FIR-086 and SHP-FIR-301, which were also conducted as open-label studies from the viewpoint of feasibility, confirmed that the efficacy and safety were consistent with those in the placebo-controlled comparative study in non-Japanese adult patients (HGT-FIR-054) and verified the effectiveness of icatibant in non-Japanese pediatric patients and Japanese adult patients. Therefore, it is considered possible to evaluate the safety, efficacy and PK of icatibant in Japanese children in the same way by conducting this study.

<Justification for Dose>

The dose was set to be the same as the dosage and administration planned for pediatric application in Japan. This dose is the same as the approved dosage and administration in the EU.

In Study HGT-FIR-086, a single dose of icatibant 0.4 mg/kg (up to 30 mg) was administered subcutaneously to pediatric patients who presented with an acute attack, and the symptoms of the attack were relieved within 2 hours after administration. Based on this result, in the application for pediatric indication in the EU, etc., a Modeling & Simulation (M&S) approach was used to set the recommended dose for each body weight category and it was approved.

Ethnic differences and age in light of the treatment response to icatibant were examined, and the results showed similar efficacy and safety between Japanese adults and non-Japanese adults as well as between adults and children. In the preliminary M&S conducted in Japanese pediatric patients, the exposure to icatibant after subcutaneous icatibant administration at body weight category-based doses in Japanese pediatric patients was predicted as lower than the exposure in non-Japanese pediatric patients after administration of icatibant at 0.4 mg/kg (up to 30 mg), but was similar to that in Japanese adult patients and within the range of the exposure, at which effects of symptom relief was observed. This was considered to indicate that the efficacy in Japanese pediatric patients is expected to be similar to that in Japanese adult patients and non-Japanese pediatric patient. On the other hand, the exposure estimated in Japanese pediatric patients is not expected to exceed the exposure for which safety has been confirmed in Japanese adults and non-Japanese children, and therefore, we consider that there is no particular safety concern in Japanese pediatric patients.

Based on the above, the doses for children in this study was set to be the same as the doses for each body weight category already approved in Europe.

The dosage and administration approved for adults in Japan is as follows: “In adults, icatibant 30 mg per dose is usually injected subcutaneously. If response is inadequate or symptoms recur, an additional injection of 30 mg may be administered at an interval of at least 6 hours. Do not administer more than 3 injections in 24 hours.” If symptoms are inadequately relieved or worsen

within 48 hours after the first dose, it will also be allowed for an attack in this study to administer up to 3 doses, including the first dose, at intervals of at least 6 hours. In the global studies in adults, icatibant was administered for up to 3 times at maximum in patients whose symptoms were not adequately relieved by single-dose administration. As a result, symptom relief was observed in all patients with no safety concerns.

Since attack symptoms generally peak by approximately 24 hours after onset [4, 5], worsening of symptoms not less than 48 hours after the first dose will be considered as a new attack episode, and a maximum of 3 doses per attack should be administered within 48 hours of the first dose.

<Justification for Methods of administration>

Icatibant is an injection solution that is administered urgently for symptom relief at the time of attacks. Therefore, the method of administration in children is intended to be self-administration outside the medical institution, such as home, as well as administration by a healthcare professional as is the case with adults. For this reason, icatibant will be administered by a healthcare professional, or the patient or his/her caregiver, e.g. the subject's family under the supervision of a healthcare professional, within 12 hours after the onset of an attack if the subject and his/her legal guardian agree and the investigator considers it appropriate after the subject receives education and training. For subsequent treatment, the subject and the subject's caregiver will be encouraged to self-administer icatibant under the supervision of a healthcare professional.

Since dose adjustment is required in pediatric patients weighing ≤65 kg, the same graduated syringe and connecter for children as that used overseas will be used.

<Justification for Endpoints>

For safety evaluation, general safety endpoints and injection site reaction, which is an important identified risk of icatibant, were selected as endpoints because no new safety risk in Japanese children is expected based on the results of Studies HGT-FIR-086 and SHP-FIR-301, etc. Immunogenicity (hypersensitivity), hypotension and cardiac dysfunction, which are potential risks of icatibant, were selected as adverse event of special interest, and presence of anti-icatibant antibodies is to be assessed for immunogenicity. Taking into consideration the fact that the subjects of this study are children, it was also determined to evaluate the effects on reproductive hormones.

For the efficacy evaluation, it was determined to evaluate the time to symptom relief using the symptom score for acute attack symptoms of HAE (severity scale of 8 symptoms related to skin and abdominal attacks or 13 symptoms including these 8 symptoms and laryngeal edema-related symptoms) by investigators, because it is expected that preschoolers will also be enrolled in this study, similarly to Study HGT-FIR-086. This endpoint has also been evaluated in the global phase 3 studies in adults and children as well as the Japanese phase 3 study in adults (HGT-FIR-054, HGT-FIR-086, and SHP-FIR-301), and the results can be compared among studies. In addition, FPS-R that enables children to visually assess pain and FLACC that enables the investigator to objectively assess pain in children with immature language ability will be used together for subjects aged 4 years and older and subjects aged less than 4 years, respectively. For these

endpoints, time to symptom relief and time to symptom minimization were defined in the same manner, taking into consideration the comparability of the results with Study HGT-FIR-086.

For PK, since the subjects of the study are children, blood sampling will be performed at 5 time points, which is considered to be the minimum to allow investigation of the PK characteristics of icatibant in Japanese pediatric patients, to reduce the burden on the subjects.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk /benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before icatibant is administered for initial attack and subsequent attacks.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator or subinvestigator, the subject's parent or legal guardian is capable of understanding and complying with protocol requirements.
2. The subject's parent or the subject's legal guardian is capable of signing and dating a written informed consent form on behalf of the subject prior to the initiation of any study procedures. Written informed assent is also obtained from the subject as much as possible.
3. The subject is in Japan and is Japanese; defined as born in Japan and having Japanese parents and Japanese maternal and paternal grandparents.
4. The subject is male or female and 2 to <18 years of age (ie, from the second birthday through the day prior to the eighteenth birthday) at the time of informed consent.
5. The subject weighs ≥12 kg at the time of the current HAE attack.
6. The subject who has a documented and confirmed diagnosis of HAE type I or II. Diagnosis may be based on historical data using the following criteria:
   a. Family history of angioedema
   b. Characteristic attack manifestations, recurrent attacks
   c. Functional C1-INH deficiency
   d. In the absence of a family history of angioedema, exclusion of other forms of angioedema (eg. ACE-induced angioedema, allergic angioedema) based on medical judgement (eg, concomitant medication, response to antihistamines or glucocorticoids, information of genetic mutation).
7. If the subject does not have a documented and confirmed diagnosis of HAE type I or II based on historical data, including C1-INH deficiency, the subject's diagnosis must be determined prior to treatment by C1-INH test results which demonstrate a functional C1-INH deficiency.
   a. HAE type I: Low amount of C1-INH protein and low level of C1-INH activity; HAE type II: Normal or increased amount of C1-INH protein and low level of C1-INH activity
   b. In the absence of a family history of angioedema, exclusion of other forms of angioedema (eg. ACE-induced angioedema, allergic angioedema) based on medical judgement (eg, concomitant medication, response to antihistamines or glucocorticoids, information of genetic mutation).

8. The current HAE attack must be in the cutaneous, abdominal, and/or laryngeal (inclusive of laryngeal and pharyngeal) areas, but no prespecified attack severity criteria are required for treatment.
9. The subject commences treatment within 12 hours after the onset of current HAE attack.
10. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study, and proves negative in the pregnancy test at screening.

*Definitions and highly effective methods of contraception are defined in Section 9.1.17 and reporting responsibilities are defined in Section 9.1.18.

7.1.1 Justification of Inclusion Criteria

Criteria 1 and 2 were set as basic matters to conduct clinical studies in pediatric subjects

Criteria 3 to 5 and 8 were set because of the specific requirements of the study population.

Criteria 6 and 7 were set for subjects with a diagnosis of hereditary angioedema, and therefore "Hereditary angioedema (HAE) guidelines (2019 revision)" [4] and " The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update" [6] diagnostic criteria.

Criteria 9 was set to suppress the variation in administration timing among subjects.

Criteria 10 was set as basic matters to conduct clinical studies.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject will require an intervention to support the airway (eg, intubation, tracheotomy, cricothyrotomy) due to the current HAE attack.
2. The subject presents with an HAE attack with laryngeal/upper respiratory tract symptoms which are considered severe in the investigator's clinical judgment and which may necessitate urgent care and/or impede the conduct of study efficacy assessments.
3. The subject has a diagnosis of angioedema other than HAE
4. The subject has evidence of stroke or coronary artery disease based on medical history at the screening examination or at pretreatment; eg, acute ischemic heart disease, unstable angina pectoris, severe coronary heart disease or congestive heart failure, that in the investigator's judgment would be a contraindication for participation in the trial (New York Heart Association [NYHA] class 3 and 4).
5. The subject has received treatment with any pain medication since the onset of the current HAE attack.

6. The subject has received replacement therapy (C1-INH products, fresh frozen plasma [FFP]) within 5 days (120 hours) from the onset of the current HAE attack.
7. The subject has received treatment with ACE inhibitors within 7 days prior to treatment.
8. The subject has used hormonal contraceptive within 90 days prior to treatment.
9. The subject has received androgen or attenuated androgens (eg, danazol, testosterone) within 90 days prior to treatment.
10. The subject has participated in another clinical study within the past 30 days before screening.
11. The subject, the subject's parent, or legal guardian is unable to understand the nature, scope, and possible consequences of the protocol, or is unlikely to comply with the protocol assessments, unable to return for follow up visits, or unlikely to complete the study for any reason.
12. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study, during the study, and within 30 days after last dose of the icatibant.
13. The subject has a history of hypersensitivity or allergies to icatibant.
14. The subject is judged by the investigator as being ineligible for any other reason; eg. a serious concomitant illness or condition.

7.2.1 Justification of Exclusion Criteria

Criteria 1, 2 and 4 were set to ensure overall safety of the study participants and because of the potential for bias in evaluation of the safety and the efficacy.

Criteria 3, 9 and 10 were set because of the potential for bias in evaluation of the safety and the efficacy.

Criteria 5 to 7 were set because of the potential for bias in evaluation of the efficacy.

Criteria 8 and 12 were set because of the potential for bias in evaluation of the safety.

Criteria 11 was set as basic matters to conduct clinical studies.

Criteria13 and 14 were set to ensure overall safety of the study participants.

7.3 Excluded Medications, Procedures, and Treatments

- Other investigational product (drug or device): within 30 days prior to screening and during the study
- Pain medication: after onset of the current HAE attack and during the hospitalization
- ACE inhibitors: within 7 days prior to treatment and during the study
- Androgens or attenuated androgens (eg, danazol, testosterone): within 90 days prior to treatment and during the study
- Hormonal contraceptives: within 90 days prior to treatment and during the study

- Replacement therapy (C1-INH products, FFP): within 5 days (120 hours) from the onset of the current HAE attack and during the hospitalization

Prophylactic therapies for HAE (eg, anti-fibrinolytics or C1-INH products) other than attenuated androgens (eg, danazol) will be allowed when it is used in a stable regimen, but therapies known to attenuate an acute HAE attack (eg, C1-INH products, FFP) must not be used during the attack being treated with icatibant unless these are required as rescue medications.

Any medicinal product may be used as rescue medication at the discretion of the investigator or subinvestigator.

For the purposes of this protocol, rescue medication is defined as any medication used after the administration of icatibant which, in the opinion of the investigator, is immediately necessary to alleviate acute symptoms which are judged by the investigator to be resultant from the current HAE attack. Rescue medication includes therapies for HAE (eg, C1-INH products, FFP) used for HAE attack and symptomatic treatment used in order to improve symptoms of angioedema (eg, pain and nausea). The determination of the necessity for rescue medication will be at the discretion of the investigator.

7.3.1 Justification of Excluded Medications

"Other investigational product (drug or device)", and "Androgens or attenuated androgens" were selected for its potential to interfere with the evaluation of safety/efficacy endpoints.

"Hormonal contraceptives" was selected for its potential to interfere with the reproductive hormones assessment.

"Pain medication", "ACE inhibitors" and "Replacement therapy" was selected for its potential to interfere with the evaluation of efficacy endpoints

7.4 Activity Control and Treatment Facilities

The investigator, the subinvestigator, and the study collaborator should instruct the subject, the subject's parent or the subject's legal guardian to adhere the following study requirements.

1. Subjects will be instructed to inform the investigator or subinvestigator before receiving treatment from another doctor, or to provide details of treatment the subject received in case of reporting afterwards. Subjects receiving treatment by another doctor will be instructed to inform another doctor of their participation in this study before the participation, as far as possible.
2. Subjects will be instructed to consult the investigator or subinvestigator before using or changing the dosage of any drug not prescribed by the investigator or subinvestigator (including vitamins supplements, over-the-counter medications, and herbal preparations). Subjects will be instructed to promptly provide the details when they use any such drug.
3. Subjects will be instructed to visit the study site at the scheduled times to undergo examinations and tests by the investigator or subinvestigator. Subjects will be instructed to

promptly inform the investigator or subinvestigator when they are unable to visit the study site as scheduled.

4. Female subjects of childbearing potential (eg, a female subject of childbearing potential is defined by the investigator's or subinvestigator's positive opinion about the subject's reproductive potential) will be instructed to use appropriate contraception from signing of informed consent to 30 days after completing the study (Section 9.1.17).

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 9.1.21.

1. Death. The subject died on study.

   Note: If the subject dies on study, the event will be considered as serious adverse event (SAE). See Section 10.2.2 for the reporting procedures.

2. Adverse event (AE). The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

   - Liver Function Test (LFT) Abnormalities
     Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 10.2.3), if the following circumstances occur at any time during study drug treatment:
     - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8 × upper limit of normal (ULN), or
     - ALT or AST >5 × ULN and persists for more than 2 weeks, or
     - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or
     - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

3. Significant protocol deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Voluntary withdrawal by the subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related adverse event), this should be specified as the reason for "voluntary withdrawal" in the eCRF.

6. Voluntary withdrawal by subject's parent/subject's legal guardian. The subject's parent/subject's legal guardian wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category.). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related adverse event), this should be specified as the reason for "voluntary withdrawal" in the eCRF.

7. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
8. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.18.

9. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
10. Other.

    Note: The specific reasons including unavoidable circumstances such as the COVID-19 pandemic should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

(1) Dosage form and manufacturing

Code name: TAK-667

Generic name: Icatibant Acetate (JAN)

Chemical name:

D-Arginyl-L-arginyl-L-prolyl-(R)-4-hydroxy-L-prolylglycyl-3-(thiophen-2-yl)-L-alanyl-L-seryl-(R)-[(1,2,3,4-tetrahydroisoquinolin-3-yl)carbonyl]-(2S,3aS,7aS)-[(hexahydroindolin-2-yl)carbonyl]-L-arginine triacetate

Dosage form: Injection

Formulation: Colorless to pale yellow clear liquid

Strength: Contains 34.14 mg of Icatibant Acetate (30.00 mg as Icatibant) in a syringe (3.0 mL)

Manufacturing: Takeda Pharmaceutical Company Limited

(2) Package and labeling

1) Package

Firazyr® 30 mg subcutaneous injection Syringe: 3.0 mL×1 Syringe

2) Labeling

Each outer box indicates the following information: the drug is for the study use only, study drug name, protocol number, the sponsor's name and address, batch number, storage condition and expiry date.

8.1.2 Storage

The study drugs are to be stored from 2 to 25°C.

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

A single, five-weight-band dosing up to a maximum of 30 mg SC administration. Injection site is abdomen in principle. If there is insufficient relief or worsening of symptoms, up to 2 additional injections are permitted per attack with a time interval of at least 6 hours within 48 hours of the initial injection. Dosage is shown in Table 8.a. Weight group will be selected based on body weight measured at baseline visit.

Subsequent treatment with icatibant for up to 2 additional acute attacks of HAE, for a total of 3 acute attacks, will be offered to subjects who present with a new attack at least 7 days after first treatment for a prior attack if the subject and the subject's parent or the subject's legal guardian consent to further treatment. The dose selection and interval for treatment of subsequent attacks will be the same as that for treatment of the initial attack (Table 8.a).

Dose is to be adjusted using a graduated syringe (sales name; BD Disposable Syringe capacity; 3 mL, sales company; Nippon Becton Dickinson) and a connecter (sales name; Dispensing Connector, sales company; Braun Aesculap Japan). The prefilled syringe is connected to a graduated syringe. Required dosage is transferred from prefilled syringe to empty graduated syringe and administrated.

Doses for an initial attack are to be administered by a healthcare professional as per instructions of investigators, or be self-administered by the subject or the subject's caregiver, e.g. the subject's family, at the study site under the supervision of a healthcare professional. In the case that icatibant is administered by whom other than healthcare professionals, if the subject and his/her legal guardian agree and the investigator considers it appropriate after the subject receives education and training, the patient or his/her caregiver, e.g. the subject's family, will be allowed to administer incatibant under the supervision of a healthcare professional. Especially for subsequent treatment, the subject and the subject's caregiver will be encouraged to self-administer icatibant under the supervision of a healthcare professional (refer to Section 8.1.3.1).

Icatibant dose and methods of administration should be recorded in eCRF (refer to Section 9.2).

Table 8.a Dosage

Weight Group*	Dose (Injection volume) of Icatibant (TAK-667)
12 to 25 kg	10 mg (1.0 mL)
26 to 40 kg	15 mg (1.5 mL)
41 to 50 kg	20 mg (2.0 mL)
51 to 65 kg	25 mg (2.5 mL)
>65 kg	30 mg (3.0 mL)

*Body weight of 12 kg or more is the subject of this study. For each weight, round to the nearest whole number for calculation.

8.1.3.1 Self-Injection Training (Optional; for Subjects Who Will Self-Administer Icatibant Only)

Subjects or the subject's caregiver, e.g. the subject's family, will be encouraged to self-administer icatibant under supervision and will receive training on the appropriate self-injection technique from a healthcare professional as per instructions of investigators prior to treatment.

The implementation status of self-administration training should be recorded in eCRF (refer to Section 9.2)

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be recorded in eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or subinvestigator will dispense the study drug to subjects according to the study procedure (refer to Appendix A).

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (site designee) will receive the pharmacy manual created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications as well as return of them to the sponsor or destruction of them.

The on-site pharmacist (site designee) will immediately return unused study drugs to the sponsor after the study is closed at the study site.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent and Assent Procedure

The requirements of the informed consent and assent are described in Section 15.2.

Informed consent of the subject's parent or the subject's legal guardian, and assent of the subject if deemed possible by the investigator or subinvestigator, must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained at screening will include date of birth, sex, race.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease being studied and eligibility criteria that resolved within 1 year prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.13). Any clinically significant conditions or diseases relevant to treatment on prior HAE attacks to be obtained as described in Section 9.1.6.

Medication history information to be obtained includes any medication relevant to eligibility criteria, except for treatments of HAE, stopped at or within 90 days prior to signing of informed consent. Medication history on prior HAE attacks to be obtained as described in Section 9.1.6.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of study drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination. Clinically significant findings will be recorded as an AE if it starts after the first dose of study drug on this study.

9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place.

9.1.5 Vital Sign Procedure

Vital signs will include body temperature, respiratory rate, sitting blood pressure (systolic and diastolic, resting more than 5 minutes), and pulse (bpm).

When vital signs are scheduled at the same time as blood draws, vital signs will be obtained before the scheduled blood draw.

9.1.6 Medical History of HAE / Current HAE Attack

(1) HAE attacks occurring before the screening

Details of HAE diagnosis (eg. time of first onset of symptom, time of diagnosis, HAE type [I or II], C1-INH activity functional/protein level, genetic mutation, family history), presence of previous icatibant administration and detail of prior HAE attacks during the 12 months prior to the screening visit (eg. frequency of attack, frequency of attack required medical interventions and detail of symptoms for each attack [time of onset, location, trigger, prodromal symptoms, severity, time of onset of relief and complete relief, and medical interventions required, start time of treatment, any clinically significant conditions or diseases relevant to treatment]) will be obtained at screening in principle and recorded in the eCRF.

(2) HAE attacks occurring after the screening

- HAE attack not treated with study drug

The subject, the subject's parent or the subject's legal guardian will note down detail of symptoms for each HAE attack not treated with study drug (time of onset, location, trigger, prodromal symptoms, severity, time of onset of relief and complete relief, and medical interventions required, start time of treatment). The investigator or subinvestigator will basically obtain this information at baseline visit prior to study drug administration for initial or subsequent attack and recorded in the eCRF.

- Current HAE attack treated with study drug

The subject, the subject's parent or the subject's legal guardian will note down detail of current HAE attack to be treated with study drug (time of onset, location, trigger, prodromal symptoms). The investigator or subinvestigator will obtain this information to establish subject eligibility at baseline visit prior to study drug administration for initial or subsequent attack and will be recorded in the eCRF.

9.1.7 Menstrual Cycle History

A menstrual cycle history will be determined historically for female subjects and will be recorded in the eCRF. The timing of the blood sampling with respect to the menstrual cycle must be known to inform the interpretation of any potential changes in reproductive hormones in adolescent females, because of the normal cyclical rise and fall of reproductive hormones of the menstrual cycle.

To assist in this determination, investigator or subinvestigator should obtain the following information and document in the eCRF.

- Age of menarche.
- Normal duration of menstrual flow.
- Normal interval in between menstrual periods.
- Date of last menstrual bleeding.
- Prospectively ask female subjects to write down subsequent dates of onset and cessation of menstrual bleeding between Day 1 and Day 8.
- Date of ovulation may be documented if subjects can identify ovulation from feeling (eg. ovulation pain, mid-cycle pain or mittelschmerz) or basal body temperature, etc.

9.1.8 Pubertal Status Determination

The investigator or subinvestigator will perform an examination for all subjects to determine whether they are prepubertal or pubertal/postpubertal. A description of the sexual maturation scale originally described by Marshall and Tanner (1969 and 1970) (Appendix C) should be referred for the determination.

9.1.9 Primary Efficacy Measurement

9.1.9.1 Investigator or Subinvestigator Symptom Score

For subjects treated at the hospital/study center, the investigator or subinvestigator will use a symptom score to assess the severities of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale. Symptom scores will be recorded on Day 1 at pretreatment and at predetermined time points after treatment. Results will be recorded in the eCRF.

Investigator-rated Symptom Score

0 = none; absence of symptoms

1 = mild (no to mild interference with daily activities)

2 = moderate (moderate interference with daily activities)

3 = severe (severe interference with daily activities)

4 = very severe (very severe interference with daily activities)

For attacks classified as cutaneous and/or abdominal, investigator-rated symptom scores will be collected for 8 symptoms: abdominal tenderness, nausea, vomiting (over 2 hours), diarrhea (over 2 hours), skin pain, erythema, skin irritation, and skin swelling.

For attacks classified as laryngeal, investigator-assessed symptom scores will be collected for 13 symptoms: abdominal tenderness, nausea, vomiting (over 2 hours), diarrhea (over 2 hours), skin

pain, erythema, skin irritation, skin swelling, dysphagia, voice change, breathing difficulties, stridor, and asphyxia.

9.1.9.2 Subject Self-assessment of Pain

Subjects who are at least 4 years of age will self-assess HAE-related pain using the FPS-R. A copy of the FPS-R is provided in Appendix D.

FPS-R self-assessment data will be recorded in a FPS-R self-assessment sheet. Subjects will record self-assessments on Day 1 at pretreatment and at predetermined time points after treatment.

Subjects or subject's parent/legal guardian will receive detailed instruction on when and how to use the FPS-R self-assessment sheet from the investigator or subinvestigator and/or clinical site personnel.

9.1.9.3 Investigator or Subinvestigator Assessment of Pain

Subjects who are below 4 years of age will undergo investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the FLACC compartmental pain scale. A copy of the FLACC scale is provided in Appendix E.

9.1.9.4 Initial Symptom Improvement Reported by Investigator and Subject

The investigator or subinvestigator will record the time when overall subject improvement of HAE symptoms is first noted. And subjects (or the subject's parent/legal guardian on behalf of the subject as appropriate) will be asked to report the time when subject feel that his/her HAE symptoms start to improve, and the investigator or subinvestigator will record in eCRF.

9.1.10 Self-Administration Assessment (Optional; for Subjects or Caregiver Who Will Self-Administer Icatibant Only)

Subjects or caregiver, e.g. the subject's family who self-administer icatibant will be asked to provide information on convenience and satisfaction with the self-administration of the study drug to treat each HAE attacks. Results will be recorded in the eCRF. The Self-Administration Assessment is located in Appendix F.

9.1.11 Reproductive Hormone Assessments

Reproductive hormone levels will be measured in all subjects. Blood samples will be collected to assess FSH, LH, estradiol, and progesterone in females, and FSH, LH, and testosterone in males.

9.1.12 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication does not include the drug provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (including vitamin supplements,

over-the-counter medications, and herbal preparations) that is used from signing of informed consent through the end of the study, and it will be recorded in the eCRF.

During the period from the end of the follow-up (Day 8) to the baseline (Day 1) for the subsequent icatibant-treated attacks, concomitant medication need not be recorded, except that information on excluded medications, medications used for SAEs, medications used for AEs leading to study discontinuation, and medications used for HAE attacks not treated with study drug will be collected at the baseline visit for the subsequent icatibant-treated attacks, and recorded in the eCRF. All medications being used at the baseline visit for subsequent icatibant-treated attacks will be collected as concomitant medications.

Rescue medication (Section 7.3) for icatibant-treated HAE attack must be recorded in the applicable page of the eCRF separately from concomitant medications.

9.1.13 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are clinically significant ongoing conditions or diseases that are present at signing of informed consent. Those include abnormalities in laboratory test, ECG, or physical examination observed at first examination, observation and assessment after obtaining informed consent, those are judged to be clinically significant by the investigator or subinvestigator. Concurrent conditions (ie, diagnosis) should be recorded.

9.1.14 Procedures for Clinical Laboratory Samples

All samples will be collected via venipuncture and in accordance with acceptable laboratory procedures. The volume of blood will be determined at each site.

Table 9.a lists the items those will be tested for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells (RBC)	ALT	Glucose
White blood cells (WBC) count with differential (%) (neutrophil, basophil, eosinophil, lymphocyte, monocyte)	Albumin	Specific gravity
	Alkaline phosphatase	pH
Hemoglobin	AST	Protein
Hematocrit	Total bilirubin	Occult blood
Platelets	Creatinine	Ketones
Mean corpuscular hemoglobin (MCH)	Creatine kinase	Clarity
Mean corpuscular hemoglobin concentration (MCHC)	Gamma-Glutamyl transferase (GGT)	Bilirubin
Mean corpuscular volume (MCV)	Chloride	Color
	Potassium	Nitrites
	Sodium	
	Calcium	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Carbon dioxide (CO_2)	
	Phosphorus	
	Blood urea nitrogen (BUN)	
	Magnesium	
	Total protein	
	Uric acid	
Other:		
Urine qualitative human chorionic gonadotropin (hCG) pregnancy test (only female subjects of childbearing potential)		
Coagulation:		
Prothrombin time (PT)		
Activated partial thromboplastin time (aPTT)		

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis (not necessary with fasting). The results of laboratory tests will be returned to the investigator or subinvestigator, who is responsible for reviewing and filing these results. Results will be recorded in the eCRF.

If subjects experience ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase (ALP), ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted. (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

If ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator or subinvestigator must contact the monitor to discuss additional testing, close monitoring, possible discontinuation of study drug, relevant subject details and possible alternative etiologies. The

abnormality should be recorded as an AE (for reporting abnormal liver function tests, please refer to Section 10.2.3).

Only female subjects of childbearing potential, defined by the investigator's or subinvestigator's positive opinion about the subject's reproductive potential, will undergo a qualitative human chorionic gonadotropin (hCG) pregnancy test. The local laboratory will perform the test.

The investigator or subinvestigator reviews and files the laboratory test results. The investigator or subinvestigator will also maintain a copy of the normal reference ranges including the archival records for the laboratory used.

9.1.15 Injection Site Reactions

Injection site reactions will be assessed by the investigator or subinvestigator at specified time points after study drug administration (1.0, 4.0, 8.0 hours after the administration, Day 2 and Day 8). Injection sites will be examined for erythema, swelling, cutaneous pain, burning sensation, itching/pruritus, and warm sensation. The injection site reaction data will be recorded on the eCRF. The diameter of any erythema or swelling should be measured to obtain the severity grading. The severity of injection site reactions will be graded as absent, mild, moderate, or severe using the scoring criteria shown in Table 9.b.

After discharge, the subject (or the subject's parent/legal guardian on behalf of the subject as appropriate) will report about injection site reactions, either in person or by telephone contact.

Table 9.b Severity Scoring for Injection Site Reactions

Injection Site Reactions	Severity		
	Mild	**Moderate**	**Severe**
Erythema	>0 to 5 cm	>5 to 10 cm	>10 cm
Swelling	>0 to 5 cm	>5 to 10 cm	>10 cm
Cutaneous Pain	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest
Burning Sensation	Mild burning sensation, which is easily tolerated	Moderate burning sensation, causing some discomfort	Severe burning sensation, causing significant discomfort
Itching/pruritus	Mild itching/pruritus, which is easily tolerated	Moderate itching/pruritus, causing some discomfort	Severe itching/pruritus, causing significant discomfort
Warm Sensation	Mild warmth to touch	Moderate warmth to touch	Significant warmth to touch

Data for injection site reactions will be collected separately from general reports of AEs. An injection site reaction not meeting SAE criteria does not need to be reported additionally as an AE.

9.1.16 Immunogenicity Evaluation

The immunogenicity of icatibant will be assessed. Serum samples for immunogenicity testing will be collected according to the study schedule (Appendix A) for determination of anti-icatibant

antibodies. Serum samples will be analyzed for anti-icatibant antibodies at a Takeda designated laboratory. Details concerning sample collection and preparation will be provided in the Study Laboratory Manual.

Samples will be stored frozen at -65°C or below if not shipped on the day of collection. Details for shipping will be provided in the Study Laboratory Manual.

9.1.17 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 30 days after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception (listed below). In addition they must be advised not to preserve or donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation), who are postmenopausal (defined as at least 2 years since last regular menses, confirmed before any study drug is administered), or who have no possibility of childbearing in the opinion of investigator or subinvestigator.

**Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, female subjects of childbearing potential must use copper intrauterine devices (IUDs) combined with male condom or female condom. Medications and devices containing hormones are excluded in this study.

The subject and the subject's parent, or the subject's legal guardian will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent/assent form stating that they understand the requirements for avoidance of pregnancy, preservation or donation of ova from providing the consent/assent until 1 month has passed from the end of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed only for female subjects of childbearing potential according to the study schedule (Appendix A) and subjects will receive continued guidance with respect to the avoidance of pregnancy.

This protocol does not condone or endorse under-age sexual activity.

9.1.18 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, eg, after or within 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Annex.

If the female subject and her parent, or the subject's legal guardian agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All pregnancies in subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.19 ECG Procedure

A resting 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval (msec), PR interval (msec), QT interval (msec), and QRS interval (msec). QTc (msec) will be calculated by the sponsor using the Fredericia's formula ($QT/RR^{0.33}$).

9.1.20 Pharmacokinetic Sample Collection and Analysis

Collect blood samples for pharmacokinetic evaluation according to the study schedule (Appendix A).

9.1.20.1 Collection of Plasma for Pharmacokinetic Sampling

Blood samples (one 1 mL sample per scheduled time) for pharmacokinetic analysis of icatibant and its metabolites (M-I and M-II) will be collected via venipuncture into vacutainers containing ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA-K2). Use of an indwelling catheter is encouraged for collection of serial blood samples for PK assessments when feasible. After mixing the vacutainers by inversion immediately, vacutainers will be centrifuged at 4°C. The plasma will be dispensed from the vacutainers to two polypropylene tubes with roughly equal volume and be stored frozen at or below -20°C in a freezer until being shipped to the analytical institute.

Details on the collection and processing of specimens are described in the Study Laboratory Manual.

For each sample, the date and time of the latest study drug administration and the actual time of blood sample collection will be recorded in the eCRF.

9.1.20.2 Bioanalytical Methods

Plasma samples will be assayed for concentrations of icatibant and its 2 major metabolites (M-I and M-II) using a validated high-performance liquid chromatography/tandem mass spectrometry (LC-MS/MS) method.

9.1.21 Documentation of Screen Failure

If the subject who signed informed consent is withdrawn at the screening visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- Death.
- AE.
- Did not meet inclusion criteria or did meet exclusion criteria. <specify reason>
- Significant protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Withdrawal by parent or legal guardian <specify reason>.
- Study termination by sponsor.
- Pregnancy
- The study is closed prior to the subject's eligible attack.
- Other <specify reason>.

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.1.22 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

During this study, the study drug will be administered by study site personnel, the subject, or caregiver, therefore, full subject compliance with treatment is anticipated.

The investigator will record all study drug administered to the subject in the eCRF.

The investigator or subinvestigator will record the implementation status of self-administration training, the administration method of this drug (administration by medical personnel, subjects, or caregivers), the usage status of the graduated syringe and connecter for pediatric administration, and the dose of study drug in the eCRF.

9.3 Schedule of Observations and Procedures

The schedule for study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

In unavoidable circumstances (eg, a widespread disease outbreak such as COVID-19 pandemic or natural disaster), exceptions may be consulted for alternative visits or assessments for conducting subject visits with approval by the Medical Monitor and/or sponsor.

9.3.1 Screening

Subjects will be screened within 180 days prior to Baseline (Day1). Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.21 for procedures for documenting screening failures.

9.3.2 Initial Icatibant-Treated Attack

9.3.2.1 Study Entrance/Baseline (Day 1:Up to 3 hours before the start of study drug administration)

The subject will visit the hospital after the onset of HAE attack.

Prescribed tests, observations, and evaluations will be performed as baseline assessment in the period from 3 hours before icatibant administration to icatibant administration and subject eligibility is confirmed based on inclusion/exclusion criteria. Efficacy assessment must be performed within 1 hour prior to treatment.

If the screening test and the pre-dose (baseline) test are performed at the same time, duplicate tests should be performed only once.

9.3.2.2 After Treatment (Day 1)

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be started administrating icatibant within 12 hours of the onset of HAE attack. Up to 2 additional injections are permitted per attack with a time interval of at least 6 hours within 48 hours of the initial injection if there is insufficient relief or worsening of symptoms.

Subjects will be hospitalized for at least 8 hours after administration and prescribed tests, observations, and evaluations will be performed. Subject can be discharged from the hospital after finishing the evaluation of 8 hours after administration. Hospitalization may be prolonged until the investigator determines that the clinical condition is stable and the subject's HAE symptoms is resolved.

When the hospitalization period extended, as a general rule, the efficacy evaluation (investigator-rated symptom score, FPS-R, FLACC scale) and injection site reaction evaluation are performed every 2 hours, including 8 hours after administration, until discharge. Initial symptom improvement (investigator and subject), adverse events, and concomitant medications will be continuously evaluated until discharge. Physical examination, vital signs, ECG, clinical laboratory tests and reproductive hormone assessments are performed only at discharge.

9.3.2.3 After Treatment (Day 2)

At 24 to 48 hours after final administration of the study drug, all subjects who received the study drug will be subjected to prescribed examinations, observations, and evaluations by telephone, and recorded in the eCRF. If hospitalization continues 48 hours after the last dose, it is not necessary to perform an evaluation that overlaps with the evaluation items of 8 hours after administration or at discharge.

9.3.2.4 Follow-up (Day 8)

On the 7th day after the first administration of the study drug, the subject comes to the hospital for follow-up. Perform prescribed examinations, observations and evaluations, and record them in the eCRF.

9.3.3 Subsequent Icatibant-Treated Attack

9.3.3.1 Study Entrance/Baseline (Day 1:Up to 3 hours before the start of study drug administration)

Further treatments with study drug for up to 2 additional acute attacks of HAE, for a total of 3 acute attacks, will be offered to subjects who present with cutaneous, abdominal or laryngeal edema attack at least 7 days after first treatment for a prior attack if the subject and the subject's parent or the subject's legal guardian consent to further treatment.

In the event that a subsequent attack occurs within the window (+1 day) allowed for performance of follow-up (Day 8) assessments associated with a prior attack, the follow-up (Day 8) assessments may also serve as the pretreatment (baseline) assessments for the subsequent attack.

The subject will visit the hospital after the onset of a HAE attack.

Prescribed tests, observations, and evaluations will be performed as baseline assessment in the period from 3 hours before icatibant administration to icatibant administration and subject eligibility is confirmed based on inclusion/exclusion criteria. Efficacy assessment must be performed within 1 hour prior to treatment.

9.3.3.2 After Treatment (Day 1 and Day 2) and Follow-up (Day 8)

Assessments listed in Appendix A will be performed in the same manner as that for the initial attack (Section 9.3.2.2 to 9.3.2.4).

9.3.4 Final Visit or Early Termination

The last visit is follow-up (Day 8) of final attack treated with study drug.

For subjects who early terminate the study during hospitalization after the start of the study drug administration, the same tests, observations and evaluations as those scheduled at 8 hours should be performed. For subjects who early terminate the study after discharge, the same tests, observations and evaluations as those scheduled at follow-up (Day 8) should be performed. In

addition, assessment of adverse events and injection site reactions, and collection of concomitant medications should be performed 7 days after initial administration of icatibant by telephone.

For all subjects receiving icatibant, the investigator must complete the end of study eCRF page.

If the subject's parent or the subject's legal guardian consent and subject assent to participation for only initial icatibant-treated attack, final visit is follow-up (Day 8) of initial icatibant-treated attack.

If the subject's parent or the subject's legal guardian consent and subject assent to participation for subsequent icatibant-treated attacks, final visit is follow-up (Day 8) for third attack treated with study drug. In case subject does not experience third attack treated with study drug, study participation will be continued until early termination or completion of the study, and final visit will be follow-up (Day 8) of final attack treated with study drug within this period.

9.3.5 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug or study procedures.

In addition, drug-device AEs related to quality or malfunction will be collected.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.) (Acute HAE attacks are not considered AEs unless meeting the criteria for an SAE. If the criteria for SAEs are met, follow the procedure for reporting SAEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, after informed consent is signed,the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the study drug, or if a sign or a symptom appears secondarily due to an AE, the worsening or complication should be recorded appropriately as a new AE. The investigator or subinvestigator should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs:

- If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a subject who has signed informed consent to participate in a study:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure / acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure (including seizure and epilepsy)	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis (including interstitial lung disease)
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
	Neuroleptic malignant syndrome / malignant hyperthermia
	Spontaneous abortion / stillbirth and fetal death
	COVID-19 related disease
	COVID-19 pneumonia

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.1.4 AEs of Special Interest

An AE of special interest (only AEs that occurred after the start of study drug administration, serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

10.1.4.1 Injection Site Reaction

- Injection site reaction – listed as important identified risk in Japan/EU RMP; Local injection site reactions were observed in almost all icatibant -treated subjects. Most injection site reactions were transient, mild to moderate in severity, and completely resolved within 4-8 hours of treatment. Injection site reactions will be evaluated by the investigator when the subject is at the hospital/study center, and the diameter of any erythema or swelling will be measured. After discharge, the subject (or the subject's parent/legal guardian on behalf of the subject as appropriate) will be interviewed about injection site reactions, either in person or by telephone contact. Injection site reaction data will be collected separately from the general AE report. Injection site reactions that do not meet the criteria for SAE need not be reported as additional AE.
- The evaluation of Injection site reaction is shown in 9.1.15.

10.1.4.2 Immunogenicity (Hypersensitivity)

- Immunogenicity (Hypersensitivity) – listed as important potential risk in Japan RMP; In clinical studies, icatibant was generally nonimmunogenic. In over repeated treatment, transient positivity in test results for the presence of anti icatibant IgG antibodies was observed in rare cases. The immunogenicity of icatibant will be assessed. Serum samples for immunogenicity testing will be collected for determination of anti-icatibant antibodies. If hypersensitivity is observed, it should be reported as an AEs of special interest.

10.1.4.3 Reproductive Hormone Level in Pubertal/ Post-Pubertal Children

- Reproductive hormone level in pubertal/ post-pubertal children – listed as important potential risk in EU RMP; Although in the juvenile toxicity studies, the effects on hormone levels, reproductive organs, and sexual maturation in juvenile/immature rats and dogs was observed, no clinically significant changes in reproductive hormones were observed during global clinical studies in pediatric HAE patients. Blood samples will be collected to assess FSH, LH, estradiol, and progesterone in females, and FSH, LH, and testosterone in males. If a clinically significant change in reproductive hormone concentration is observed, it is reported as an AEs of special interest with clinical symptoms.

10.1.4.4 Hypotension and Cardiac Dysfunction

- Hypotension and cardiac dysfunction – listed as important potential risk in Japan RMP; In vitro studies have shown that icatibant activates human mast cells and decrease of blood pressure was observed in a high-volume bolus intravenous injection study of icatibant. In addition, the bradykinin antagonism of icatibant may pose a potential risk to patients with cardiovascular disease. Although no clinically significant hypotensive action and safety concerns for cardiovascular system was observed in clinical studies, hypotension and cardiac dysfunction will be assessed by standard safety testing including vital signs and 12-lead ECG. If clinically significant hypotension and cardiac dysfunction are observed, it is reported as an AEs of special interest.

10.1.5 Intensity of AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.8 Start Date and Time

The start date and time of the AE is the date and time that the first signs/symptoms were noted by the subject and/or investigator.

The start date and time of AEs will be determined using the following criteria;

AEs	Start Date and Time
Any signs/symptoms/diseases (diagnosis)	The date and time that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date and time when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date and time when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date and time that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings.	The date and time of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms.	The date and time of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.9 Stop Date and Time

The stop date and time of the AE is the date and time at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.10 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.11 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, or the AE occurred before the study drug administration.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.1.13 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product and/or device.

An investigator who is made aware of or identifies a potential product complaints should immediately report the event to Takeda in accordance with the contact list provided to the site. Whenever possible, the associated product should be maintained in accordance with pharmacy manual pending further guidance from a Takeda representative.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the informed consent to participate in the study. Routine collection of AEs will continue until the end of the study (Day 8).

During the period from the end of the follow-up (Day 8) to the onset of icatibant-treated subsequent HAE attacks, as a general rule, this period is excluded from the collection period of AEs, only SAEs and AEs leading to study discontinuation are detailed in eCRF. All AEs ongoing at the time of the onset of icatibant-treated subsequent HAE attacks will be collected and recorded in the eCRF.

Collection of device defects will commence from the time that the subject is first administered study drug. Routine collection of device defects will continue until the end of the study.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a SAE that occurs prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-SAEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs after the first exposure to study drug, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.

3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

A clinically relevant worsening of the signs and symptoms of an attack treated with icatibant is considered to be related to the underlying disease of HAE, and is collected in the eCRF separately from general reports of AEs unless meeting the criteria of an SAE.

10.2.1.3 AEs of Special Interest

If the subject experiences immunogenicity (hypersensitivity), a clinically significant change in reproductive hormone concentration in pubertal/ post-pubertal children, or hypotension and cardiac dysfunction, during the treatment period or the safety follow-up period as described in Section 10.1.4, the investigator or the subinvestigator will record it in the eCRF and report it to the sponsor within 1 working day after the occurrence of the event. If necessary, prepare the AEs report as a backup, and submit it to the sponsor/designated person (see attached annex for contact information).

If an injection site reaction occurs during the study, the investigators should document it following 9.1.15.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

The investigator or the subinvestigator will report the SAE to the sponsor within 24 hours after the occurrence of the SAE, using the eCRF. If necessary, prepare the SAE report as a backup, and submit it to the sponsor/designated person (see attached annex for contact information). The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s)
- Causality assessment.

The investigator should submit the original copy of the SAE form to the sponsor.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the monitor or the sponsor's designee for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.14 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form (copy) or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs /the head of the study site . Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs.The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs.

- Results of pharmacokinetics conducted at the analytical institute
- Results of immunogenicity (anti-icatibant antibodies)

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the

identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be finalized the first versoin prior to the first subject enrolled and finalized amendments prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

13.1.1.1 Safty Analysis Sets

The safety analysis set will be defined as all subjects who received at least 1 dose of study drug.

13.1.1.2 Full Analysis Set

The full analysis set will be defined as all subjects who received at least 1 dose of study drug. The definition of full analysis set is the same as the safety analysis set in this study.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the safety analysis set.

13.1.3 Efficacy Analysis

Secondary endpoints and analytical methods

[Secondary Endpoints]

- Time to onset of symptom relief and time to minimal symptom, as measured by investigator- and subject-reported outcomes.
  - For all subjects (2 to <18 years of age): investigator assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator-rated symptom score.
    - The time to onset of symptom relief, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which at least a 20% improvement is observed in the average post-treatment score with no worsening of any single component score.
    - The time to minimal symptoms, defined as the duration of time in hours from the time of icatibant administration to the earliest time post-treatment when all symptoms are either mild or absent based on the investigator-rated symptom score.

- For subjects ≥4 to <18 years of age only: subject self-assessment of HAE-related pain using the FPS-R.
  - ✧ The time to onset of symptom relief, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the post-treatment score improved by at least 1 level.
  - ✧ The time to minimal symptoms, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the post-treatment score improved to 0.
- For subjects 2 to <4 years of age only: investigator assessment of HAE-related pain using the FLACC scale.
  - ✧ The time to onset of symptom relief, defined as the earliest time at which a 20% improvement is observed in the total post-treatment score.
  - ✧ The time to minimal symptoms, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the total post-treatment score improved to 0.

- The incidence of rescue medication use.
- The proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with SC icatibant using investigator-rated symptom scores.
- Time to initial symptom improvement reported by investigator or subject
  - ✧ Time to initial symptom improvement reported by investigator, defined as the duration of time in hours from icatibant administration until the time when overall subject improvement was first noted by investigator.
  - ✧ Time to initial symptom improvement reported by subject, defined as the duration of time in hours from icatibant administration until the time when overall subject improvement was first noted by subject, subject's parent or subject's legal guardian.

[Analytical methods]

All efficacy endpoints will be summarized by icatibant-treated attacks using the full analysis set and listed. For the time-to-event endpoints, the survival function (e.g. proportion of subjects not achieving symptom relief) for each assessment time will be calculated by Kaplan-Meier method using the first icatibant-treated attacks within each subject. The second and third icatibant-treated attacks will be listed. Assuming independency in recurrent events within a subject, the survival function for each assessment time will be also calculated by Kaplan-Meier method using all icatibant-treated attacks. Due to the small sample size, no statistical inferences (statistical test nor confidence interval) will be performed.

13.1.4 Pharmacokinetic Analysis

Secondary endpoints and analytical methods

[Secondary Endpoints]

Plasma concentrations of icatibant and its major metabolites (M-I and M-II) at 0.5, 1.0, 2.0, and 4.0 hours after the first SC injection for an initial attack.

[Analytical methods]

Plasma concentrations of icatibant and its metabolites (M-I and M-II) will be summarized at each time point.

Data collected in this study will be combined with those from global studies, and the population PK modeling and simulations will be performed. Individual pharmacokinetic parameters (e.g. C_{max} and AUC) will be estimated by population PK analysis, if possible. Analysis plan and report of population pharmacokinetic analysis will be provided separately from the clinical study report.

13.1.5 Safety Analysis

Primary endpoints and analytical methods

[Primary Endpoints]

- Frequency and severity of TEAEs , including injection site reactions

[Analytical methods]

The following analysis will be performed using the safety analysis set. TEAE is defined as an AE that occurs on or after administration of icatibant for each attack and until the end of follow-up period (Day 8). TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and tabulated by the system organ class (SOC) and the Preferred Term (PT), and by icatibant-treated attacks and the total.

Injection site reactions will be summarized by icatibant-treated attacks and the total, and by severity.

Secondary endpoints and analytical methods

[Secondary Endpoints]

- Resting 12-lead electrocardiogram parameters in comparison to baseline
- Vital sign measurements in comparison to baseline
- Clinical laboratory parameters (serum chemistry, hematology and urinalysis) in comparison to baseline
- Reproductive hormone levels in comparison to baseline
- Immunogenicity (presence of anti-icatibant antibodies) in comparison to baseline

[Analytical methods]

For continuous values of laboratory parameters, vital signs and other safety parameters, summary statistics will be provided for observed values and change from baseline at each evaluation time

point and icatibant-treated attack. Pre- and post-dose shift tables will be provided for categorical variables.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Total of at least 3 subjects*

* The enrollment will be continued until the end of the enrollment period and the sample size may exceed 3 subjects.

[Justification for Determination of Sample Size]

The planned sample size chosen of 3 subjects administered icatibant in this study is based on the feasibility and is not statistically determined.

Although there have been no accurate reports regarding the number of pediatric HAE patients in Japan, it is estimated approximately 30 to 50 patients based on the population estimate and the percentage of children among Japanese HAE patients confirmed in the latest Japanese HAE survey. However, comprehensive feasibility assessment for medical institutions across Japan found much less candidate subjects and only few clinical sites possible to conduct the study due to some hurdles in implementation. In addition, considering a difficulty to obtain informed consent in a pediatric study, the number of patients to be enrolled was assumed to be 3.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and head of the study site guarantee access to source documents by the sponsor or its designee (contract research organization: CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee , including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster) that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. Deviations from the protocol-specified procedures will be recorded as related to unexpected circumstances (eg, COVID-19). There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, (eg, the PMDA). If the study site is contacted for an inspection by a regulatory body, the sponsor should be

notified immediately. The investigator and head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB Approval

IRBs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form/assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject informed consent/assent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form /assen form) reviewed; and state the approval date. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form/assent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject/parent/legal guardian incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent/Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. An assent document describes the study, using a language

appropriate to the subject's age and development, to potential subjects with enough mental capacity to understand what it means to participate in a clinical study, and is used to obtain the subject's assent (a pediatric subject's consent, which is not a regulatory requirement) separately from the subject's parent's, or the subject's legal guardian's consent. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent and assent forms. The informed consent and assent forms must be approved by both of the IRB and sponsor prior to use.

The subject assent form must be written in a language appropriate to the potential subject's age and development. The informed consent form must be written in a language fully comprehensible to a subject's parent or the subjects' legal guardian. It is the responsibility of the investigator or subinvestigator to explain the subject assent form to the subject using a language and terms comprehensible and to explain the detailed elements of the informed consent form to the subject's parent, or the subject's legal guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject and the subject's parent, or the subject's legal guardian must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject's parent or the subject's legal guardian determines the subject will participate in the study, then the informed consent form must be signed and dated by the subject's parent or the subject's legal guardian at the time of consent and prior to the subject entering into the study.

Whenever possible, the subject's own assent should be obtained in addition to the subject's parent's or the subject's legal guardian's consent. The subject's assent will be preferably obtained in writing, if he/she is a junior high school student or of a higher age. Whenever a written assent is not provided, though preferable also for subjects aged below junior high school students, the subject's oral assent must be documented in the informed consent form signed by the subject's parent or the subject's legal guardian. The subject's parent or the subject's legal guardian should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator or subinvestigator must also sign and date the informed consent form and subject assent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form, and the subject assent form (if applicable, the same hereinafter) will be stored in the investigator's site file. The investigator or subinvestigator must document the dates the subject's parent or the subject's legal guardian signs the informed

consent form and the date the subject signs the subject assent form in the subject's medical record. Copies of the signed informed consent form and the signed subject assent form shall be given to the subject, the subject's parent, or the subject's legal guardian.

All revised informed consent/assent forms must be reviewed and signed by relevant subjects, the relevant subject's parent or the subject's legal guardian in the same manner as the original informed consent/assent. The date the revised consent/assent was obtained should be recorded in the subject's medical record, and the subject, the subject's parent, or legal guardian should receive a copy of the revised informed consent/assent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, PMDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject, the subject's parent, or the subject's legal guardian as part of the informed consent /assent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility name, investigator's site city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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Appendix A [redacted]

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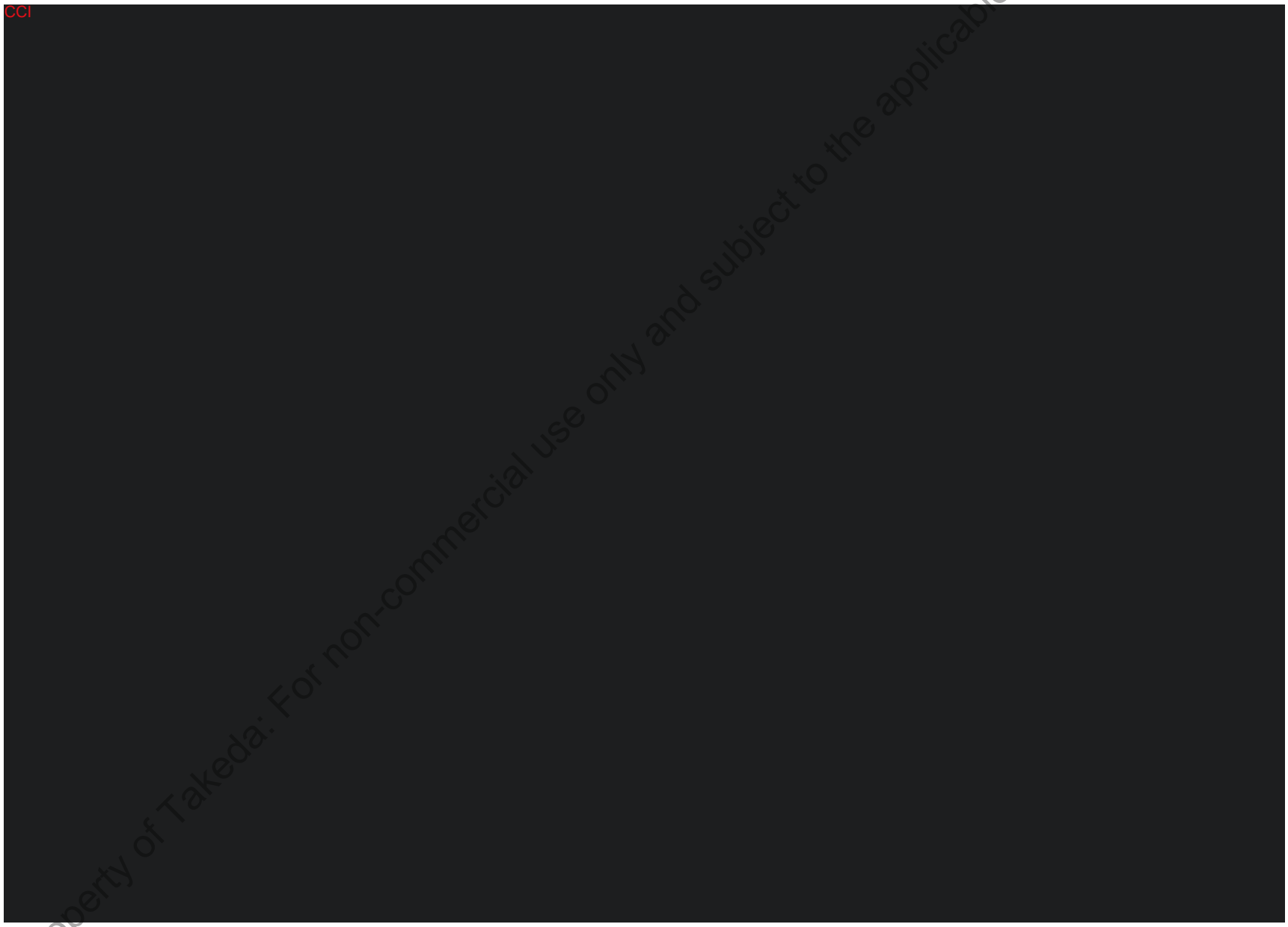

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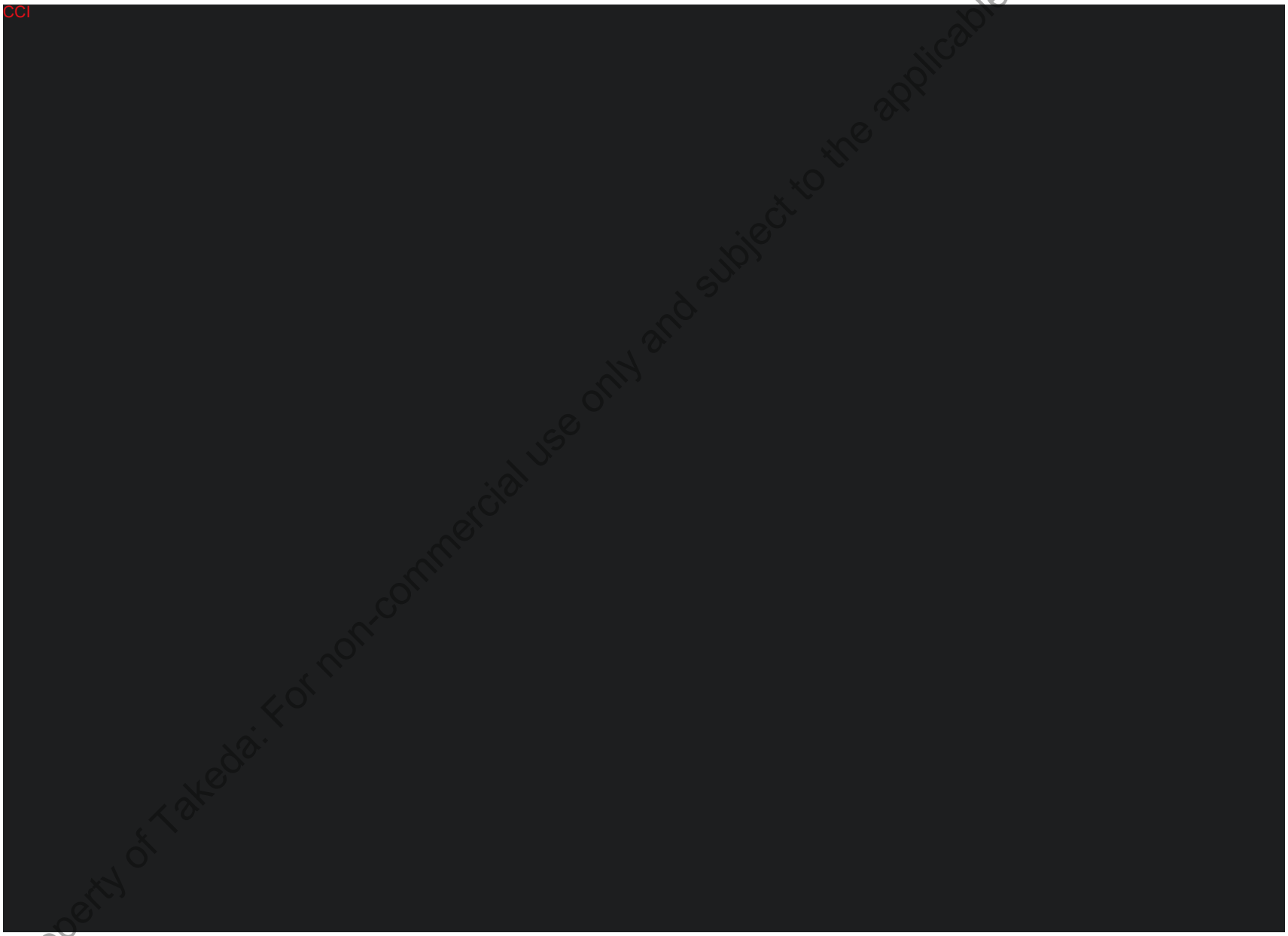

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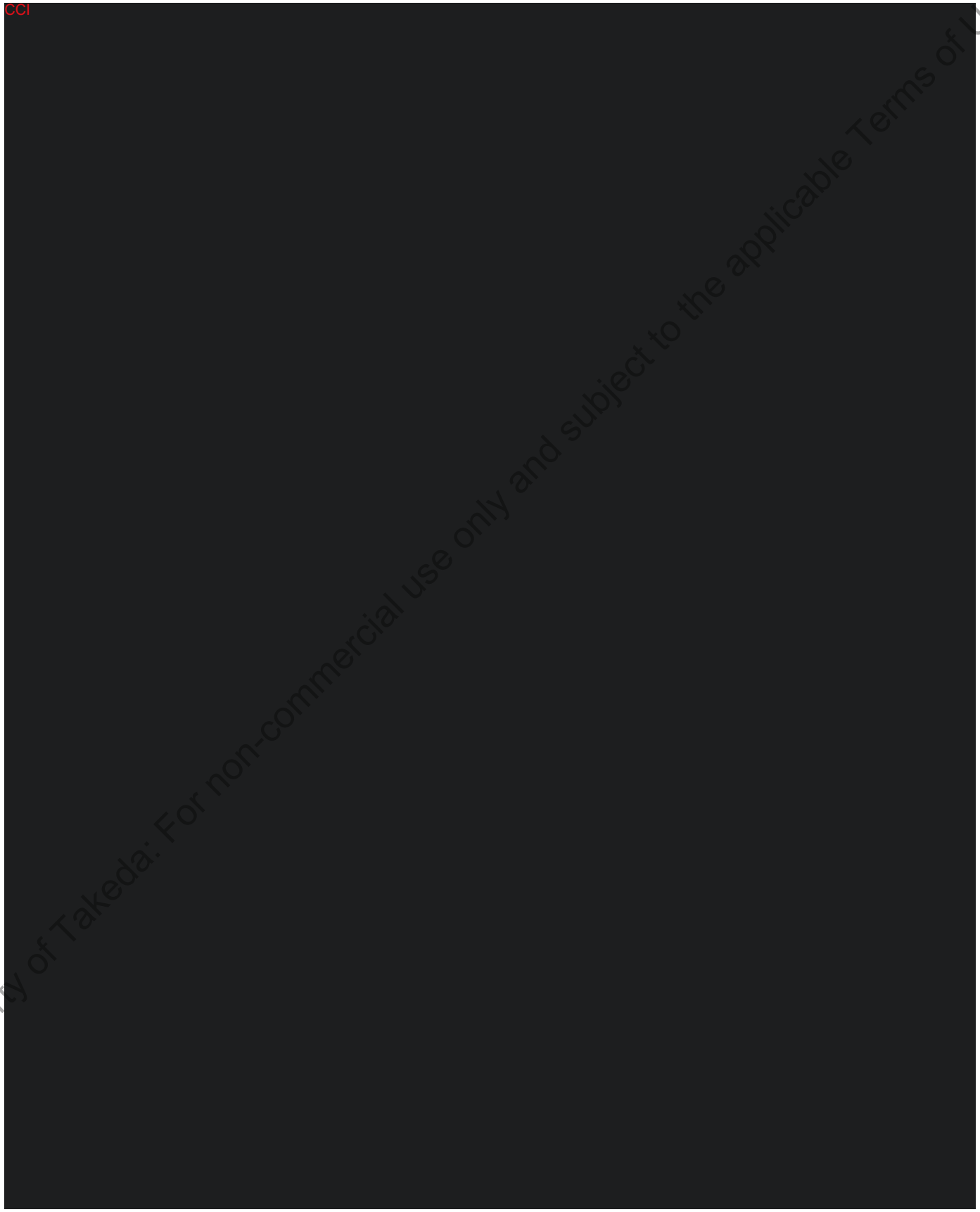

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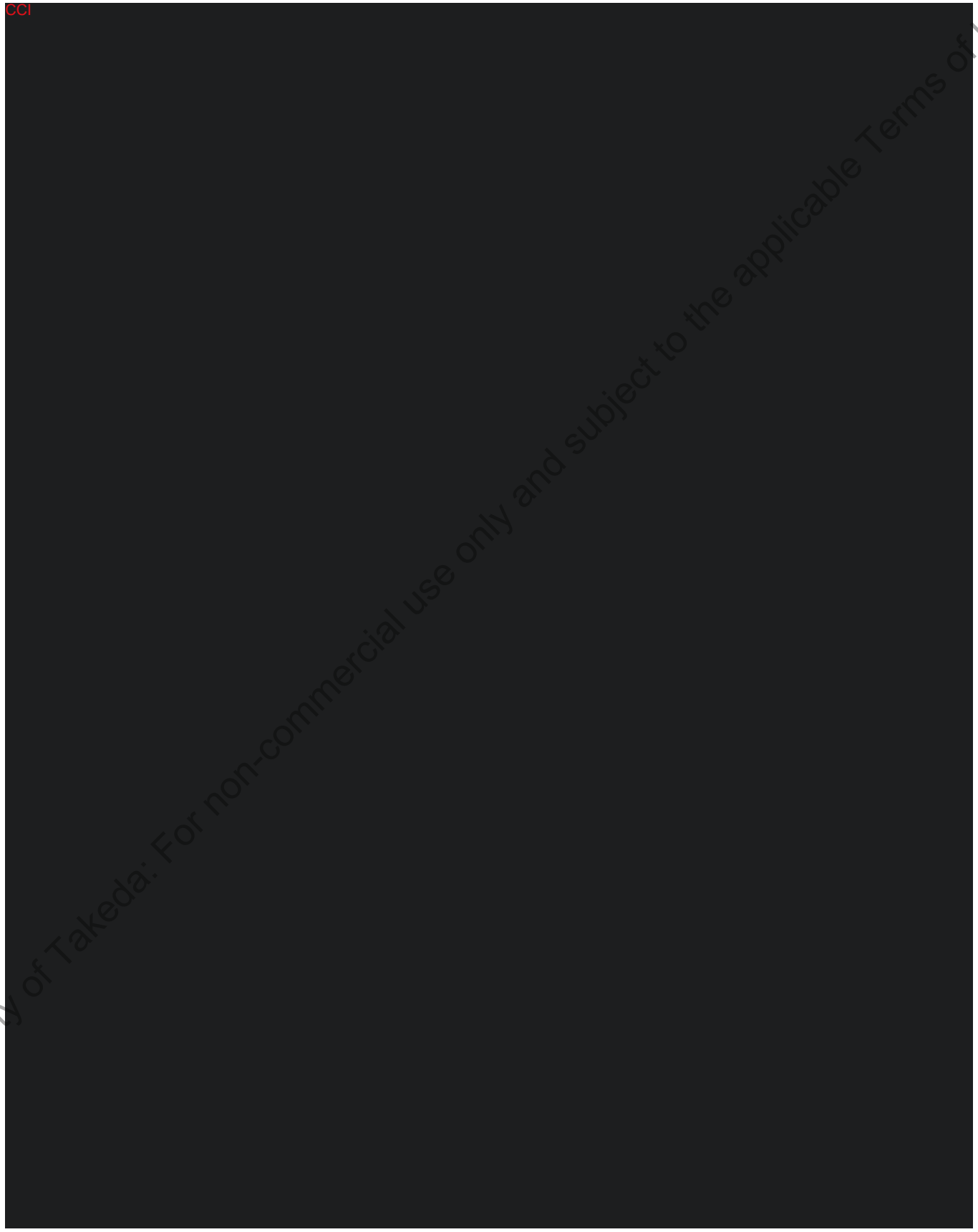

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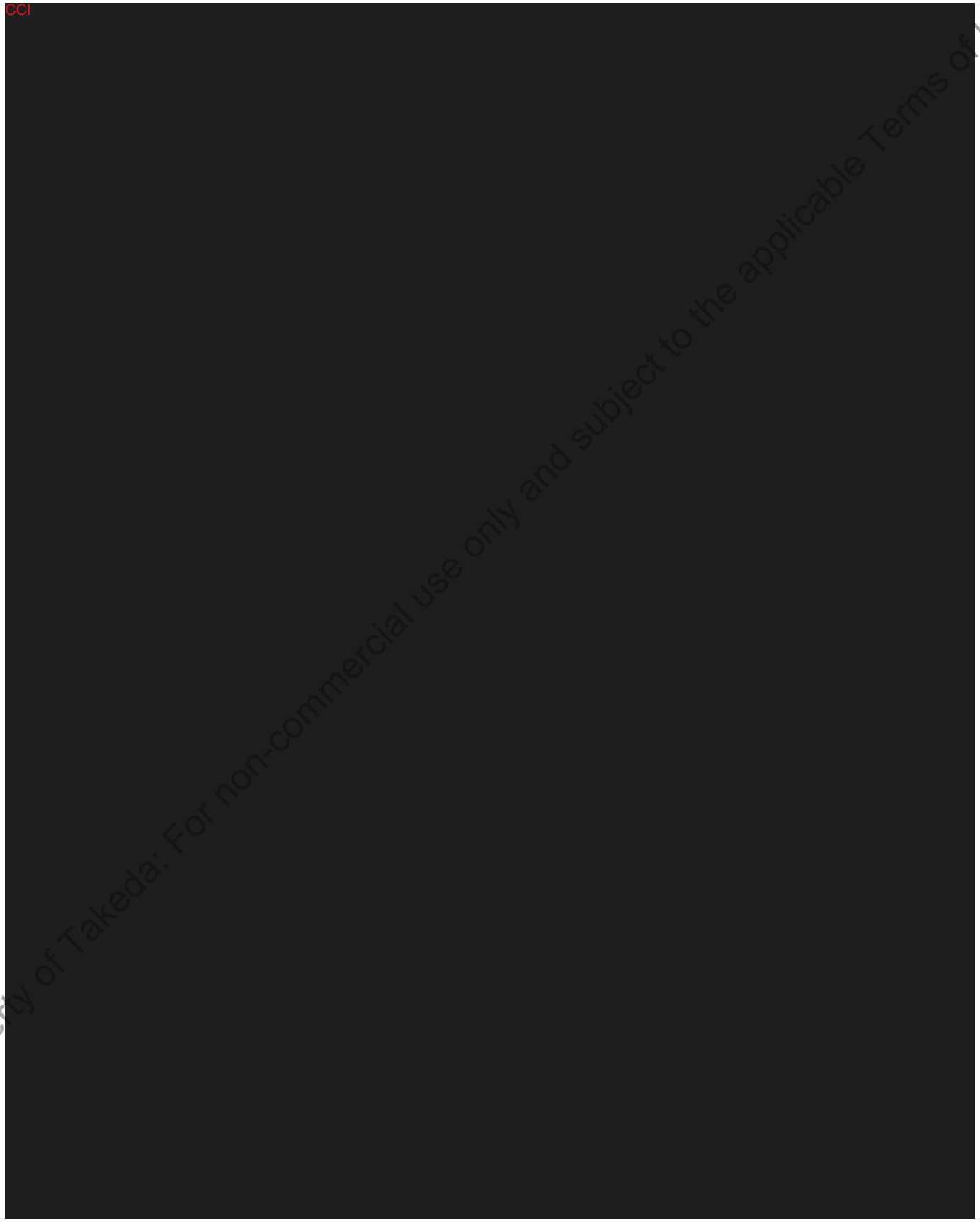

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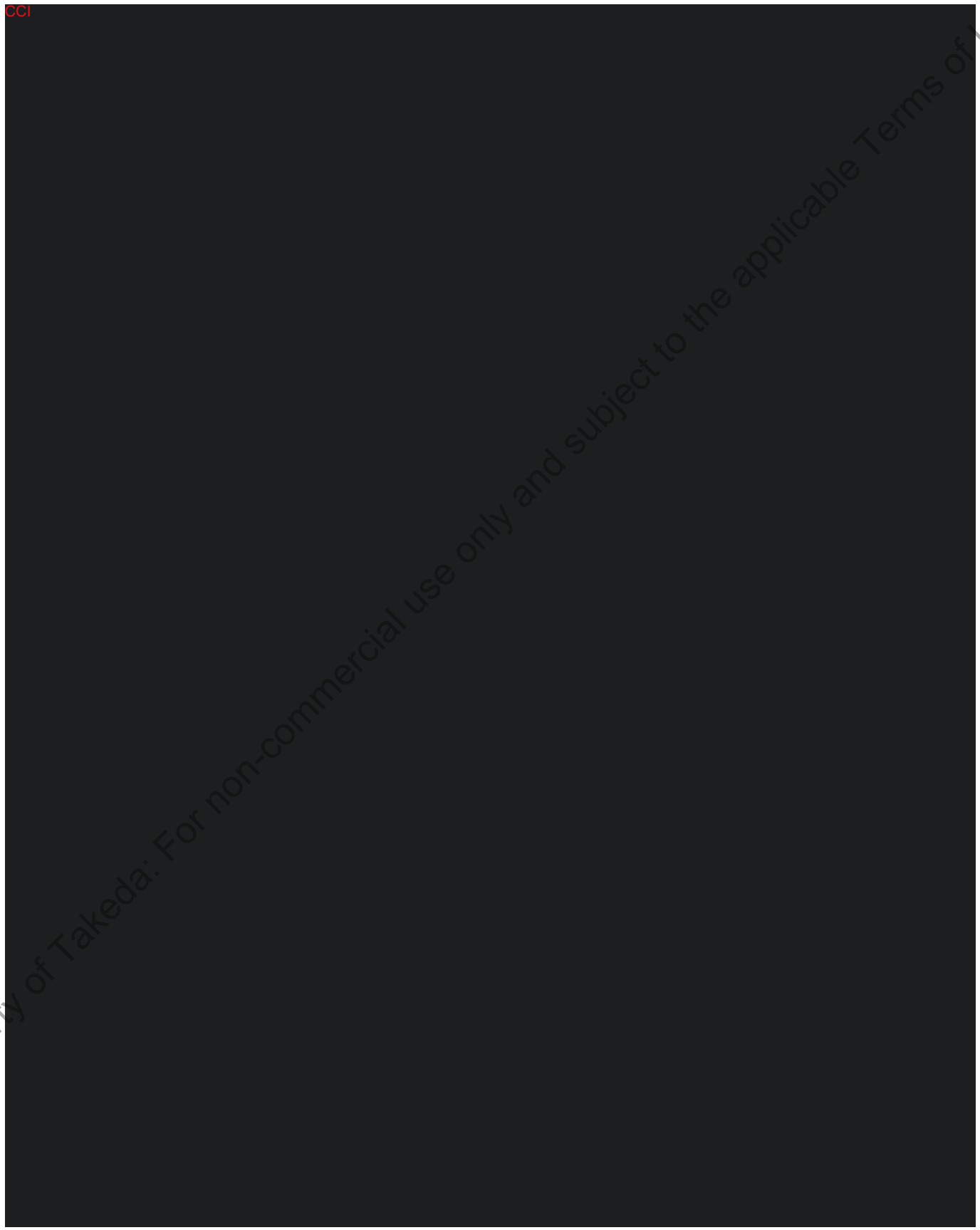

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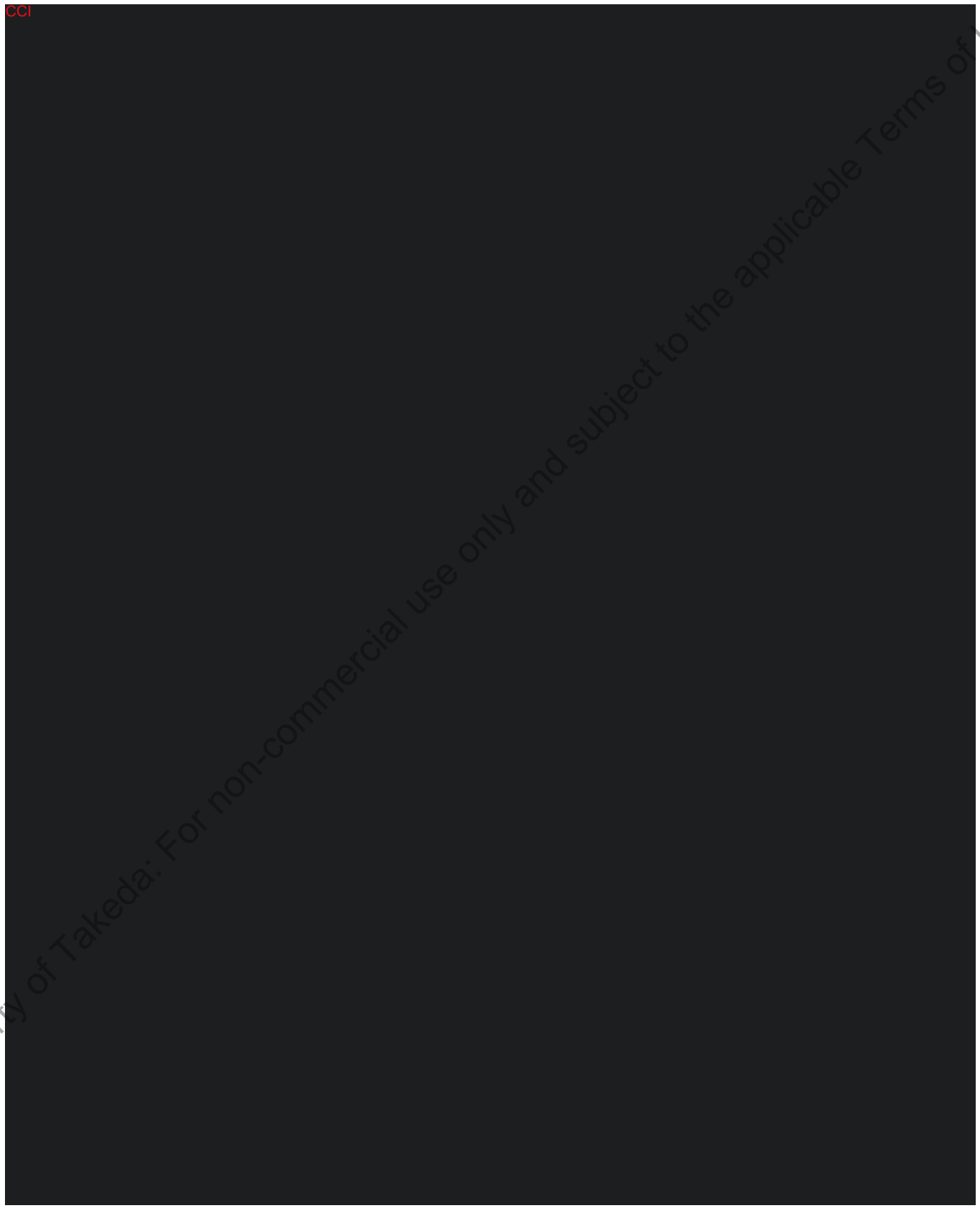

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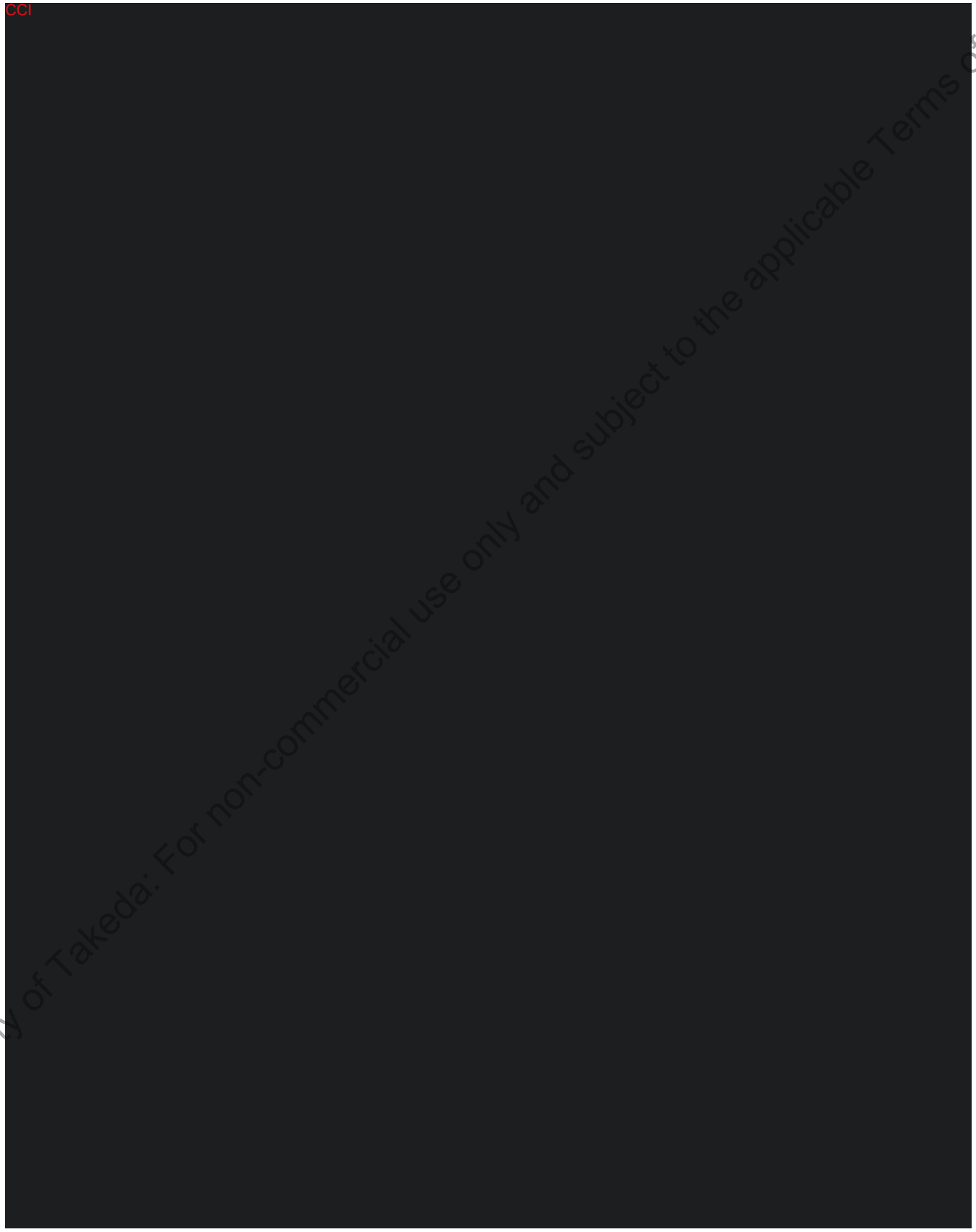

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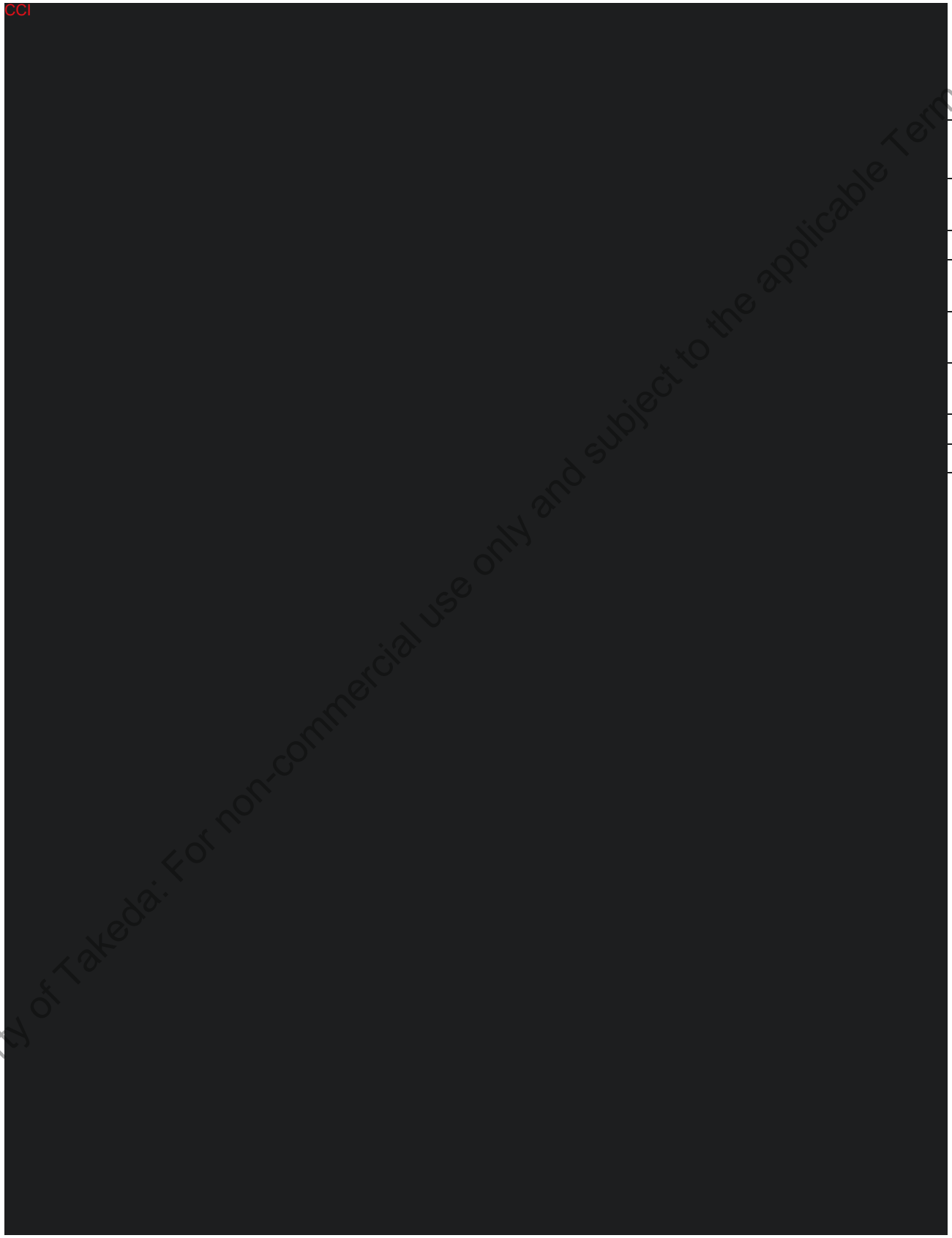

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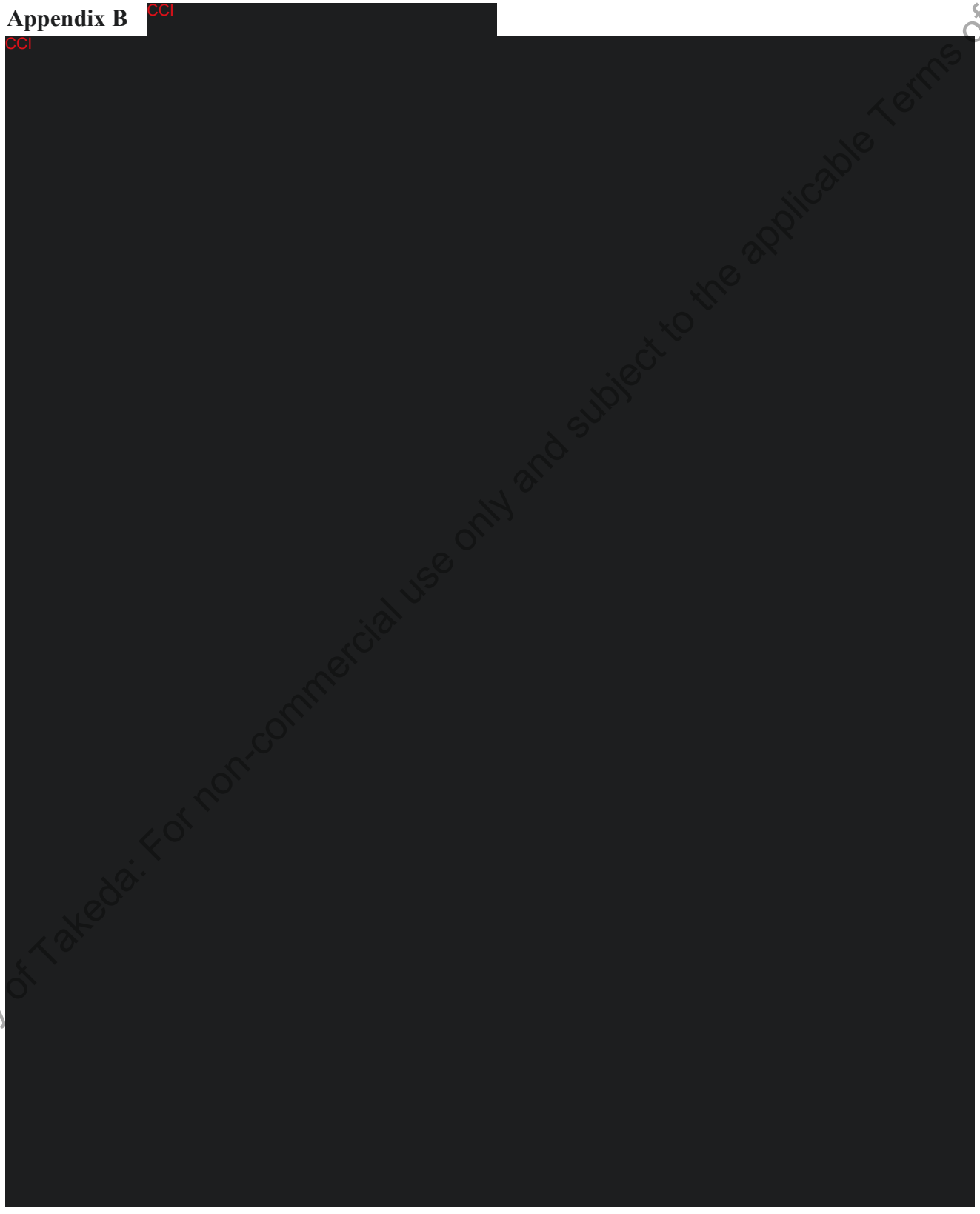

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Appendix D

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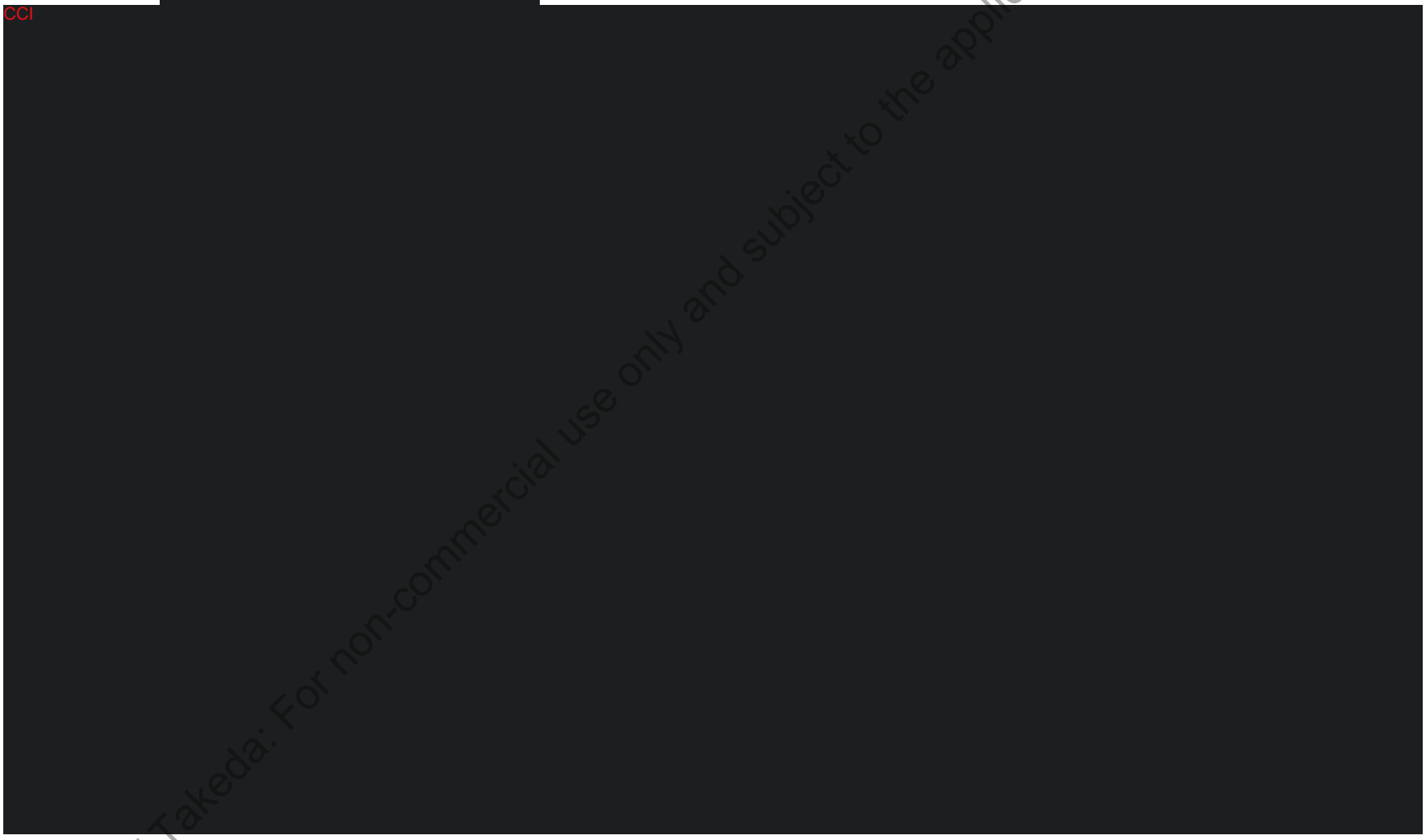

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Appendix F

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Appendix G [redacted]

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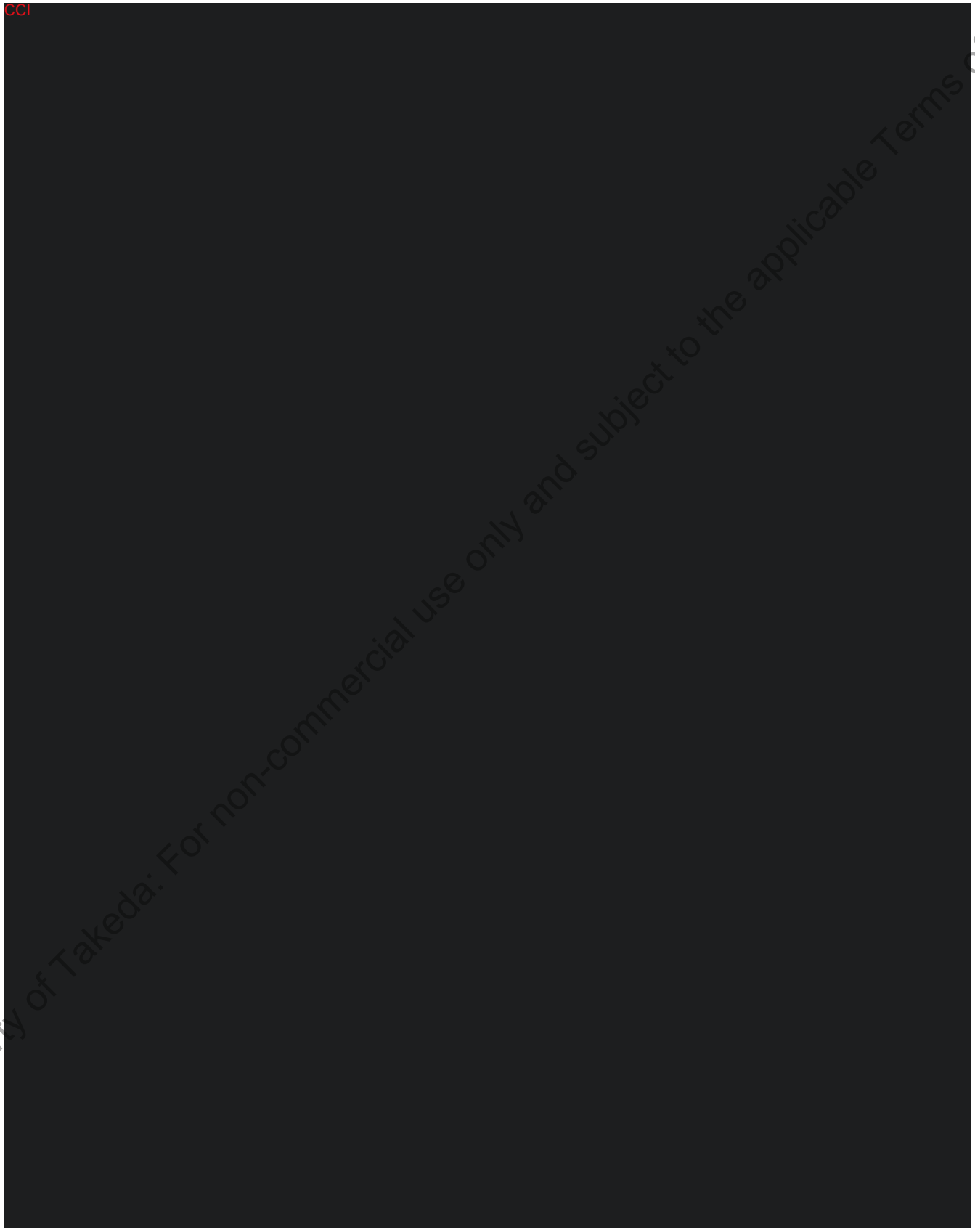

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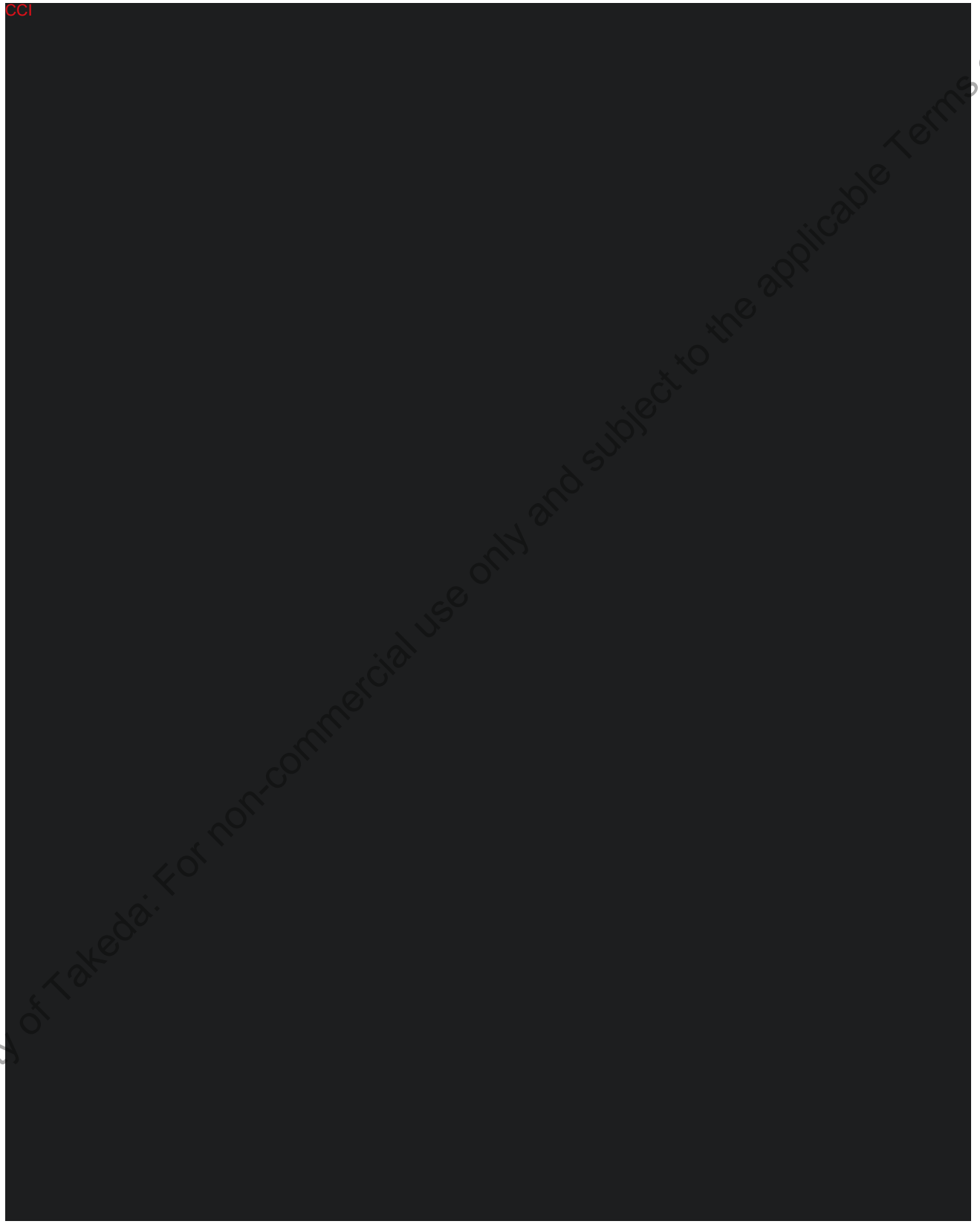

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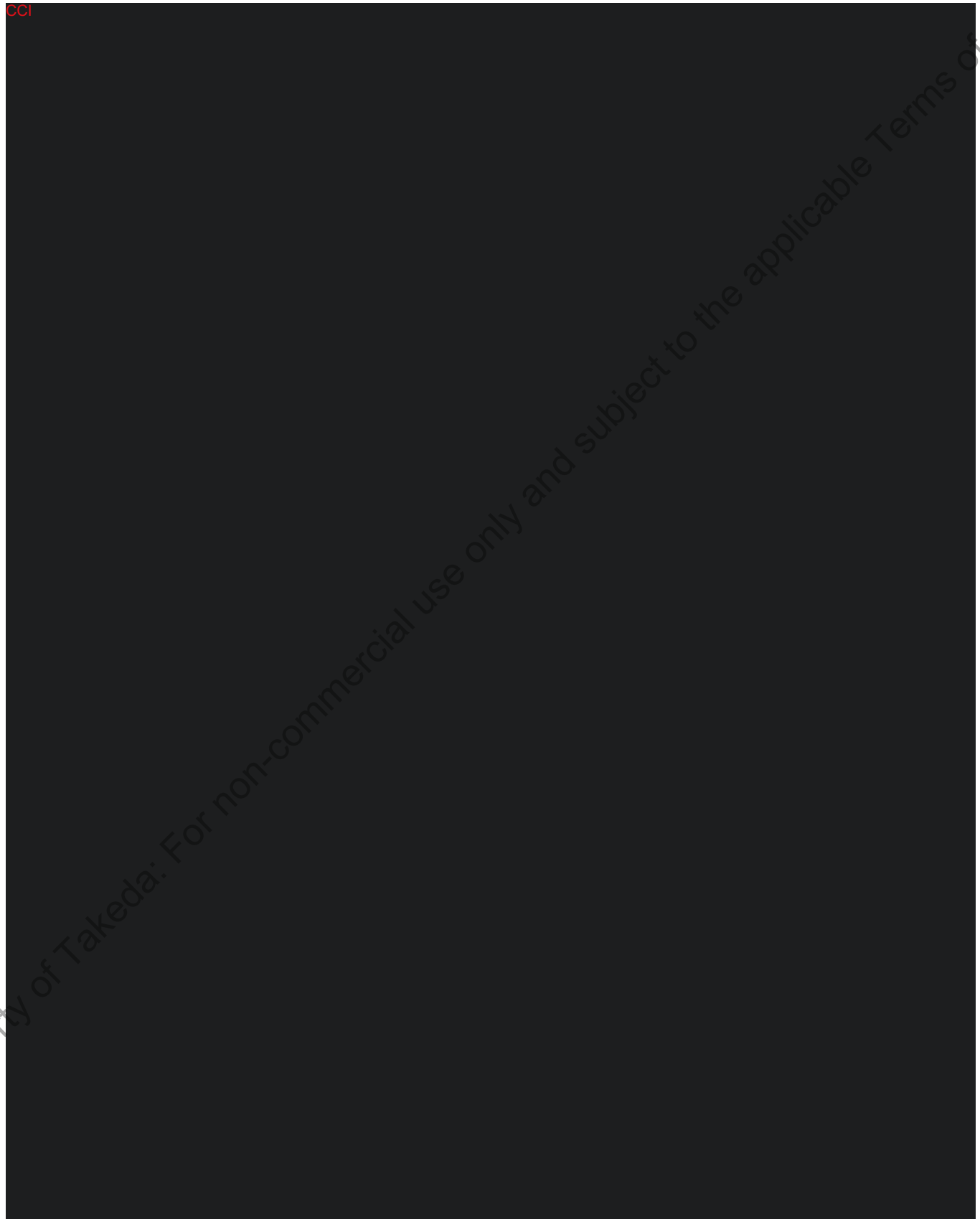

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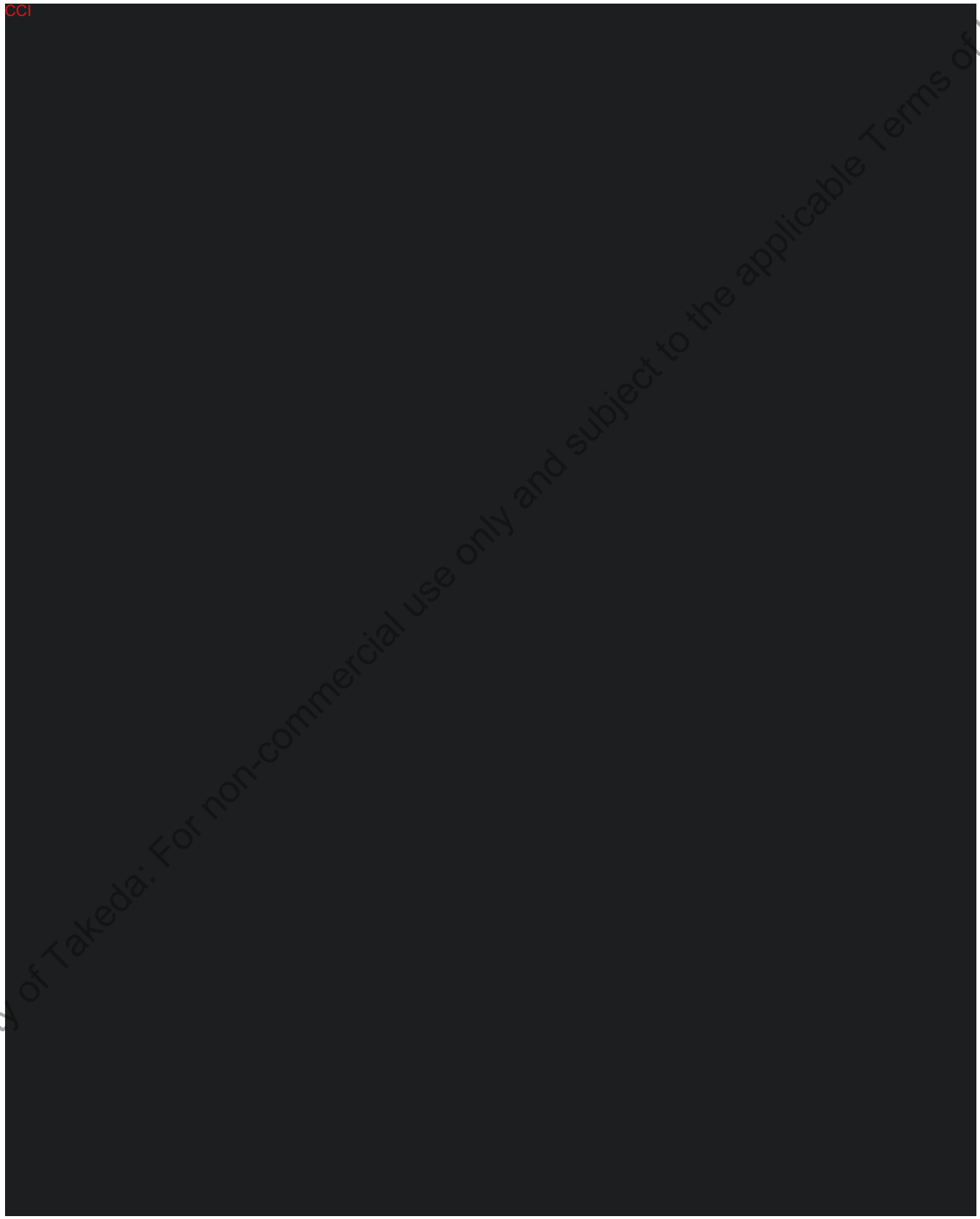

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