Clinical Study Protocol

NCT Number: NCT05526391

Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous TAK-341 in Subjects With Multiple System Atrophy

Study Number: TAK-341-2001

Document Version and Date: Amendment 3, 29 Nov 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous TAK-341 in Subjects With Multiple System Atrophy

Phase 2 Study of TAK-341 for Multiple System Atrophy

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Ave Lexington, MA 02421		
Study Number:	TAK-341-2001		
IND Number:	158317	**EudraCT Number:**	2022-000336-28
Compound:	TAK-341		
Date:	29 November 2023	**Version/Amendment Number:**	Amendment 3

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
29 November 2023	Amendment 3	Substantial	Global
03 November 2022	Amendment 2 FR v1	Nonsubstantial	France
17 October 2022	Amendment 2 DE v1	Nonsubstantial	Germany
22 September 2022	Amendment 2 GB v1	Nonsubstantial	United Kingdom
15 June 2022	Amendment 2	Substantial	Global
18 April 2022	Amendment 1	Substantial	Global
14 February 2022	Initial protocol	Substantial	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center (TDC)–sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and in relevant guidelines provided to the site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	Fax: Takeda Pharmacovigilance (Non-Oncology) US and Canada: +1 224-554-1052 Rest of World: +1 224-554-1052 BELLSYSTEM24, Inc Japan cases: 0120-490-849 Only when fax is not possible and EDC/RAVE is not available within 24 hours of receiving the event, please email the serious adverse event forms: - Non-Oncology US and Canada: PVSafetyAmericas@takeda.com - Non-Oncology Rest of World: PharmacovigilanceMailbox@Takeda.com - Japan cases: Takeda@e-medinfo.com
Medical monitor (provides medical advice on the protocol and study drug)	PPD Phone: +1 800-201-8725
Responsible medical officer (carries overall responsibility for the conduct of the study)	PPD, MD PPD Takeda Pharmaceuticals 40 Landsdowne St Cambridge, MA 02139 PPD

EDC: electronic data capture.

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP): 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 and other signatories can be found on the signature page.

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

PPD, MD	Date
PPD Neuroscience Therapeutic Area	
PPD, PhD	Date
PPD, Statistics Neuroscience Global Statistics	
PPD, PhD	Date
PPD Quantitative Clinical Pharmacology	

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, prescribing information 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, life, dignity, integrity, confidentiality of personal information, 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.
- ICH E6(R2) GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.2 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix C).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 CCI

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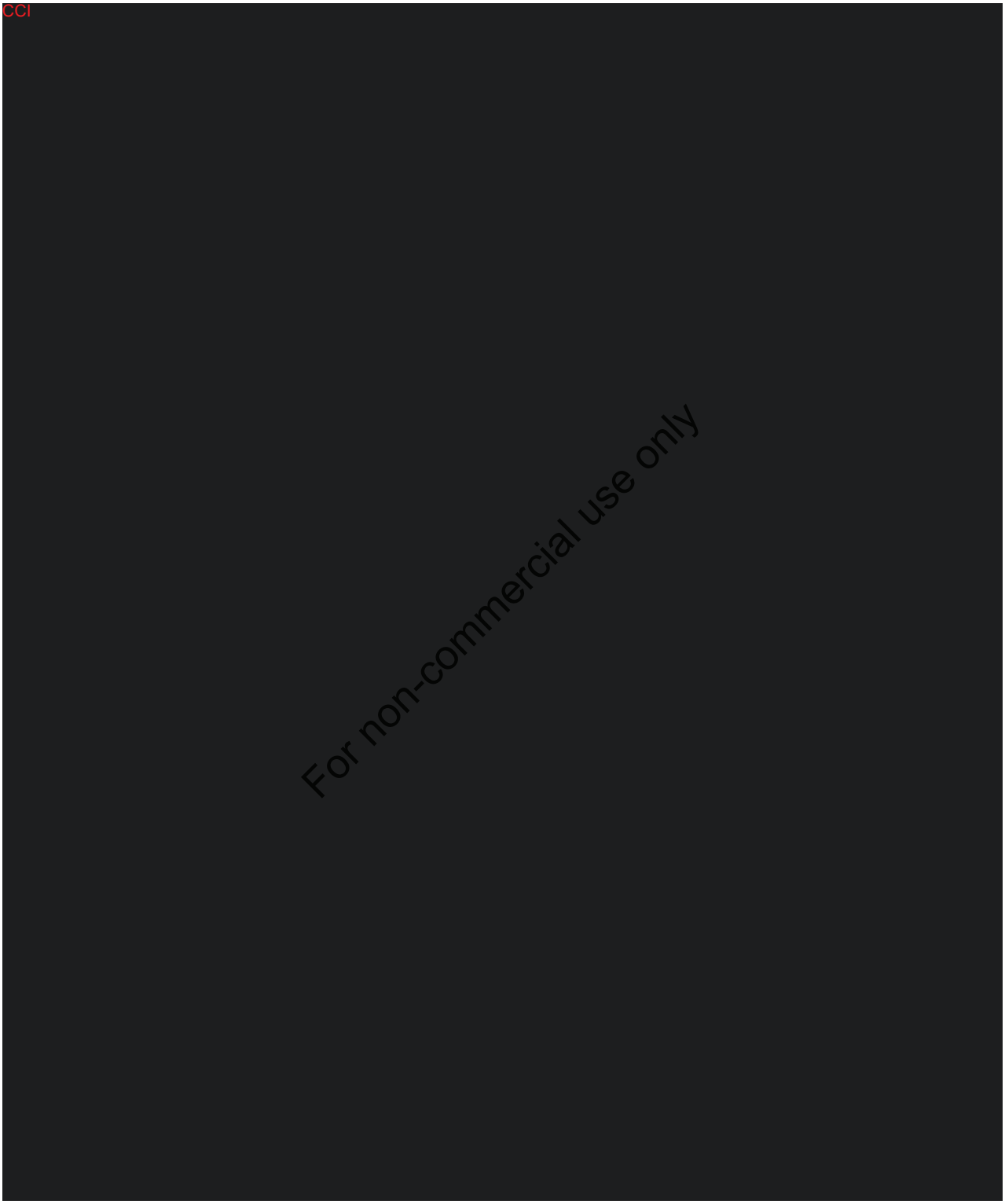

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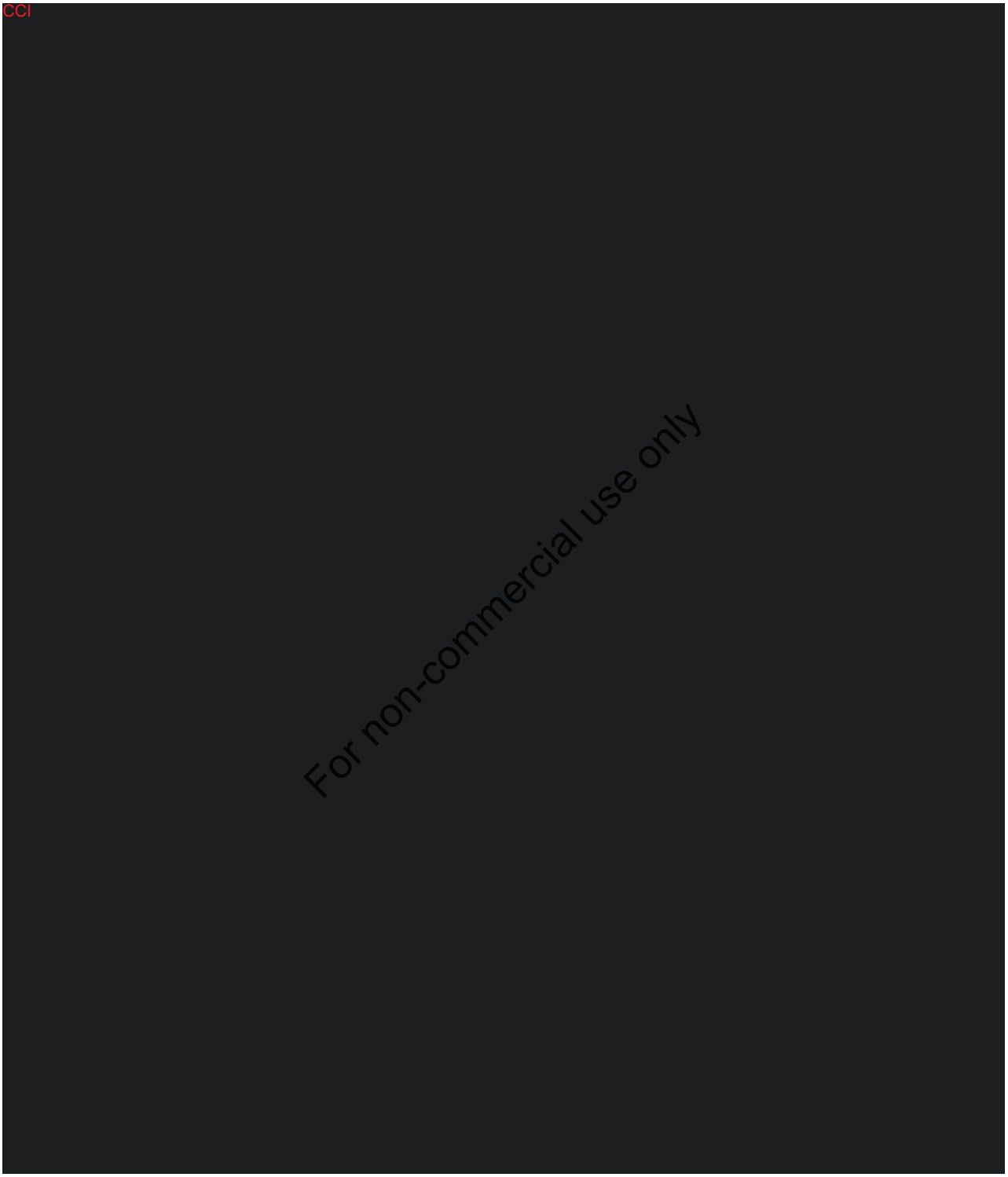

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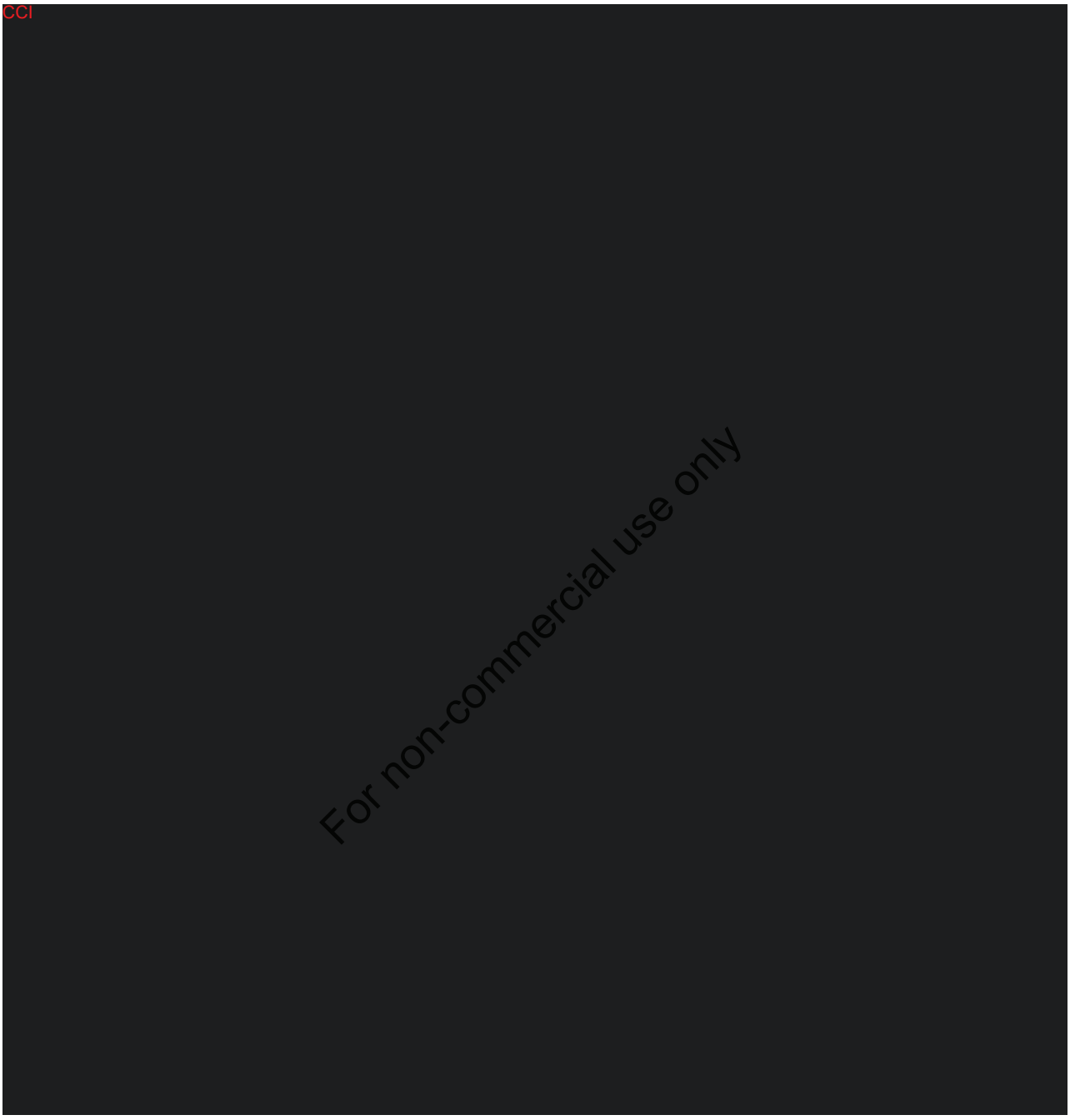

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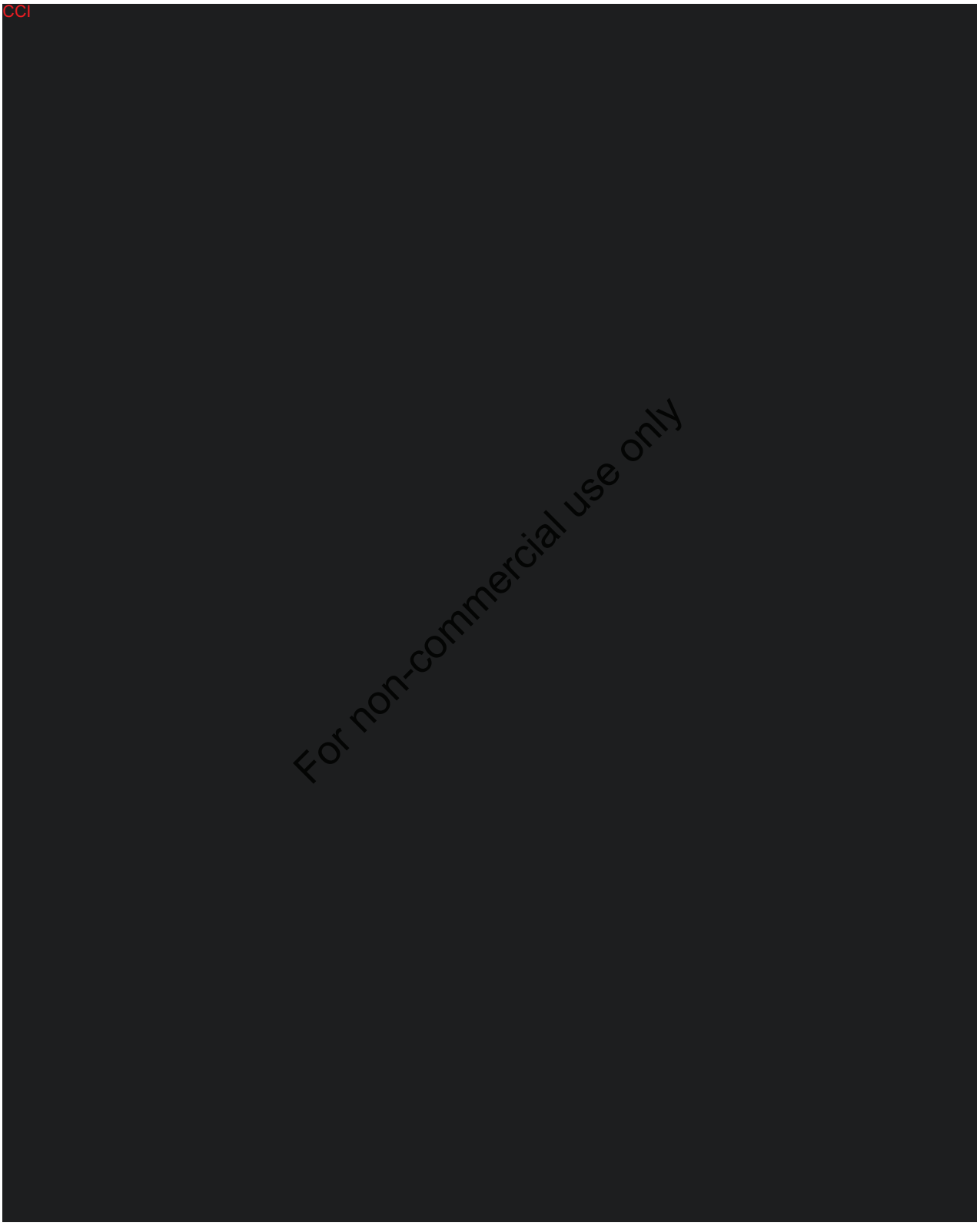

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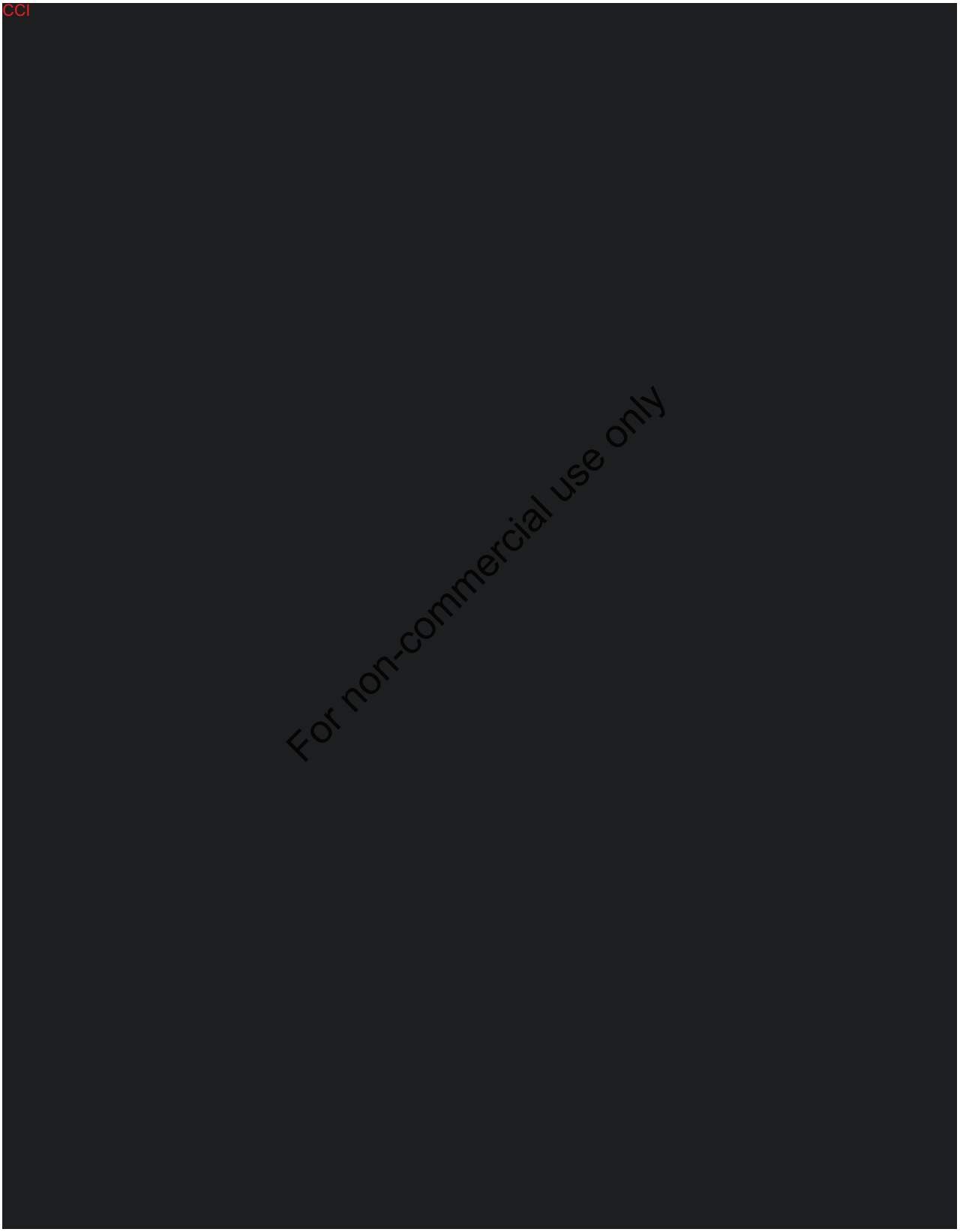

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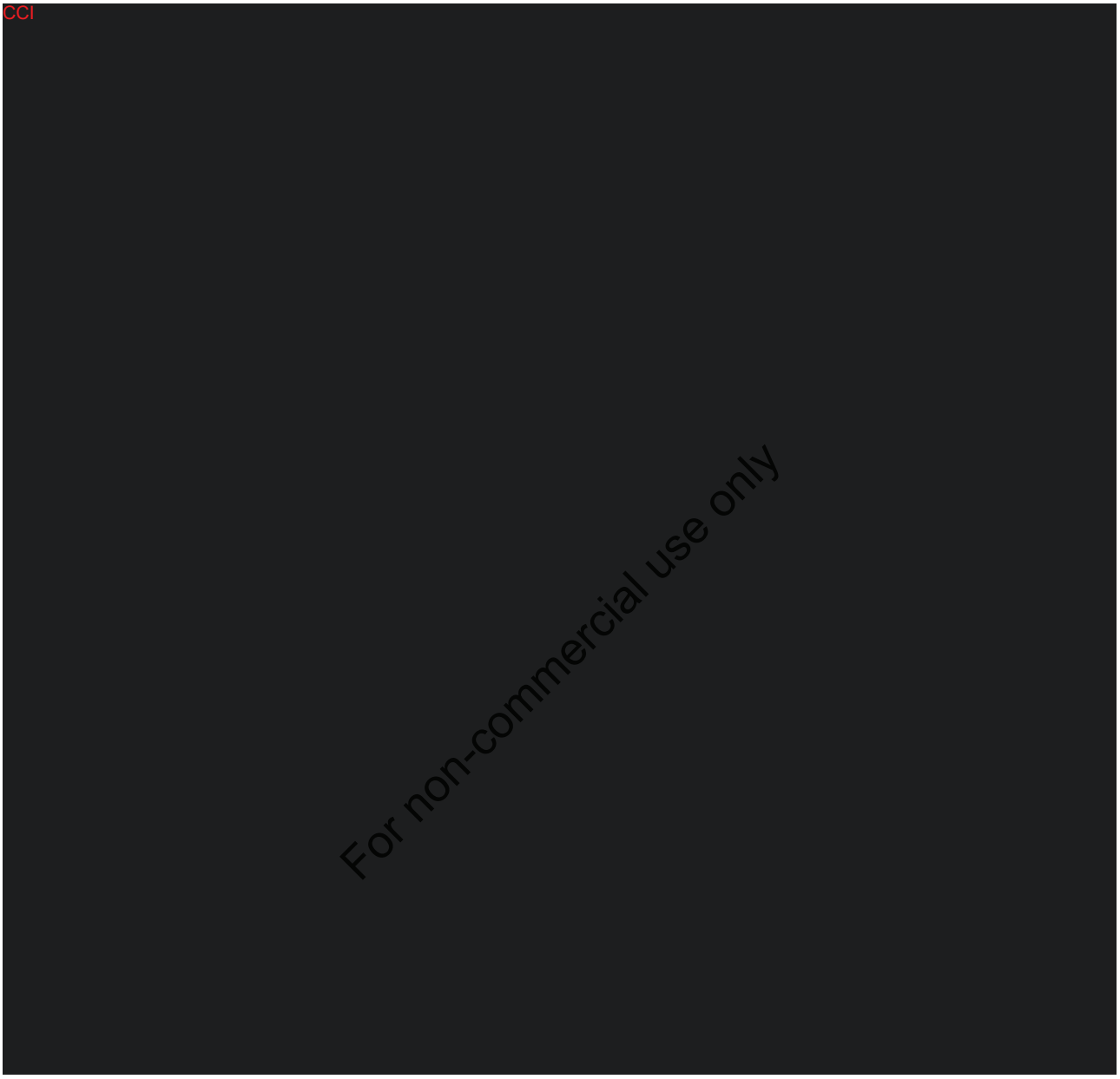

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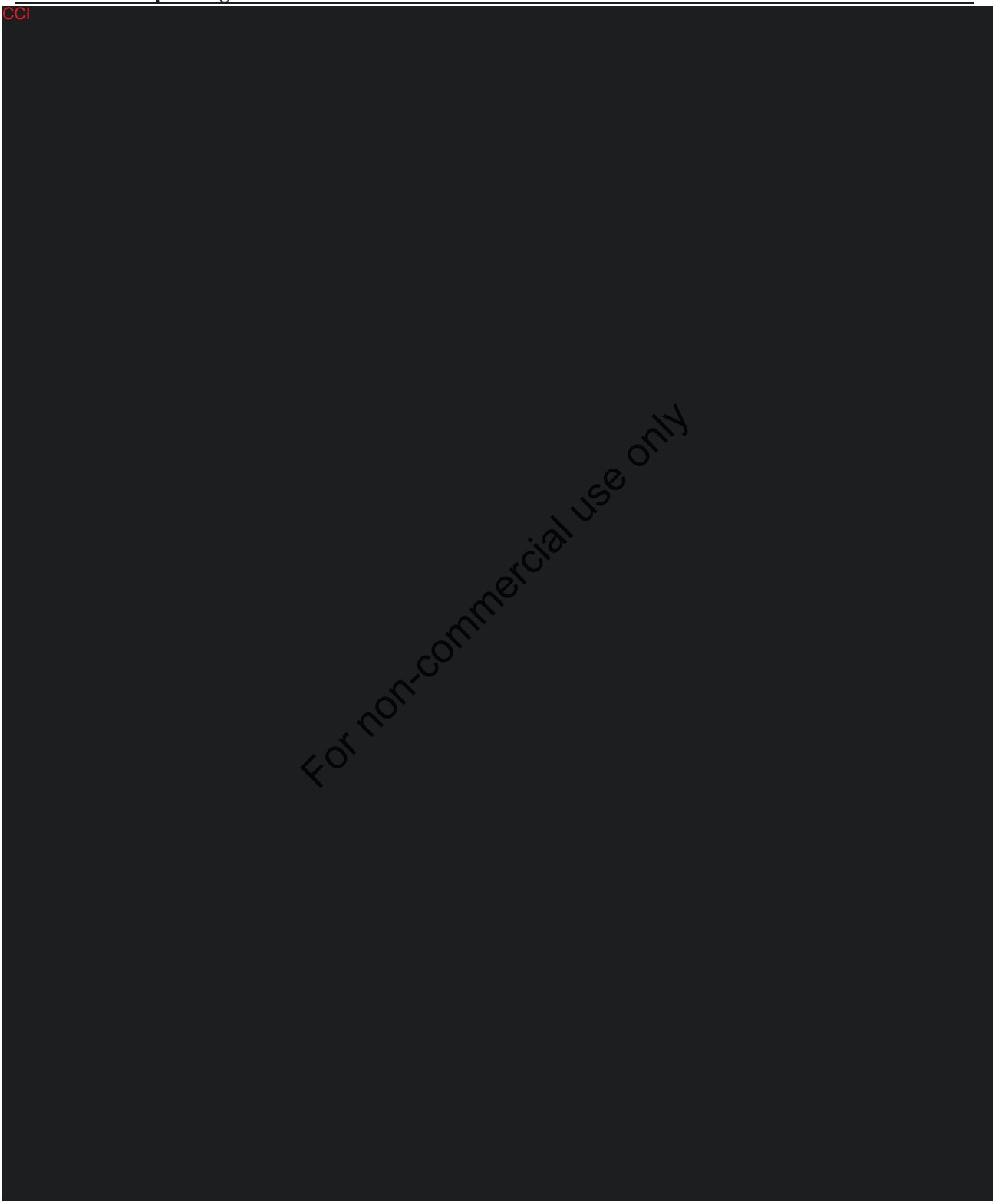

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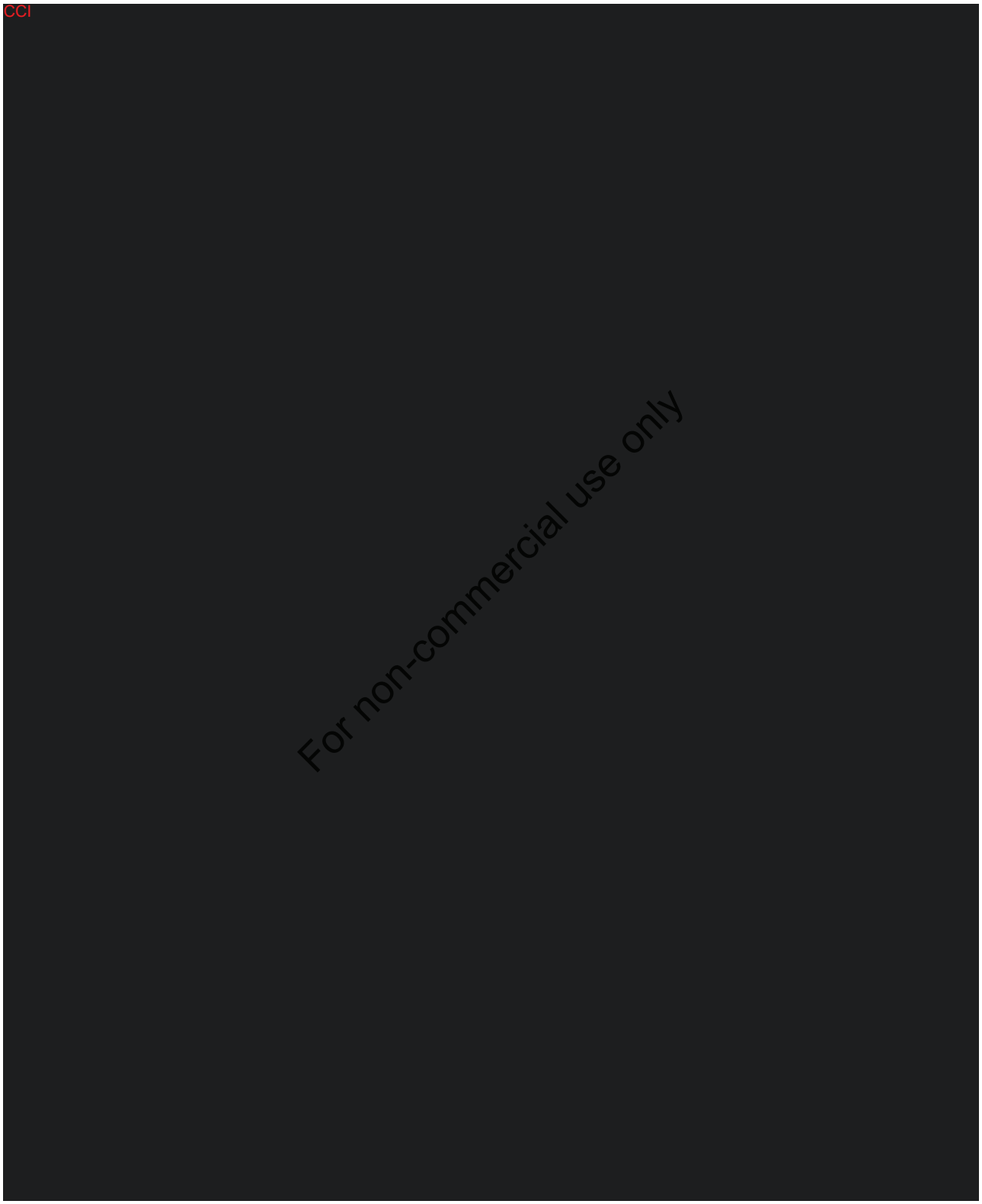

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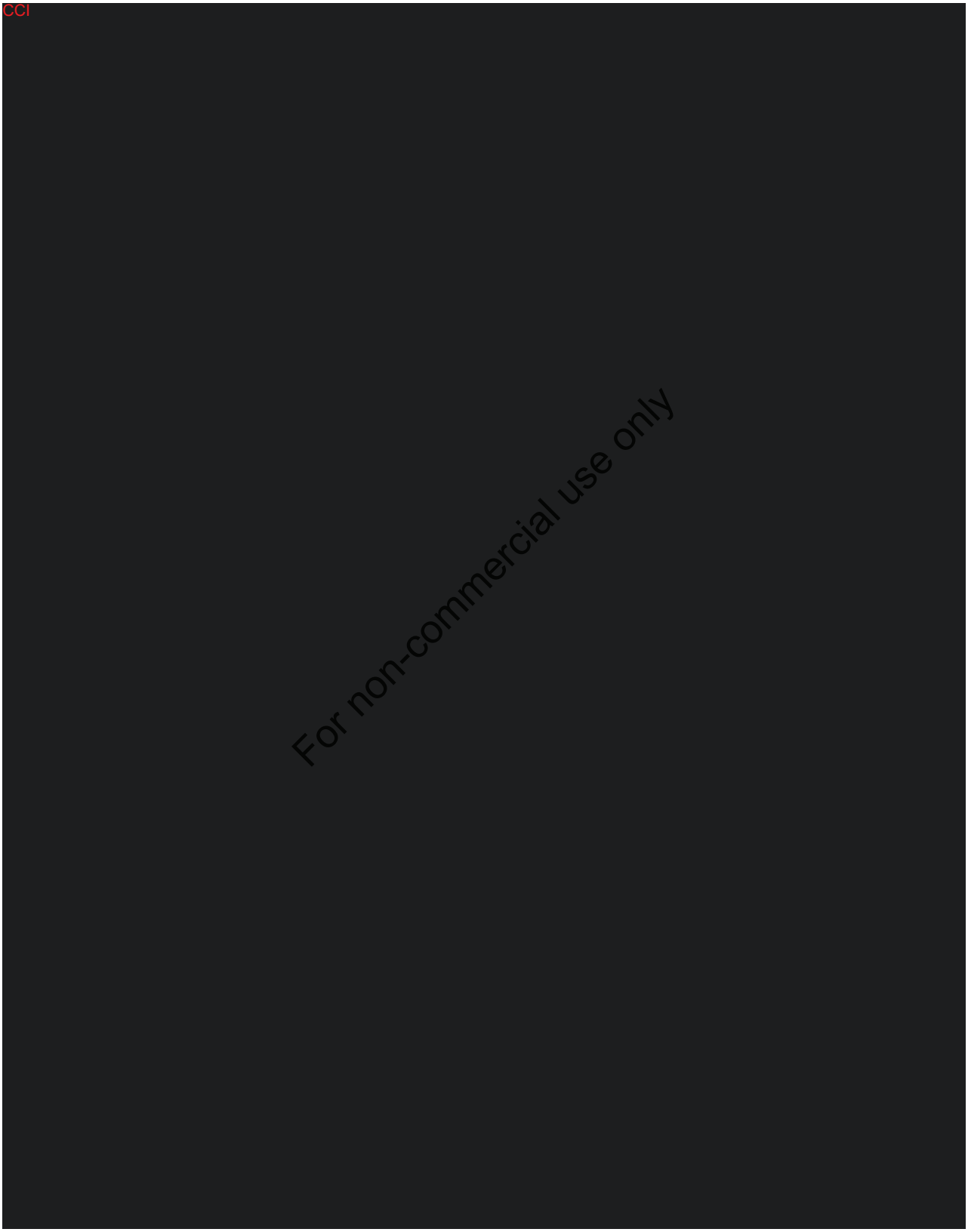

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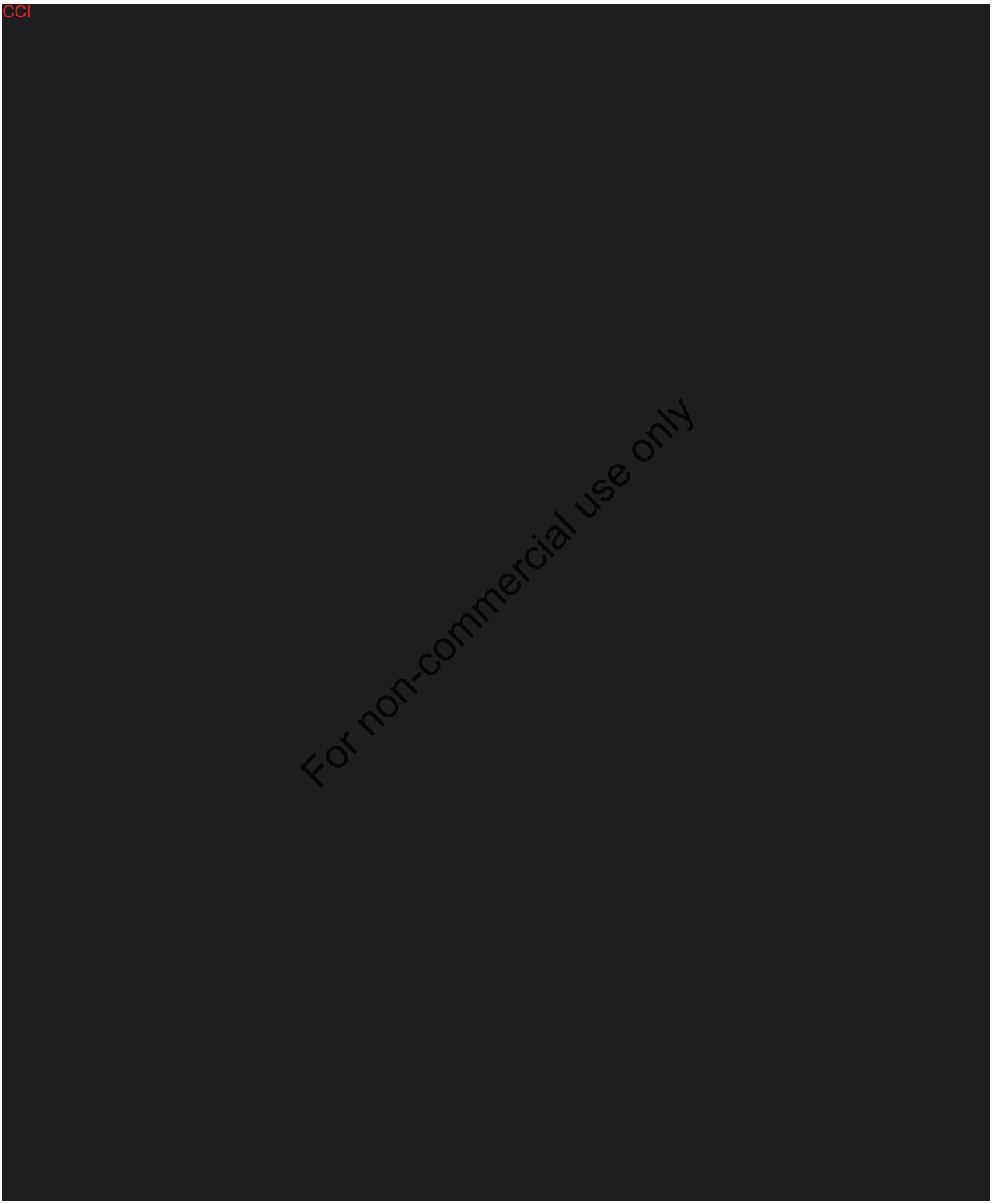

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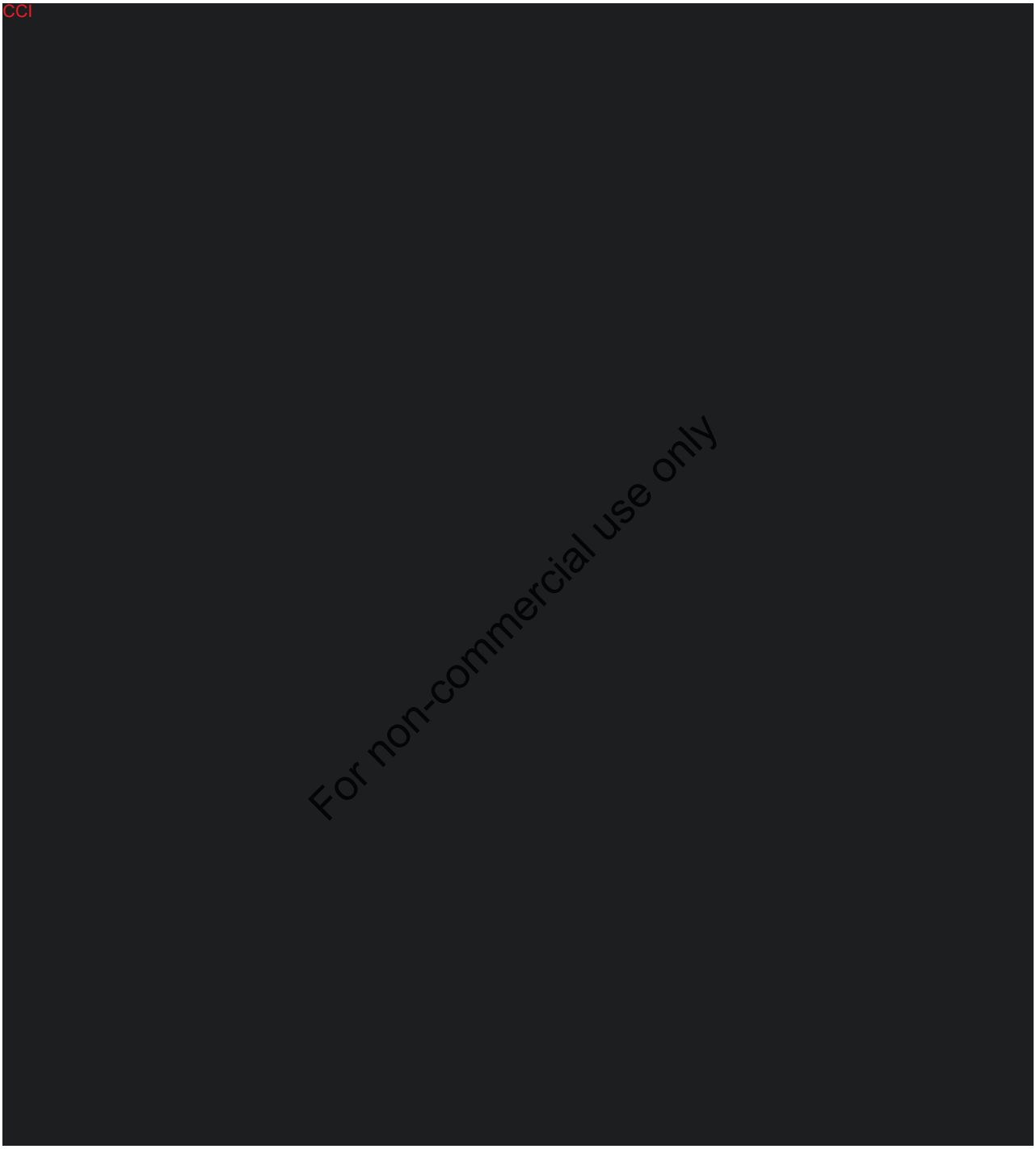

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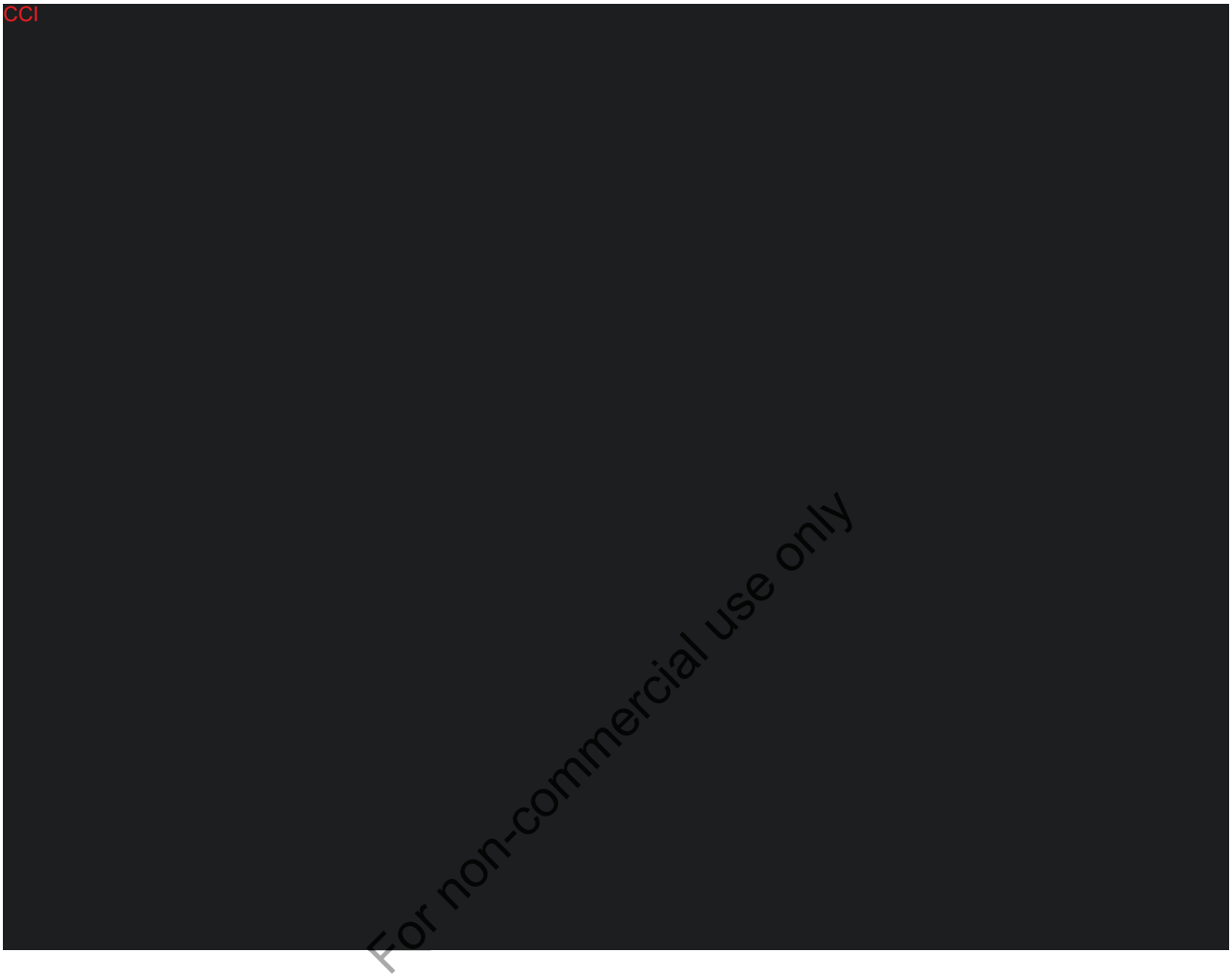

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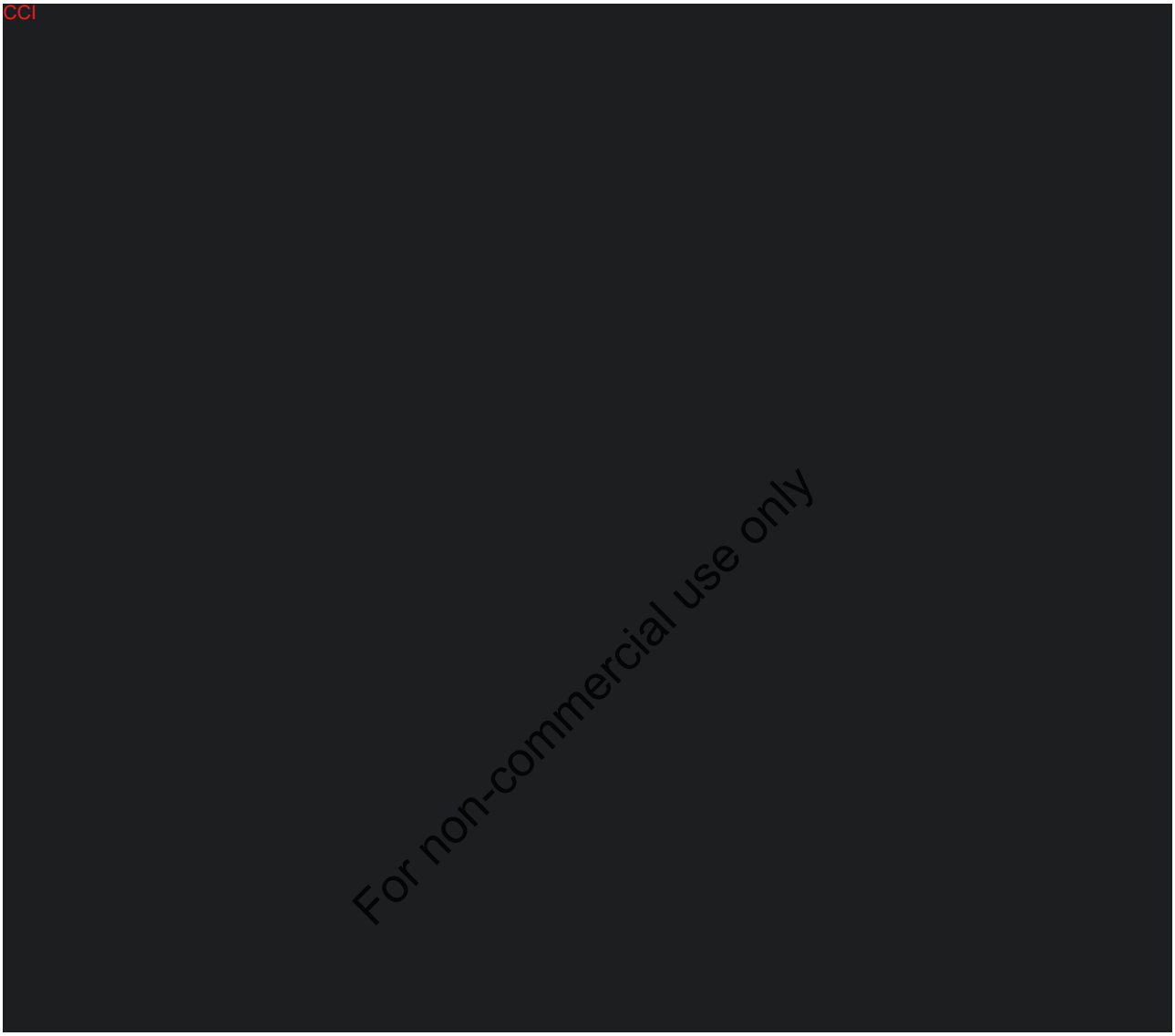

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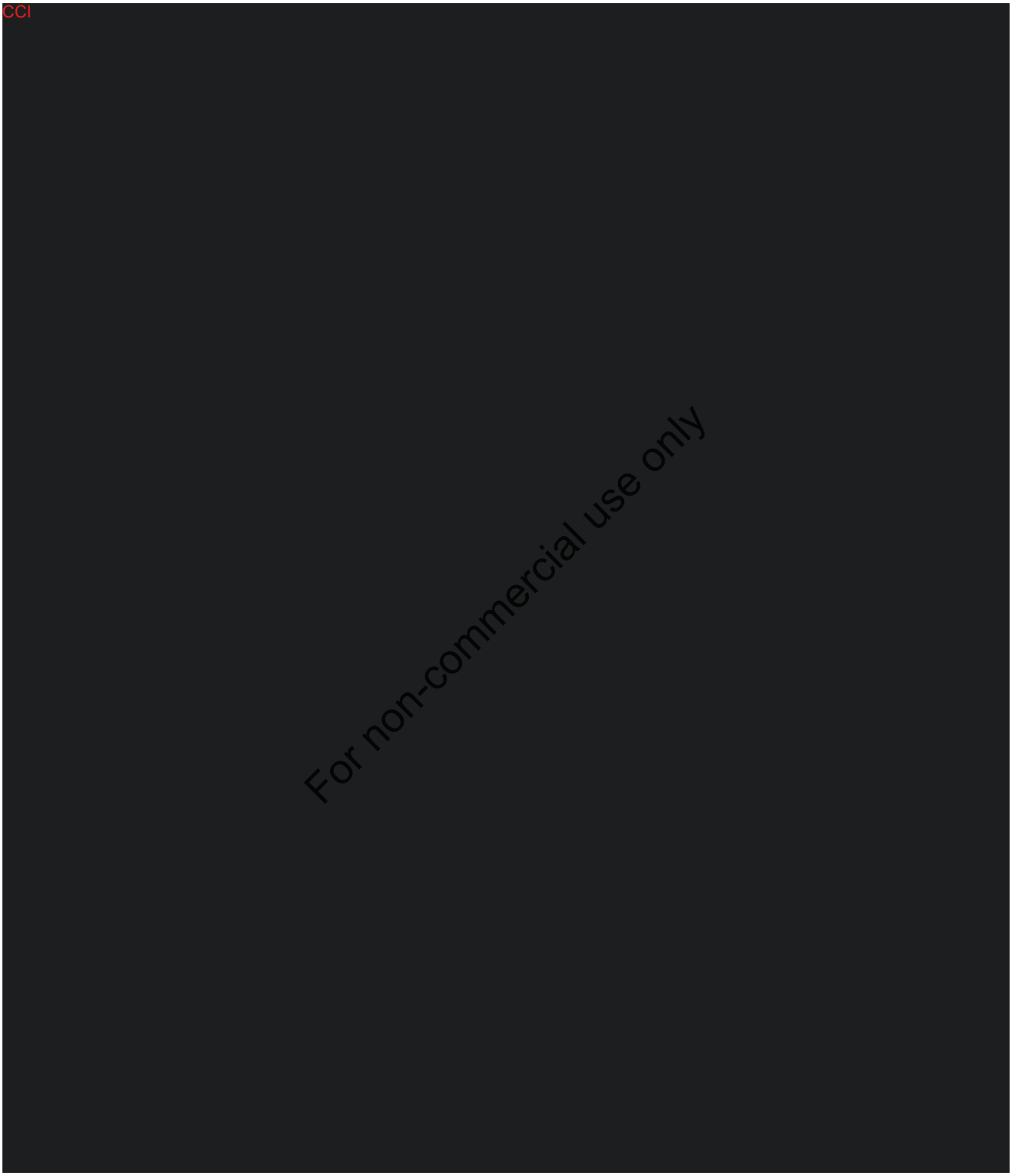

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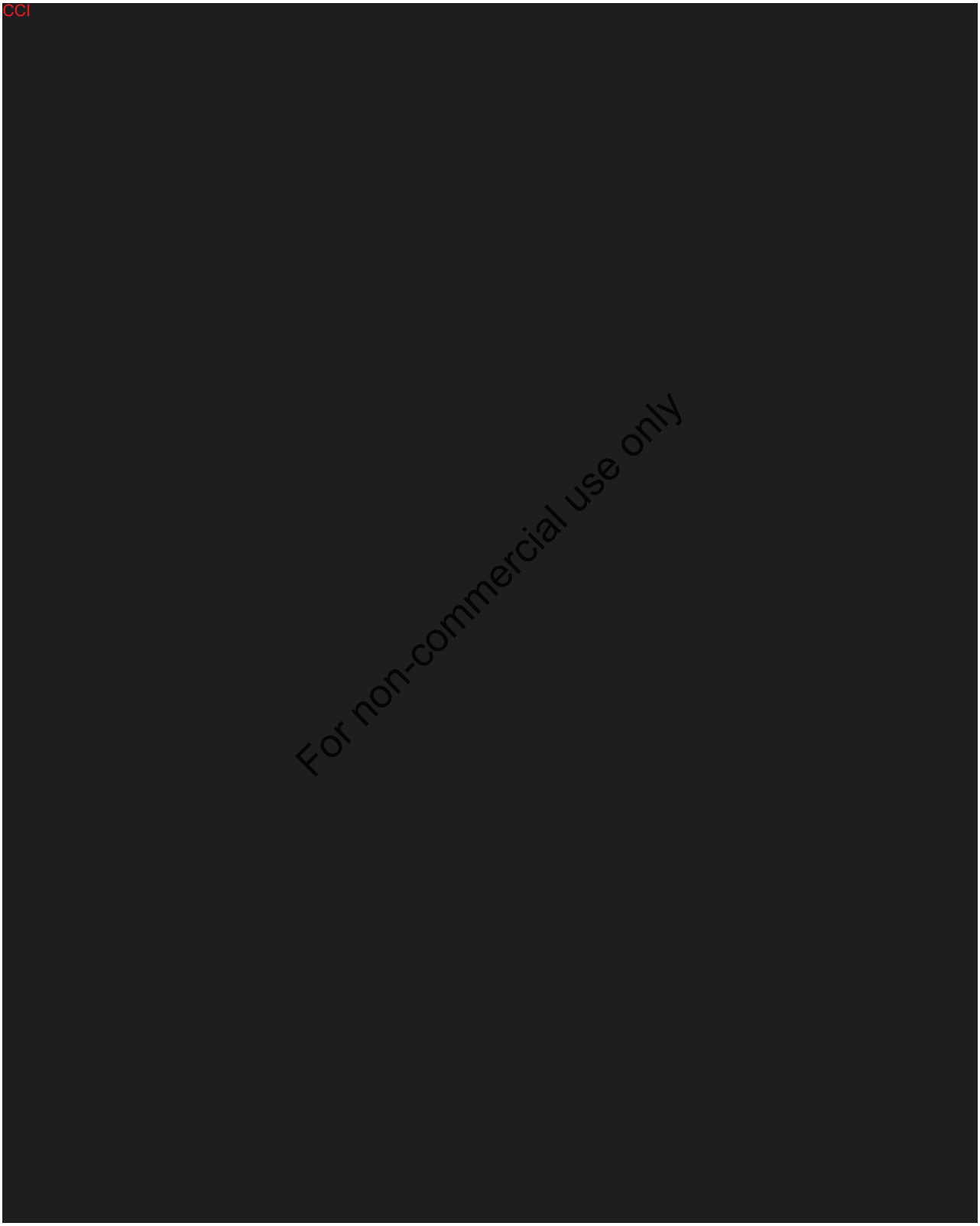

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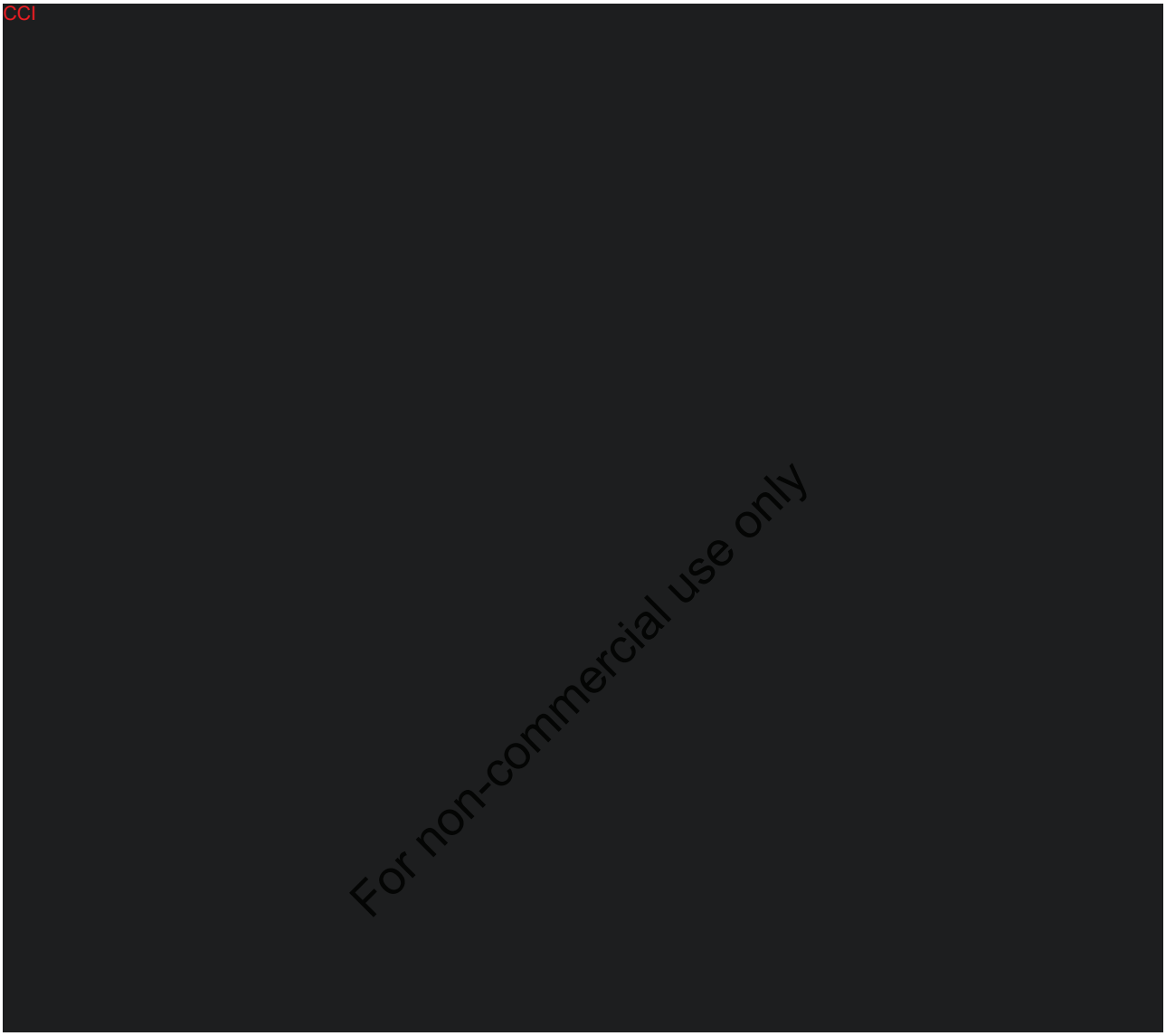

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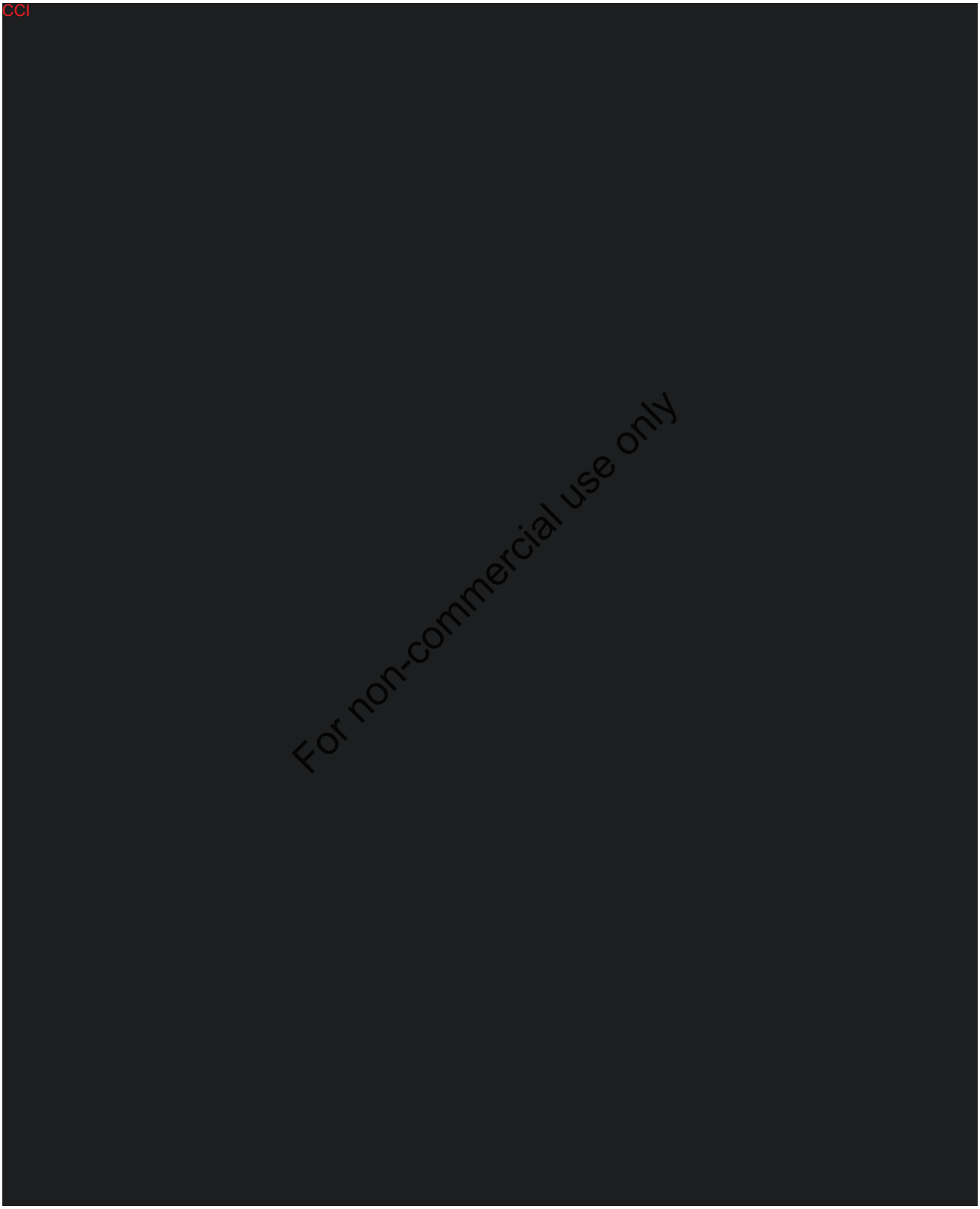

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-341	
Title of Protocol: A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenous TAK-341 in Subjects With Multiple System Atrophy	**IND No.:** 158317	**EudraCT No.:** 2022-000336-28
Study Number: TAK-341-2001	**Phase:** 2	

Study Design:

This study is a multicenter, randomized, double-blind, placebo-controlled phase 2 study to assess the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of TAK-341 administered as multiple intravenous (IV) infusions every 4 weeks (Q4W) over 52 weeks in male and female subjects with possible or probable multiple system atrophy (MSA), aged at least 40 years.

The study comprises a screening period of up to 42 days (6 weeks), a 52-week double-blind treatment period, and a follow-up safety visit approximately 90 days after the final infusion. Each subject will receive a total of 13 IV infusions of TAK-341 or placebo for approximately 60 minutes, with approximately 4 weeks between infusions (ie, Q4W dosing). An early PK cohort consisting of the first approximately CCI subjects will be randomized CCI to receive either TAK-341 or placebo. Dosing in subjects in the early PK cohort will be initiated at CCI Q4W. CCI After the early PK cohort is fully enrolled, further subjects will be enrolled into the main cohort. Subjects in the main cohort will receive CCI TAK-341 or placebo CCI CCI

The overall study duration (screening/enrollment, treatment period, and follow-up) will be up to approximately

67 weeks per subject.

The total Unified Multiple System Atrophy Rating Scale (UMSARS) will be administered to all subjects. The primary objective is to evaluate the effect of TAK-341 as compared to placebo on impairment in MSA subjects as measured by a modified UMSARS consisting of the UMSARS Part I, minus the sexual function item, with the 0 (normal) and 1 (mild) ratings on each item collapsed during the analysis process.

Early PK Cohort

Approximately CCI subjects in this cohort will receive 13 infusions over approximately 52 weeks. At Visit 2 (Day 1), eligible subjects will be randomized CCI to receive CCI TAK-341 (CCI dug product) or placebo (IV saline) in double-blinded fashion. CCI [redacted] Subjects will continue to receive Q4W infusions after the collection of early PK data, for a total of 13 infusions.

PK, safety, immunogenicity, and tolerability data from the early PK cohort from baseline through Day 85 will be evaluated once PK data from Visit 5 has been collected in all subjects in the early PK cohort. CCI [redacted]

Main Cohort

Approximately CCI subjects in this cohort will receive 13 infusions over approximately 52 weeks. Enrollment and dosing of subjects in the main cohort will continue while the PK data from the early PK cohort are being collected, analyzed, and final dose decision is made. At Visit 2 (Day 1), eligible subjects were randomized CCI to receive TAK-341 CCI or placebo (IV saline) in double-blinded fashion until the final dose was selected. After the final dose was selected, eligible subjects will be randomized CCI to receive TAK-341 CCI or placebo (IV saline) in double-blinded fashion. CCI [redacted]

All Subjects

All subjects will be treated with either TAK-341 or placebo Q4W for a total of approximately 52 weeks up to Visit 14 (Day 337; Infusion #13). For all subjects, sparse PK sampling (blood) will be performed at Visit 2 (Day 1; Infusion #1), Visit 5 (Day 85; Infusion #4), Visit 8 (Day 169; Infusion #7), and Visit 14 (Day 337; Infusion #13) except for subjects in the early PK cohort, CCI [redacted]. All subjects will undergo predose and end-of-infusion PK sampling on Visit 3 (Day 29; Infusion #2) and Visit 11 (Day 253; Infusion #10). A single PK sample

will be collected at Visit 15 (Day 365) and at the follow-up safety visit (Visit 16; Day 427) or the early termination visit. CCI [redacted] All subjects will undergo lumbar puncture on Visit 2 (Day 1, pre-dose) and Visit 15 (Day 365, trough). ADA data will be monitored on an ongoing basis.

MSA Study Population

- Possible or probable MSA (per Gilman et al, 2008 criteria).
- UMSARS Part I score ≤21 (excluding Item #11, sexual function) with a score ≤2 on Items #2 (swallowing), #7 (walking), and #8 (falling) at screening visit (Visit 1).
- UMSARS Part IV disability score ≤3 at screening visit (Visit 1).
- Subject has a Montreal Cognitive Assessment (MoCA) ≥18. Additionally, subject has sufficiently intact cognition to complete study assessments and follow study instructions, per investigator's judgment.
- Informed consent understood and signed by the subject (or, when applicable, the subject's legally acceptable representative).

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Primary Objective:

- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on UMSARS Part I, minus the sexual function item, with collapse of the normal and mild ratings on each item.

Secondary Objectives:

- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the 11-item UMSARS specified by Palma et al 2021.
- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the total UMSARS (UMSARS Part I + Part II).
- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the Part I UMSARS minus the sexual function item (without collapse of ratings of scale items).
- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the Part II UMSARS.
- To evaluate the efficacy of TAK-341 versus placebo on the Clinical Global Impression-Severity (CGI-S) scale.
- To evaluate the efficacy of TAK-341 versus placebo on the Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction (SCOPA-AUT).
- To evaluate the efficacy of TAK-341 versus placebo, as measured by overall survival at 52 weeks.
- To evaluate the effect of TAK-341 versus placebo on levels of CSF free αSYN, as measured by the change from baseline to Week 52.
- To assess the serum PK and CSF concentrations of TAK-341 in subjects with MSA.

Safety Objectives:

- To assess the safety and tolerability of TAK-341 in subjects with MSA.
- To assess the immunogenicity of TAK-341 in subjects with MSA.

Exploratory Objectives:

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[redacted]

[z] CCI [redacted]

Subject Population:
Subjects aged at least 40 years with possible or probable MSA per the Gilman et al, 2008 criteria. The subject's onset of first MSA symptoms (including parkinsonism, cerebellar symptoms, orthostatic or urinary symptoms) should have occurred ≤4 years before screening, as assessed by the investigator. In addition, their anticipated life expectancy would need to be ≥3 years, per investigator judgment. Subjects will also need to demonstrate an UMSARS Part I score ≤21 (excluding Item #11, sexual function) with a score ≤2 on Item #2 (swallowing), #7 (walking), and #8 (falling); an UMSARS Part IV disability score ≤3; and a MoCA score ≥18 with sufficiently intact cognition to complete study and follow study instructions according to the investigator's judgment. The subject (or, when applicable, the subject's legally acceptable representative) must be able to provide informed consent.

Number of Subjects:	**Number of Sites:**
Approximately 138.	Approximately 55 enrolling sites in North America, Europe, and Asia.
Dose Level(s): *Early PK cohort dose (before final dose selection):* CCI [redacted] *Main cohort dose (before final dose selection):* TAK-341 CCI [redacted] Q4W per infusion. *Final selected dose for both early PK cohort and main cohort:* CCI [redacted] Q4W per infusion *Comparator:* placebo (IV saline).	**Route of Administration:** *Study drug (TAK-341):* IV infusion, CCI [redacted]. *Placebo (IV saline):* IV infusion, CCI [redacted].
Duration of Treatment: Single dose approximately Q4W over 52 weeks (total of 13 infusions). CCI [redacted]	**Period of Evaluation:** 52 weeks (endpoint evaluation). CCI [redacted]

Criteria for Inclusion:

General

1. The subject (or, when applicable, the subject's legally acceptable representative) signs an informed consent form indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts (additionally *for subjects in Germany or Austria*: the subject has been informed of the nature, significance, and implications of the clinical study and is willing and able to understand and fully comply with study procedures and requirements (including digital tools and applications) in the opinion of the investigator. If the subject becomes incompetent over the course of the study, a legally authorized court-appointed representative or an appointed agent in health matters (ie, legally acceptable representative) will need to be identified and the subject will need to provide assent, in accordance with the local regulations, guidelines, and the institutional review board (IRB)/independent ethics committee (IEC) to provide informed consent on the subject's behalf to continue in the clinical study).
2. The subject is an outpatient of either sex, at least 40 years old, at the time of consent.
3. Subjects must, in the opinion of the investigator, be able to participate in all scheduled evaluations, likely to be compliant, and likely to complete all required tests, including neuroimaging brain scans and lumbar punctures.

4. The subject has a body mass index ≥18 and ≤35 kg/m^2 at screening.

Diagnostic

5. The subject has a diagnosis of possible or probable MSA using the modified Gilman et al, 2008 diagnostic criteria.
6. The subject's onset of first MSA symptoms (including parkinsonism, cerebellar symptoms, orthostatic or urinary symptoms) occurred ≤4 years before screening, as assessed by the investigator.
7. The subject's anticipated life expectancy is ≥3 years, per investigator judgment.
8. The subject has an UMSARS Part I score of ≤21 (excluding Item #11, sexual function) at screening visit (Visit 1), and additionally has:
    a) Severity score ≤2 on the swallowing item (#2) at screening visit (Visit 1).
    b) Severity score ≤2 on the ambulation item (#7) at screening visit (Visit 1).
    c) Severity score ≤2 on the falling item (#8) at screening visit (Visit 1).
9. The subject has an UMSARS Part IV disability score ≤3 at screening visit (Visit 1).
10. Subject has a MoCA ≥18. Additionally, subject has sufficiently intact cognition to complete study assessments and follow study instructions, per investigator's judgment.
11. A male subject who is nonsterilized (fertile) and sexually active with a female partner of childbearing potential is eligible to participate if he agrees to use a barrier method of contraception (ie, condom with or without spermicide) from the signing of informed consent throughout the study and for 90 days plus 5 half-lives (total of 190 days) after the last dose. In addition, they must be advised not to donate sperm during this period. The female partner of a male subject should also be advised to use a highly effective method of contraception.
12. Female subjects are eligible to participate if (a) they are not pregnant or nursing, and (b) they are of nonchildbearing potential or agree to use highly effective contraception from the signing of informed consent throughout the study and for 30 days plus 5 half-lives (total of 130 days) after the last dose of study drug.

Criteria for Exclusion:

Medical History

1. The subject has serious or unstable clinically significant illness including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic or autoimmune (eg, multiple sclerosis), hematologic, or other major disease, which, in the judgment of the investigator, is poorly controlled or otherwise likely to deteriorate, compromises the subject's safety or ability to complete the study, or compromises the interpretation of the study results.
2. The subject has other medical problems (neurological, visual, orthopedic, psychiatric) that, in the opinion of the investigator, may significantly interfere with completion of the study or interpretation of study endpoints or may confound diagnosis.
3. The subject has a disorder that is likely to interfere with drug disposition and elimination.
4. In the opinion of the investigator, the subject has a diagnosis of depression or other psychiatric disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), AND this disorder is poorly controlled AND of sufficient severity to interfere with completion of the study or interpretation of the endpoints.
5. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year before screening. CCI [redacted]
6. The subject has a history of alcohol or substance use disorder (except tobacco use disorder), as defined by the DSM-5, within 1 year before screening or between screening and randomization, or, in the opinion of the

investigator the subject's current or past use of substances may interfere with performance on the assessments.

7. The subject has a positive finding on an alcohol or illicit drug screen. A positive result for cannabis or prescription medications does not require exclusion.
8. The subject has undergone surgery for the treatment of MSA (eg, pallidotomy, deep brain stimulation, fetal tissue transplantation).
9. The subject has a history of epilepsy or seizures, except self-limited febrile childhood seizures.
10. The subject has any contraindication to lumbar puncture (as assessed by the Investigator) CCI [redacted]
11. The subject has hypersensitivity to TAK-341 or any excipients used in its formulation.
12. The subject has a history of cancer in the past 5 years (does not apply to participants with carcinoma in situ that has been resolved without further treatment, or basal cell carcinoma; these subjects may be included after approval by the sponsor or designee).

Diagnostic Assessments

13. Any clinically significant abnormality as determined by investigator at screening or between screening and randomization in physical examination findings, vital signs, electrocardiograms (ECGs), or clinical laboratory test results that may compromise the subject's safety or ability to complete the study or compromise the interpretation of the study results.
14. Presence of any contraindications to MRI as assessed by the Investigator CCI [redacted]
15. Ophthalmic abnormalities. CCI [redacted]
16. The subject has any of the following at the screening visit: estimated glomerular filtration rate (determined with the Chronic Kidney Disease Epidemiology Collaboration equation) <50 mL/min; QT interval with

Fridericia correction method >450 ms for male subjects and >470 ms for female subjects; a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >1.5 × the upper limit of normal.

17. Clinically significant vital sign abnormalities at screening or Visit 2 (Day 1), defined as (a) systolic blood pressure ≥160 mm Hg, (b) diastolic blood pressure ≥90 mm Hg (blood pressure assessed with the subject at rest in the seated position; may be repeated up to 3 times), or (c) pulse rate <45 or >100 beats per minute (subject at rest in the seated position; may be repeated up to 3 times).
18. The subject has a positive hepatitis B surface antigen test result, known or suspected active hepatitis C infection, or known history of HIV infection.
CCI [redacted]
19. The subject has a brain MRI that shows clinically significant evidence of malignant, ischemic, hemorrhagic, demyelinating, structural, or degenerative brain disease (other than MSA) that may confound diagnosis or compromise subject safety during the study, or the subject has findings that compromise the safety of lumbar puncture.
20. The subject has a current blood clotting or bleeding disorder, including clinically significant abnormal findings in laboratory tests of coagulation.

Other

21. The subject has poor venous access, such that IV drug delivery or PK/safety blood sampling would be difficult.
22. The subject has participated in another study investigating active or passive immunization against αSYN for PD or MSA (CCI [redacted]).
23. The subject has had immunoglobulin G therapy for any reason within 6 months before screening.
24. The subject's participation in a previous study of a disease-modifying therapy (with proven receipt of active treatment) will compromise the interpretability of the data from the present study, per consultation with medical monitor or designee. CCI [redacted]
25. The subject has received any investigational compound that, in the opinion of the investigator or sponsor, may not have completely washed out before the screening visit or may affect the safety or efficacy evaluations. Complete washout is defined as not having received investigational product 90 days before screening or 5 half lives of the investigational product, whichever is longer.
26. The subject has a positive pregnancy test result at screening or Visit 2 (Day 1).
27. The subject is an immediate family member, is a study site employee, or is in a dependent relationship (eg, as a spouse, parent, child, or sibling) with a study site employee who is involved in the conduct of this study.
28. The subject has donated 400 mL or more of his or her blood volume within 90 days before the start of the screening visit.
29. Austrian participants without capacity of consent (ie, ability to understand and process information relevant to making an informed, voluntary decision to participate in research).

Main Criteria for Evaluation and Analyses:

The primary endpoint includes efficacy as assessed by a modified UMSARS (ie, UMSARS Part I, minus the sexual function item, with the 0 [normal] and 1 [mild] ratings on each item collapsed during the analysis process) with TAK-341 compared with placebo (change from baseline over 52 weeks).

Secondary endpoints will include PK and efficacy as assessed by the total UMSARS (UMSARS Part I + Part II), Part I UMSARS minus the sexual function item, Part II UMSARS, SCOPA-AUT, CGI-S, overall survival at 52 weeks, and levels of CSF free αSYN.

Safety endpoints will include incidence of treatment-emergent adverse events; incidence of clinically significant

abnormal values (in clinical laboratory evaluations, vital signs, ECG parameters, and the C-SSRS); findings from clinical laboratory evaluations, vital sign assessments, ECG, C-SSRS, physical examination, neurological examination, CCI ; and incidence of antidrug antibodies (ADAs).

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Statistical Considerations:

Safety, tolerability, PK, and pharmacodynamics will be summarized descriptively with tables, listings, and graphs, as appropriate. Adverse events will be listed and will be summarized by using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term and by treatment regimen. The main presentation period of adverse events will be the time from first dose to follow-up. In addition, to capture adverse events related to CSF sampling, adverse events will also be presented separately for each CSF sampling time point.

Serum PK parameters will be determined for TAK-341 CCI The results of population PK and PK/pharmacodynamics analysis will be reported separately.

Summary statistics will be provided for the observed values of the efficacy measures at baseline and each of the postdose visits by treatment groups. Change from baseline will also be summarized with descriptive statistics by treatment groups.

The primary analysis will be performed using CCI .

The analysis of change from baseline for the secondary outcomes of UMSARS and SCOPA-AUT total score will be analyzed in the same manner as the primary analysis. CCI

Drug effects on change from baseline for all endpoints will be assessed using CCI

CCI

The final analyses for the primary endpoint will be conducted after all enrolled subjects enrolled have had the opportunity to complete 52 weeks of treatment (total of 13 infusions) with TAK-341 or placebo.

Sample Size Justification: A sample size of approximately 138 randomized subjects with MSA would be sufficient to detect an approximately CCI difference between TAK-341 and placebo in the mean change from baseline on a modified UMSARS score (UMSARS Part I minus the sexual function item, with collapsing of 'normal and mild' ratings during analysis). CCI [redacted].

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Contract Research Organization Obligations Listing, located in the trial master file. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The study is being funded by Takeda. Payments for the conduct of the study that will be made to study sites and, if applicable, investigators and/or other study staff will be specified in the Clinical Study Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the study starts at their study site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the study at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

αSYN	α-synuclein
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC_{τ}	area under the serum concentration-time curve during a dosing interval
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CCI	[redacted]
CGI-S	Clinical Global Impression-Severity
C_{max}	maximum observed concentration
CNS	central nervous system
COVID-2019	coronavirus disease 2019
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCV	hepatitis C virus
ICH	International Council for Harmonisation
ID	identification (number)
IEC	independent ethics committee
IVRS/IWRS	interactive voice response system/interactive web response system
IP	investigational product
IRB	institutional review board
IV	intravenous
LFT	liver function test
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance image, magnetic resonance imaging
CCI	[redacted]

MSA	multiple system atrophy
MSA-C	multiple system atrophy with predominant cerebellar ataxia
MSA-P	multiple system atrophy with predominant parkinsonism
CCI	[redacted]
CCI	[redacted]
PD	Parkinson disease
CCI	[redacted]
PK	pharmacokinetic(s)
CCI	[redacted]
PRO	patient-reported outcome
PTE	pretreatment event
Q4W	every 4 weeks
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
CCI	[redacted]
SCOPA-AUT	Scales for Outcomes in Parkinson's Disease–- Autonomic Dysfunction
SUSAR	suspected unexpected serious adverse reaction
TDC	Takeda Development Center
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of the maximum observed concentration
ULN	upper limit of normal
UMSARS(-I to IV)	Unified Multiple System Atrophy Rating Scale(-Parts I to IV)
CCI	[redacted]
US	United States

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

TAK-341 is being developed as a therapeutic antibody for the treatment of patients with multiple system atrophy (MSA) and Parkinson disease (PD).

TAK-341 is an α-synuclein (αSYN)–specific, CCI monoclonal antibody CCI [redacted] Abnormal accumulation of aggregated αSYN in the central nervous system (CNS) and peripheral autonomic nervous system is a pathological hallmark of a group of diseases known as α-synucleinopathies, which include PD, MSA, dementia with Lewy bodies, and pure autonomic failure. MSA is the most rapidly progressing of the α-synucleinopathies. In patients with MSA, αSYN accumulates primarily in oligodendrocytes, forming glial cytoplasmic inclusions. The symptoms reflect the progressive loss of function and death of different types of nerve cells in the brain and spinal cord.

CCI [redacted]

[redacted]

MSA is a rare, rapidly progressing, largely sporadic, fatal neurodegenerative disorder characterized by a combination of parkinsonism, ataxia, and severe autonomic dysfunction (eg, orthostatic hypotension; urinary incontinence/incomplete bladder emptying; erectile dysfunction; decreased sweating; salivation; dysphonia; and respiratory symptoms including stridor, sleep-disordered breathing, and respiratory insufficiency) with a relentless worsening of motor and nonmotor symptoms during an average timeframe of 6 to 10 years to death, with more rapid progression at the onset.

Patients with MSA have a mean age of onset of 55 to 60 years, with rapid and progressive loss of motor function over 5 to 10 years. Approximately 50% of patients require walking aids within 3 years after the onset of motor symptoms and 60% require a wheelchair after 5 years. The median time before the patient is bedridden is 6 to 8 years. People with MSA often develop pneumonia in the later stages of the disease and may suddenly die from cardiac or respiratory issues.

The MEDI1341/TAK-341 nomenclature in this protocol reflects the specific formulation used. Prior nonclinical and phase 1 clinical studies in this program were conducted using intravenous (IV) administration of MEDI1341, developed by AstraZeneca. This current study and further clinical development in this program will be conducted using IV administration of TAK-341, [redacted]

4.1.1 Clinical Background

Clinical studies with MEDI1341 comprised 1 completed phase 1 single ascending dose (SAD) study (D6340C00001) conducted in 49 healthy adult subjects and 1 completed multiple ascending dose (MAD) study (D6340C00002) in subjects with PD. [redacted]

CCI [redacted]

Given the available unblinded safety data from the SAD and MAD studies, MEDI1341 appeared to be safe and well tolerated.

Refer to the investigator's brochure for additional details.

4.2 Rationale for the Proposed Study

There are currently no marketed or available therapies in the United States (US) that can slow or prevent the progression of MSA. TAK-341 may, therefore, potentially address a great unmet medical need for patients with MSA.

Phase 1 studies have demonstrated acceptable PK characteristics and target engagement and no safety issues to date. This study will be the first phase 2 study to test the efficacy and safety of TAK-341 in subjects with MSA.

The objective of the current phase 2 study is to evaluate the efficacy, safety, tolerability, PK, and pharmacodynamics of IV TAK-341 in patients with MSA to support further development of TAK-341 as a potential treatment for MSA. The available nonclinical pharmacology, PK, and toxicology data, in addition to the data from the two phase 1 studies (ie, SAD in healthy volunteers and MAD in subjects with PD) support the current trial design. Several key aspects were considered to formulate the study design. First, the efficacy profile of repeated fixed-dose TAK-341 will be evaluated for the first time in subjects with MSA and compared with that of subjects receiving placebo control.

CCI [redacted]

CCI [redacted]

4.3 Benefit-Risk Profile

The benefit-risk profile supports continued development of TAK-341.

MSA is a lethal condition with a life expectancy of 6 to 10 years after symptom onset (Fanciulli and Wenning 2015). CCI [redacted]. Potential risks of TAK-341 include CCI [redacted]. These risks and their mitigation strategies are summarized next.

- CCI [redacted]
- As with any monoclonal antibody, infusion reactions and hypersensitivity reactions, including anaphylaxis, are possible. CCI [redacted]
- CCI [redacted]
- [redacted]
- This study includes CSF collection CCI [redacted]. CSF collection is an established procedure with typical risks associated with lumbar puncture, including headache, infection, bleeding, and intracranial structural pathology producing raised intracranial pressure. These risks will be mitigated by the exclusion of subjects with any contraindications to lumbar puncture (please see the exclusion criteria; Section 7.2). CCI [redacted]

CCI [redacted]

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on Unified Multiple System Atrophy Rating Scale (UMSARS) Part I, minus the sexual function item, with collapse of the normal and mild ratings on each item.

5.1.2 Secondary Objectives

- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the 11-item UMSARS specified by Palma et al. 2021.
- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the total UMSARS (UMSARS Part I + Part II).
- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the Part I UMSARS minus the sexual function item (without collapse of ratings of scale items).
- To evaluate the efficacy of TAK-341 versus placebo, as measured by the change from baseline to Week 52 on the Part II UMSARS.
- To evaluate the efficacy of TAK-341 versus placebo on the Clinical Global Impression-Severity (CGI-S) scale.
- To evaluate the efficacy of TAK-341 versus placebo on the Scales for Outcomes in Parkinson's Disease–- Autonomic Dysfunction (SCOPA-AUT).
- To evaluate the efficacy of TAK-341 versus placebo, as measured by overall survival at 52 weeks.
- To evaluate the effect of TAK-341 versus placebo on levels of CSF free αSYN, as measured by the change from baseline to Week 52.
- To assess the serum PK and CSF concentrations of TAK-341 in subjects with MSA.

5.1.3 Safety Objectives

- To assess the safety and tolerability of TAK-341 in subjects with MSA.
- To assess the immunogenicity of TAK-341 in subjects with MSA.

5.1.4 Exploratory Objectives

CCI

[redacted]

5.2 CCI

[redacted]

5.3 Endpoints

5.3.1 Primary Endpoint

- Change from baseline to Week 52 on UMSARS Part I, minus the sexual function item, with collapse of the normal and mild ratings on each item with TAK-341 compared with placebo.

5.3.2 Secondary Endpoints

- Change from baseline to Week 52 on the 11-item UMSARS specified by Palma et al. 2021 al 2021 with TAK-341 compared with placebo.
- Change from baseline to Week 52 on the UMSARS total score (UMSARS Part I + Part II) with TAK-341 compared with placebo.
- Change from baseline to Week 52 on the UMSARS Part I score minus the sexual function item (without collapse of ratings of scale items) with TAK-341 compared with placebo.
- Change from baseline to Week 52 on the UMSARS Part II score with TAK-341 compared with placebo.
- CGI-S score with TAK-341 compared with placebo.
- Change from baseline to Week 52 on the SCOPA-AUT total score with TAK-341 compared with placebo.
- Overall survival at 52 weeks with TAK-341 compared with placebo.
- Change from baseline to Week 52 on levels of CSF free αSYN with TAK-341 compared with placebo.
- Serum PK parameters, if feasible, will include but not be limited to the following:
  - C_{max}.
  - t_{max}.
  - Area under the serum concentration-time curve during a dosing interval (AUC_{τ}).
- CSF concentrations of TAK-341.

5.3.3 Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs).
- Incidence of clinically significant abnormal values for clinical laboratory evaluations, vital signs, ECG parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS).
- Findings from clinical laboratory evaluations, vital signs, ECG, C-SSRS, physical examination, neurological examination, CCI [redacted]
- Incidence of ADAs.

5.3.4 Exploratory Endpoints

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled phase 2 study to assess the efficacy, safety, tolerability, PK, and pharmacodynamics of TAK-341 administered as multiple IV infusions Q4W over 52 weeks in male and female subjects with possible or probable MSA, aged at least 40 years.

The study comprises a screening period of up to 42 days (6 weeks), a 52-week double-blind treatment period, and a follow-up safety visit approximately 90 days after the final infusion. Each subject will receive a total of 13 IV infusions of TAK-341 or placebo CCI [redacted], with approximately 4 weeks between infusions (ie, Q4W dosing). CCI [redacted]

CCI . Dosing in subjects in the early PK cohort will be initiated at CCI Q4W. Additional PK assessments for the early PK cohort subjects are described below (intensive serial serum PK sampling). After the early PK cohort is fully enrolled, further subjects will be enrolled into the main cohort. Subjects in the main cohort will receive CCI TAK-341 or placebo CCI

CCI

The overall study duration (screening/enrollment, treatment period, and follow-up) will be up to approximately 67 weeks per subject.

The total UMSARS will be administered to all subjects. The primary objective is to evaluate the effect of TAK-341 as compared to placebo on impairment in MSA subjects as measured by a

modified UMSARS consisting of the UMSARS Part I, minus the sexual function item, with the 0 (normal) and 1 (mild) ratings on each item collapsed during the analysis process.

Early PK Cohort

Approximately CCI subjects in this cohort will receive 13 infusions over approximately 52 weeks. At Visit 2 (Day 1), eligible subjects will CCI [redacted] Once subjects receive Infusion #3 at Visit 4 (Day 57), intensive serial serum PK sampling will be conducted until the predose assessment for Infusion #4 at Visit 5 (Day 85). The early PK cohort will also undergo lumbar puncture on Visit 5 (Day 85), before dosing of Infusion #4. CCI [redacted]
Subjects will continue to receive Q4W infusions after the collection of early PK data, for a total of 13 infusions.

CCI [redacted]

Main Cohort

Approximately CCI subjects in this cohort will receive 13 infusions over approximately 52 weeks. Enrollment and dosing of subjects in the main cohort will continue while the PK data from the early PK cohort are being collected, analyzed, and final dose decision is made. At Visit 2 (Day 1), eligible subjects were randomized CCI to receive TAK-341 CCI or placebo (IV saline) in double-blinded fashion until the final dose was selected. After the final dose was selected, eligible subjects will be randomized CCI to receive TAK-341 CCI or placebo (IV saline) in double-blinded fashion. Randomization of subjects will be stratified by diagnostic certainty (probable and possible MSA). CCI [redacted]

CCI [redacted]

All Subjects

All subjects will be treated with either TAK-341 or placebo Q4W for a total of approximately 52 weeks up to Visit 14 (Day 337; Infusion #13). For all subjects, sparse PK sampling (of blood) will be performed at Visit 2 (Day 1; Infusion #1), Visit 5 (Day 85; Infusion #4), Visit 8 (Day 169; Infusion #7), and Visit 14 (Day 337; Infusion #13) except for subjects in the early PK cohort, CCI [redacted]

MSA Study Population

- Possible or probable MSA (per Gilman et al, 2008 criteria) (Gilman et al. 2008) (Appendix F).
- UMSARS Part I score ≤21 (excluding Item #11, sexual function) with a score ≤2 on Items #2 (swallowing), #7 (walking), and #8 (falling) at screening visit (Visit 1).
- UMSARS Part IV disability score ≤3 at screening visit (Visit 1).
- Sufficiently intact cognition to follow instructions and complete study assessments throughout the duration of the study, per investigator judgment.
- Informed consent understood and signed by the subject (or, when applicable, the subject's legally acceptable representative).

CCI [redacted]

[redacted]

Figure 6.a [redacted]

[redacted]

6.2 Justification for Study Design, Dose, and Endpoints

This study will enroll approximately 138 subjects with possible or probable MSA per the Gilman et al, 2008 criteria (Gilman et al. 2008). The subject's onset of first MSA symptoms (including parkinsonism, cerebellar symptoms, orthostatic or urinary symptoms) should have occurred ≤4 years before screening. [redacted]

[redacted]

CCI [redacted]

A double-blind treatment period of 52 weeks was chosen to maximize the likelihood of observing efficacy while maintaining feasibility and keeping drop-out rates sufficiently low.

CCI [redacted]

An early PK cohort consisting of the first approximately CCI subjects with MSA will provide intensive serial serum PK samples after the third monthly dose at Day 57; samples will be collected through immediately before the fourth dose at Day 85 CCI [redacted]

In addition to the intensive PK sample collection in the early PK cohort, all subjects will provide sparse PK serum samples on Days 1, 29, 85, 169, 253, and 337, and the PK data from all subjects will be analyzed by using a population PK approach.

CCI [redacted]

CCI [redacted]

The total UMSARS (Appendix G) will be administered to all subjects. The primary objective is to evaluate the effect of TAK-341 as compared to placebo on impairment in MSA subjects as measured by a modified UMSARS, CCI [redacted]; this scale consists of the UMSARS Part I, minus the sexual function item, with the 0 (normal) and 1 (mild) ratings on each item collapsed during the analysis process.

In addition, this study will evaluate a number of additional UMSARS versions as secondary CCI [redacted] endpoints (eg, Palma et al. 2021).

Other secondary objectives will include assessment of SCOPA-AUT, CGI-S, overall survival at 52 weeks, and CSF free αSYN levels, and serum PK and CSF concentrations of TAK-341.

All subjects will undergo lumbar puncture at baseline and at 12 months for the purpose of evaluating CSF PK and pharmacodynamics (free αSYN levels) and CSF biomarkers. CCI [redacted]

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 benefit-risk profile for TAK-341, such that the benefit-risk profile is no longer acceptable for subjects participating in the study.
- The data monitoring committee recommends that the study should be suspended or terminated.
- Significant violation of 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 Site(s)

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) 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.

6.3.4 Duration of an Individual Subject's Study Participation

Subjects may continue treatment unless a safety issue is identified that requires subject discontinuation or study termination. Subjects will discontinue treatment if they have an unacceptable TAK-341-related toxicity.

Subjects will be followed up to 90 days after the last dose/final infusion of TAK-341 or placebo to permit the detection of any delayed treatment-emergent AEs.

6.3.5 End of Study/Study Completion Definition and Planned Reporting

The end of the study is defined as the date of the last visit of the last subject participating in the study.

Primary Completion/Study Completion

The final analyses for the primary endpoint and final CSR will be conducted after all enrolled subjects have had the opportunity to complete 52 weeks of treatment (total of 13 infusions) with TAK-341 or placebo.

6.3.6 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary: Change from baseline to Week 52 on UMSARS Part I, minus the sexual function item, with collapse of the normal and mild ratings on each item with TAK-341 compared with placebo.	Refer to Section 9.1.7.1.	Up to 52 weeks
Secondary: Change from baseline to Week 52 on the 11-item UMSARS specified by Palma et al. 2021, with TAK-341 compared with placebo.	Refer to Section 9.1.7.1.	Up to 52 weeks
Secondary: Change from baseline to Week 52 on the UMSARS total score (UMSARS Part I + Part II) with TAK-341 compared with placebo.	Refer to Section 9.1.7.1.	Up to 52 weeks
Secondary: Change from baseline to Week 52 on the UMSARS Part I score minus the sexual function item (without collapse of ratings of scale items) with TAK-341 compared with placebo.	Refer to Section 9.1.7.1.	Up to 52 weeks
Secondary: Change from baseline to Week 52 on the UMSARS Part II score with TAK-341 compared with placebo.	Refer to Section 9.1.7.1.	Up to 52 weeks
Secondary: CGI-S score with TAK-341 compared with placebo.	Refer to Section 9.1.7.1.	Up to 52 weeks
Secondary: Change from baseline to Week 52 on the SCOPA-AUT total score with TAK-341 compared with placebo.	Refer to Section 9.1.7.4	Up to 52 weeks
Secondary: Overall survival at 52 weeks with TAK-341 compared with placebo.	Refer to Section 13.1.3	Up to 52 weeks
Secondary: Change from baseline to Week 52 on levels of CSF free αSYN with TAK-341 compared with placebo.	Refer to Section 9.1.15.2.1 and 9.1.15.2.2	Up to 52 weeks
Secondary: Serum PK parameters, if feasible, but not limited to C_{max}, t_{max}, and AUC_{τ}.	Refer to Section 9.1.15.1.1.	Up to 52 weeks
Secondary: CSF concentrations of TAK-341.	Refer to Section 9.1.15.1.2.	Up to 52 weeks

αSYN: α-synuclein; AUC_{τ}: area under the serum concentration-time curve during a dosing interval; CGI-S: Clinical Global Impression-Severity; C_{max}: maximum observed serum concentration; CSF: cerebrospinal fluid; SCOPA-AUT: Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction; t_{max}: time of first occurrence of maximum observed concentration; UMSARS: Unified Multiple System Atrophy Rating Scale.

6.3.7 Total Study Duration

It is anticipated that this study will last for approximately 30 months.

6.4 Post-Trial Access

CCI

[redacted]

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All eligibility criteria, including test results, need to be confirmed before randomization/first dose.

7.1 Inclusion Criteria

General

1. The subject (or, when applicable, the subject's legally acceptable representative) signs an informed consent form indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts (additionally *for subjects in Germany or Austria*: the subject has been informed of the nature, significance, and implications of the clinical study and is willing and able to understand and fully comply with study procedures and requirements (including digital tools and applications) in the opinion of the investigator. If the subject becomes incompetent over the course of the study, a legally authorized court-appointed representative or an appointed agent in health matters (ie, legally acceptable representative) will need to be identified and the subject will need to provide assent, in accordance with the local regulations, guidelines, and the IRB/IEC to provide informed consent on the subject's behalf to continue in the clinical study).
2. The subject is an outpatient of either sex, at least 40 years old, at the time of consent.
3. Subjects must, in the opinion of the investigator, be able to participate in all scheduled evaluations, likely to be compliant, and likely to complete all required tests, including neuroimaging brain scans and lumbar punctures.
4. The subject has a body mass index (BMI) ≥18 and ≤35 kg/m^2 at screening.

Diagnostic

5. The subject has a diagnosis of possible or probable MSA using the modified Gilman et al, 2008 diagnostic criteria (Gilman et al. 2008) (Appendix F).
6. The subject's onset of first MSA symptoms (including parkinsonism, cerebellar symptoms, orthostatic or urinary symptoms) occurred ≤4 years before screening, as assessed by the investigator.
7. The subject's anticipated life expectancy is ≥3 years, per investigator judgment.
8. The subject has an UMSARS Part I score of ≤21 (excluding Item #11, sexual function) at screening visit (Visit 1), and additionally has:
   a) Severity score ≤2 on the swallowing item (#2) at screening visit (Visit 1).

b) Severity score ≤2 on the ambulation item (#7) at screening visit (Visit 1).

c) Severity score ≤2 on the falling item (#8) at screening visit (Visit 1).

9. The subject has an UMSARS Part IV disability score ≤3 at screening visit (Visit 1).
10. Subject has a MoCA ≥18. Additionally, subject has sufficiently intact cognition to complete study assessments and follow study instructions, per investigator's judgment.
11. A male subject who is nonsterilized (fertile) and sexually active with a female partner of childbearing potential is eligible to participate if he agrees to use a barrier method of contraception (ie, condom with or without spermicide) from the signing of informed consent throughout the study and for 90 days plus 5 half-lives (total of 190 days) after the last dose. In addition, they must be advised not to donate sperm during this period. The female partner of a male subject should also be advised to use a highly effective method of contraception.
12. Female subjects are eligible to participate if (a) they are not pregnant or nursing and (b) they are of nonchildbearing potential or agree to use highly effective contraception from the signing of informed consent throughout the study and for 30 days plus 5 half-lives (total of 130 days) after the last dose of study drug.

> Definitions and highly effective methods of contraception are defined in Section 9.1.16.3 and reporting responsibilities are defined in Section 9.1.17.

7.2 Exclusion Criteria

Medical History

1. The subject has serious or unstable clinically significant illness including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic or autoimmune (eg, multiple sclerosis), hematologic, or other major disease, which, in the judgment of the investigator, is poorly controlled or otherwise likely to deteriorate, compromises the subject's safety or ability to complete the study, or compromises the interpretation of the study results.
2. The subject has other medical problems (neurological, visual, orthopedic, psychiatric) that, in the opinion of the investigator, may significantly interfere with completion of the study or interpretation of study endpoints or may confound diagnosis.
3. The subject has a disorder that is likely to interfere with drug disposition and elimination.
4. In the opinion of the investigator, the subject has a diagnosis of depression or other psychiatric disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), AND this disorder is poorly controlled AND of sufficient severity to interfere with completion of the study or interpretation of the endpoints.
5. The subject is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the subject has attempted suicide within the past year before screening. Subjects who have positive answers on Item 4 or 5 on the C-SSRS (based on the past year) before randomization are excluded.

6. The subject has a history of alcohol or substance use disorder (except tobacco use disorder), as defined by the DSM-5, within 1 year before screening or between screening and randomization, or, in the opinion of the investigator, the subject's current or past use of substances may interfere with performance on the assessments.
7. The subject has a positive finding on an alcohol or illicit drug screen. A positive result for cannabis or prescription medications does not require exclusion.
8. The subject has undergone surgery for the treatment of MSA (eg, pallidotomy, deep brain stimulation, fetal tissue transplantation).
9. The subject has a history of epilepsy or seizures, except self-limited febrile childhood seizures.
10. The subject has any contraindication to lumbar puncture (as assessed by the Investigator) CCI [redacted]
11. The subject has hypersensitivity to TAK-341 or any excipients used in its formulation.
12. Subject has a history of cancer in the past 5 years (does not apply to participants with carcinoma in situ that has been resolved without further treatment, or basal cell carcinoma; these subjects may be included after approval by the sponsor or designee).

Diagnostic Assessments

13. Any clinically significant abnormality as determined by investigator at screening or between screening and randomization in physical examination findings, vital signs, ECGs, or clinical laboratory test results that may compromise the subject's safety or ability to complete the study or compromise the interpretation of the study results.
14. Presence of any contraindications to MRI as assessed by the Investigator CCI [redacted]

CCI [redacted]

15. Ophthalmic abnormalities. CCI [redacted]

16. The subject has any of the following at the screening visit: estimated glomerular filtration rate (determined with the Chronic Kidney Disease Epidemiology Collaboration equation) <50 mL/min; QT interval with Fridericia correction method >450 ms for male subjects and >470 ms for female subjects; a serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >1.5 × the upper limit of normal (ULN).
17. Clinically significant vital sign abnormalities at screening, defined as (a) systolic blood pressure ≥160 mm Hg, (b) diastolic blood pressure ≥90 mm Hg (blood pressure assessed with the subject at rest in the seated position; may be repeated up to 3 times), or (c) pulse rate <45 or >100 beats per minute (subject at rest in the seated position; may be repeated up to 3 times).
18. The subject has a positive hepatitis B surface antigen test result, known or suspected active hepatitis C infection, or known history of HIV infection.

CCI [redacted]

19. The subject has a brain MRI that shows clinically significant evidence of malignant, ischemic, hemorrhagic, demyelinating, structural, or degenerative brain disease (other than MSA) that may confound diagnosis or compromise subject safety during the study, or the subject has findings that compromise the safety of lumbar puncture per investigator judgment.
20. The subject has a current blood clotting or bleeding disorder, including clinically significant abnormal findings in laboratory tests of coagulation.

Other

21. The subject has poor venous access such that IV drug delivery or PK/safety blood sampling would be difficult.

22. The subject has participated in another study investigating active or passive immunization against αSYN for PD or MSA ([redacted]).
23. The subject has had immunoglobulin G therapy for any reason within 6 months before screening.
24. The subject's participation in a previous study of a disease-modifying therapy (with proven receipt of active treatment) will compromise the interpretability of the data from the present study, per consultation with medical monitor or designee. [redacted]
25. The subject has received any investigational compound that, in the opinion of the investigator or sponsor, may not have completely washed out before the screening visit or may affect the safety or efficacy evaluations. Complete washout is defined as not having received investigational product 90 days before screening or 5 half lives of the investigational product, whichever is longer. See Table 7.a for further information.
26. The subject has a positive pregnancy test result at screening.
27. The subject is an immediate family member, is a study site employee, or is in a dependent relationship (eg, as a spouse, parent, child, or sibling) with a study site employee who is involved in the conduct of this study.
28. The subject has donated 400 mL or more of his or her blood volume within 90 days before the start of the screening visit.
29. Austrian participants without capacity of consent (ie, ability to understand and process information relevant to making an informed, voluntary decision to participate in research).

7.3 Excluded and Allowed Medications and Treatments

Once screened, subjects must be instructed not to initiate the use of any medications, including over-the-counter products, without first consulting with the investigator.

Excluded and allowed medications and treatments are shown in Table 7.a.

Table 7.a Excluded and Allowed Medications and Treatments

	Regular Use	Episodic Use	Comments or Exceptions
Commercial vaccines, including COVID-19 vaccines	Not allowed within 1 week of any administration of TAK-341/placebo. Otherwise allowed.	Not applicable.	Not allowed: any commercially available vaccine (including vaccines available under emergency authorization) within 1 week of any administration of TAK-341.

Table 7.a Excluded and Allowed Medications and Treatments

	Regular Use	Episodic Use	Comments or Exceptions
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Any investigational drug	Not allowed.	Not allowed.	Must have stopped investigational drug CCI [redacted] Subjects whose previous participation in a study of a disease-modifying therapy would compromise interpretability of data from the present study are excluded, per investigator and/or sponsor judgment and should be discussed with the medical monitor. CCI [redacted] Subjects who received placebo in prior studies of disease-modifying therapies can participate, if placebo assignment is documented.
CCI [redacted]	[redacted]	[redacted]	[redacted]

Table 7.a Excluded and Allowed Medications and Treatments

	Regular Use	Episodic Use	Comments or Exceptions
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 7.a Excluded and Allowed Medications and Treatments

	Regular Use	Episodic Use	Comments or Exceptions
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cannabis and cannabis-derived products	Allowed under some circumstances. (see comments)	Not allowed	Allowed if subjects have been using cannabis and cannabis-derived products at a relatively stable level for at least 30 days before randomization for a valid medical reason endorsed by a medical professional. Otherwise, washout of at least 30 days before randomization is needed. Subjects must abstain from use of these products for at least 24 hours before any study-related assessments.
Herbal remedies that are psychoactive (eg, kava, valerian, ginkgo biloba)	Allowed under some circumstances (see comments).	Allowed under some circumstances.	Herbal remedies may be permitted conditionally on approval from the investigator and sponsor if the remedies are judged to be unlikely to affect the outcome measures, are deemed to be safe, and do not interfere with study procedures. In addition, the dosing regimen should be stable for the duration of the study.
Acetaminophen	Allowed under some circumstances (see comments).	Allowed under some circumstances (see comments).	Acetaminophen is allowed at approved (per label) doses.
CCI [redacted]	[redacted]	[redacted]	[redacted]

Table 7.a Excluded and Allowed Medications and Treatments

	Regular Use	Episodic Use	Comments or Exceptions
Other prescription drugs	Allowed under some circumstances (see comments).	Allowed under some circumstances (see comments).	Use is permitted only if the drug is prescribed or used for ongoing nonexclusionary medical conditions or health reasons. The dosing regimen should be stable for 30 days before randomization and is expected to remain stable for the duration of the study, and the medication or supplement should not interfere with study procedures or compromise subject safety.
CCI [redacted]	[redacted]	[redacted]	[redacted]

CNS: central nervous system; COMT: catechol-o-methyl-transferase; COVID-19: coronavirus disease 2019; MAO-B: monoamine oxidase B; MSA: multiple system atrophy.

7.4 On-Study Restrictions

7.4.1 Diet, Fluid, and Activity Control

7.4.1.1 Meals and Dietary Restrictions

Alcohol use is prohibited for 48 hours before the screening visit, for 48 hours before Visit 2 (Day 1; baseline visit), for 48 hours before Visit 8, for 48 hours before Visit 14, and for 48 hours before the visit at the end of the treatment period (Visit 15). If they consume alcohol, subjects are advised to consume only moderate levels of alcohol for the duration of the study, defined as less than 3 units (1 unit = 25 mL spirits, 125 mL wine, or 250 mL beer or lager) in any 24-hour period for men and less than 2 units in any 24-hour period for women.

7.4.1.2 Other Restrictions

- Subjects must refrain from blood and plasma donation during the study and for up to 2 months after the final follow-up visit.
- Male subjects who are biologically capable of fathering children must agree and commit to use of an adequate form of barrier contraception and refrain from sperm donation for the duration of the treatment period and for 90 days plus 5 half-lives (total of 190 days) after the last administration of study drug. A male subject is considered capable of fathering children even if his sexual partner is sterile or using contraceptives (detailed contraception guidance per sponsor standard).
- Female subjects of childbearing potential who are sexually active with a nonsterilized (fertile) male partner must agree and commit to use of a highly effective method of

contraception for the duration of the treatment period and for 30 days plus 5 half-lives (total of 130 days) after last administration of study drug.

- If subjects are confined to the clinic, facility rules and study restrictions must be followed.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for early discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For subjects with screen failure, refer to Section 9.1.22.

1. Pretreatment event (PTE) or TEAE. The subject has experienced a PTE or a TEAE that may require early termination if continued participation would impose an unacceptable risk to the subject's health or if the subject is unwilling to continue because of the PTE or TEAE.
   - 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), if the following circumstances occur at any time during study drug treatment:
     - ALT or AST >8 × ULN, or
     - ALT or AST >5 × ULN and persists for longer 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 the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
   - Subject experiences any of the events on the Takeda medically significant list (see Section 10.1.5; no AEs of special interest are defined for this study).
2. Significant protocol deviation. It is discovered after randomization that the subject did not meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not attend visits, and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw (the subject) 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.
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

6. 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 9.1.17.

7. 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.

8. Other.

   Note: The specific reasons should be recorded in the specify field of the eCRF.

Subjects who withdraw early from study or study drug should perform the early-termination visit and should also complete the follow-up safety visit (90 days after final infusion).

For subjects in Germany or Austria: If a subject becomes incompetent over the course of the study and a court-appointed representative or an appointed agent in health matters is not identified, the participant may be withdrawn from the study.

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.

Subjects who withdraw early from study or study drug should perform the early-termination visit and should also complete the follow-up safety visit (90 days after final infusion).

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 in the following subsections.

8.1.1.1 Study Drug

Details regarding the dosage form description of the active drug and matching placebo can be found in the pharmacy manual and the investigator's brochure. Study drug will be packaged to support enrollment and replacement subjects as required.

CCI [redacted]

8.1.1.2 Sponsor-Supplied Drug

Takeda will supply TAK-341 drug product.

8.1.2 Storage

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. CCI [redacted]

8.1.3 Dose and Regimen

TAK-341 or placebo will be administered as an IV infusion CCI [redacted], Q4W during the 52-week double-blind period (total of 13 infusions). CCI [redacted]

The starting dose of the early PK cohort will be TAK-341 CCI [redacted] per infusion Q4W. The dose may be changed after preliminary analysis of data from the early PK cohort.

The initial dose of the main cohort (before final dose selection) was TAK-341 CCI [redacted] per infusion Q4W.

The final selected dose for both main and early PK cohorts is TAK-341 CCI [redacted] per infusion Q4W.

TAK-341 will be supplied by the sponsor (or designee). CCI [redacted]

The IP will be administered as an IV infusion via an IV bag CCI [redacted], The investigator will be provided with adequate quantities of IP using designated distribution centers.

The dose of IP for administration must be prepared by the investigator's or site's designated unblinded IP managers or unblinded designees using aseptic technique. Unblinded staff should not have any contact with study subjects.

Refer to the label/pharmacy manual for additional details regarding IP storage and administration of IV flush procedures.

IP Preparation

The dose of IP for administration must be prepared by the investigator's or site's designated IP manager (or designee) using aseptic technique. Further details regarding details of IP dose preparation, storage temperature, storage time, and administration are provided in the label/pharmacy manual.

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 documented on an overdose page of the eCRF 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 10.2.5.

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

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the randomization schedule allocated to each study site.

All subjects will receive IV infusions of TAK-341 or placebo Q4W during the 52 weeks of the double-blind period (total of 13 infusions).

Subjects in the early PK cohort consisting of the first approximately CCI TAK-341 infusion Q4W or placebo (IV saline), in double-blinded fashion. CCI

Subjects in the main cohort will be randomized CCI to receive CCI TAK-341 infusion Q4W (final selected dose) or placebo (IV saline) in double-blinded fashion. CCI

Subjects will be assigned to receive their treatment according to the randomization schedule produced by the interactive voice response system/interactive web response system (IVRS/IWRS) vendor.

The exact dosing date and time (ie, start and end of infusion) of each infusion will be collected for all subjects.

8.3 Randomization Code Creation and Storage

The IVRS/IWRS system will generate the randomization schedule. All randomization information will be stored in a secured area accessible only by authorized personnel.

Randomization will be performed after eligibility is confirmed through all predosing procedures.

8.4 Study Drug Blind Maintenance

The study drug blind will be maintained using the IVRS/IWRS.

Since the maintenance of the blind may be compromised because of results from drug concentrations and/or pharmacodynamics assessments, such results should not be disclosed before the blind is broken. In the event that results must be reported to the investigator before the blind is broken, all efforts should be made to maintain the blind (eg, changing a medication identification [ID] number to prevent identification of subjects by the laboratory site personnel). Detailed procedures for measuring subjects' drug concentration levels (including reporting results) are provided in the separately created procedure for directions on handling of biological samples for measuring drug concentrations.

CCI [redacted]

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, before unblinding. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator should attempt to contact the sponsor and medical monitor before unblinding a subject's intervention assignment unless this could delay emergency treatment for the subject. The investigator has the final decision and unilateral right for unblinding. In case of a safety concern (eg, SAEs or suspected unexpected serious adverse reactions [SUSARs]), a designated subinvestigator may be unblinded to a subject's treatment assignment in place of the principal investigator in accordance with site procedure; in such cases, the principal investigator or designee will still perform the decision to unblind.

For unblinding a subject, the study drug blind can be obtained by the investigator by accessing the IVRS/IWRS.

The medical monitor and sponsor must be notified as soon as possible if the study drug blind is broken, but this communication should not delay any urgent medical treatment. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information must be recorded in the eCRF.

In case of an unblinding event, the staff member that was unblinded must report that there was an unblinding event to the clinical team. The unblinding events and the specifics to the unblinding (eg, subject's treatment assignment) must not be shared with the Blinded Clinical team and are ONLY to be provided to the Unblinded team to protect the Clinical monitoring teams.

If the unblinding procedure is performed for safety reasons (eg, SAEs or SUSARs), study drug must be stopped immediately, and the subject must be withdrawn from the study.

The data monitoring committee evaluating safety data from the entire study will be independent.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee for destruction. Destruction at site will be permitted if/when a standard operating procedure exists after the investigator or designee requests and receives the sponsor's approval.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all deliveries of sponsor-supplied drug to the site, site inventory, dispensation and use by each subject, and returns to the sponsor or designee.

On receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and the medication is in good condition. If quantity and conditions are acceptable, the investigator or designee should acknowledge receipt of the shipment. If there are any discrepancies between the packing list and the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to the following:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

- Ensuring that a site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, reviews the randomization schedule and subject dosing log before dosing on Day 1 and after dosing to ensure all subjects received the correct dose of study drug,
- Filing all study medication documentation in the investigator's essential document file.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IVRS/IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

In the event of the expiry date of sponsor-supplied drug is extended for drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

Refer to the pharmacy manual for additional information related to the study drug. In instances where the protocol and pharmacy manual conflict, the text in the pharmacy manual shall supersede the text in the protocol.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. They apply to all subjects except where indicated. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. CCI [redacted]

This study allows for the use of home health visits or in-clinic visits to assist with the collection of data at specified time points after Infusion #3 (Visit 4) for the early PK cohort. CCI [redacted] Home health visits must comply with national and local laws and regulations; these visits will be documented in the subject's medical record, and the data will be entered into the eCRF. For additional details, please refer to Section 9.1.24.

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained before the subject enters the study and before any protocol-directed procedures are performed.

A unique screening ID number will be generated by the IVRS/IWRS and assigned to each subject after informed consent is signed and the site registers the subject in the IVRS/IWRS. This ID number will be used throughout the study.

Subjects consenting via consent, where available, will sign the consent forms (paper consent forms will be used instead if required by local regulations); or, when applicable, the subject's legally acceptable representative will sign (or sign) the consent forms.

The investigational site is responsible for the consenting process. The requirements of informed consent are described in Section 15.2.

For subjects in Germany or Austria: Invasive diagnostics not necessary for subject safety and wellbeing (eg, lumbar puncture for PK assessment) are not allowed in subjects who become incapable of giving informed consent.

9.1.1.1 CCI [redacted]

[redacted]

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth/age and/or age (collected according to the country's convention), sex, Hispanic ethnicity (US only), race as described by the subject, height, weight, and smoking status of the subject at screening.

Medical history-taking will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before his or her signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.12). CCI [redacted]

Medication history for investigational drugs should be obtained from the time of onset of MSA symptoms to ensure compliance with the requirements in Table 7.a. Medication history information to be obtained for noninvestigational drugs includes any medication relevant to eligibility criteria stopped at or within 30 days before signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before the first dose of study drug at screening) will consist of an assessment of the following body systems: (1) head, eyes; ears, nose, and throat; (2) cardiovascular system; (3) respiratory system; (4) gastrointestinal system; (5) dermatologic system; (6) extremities; (7) musculoskeletal system; (8) lymph nodes; and (9) other.

An abbreviated physical examination may be performed after the screening visit at designated visits (see Appendix A, footnote h). All subsequent physical examinations should include assessment for clinically significant changes from the baseline/screening assessment.

Physical examination must be conducted at any visit if clinically indicated.

9.1.4 Neurological Examination Procedure

A separate neurological examination will be performed and documented in the eCRF. This will include testing of mental status, gait, cerebellar function, cranial nerve function, upper and lower extremity motor strength, reflexes, and sensation.

Neurological examination must be conducted at any visit if clinically indicated.

9.1.5 Weight, Height, and BMI

Subjects' weight and height should be measured while they are wearing indoor clothing and with their shoes off. BMI is calculated using metric units, where height is recorded in centimeters without decimal places, and weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as follows:

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2.$$

Note: Although height is reported in centimeters, the BMI formula uses meters for height. Meters can be determined from centimeters by dividing by 100. For example, if height = 176 cm (1.76 meters) and weight = 79.2 kg, then BMI = $79.2/1.76^2 = 25.56818$ kg/m^2.

The values should be reported to 1 decimal place by rounding. Thus, in the current example, BMI would be reported as 25.6 kg/m^2. Because BMI is used as an exclusion criterion, the determination for inclusion/exclusion must be made after rounding.

9.1.6 Vital Sign Procedure

The investigator will review all vital signs for real-time safety monitoring purposes. Vital signs will include body temperature, respiratory rate, seated blood pressure (systolic and diastolic), and seated pulse (beats per minute); measurements should be taken after the subject has been sitting for at least 5 minutes. Whenever possible, the same method (eg, same size cuff, manual or automated; same arm) should be used for all measurements for each individual subject and should be the same for all subjects.

Blood pressure and heart rate may be repeated up to 3 times at screening.

When vital signs are scheduled at the same time as blood collections, blood collection will take priority, and vital signs will be assessed within 0.5 hour before or after the scheduled blood collection.

9.1.7 Clinical Efficacy Assessments and Procedures

9.1.7.1 UMSARS-I to IV (Total and Modified Versions)

The UMSARS (Wenning et al. 2004) is included in this study as a primary and secondary endpoint to allow for evaluation of disease stability over the duration of the study.

A copy of the total UMSARS scale is provided. A version of the instrument relevant to the individual subject's native language should be used.

The total UMSARS (Appendix G) will be administered to all subjects at the time points described in the schedule of study activities (Appendix A).

The primary objective is to evaluate effect on a modified UMSARS consisting of the UMSARS Part I, minus the sexual function item, with the 0 (normal) and 1 (mild) ratings on each item collapsed during the analysis process.

A secondary endpoint will evaluate the effect on an 11-item UMSARS specified in Palma et al. 2021 (Palma et al. 2021).

CCI [redacted]

The UMSARS is a 4-part, multimodal rating scale developed and validated to assess the severity of and to follow the course of MSA (Wenning et al. 2004). The UMSARS is a scale containing both impairment and disability sections. One major advantage of UMSARS is that it was developed as a compound scale to capture the multiple aspects of MSA. It assesses both motor and autonomic disability (Part I historical) and motor impairment (Part II motor examination).

The 4 parts or components of the scale are as follows:

- UMSARS Part I (historical review) is a 12-item scale that was adapted from the Unified Parkinson's Disease Rating Scale (UPDRS) and is used to assess activities related to motor disability (first 8 items) and 4 novel items related to autonomic dysfunction. Each item is scored from 0 (normal) to 4 (severe). The investigator rates the average functional situation for the past 2 weeks (unless specified) according to findings from the subject and caregiver interview and will indicate the score that best fits with the subject's status. The functional history is rated independently from the nature of the signs.
- UMSARS Part II (motor examination) is a 14-item scale. Most of the items (eg, speech, rapid alternating movements of the hands, finger taps, leg agility) measure the functional impairment of selected complex movements, and only a few items directly refer to specific parkinsonian (tremor at rest) or cerebellar (ocular motor dysfunction, heel-shin test) features. The motor examination section of UMSARS was based on modified UPDRS-III items in addition to novel items such as heel-knee-shin ataxia. The construction process was directed

by the perceived need to measure functional disability independent of the underlying motor deficits, which may include not only parkinsonism and cerebellar ataxia but also dystonic, myoclonic, and pyramidal features. Each item is scored from 0 (normal) to 4 (severe). The investigator rates the worst-affected limb.

- UMSARS Part III (autonomic examination) captures the cardinal autonomic feature of MSA, ie, orthostatic hypotension. Supine blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing. Orthostatic symptoms may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, and neck and coat-hanger ache.
- UMSARS Part IV (global disability scale) is a 5-grade scale ranging from 1 (completely independent) to 5 (totally dependent, helpless, and bedridden).

9.1.7.2 CCI

[redacted]

9.1.7.3 Global Impression Scales

CCI [redacted]

The CGI-S is used to assess the clinician's impression of the subject's clinical condition. The clinician should use his or her total clinical experience with this subject population and rate the current severity of the subject's illness on a 7-point scale ranging from 1 for normal, not at all ill to 7 for among the most extremely ill patients. This rating is based on current observed and reported symptoms, behavior, and function and should reflect the severity level at the time of the assessment.

CCI [redacted]

9.1.7.4 SCOPA-AUT

The SCOPA-AUT is a patient-reported outcome that assesses autonomic function. Autonomic function is a critical symptom domain for MSA. Autonomic PROs are generally included in MSA trials (eg, Lundbeck).

The scale is self-completed by patients and consists of 25 items assessing the following domains: gastrointestinal (7 items), urinary (6 items), cardiovascular (3 items), thermoregulatory (4 items), pupillomotor (1 item), and sexual (2 items for men and 2 items for women). The score for each item ranges from 0 (never experiencing the symptom) to 3 (often experiencing the symptom).

9.1.7.5 CCI [redacted]

[redacted]

9.1.7.6 Orthostatic Blood Pressure

Orthostatic blood pressure and heart rate will be collected at each visit as per the instructions in UMSARS Part III: Autonomic Examination (Appendix G). When UMSARS is being performed at the same visit, UMSARS Part III can serve as the assessment of orthostatic blood pressure and heart rate if performed before IP administration (ie, orthostatic vitals do not need to be performed twice in the same visit). When the orthostatic blood pressure and heart rate are collected via the UMSARS, then these measures should not be recorded in the electronic data capture (EDC) as well (ie, to prevent duplicate collection).

Refer to the UMSARS Part III (autonomic examination) description provided in Section 9.1.7.1.

9.1.7.7 Orthostatic Heart Rate

See section 9.1.7.6. Refer to the UMSARS Part III (autonomic examination) description provided in Section 9.1.7.1.

When the orthostatic blood pressure and heart rate are collected via the UMSARS, then these measures should not be recorded in the electronic data capture (EDC) as well (ie, to prevent duplicate collection).

9.1.7.8 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) is a 30-point test that has been validated as a tool for the detection of mild cognitive impairment. Several cognitive domains are tested: short-term memory recall, visuospatial abilities, executive functions, attention, concentration, working memory, language, and orientation in time and place.

The MoCA is an interviewer-administered performance outcome measure.

CCI [redacted]

9.1.7.9 CCI [redacted]

[redacted]

CCI [redacted]

9.1.7.10 CCI [redacted]

9.1.7.11 CCI [redacted]

9.1.8 CCI

[redacted]

9.1.9 CCI

[redacted]

9.1.10 CSF Sampling Procedures

Imaging procedures may be optionally performed if not contraindicated and per local procedures during screening, to assess the feasibility of lumbar puncture, depending on the investigator's judgment. When performed, imaging procedures should be performed before lumbar puncture.

Lumbar puncture for CSF sampling will be performed as specified in the schedule of study activities (Appendix A; Section 9.1.15.1.2 for PK CSF sampling; Section 9.1.15.2.2 for biomarker CSF sampling); this will be done at the clinical site according to the standard operating procedure. CCI [redacted]; all subjects will receive a lumbar puncture at Visit 2 and 15. Results from the screening CCI [redacted] should be available and reviewed before the Visit 2 lumbar puncture, and the CCI [redacted] should be reviewed before the Visit 15 lumbar puncture for CSF sampling.

Lumbar puncture for CSF sampling should ideally be performed at the same time of day as the baseline lumbar puncture (±4 hours) prior to dosing.

For subjects in Germany or Austria: Invasive diagnostics not necessary for subject safety and wellbeing (eg, lumbar puncture for PK assessment) are not allowed in subjects who become incapable of giving informed consent.

9.1.11 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 is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed [e]consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.12 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at the signing of informed consent. These include clinically significant laboratory, ECG, or physical or neurological examination abnormalities noted at the screening examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.13 Maximum Blood Volumes

The maximum volume of blood to be collected at any single visit is approximately CCI [redacted] mL for the main cohort, early PK cohort, CCI [redacted]. The maximum total volume of blood over the course of the study is approximately CCI [redacted] mL for the main cohort (excluding subjects in the early PK cohort, CCI [redacted]; and CCI [redacted] mL for the early PK cohort subjects, CCI [redacted]

CCI [redacted]. The maximum total volume of CSF to be collected over the course of the study is approximately CCI [redacted]

9.1.14 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be obtained on the days stipulated in Appendix A and Appendix B. It is not necessary that the subjects fast before these blood samples are collected. Additional laboratory safety tests may be added to the blood samples previously collected to obtain additional safety information, at the investigator's discretion. (eg, creatinine kinase isoenzymes may be added to a serum chemistry panel for which a sample was already drawn.)

Details of these procedures and required safety monitoring will be given in the laboratory manual and/or collection flow chart.

Table 9.a lists the tests that will be performed for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cell count White blood cell count with differential (absolute counts) Hemoglobin Hematocrit Platelets **Coagulation** Prothrombin time/international normalized ratio Activated partial thromboplastin time	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Total bilirubin Total protein Creatinine Blood urea nitrogen (blood urea in China) Creatine kinase γ-Glutamyl transferase Potassium Sodium Glucose Chloride Bicarbonate Calcium Phosphorus Cholesterol Triglycerides Globulins	pH Specific gravity Protein Glucose Blood Nitrite Microscopic analysis (only if dipstick results are positive): white blood cell count, red blood cell count, epithelial cells, casts
Other		
Antidrug antibody		

Serum	Urine/Blood	Breath Test
eGFR [a] Vitamin B12 Folic acid Hepatitis B surface antigen Antibody to HCV; if positive, reflex qPCR for HCV viral RNA. Female subjects: β-hCG (for pregnancy) [b] Female subjects aged ≤60 years: follicle-stimulating hormone Samples for biomarkers (αSYN)	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates Urine pregnancy (optional substitute for serum pregnancy at postscreening visits) [b]	Alcohol breathalyzer screen

αSYN: α-synuclein; β-hCG: beta-human chorionic gonadotropin; eGFR: estimated glomerular filtration rate; HCV: hepatitis C virus; qPCR: quantitative polymerase chain reaction.

[a] Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

[b] Serum pregnancy testing (β-hCG) is the preferred standard. After the screening visit, if serum pregnancy testing is not available or if results cannot be obtained in time for dosing, then a urine pregnancy test may be substituted, contingent on the investigator's judgment.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

The investigator will report the results of hepatitis B surface antigen and anti-HCV antibody tests, urine drug, and, if applicable, serum follicle-stimulating hormone (FSH) (for female subjects only) directly to subjects. The sponsor will confirm the overall test results (as positive or negative), rather than detailed results, for subjects to be administered the study drug. In the event that the result of positive is detected, the details will be identified and eligibility will be judged.

If subjects experience ALT or AST >3 × ULN, follow-up laboratory tests (at a minimum: serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase, and international normalized ratio) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. (Refer to Sections 7.5 and 10.2.6 for the appropriate guidance on reporting abnormal LFT results.)

If ALT or AST remains elevated >3 × ULN on these 2 consecutive occasions, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details, and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.6).

For subjects who have clinically significant LFT abnormalities but have not reached the aforementioned criteria, the investigator and the sponsor will discuss if discontinuation is necessary.

The investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

All clinically significant laboratory abnormalities must be recorded as an AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.15 PK and Biomarker Sample Collection and Analysis

Samples for PK and biomarker analysis will be collected at the time points stipulated in the schedules of study activities (Appendix A and Appendix B). Please refer to the laboratory manual and/or collection flow chart for information on the collection, processing, and shipment of samples to the central laboratory.

The decision as to which collected samples will be assayed for evaluation of PK and biomarkers will be determined by the sponsor.

Primary specimen collection parameters are provided in Table 9.b.

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for TAK-341 PK	Serum	Serum sample for PK analysis	Mandatory
CSF sample for TAK-341 concentration	CSF (LP)	CSF sample for concentration analysis	Mandatory
CCI [redacted]	[redacted]	[redacted]	[redacted]
CSF samples for free α-synuclein measurement	CSF (LP)	CSF sample for biomarker analysis for secondary endpoint	Mandatory
CCI [redacted]	[redacted]	[redacted]	[redacted]
CCI [redacted]	[redacted]	[redacted]	[redacted]
Blood samples for ADA measurements	Serum	Blood sample for ADA analysis	Mandatory
CCI [redacted]	[redacted]	[redacted]	[redacted]

ADA: antidrug antibody; CSF: cerebrospinal fluid; LP: lumbar puncture; PK: pharmacokinetic(s).

9.1.15.1 PK Measurements

The PK parameters of TAK-341 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following PK parameters will be calculated from serum and/or CSF concentrations of TAK-341, if feasible, unless otherwise specified.

Symbol/Term	Definition
Serum	
C_{max}	Maximum observed serum concentration
AUC_{τ}	Area under the serum concentration-time curve during a dosing interval
t_{max}	Time of first occurrence of maximum observed concentration
CSF	
$Ratio_{CSF/serum\ concentration}$	Ratio of the CSF to serum concentration values

CSF: cerebrospinal fluid.

Additional PK parameters may be calculated as appropriate. A detailed PK analysis plan will be prepared before PK parameter computation. Actual sampling times, rather than scheduled sampling times, will be used in all data presentations.

PK blood samples collected outside of the predetermined time windows will not be considered a protocol deviation since actual sample times are used.

9.1.15.1.1 Serum for PK Measurements

Blood samples for PK analysis of TAK-341 will be collected into blood collection tubes (vacutainers). The serum prepared from blood samples may be archived for additional analysis of potential metabolites.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted on the basis of the preliminary emerging concentration data collected from prior subject(s), but the total number of samples collected per subject should not exceed the planned number.

Instructions for collecting, processing, and shipping of PK samples are provided in the laboratory manual/study manual/collection flow chart. If possible, blood samples for PK analysis should be obtained from the arm opposite to that used for study drug or placebo infusion.

Details regarding bioanalytical methods will be provided in the laboratory manual/collection flow chart and/or other study documentation.

For PK sampling schedules, refer to Table 9.c.

Table 9.c Sampling of Blood Samples for PK Analysis (All Subjects)

Analyzed Substances	Samples	Study Day		Blood Sampling Time Points
		All Subjects (Both Early PK and Main Cohorts)		
TAK-341	Serum	Days 1, 169, and 337 (or early termination)	Predose	Right before end of infusion (CCI) 6±2 hours after start of infusion 24±4 hours after start of infusion [a]
		Day 29 and 253	Predose	Right before end of infusion (CCI)
		Day 365 and 427 or ET	Single sample	
		Main Cohort		
		Day 85	Predose	Right before end of infusion (CCI) 6±2 hours after start of infusion 24±4 hours after start of infusion [a]
		Early PK Cohort, CCI		
		Days 57 and 85 [b, c]	Predose	Day 57 only: Right before end of infusion (CCI) CCI [c] CCI [c] CCI [c] CCI [c] CCI [c]

ET: early termination; PK: pharmacokinetic(s).

[a] PK blood collection 24 hours after the start of infusion will be performed only for subjects staying overnight.

[b] CCI

9.1.15.1.2 CSF for PK Measurements

CSF samples for PK analysis of TAK-341 will be collected from subjects as specified in the schedule of study activities (Appendix A) at the clinical site according to the standard operating procedure.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted on the basis of the preliminary emerging concentration data collected from prior subject(s), but the total number of samples collected per subject should not exceed the planned number (3 samples).

Lumbar puncture for CSF sampling should ideally be performed at the same time of day as the baseline lumbar puncture (±4 hours) prior to dosing.

Instructions for collecting, processing, and shipping of CSF PK samples are provided in the laboratory manual and/or collection flow chart.

Details regarding bioanalytical methods will be provided in the laboratory manual/collection flow chart and/or other study documentation.

9.1.15.2 Biomarker Measurements

Assessments for plasma and CSF biomarkers will be performed at the time points described in the schedule of study activities (Appendix A. The endpoints include, but are not limited to the cci [redacted] in plasma and CSF and levels of CSF free αSYN.

Additional biomarker bioanalytics may be included, if appropriate.

9.1.15.2.1 Plasma for Biomarker Analysis

Blood samples for analysis of αSYN and cci [redacted]. The laboratory manual and/or collection flow chart will contain the details on sample handling and aliquoting.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted on the basis of preliminary emerging concentration data collected from prior subjects. The total number of samples collected per subject will not exceed the number previously stated.

Instructions for collecting, processing and shipping of biomarker samples are provided in the laboratory manual and/or collection flow chart.

Details regarding bioanalytical methods will be provided in the laboratory manual/collection flow chart and/or other study documentation.

9.1.15.2.2 CSF for Biomarker Analysis

CSF levels of free αSYN and other biomarkers (cci [redacted]) will be measured to confirm the pharmacodynamic and disease related biomarker effects of TAK-341 in the CNS of subjects with MSA. Samples will be collected by trained personnel at the clinical site according to the standard operating procedure. Additional biomarker assessments may be performed, if appropriate.

Lumbar puncture for CSF sampling should ideally be performed at the same time of day as the baseline lumbar puncture (±4 hours) prior to dosing.

Instructions for collecting, processing, and shipping of CSF biomarker samples are provided in the laboratory manual and/or collection flow chart.

Details regarding bioanalytical methods will be provided in the laboratory manual/collection flow chart and/or other study documentation.

9.1.16 Contraception and Pregnancy Avoidance Procedure

9.1.16.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 190 days (90 days PLUS 5 half-lives) after last dose of study drug, nonsterilized (fertile)** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective contraception below.

*Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as continuous amenorrhea of at least 12 months and an FSH>40 IU/L, confirmed before any study drug is implemented.

**Fertile men: For the purpose of this study, a person of male birth sex is considered a fertile man after puberty unless permanently sterile by bilateral orchidectomy.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign the consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study and for 190 days after the last dose of study drug.

9.1.16.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 130 days (30 days PLUS 5 half-lives) after last dose of study drug, female subjects of childbearing potential* who are sexually active with a non-sterilized male partner** must use a highly effective method of contraception (from the list in Section 9.1.16.3).

In addition, they must be advised not to donate ova during this period.

9.1.16.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent

sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Fertile men: For the purpose of this study, a person of male birth sex is considered a fertile man after puberty unless permanently sterile by bilateral orchidectomy.

The following information applies for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, the only acceptable methods of contraception are:
    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation
        - Oral
        - Injectable
        - Implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner (highly effective provided that partner is the sole sexual partner of the WOCBP trial participant and the vasectomized partner has received medical assessment of the surgical success).
    - Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of the risk associated with the trial intervention[s]. Reliability of abstinence should be evaluated in relation to trial duration and the preferred and usual lifestyle of the trial participant.)
2. Unacceptable methods of contraception are the following:
    - Periodic abstinence
        - Calendar

  - Symptothermal
  - Post-ovulation
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method (LAM)

Note also that female and male condoms should not be used together.

3. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.
4. During the course of the study, regular serum/urine beta-human chorionic gonadotropin (β-hCG) pregnancy tests will be performed only for women of childbearing potential and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) Contraceptive requirements of the study.
   b) Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
   c) Assessment of subject compliance through questions such as:
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
5. In addition to a negative serum β-hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), and a negative serum/urine β-hCG pregnancy test 1 day or the same day before receiving any dose of study medication.

9.1.17 Pregnancy

If any female subject is found to be pregnant during administration of active study drug, eg, after baseline/Day 1 or within 130 days of the last dose of active study drug, she should be withdrawn, and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 190 days (5 half-lives plus 90 days) after the last dose should also be recorded after obtaining authorization from the subject's partner. The pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.1.

Should the pregnancy occur during or after the administration of blinded drug, the investigator must inform subjects of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to receive placebo need not be followed up.

If the female subject and/or female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject or female partner of the subject was participating in a clinical study at the time she became pregnant and provide details about the study drug the subject received (blinded or unblinded, as applicable).

All pregnancies, including those in female partners of male subjects and in subjects receiving active study drug, will be followed up to their final outcome by using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.18 ECG Procedure

The investigator or designee will review all 12-lead ECG data, including estimates of ECG intervals, for real-time safety monitoring purposes, and an assessment of normality/abnormality will be recorded in the eCRF.

For both screening and safety ECGs, a standard 12-lead ECG will be recorded. The following parameters will be recorded by a central reader from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, QRS interval, and QT interval with Fridericia correction, and QT interval with Bazett correction.

All stationary 12-lead ECG machines will be supplied by the site. Subjects should be in a supine position after a rest period of approximately 10 minutes for the ECG recordings. Should technical difficulties occur during recording of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

If an ECG is scheduled at the same time as blood collection or vital sign assessment, the ECG will be obtained within 0.5 hour before the scheduled blood collection or vital sign assessment.

ECG assessments must be conducted at any visit if clinically indicated.

9.1.19 Immunogenicity Sample Collection

CCI [redacted]

Blood samples for the assessment of ADAs will be collected at the time points specified in the schedule of study activities (Appendix A). Samples must be collected before the study drug is administered on a dosing day and can optionally be collected at unscheduled visits for a subject

who experiences an AE considered by the investigator to be consistent with hypersensitivity/infusion-related reaction. A sample may be assessed for neutralizing ADAs if a positive ADA is detected.

A validated electrochemiluminescence assay will be used for the detection of ADAs to TAK-341 in human serum.

9.1.20 CCI

[redacted]

9.1.21 C-SSRS

The C-SSRS is a standard rating scale that is used to assess suicidal behavior and ideation in subjects during participation in a clinical trial of centrally acting drugs. The tool is administered via interview with the subject.

The C-SSRS will be used to assess suicidality over the year preceding screening and over the subject's lifetime. At screening, the baseline screening version of the scale will be used, and at subsequent visits the "since last visit version of the scale" will be used. Versions of the instrument relevant to the subject's native language should be used.

For timing of postscreening C-SSRS assessments, refer to the schedule of study activities (Appendix A).

9.1.22 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of screen failure.

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

- PTE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Screening ID numbers assigned to subjects in whom screening fails should not be reused.

Subjects in whom screening fails can be rescreened, with approval of the sponsor or designee (eg, medical monitor). Assessments required in the rescreening visit would be agreed on between investigator and sponsor. Subjects should be assigned a new screening ID number.

9.1.23 Documentation of Randomization

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

If the subject is found to be ineligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.24 Home Health Visits

This study allows for the use of home health visits or in-clinic visits to assist with the collection of data at specified time points after Infusion #3 (Visit 4) for the early PK cohort.

For home healthcare visits, collection of clinical laboratory samples (blood specimen collection) may be performed by the investigator, qualified site staff, or qualified home healthcare provider who can visit the study subject's residence.

Home healthcare visits will be documented in the study records and eCRF.

9.1.25 Alternative Approaches to Study Procedures and Data Collection Due to Coronavirus Disease-2019 or Other Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that effect the ability to conduct study procedures according to the schedules of study activities (Appendix A and Appendix B), contingency measures may be implemented. In acknowledgement of FDA guidance (fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency, Accessed 12 June 2020), as well as study site, hospital, local, state, and national restrictions established during these kinds of circumstances, the following measures are being taken for the current study:

- Other than the final visit, alternative methods for conducting subject visits (eg, telephone visits, video conferencing, or in-home study visits conducted by site personnel contingent on local regulations) may be used with approval by the sponsor or designee.
  - Approval may be granted to omit collection of certain study assessments, and visit windows may be extended.
  - When approval is given for a subject to miss an in-person study visit, a study site physician will speak directly with the subject by telephone or other medium (eg, computer-based video communication) during each visit window to assess the subject's safety and overall clinical status.
  - At minimum, the study site physician or other qualified site personnel should conduct the following assessments within specified visit windows: AE assessments, documentation of concomitant medication(s), administration of the C-SSRS, and assessment of clinical symptoms.
  - Other study assessments may be performed using an alternative method as feasible and may involve audio or video recording where allowed by local regulation. In some cases, audio and/or video recording of subject interviews may not be possible. This will be documented in the study records.
  - Sites may seek approval to extend a visit window to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such departures will be recorded in the study records.
  - The maximum interval between successive study visits may be no longer than 8 weeks.
- The final visit should be performed in person. When it is not possible for the subject to come to the study site, the preferred alternative for the final visit is for qualified study site personnel to go to the subject's residence and conduct the protocol-specified procedures at that location. Assessments collected at a subject's residence should comply with applicable local regulations.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the schedule of study activities) due to the coronavirus disease 2019 (COVID-19)

pandemic must be documented in the study records as related to COVID-19. Data collected using alternative methods may be handled differently in the final data analyses.

Subjects who discontinue from screening because of COVID-19–related factors but were otherwise qualified to participate in the trial may be rescreened if the sponsor's clinician agrees.

Missed or delayed clinic visits or subject withdrawals due to COVID-19 must be recorded on the eCRF.

If a subject chooses to withdraw from study participation because of personal concerns related to the COVID-19 pandemic (other than a COVID-19–related AE), this should be specified as the reason for subject withdrawal in the eCRF.

9.2 Overnight Stay/Treatment Compliance

Study drug will be administered or dispensed only to eligible subjects under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Subjects will report to the clinical site at check-in and will leave after completion of all study-related procedures on the days specified in the schedule of study activities (Appendix A).

All subjects can be offered an overnight stay (ie, optional overnight stay) at Visit 2 (Day 1), Visit 8 (Day 169), and Visit 15 (Day 365), at the investigator's discretion.

Subjects in the early PK cohort can additionally be offered an overnight stay at Visit 4 (Day 57) and Visit 5 (Day 85), at the investigator's discretion CCI [redacted]

9.3 Schedule of Observations and Procedures

The schedules for all study-related procedures for all evaluations are shown in Appendix A and Appendix B. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening

Subjects will be screened within 1 to 42 days before baseline/randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.22 for procedures for documenting screening failures.

Procedures to be completed at screening are listed in Appendix A.

Subjects who initially fail screening may be rescreened, with approval of the sponsor or designee (eg, medical monitor). Assessments required in the rescreening visit would be agreed on between the investigator and sponsor. Subjects should be assigned a new screening ID number.

9.3.2 Treatment Period

9.3.2.1 Baseline Procedures/Randomization

Baseline procedures/randomization will occur on Day 1.

Procedures to be completed at baseline are listed in Appendix A.

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IVRS/IWRS, as described in Section 8.2. The first dose of study drug will be administered as described in Section 6.1. The procedure for documenting screening failures is provided in Section 9.1.22.

Randomization of subjects will be stratified by diagnostic certainty (probable and possible MSA).

9.3.2.2 Treatment Period

Procedures to be completed during the treatment period are listed in Appendix A and Appendix B.

9.3.3 Final Efficacy Visit (Visit 15) or Early Termination Visit

The final efficacy visit will be performed at Visit 15 (Day 365) or at the early-termination visit. Subjects who withdraw early from study or study drug (ie early-termination subjects) should perform the early-termination visit and should also complete the follow-up safety visit (90 days after final infusion).

Procedures to be completed at this visit are listed in Appendix A.

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

9.3.4 Follow-up Visit

The follow-up safety visit occurs 90 days after the final infusion.

Procedures to be completed at this visit are listed in Appendix A.

9.3.5 Unscheduled Visit

Subjects may return to the study center for unscheduled visits as needed. Unscheduled study visits can be performed when the subject has a study-related issue between regular study visits.

The following procedures should be performed during this visit:

- Documentation of concomitant medications.
- AE assessment.
- Pregnancy test (for female subjects of childbearing potential)
- Other procedures, including dose adjustments, as deemed appropriate by the investigator.

9.3.6 Poststudy Care

Refer to Section 6.4 for information regarding post-trial access of TAK-341. The subject should be returned to the care of a physician and standard therapies as required.

9.4 Biological Sample Retention and Destruction

Refer to the sample management plan.

The CSF, serum, and plasma samples will be labeled with a unique sample identifier. The code numbers will be kept secure by, or on behalf, of the sponsor.

Specimens for genetic analysis will be collected as described in Section 9.1.20. After extraction and purification, the genetic material will be preserved, retained, and initially stored at CCI [redacted] and then preserved and retained for long-term storage at CCI [redacted] up to but not longer than 15 years or as required by applicable law. The sponsor has established a system to protect the subjects' personal information to ensure optimal protection of confidentiality and has defined standard processes for sample and data collection, storage, analysis, and destruction.

When subjects request disposal of a stored sample during the retention period, the site will ask the vendor to destroy the sample via the sponsor according to the procedure. The vendor will destroy the sample in accordance with the procedure and notify the site and sponsor.

Subjects who consented and provided a genetic sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time. The investigator or designee should notify the sponsor of consent withdrawal.

10.0 PTEs AND AEs

Key safety measures include the following:

- Findings from physical and neurological examinations.
- Subject reports of any AEs.
- Vital signs (blood pressure, pulse rate, body temperature, and respiration rate) as specified in the study manual).
- Findings on 12-lead ECGs.
- Results of clinical safety laboratory assessments (clinical chemistry, hematology, coagulation, urinalysis, pregnancy test [women only]).
- CCI [redacted]
- Brain MRI without contrast.
- C-SSRS results.

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

10.1.3 Additional Points to Consider for PTEs and TEAEs

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 PTEs or TEAEs.)
- 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 collection) should be recorded as an AE.

Diagnoses Versus 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 retest 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 [e]consent) are considered concurrent medical conditions and should NOT be recorded as AEs. Baseline evaluations (eg, laboratory tests, ECG, radiography, etc) should NOT be recorded AEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or as a TEAE. 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 from baseline (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 a PTE after the start of study drug, the worsening or complication should be recorded as a TEAE. Investigators should ensure that the TEAE term recorded captures the change in the PTE (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 before 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 distinguish 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 eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

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

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 (Section 10.1.5; not defined for this study).

PTEs that fulfill 1 or more of the aforementioned serious criteria are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.5 and 10.3).

10.1.5 AEs of Special Interest

No AEs of special interest have been defined for this study.

10.1.6 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.

10.1.7 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.

10.1.8 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.

10.1.9 Start Date

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

10.1.12 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: This is to be used only 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.
- Dose interrupted: The dose was interrupted because of the particular AE.

10.1.13 Outcome

- Recovered/resolved: The subject's condition 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 and/or significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal: The AE that are considered as the cause of death.
- Unknown: The course of the AE cannot be followed up because of hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE and PTE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first given study drug (Visit 2; Day 1; baseline visit) or until screen failure. For subjects who discontinue before study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of TEAEs will commence from the time that the subject is first given study drug (Visit 2; Day 1; baseline visit). Routine collection of TEAEs will continue until the follow-up safety visit (90 days after the final infusion at Visit 16).

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 an SAE 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. Nonserious PTEs, related or unrelated to the study procedure, do not need to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, 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) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Management of IP-Related Toxicities

The investigator is responsible for ensuring that expertise and facilities are available for the management of all suspected IP-related toxicities in accordance with local procedures and accepted standards of medical practice. There is no specific antidote to TAK-341. In case of suspected IP-related toxicity, an appropriate level of vital sign monitoring should be instituted; symptomatic and supportive treatment should be provided according to the judgement of the investigator. Treatment of suspected IP-related toxicity may be guided by further investigations, and referral to a specialist high-dependency unit may be warranted.

In the case of suspected IP-related toxicity that occurs during the course of an IP infusion, the investigator should exercise medical judgement with respect to the nature, severity, and seriousness of the event and give careful consideration to discontinuing further IP administration.

Any case of suspected IP-related toxicity should be reported as an AE (Section 10.2.1) or SAE (Section 10.2.5).

10.2.3 Management of Reactions to Dose Administration/Infusion

As with any antibody, allergic/hypersensitivity reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available and study personnel must be trained to recognize and treat anaphylaxis. Before administration of TAK-341, medications and resuscitation equipment for the emergency management of an anaphylactic reaction must be available.

If a subject experiences an infusion reaction during infusion of TAK-341, appropriate medications may be administered as per local standards of care. As an alternative, or in addition, the infusion of study drug may be stopped, per investigator judgment.

Any such activities must be recorded appropriately. If an infusion reaction occurs in any subject, the investigator should immediately contact the medical monitor.

10.2.4 Potential Infusion-Related Events

AEs that may be related to infusion of monoclonal antibodies usually occur during administration of the IP or within the first 24 hours after the infusion. They may be characterized by a complex of symptoms, including general symptoms (eg, flulike illness, chills, and headache), cardiorespiratory symptoms (eg, hypotension, acute respiratory distress syndrome, acute coronary syndromes, arrhythmias, and shock), or allergic/hypersensitivity symptoms (eg, urticaria, angioedema, and bronchospasm). If these occur in any subject they should be reported immediately to the medical monitor. The specific key signs/symptoms should be captured as part of the AE reporting, along with the timing of events related to the infusion. If the investigator considers the AE to be an SAE it should be reported as such (see Section 10.2.5).

10.2.5 Collection and Reporting of SAEs

All AEs spontaneously reported by the subject or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.2.1 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported (see Section 10.2.1 for the period of observation) by the investigator to the Takeda Global Patient Safety Evaluation department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an EDC SAE report. If transmission of an EDC SAE report is not feasible within 24 hours of becoming aware of the

event, then a facsimile (fax) of the completed Takeda paper-based SAE form should be submitted to the fax number provided in this section.

SAE Reporting Contact Information			
Fax number:	**US and Canada** +1-224-554-1052	**Rest of World** +1-224-554-1052	**Japan** 0120-490-849
Email address:	PVSafetyAmericas@takeda.com	PharmacovigilanceMailbox@Takeda.com	Takeda@e-medinfo.com

SAE: serious adverse event; PV: pharmacoviligance; US: United States.

In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of SAE forms with a portable document format (or PDF) attachment should be used only when fax is not possible and EDC/RAVE is not available within 24 hours of receipt of the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via email within 1 business day.

If SAEs are reported via fax or by email, EDC must be updated as soon as possible with the appropriate information. Information in the SAE report or form must be consistent with the data provided on the eCRF.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

Reporting of serious PTEs will follow the procedure described for SAEs.

10.2.6 Reporting of Abnormal Liver-Associated Test Results

If a subject is noted to have ALT or AST elevated >3 × ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed will be recorded.

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 per Section 10.2.5. The investigator must contact the medical monitor 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. In addition, an LFT increases eCRF must be completed and transmitted with the Takeda SAE form (per Section 10.2.5).

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 will transmit a follow-up EDC SAE report (or a paper-based SAE form in an EDC SAE report is not feasible) or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory test results, 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 or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all SUSARs and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. 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 or IEC.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent Data Monitoring Committee

The data monitoring committee will be independent. The data monitoring committee evaluate safety data from the entire study on a regular basis per its charter. The charter for the data monitoring committee will be finalized before the start of the 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 Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs 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.

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. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date/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.

After the study database is locked, 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. The principal investigator must review the data change for completeness and accuracy and must sign and date the change.

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 subjects' 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

Procedure for All Countries Except for Japan

The investigator agrees 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 (including consent forms to use digital tools and applications, if applicable); subject authorization forms regarding the use of personal health information (if separate from the informed [e]consent forms); copies of all paper CRFs and query responses/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. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) Section 5.5.11 states that the study records should be retained until an amount of time specified by applicable regulatory

requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

Procedure for Japan

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; subject authorization forms regarding the use of personal health information (if separate from the informed consent forms); copies of all paper CRFs and query responses/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. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator and the head of the study site to retain essential documents specified in ICH E6(R2) (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6(R2) Section 5.5.11 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and/or the head of the study site and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

13.1.1 Analysis Sets

13.1.1.1 Safety Analysis Set

The safety analysis set will include all subjects who were randomized and received at least 1 dose of the study drug. Subjects in this analysis set will be used for demographics, baseline characteristics, and safety summaries.

13.1.1.2 Efficacy Analysis Set

The efficacy analysis set will include all subjects who received at least 1 dose of the study drug and who have at least 1 evaluable postdose efficacy measure.

13.1.1.3 PK Analysis Set

The PK analysis set will consist of subjects who receive at least 1 dose of study drug and who have at least 1 measurable serum or CSF (as applicable) concentration of TAK-341.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be listed and summarized by each treatment group and overall using the safety analysis set.

13.1.3 Efficacy Analysis

Summary statistics will be provided for the observed values of the efficacy measures at baseline and each of the postdose visits by treatment groups. Change from baseline will also be summarized with descriptive statistics by treatment groups.

The primary analysis will be performed using a CCI [redacted]. Additional analyses to address sensitivity to missing data will be specified in the SAP. Baseline covariates will be included in all models as appropriate.

The analysis of change from baseline for the secondary outcomes of UMSARS and SCOPA-AUT total score will be analyzed in the same manner as the primary analysis. CCI [redacted]

Drug effects on change from baseline for all endpoints will be assessed using 2-sided tests. In all analyses, the interaction terms and covariates will be added as appropriate.

13.1.4 PK Analysis

PK will be summarized descriptively with tables, listings, and graphs, as appropriate.

Serum PK parameters will be determined for TAK-341 CCI [redacted] CSF free αSYN reduction in all subjects may also be evaluated by using a population PK/pharmacodynamics modeling approach. The results of population PK and PK/pharmacodynamics analysis will be reported separately.

13.1.5 Pharmacodynamic/Biomarker Analysis

Pharmacodynamic effects on levels of CSF free αSYN (secondary objective/endpoint) and other CSF and plasma biomarkers will be summarized descriptively with tables, listings, and graphs, as appropriate.

13.1.6 Immunogenicity Analyses

The proportion of subjects with positive ADAs (transient and persistent) (and the proportion of subjects with positive neutralizing ADA, if applicable) during the study will be summarized. The effect of immunogenicity on PK, safety, and efficacy will be examined.

13.1.7 Safety Analysis

AEs will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated.

Safety and tolerability will be summarized descriptively with tables, listings, and graphs, as appropriate.

AEs will be listed and will be summarized by using the MedDRA System Organ Class and Preferred Term and by treatment regimen. The main presentation period of AEs will be the time from first dose to follow-up. In addition, to capture AEs related to CSF sampling, AEs will also be presented separately for each CSF sampling time point.

PK, safety, immunogenicity, and tolerability data from baseline through Day 85 from CCI (early PK cohort) will be evaluated.

The independent data monitoring committee will evaluate safety data from the entire study on a regular basis per its charter.

13.2 CCI

[redacted]

13.3 Determination of Sample Size

A sample size of approximately 138 randomized subjects with MSA would be sufficient to detect an approximately CCI difference between TAK-341 and placebo in the mean change from baseline on a modified UMSARS score (UMSARS Part I minus the sexual function item, with collapsing of 'normal and mild' ratings during analysis). CCI [redacted]

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 the study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), 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.

Alternative approaches may be used to ensure data quality, data integrity, and subject safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. Additional details are in the monitoring plan.

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 that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

PK blood samples collected outside of the predetermined time windows will not be considered a protocol deviation since actual sample times are used.

Procedure for Sites in Japan Only

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 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 and 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, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and 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 C. The principles of the Declaration of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/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 or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members because of privacy and conflict-of-interest concerns should instead provide a Federalwide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy

of the informed consent 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 or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent form must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed [e]consent form) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will ship study drug and/or notify the site after the sponsor has confirmed the adequacy of site regulatory documentation, and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification, no protocol activities, including screening may occur.

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

Subject incentives should not exert undue influence on participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written and/or 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. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study, including the use of electronic devices and associated technologies (if applicable). The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The informed consent form will detail the requirements of the subject 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 or IEC approval of the informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective

subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject, or the subject's legally acceptable representative, 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, or the subject's legally acceptable representative, determines the subject will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters the study. The subject, or the subject's legally acceptable representative, should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink in the case of written informed consent. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent or after receipt of subject signature (in the case of consent) and before the subject enters the study.

Once signed, the original informed consent form, or certified copy (if applicable), subject authorization form (if applicable), and subject information sheet (if applicable) will be maintained by the study site. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be provided to the subject.

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

(*For subjects in Germany or Austria*: If the subject becomes incompetent over the course of the study, a legally authorized court-appointed representative or an appointed agent in health matters (ie, legally acceptable representative) will need to be identified and the subject will need to provide assent, in accordance with the local regulations, guidelines, and the IRB/IEC to provide informed consent on the subject's behalf to continue in the clinical study. If a court-appointed representative or an appointed agent in health matters is not identified, the subject may be withdrawn from the study. Invasive diagnostics not necessary for subject safety and well-being (eg, lumbar puncture for PK assessment) are not allowed in subjects who become incapable of giving informed consent).

Subjects who consented and provided a blood sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. The investigator or designee should notify the sponsor of consent withdrawal.

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 ID number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique ID number.

In the event that a serious data breach is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventative actions in response. These actions will be documented and the relevant regulatory agency or agencies will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study subjects, this would be done through the investigator.

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, US FDA, UK MHRA, PMDA of Japan), the sponsor's designated auditors, and the appropriate IRBs and IECs 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 as part of the informed consent 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 Clinical Trial Disclosures and Publication

15.4.1 Clinical Trial Registration and Results Disclosure

To ensure that information about clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at minimum, register all interventional clinical trials before the start of the study and disclose the results of those trials in a manner and timeframe compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on ClinicalTrials.gov, other clinical trial registries and/or databases as required by law, and on Takeda's corporate website(s).

15.4.2 Publication

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.

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 venue (eg, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

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.

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CCI [redacted]

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Appendix A CCI

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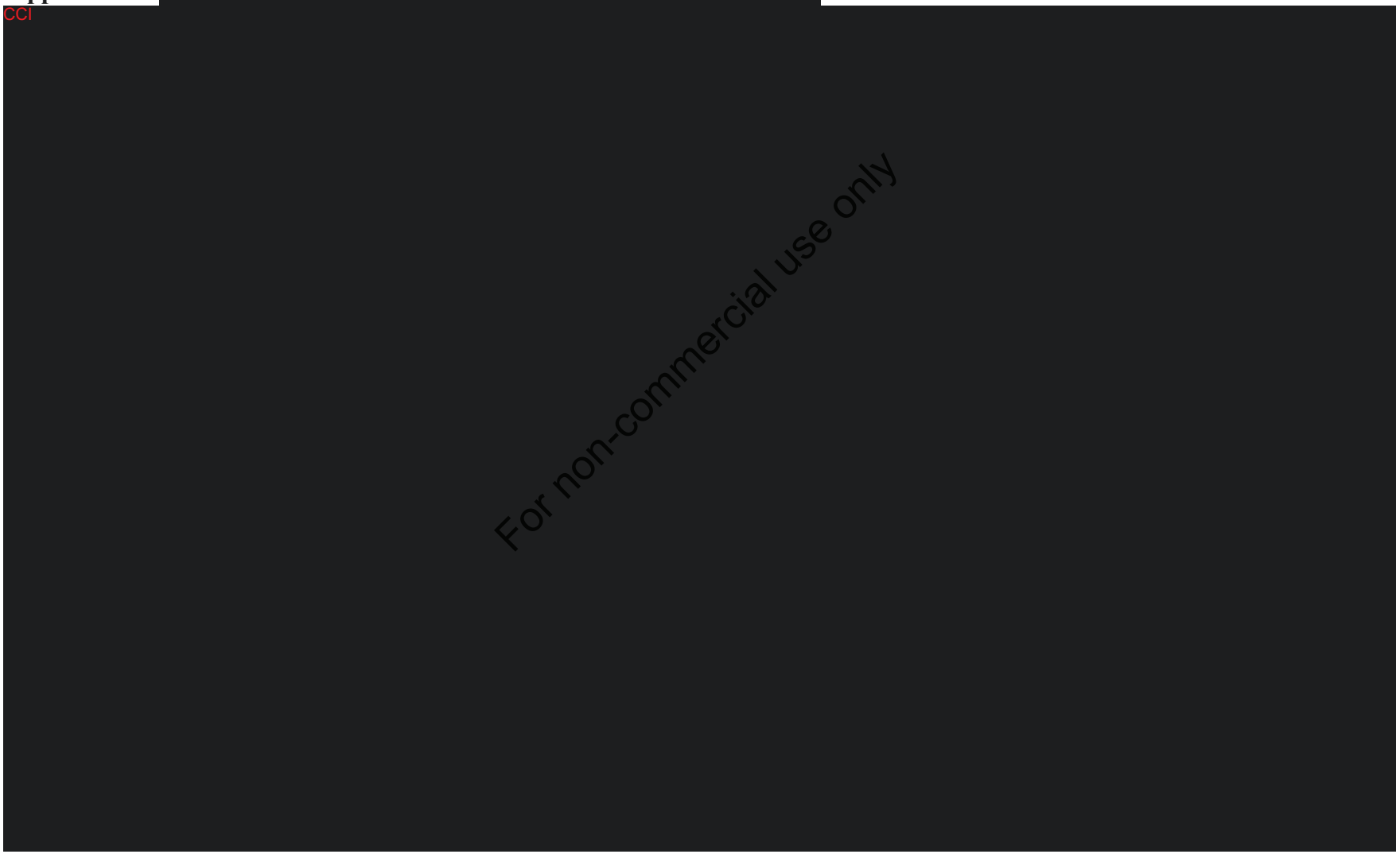

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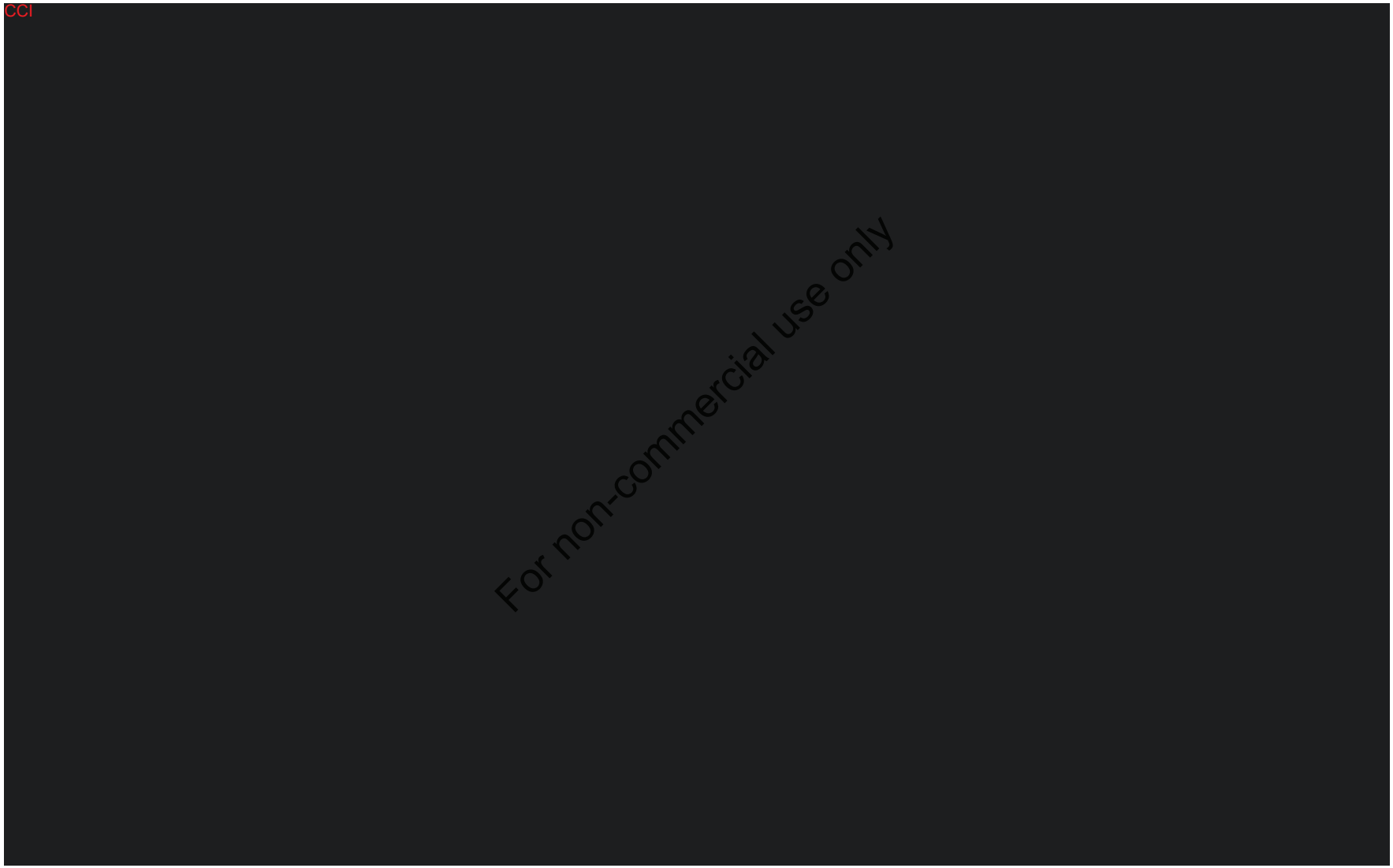

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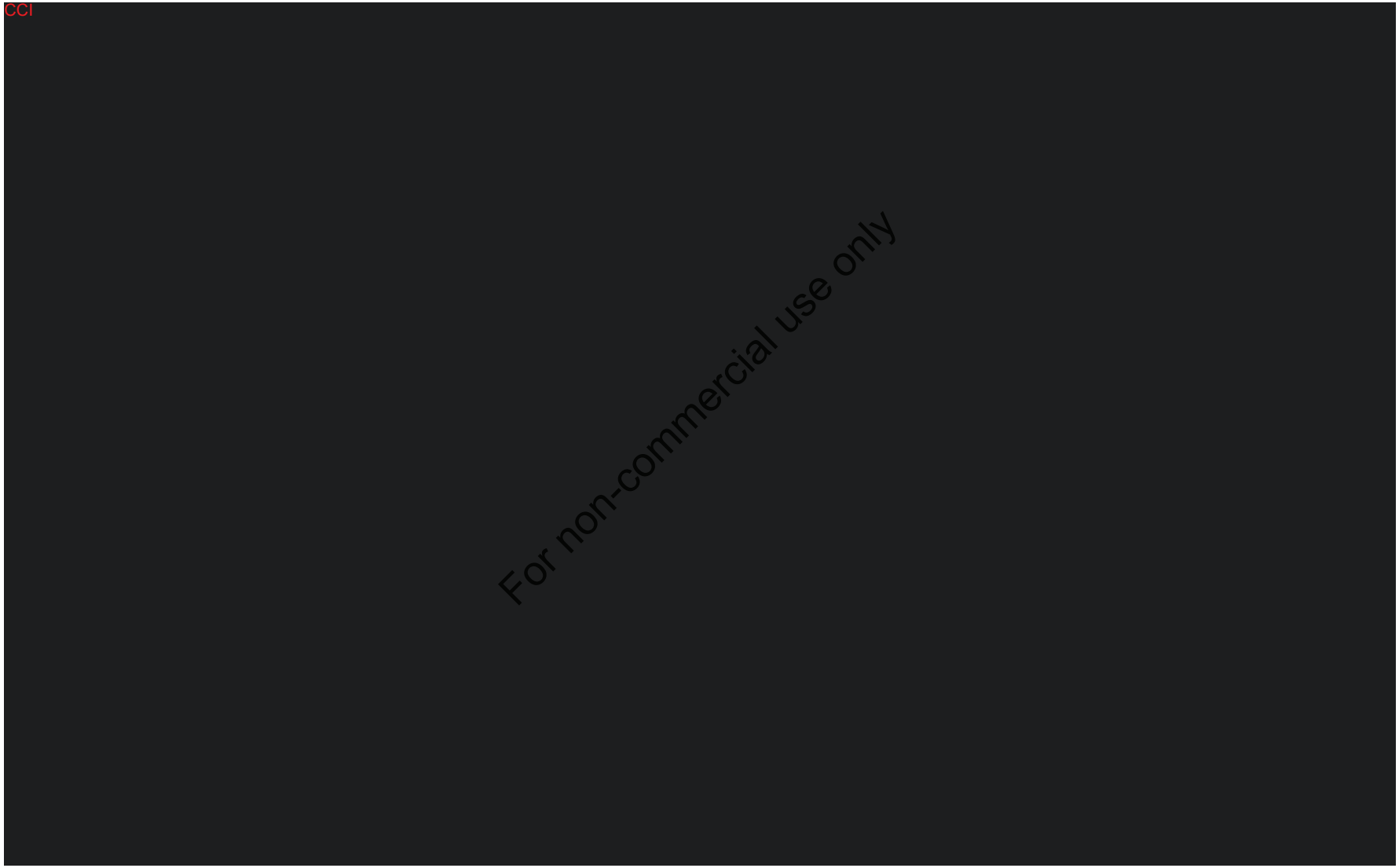

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Appendix B

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Appendix C Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study (for applicable countries).

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix D Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing an informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the

subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of genetic testing will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:

    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may affect the scientific integrity of the research; and

    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed [e]consent) from screening throughout the duration of the study, and for 30 days plus 5 half-lives (total of 130 days). Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 90 days plus 5 half-lives (total of 190 days). If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix E CCI

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Appendix F MSA Diagnostic Criteria (Gilman et al. 2008)

Criteria for the Diagnosis of Probable MSA

A sporadic, progressive, adult (>30 years)–onset disease characterized by the following:

- Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in male subjects) or an orthostatic decrease of blood pressure within 3 minutes of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, and
- Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability), or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction).

Criteria for Possible MSA

A sporadic, progressive, adult (>30 years)–onset disease characterized by the following:

- Parkinsonism (bradykinesia with rigidity, tremor, or postural instability), or
- A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction), and
- At least 1 feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in male subjects, or significant orthostatic blood pressure decline that does not meet the level required for improbable MSA), and

Criteria for Possible MSA

At least 1 of the following additional features:

Possible MSA with predominant parkinsonism (MSA-P) or MSA with predominant cerebellar ataxia (MSA-C)

- Babinski sign with hyperreflexia.
- Stridor.

Possible MSA with predominant parkinsonism (MSA-P)

- Rapidly progressive parkinsonism.
- Poor response to levodopa.
- Postural instability within 3 years of motor onset.
- Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction.
- Dysphagia within 5 years of motor onset.
- Atrophy on MRI of the putamen, middle cerebellar peduncle, pons, or cerebellum.
- Hypometabolism on fluorodeoxyglucose (FDG)–positron emission tomography (PET) in the putamen, brainstem, or cerebellum.

Possible with predominant cerebellar ataxia (MSA-C)

- Parkinsonism (bradykinesia and rigidity).
- Atrophy on MRI of the putamen, middle cerebellar peduncle, or pons.
- Hypometabolism on FDG-PET in the putamen.
- Presynaptic nigrostriatal dopaminergic denervation on single-photon emission computerized tomography or PET.

Appendix G Total UMSARS Scale (Wenning et al. 2004)

Administer all items from UMSARS Parts I, II, III, and IV.

Part I: Historical Review

Instructions for Part I items: Rate the average functional situation for the past 2 weeks (unless specified) according to the patient and caregiver interview. Indicate the score that best fits with the patient status. Rate the function independently from the nature of the signs.

UMSARS 1 – Question 1. Speech

0 Not affected.

1 Mildly affected. No difficulties being understood.

2 Moderately affected. Sometimes (less than half of the time) asked to repeat statements.

3 Severely affected. Frequently (more than half of the time) asked to repeat statements.

4 Unintelligible most of the time.

UMSARS 1 – Question 2. Swallowing

0 Normal.

1 Mild impairment. Choking less than once a week.

2 Moderate impairment. Occasional food aspiration with choking more than once a week.

3 Marked impairment. Frequent food aspiration.

4 Nasogastric tube or gastrostomy feeding.

UMSARS 1 – Question 3. Handwriting

0 Normal

1 Mildly impaired, all words are legible.

2 Moderately impaired, up to half of the words are not legible.

3 Markedly impaired, the majority of words are not legible.

4 Unable to write.

UMSARS 1 – Question 4. Cutting food and handling utensils

0 Normal.

1 Somewhat slow and/or clumsy, but no help needed.

2 Can cut most foods, although clumsy and slow; some help needed.

3 Food must be cut by someone, but can still feed slowly.

4 Needs to be fed.

UMSARS 1 – Question 5. Dressing

0 Normal.

1 Somewhat slow and/or clumsy, but no help needed.

2 Occasional assistance with buttoning, getting arms in sleeves.

3 Considerable help required, but can do some things alone.

4 Completely helpless.

UMSARS 1 – Question 6. Hygiene

0 Normal.

1 Somewhat slow and/or clumsy, but no help needed.

2 Needs help to shower or bathe; or very slow in hygienic care.

3 Requires assistance for washing, brushing teeth, combing hair, using the toilet.

4 Completely helpless.

UMSARS 1 – Question 7. Walking

0 Normal.

1 Mildly impaired. No assistance needed. No walking aid required (except for unrelated disorders).

2 Moderately impaired. Assistance and/or walking aid needed occasionally.

3 Severely impaired. Assistance and/or walking aid needed frequently.

4 Cannot walk at all even with assistance.

UMSARS 1 – Question 8. Falling (rate the past month)

0 None.

1 Rare falling (less than once a month).

2 Occasional falling (less than once a week).

3 Falls more than once a week.

4 Falls at least once a day (if the patient cannot walk at all, rate 4).

UMSARS 1 – Question 9. Orthostatic symptoms

0 No orthostatic symptoms.*

1 Orthostatic symptoms are infrequent and do not restrict activities of daily living.

2 Frequent orthostatic symptoms developing at least once a week. Some limitation in activities of daily living.

3 Orthostatic symptoms develop on most occasions. Able to stand >1 min on most occasions. Limitation in most of activities of daily living.

4 Symptoms consistently develop on orthostasis. Able to stand <1 min on most occasions. Syncope/presyncope is common if patient attempts to stand.

*Syncope, dizziness, visual disturbances or neck pain, relieved on lying flat.

UMSARS 1 – Question 10. Urinary function*

0 Normal.

1 Urgency and/or frequency, no drug treatment required.

2 Urgency and/or frequency, drug treatment required.

3 Urge incontinence and/or incomplete bladder emptying needing intermittent catheterization.

4 Incontinence needing indwelling catheter.

*Urinary symptoms should not be due to other causes.

UMSARS 1 – Question 11. Sexual function

0 No problems.

1 Minor impairment compared to healthy days.

2 Moderate impairment compared to healthy days.

3 Severe impairment compared to healthy days.

4 No sexual activity possible.

UMSARS 1 – Question 12. Bowel function

0 No change in pattern of bowel function from previous pattern.

1 Occasional constipation but no medication needed.

2 Frequent constipation requiring use of laxatives.

3 Chronic constipation requiring use of laxatives and enemas.

4 Cannot have a spontaneous bowel movement.

Part II: Motor Examination Scale

Instructions for Part II items: Always rate the worst affected limb.

UMSARS Part II – Question 1. Facial expression

0 Normal.

1 Minimal hypomimia, could be normal ("Poker face").

2 Slight but definitely abnormal diminution of facial expression.

3 Moderate hypomimia; lips parted some of the time.

4 Masked or fixed facies with severe or complete loss of facial expression, lips parted 0.25 inch or more.

UMSARS Part II – Question 2. Speech

The patient is asked to repeat several times a standard sentence.

0 Normal.

1 Mildly slow, slurred, and/or dysphonic. No need to repeat statements.

2 Moderately slow, slurred, and/or dysphonic. Sometimes asked to repeat statements.

3 Severely slow, slurred, and/or dysphonic. Frequently asked to repeat statements.

4 Unintelligible.

UMSARS Part II – Question 3. Ocular motor dysfunction

Eye movements are examined by asking the subject to follow slow horizontal finger movements of the examiner, to look laterally at the finger at different positions, and to perform saccades between two fingers, each held at an eccentric position of approximately 30°. The examiner assesses the following abnormal signs: (1) broken-up smooth pursuit, (2) gaze-evoked nystagmus at an eye position of more than 45 degrees, (3) gaze-evoked nystagmus at an eye position of less than 45 degrees, (4) saccadic hypermetria. Sign 3 suggests that there are at least two abnormal ocular motor signs, because Sign 2 is also present.

0 None.

1 One abnormal ocular motor sign.

2 Two abnormal ocular motor signs.

3 Three abnormal ocular motor signs.

4 Four abnormal ocular motor signs.

UMSARS Part II – Question 4. Tremor at rest (rate the most affected limb)

0 Absent.

1 Slight and infrequently present.

2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 Moderate in amplitude and present most of the time,

4 Marked in amplitude and present most of the time.

UMSARS Part II – Question 5. Action tremor

Assess postural tremor of outstretched arms (A) and action tremor on finger pointing (B). Rate maximal tremor severity in Task A and/or B (whichever is worse), and rate the most affected limb.

0 Absent.

1 Slight tremor of small amplitude (A). No interference with finger pointing (B).

2 Moderate amplitude (A). Some interference with finger pointing (B).

3 Marked amplitude (A). Marked interference with finger pointing (B).

4 Severe amplitude (A). Finger pointing impossible (B).

UMSARS Part II – Question 6. Increased tone (rate the most affected limb)

Judged on passive movement of major joints with patient relaxed in sitting position; ignore cogwheeling.

0 Absent.

1 Slight or detectable only when activated by mirror or other movements.

2 Mild to moderate.

3 Marked, but full range of motion easily achieved.

4 Severe, range of motion achieved with difficulty.

UMSARS Part II – Question 7. Rapid alternating movements of hands.

Pro-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately, rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cerebellar incoordination. Rate functional performance regardless of underlying motor disorder.

0 Normal.

1 Mildly impaired.

2 Moderately impaired.

3 Severely impaired.

4 Can barely perform the task.

UMSARS Part II – Question 8. Finger taps

Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand at least 15 to 20 seconds. Rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cerebellar incoordination. Rate functional performance regardless of underlying motor disorder.

0 Normal.

1 Mildly impaired.

2 Moderately impaired.

3 Severely impaired.

4 Can barely perform the task.

UMSARS Part II – Question 9. Leg agility

Patient is sitting and taps heel on ground in rapid succession, picking up entire leg. Amplitude should be approximately 10 cm, rate the worst affected leg. Note that impaired performance on this task can be caused by bradykinesia and/or cerebellar incoordination. Rate functional performance, regardless of underlying motor disorder.

0 Normal.

1 Mildly impaired.

2 Moderately impaired.

3 Severely impaired.

4 Can barely perform the task.

UMSARS Part II – Question 10. Heel-knee-shin test

The patient is requested to raise one leg and place the heel on the knee, and then slide the heel down the anterior tibial surface of the resting leg toward the ankle. On reaching the ankle joint, the leg is again raised in the air to a height of approximately 40 cm and the action is repeated. At least three movements of each limb must be performed for proper assessment. Rate the worst affected limb.

0 Normal.

1 Mildly dysmetric and ataxic.

2 Moderately dysmetric and ataxic.

3 Severely dysmetric and ataxic.

4 Can barely perform the task.

UMSARS Part II – Question 11. Arising from chair

Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.

0 Normal.

1 Clumsy, or may need more than one attempt.

2 Pushes self up from arms of seat.

3 Tends to fall back and may have to try more than once but can get up without help.

4 Unable to arise without help.

UMSARS Part II – Question 12. Posture

0 Normal.

1 Not quite erect, slightly stooped posture; could be normal for older person.

2 Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 Severely stooped posture with kyphosis; can be moderately

UMSARS Part II – Question 13. Body sway

Rate spontaneous body sway and response to sudden, strong posterior displacement produced by pull on shoulder while patient erect with eyes open and feet slightly apart. Patient has to be warned.

0 Normal.

1Slight body sway and/or retropulsion with unaided recovery.

2 Moderate body sway and/or deficient postural response; might fall if not caught by examiner.

3 Severe body sway. Very unstable. Tends to lose balance spontaneously.

4 Unable to stand without assistance.

UMSARS Part II – Question 14. Gait

0 Normal.

1 Mildly impaired.

2 Moderately impaired. Walks with difficulty, but requires little or no assistance.

3 Severely impaired. Requires assistance.

4 Cannot walk at all, even with assistance.

Part III: Autonomic Examination

Instructions for Part III items: Supine blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing. Orthostatic symptoms may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, neck and "coat-hanger" ache.

UMSARS Part III

Systolic blood pressure

Supine
Standing (2 minutes)
Unable to record

Diastolic blood pressure

Supine
Standing (2 minutes)
Unable to record

Heart rate

Supine
Standing (2 minutes)
Unable to record

Orthostatic symptoms

Yes
No

Part IV: Global Disability Scale

UMSARS Part IV

1. Completely independent. Able to do all chores with minimal difficulty or impairment. Essentially normal. Unaware of any difficulty.

2. Not completely independent. Needs help with some chores.

3. More dependent. Help with half of chores. Spends a large part of the day with chores.

4. Very dependent. Now and then does a few chores alone or begins alone. Much help needed.

5. Totally dependent and helpless. Bedridden.

Appendix H Protocol History

Date	Amendment Number	Amendment Type (for regional Europe purposes only	Region
29 November 2023	Amendment 3	Substantial	Global
03 November 2022	Amendment 2 FR v1	Nonsubstantial	France
17 October 2022	Amendment 2 DE v1	Nonsubstantial	Germany
27 September 2022	Amendment 2 GB v1	Nonsubstantial	United Kingdom
15 June 2022	Amendment 2	Substantial	Global
18 April 2022	Amendment 1	Substantial	Global
14 February 2022	Initial protocol	Not applicable	Global

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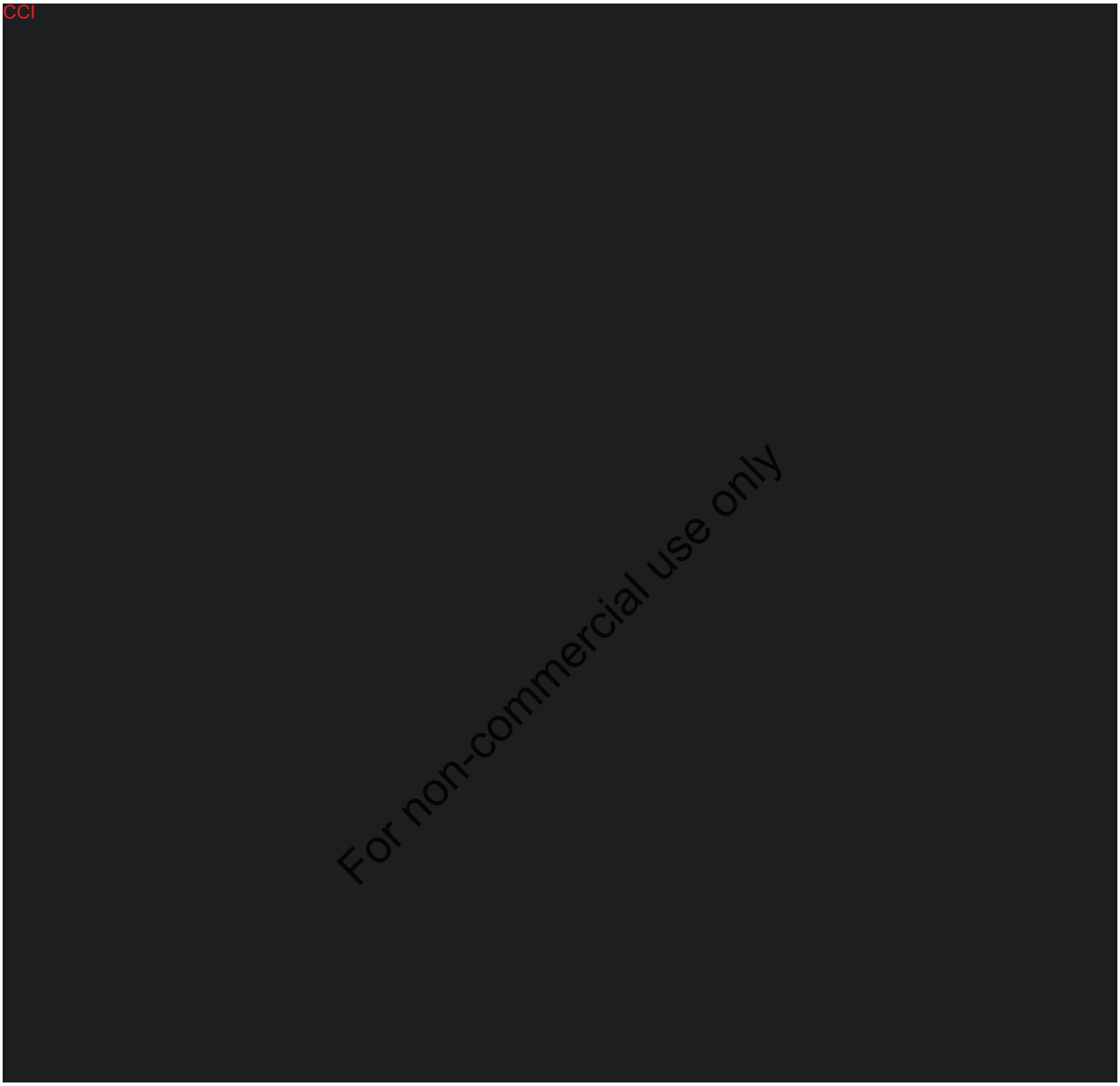

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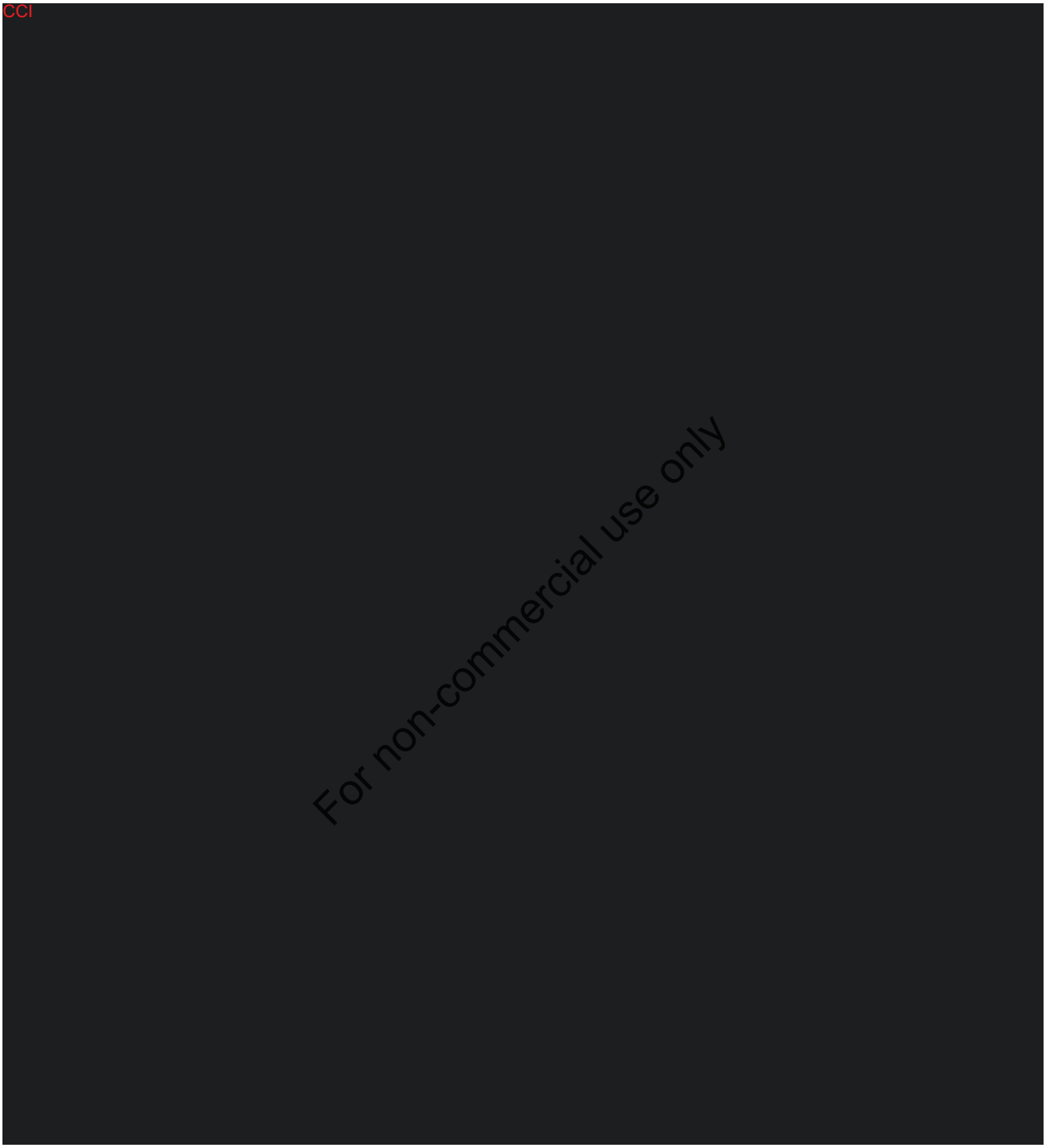

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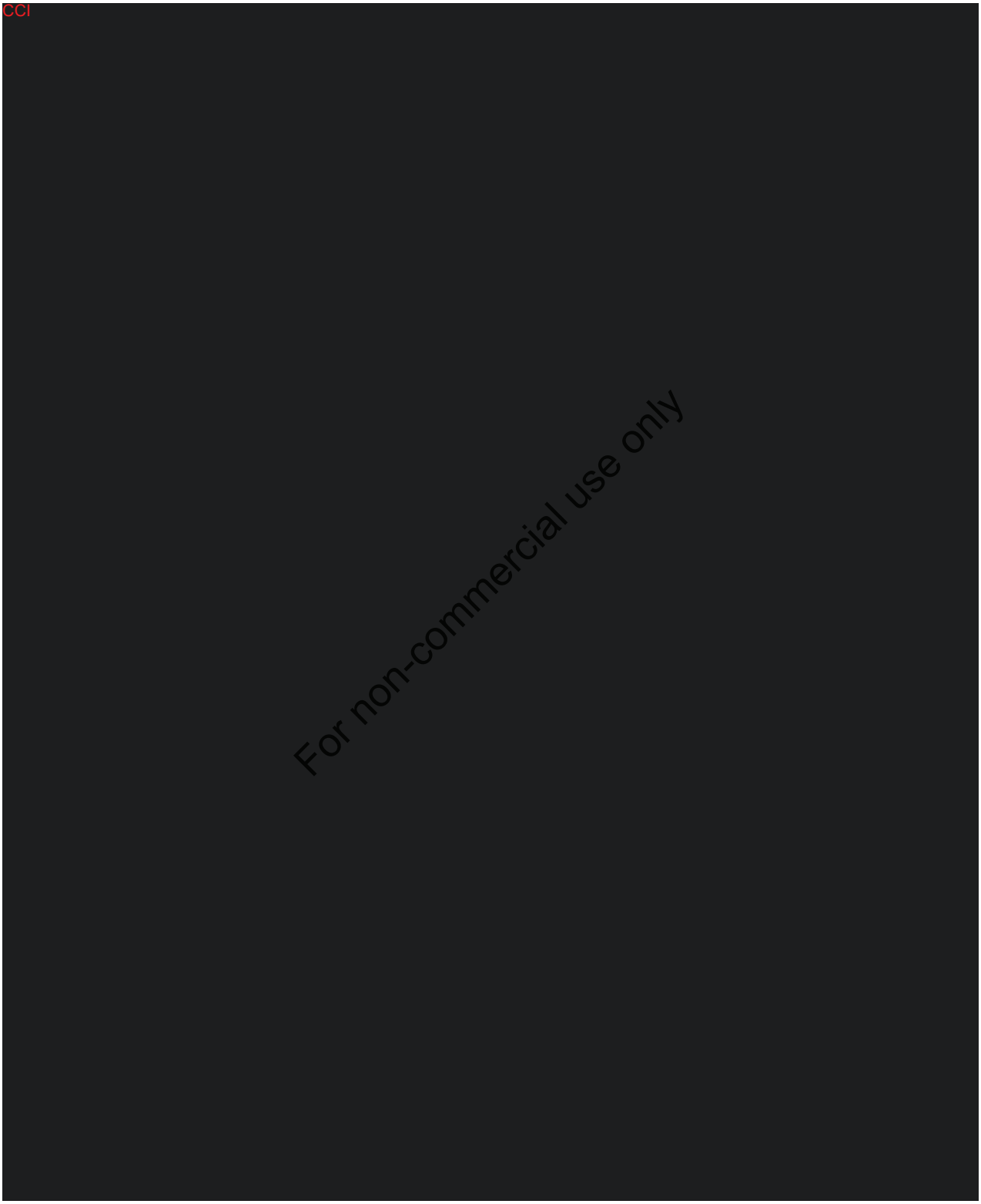

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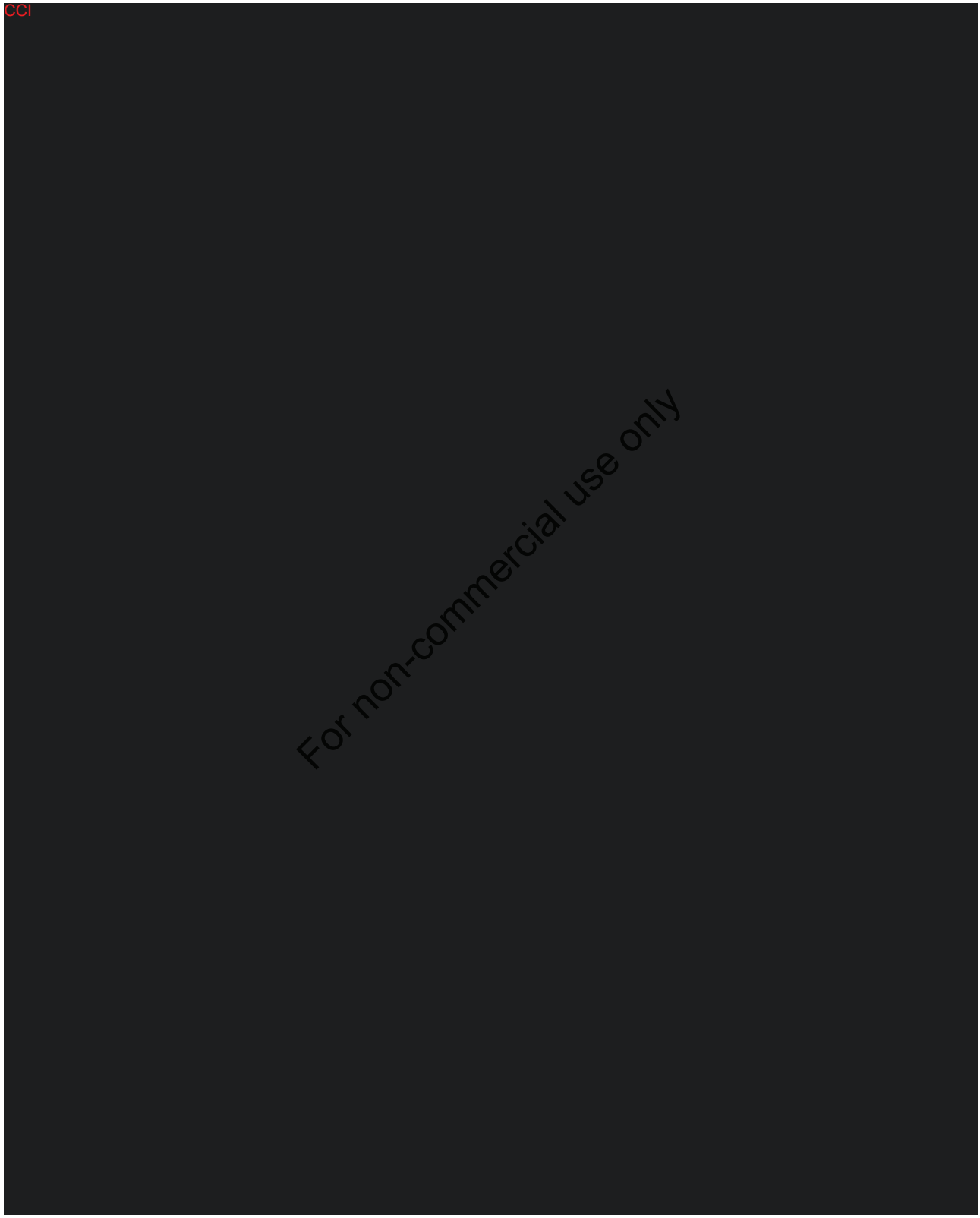

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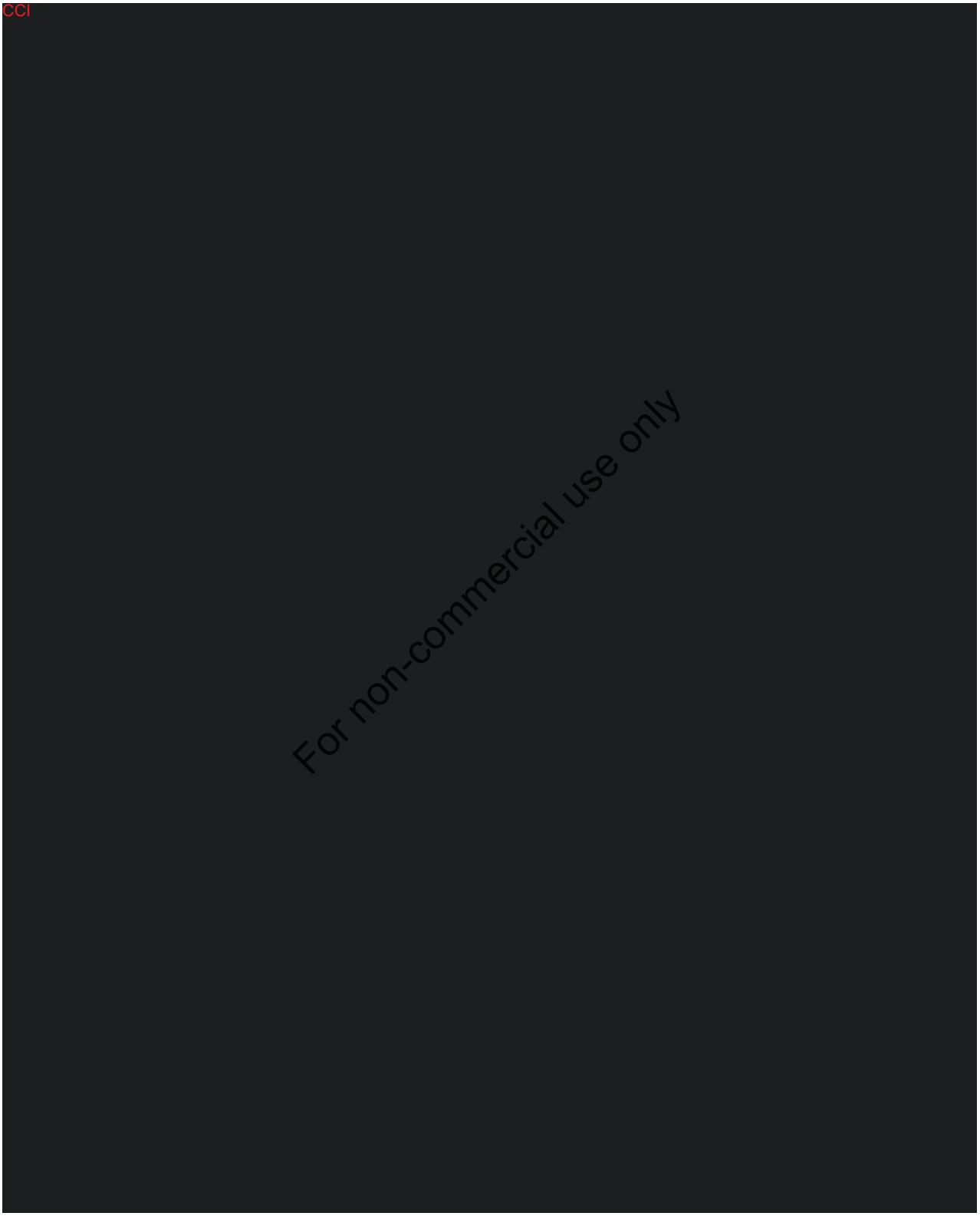

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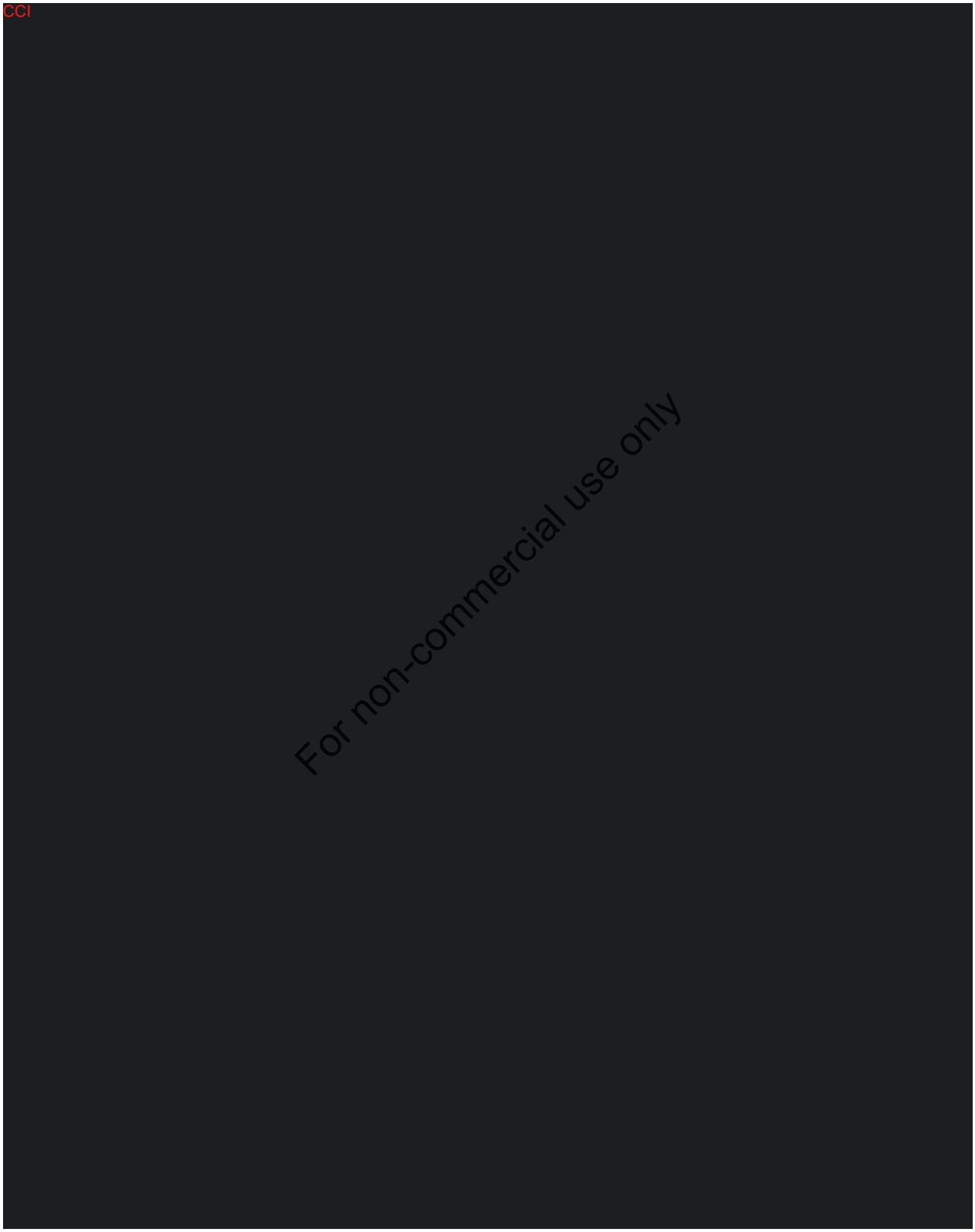

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Signature Page for TAK-341-2001_Protocol Amend 3_2023-11-29

Title: A Randomized, Double-blind, Placebo-Controlled, Phase 2 Study to Evaluate

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