Clinical Study Protocol

NCT Number: NCT06323356

Title: A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-279 in Adult Subjects With Generalized Pustular Psoriasis or Erythrodermic Psoriasis

Study Number: TAK-279-PsO-3005

Document Version and Date: Amendment 5/ 08-OCT-2024

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-279 in Adult Subjects With Generalized Pustular Psoriasis or Erythrodermic Psoriasis

A Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-279 in Subjects With Generalized Pustular Psoriasis or Erythrodermic Psoriasis

Sponsor:	Takeda Pharmaceutical Company Limited 4-1-1, Doshomachi, Chuo-ku Osaka, Japan 540-8645		
Study Number:	TAK-279-PsO-3005		
Study Phase:	3		
IND Number:	Not Applicable	**EudraCT/CTIS Number:**	Not Applicable
Investigational Product:	TAK-279		
Date:	08 October 2024	**Version/Amendment Number:**	Amendment 5

Amendment History:

Date	Amendment Number	Region
18 October 2023	Initial version	All Sites
16 November 2023	Amendment 1	All Sites
26 January 2024	Amendment 2	All Sites
22 March 2024	Amendment 3	All Sites
10 July 2024	Amendment 4	All Sites
08 October 2024	Amendment 5	All Sites

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APPROVALS

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual subjects 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) Good Clinical Practice (GCP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations

SIGNATURES OF THE RESPONSIBLE TAKEDA MEDICAL OFFICER AND OTHER SIGNATORY (IES)

The electronic signature of the of the following individuals is provided below.

[redacted], Clinical Science	
[redacted], Statistical & Quantitative Sciences	
[redacted], Quantitative Clinical Pharmacology	Not applicable

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INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the Investigator's Brochure (IB), 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 of Technical Requirements for Pharmaceuticals for Human Use GCP.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) as defined in this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the Investigator as described in this protocol.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a potential subject to obtain their informed consent to participate.

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I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Summary of Changes Since the Last Version of the Approved Protocol			
Protocol Amendment 5			
Amendment Date: 08 October 2024			**Japan**
Overall Reason for the Amendment The reason for this protocol update is to allow T-SPOT at local laboratories.			
Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of Change(s)**	**Rationale for Change(s)**	**Section**
1	Added the acceptance of T-SPOT at local laboratories	To allow T-SPOT at local laboratories	Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 5.2 Exclusion Criteria Section 8.3.4 Clinical Safety Laboratory Tests

See Section 10.8 for protocol history, including all previous amendments.

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ADMINISTRATIVE INFORMATION

CONTACTS

See Annexes.

ADDITIONAL INFORMATION

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

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Send it to the following email address:

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Pharmaceutical Company Limited
4-1-1, Doshomachi, Chuo-ku, Osaka, Japan 540-8645</td><td colspan="2">Compound:
TAK-279</td></tr>
<tr><td>Study Number:
TAK-279-PsO-3005</td><td>Phase:
3</td><td>IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td colspan="4">Title of Protocol:
A Phase 3, Open-Label, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-279 in Adult Subjects With Generalized Pustular Psoriasis or Erythrodermic Psoriasis</td></tr>
<tr><td colspan="4">Short title:
A Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-279 in Subjects With Generalized Pustular Psoriasis or Erythrodermic Psoriasis</td></tr>
<tr><td colspan="4">Number of subjects (total and per treatment arm):
Approximately 20 subjects will be enrolled to receive TAK-279 (approximately10 each for generalized pustular psoriasis [GPP] and erythrodermic psoriasis [EP], respectively).</td></tr>
<tr><td colspan="4">Number of subjects (total and per treatment arm):
Approximately 20 subjects will be enrolled to receive TAK-279 (10 each for generalized pustular psoriasis [GPP] and erythrodermic psoriasis [EP], respectively).</td></tr>
<tr><td colspan="4">Investigator(s): Multicenter study</td></tr>
<tr><td colspan="4">Site(s) and Region(s): Japan, with approximately 20 sites</td></tr>
<tr><td colspan="4">Study period (planned):
The maximum study duration per subject is 61 weeks, including up to 35 days for the screening period, a 52-week treatment period, and a 4-week safety follow-up period.</td></tr>
<tr><td colspan="4">Objectives and Endpoints</td></tr>
<tr><td colspan="4"><table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary objective:
To evaluate the efficacy of TAK-279 30 mg orally administered QD for 16 weeks in subjects with GPP or EP.</td><td>Coprimary Efficacy Endpoints:
• Static Physician’s Global Assessment (sPGA) 0/1 response: Assessed as proportion of subjects achieving an sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at Week 16
• PASI-75 response: Assessed as proportion of subjects achieving ≥75% improvement from baseline in PASI score at Week 16</td></tr>
</table></td></tr>
</table>

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	Secondary objective: To evaluate the efficacy of TAK-279 30 mg orally administered QD for 52 weeks in subjects with GPP or EP.	**Secondary Efficacy Endpoints:** • sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at Weeks 52 • Durable sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at both the Week 16 and Week 52 visits • Enhanced sPGA response: Proportion of subjects achieving an sPGA of clear (0) at Weeks 16 and 52 • Simplified sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) at Weeks 16 and 52 • Simplified durable sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) at both the Week 16 and Week 52 • PASI-75 response: Proportion of subjects achieving PASI-75 at Weeks 52 • PASI-90 response: Proportion of subjects achieving PASI-90 at Weeks 16 and 52 • PASI-100 response: Proportion of subjects achieving PASI-100 at Weeks 16 and 52 • Durable PASI-75 response: Proportion of subjects achieving PASI-75 at both the Week 16 and Week 52 visits • Durable PASI-90 response: Proportion of subjects achieving PASI-90 at both the Week 16 and Week 52 visits • Scalp-specific Physician's Global Assessment (ssPGA) response: Proportion of subjects achieving an ssPGA of absence of disease (0) or very mild disease (1) with a ≥2-point decrease from baseline at Weeks 16 and 52 (for subjects with a baseline ssPGA ≥3, baseline PSSI ≥12, and SSA involvement ≥30%) • Change from baseline in ssPGA at Weeks 16 and 52 • Proportion of subjects achieving a Physician's Global Assessment (PGA) of the hands and/or feet of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at	

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		Weeks 16 and 52 (for subjects with a baseline PGA of the hands and/or feet ≥3) • Dermatology Life Quality Index (DLQI) response: Proportion of subjects with a DLQI score of 0/1 at Weeks 16 and 52 (for subjects with a baseline DLQI score ≥2) • Change from baseline in DLQI at Weeks 16 and 52 • Change from baseline in Nail Psoriasis Severity Index (NAPSI) at Weeks 16 and 52, among subjects with nail involvement at baseline • Change and percent change from baseline in BSA affected by psoriasis at Weeks 16 and 52 **Secondary Efficacy Endpoints for GPP:** • Generalized Pustular Psoriasis Global Assessment (GPPGA) Pustulation Subscore response: Proportion of subjects achieving a GPPGA Pustulation Subscore of no visible pustules (0) at Weeks 16 and 52 • GPPGA 0/1 response: Proportion of subjects achieving a GPPGA of clear (0) or almost clear at Weeks 16 and 52 • Enhanced GPPGA response: Proportion of subjects achieving a GPPGA of clear (0) at Weeks 16 and 52 • Generalized Pustular Psoriasis Area and Severity Index (GPPASI)-75 response: Proportion of subjects achieving ≥75% improvement from baseline in GPPASI score at Weeks 16 and 52 • Change from baseline in JDA severity score at Weeks 16 and 52	
	Safety objective: To assess the safety and tolerability of TAK-279 30 mg orally administered QD in subjects with GPP or EP.	**Safety Endpoints:** • Incidence of treatment-emergent adverse events (TEAEs) • Changes in clinical laboratory parameters, vital signs, and electrocardiogram (ECG) • Adverse events of special interest (AESIs)	

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Rationale:

Although a number of therapies exist for the treatment of GPP and EP, there remains significant unmet need for oral therapies that have comparable efficacy to those of the biologic agents while offering long-term safety.

TAK-279 is a highly selective oral allosteric inhibition of TYK2. TAK-279 is selective for the allosteric site on TYK2, which may allow greater inhibition of the target while retaining a favorable benefit-risk profile by minimizing off-target effects on other JAKs. The results of the completed Study 4858-201 suggested the efficacy of TAK-279 in psoriasis vulgaris. In addition, drug with approved TYK2 inhibitory activity similar to TAK-279 has been shown to be effective for GPP and EP. Based on these results, TAK-279 is expected to be effective for GPP and EP. TAK-279 is an oral drug that is easier to administer, and it has the potential to demonstrate clinical efficacy and a favorable safety and tolerability profile for the treatment of GPP and EP.

Study intervention, dose, and mode of administration: TAK-279 30 mg tablet for oral administration.

Overall Design and Methodology:

This is a phase 3, open-label, multicenter study to evaluate the efficacy, safety, and tolerability of TAK-279 once daily (QD) for 52 weeks in Japanese subjects with GPP or EP.

Approximately 20 male and female subjects, aged 18 years and older, with GPP or EP will be enrolled in this study. To be eligible for the study, subjects must have a diagnosis of GPP or EP prior to the screening visit. In addition, subjects will need to have the following characteristics: For GPP, total JDA severity score <14 and BSA involvement ≥10% at screening and BSA involvement ≥10% on Day 1. For EP, a history of plaque-type of psoriasis and BSA involvement ≥80% at screening and Day 1. For both populations, eligible for phototherapy or systemic therapy.

Screening Period:

The screening period will be a maximum of 35 days and no fewer than 1 day. Key activities during screening include collection of PASI, sPGA, and BSA (and JDA severity score in patients with GPP), collection of ECG, and collection of serum blood samples. Consenting subjects will be screened for eligibility in a clinical setting before enrollment.

All subjects who sign an informed consent form at screening and fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study.

Treatment Period:

Of the approximately 20 planned subjects, approximately 10 will be enrolled in each of the GPP and EP cohorts. The study will be conducted at approximately 20 sites located in Japan. All subjects who are eligible by screening will receive initiate treatment with TAK-279 30 mg orally QD on Day 1 up to Week 52. Subjects will attend a total of 16 scheduled study visits: Day 1, Weeks 1, 2, 4 and every 4 weeks thereafter through Week 52 (end of treatment [EOT]).

Efficacy will be assessed using PASI, 5-point sPGA, and percentage BSA involvement. For subjects with scalp psoriasis at Day 1, 5-point ssPGA will be assessed during the study period. For subjects with nail psoriasis at Day 1, NAPSI will be assessed during the study period. For subjects with hands and/or feet psoriasis involvement at Day 1, PGA of the hands and/or feet will be assessed during the study period. For subjects with GPP, GPPASI and GPPGA will be assessed during the study period. Patient-reported outcome assessments will include DLQI.

Safety will be assessed by collecting TEAEs, including AESIs; recording vital signs; performing complete and targeted physical examinations; and evaluating ECG and clinical laboratory results. Signs of depression and suicidal ideation and behavior will be monitored with the 8-item Patient Health Questionnaire (PHQ-8) and Columbia-Suicide Severity Rating Scale (C-SSRS), respectively.

The full benefit-risk profile of TAK-279 has not been established. However, based on the current understanding of the safety profile from nonclinical studies, clinical data from completed and ongoing clinical studies, as well as the scientific literature, TAK-279 appears to be well tolerated with early evidence of efficacy on clinically significant outcomes.

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A major adverse cardiovascular events (MACE)Adjudication Committee with representation including a cardiologist will be established to review certain cardiovascular adverse events (AEs). Respective details will be in separate MACE Adjudication Committee related materials.

No interim analysis is planned in this study.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

Subject eligibility is determined according to the following criteria evaluated during the screening period or as specified below:

Subject Willingness:

1. Subject 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.
2. Subject has provided written informed consent and any required privacy authorization before the initiation of any study procedures.

Disease Characteristics:

For GPP

3. Subject has a diagnosis of GPP based on the diagnostic criteria of the JDA (Appendix 1) prior to the screening visit.
4. Subject has been on a stable treatment regimen for GPP for at least 2 weeks prior to Day 1.
5. Subject has a total JDA severity score <14 at screening.
6. Subject has erythema with pustules covering ≥10% of his or her BSA at screening and Day 1.
7. Subject must be a candidate for phototherapy or systemic therapy.

For EP

8. Subject has a diagnosis of EP prior to the screening visit.
9. Subject has a history of plaque-type of psoriasis.
10. Subject has plaque psoriasis covering ≥80% of his or her BSA at screening and Day 1.
11. Subject must be a candidate for phototherapy or systemic therapy.

Age and Reproductive Status:

12. Subject is aged 18 years or older at the time of consent.
13. Subject meets the following birth control requirement:

    A surgically sterile female subject; or a female subject of nonchildbearing potential with laboratory confirmation of postmenopausal status (ie, follicle-stimulating hormone levels >40 mIU/mL); or, if sexually active with a nonsterilized individual who produces sperm, an individual with potential for pregnancy who agrees to use a highly effective method of contraception from the signing of informed consent throughout the duration of the study and for 10 days after the last dose.

Exclusion Criteria:

A subject will be excluded from the study if any of the following exclusion criteria are met at screening or as specified below:

Target Disease-Related Exclusions:

1. Subject has evidence of predominantly guttate psoriasis, predominantly inverse, or drug-induced psoriasis.
2. Subject requires systemic treatment, other than nonsteroidal anti-inflammatory drugs or non-prohibited therapies, during the study period for an immune-related disease (eg, inflammatory bowel disease).

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3. Subject has a history of excessive sun exposure, has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study period. Use of sunscreen products and protective apparel is recommended when sun exposure cannot be avoided.
4. Subject has concomitant comorbid skin condition that, in the opinion of the investigator, would interfere with the study assessments.

Recent/Concurrent Infectious Disease Exclusions:

5. Tuberculosis (TB):
   a) Subject has history of active TB infection, regardless of treatment status.
   b) Subject has signs or symptoms of active TB (including but not limited to chronic fever, chronic productive cough, night sweats, or weight loss) as judged by the investigator.
   c) Subject has evidence of latent TB infection (LTBI) as evidenced by a positive T-SPOT result OR 2 indeterminate results and subject does not have documentation of appropriate LTBI prophylaxis or is not able or not willing to initiate appropriate LTBI prophylaxis. Subject remains eligible if there are no signs/symptoms of active TB AND documentation of no history of active TB can be provided AND (1) subject can provide documentation of prior and complete treatment for LTBI (appropriate in duration and type per current guidelines) or (2) subject has a positive T-SPOT result or 2 indeterminate T-SPOT results but has initiated prophylaxis (appropriate in duration and type per current guidelines) at least 3 weeks prior to Day 1.

      Note: TB prophylaxis regimens should be administered according to guidelines; however, because of potential interactions with TAK-279, rifampin should not be used. TB testing should be conducted using T-SPOT submitted to central laboratory or measured at local laboratories unless alternate or additional tests are required per guidelines.

   d) Subject has had any imaging study during or 6 months prior to screening, including x-ray, chest computed tomography, magnetic resonance imaging, or other chest imaging suggesting evidence of current active or a history of active TB. X-ray is required for all subjects regardless of T-SPOT results unless the subject has had normal chest imaging in the 6 months prior to screening.
6. Herpes infections:
   a) Subject has active herpes virus infection, including herpes zoster or herpes simplex 1 and 2 (demonstrated on physical examination and/or medical history) at screening or Day 1.
   b) Subject has history of serious herpetic infection that includes any episode of disseminated disease, multidermatomal herpes zoster, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (defined as 2 episodes within 2 years).
7. Non-herpetic viral diseases:
   a) Subject has presence of hepatitis C virus (HCV) antibody and a positive confirmatory test result for HCV RNA (nucleic acid test or polymerase chain reaction).
   b) Subject has presence of positive hepatitis B surface antigen (HBsAg+), or indeterminant hepatitis B surface antigen, presence of hepatitis B virus DNA (regardless of serology), or positive anti-hepatitis B core antibody without concurrent positive hepatitis B surface antibody (HBcAb+ and HBsAb-).
   c) Subject has positive results for human immunodeficiency virus by serology, regardless of viral load.
8. Other infectious diseases:
   a) Subject has a history of active infection or febrile illness within 7 days prior to Day 1, as assessed by the investigator.
   b) Subject has history of symptoms suggestive of systemic or invasive infection within 30 days prior to Day 1.
   c) Subject has a history of bacterial, viral, or fungal infection that required hospitalization or treatment with intravenous antimicrobial therapy within 8 weeks prior to Day 1, or oral antimicrobial therapy within 30 days prior to Day 1.

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d) Subject has a history of chronic or recurrent bacterial disease, including but not limited to chronic pyelonephritis or cystitis, chronic bronchitis/pneumonitis, osteomyelitis, or chronic skin ulcerations/infections or fungal infections (except superficial nailbed mycosis).

e) Subject has a history of an infected joint prosthesis unless that prosthesis has been removed or replaced at least 60 days prior to Day 1.

f) Subject has a history of opportunistic infections (eg, Pneumocystis jirovecii pneumonia, histoplasmosis, coccidiomycosis).

g) Subject had a bacterial infection within 60 days prior to Day 1 for which he or she did not receive treatment.

Noninfectious Disorders Exclusions:

9. Subject has any clinically significant medical condition, evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, or immunologic), or vital signs/physical/laboratory/ECG abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results. These include but are not limited to:

a) Subject has a history of known or suspected condition/illness that is consistent with compromised immunity, including but not limited to any identified congenital or acquired immunodeficiency; splenectomy.

b) Subject had a major surgery within 60 days prior to Day 1 or has a major surgery planned during the study.

c) Subject has unstable, poorly controlled, or severe hypertension at screening, confirmed by 2 repeat assessments.

d) Subject has a history of Class III or IV congestive heart failure as defined by New York Heart Association criteria.

e) Subject has a history of cancer or lymphoproliferative disease, with the exception of successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.

f) For subjects with asthma, chronic obstructive pulmonary disease, or other pulmonary illnesses, subject has been hospitalized in the past 3 months, has ever required intubation for treatment, currently requires oral corticosteroids, or has required more than 1 course of oral corticosteroids within 6 months prior to Day 1.

g) Subject has any of the following cardiovascular disease history:

- A new diagnosis of atrial fibrillation or an episode of atrial fibrillation with rapid ventricular response or other dysrhythmia, non-acute cardiac hospitalization (eg, pacemaker implantation), pulmonary embolism, or deep venous thrombosis within the past 6 months prior to screening.
- Any history of cerebrovascular event, myocardial infarction, coronary stenting, or aorto-coronary bypass surgery. If, however, the investigator determines there are no suitable treatment alternatives available for the subject and it has been at least 6 months since the occurrence of any such event, the subject may enroll.

h) Subject has ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the subject if he or she participated in the study, in the opinion of the investigator.

i) Subject has significant/uncontrolled psychiatric illness, in the opinion of the investigator.

j) Subject has any lifetime history of suicidal ideation, suicidal behavior, or suicidal attempts by 1) medical history; or 2) by C-SSRS documentation or by answering "yes" to Question 5 for suicidal ideation on the C-SSRS at screening; or 3) is clinically deemed to have a suicide risk by the investigator.

k) Subject has a PHQ-8 score of 15 or above at screening.

l) Subject has a history of clinically significant drug or alcohol abuse within 12 months prior to Day 1.

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Prohibited Psoriasis Treatments Exclusions:

For the below prohibited psoriasis treatments, the washout period prior to Day 1 is within the time frame indicated or 5 half-lives, whichever is longer.

10. Subject has received any of the following biologics or biosimilar versions within the time frame indicated:
    a) Antibodies to IL-12/-23, IL-17, IL-23, or IL-36 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, guselkumab, risankizumab, or spesolimab) within 6 months prior to Day 1.
    b) TNF inhibitor(s) (eg, etanercept, adalimumab, infliximab, certolizumab) within 2 months prior to Day 1.
    c) Agents that modulate integrin pathways to impact lymphocyte trafficking (eg, natalizumab) or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, or visilizumab) within 3 months prior to Day 1.
    d) Rituximab or other immune cell-depleting therapy (eg, granulocyte and monocyte adsorptive apheresis) within 6 months prior to Day 1.
11. Subject has used medicated shampoo and/or body wash, including formulations containing but not limited to salicylic acid, corticosteroids, coal tar, vitamin D_3 analogues, or other compounds used for the management of psoriasis within 2 weeks prior to Day 1.
12. Subject has used any topical medication that could affect psoriasis presentation (including but not limited to corticosteroids, salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, retinoids, vitamin D analogues [such as calcipotriol], methoxsalen, trimethylpsoralen, calcineurin inhibitors [eg, tacrolimus], tapinarof, roflumilast, JAK inhibitors, or tar) within 2 weeks prior to Day 1.

    Note: Low-potency topical steroids (World Health Organization Class VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours before any study visit. Low-potency topical steroids may be used to treat acute non-psoriatic conditions (eg, contact dermatitis) on all body regions for no more than 2 weeks but should not be used within 24 hours before any study visit. Low-potency topical steroids co-formulated with other topicals that may affect the presentation of psoriasis are not permitted. Bland emollients (defined as emollients containing only ingredients that are pharmacologically inactive) are allowed on all body regions but should not be used within 24 hours before any study visit.
13. Subject has used any systemic nonbiologic treatment that could affect psoriasis presentation (including oral, intravenous, intramuscular, intra-articular, intrathecal, or intralesional corticosteroids; oral retinoids; immunosuppressive/immunomodulating medication; methotrexate; azathioprine; 6-thioguanidine; mercaptopurine; mycophenolate mofetil; hydroxyurea; cyclosporine; 1,25-dihydroxyvitamin D_3 analogues; psoralens; sulfasalazine; fumaric acid derivatives; JAK inhibitors [including deucravacitinib and upadacitinib]; apremilast) within 4 weeks prior to Day 1, or 5 half-lives, whichever is longer.

    Note: Intranasal corticosteroids, inhaled corticosteroids, and eye and ear drops containing corticosteroids are permitted. Use of prednisone or its equivalent at a daily dose ≤10 mg/day is permitted.
    For subjects with GPP, one of following agent is permitted under stable dose: methotrexate, or retinoids.
    For subjects with EP, concomitant use of methotrexate, or retinoids is permitted under stable dose until Week 2.
14. Subject has used leflunomide within 6 months prior to Day 1.
15. Subject has received phototherapy (including ultraviolet B [UV-B], psoralen and ultraviolet A [PUVA], tanning beds, therapeutic sunbathing) or excimer laser within 4 weeks prior to Day 1.
16. Subject has used botanical preparations (eg, herbal supplements or traditional medicines, including traditional Chinese medicines derived from plants, minerals, or animals) intended to treat psoriasis or other immunological diseases within 4 weeks prior to Day 1.
17. Subject has any previous exposure to TAK-279 (also known as NDI-034858), or subject participated in any study that included a TYK2 inhibitor (eg, deucravacitinib, VTX958, GLPG3667, etc.), unless subject has documentation of post-trial unblinding that confirms the subject did not receive a TYK2 inhibitor.

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Other Prohibited Concomitant Medications Exclusions:

For the below prohibited psoriasis treatments, the washout period prior to Day 1 is within the time frame indicated or 5 half-lives, whichever is longer.

18. Subject has received lithium, antimalarials, or intramuscular gold therapy within 4 weeks prior to Day 1.
19. Subject is currently being treated with strong or moderate cytochrome P450 3A4 (CYP3A4) inhibitors (such as itraconazole) or strong or moderate CYP3A4 inducers (such as rifampin, carbamazepine, or phenytoin), or has received strong or moderate CYP3A4 inhibitors or strong or moderate CYP3A4 inducers within 4 weeks or 5 half-lives of the inducer or inhibitor, whichever is longer, prior to Day 1, or is anticipated to require treatment with strong or moderate CYP3A4 inducers or inhibitors during the study period (see Appendix 3).

    Note: This includes consumption of food or beverages containing grapefruit and/or Seville oranges within 1 week of Day 1. Subjects must be counseled to avoid food or beverages containing grapefruit and/or Seville oranges for the duration of the study.
20. Subject has received any live-attenuated vaccine within 60 days prior to Day 1 or plans to receive a live-attenuated vaccine during the study and up to 4 weeks after the last study drug administration.

    Note: Non–live-attenuated vaccines or boosters for coronavirus disease-2019 (COVID-19) or influenza are permitted during the study.
21. Subject received an investigational antibody or biologic therapy within 6 months prior to Day 1.
22. Subject is currently receiving a nonbiological study drug or device or has received one within 4 weeks prior to Day 1.
23. Subject is currently enrolled in a clinical study or anticipates enrollment in a clinical study during the course of the study.

Laboratory/Physical Exclusions:

24. Subject has any of the following laboratory values at the screening visit:
    a) AST or ALT values >3 times the ULN
    b) Total bilirubin (unconjugated and/or conjugated) >1.5 times the ULN
    c) Hemoglobin <9.0 g/dL (<90.0 g/L)
    d) Absolute white blood cell count $<3.0 \times 10^9$/L ($<3000/mm^3$)
    e) Absolute neutrophil count of $<1.0 \times 10^9$/L ($<1000/mm^3$)
    f) Absolute lymphocyte count of $<0.5 \times 10^9$/L ($<500/mm^3$)
    g) Platelet count $<100 \times 10^9$/L ($<100,000/mm^3$)
    h) Thyroid-stimulating hormone (TSH) outside the normal reference range **AND** free thyroxine (T4) or triiodothyronine (T3) outside the normal reference range
    i) Estimated creatinine clearance <45 mL/min based on the Cockcroft-Gault calculation.
    j) Creatine phosphokinase (CPK) > ULN. CPK may be repeated once; if repeat value is Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or lower (or $\leq 2.5 \times$ ULN) and no higher than the initial value, subject remains eligible. Investigators should assess the subject for modulating factors including concomitant medications or vigorous exercise that may affect CPK levels.
25. Subject has any other significant laboratory abnormalities that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
26. Subject does not tolerate venipuncture or inability to be venipunctured.

Allergies and Adverse Drug Reactions Exclusions:

27. Subject has history of significant drug allergy (such as anaphylaxis).
28. Subject has a known or suspected allergy to TAK-279 or any of its components (see Section 6.1).

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Other Exclusions:

29. Subject has a positive pregnancy test result or plans to become pregnant during the study period, or subject is pregnant or lactating/nursing.
30. Subjects who have given greater than 500 mL of blood or plasma within 30 days of screening (during a clinical study or at a blood bank donation) or plans to donate blood during the course of the study.
31. Subject is compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness, or is committed to an institution by virtue of an order issued either by judicial or administrative authorities (ie, prison).
32. Subject is a study site employee, an immediate family. member (eg, spouse, parent, child, sibling), or is in a dependent relationship with study site employee who is involved in the conduct of this study, or may consent under duress.

Intervention groups and duration including maximum duration of subject participation in the study:

The maximum study duration per subject is 61 weeks, including:

- Up to 35 days for the screening period,
- Up to 52-week treatment period,
- A 4-week safety follow-up period.

Statistical analysis

Analysis Sets:

Full Analysis Set (FAS): All subjects who received at least 1 dose of TAK-279.

Per-protocol Set (PPS): All subjects who received at least 1 dose of TAK-279, did not have any important protocol deviations, and whose primary endpoints were evaluable.

Safety Analysis Set: All subjects who received at least 1 dose of TAK-279.

Efficacy Analyses

Coprimary Efficacy Endpoints:

For each coprimary efficacy endpoint, frequency distribution will be provided with proportion and the two-sided 95% confidence interval by disease (GPP and EP) in the FAS. The confidence interval will be calculated using Clopper-Pearson method.

Secondary Efficacy Endpoints:

The following analysis will be performed by disease (where applicable) in the FAS.

- For continuous endpoints, descriptive statistics and two-sided 95% confidence interval of mean will be provided for observed values (baseline and post-baseline visits) and changes from baseline (each post-baseline visit - baseline). For endpoints with multiple visits, these will be provided by visit.
- For binary endpoints, frequency distribution will be provided with proportion and the two-sided 95% confidence interval. For endpoints with multiple visits, these will be provided by visit.

Safety Analyses:

The following analysis will be performed by disease in the safety analysis set.

A TEAE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The frequency distribution will be provided using the system organ class and the preferred term.

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute (NCI) CTCAE, Version 5.0 or higher, and will be listed.

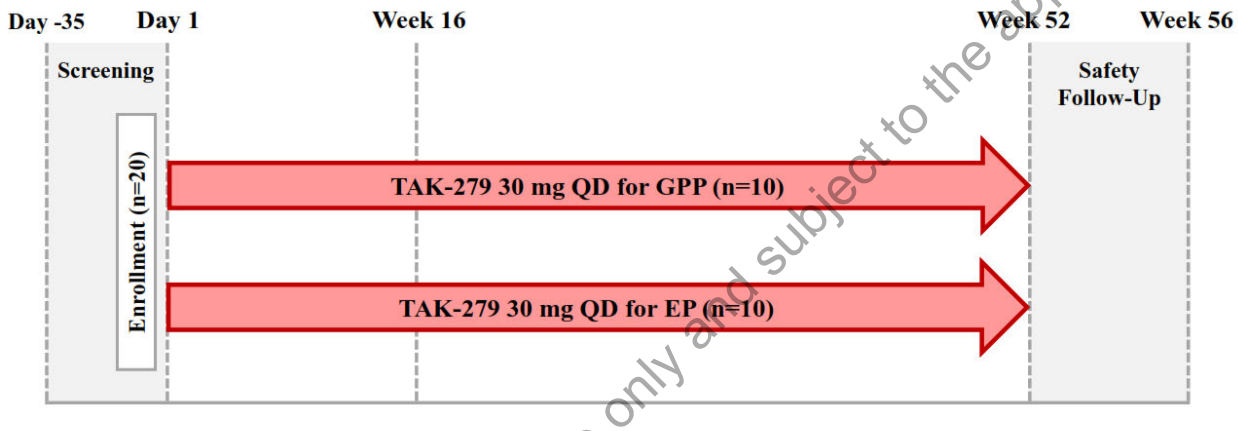
Clinical laboratory results, vital signs, and ECGs will also be summarized. For continuous endpoints, the observed values and the changes from baseline will be summarized for each visit using descriptive statistics. Case plots will also be presented for the observed values. For categorical endpoints, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

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Sample Size Determination:
For each disease (GPP and EP), the targeted sample size is approximately 10 subjects based on enrollment feasibility of this population in Japan, rather than statistical perspective (e.g., power calculation). Consequently, the targeted sample size is approximately 20 subjects in total.

1.2 Schema

Figure 1.a Study Schema



GPP: Generalized Pustular Psoriasis; EP: Erythrodermic Psoriasis; QD: once daily.

1.3 Schedule of Activities (SoA)

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form (ICF). No treatment or trial-related procedures will be initiated before the informed consent is signed.

The screening evaluation will be performed according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively). If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Study procedures are outlined in Table 1.a and Table 1.b.

Patient-reported outcome assessments must be completed prior to the clinician-reported outcome efficacy assessments, other laboratory procedures, and study drug administration, unless specified otherwise. Examples of the assessments and questionnaires used in this study are presented in the Appendices.

Every attempt should be made to adhere to the visit schedule. If an unscheduled visit (eg, an additional visit not specified in Table 1.a) is unavoidable or necessary, the investigator may allow it at his or her discretion. All study-specific unscheduled visits should be documented in the subject's record and the appropriate clinical data should be recorded.

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Table 1.a Schedule of Activities

Study Visits	Screening Period	Treatment Period														FU
	Screening Visit	Day 1	Weeks 1, 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32	Week 36	Week 40	Week 44	Week 48	Week 52 (EOT)/ET	Week 56 (EOS)
Windows (days)	-35 to -1 [a]	-	(±2)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)
Administrative Procedures																
Informed consent	X															
Inclusion and exclusion criteria	X	X														
Demographics	X															
Medical and surgical history	X	X														
Psoriasis-related history and prior treatment	X															
Active scalp, nail, hands and/or feet psoriasis (yes/no) [b]		X														
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
On-site study drug administration [c]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense study drug		X	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of study drug			X	X	X	X	X	X	X	X	X	X	X	X	X	X [d]
Subject diary distribution/collection/ review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [d]

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Table 1.a Schedule of Activities

Study Visits	Screening Period	Treatment Period														FU
	Screening Visit	Day 1	Weeks 1, 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32	Week 36	Week 40	Week 44	Week 48	Week 52 (EOT)/ET	Week 56 (EOS)
Windows (days)	-35 to -1 [a]	-	(±2)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)
Clinical Procedures and Laboratory Assessments																
Adverse events evaluation [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body height and weight [f]	X [f]	X		X	X		X		X		X				X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination	X						X									X
Targeted physical examination		X	X	X	X	X		X	X	X	X	X	X	X	X	
12-lead ECG	X	X		X			X		X						X	X
TB test [h]	X															
Chest X-ray [i]	X															
Serology (HIV, HBV [HBsAg, anti-HBc, HBV DNA], HCV) [j]	X															
TSH and reflex free T4 and T3	X															
Clinical laboratory tests (hematology, chemistry, urinalysis, FSH [k], CRP levels)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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Study Visits	Screening Period	Treatment Period														FU
	Screening Visit	Day 1	Weeks 1, 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32	Week 36	Week 40	Week 44	Week 48	Week 52 (EOT)/ET	Week 56 (EOS)
Windows (days)	-35 to -1 [a]	-	(±2)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)
Fasting lipid panel [l]		X		X			X		X						X	X
Clinician-Reported Outcomes Assessments																
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ssPGA (for subjects with scalp psoriasis at Day 1) [b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PSSI (for subjects with scalp psoriasis at Day 1) [b]		X														
GPPGA [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
GPPASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
JDA severity score	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NAPSI (for subjects with nail psoriasis at Day 1) [b]		X	X [n]	X	X	X	X	X	X	X	X	X	X	X	X	
PGA of hands and/or feet (for subjects with hands and/or feet psoriasis at Day 1) [b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS [o]	X	X	X [p]		X		X		X			X			X	X

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Table 1.a Schedule of Activities

Study Visits	Screening Period	Treatment Period														FU
	Screening Visit	Day 1	Weeks 1, 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32	Week 36	Week 40	Week 44	Week 48	Week 52 (EOT)/ET	Week 56 (EOS)
Windows (days)	-35 to -1 [a]	-	(±2)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)
Patient-Reported Outcomes																
DLQI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PHQ-8	X	X			X		X		X			X			X	X
PK, Biomarker, and Other Evaluations																
Plasma samples for TAK-279 PK concentration [q]	Refer to Table 1.b															
Serum for biomarker analysis		X		X	X	X	X		X			X			X	

anti-HBc: antibody to hepatitis B core antigen; BSA: body surface area; CRP: C reactive protein; C-SSRS: Columbia-Suicide Severity Rating Scale; DLQI: Dermatology Life Quality Index; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; ET: early termination; FSH: follicle-stimulating hormone; FU: follow-up; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; ICF: informed consent form; LTBI: latent tuberculosis infection; MRI: magnetic resonance imaging; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index; PASI-75: 75% improvement from baseline in PASI; PHQ-8: Eight-item Patient Health Questionnaire; PK: pharmacokinetic; PsA: psoriatic arthritis; QD: once daily; sPGA: static Physician's Global Assessment; ssPGA: scalp-specific Physician's Global Assessment; T4: thyroxine; T3: triiodothyronine; TSH: thyroid-stimulating hormone.

[a] Screening period must be no more than 35 days but no fewer than 1 day from Day 1 visit.

[b] At baseline, investigators will be asked to assess for presence of active psoriasis of scalp, nails, and hands/feet. For subjects with active scalp psoriasis, investigators will be asked to assess ssPGA and PSSI at Day 1, and ssPGA at subsequent visits per SoA. For subjects with active nail psoriasis, investigators will be asked to assess NAPSI per SoA. For subjects with active hand/foot psoriasis, investigators will be asked to assess PGA of the hands and/or feet per SoA.

[c] Study products will be taken at home for 52 weeks, except on visit days, when the first study drug administration of the day and visit days will be administered on site. No study drug administration will occur on the day of the Week 52 visit.

[d] For subjects who complete EOS after ET only.

[e] Collection of adverse events (AEs) begins after signing the ICF.

[f] Height will be measured only at screening.

[g] For female subjects of childbearing potential only. Serum pregnancy test to be performed at screening, with urine pregnancy test at subsequent visits.

[h] TB testing should be conducted using T-SPOT submitted to central laboratory or measured at local laboratories. For subjects who have documentation of LTBI and who have completed a course of prophylaxis (appropriate in duration and type per current local country guidelines), T-SPOT does not need to be repeated.

[i] Chest X-ray not required for patients with normal chest imaging (chest X-ray, dedicated computed tomography, or MRI of the chest) within the 6 months prior to screening.

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Table 1.a Schedule of Activities

Study Visits	Screening Period	Treatment Period													FU
	Screening Visit	Day 1	Weeks 1, 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Weeks 28, 32	Week 36	Week 40	Week 44	Week 48	Week 52 (EOT)/ET	Week 56 (EOS)
Windows (days)	-35 to -1 [a]	-	(±2)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)

[j] Eligible subjects who are negative for HBV-DNA at Screening test and are of the #3 and #5 types in Appendix 2 should be continued to undergo HBV DNA testing at a central laboratory once per month for the first 6 months and every 3 months thereafter, after initiation of study drug.
[k] FSH must be obtained to confirm postmenopausal state in subjects <60 years old with absence of menses for ≥12 months with no alternative medical cause (see Section 10.4 for additional details).
[l] Study treatment may be taken without regard to meals; however, subjects are required to fast for a minimum of 8 hours before visits on which fasting lipid samples will be drawn.
[m] GPPGA, GPPASI, JDA severity score will be assessed only for GPP subject.
[n] NAPSI will be assessed at not Week 1 but Week 2.
[o] C-SSRS 'Baseline' version (Appendix 14) will be used for screening assessment and 'Since Last Visit' version (Appendix 15) will be used for all subsequent assessments.
[p] C-SSRS will be assessed at not Week 1 but Week 2.
[q] Blood samples for PK analyses will be collected predose and post dose according to the timepoints specified in Table 1.b.

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Table 1.b Schedule of Activities – Sampling Timepoints for TAK-279 PK Analysis

Study Visits	Screening Period	Treatment Period											FU
	Screening Visit	Day 1	Week 1	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 32	Week 40	Week 52 (EOT)/ET	Week 56 (EOS)
Windows (days)	**-35 to -1 [a]**	**-**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±3)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**	**(±7)**
Predose PK sample collection [b]		X			X	X	X	X	X		X	X	
Postdose PK sample collection at approximately 3-4 hours after dosing						X							

EOS: end-of-study; EOT: end-of-treatment; ET: early termination; FU: follow-up; PK: pharmacokinetic.
[a] Screening period must be no more than 35 days but no fewer than 1 day from Day 1 visit.
[b] Predose PK samples are collected prior to study drug administration on site visit days. At Week 52, there is no dose administered at the study site. For this visit only, the PK sample can be collected at any time during the visit.

2.0 INTRODUCTION

2.1 Study Rationale

TAK-279 is an oral inhibitor of tyrosine kinase (TYK2) that binds to the JH2 pseudokinase domain, resulting in highly selective TYK2 kinase activity compared to the other homologous proteins in the Janus kinase (JAK) family of nonreceptor tyrosine kinases (JAK1, JAK2, and JAK3).

TYK2 catalyzes the phosphorylation of signal transducers and activators of transcription (STAT) proteins downstream of several cytokine receptors, including the interleukin (IL)-23 receptor, as well as the Type I interferon receptor and the IL-12 receptor (Watford et al. 2004). The activation of TYK2 dependent receptors by their cytokine ligands results in the activation of STAT dependent transcription and cellular functional responses specific for the receptors and cell types they are expressed on (Stark and Darnell 2012). The cytokine signaling pathways regulated by TYK2 play key roles in several immune-mediated disorders. Most relevant for psoriasis pathogenesis, the cytokine IL-23 is central to the expansion and survival of Th17 cells and innate lymphoid cells, both of which have been shown to play key pathogenic roles in autoimmunity (Sutton et al. 2012). IL-23 stimulation drives the production of key proinflammatory cytokines by Th17 cells, including IL-17A, IL-17F, and IL-22, all of which are effector molecules in psoriatic skin.

Although a number of therapies exist for the treatment of generalized pustular psoriasis (GPP) and erythrodermic psoriasis (EP) in Japan, there remains significant unmet need for oral therapies that have comparable efficacy to those of the biologic agents while offering long-term safety.

TAK-279 is a highly selective oral allosteric inhibition of TYK2. TAK-279 is selective for the allosteric site on TYK2, which may allow greater inhibition of the target while retaining a favorable benefit-risk profile by minimizing off-target effects on other JAKs. The results of the completed Study 4858-201 suggested the efficacy of TAK-279 in psoriasis vulgaris. In addition, drug with approved TYK2 inhibitory activity similar to TAK-279 has been shown to be effective for GPP and EP. Based on these results, TAK-279 is expected to be effective for GPP and EP. TAK-279 is an oral drug that is easier to administer, and it has the potential to demonstrate clinical efficacy and a favorable safety and tolerability profile for the treatment of GPP and EP. For additional information, see the IB for TAK-279.

2.2 Background

2.2.1 Generalized Pustular Psoriasis and Erythrodermic Psoriasis

Psoriasis is a chronic, systemic immune-mediated inflammatory disease characterized by development of erythematous, scaly, skin plaques. Psoriasis is generally classified into five disease types of plaque psoriasis, guttate psoriasis, pustular psoriasis, EP and psoriatic arthritis (PsA) in Japan.

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Plaque psoriasis is the most common type of psoriasis prevalent worldwide, with 1% to 2% of the population affected (Armstrong and Read 2020). The Psoriasis Area and Severity Index (PASI), total BSA affected, and the sPGA are widely accepted tools for assessing psoriasis severity (Greb et al. 2016; Oji and Luger 2015). The primary goal of psoriasis therapies is clearance of psoriatic plaques, with a benchmark level of treatment response in most current clinical studies of 75% improvement from baseline in PASI (PASI-75) at Week 12 or 16. This benchmark is readily achieved by the majority of patients treated with biologic therapies targeting tumor necrosis factor (TNF) α, IL-12/23, IL-23, and IL-17 (Gisondi et al. 2020; Menter et al. 2019).

GPP is a rare, severe neutrophilic skin disorder characterized by sudden widespread eruption of superficial sterile pustules with or without systemic inflammation. GPP flares can be life-threatening if untreated due to potential severe complications such as cardiovascular failure and serious infections (Krueger et al. 2022). Erythrodermic psoriasis (EP), a rare variant of plaque psoriasis, accounts for 1–2% patients with psoriasis, is clinically defined as prominent erythema and scaling affecting at least 75–90% of the body surface area (BSA). Due to the extensive cutaneous involvement, EP patients can present with systemic symptoms, such as pruritus, fever, chills, dehydration, arthralgia, asthenia and lymphadenopathy (Lo and Tsai 2021).

While there are multiple biologic agents approved for the treatment of moderate-to-severe plaque psoriasis, there are a very limited number of oral small molecule therapies available to patients. Some patients can be treated with oral immunosuppressive drugs; however, these treatments generally exhibit limited efficacy (Menter et al. 2019). Recently, the Food and Drug Administration has approved deucravacitinib, an oral, selective, allosteric tyrosine kinase 2 (TYK2) inhibitor, similar to TAK-279, for the treatment of moderate-to-severe psoriasis. Deucravacitinib was approved by the European Medicines Association and is currently under regulatory review by other health authorities around the world for the treatment of moderate-to-severe plaque psoriasis. In Japan, deucravacitinib was approved with indications of plaque psoriasis, GPP, and EP. The current standard of care for GPP and EP includes immune-suppressants and -modulators (e.g., cyclosporine, methotrexate, TNF-a inhibitors, IL-17 inhibitors, IL-12/23 antagonists), and etretinate (retinoid). Granulocyte and monocyte absorption apheresis is also used for treating GPP.

But, there are still strong unmet medical needs for the refractory patients even if several treatment options are available, and clinical experience and better understanding of the disease pathology are being accumulated.

2.2.2 TAK-279

TAK-279 (formerly NDI-034858) is a small molecule allosteric inhibitor of the non-receptor TYK2. TYK2 is a critical intracellular component of the JAK-STAT signaling cascade, which is activated downstream of several cytokine receptors upon ligand binding, including the IL-23, IL-12, and Type I interferon (Watford et al. 2004). TYK2 and the cytokines that depend on

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TYK2 have been implicated in a range of autoimmune diseases. TAK-279 is being developed for the treatment of immune-related conditions.

The activation of TYK2-dependent receptors by their cytokine ligands results in the activation of STAT-dependent transcription and cellular functional responses specific for the receptors and cell types they are expressed on (Stark and Darnell 2012). The cytokine signaling pathways regulated by TYK2 play key roles in several immune-mediated disorders.

The cytokine IL-12 is essential for the development of Type 1 T-helper cells, which produce interferon-gamma, a major effector molecule in systemic autoimmune disorders such as systemic lupus erythematosus (Chasset and Arnaud 2018; Trinchieri 1993). The cytokine IL-23 is central for the expansion and survival of Th17 cells and innate lymphoid cells, both of which have been shown to play key pathogenic roles in autoimmunity (Sutton et al. 2012). IL-23 stimulation drives the production of key proinflammatory cytokines by Th17 cells, including IL-17A, IL-17F, and IL-22, all of which are effector molecules important for the pathogenesis of conditions such as psoriasis, PsA, spondyloarthritis and inflammatory bowel disease.

2.3 Drug Interactions

The following summarizes the known drug-drug interaction (DDI) potential for TAK-279.

- Following 50 mg TAK-279 single dose administration with multiple doses of 200 mg itraconazole (strong cytochrome P450 [CYP] 3A4 inhibitor), the geometric mean ratio for the area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) was 2.14 (90% confidence interval [CI]: [1.60-2.87]) (Study 4858-105).
- Preliminary results from the ongoing Study TAK-279-1002 showed that coadministration of 50 mg TAK-279 single dose with multiple 500 mg doses of erythromycin increased plasma TAK-279 $AUC_{0-\infty}$ by approximately 133%, when compared with TAK-279 administered alone.
- Preliminary results from the ongoing Study TAK-279-1002 showed that coadministration of 50 mg TAK-279 single dose with multiple 100 mg doses of phenytoin decreased plasma TAK-279 $AUC_{0-\infty}$ by 66%, when compared with TAK-279 administered alone.

Based on the initial physiologically based pharmacokinetic (PBPK) model, for a moderate CYP3A4 inducer (efavirenz), TAK-279 area under the concentration-time curve (AUC) is predicted to decrease by 50%. Therefore, strong and moderate CYP3A4 inhibitors and inducers are excluded in this study.

The PBPK model was also used prospectively to predict the likely outcomes of interaction with sensitive CYP2C8 (rosiglitazone), CYP3A4 (midazolam), UGT1A1 (raltegravir), P-gp (digoxin), and MATE-1/2-K (metformin) probe substrates following multiple 50 mg doses of TAK-279. No clinically significant DDIs (AUC and maximum concentration ratios <1.25 fold) were predicted following coadministration of multiple doses of 50 mg QD TAK-279, with sensitive CYP2C8, CYP3A4, UGT1A1 and P-gp probe substrates. A weak (≥1.25 to <2-fold change in AUC) interaction was predicted following coadministration of multiple doses of 50 mg QD TAK-279

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with sensitive MATE1/2-K probe substrate metformin. Therefore, the likelihood of DDI of TAK-279 with these substrates is expected to be low in vivo.

Further details can be found in the IB.

2.4 Benefit/Risk Assessment

2.4.1 Known Potential Benefits

TYK2 mediates signaling of inflammatory cytokines of both adaptive (IL-12, IL-23) and innate (type I IFN) immune responses that play key roles in several immune-mediated disorders including psoriasis (Chasset and Arnaud 2018; Trinchieri 1993). Monoclonal antibody therapeutics directed against IL-23 or IL-17 cytokines have been approved for clinical use in adults with psoriasis. For example, recently approved antibodies against IL-23 (guselkumab) or IL-17A (secukinumab) are approved for plaque psoriasis and produce a response of PASI-75 at 12 weeks in 75% to 91% of patients with psoriasis (Bilal et al. 2018). Additionally, deucravacitinib, an oral small molecule allosteric inhibitor of TYK2, was approved by the Food and Drug Administration (FDA) in the US in 2022 based on results from 2 phase 3 studies demonstrating PASI-75 in 58.4% (Armstrong et al. 2023) and 53% (Strober et al. 2023) of patients. And deucravacitinib was also approved in Japan in 2022 for plaque psoriasis, GPP and EP based on the above results and Japan phase 3 study's result.

TAK-279, also an allosteric inhibitor of TYK2, has demonstrated early clinical efficacy in a phase 2b trial Study 4858-201 in moderate-to-severe psoriasis. In this study, TAK-279 demonstrated a dose-response for PASI-75 at Week 12, with over two-thirds of patients achieving PASI-75 at doses of 15 and 30 mg. In addition, at the 30 mg dose, 33% of patients achieved PASI-100 at Week 12. Similar results were achieved for the Physician's Global Assessment (PGA), with half of subjects receiving doses of 15 and 30 mg achieving PGA 0/1 and 33% of subjects receiving the 30 mg dose achieving a PGA 0. To date, TAK-279 has been well tolerated with no major safety signals identified.

Thus, both the phase 2 clinical data from TAK-279 and pivotal data from phase 3 studies of deucravacitinib, another allosteric TYK2 inhibitor, support the potential for TAK-279 to treat not only moderate-to-severe plaque psoriasis, but also GPP and EP.

2.4.2 Potential Risks

Based on the review of the clinical data from the completed studies, the potential risks of TAK-279 include:

- Infections (severe or serious or opportunistic) (clinical data).
- Creatine phosphokinase (CPK) elevation National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (severe) >5× upper limit of normal (ULN) (clinical data).
- Abnormal liver function tests (nonclinical and clinical data).

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The potential risks of TAK-279 based on non-specific JAK inhibitor class effects only include the below events; of note, the TAK-279 clinical program experience to date does not suggest an increased risk of these events:

- Major adverse cardiovascular events (MACE), defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.
- Thromboembolic events.
- Malignancies.

2.4.3 Proposed Risk Mitigation Strategy

Risk mitigations for monitoring subject safety include:

- Infections:
  - Excluding subjects with active, chronic, or recurrent infections; a history of opportunistic infection; or a history of primary or secondary immunodeficiency.
  - Discontinue or temporarily hold dosing in subjects with serious, severe, or opportunistic infections until resolution.
  - Serious/severe and opportunistic infections must be reported as adverse event of special interests (AESIs) with immediate notification to the sponsor and medical monitor.
- CPK elevation:
  - Immediately discontinue or hold dosing for subjects with Grade 3 or higher CPK elevation until a complete evaluation is completed and report as an AESI.
  - Immediately discontinue subjects with a confirmed case of rhabdomyolysis.
- Abnormal liver function tests **:
  - Immediately hold dosing and investigate further once the following criteria is met: ALT or AST ≥3 × ULN in conjunction with elevated total bilirubin ≥2 × ULN. Immediately notify the sponsor and report the event as a serious adverse event (SAE).
  - All abnormal liver function tests ≥ Grade 2 will be reported as AESIs.

** Bilirubin elevation monitoring included under abnormal liver function tests.

- Thromboembolic events:
  - Thromboembolic events, defined as pulmonary embolism, deep vein thrombosis, and other venous and arterial thromboembolic events (eg, noncardiac, non-neurologic, fatal, and nonfatal) will be reported as AESIs.

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- Malignancies:
  - All malignancies, including nonmelanoma skin cancer (NMSC), malignancies other than NMSC, and lymphomas will be reported as AESIs.
- MACE:
  - All MACE, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke will be reported as AESIs.
  - Immediate notification to the sponsor within 24 hours of onset of a potential MACE.
- Monitoring:
  - Ongoing monitoring of periodic or ad hoc data for benefit-risk assessment including events of interest (MACE)
  - Depression with suicidality is not a risk specifically associated with the TAK-279 mechanism, namely TYK2 inhibition, and has not been observed in the TAK-279 clinical trials to date but has been previously observed in psoriasis clinical trials. Given this, the study will include ongoing monitoring of subjects in the study to identify and assess suicidality (Columbia Suicide Severity Rating Scale [C-SSRS]) and depression (8-item Patient Health Questionnaire; PHQ-8) and discontinue or temporarily hold dosing in subjects at risk of suicidality.
- Hepatitis B Virus (HBV) DNA
  - Severe hepatitis development due to reactivation of HBV-DNA with the use of potent immunosuppressants has been reported. Thus, according to guidelines, quantitative HBV-DNA measurements should be performed once per month for the first 6 months and every 3 months thereafter, even if the screening test is negative for HBV-DNA.
  - If recurrence of HBV infection is suspected or the HBV DNA level is confirmed to be 20 IU/mL (1.3 LogIU/mL)/lower limit of quantification or higher in laboratory test results, as follows:
    - Record the HBV DNA test results as an adverse event (AE).
    - Consult with experts in Hepatitis B about initiating treatment (e.g. nucleotide analogues) and continuation of TAK-279 administration.
- An independent panel of experts (cardiologist) to adjudicate events of interest (eg, MACE), see Section 10.1.5.1.

2.4.4 Risk Benefit Conclusions

The full benefit-risk profile of TAK-279 has not been established. However, based on the current understanding of the safety profile from nonclinical studies, clinical data from completed and ongoing clinical studies, as well as the scientific literature, TAK-279 appears to be well tolerated with early evidence of efficacy on clinically significant outcomes. Refer to the latest version of

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the TAK-279 IB for the overall benefit/risk assessment and the most current information regarding drug metabolism, pharmacokinetics (PK), efficacy, and safety of TAK-279.

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1 Objectives

3.1.1 Primary Objective

To evaluate the efficacy of TAK-279 30 mg orally administered QD for 16 weeks in subjects with GPP or EP.

3.1.2 Secondary Objective

To evaluate the efficacy of TAK-279 30 mg orally administered QD for 52 weeks in subjects with GPP or EP.

3.1.3 Safety Objective

To assess the safety and tolerability of TAK-279 30 mg orally administered QD in subjects with GPP or EP.

3.1.4 Exploratory Objectives

1. [redacted]
2. [redacted]

3.2 Endpoints

3.2.1 Coprimary Efficacy Endpoints

- Static Physician's Global Assessment (sPGA) 0/1 response: Assessed as proportion of subjects achieving an sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at Week 16
- PASI-75 response: Assessed as proportion of subjects achieving ≥75% improvement from baseline in PASI score at Week 16

3.2.2 Secondary Efficacy Endpoints

- sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at Weeks 52

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- Durable sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at both the Week 16 and Week 52 visitsEnhanced sPGA response: Proportion of subjects achieving an sPGA of clear (0) at Weeks 16 and 52
- Simplified sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) at Weeks 16 and 52
- Simplified durable sPGA 0/1 response: Proportion of subjects achieving an sPGA of clear (0) or almost clear (1) at both the Week 16 and Week 52
- PASI-75 response: Proportion of subjects achieving PASI-75 at Weeks 52
- PASI-90 response: Proportion of subjects achieving PASI-90 at Weeks 16 and 52
- PASI-100 response: Proportion of subjects achieving PASI-100 at Weeks 16 and 52
- Durable PASI-75 response: Proportion of subjects achieving PASI-75 at both the Week 16 and Week 52 visits
- Durable PASI-90 response: Proportion of subjects achieving PASI-90 at both the Week 16 and Week 52 visits
- Scalp-specific Physician's Global Assessment (ssPGA) response: Proportion of subjects achieving an ssPGA of absence of disease (0) or very mild disease (1) with a ≥2-point decrease from baseline at Weeks 16 and 52 (for subjects with a baseline ssPGA ≥3, baseline psoriasis scalp severity index (PSSI) ≥12, and scalp surface area (SSA) involvement ≥30%)
- Change from baseline in ssPGA at Weeks 16 and 52
- Proportion of subjects achieving a PGA of the hands and/or feet of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at Weeks 16 and 52 (for subjects with a baseline PGA of the hands and/or feet ≥3)
- Dermatology Life Quality Index (DLQI) response: Proportion of subjects with a DLQI score of 0/1 at Weeks 16 and 52 (for subjects with a baseline DLQI score ≥2)
- Change from baseline in DLQI at Weeks 16 and 52
- Change from baseline in Nail Psoriasis Severity Index (NAPSI) at Weeks 16 and 52, among subjects with nail involvement at baseline
- Change and percent change from baseline in BSA affected by psoriasis at Weeks 16 and 52

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3.2.3 Secondary Efficacy Endpoints for Generalized Pustular Psoriasis

- Generalized Pustular Psoriasis Global Assessment (GPPGA) Pustulation Subscore response: Proportion of subjects achieving a GPPGA Pustulation Subscore of no visible pustules (0) at Weeks 16 and 52
- GPPGA 0/1 response: Proportion of subjects achieving a GPPGA of clear (0) or almost clear (1) at Weeks 16 and 52
- Enhanced GPPGA response: Proportion of subjects achieving a GPPGA of clear (0) at Weeks 16 and 52
- Generalized Pustular Psoriasis Area and Severity Index (GPPASI)-75 response: Proportion of subjects achieving ≥75% improvement from baseline in GPPASI score at Weeks 16 and 52
- Change from baseline in JDA severity score at Weeks 16 and 52

3.2.4 Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Changes in clinical laboratory parameters, vital signs, and electrocardiogram (ECG)
- AESIs (see Section 8.3.8.7)

3.2.5 Exploratory Endpoints

- [redacted]
- [redacted]

3.3 Estimands

Not Applicable.

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4.0 STUDY DESIGN

4.1 Overall Design

This is a phase 3, open-label, multicenter study to evaluate the efficacy, safety, and tolerability of TAK-279 once daily (QD) for 52 weeks in Japanese subjects with GPP or EP.

Approximately 20 male and female subjects, aged 18 years and older, with GPP or EP will be enrolled in this study. To be eligible for the study, subjects must have a diagnosis of GPP or EP prior to the screening visit. In addition, subjects will need to have the following characteristics: For GPP, total JDA severity score <14 and BSA involvement ≥10% at screening and BSA involvement ≥10% on Day 1. For EP, a history of plaque-type of psoriasis and BSA involvement ≥80% at screening and on Day 1. For both populations, eligible for phototherapy or systemic therapy.

This study will consist of 3 parts, including a screening period of up to 35 days, a treatment period of up to 52 weeks, and a safety follow-up period of 4 weeks. Thus, the maximum study duration per subject is expected to be 61 weeks. Details are provided in Section 4.1.1, Section 4.1.2, and Section 4.1.3.

4.1.1 Screening Period

The screening period will be a maximum of 35 days and at least 1 day. Activities during screening will proceed according to the schedule of activities (SoA; Table 1.a). Consenting subjects will be screened for eligibility in a clinical setting before enrollment.

All subjects who sign an informed consent form (ICF) at screening and fulfill all of the inclusion criteria and none of the exclusion criteria (see Section 5.0) will be accepted into the study.

4.1.2 Treatment Period

Of the approximately 20 planned subjects, approximately 10 will be enrolled in each of the GPP and EP cohorts. The study will be conducted at approximately 20 sites located in Japan. All subjects who are eligible by screening will receive initiate treatment with TAK-279 30 mg orally QD on Day 1 up to Week 52. Subjects will attend a total of 16 scheduled study visits: Day 1, Weeks 1, 2, 4 and every 4 weeks thereafter through Week 52 (end of treatment [EOT]).

A MACE Adjudication Committee with representation including a cardiologist will be established to review certain cardiovascular AEs. See Section 10.1.5.1 and details will be in separate MACE Adjudication Committee related materials.

4.1.3 Follow-up Period

The treatment period will be followed by a 4-week safety follow-up period. Subjects will also attend a follow-up visit at Week 56/end of study (EOS), or at early termination (ET).

For a schematic of the study design, see Section 1.2. For the SoA, see Section 1.3.

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4.2 Scientific Rationale for Study Design

The proposed design of this phase 3 study is considered appropriate for confirming the efficacy, safety, and tolerability of TAK-279 in subjects with GPP or EP.

The severity of GPP and EP is severe, and the number of patients is extremely limited. Therefore, in consideration of the feasibility of conducting a clinical study in Japan, a study with a design of open-label and uncontrolled will be conducted to evaluate the efficacy and safety of TAK-279.

The treatment duration of 52 weeks is proposed to be sufficient to provide evidence supporting the long-term efficacy of TAK-279. The timing of the primary endpoint at Week 16 is consistent with that used in other major studies of systemic therapy in moderate-to-severe psoriasis, and consistent with the phase 2b primary endpoint timepoint of Week 12, at which a significant proportion of subjects on TAK-279 achieved PASI-75. The proposed coprimary endpoints for phase 3, PASI-75 and a sPGA of clear (0) or almost clear (1) with a ≥2-point decrease from baseline at Week 16, are standard measures in clinical studies for demonstrating efficacy of systemic psoriasis treatments in subjects with stable, chronic, moderate-to-severe psoriasis.

4.3 Justification for Dose

The dose of 30 mg QD was selected based on information from studies to date, including the efficacy and safety results from the phase 2b 4858-201 study in moderate-to-severe plaque psoriasis conducted by Nimbus Therapeutics. In that study, there was a dose-dependent response in the proportion of subjects achieving PASI response among dose cohorts, with similar percentages of patients achieving PASI-75 and PASI-90 at doses of 15 and 30 mg QD. Additionally, there was no evidence of a plateau in PASI-100 response (15.1% in the 15 mg dose group and 32.7% in the 30 mg dose group). [redacted] There were no dose-related safety signals identified in the study, including no significant difference in infection rates between the 15 and 30 mg doses (22.6% in the 15 mg dose cohort and 26.9% in the 30 mg dose cohort). Therefore, the 30 mg dose provides a favorable benefit/risk profile for patients with GPP or EP. The half-life ($t_{1/2}$) of TAK-279, ranged from 17.1 to 37.4 hours, supports QD dosing.

4.4 End of Study/Study Completion Definition

4.4.1 EOT

EOT is a subject-level time point that indicates the end of the subject's treatment in the study at ET or permanent discontinuation from study drug, or at Week 52.

4.4.2 EOS

EOS is a subject-level time point that occurs after a subject completes Week 56.

For subjects who are discontinued permanently from study drug and choose not to continue participation for any reason, EOS occurs after the ET visit followed by the 4-week safety follow

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up; if subjects are discontinued permanently from study drug but continue in the study, EOS will be the last visit completed or Week 56, whichever comes first.

Once EOS has been reached for all subjects, there will be a final database lock followed by a final analysis of all safety, PK, and efficacy data.

4.4.3 Study Completion

The study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the study, withdraws consent from overall study participation, is lost to follow-up (ie, the investigator is unable to contact the subject), or the sponsor ends the study, whichever occurs first.

5.0 STUDY POPULATION

The study population comprises adults with GPP or EP.

Informed consent must be obtained before any screening procedures, other than activities the Institutional Review Board (IRB) has specifically approved for use as prescreening procedures. Specifically, informed consent must be obtained before beginning test procedures outlined in the SoA (Table 1.a and Table 1.b). Informed consent requirements are described in Section 10.1.3.

All entry criteria, including test results, must be confirmed before enrollment. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Investigators must account for all individuals who sign ICFs, regardless of the outcome of the screening, by completing the required electronic case report forms (eCRFs).

Rescreening will be allowed under circumstances described in Section 5.4.

5.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria evaluated during the screening period or as specified below:

Subject Willingness:

1. Subject 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.
2. Subject has provided written informed consent and any required privacy authorization before the initiation of any study procedures.

Disease Characteristics:

For GPP

3. Subject has a diagnosis of GPP based on the diagnostic criteria of the JDA (Appendix 1) prior to the screening visit.
4. Subject has been on a stable treatment regimen for GPP for at least 2 weeks prior to Day 1.

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5. Subject has a total JDA severity score <14 at screening.
6. Subject has erythema with pustules covering ≥10% of his or her BSA at screening and Day 1.
7. Subject must be a candidate for phototherapy or systemic therapy.

For EP

8. Subject has a diagnosis of EP prior to the screening visit.
9. Subject has a history of plaque-type of psoriasis.
10. Subject has plaque psoriasis covering ≥80% of his or her BSA at screening and Day 1.
11. Subject must be a candidate for phototherapy or systemic therapy.

Age and Reproductive Status:

12. Subject is aged 18 years or older at the time of consent.
13. Subject meets the following birth control requirement:

    A surgically sterile female subject; or a female subject of nonchildbearing potential with laboratory confirmation of postmenopausal status (ie, follicle-stimulating hormone levels >40 mIU/mL); or, if sexually active with a nonsterilized individual who produces sperm, an individual with potential for pregnancy who agrees to use a highly effective method of contraception from the signing of informed consent throughout the duration of the study and for 10 days after the last dose.

5.2 Exclusion Criteria

A subject will be excluded from the study if any of the following exclusion criteria are met at screening or as specified below:

Target Disease-Related Exclusions:

1. Subject has evidence of predominantly guttate psoriasis, predominantly inverse, or drug-induced psoriasis.
2. Subject requires systemic treatment, other than nonsteroidal anti-inflammatory drugs or non-prohibited therapies, during the study period for an immune-related disease (eg, inflammatory bowel disease).
3. Subject has a history of excessive sun exposure, has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study period. Use of sunscreen products and protective apparel is recommended when sun exposure cannot be avoided.
4. Subject has concomitant comorbid skin condition that, in the opinion of the investigator, would interfere with the study assessments.

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Recent/Concurrent Infectious Disease Exclusions:

5. TB:
   a) Subject has history of active TB infection, regardless of treatment status.
   b) Subject has signs or symptoms of active TB (including but not limited to chronic fever, chronic productive cough, night sweats, or weight loss) as judged by the investigator.
   c) Subject has evidence of latent TB infection (LTBI) as evidenced by a positive T-SPOT result OR 2 indeterminate results and subject does not have documentation of appropriate LTBI prophylaxis or is not able or not willing to initiate appropriate LTBI prophylaxis. Subject remains eligible if there are no signs/symptoms of active TB AND documentation of no history of active TB can be provided AND (1) subject can provide documentation of prior and complete treatment for LTBI (appropriate in duration and type per current guidelines) or (2) subject has a positive T-SPOT result or 2 indeterminate T-SPOT results but has initiated prophylaxis (appropriate in duration and type per current guidelines) at least 3 weeks prior to Day 1.

      Note: TB prophylaxis regimens should be administered according to guidelines; however, because of potential interactions with TAK-279, rifampin should not be used. TB testing should be conducted using T-SPOT submitted to central laboratory or measured at local laboratories unless alternate or additional tests are required per guidelines.
   d) Subject has had any imaging study during or 6 months prior to screening, including x-ray, chest computed tomography, magnetic resonance imaging, or other chest imaging suggesting evidence of current active or a history of active TB. X-ray is required for all subjects regardless of T-SPOT results unless the subject has had normal chest imaging in the 6 months prior to screening.
6. Herpes infections:
   a) Subject has active herpes virus infection, including herpes zoster or herpes simplex 1 and 2 (demonstrated on physical examination and/or medical history) at screening or Day 1.
   b) Subject has history of serious herpetic infection that includes any episode of disseminated disease, multidermatomal herpes zoster, herpes encephalitis, ophthalmic herpes, or recurrent herpes zoster (defined as 2 episodes within 2 years).
7. Non-herpetic viral diseases:
   a) Subject has presence of hepatitis C virus (HCV) antibody and a positive confirmatory test result for HCV RNA (nucleic acid test or polymerase chain reaction).
   b) Subject has presence of positive hepatitis B surface antigen (HBsAg+), or indeterminant hepatitis B surface antigen, presence of hepatitis B virus DNA (regardless of serology), or positive anti-hepatitis B core antibody without concurrent positive hepatitis B surface

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antibody (HBcAb+ and HBsAb-). (Details for eligibility are provided in Appendix 2 as a table.)

c) Subject has positive results for HIV by serology, regardless of viral load.

8. Other infectious diseases:

a) Subject has a history of active infection or febrile illness within 7 days prior to Day 1, as assessed by the investigator.

b) Subject has history of symptoms suggestive of systemic or invasive infection within 30 days prior to Day 1.

c) Subject has history of bacterial, viral, or fungal infection that required hospitalization or treatment with intravenous antimicrobial therapy within 8 weeks prior to Day 1, or oral antimicrobial therapy within 30 days prior to Day 1.

d) Subject has a history of chronic or recurrent bacterial disease, including but not limited to chronic pyelonephritis or cystitis, chronic bronchitis/pneumonitis, osteomyelitis, or chronic skin ulcerations/infections or fungal infections (except superficial nailbed mycosis).

e) Subject has a history of an infected joint prosthesis unless that prosthesis has been removed or replaced at least 60 days prior to Day 1.

f) Subject has a history of opportunistic infections (eg, *Pneumocystis jirovecii* pneumonia, histoplasmosis, coccidiomycosis).

g) Subject had a bacterial infection within 60 days prior to Day 1 for which he or she did not receive treatment.

Noninfectious Disorders Exclusions:

9. Subject has any clinically significant medical condition, evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, or immunologic), or vital signs/physical/laboratory/ECG abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results. These include but are not limited to:

a) Subject has a history of known or suspected condition/illness that is consistent with compromised immunity, including but not limited to any identified congenital or acquired immunodeficiency; splenectomy.

b) Subject had a major surgery within 60 days prior to Day 1 or has a major surgery planned during the study.

c) Subject has unstable, poorly controlled, or severe hypertension at screening, confirmed by 2 repeat assessments.

d) Subject has a history of Class III or IV congestive heart failure as defined by New York Heart Association criteria.

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e) Subject has a history of cancer or lymphoproliferative disease with the exception of successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix.

f) For subjects with asthma, chronic obstructive pulmonary disease, or other pulmonary illnesses, subject has been hospitalized in the past 3 months, has ever required intubation for treatment, currently requires oral corticosteroids, or has required more than 1 course of oral corticosteroids within 6 months prior to Day 1.

g) Subject has any of the following cardiovascular disease history:

- A new diagnosis of atrial fibrillation or an episode of atrial fibrillation with rapid ventricular response or other dysrhythmia, non-acute cardiac hospitalization (eg, pacemaker implantation), pulmonary embolism, or deep venous thrombosis within the past 6 months prior to screening.
- Any history of cerebrovascular event, myocardial infarction, coronary stenting, or aorto-coronary bypass surgery. If, however, the investigator determines there are no suitable treatment alternatives available for the subject and it has been at least 6 months since the occurrence of any such event, the subject may enroll.

h) Subject has ECG abnormalities that are considered clinically significant and would pose an unacceptable risk to the subject if he or she participated in the study, in the opinion of the investigator.

i) Subject has significant/uncontrolled psychiatric illness, in the opinion of the investigator.

j) Subject has any lifetime history of suicidal ideation, suicidal behavior, or suicidal attempts by 1) medical history; or 2) by C-SSRS documentation or by answering "yes" to Question 5 for suicidal ideation on the C-SSRS at screening; or 3) is clinically deemed to have a suicide risk by the investigator.

k) Subject has a PHQ-8 score of 15 or above at screening.

l) Subject has a history of clinically significant drug or alcohol abuse within 12 months prior to Day 1.

<u>Prohibited Psoriasis Treatments Exclusions:</u>

For the below prohibited psoriasis treatments, the washout period prior to Day 1 is within the time frame indicated or 5 half-lives, whichever is longer.

10. Subject has received any of the following biologics or biosimilar versions within the time frame indicated:

a) Antibodies to IL-12/-23, IL-17, IL-23, or IL-36 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, guselkumab, risankizumab, or spesolimab) within 6 months prior to Day 1.

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b) TNF inhibitor(s) (eg, etanercept, adalimumab, infliximab, certolizumab) within 2 months prior to Day 1.

c) Agents that modulate integrin pathways to impact lymphocyte trafficking (eg, natalizumab) or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, or visilizumab) within 3 months prior to Day 1.

d) Rituximab or other immune cell-depleting therapy (eg, granulocyte and monocyte adsorptive apheresis) within 6 months prior to Day 1.

11. Subject has used medicated shampoo and/or body wash, including formulations containing but not limited to salicylic acid, corticosteroids, coal tar, vitamin D_3 analogues, or other compounds used for the management of psoriasis within 2 weeks prior to Day 1.

12. Subject has used any topical medication that could affect psoriasis presentation (including but not limited to corticosteroids, salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, retinoids, vitamin D analogues [such as calcipotriol], methoxsalen, trimethylpsoralen, calcineurin inhibitors [eg, tacrolimus], tapinarof, roflumilast, JAK inhibitors, or tar) within 2 weeks prior to Day 1.

    Note: Low-potency topical steroids (World Health Organization Class VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours before any study visit. Low-potency topical steroids may be used to treat acute non-psoriatic conditions (eg, contact dermatitis) on all body regions for no more than 2 weeks but should not be used within 24 hours before any study visit. Low-potency topical steroids co-formulated with other topicals that may affect the presentation of psoriasis are not permitted. Bland emollients (defined as emollients containing only ingredients that are pharmacologically inactive) are allowed on all body regions but should not be used within 24 hours before any study visit.

13. Subject has used any systemic nonbiologic treatment that could affect psoriasis presentation (including oral, intravenous, intramuscular, intra-articular, intrathecal, or intralesional corticosteroids; oral retinoids; immunosuppressive/immunomodulating medication; methotrexate; azathioprine; 6-thioguanidine; mercaptopurine; mycophenolate mofetil; hydroxyurea; cyclosporine; 1,25-dihydroxyvitamin D_3 analogues; psoralens; sulfasalazine; fumaric acid derivatives; JAK inhibitors [including deucravacitinib and upadacitinib]; apremilast) within 4 weeks prior to Day 1 or 5 half-lives, whichever is longer.

    Note: Intranasal corticosteroids, inhaled corticosteroids, and eye and ear drops containing corticosteroids are permitted. Use of prednisone or its equivalent at a daily dose ≤10 mg/day is permitted.
    For subjects with GPP, one of following agent is permitted under stable dose: methotrexate, or retinoids.
    For subjects with EP, concomitant use of methotrexate, or retinoids is permitted under stable dose until Week 2.

14. Subject has used leflunomide within 6 months prior to Day 1.

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15. Subject has received phototherapy (including ultraviolet B [UV-B], psoralen and ultraviolet A [PUVA], tanning beds, therapeutic sunbathing) or excimer laser within 4 weeks prior to Day 1.
16. Subject has used botanical preparations (eg, herbal supplements or traditional medicines, including traditional Chinese medicines derived from plants, minerals, or animals) intended to treat psoriasis or other immunological diseases within 4 weeks prior to Day 1.
17. Subject has any previous exposure to TAK-279 (also known as NDI-034858), or subject participated in any study that included a TYK2 inhibitor (eg, deucravacitinib, VTX958, GLPG3667, etc.), unless subject has documentation of post-trial unblinding that confirms the subject did not receive a TYK2 inhibitor.

Other Prohibited Concomitant Medications Exclusions:

For the below prohibited concomitant medications, where applicable, the washout period prior to Day 1 is within the time frame indicated or 5 half-lives, whichever is longer.

18. Subject has received lithium, antimalarials, or intramuscular gold therapy within 4 weeks prior to Day 1.
19. Subject is currently being treated with strong or moderate cytochrome P450 3A4 (CYP3A4) inhibitors (such as itraconazole) or strong or moderate CYP3A4 inducers (such as rifampin, carbamazepine, or phenytoin), or has received strong or moderate CYP3A4 inhibitors or strong or moderate CYP3A4 inducers within 4 weeks or 5 half-lives of the inducer or inhibitor, whichever is longer, prior to Day 1, or is anticipated to require treatment with strong or moderate CYP3A4 inducers or inhibitors during the study period (see Appendix 3).

    Note: This includes consumption of food or beverages containing grapefruit and/or Seville oranges within 1 week of Day 1. Subjects must be counseled to avoid food or beverages containing grapefruit and/or Seville oranges for the duration of the study.
20. Subject has received any live-attenuated vaccine within 60 days prior to Day 1 or plans to receive a live-attenuated vaccine during the study and up to 4 weeks after the last study drug administration.

    Note: Non–live-attenuated vaccines or boosters for coronavirus disease-2019 (COVID-19) or influenza are permitted during the study.
21. Subject received an investigational antibody or biologic therapy within 6 months prior to Day 1.
22. Subject is currently receiving a nonbiological study drug or device or has received one within 4 weeks prior to Day 1.
23. Subject is currently enrolled in a clinical study or anticipates enrollment in a clinical study during the course of the study.

Laboratory/Physical Exclusions:

24. Subject has any of the following laboratory values at the screening visit:

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a) AST or ALT values >3 times the ULN

b) Total bilirubin (unconjugated and/or conjugated) >1.5 times the ULN

c) Hemoglobin (Hgb) <9.0 g/dL (<90.0 g/L)

d) Absolute white blood cell count $<3.0 \times 10^9$/L ($<3000/mm^3$)

e) Absolute neutrophil count of $<1.0 \times 10^9$/L ($<1000/mm^3$)

f) Absolute lymphocyte count of $<0.5 \times 10^9$/L ($<500/mm^3$)

g) Platelet count $<100 \times 10^9$/L ($<100,000/mm^3$).

h) Thyroid-stimulating hormone (TSH) outside the normal reference range **AND** free thyroxine (T4) or triiodothyronine (T3) outside the normal reference range

i) Estimated creatinine clearance <45 mL/min based on the Cockcroft-Gault calculation.

j) CPK > ULN. CPK may be repeated once; if repeat value is CTCAE Grade 1 or lower (or ≤2.5 × ULN) and no higher than the initial value, subject remains eligible. Investigators should assess the subject for modulating factors including concomitant medications or vigorous exercise that may affect CPK levels.

25. Subject has any other significant laboratory abnormalities that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.
26. Subject does not tolerate venipuncture or inability to be venipunctured.

Allergies and Adverse Drug Reactions Exclusions:

27. Subject has history of significant drug allergy (such as anaphylaxis).
28. Subject has a known or suspected allergy to TAK-279 or any of its components (see Section 6.1).

Other Exclusions:

29. Subject has a positive pregnancy test result or plans to become pregnant during the study period, or subject is pregnant or lactating/nursing.
30. Subjects who have given greater than 500 mL of blood or plasma within 30 days of screening (during a clinical study or at a blood bank donation) or plans to donate blood during the course of the study.
31. Subject is compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness, or is committed to an institution by virtue of an order issued either by judicial or administrative authorities (ie, prison).
32. Subject is a study site employee, an immediate family member (eg, spouse, parent, child, sibling), or is in a dependent relationship with study site employee who is involved in the conduct of this study, or may consent under duress.

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5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Study treatment may be taken without regard to meals; however, subjects are required to fast for a minimum of 8 hours before visits on which fasting lipid samples will be drawn (Day 1 and Weeks 4, 16, 24, 52, and 56). Restrictions on the consumption of other products with known pharmacological effects are also described in Section 6.7.2.

5.3.2 Skin Care

General skin care measures (with above restrictions for topical treatments) that are standard for patients with GPP or EP are permitted. Subjects should avoid excessive sun exposure and avoid risks that are known to induce flare of psoriasis. Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

5.4 Screening

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

5.4.1 Screen Failures

An individual who has provided informed consent to participate in the study may be categorized as a screen failure for any of the following reasons:

- Screen Failure (Did Not Meet Eligibility Criteria)
- Adverse Event
- Lost to Follow-up
- Pregnancy
- Withdrawal by Subject
- Study Terminated by Sponsor
- Other (Specify)

Subjects are **not** considered screen failures if they were enrolled but not treated. See Section 7.2.

Information about screen failures should be collected, including subject identification (ID), screening disposition (including the reason for screen failure), demography, inclusion/exclusion criteria, and AEs (if applicable). If a potential subject experiences an SAE during screening, all of the subject's screening data must be available for collection.

Subject ID numbers assigned to subjects who do not meet eligibility criteria should not be reused.

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5.4.2 Rescreening

An individual who has been designated a screen failure may be rescreened once. Additional proposed rescreening requires discussion with the medical monitor. Subjects cannot be rescreened once it is confirmed that they do not meet eligibility criteria unless the screen failure was due to a temporary condition (eg, recent upper respiratory infection, poorly controlled blood pressure with subsequent medication adjustment) or incomplete information at the time of eligibility confirmation that would make rescreening appropriate at a later date. All reasons for rescreening must be discussed and approved prospectively with the medical monitor.

All procedures included in the screening visit, including signature of a new ICF, should be performed. TB testing, chest x-ray, hepatitis panels, and HIV testing do not need to be repeated if rescreening is within the last 3 months of initial screening and there have been no pertinent changes to the subject's medical history or risk assessment. Subjects will receive a new screening ID upon rescreening.

5.5 Criteria for Temporarily Delaying <Enrollment/Randomization/Administration of Study Intervention>

Not Applicable.

5.6 Enrollment

A subject is defined as enrolled when all of the following have occurred:

- the subject has provided informed consent (that is, in writing, documented via a signed and dated ICF)
- the subject has completed screening, having satisfied all entry criteria.

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6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Intervention(s) Administered

This study intervention refers to the investigational product that is intended to be administered to a subject according to the study protocol. Study drug will be provided by the sponsor.

In this study, the intervention is:

- Study drug: TAK-279 tablet

Regarding the dosage form description and strengths, or composition for the extemporaneous preparation of the study drug administered in this study is presented in Table 6.a.

Table 6.a Study Intervention Administered: Drug

Intervention Label	TAK-279
Intervention Name	TAK-279
Former Name(s) or Alias(es)	NDI-034858
Intervention Description	Details provided in the IB. Excipients are as follows: Hypromellose acetate succinate, microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate and Opadry QX.
Type	Drug
Dose Formulation	White to offwhite oval shaped Tablet
Unit Dose Strength(s)	30 mg
Dosage Level(s)	30 mg QD
Route of Administration	Oral
Use	Experimental
Classification	Drugs
Authorization Status	Not Authorized in Any Region
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in HDPE bottle.
Storage conditions	15°C to 25°C (59°F-77°F)

The study drugs will be administered orally for 52 weeks as described in Table 6.b in accordance with the schedule. On study visit days, the study drug will be administered at the study site after completion of all tests scheduled for the visit. The date and time of each study drug administration will be collected by the study site (during the visit). On the Week 52 visit, no study drug will be administered.

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Table 6.b Study Cohorts

Cohorts	Study treatments
Generalized Pustular Psoriasis	TAK-279 tablet 30 mg QD p.o. (up to Week 52)
Erythrodermic Psoriasis	TAK-279 tablet 30 mg QD p.o. (up to Week 52)

QD: once daily, p.o.: oral
The study drug should be taken with approximately 240 mL of water.

6.2 Preparation, Handling, Storage, and Accountability

6.2.1 Accountability Throughout the Study

The investigator or designee must ensure that the sponsor-supplied study drug is used in accordance with the protocol and is only dispensed to subjects enrolled in the study.

To document appropriate use of sponsor-supplied study drug (Section 6.1), the investigator or designee must maintain 100% accountability for all sponsor-supplied study interventions that the site receives and dispenses during his or her entire participation in the study.

Proper drug accountability includes, but is not limited to:

- The investigator or designee must maintain records of all sponsor-supplied study interventions delivery to the site, current site inventory, dispensing for use by each subject, and return to the sponsor or designee.
- The investigator or designee must record this inventory on a sponsor-approved drug accountability log.
- Based on entries in the log, it must be possible to reconcile study products delivered with those used and returned.
- All study drugs must be accounted for, and all discrepancies investigated and documented to the sponsor's satisfaction.
- All study interventions not returned to the site by a subject must be investigated by the site and appropriately documented on the log.
- If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Further guidance and information for handling and storage of study drug is provided in the corresponding pharmacy manual.

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6.2.2 Receiving Product at the Site

Investigators will be provided with sufficient quantity of study drug to carry out this protocol for the agreed number of subjects.

On receipt of sponsor-supplied study drugs, 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. This will include an examination of temperature-monitoring devices.

The investigator or designee will confirm receipt of the study drugs and document the contents and condition of the shipment. If there are any discrepancies between the packing list and the actual product received, the sponsor must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

6.2.3 Handling and Storage at the Site

The investigator bears the overall responsibility for ensuring that the study drugs are stored in an appropriate location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

An appropriate storage location is one that is secure, with access that is limited to the investigator and authorized site staff, and that is environmentally controlled (manually or automated) in accordance with labeled storage requirements.

Study drug must remain in the original container until dispensed.

The investigator is responsible for ensuring that the study intervention is maintained according to the requirements described in Table 6.a.

The investigator is responsible for ensuring that the study drug is maintained within an established temperature range, that the temperature is monitored throughout the duration of the study, and that records are maintained.

A daily temperature log of the drug storage area must be maintained every working day. The required storage condition for all study drugs is between 15°C to 25°C (59°F-77°F). The temperature should be monitored continuously by a datalogger or a similar device.

The sponsor must be notified immediately on discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the study intervention and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

Study drugs must be kept in these conditions until they are used or returned to the sponsor for destruction. Further instructions will be provided in the pharmacy manual.

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The sponsor should be notified immediately if there are any changes to the storage area of the study intervention that could affect the integrity of the product(s), (eg, fumigation of a storage room).

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

6.2.4 Labeling

Changes to sponsor-supplied packaging, including the addition of labels prior to dosing, may not be made without full agreement in advance by the sponsor. Such additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the study intervention to satisfy Japan or institutional requirements, but *must not*:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

6.2.5 Preparation

Not applicable.

6.2.6 Dispensing/Administration

The investigator has overall responsibility for dispensing the study drug.

Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or their designee will administer the study intervention only to subjects enrolled in this study, and following the procedures set out in the study protocol. Each subject will be given only the study intervention carrying their treatment assignment.

6.2.7 Destruction or Return

The investigator is responsible for ensuring that all study supplies are retrieved from subjects.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied product accountability and reconciliation before sponsor-supplied products are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied study interventions' accountability, and destruction. Originals will be sent to the sponsor or designee.

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The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

Further instructions regarding the final disposition of unused study drugs will be provided in the pharmacy manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

This is not a randomized study; therefore, no randomization schedule will be generated.

6.3.2 Blinding the Treatment Assignment

Not applicable.

6.3.3 Unblinding

Not Applicable.

6.4 Study Intervention Compliance

Study treatment compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning, review of the subject's bottles, and by maintaining adequate study drug dispensing and return records.

Subjects who are significantly noncompliant with treatment will be counseled and could be discontinued from the study, at the discretion of the investigator, following consultation with the sponsor. A subject is considered significantly noncompliant if treatment has been interrupted for ≥14 days consecutively prior to Week 24 and for ≥21 days consecutively thereafter. A subject will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of study drug in the same time frame, as judged by the investigator.

6.5 Continued Access to Study Intervention After the End of the Study

No continued access is planned for this study.

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

6.6 Treatment of Overdose

In this study, an overdose is defined as a known deliberate or accidental administration of the study intervention, either to or by a study subject, at a dose above that assigned to that individual subject.

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

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In addition, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the subject to determine, in consultation with the medical monitor, whether study intervention should be interrupted.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.

All cases of overdose must be documented, including the quantity of the excess dose. Although overdose cases are not per se AEs, they should be reported, regardless of whether the subject manifested any signs or symptoms (considered AEs). If there are signs and symptoms meeting the criteria for reporting as AEs or SAEs, they should also be reported, as described in Section 10.3.4.

6.7 Prior and Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products, and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded in the subject's source and study electronic data capture (EDC) system. In addition, the last use of any prohibited medications before Day 1 must be recorded within the time frames described in the exclusion criteria. Additionally, the subject's lifetime GPP/EP medication history will be collected at screening.

6.7.1 Rescue Medicine

The use of rescue medications is not allowed at any time during the study.

6.7.2 Excluded Procedures and Treatments

The prohibited medications listed in Table 6.c are not to be used from the defined washout periods before the first administration of study treatment at the Day 1 visit through the last study visit. Subjects who start prohibited medications (systemic or topical) or therapies during the study may be discontinued from study treatment. For the prohibited therapies in Table 6.c, where applicable, the washout period prior to Day 1 is within the time frame indicated or 5 half-lives, whichever is longer. Investigators are responsible for ensuring adequate washout based on the label half-life.

Investigators should contact the medical monitor as soon as possible when any prohibited medication or therapy is initiated, to discuss the appropriate steps.

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Table 6.c Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
TAK-279/NDI-034858	Lifetime
Antibodies to IL-12/-23, IL-17, IL-23, or IL-36 (eg, ustekinumab, secukinumab, tildrakizumab, ixekizumab, guselkumab, risankizumab, spesolimab or biosimilar versions)	6 months
Rituximab or other immune cell-depleting agents	6 months
Agents that modulate integrin pathways to impact lymphocyte trafficking (eg, natalizumab), or agents that modulate B cells or T cells (eg, alemtuzumab, abatacept, or visilizumab)	3 months
An investigational antibody or biologic therapy	6 months
TNF inhibitor(s) (eg, etanercept, adalimumab, infliximab, certolizumab, or biosimilar versions)	2 months
Nonbiological study drug or device	4 weeks
Any live-attenuated vaccine Note: Non–live-attenuated vaccines or boosters for COVID-19 and influenza are permitted during the study.	60 days
Systemic nonbiologic treatment that could affect psoriasis (including oral, intravenous, intramuscular, intra-articular, intrathecal, or intralesional corticosteroids; oral retinoids; immunosuppressive/immunomodulating medication; methotrexate; azathioprine; 6-thioguanidine; mercaptopurine; mycophenolate mofetil; hydroxyurea; cyclosporine; 1,25-dihydroxyvitamin D_3 analogues; psoralens; sulfasalazine; fumaric acid derivatives; JAK inhibitors [including deucravacitinib and upadacitinib]; apremilast) Note: Intranasal corticosteroids, inhaled corticosteroids, and eye and ear drops containing corticosteroids are also permitted.	4 weeks
Leflunomide	6 months
Strong or moderate CYP3A4 inhibitors (such as itraconazole) or strong or moderate CYP3A4 inducers (such as rifampin, carbamazepine, or phenytoin); see Appendix 3 for a list of prohibited medications in these classes. Note: Subject is currently being treated with or is anticipated to require treatment with strong or moderate CYP3A4 inducers or inhibitors during the study period will be excluded.	4 weeks or 5 half-lives (whichever is longer)
Lithium, antimalarials, or intramuscular gold therapy	4 weeks
Phototherapy (including UV-B, PUVA, tanning beds, therapeutic sunbathing) or excimer laser	4 weeks
Shampoo and/or body wash that contains salicylic acid, corticosteroids, coal tar, vitamin D_3 analogues, or other compounds.	2 weeks
Topical medication that could affect psoriasis (including but not limited to corticosteroids, salicylic acid, urea, alpha- or beta-hydroxy acids, anthralin, retinoids, vitamin D analogues [such as calcipotriol] , methoxsalen, trimethylpsoralen, calcineurin inhibitors [tacrolimus], tapinarof, roflumilast, JAK inhibitors, or tar)	2 weeks
Food or beverage containing grapefruit and/or Seville oranges. Note: Subjects must be counseled to avoid food or beverages containing grapefruit and/or Seville oranges for the duration of the study	1 week

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Table 6.c Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Botanical preparations (eg, herbal supplements or traditional medicines, including traditional Chinese medicines derived from plants, minerals, or animals) intended to treat psoriasis or other immunological diseases	4 weeks

COVID-19: coronavirus disease 2019; CYP3A4: cytochrome P450 3A4; IL: interleukin; JAK: Janus kinase; PUVA: psoralen-ultraviolet-A; TNF: tumor necrosis factor; TYK: tyrosine kinase; UV: ultraviolet.

6.7.3 Permitted Concomitant Medications and Procedures

6.7.3.1 *Emollients*

Subjects can apply a bland (defined as emollients containing only ingredients that are pharmacologically inactive) emollient of their choice on their skin, including on psoriasis lesions. However, subjects must not apply emollient within 24 hours before any study visit.

Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different). The commercial name of the selected emollient(s) will be recorded. No other products may be applied to psoriasis lesions during the study except as defined in Section 6.7.3.2.

6.7.3.2 *Other Permitted Therapies*

The following therapies are permitted:

- Intranasal corticosteroids, inhaled corticosteroids, and eye and ear drops containing corticosteroids are permitted.
- Use of prednisone or its equivalent at a daily dose ≤10 mg/day is permitted.
- For subjects with GPP, one of following agent is permitted under stable dose: methotrexate, or retinoids.
- For subjects with EP, concomitant use of methotrexate, or retinoids is permitted under stable dose until Week 2.
- Low-potency topical steroids (World Health Organization Class VI and VII) are permitted on the palms, soles, face, and intertriginous areas but should not be used within 24 hours before any study visit. Low-potency topical steroids may be used to treat acute non-psoriatic conditions (eg, contact dermatitis) on all body regions for no more than 2 weeks but should not be used within 24 hours before any study visit. No rescue medications are permitted during the course of the study.

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- Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided. However, on the day of scheduled visits, subjects must not apply sunscreen products before their scheduled visit time.
- Non–live-attenuated vaccines or boosters for COVID-19 and influenza are permitted during the study.
- The use of a stable dose of chronic medication not otherwise excluded per Section 6.7.2 is permitted, provided the subject received the dose at least 4 weeks prior to Day 1 and is planning to maintain throughout the study.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

This section describes the circumstances under which individual subjects would withdraw or be discontinued from the study intervention or from the study itself.

Section 10.1.12 describes circumstances in which specific sites or the study itself would be discontinued.

7.1 Discontinuation of Study Drug

In rare instances, it may be necessary for a subject to permanently discontinue study drug. If the study drug is permanently discontinued, the subject should remain in the study to be evaluated for safety follow-up. Data to be collected at the time of discontinuation of study intervention (EOT/ET visit) and at safety follow-up (EOS) visit are listed in the SoA (Section 1.3).

NOTE: Subjects who do not qualify for the study (screen failures) are not considered to have discontinued; instead see Section 5.4.1.

Potential circumstances for which a subject may permanently discontinue study drug include:

- **AE**. The subject has experienced an AE that may require discontinuation of study drug or ET if continued intervention or participation impose an unacceptable risk to the subject's health, in the opinion of the investigator, or the subject is unwilling to continue because of the AE.
- **Death.**
- **Protocol deviation**. The discovery after enrollment 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.
- **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.

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- **Withdrawal by subject.** The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (eg, 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. In such cases, please refer to further guidance regarding subject withdrawal in Section 7.2.

- **Study terminated by sponsor.**
- **Pregnancy.** The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must discontinue study drug immediately, but continue to be followed (see Section 10.4.3).

- **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.

7.1.1 Temporary Interruption of Study Drug

Study treatment should be interrupted if the following events occur. All such events should be discussed with the medical monitor.

- First serious infection requiring systemic therapy. Study drug may be reinitiated upon approval of medical monitor and sponsor.
  Note: a second serious instance of serious infection or a first opportunistic infection requires permanent discontinuation; see Section 7.1.2.
- CPK elevation of Grade >3 or higher.

Study procedures should be continued to be evaluated for safety, PK, and other parameters even in the event of temporary dosing interruption. The medical monitor should be contacted for consultation, including whether it may be appropriate to exclude any of the planned procedures. In the event a decision is made to permanently discontinue dosing, attempts should be made to continue to follow the subject for the full duration of the study. If a decision is made to permanently discontinue a subject from the study, please refer to the data to be collected at the ET visit of the SoA.

7.1.2 Permanent Discontinuation of Study Drug

Study treatment must be discontinued if the following events occur. All such events must be discussed with the medical monitor:

- If during the study the investigator and/or sponsor deem that continued participation in the study poses unacceptable risk to the subject.
- If during the study a subject has unstable cardiovascular disease, defined as a clinical cardiovascular event (including but not limited to acute coronary syndrome, cerebrovascular event, myocardial infarction, deep vein thrombosis, or pulmonary embolism) or a cardiac

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hospitalization (coronary stenting or aorto-coronary bypass surgery), the study drug must be discontinued.

- If during the study a subject has 2 occurrences of serious infection or 1 occurrence of opportunistic infection.
- If during the study a subject develops any malignancy including localized nonmelanoma skin cancer (NMSC) or carcinoma in situ of the cervix, the study drug will be discontinued. However, if the investigator determines there are no suitable treatment alternatives available for the subject who develops a localized NMSC or carcinoma in situ of the cervix, and the investigator has carefully evaluated and documented the benefit-risk assessment of the subject's continuation, the subject may be permitted to continue after discussion with and approval by the medical monitor.
- If during the study a subject has a confirmed case of rhabdomyolysis.
- If during the study a subject has abnormal liver-associated test results, then the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. Suggested hepatic investigations are listed in Table 10.f and criteria for considering discontinuation of study drug are shown in Figure 10.b.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject with the medical monitor when possible.

7.2.1 Discontinuation of Study Drug and Discontinuation of Study (Withdrawal of Informed Consent)

All attempts should be made to determine the date of the last dose and the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (eg, 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).

At the time of discontinuing from the study, if possible, an ET visit should be conducted, as shown in the SoA (Section 1.3), as soon as possible, preferably within 2 weeks after the last dose of the study drug. The primary criterion for termination must be recorded by the investigator. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Subjects who withdraw from the study will not be replaced.

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7.2.2 Discontinuation of Study Drug and Continuation of Study

During the study, subjects who terminate study drug treatment early but choose not to withdraw their consent are encouraged to continue to complete the study. Subjects should complete an ET visit as soon as possible, preferably within 2 weeks after the last dose of the study drug, at which time any remaining study drug should be collected. If subject cannot visit the site within 2 weeks, subjects should follow regular visit schedules and adhere to study procedures except for PK collection; additionally, study drug will not be dispensed at subsequent visits. In this regard, the scheduled visit at which subjects visit the site will be handled as the ET visit.

Subjects who discontinue study drug will not be replaced.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the study with a primary reason of "lost to follow-up."

8.0 STUDY ASSESSMENTS AND PROCEDURES

Written informed consent must be obtained (signed and dated) before study assessments and procedures can be performed, as described in Section 10.1.3.

The following sections describe the study procedures and data to be collected at planned time points per the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the samples. Whenever possible, the same person should perform each assessment.

Digital technologies in use as part of this study include electronic clinical outcome assessments (eCOAs).

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As part of the study procedures:

- All tools and technologies that study sites and subjects will use, and procedures for completing these assessments, will be detailed and training provided.
- Usage instructions and support will be provided including access to a help desk for questions.

Detailed logistical, operational, or site/subject procedures will be described in separate study manuals.

8.1 Demographics, Medical History, and Medication History

8.1.1 Demographics

Qualified site personnel will collect subject demographic information prior to the subject receiving the first dose of study intervention, which will include:

- Age/date of birth at the time of informed consent
- Sex
- Race, ethnicity (where permitted or required).
- Height, weight, alcohol use, and smoking status of the subject at screening.

  Note: as permitted by site-specific guidelines or regulations.

8.1.2 Medical History

Medical history, including concurrent medical conditions, will be collected.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or before the subject signed the ICF. Ongoing conditions are considered concurrent medical conditions.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, ECG, physical examination, and/or vital signs abnormalities noted at baseline, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

Any significant conditions or diseases relevant to the proposed indication include disease name, treatment name.

8.1.2.1 *Medical Records*

For a subject to be considered eligible for study participation, medical history must be collected. Every attempt should be made to obtain the subject's medical records. In doing so, if medical records are obtained from other institutions, the site/center must obtain consent from the subject. After consent is obtained, the site/center will be responsible in parallel with the subject for records to be sent to the site. Sites should make every attempt to obtain and review the subject's

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medical records. If the site cannot obtain medical records for any reason, subject-reported history is acceptable. Once the records and/or history are obtained, the investigator along with study staff will review the subject's history within the screening period to determine eligibility for randomization into the study.

8.1.3 History of psoriasis Arthritis and Active psoriasis

At the time of screening, history of PsA will be documented.

Additionally, at Day 1, investigators will assess whether the subject has active scalp psoriasis, active nail psoriasis, and/or active hand/foot psoriasis. Only subjects with active scalp psoriasis at Day 1 will subsequently be administered the ssPGA and PSSI at Day 1 and ssPGA subsequently per SoA. Only subjects with active nail psoriasis at Day 1 will be administered NAPSI at Day 1 and subsequently per the SoA. Only subjects with active hand/foot psoriasis at Day 1 will be administered the PGA of the hands/feet at Day 1 and subsequently per SoA.

Note: subjects with a history of these conditions but without the presence of active lesions will NOT be administered these assessments.

8.1.4 Prior and Concomitant Treatments/Medications

Prior and concomitant treatments and medications will be collected and recorded in the subject's source document.

Such treatments/medications include, but are not limited to:

- medications or vaccines
- over-the-counter or prescription medicines
- recreational drugs
- vitamins
- herbal supplements
- medications relevant to the eligibility criteria
- other specific categories of interest

Concomitant medications/treatments are defined as those given in addition to the study intervention between the signing of the ICF and subject completion.

Concomitant medications may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.2 Efficacy Assessments

The planned time points for all efficacy assessments are provided in the SoA (Table 1.a).

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8.2.1 Clinician-Reported Outcome Assessments

Clinical evaluations of GPP and EP will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. Identified site personnel will be appropriately qualified based on agreed-upon requirements and fully trained/certified prior to administration of the clinician reported outcome assessments. Details will be described in separate study manuals. To ensure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

8.2.1.1 *Psoriasis Area and Severity Index (PASI)*

PASI scores will be evaluated at the visits specified in Table 1.a. This index quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of BSA affected (Fredriksson and Pettersson 1978). The PASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration, and desquamation/scaling (each scored from 0 to 4 separately) for each of 4 body regions, with adjustments for the percentage of BSA (using BSA multiplier) involved for each body region and for the proportion of the body region to the whole body. Refer to Appendix 4 for a complete description of this scale.

8.2.1.2 *Static Physician's Global Assessment (sPGA)*

The sPGA of disease severity will be assessed at the visits specified in Table 1.a. The sPGA is a 5-point scale of an average assessment of the current state of the disease based on erythema, scaling, and induration. Lesions will be graded separately for erythema, induration, and scaling and the average score, rounded to the nearest whole number, will be the final sPGA score. A detailed description of sPGA scores is provided in Appendix 5.

8.2.1.3 *Body Surface Area (BSA)*

The overall BSA affected by plaque psoriasis will be evaluated (from 0% to 100%) at the visits specified in Table 1.a. The palmar surface of 1 hand (using the subject's hand and including the palm and fingers) represents 1% of his or her total BSA (Thomas and Finlay 2007). A detailed description of BSA scores is provided in Appendix 6.

8.2.1.4 *Scalp-Specific Physician's Global Assessment (ssPGA)*

The ssPGA will be evaluated at the visits specified in Table 1.a only for subjects with active scalp psoriasis at Day 1. Scalp lesions will be evaluated in terms of clinical signs of erythema, induration, and scale and scored on 5-point ssPGA scale as detailed in Appendix 7 (Foley et al. 2018).

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8.2.1.5 *Psoriasis Scalp Severity Index (PSSI)*

The PSSI is a clinician-reported outcome that measures the extent (% Scalp Surface Area affected) and severity of scalp psoriasis by assessing the following clinical symptoms: erythema, induration, and desquamation (scaling). The extent of the scalp affected by psoriasis is measured using a 6-point scale ranging from 1 to 6 where 1 = <10%, 2 = 10% to 29%, 3 = 30% to 49%, 4 = 50% to 69%, 5 = 70% to 89%, and 6 = 90% to 100%. Severity of each of the scalp psoriasis clinical symptoms is measured using a 5-point Likert scale ranging from 0 (absent) to 4 (severest possible). The total score (0 to 72) is a based on the sum of the severity (clinical symptoms) scores multiplied by the extent (scalp surface area) score. Higher scores will indicate greater psoriatic disease severity (Thaçi et al. 2001). For pertinent endpoints, scalp surface area (SSA) involvement will be derived from the PSSI. A description of the PSSI is provided in Appendix 8.

8.2.1.6 *Generalized Pustular Psoriasis Global Assessment (GPPGA)*

The GPPGA will be evaluated at the visits specified in Table 1.a. GPPGA is common endpoints in clinical studies of GPP, and is skin-based scoring systems. The GPPGA is a clinician assessment of overall GPP severity based on a modified PGA, and the severity of pustules, erythema, and scaling of GPP lesions are assessed. The five grades of severity for erythema, scaling, and pustulation correspond to 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. The GPPGA score is based on averaging the individual scores for erythema, scaling, and pustulation (Burden et al. 2022; Reich et al. 2022). A detailed description of GPPGA scores is provided in Appendix 9.

8.2.1.7 *Generalized Pustular Psoriasis Area and Severity Index (GPPASI)*

The GPPASI will be evaluated at the visits specified in Table 1.a. GPPASI is common endpoints in clinical studies of GPP, and is skin-based scoring systems. GPPASI is a modified composite index and an adaptation of the PASI score. The induration component has been substituted with a pustule component, with an overall score range from 0 (least severe) to 72 (most severe). The five grades of severity for erythema, scaling, and pustulation correspond to 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe. The score for each body region is calculated (the product of the sum of severity scores and its corresponding BSA score for erythema, scaling, and pustulation, multiplied by a weighting factor for each body region) and then the total GPPASI score determined (the sum of the individual scores from all body regions (Burden et al. 2022; Reich et al. 2022). A detailed description of GPPASI scores is provided in Appendix 10.

8.2.1.8 *JDA severity score*

The JDA severity will be evaluated at the visits specified in Table 1.a. The Japanese Dermatological Association severity index (JDASI) assesses the systemic symptoms by laboratory changes. With the JDASI the skin is evaluated using three criteria (1) erythema area (overall), (2) erythema area with pustules and (3) oedema area. Scoring ranges from 3 to 0 (severe, moderate, mild, none) with a maximum of nine points. For systemic involvement pyrexia, white blood cell count, C reactive protein (CRP) and serum albumin with scores ranging from 2 to 0 (maximum 8 points) are assessed. The total JDASI score of GPP is the sum of both

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categories and categorizes as severe (17–11 points), moderate (10–7 points) or mild (0–6 points) (Reich et al. 2022). A detailed description of JDA severity scores is provided in Appendix 11.

8.2.1.9 *PGA of Hands and/or Feet*

The PGA of hands and/or feet will be evaluated at the visits specified in Table 1.a only for subjects with hands and/or feet psoriasis involvement at Day 1. This is a 5-point scale and a score of 0 to 4 should be assigned, based on the category that best describes the severity of active psoriasis of the subject's hands and feet (Foley et al. 2018). A detailed description of the PGA of hands and feet scores is provided in Appendix 12.

8.2.1.10 *Nail Psoriasis Severity Index (NAPSI)*

The NAPSI will be evaluated at the visits specified in Table 1.a only for subjects with nail psoriasis at Day 1. The NAPSI is a grading system for nail psoriasis that includes extent of involvement and location in the nail unit of the psoriatic pathologic changes. The nail is divided with imaginary horizontal and longitudinal lines into quadrants. Each quadrant of the nail is evaluated for the presence or absence of nail matrix disease (pitting, leukonychia, red spots in lunula, nail plate crumbling) and for nail bed disease (oil drop [salmon patch] discoloration, onycholysis, nail bed hyperkeratosis, and splinter hemorrhage). Each nail is given a score for nail bed psoriasis (0-4) and nail matrix psoriasis (0-4) depending on the presence of any of the features of nail psoriasis in that quadrant. The sum of the scores for all of the fingernails is the nail psoriasis severity score for that subject at that time. The sum of the scores from all fingernails is 0-80 (Rich and Scher 2003). Refer to Appendix 13 for a complete description of the NAPSI.

8.2.2 Patient-Reported Outcomes (PRO)

Subjects will complete Patient-Reported Outcomes (PRO) assessments, on the site electronic device on site visit days.

PHQ-8 safety-related PRO assessment is described in Section 8.3.7, respectively.

8.2.2.1 *Dermatology Life Quality Index Questionnaire (DLQI)*

The DLQI is a subject-administered, 10-question validated QoL questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include 0 (not at all), 1 (a little), 2 (a lot), and 3 (very much) and unanswered ("not relevant") responses were scored as "0". Total scores range from 0 to 30, with higher score indicating greater quality of life is impairment. The questionnaire is provided in Appendix 16.

8.3 Safety Assessments

Safety will be assessed by monitoring for the following:

- TEAEs.

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- Physical examinations (general and targeted).
- Vital signs (body temperature, blood pressure, and pulse).
- ECG parameters.
- Clinical laboratory parameters.
- Assessing C-SSRS Appendix 14 and Appendix 15) and PHQ-8 (Appendix 17).
- AESIs (see Section 8.3.8.7).

Planned time points for all safety assessments are provided in the SoA (Table 1.a).

8.3.1 Physical Examinations

8.3.1.1 *Complete physical examination*

The following sites/systems at the least will be included in the physical examination, which will be performed at the visits specified in Table 1.a and include the following body systems:

- General appearance
- Dermatological (except plaque psoriasis)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Investigators should pay special attention to clinical signs related to previous serious illnesses.

All subsequent physical examinations should assess clinically significant changes from the baseline physical examination.

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation.

8.3.1.2 *Targeted physical examination*

The following sites/systems will at least be included in the targeted physical examination that will be performed at the visits specified in Table 1.a:

- General appearance

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- Dermatological (except plaque psoriasis)
- Respiratory
- Cardiovascular
- Abdominal

If deemed appropriate by the investigator based on the subject's condition, a complete physical examination as described in Section 8.3.1 can be performed instead of a targeted examination.

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation.

8.3.2 Vital Signs

Vital signs will be collected at the visits specified in Table 1.a and will include:

- Body temperature (oral measurement).
- Respiratory rate.
- Sitting blood pressure (systolic and diastolic, resting more than 5 minutes).
- Pulse (bpm),

Blood pressure and pulse measurements will be assessed in sitting position, after 5 minutes rest in a quiet setting without distractions (eg, television, cell phones) with a completely automated device. Blood pressure should be determined by cuff (using the same method, the same cohort, and the same position throughout the study). Manual techniques will be used only if an automated device is not available. One reading of blood pressure and pulse will be taken at the scheduled time points.

The investigator will record the vital sign results, and assess whether a change in vital signs from baseline may be deemed clinically significant and whether the change should be considered and recorded as an AE.

8.3.2.1 *Weight and Height*

Weight and height will be measured and recorded at the visits specified in Table 1.a. Height will only be recorded at the screening visit.

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

8.3.3 Electrocardiograms

A single, standard 12-lead ECG will be performed locally as a safety assessment at the visits specified in Table 1.a. All ECGs will be performed with the subject in the supine or semisupine

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position and after resting comfortably for at least 5 minutes. The time that the ECG was collected will be recorded. A copy of the ECG tracing should be kept in the subject's records.

Clinically significant findings in the ECG may exclude a subject from study participation at the investigator's discretion.

8.3.4 Clinical Safety Laboratory Tests

All protocol-required laboratory tests, as defined in Table 8.a, must be conducted in accordance with the laboratory manual and the SoA (Table 1.a). Details about these procedures and required safety monitoring will be given in the laboratory manual.

The maximum volume of blood at any single visit and the approximate total volume of blood for the study subject will be provided in laboratory manual/ICF.

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Table 8.a Clinical Laboratory Tests

Laboratory testing	Tests included
Hematology	aPTT, HCT, Hgb, INR, MCH, MCHC, MCV, MPV, PLT, PT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Chemistry	Albumin, alkaline phosphatase, ALT, AST, calcium, CPK, creatinine (enzymatic), GGT, glucose random, potassium, sodium, total bilirubin, direct bilirubin if total bilirubin >ULN, urea (BUN), uric acid
Urinalysis	Color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen Quantitative analysis of albumin and creatinine as well as albumin:creatinine ratio Microscopic analysis (as required)
Fasting lipids	Cholesterol (total, LDL, and HDL), triglycerides (all fasting)
Others	
Hepatitis B (test once per month for the first 6 months and every 3 months thereafter)	HBV [HBsAg, anti-HBc, anti-HBs, hepatitis B virus DNA] (for subjects of the #3 and #5 types in Appendix 2 after initiation of study drug)
CRP	
Other screening tests	HCV [with reflex to HCV RNA if positive] HIV FSH levels (for female subjects only) Serum pregnancy test (β-hCG) at screening or urine dipstick test at subsequent visits for subjects of childbearing potential Tuberculosis test (T-SPOT) Note: If required per guidelines, additional TB testing can be performed by local laboratory. TSH and reflex free T4 and T3 Calculated creatinine clearance

ALT: alanine aminotransferase; anti-HBc: antibody to hepatitis B core antigen; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; β-hCG: β-human chorionic gonadotropin; BUN: blood urea nitrogen; CPK: creatine phosphokinase; CRP: C reactive protein; FSH: follicle-stimulating hormone; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigens; HBV: hepatitis B virus; HCT: hematocrit; HCV: hepatitis C virus; HDL: high density lipoprotein; Hgb: hemoglobin; HIV: human immunodeficiency virus; INR: international normalized ratio; LDH: lactate dehydrogenase; LDL: low-density lipoprotein; MCH: mean corpuscular Hgb; MCHC: mean corpuscular Hgb concentration; MCV: mean corpuscular volume; MPV: mean platelet volume; PLT: platelets; PT: prothrombin time; RBC: red blood cell (count); T3: triiodothyronine; T4: thyroxine; TSH: thyroid stimulating hormone; ULN: upper limit of normal; WBC: white blood cell (count).

Laboratory safety tests (eg, hematology, serum chemistries including liver tests, and urinalysis) will be performed by a central laboratory designated by the sponsor. Local laboratories may only

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be used T-SPOT or in cases when the central laboratory results will not be available, and the results are needed immediately to determine what actions to take for safety reasons.

The central laboratory will return these results, along with their reference ranges, to the investigator. The investigator is responsible for reviewing the laboratory report, documenting this review, and filing the laboratory report with the source documents.

Abnormal laboratory findings associated with the subject's known prior medical conditions should not be considered clinically significant or reported as AE, unless judged by the investigator to be more severe than expected for the subject's known prior medical conditions.

Clinically significant abnormal laboratory values obtained during participation in the study or within 4 weeks after the last dose of study intervention should be repeated until the values return to normal or the baseline value or are no longer considered clinically significant by the investigator or medical monitor. The investigator should evaluate whether the laboratory result meets the AE criteria in Section 10.3.

Abnormal clinical laboratory values that are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified. For subjects with treatment-emergent abnormal liver test results, see Section 10.5 for additional monitoring, evaluation, and follow-up recommendations.

Eligible subjects with negative for hepatitis B virus (HBV) DNA at screening should be continued to undergo HBV DNA testing at a laboratory once per month for the first 6 months and every 3 months thereafter after initiation of study drug. As a result, recurrence of HBV infection is suspected or the HBV DNA level is confirmed to be 20 IU/mL (1.3 LogIU/mL)/lower limit of quantification or higher, investigators will record the HBV DNA test results as an AE and consult with experts in Hepatitis B about initiating treatment (e.g. nucleotide analogues) and continuation of study drug.

Follow-up safety monitoring will be conducted at the investigator's discretion. Results determined by the investigator to be SAEs or AESI should be reported to the sponsor following the procedures described in Section 8.3.8.4.

8.3.5 Pregnancy Testing

A urine and/or serum beta- human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all subjects of childbearing potential at times described in Table 1.a and at other timepoints at the discretion of the investigator if pregnancy is suspected. Pregnancy test may be conducted locally at the study site when central serum pregnancy test is not available.

If a subject becomes pregnant during the study after confirming a positive pregnancy test via highly sensitive serum testing, the subject will be immediately discontinued from study

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intervention and encouraged to continue to be followed for safety unless they have withdrawn consent for further study participation for other reasons.

If a subject becomes pregnant during the study, the pregnancy must be followed as described in Section 10.4.3.

8.3.6 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be performed at the visits specified in Table 1.a. The C-SSRS is an assessment tool that evaluates suicidal ideation and behavior. It includes 5 levels of suicidal ideation, 5 levels of suicidal behavior, and the category self-injurious behavior, no suicidal intent. The Baseline version will be used at screening (Appendix 14) and the Since Last Visit version will be used at subsequent visits (Appendix 15) (Posner et al. 2007).

The C-SSRS is a clinical outcome assessments (COA) that must be administered by study investigator or properly trained designee. A training certificate for the administer(s) will be on file at the investigator's site.

The investigator must review the completed C-SSRS. If needed, the medical monitor will be consulted, and the subject may be referred to a qualified mental health care provider or to appropriate emergency room for further evaluation.

Refer to Appendix 14 and Appendix 15 for the questionnaires.

8.3.7 8-item Patient Health Questionnaire (PHQ-8)

The PHQ-8 is a COA and will be evaluated at the visits specified in Table 1.a. The PHQ-8 is established as a valid diagnostic and severity measure for depressive disorders (Kroenke et al. 2009). Each of the 8 questions is based on a 2-week recall period and scored on a scale of 0 to 3. The scores for each item are summed to produce a total score between 0 and 24 points. A total score of 0 to 4 represents no significant depressive symptoms. A total score of 5 to 9 = mild depressive symptoms; 10 to 14 = moderate; 15 to 19 = moderately severe; and 20 to 24 = severe. If deemed clinically necessary based on a significant change in PHQ-8 or a PHQ-8 value consistent with potential new depression, the medical monitor will be consulted, and the subject may be referred to a qualified mental health care provider or to appropriate emergency room for further evaluation. The questionnaire is provided in Appendix 17.

8.3.8 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Section 10.2.

The investigator and any qualified designees are responsible for collecting, detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for follow-up of these events (see Section 10.3.4).

The COAs/PROs listed in Section 8.2.1, Section 8.2.2, Section 8.3.6, and Section 8.3.7 will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with these instruments, then proper follow-up with the subject for medical evaluation should be undertaken. If it is determined through this

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follow-up that an AE not previously reported has been identified, normal reporting requirements should be applied.

8.3.8.1 *Time Period for Collecting Adverse Event and Serious Adverse Event Information*

All AEs (including pretreatment and treatment emergent) will be collected from the signing of the ICF until the completion of the last follow-up visit at the time points specified in the SoA (Section 1.3). However, subjects who discontinued from study drug prematurely are encouraged to continue on study, and at minimum to have a safety follow-up visit 4 weeks after last dose, unless they have withdrawn consent for further study participation for other reasons.

All SAEs will be recorded and reported to the sponsor or designee immediately. Under no circumstance should this exceed 24 hours. The investigator will also submit any updated SAE data within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor via the reporting method described in Section 10.3.4.7.

8.3.8.2 *Method of Detecting Adverse Events and Serious Adverse Events*

At each study visit specified in the SoA (Section 1.3), subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences without introducing bias. Subjects and investigators may report AEs occurring at any time during the study.

8.3.8.3 *Follow-up of Adverse Events and Serious Adverse Events*

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All subjects experiencing AEs, whether considered associated with the use of the study drug or not, will be documented.

All AEs (including SAEs) must be monitored until the end of the study or until the event resolves, stabilizes, is otherwise explained, or the subject is lost to follow-up as defined in Section 7.3.

Information to be documented for each event is defined in Section 10.3.4.

Further information on follow-up procedures is provided in Section 10.3.4.6.

8.3.8.4 *Regulatory Reporting Requirements for Serious Adverse Events*

An SAE should be recorded and reported by the investigator to the sponsor or designee within 24 hours of first onset or notification of the event. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

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Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met. The sponsor has a legal responsibility to notify the regulatory authority about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB or other required study documents and will notify the IRB, if appropriate according to requirements.

The sponsor or designee must prepare safety reports for suspected unexpected serious adverse reactions (SUSARs) according to regulatory requirements and sponsor policy and forward them to investigators as necessary.

8.3.8.4.1 Reporting of Abnormal Liver-associated Test Results

For any subject with AST or ALT ≥3× ULN **and** total bilirubin ≥2× ULN **or** INR >1.5× ULN, report the event as an SAE, irrespective of an alternative etiology being identified, contact the medical monitor and Takeda trial clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Section 10.5.

8.3.8.5 *Pregnancy in a Subject or Subject's Partner During the Study*

See Section 10.4.3.

8.3.8.6 *Deaths*

Any death that occurs during the study will be reported per SAE reporting procedure, and should be carefully followed up to assess and identify the cause for death.

8.3.8.7 *Adverse Events of Special Interest*

If the AESI that occurs during the treatment period or the follow up period is considered to be clinically significant based on the criteria below, it should be reported by the investigator to the sponsor immediately or within 24 hours of/after the first onset or subject's notification of the event. Reporting urgency depends on the level of emergency.

The following are AESIs:

- Infections that are severe or serious or opportunistic.
- CPK elevation CTCAE Grade 3 or higher (severe) >5× ULN
- Abnormal liver function tests ≥ Grade 2.
- MACE, defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

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- Thromboembolic events.
- Malignancies.
- Gastrointestinal perforation
- Cytopenias (anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia; clinically significant or not), defined by the following ranges:
  - Hemoglobin <9.0 g/dL (<90.0 g/L).
  - White blood cell count $<3.0 \times 10^9$/L ($<3000/mm^3$).
  - Absolute neutrophil count $<1.0 \times 10^9$/L ($<1000/mm^3$).
  - Absolute lymphocyte count $<0.5 \times 10^9$/L ($<500/mm^3$).
  - Platelet count $<100 \times 10^9$/L.
- Renal dysfunction.
- Hypersensitivity reaction.

AESIs should be reported as detailed in Section 8.3.8.1. All serious AESIs will be reported into the safety database.

8.3.8.8 *Special Situation Reporting (SSR)*

Special situation reportings (SSRs) are defined as medication errors, and uses outside what is foreseen in the protocol, including overdose, misuse and abuse of the product. SSRs may or may not be associated with an AE/SAE. SSRs must be reported to Takeda Global Patient Safety Evaluation, using a paper SSR form within 7 calendar days of awareness. If an SSR is associated with an SAE or AESI, the SAE/AESI must be reported to Takeda Global Patient Safety Evaluation within 24 hours of awareness.

8.4 Pharmacokinetics

8.4.1 Collection of Blood for PK Sampling

Subjects will undergo PK sampling as specified in Table 1.b, to quantify the level of TAK-279 in plasma. Sparse PK samples will be collected in all subjects.

On all days of PK collection, the time(s) of study drug administration must be recorded (including the administration prior to predose PK collection and any other situations where dosing occurred outside the study site). On the days of PK collection, administration of study drug must occur under the supervision of the investigator (or designee) after the predose PK sample is obtained.

The actual date and time of each blood sample collection will be recorded.

Details about the collection, processing, handling, storage, and shipping of plasma samples will be provided in the laboratory manual.

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8.4.2 Bioanalytical Methods

[redacted] will be used for the determination of TAK-279 concentration in plasma samples.

8.5 Biomarkers and Other Analyses

Serum samples will be collected as specified in Table 1.a. [redacted]

These exploratory biomarkers will not be reported in the clinical study report (CSR).

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of blood samples will be provided in the laboratory manual.

Leftover samples may be retained and stored for other possible additional future analysis and assay development if allowed by guidelines and regulations. Any retained samples will be de-identified and will not be labeled with subject identifying information. Leftover samples will be destroyed either after 15 years from the end of the study or as required by applicable law.

Collection of samples for exploratory biomarkers are dependent on guidelines and regulations (including feasibility of sample or data export) in addition to IRB approval. The biomarker sample analyses will be performed if or when required. Because of continually evolving advances in precision medicine, the method and laboratory that will be recommended for the biomarker analysis cannot always be anticipated, but will be specified, if required by guidelines and regulations.

8.6 Electronic Diaries

Not applicable.

9.0 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared and finalized before database lock. The SAP will provide further details regarding the definition of analysis variables and the statistical analysis methodology to address all study objectives.

9.1 Statistical Hypotheses

No statistical hypothesis testing will be performed in this study.

9.2 Analysis Sets

In this study, 4 analysis sets are defined: the full analysis set (FAS), per-protocol set (PPS), the safety analysis set and PK analysis set.

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FAS

This set will consist of all subjects who received at least 1 dose of TAK-279.

PPS

This set will consist of all subjects who received at least 1 dose of TAK-279, and did not have any important protocol deviations affecting the efficacy evaluations.

Safety Analysis Set

This set will consist of all subjects who received at least 1 dose of TAK-279.

PK Analysis Set (PKAS)

This set will consist of all subjects who received at least 1 dose of TAK-279 and had at least 1 measurable TAK-279 plasma concentration value after the first study treatment dose. Analysis of PK will be based on the PKAS.

9.3 Baseline

The baseline will be defined as the last non-missing assessment prior to the first study drug administration (including unscheduled assessments).

9.4 Efficacy Analyses

9.4.1 Coprimary Efficacy Endpoints

For each coprimary efficacy endpoint, the following analysis will be performed by disease (GPP and EP, the same hereinafter).

9.4.1.1 *Primary Analysis*

Frequency distribution will be provided with proportion and the two-sided 95% confidence interval in the FAS. The confidence interval will be calculated using Clopper-Pearson method. For sPGA 0/1 response, subjects with 0 or 1 score at baseline will be excluded from the analysis.

9.4.1.2 *Supplementary Analysis*

To confirm robustness of the results, the same analysis as the primary analysis will be performed in the PPS.

9.4.1.3 *Strategy for Addressing Intercurrent Events*

The expected intercurrent events (ICEs) prior to Week 16 are listed below:

- Permanent treatment discontinuation due to AEs
- Permanent treatment discontinuation due to lack of efficacy
- Permanent treatment discontinuation due to other reasons

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- Initiation of a protocol-prohibited medication/therapy that could improve psoriasis (e.g., GPP or EP)

A composite strategy will be implemented to address these ICEs. Specifically, nonresponder imputation will be used for coprimary efficacy endpoints for subjects who permanently discontinue treatment prior to Week 16, initiate a protocol-prohibited therapies or procedures that could improve psoriasis during the first 16 weeks of treatment, or who have otherwise missing endpoint data at the specified timepoint.

9.4.2 Secondary Efficacy Endpoints

The following analysis will be performed by disease (where applicable) in the FAS.

- For continuous endpoints other than BSA affected by psoriasis, PASI and GPPASI, descriptive statistics and two-sided 95% confidence interval of mean will be provided for observed values (baseline and post-baseline visits) and changes from baseline (each post-baseline visit's value – baseline value). For endpoints with multiple visits, these will be provided by visit.
- For BSA affected by psoriasis, PASI and GPPASI, descriptive statistics and two-sided 95% confidence interval of mean will be provided for observed values, changes from baseline and percent changes from baseline ([each post-baseline visit's value - baseline value] / [baseline value] x 100) by visit.
- For binary endpoints, frequency distribution will be provided with proportion and the two-sided 95% confidence interval. The confidence interval will be calculated using Clopper-Pearson method. For endpoints with multiple visits, these will be provided by visit.

9.5 Safety Analyses

The following analysis will be performed by disease in the safety analysis set.

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to NCI CTCAE, Version 5.0 or higher, and will be listed.

9.5.1 Treatment-emergent Adverse Event

TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The frequency distribution will be provided using the system organ class (SOC) and the preferred term as follows:

- The frequency of all TEAEs
- The frequency of drug-related TEAEs
- The frequency of TEAEs by intensity
- The frequency of drug-related TEAEs by intensity

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- The frequency of TEAEs leading to study drug discontinuation
- The frequency of serious TEAEs
- The frequency of TEAEs of special interest

9.5.2 Clinical Laboratory Results, Vital Signs, and ECGs

For continuous endpoints, the observed values and the changes from baseline will be summarized for each visit using descriptive statistics. Case plots will also be presented for the observed values.

For categorical endpoints, shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

9.6 PK Analysis

No formal noncompartmental PK analyses will be performed on concentration-time data. Summary statistics of TAK-279 plasma concentrations will be summarized using the PKAS. Individual concentration-time data will be included in listings.

[redacted]

9.7 Exploratory Biomarkers

[redacted]

9.8 Other Analyses

Demographics and other baseline characteristics will be summarized by disease (GPP and EP) in the FAS.

9.9 Interim/Intermediate Analysis

No interim analysis is planned in this study.

9.10 Determination of Sample Size

For each disease (GPP and EP), the targeted sample size is approximately 10 subjects based on enrollment feasibility of this population in Japan, rather than statistical perspective. Consequently, the targeted sample size is approximately 20 subjects in total.

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10.0 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted with the highest respect for the individual 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 regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Section 10.1.11. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national laws and regulations.

10.1.2 Financial Disclosure

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 sub-investigators 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 sub-investigator 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 prior to the start of the study at their site.

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

10.1.3 Informed Consent Process

10.1.3.1 *Informed Consent Requirements in This Study*

The goal of the informed consent process is to provide a potential subject or their legally authorized representative with sufficient information about the research to allow for an informed decision about their voluntary participation in the research study. The informed consent process must facilitate the subject's comprehension of the information and allow adequate opportunity for the subject to ask questions and consider whether or not to participate. This process may extend beyond a subject's initial consent due to changing circumstances within the study, the therapeutic landscape, or the subject's situation.

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When a subject consents to participate in the study, their informed consent must be documented in writing via a signed and dated ICF. The date of the informed consent will also be collected along with the current protocol version.

10.1.3.2 *Standards the Informed Consent Follows*

Informed consent documents must 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 ICF and related materials subject authorization form (if applicable), and subject information sheet (if applicable):

- explain the nature of the study, its objectives, potential risks and benefits.
- describe the subject's rights and responsibilities, including what the study will require of the subject.
- 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.
- state the fact the subject is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

10.1.3.3 *Who Creates the Informed Consent Materials*

The sponsor will provide sample ICFs, subject authorization form (if applicable), and subject information sheet (if applicable) to the investigator.

The investigator is responsible for the preparation, content, and IRB approval of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable).

The principal investigator will provide the sponsor with a copy of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) that was reviewed by the IRB and received their favorable opinion/approval. A copy of the IRB's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB requires modification of the sample documents that the sponsor provided, the documentation supporting this requirement must be provided to the sponsor. Both the IRB and the sponsor must approve the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) before use.

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10.1.3.4 *Who Conducts the Informed Consent Process*

It is the responsibility of the investigator and the study personnel to:

- explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject.
- answer all of the subject's questions about the study.
- provide the subject ample time to decide whether or not to participate in the study.
- obtain written and/or electronic informed consent from all subjects prior to any study-related procedures including screening assessments.

Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

If the subject, or the subject's legally acceptable representative, determines they will participate in the study, then they must sign and date the ICF, subject authorization form (if applicable) at the time of consent and prior to entering into the study.

The investigational site is responsible for the consenting process.

A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be provided to the subject or the subject's legally authorized representative.

The investigator must also sign and date the ICF at the time of consent and before the subject enters the study.

The signed ICF must remain in each subject's study file at the site and must be available for verification at any time.

The investigator must document the date the subject signs the ICF in the subject's source documents.

10.1.3.5 *Reconsent*

Subjects are required to re-consent if changes are made to the protocol or if new information is made available that may affect the willingness of current subjects (those who are already enrolled and actively participating) to continue in the clinical investigation. Re-consent should be obtained as described in Section 10.1.3.1.

Re-consent is needed for subjects who rescreen (see Section 5.4.2).

Updated ICFs, individual consents, individual assents, individual re-consents and re-assents will be placed in the Study Master File.

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10.1.4 Data Protection

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their source documents and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market TAK-279; national regulatory authorities; and the IRB which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities. Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under laws governing privacy.

The results of studies containing subjects' unique identifying number, relevant source documents, and possibly initials and dates of birth, where allowed per law, may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that their personal study-related data will be used by the sponsor in accordance with data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the ICF.
- The subject must be informed that their source documents may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

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 preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) 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.

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10.1.5 Committees Structure

10.1.5.1 *MACE Adjudication Committee*

A MACE Adjudication Committee with representation including a cardiologist will be established to review certain cardiovascular AEs. Details will be in a separate MACE Adjudication Committee charter, which will describe the roles and responsibilities of the MACE Adjudication Committee.

10.1.5.2 *IRB Approval*

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

The sponsor or designee will supply relevant documents for submission to the respective IRBs for the protocol's review and approval. This protocol, the IB, a copy of the ICF, 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 IRBs for approval.

The IRB's written approval of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before signing a contract for the clinical study).

The IRBs approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) 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 notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

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

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRBs and sponsor.

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10.1.6 Dissemination of Clinical Study Data

10.1.6.1 *Study Results Disclosure*

In order to ensure that information on clinical studies reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical studies before study start and disclose the results of those studies 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/databases as required by law, and on Takeda's corporate website(s).

10.1.7 Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Guidelines.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CRO]).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator unless regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7.1 *Protocol Deviations*

The investigator may deviate from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a such a deviation, the principal investigator should notify the sponsor and the head of the study site about the deviation 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 to avoid

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future deviations. 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 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, 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.

10.1.7.2 *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 head of the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject source documents, informed consent documentation, documentation of subject authorization to use personal health information, 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 regulations.

10.1.7.3 *Audits*

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. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately.

The investigator and head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 10.1.8.

10.1.8 Source Documents

All key data must be recorded in the subject's source documents unless otherwise noted in the protocol. Source documents may be paper or electronic, including data obtained using electronic devices and associated technologies. Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, appointment books, diaries, COAs, original

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clinical laboratory reports, histology reports, pathology reports, X-rays. The COAs will handle data captured in the eCOA by the electronic device as source documents. The investigator is responsible for maintaining adequate and accurate source documents.

The investigator must provide direct access to inspect facilities, including original source records relevant to this study (regardless of media), to: the sponsor or its authorized representatives; the respective national, regulatory authorities; the IRB; and auditors. These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency or an auditor. The ICF includes a statement granting this access to source data.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.1.8.1 *Electronic Case Report Forms*

Completed eCRFs are required for each subject who has completed the consent process. The eCRFs are designed to record all observations and other data pertinent to the clinical investigation unless otherwise noted in the protocol.

The sponsor or its designee will supply study sites with access to eCRFs. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. eCRFs must be completed in English.

The investigator or the investigator's designee (ie, authorized site personnel, as stated in the site delegation log) must enter data from the source documents (Section 10.1.8) into the eCRF with guidance from the study CRF Completion Guidelines.

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

A study monitor from the sponsor or its designee will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Auditors, IRB members, or regulatory inspectors may also check the eCRF entries against the source documents.

Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, ID of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should also be included. The principal

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investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values.

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.

10.1.8.2 *Documentation and Retention of Records*

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. A definition of what constitutes source data and its origin can be found in the source data acknowledgment or monitoring guidelines.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous source documents or transfer records, depending on the study. Also, current source documents must be available.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8.3 *Data Handling*

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 MedDRA. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

10.1.8.4 *Record Retention*

The investigator and the head of the study site agree to keep the records stipulated in Section 10.1.8.2. Those documents include (but are not limited to) the study-specific documents, the ID log of all participating subjects, source documents, all original signed and dated ICF, all 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. The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor

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requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

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

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

10.1.9 Study and Site Start and Closure

10.1.9.1 *First Act of Recruitment*

The first act of recruitment is the first site open. For clinical study disclosure purposes, the study start date is the date when the first subject signed the ICF.

10.1.9.2 *Study/Site Termination*

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. The sponsor reserves the right to close the study site at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination:
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB or health authorities, the sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
  - Total number of subjects included earlier than expected

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If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO (s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

A more detailed list of specific safety parameters for site or study termination is provided in Section 10.1.12.

10.1.10 Publication Policy

During this study, until the open access period, only Takeda may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation.

Both during and after this study, all public disclosures containing data/information from this study must undergo ***review and receive written approval*** by the appropriate Takeda representative(s) ***before*** any public disclosure (including but not limited to submission, presentation, posting on online platforms for archiving, and distribution of unpublished preprints).

This policy applies to all publication types, including: abstracts and presentations (oral and poster, including invited presentations) for scientific congresses; articles (original research manuscripts, review articles, invited articles), letters to the editor, and editorials, in scientific peer-reviewed journals; print, electronic and enhanced multimedia publications associated with traditional congress and journal publishing (such as, but not limited to, audio, visual/graphical or video abstracts or manuscript summaries; video or animated posters; augmented reality, etc.); books and book chapters.

Authorship will be determined in line with the requirements of the International Committee of Medical Journal Editors (ICMJE) Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals, unless otherwise required by the journal or forum where the publication appears.

All publications must be developed with a dataset (such as statistical tables and listings, a CSR, and/or final report) that has been verified by a qualified Takeda employee per Takeda's internal standards. Data relevant to the development of Takeda publications must be shared with all authors via a secure site.

Publications derived from this study may never contain subjects' direct identifiers (such as subject ID, initials) but may contain indirect/quasi identifiers (for example sex/gender, age/birth date, geographic indicators). Publications derived from this study may not include products' direct identifiers (lot numbers or batch numbers) unless specifically required by the journal or conference guidelines and if approved by Takeda.

Takeda requires the submission of all manuscripts resulting from this study, regardless of the intended audience or language, to journals that offer public availability via an Open Access platform.

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10.1.11 Responsibilities of the Sponsor and the Investigator

10.1.11.1 *Sponsor Responsibilities*

10.1.11.1.1 Study-related Responsibilities

The sponsor will perform all study-related activities. 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 sub-investigators 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 sub-investigator 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 sub-investigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the study.

10.1.11.1.2 Insurance

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a 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.

10.1.11.2 *Investigator Responsibilities*

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all other applicable laws and regulations.

The investigator agrees to assume the following responsibilities:

- Conduct the appropriate study in accordance with the protocol and GCP considering the rights, safety, and wellbeing of human subjects.
- When a part of the important activities related to the study are delegated to the sub-investigator or the study collaborator, prepare the lists of activities to be delegated and responsible personnel, submit the lists to the head of the study in advance to get them accepted.
- Prepare a written ICF and other written information, and update as appropriate.
- Confirm the contents of the clinical study agreement.

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- Provide necessary information on the protocol, medications and responsibilities of individual personnel to the investigator and study collaborator, and provide guidance and supervision.
- Screen subjects who meet the requirements of the protocol, provide the explanation of the study in writing and obtain the written or electronic consent.
- Assume responsibility for all the medical judgement related to the study.
- Ensure in collaboration with the head of the study that sufficient medical care on all clinically significant AEs related to the study are provided to subjects throughout and beyond the period when subjects participate in the study.
- If a subject consults other medical institution or other department, notify the physician of the medical institution or department of the subject's participation in the study upon obtaining the consent of the subject, as well as the end and termination of the study in writing, and document such records.
- In case of urgent report of a SAE, immediately notify the head of the study and the sponsor in writing.
- Prepare correct and complete eCRFs, and submit them to the sponsor with electronic signature.
- Check and confirm the contents of eCRFs entered by the sub-investigator or transcribed from the source data by the study collaborator, and submit them to the sponsor with electronic signature.
- Discuss any proposal from the sponsor including update of the protocol.
- Notify the director of the site of the end of the study in writing.
- Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

10.1.11.2.1 Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRBs and provide them with a detailed written explanation. The investigator will also return all study intervention, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with IRBs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter

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studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.1.11.2.2 Principal Investigator/Coordinating Investigator

The sponsor's responsible medical officer/medical expert, will review and approve the final CSR.

The principal investigator may be designated to review and sign the final CSR and by doing so agrees that it accurately describes the results of the study, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.1.12 Site Termination or Suspension

10.1.12.1 *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.

10.1.12.2 *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 ET of the study:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-279, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Termination of study by the sponsor.

10.1.12.3 *Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)*

In the event that the sponsor, an IRB, or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for ET 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.

10.2 Clinical Laboratory Tests

Table 8.a lists the tests that will be obtained for each laboratory specimen. These tests will be performed by the central laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by regulations.

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10.2.1 Clinical Laboratory Assessments and Other Safety Assessments

A change in the value of a clinical laboratory parameter, physical examination finding, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of study intervention, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further change of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the study intervention, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), physical examination, vital sign, or ECG values that were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the subject, whether a change in a clinical laboratory value, physical examination, vital sign, or ECG parameter is clinically significant and represents an AE. The assessment of clinical significance is recorded on the eCRF related to the assessment (for example, the clinical laboratory value eCRF), but an event that is also classified as an AE will be recorded on the AE page.

10.2.2 Biological Sample Retention and Destruction

In this study, specimens for biomarker analysis will be collected as described in Section 8.5. Details are provided in the study laboratory manual.

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10.3 Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Table 10.a AE Subtypes Defined in This Section

Type	Nested Subtypes	Report Within [a]	Sponsor Reports [b]
AE – collection timing per SoA—Section 1.3		NE	NE
	AESI—Section 8.3.8.7, Section 10.3.3.2	24 hours	TBD [c]
	TEAE—Section 10.3.4.9	NE	NE
	SAE—Section 8.3.8.4	24 hours	TBD [c]
	Related AE—any study intervention (whether the investigational product or another intervention)—Section 6.1, Section 10.3.4.3	NE	NE
	Related AE (ADR) (related to the investigational product)	NE	NE
	Expected AE—Section 10.3.4.7	NE	NE
	Unexpected AE—Section 10.3.4.8	NE	NE
	SUSAR (ie, related to investigational product)—Section 10.3.5.2 • Fatal/life-threatening • Nonfatal/non-life-threatening	 24 hours 24 hours	 7 days 15 days

ADR: adverse drug reaction; AE: adverse event; AESI: adverse event of special interest; CRO: clinical research organization; NE: not expedited; SAE: serious adverse event; SUSAR: suspected, unexpected serious adverse reaction; TBD: to be determined;
TEAE: treatment-emergent adverse event.
The specific timeframes on this chart apply to expedited AE/SAE reporting periods.
[a] This is the required, expedited reporting period for the site to report the event to the sponsor/CRO.
[b] This is the required, expedited reporting period for the sponsor to notify other parties including but not limited to regulatory agencies.
[c] To be evaluated at the sponsor. Reporting requirements vary.

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10.3.1 Definition of Adverse Event

AE Definition
An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of the study intervention, whether or not the occurrence is considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study intervention. An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of study drug or a concomitant medication. (Repeated or additional noninvasive testing [eg, laboratory or ECG retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.) **AE onset and resolution dates** are defined as follows: • Start date: the date when the first signs/symptoms were noted by the subject and/or investigator • End date: the date when the subject recovered, the event resolved but with sequelae, or the subject died

Events Meeting the AE Definition
• New condition detected or diagnosed after the use of the study intervention(s), even though it may have been present before the start of the study • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition • Event that is of greater intensity, frequency, or duration than expected for the individual subject or an event with a reasonable possibility that it was related to the study intervention (See Section 10.3.4 for guidance.) • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, physical examinations, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), including those that worsen from baseline • Signs, symptoms, and/or clinical sequelae resulting from a lack of efficacy (NOT the lack of efficacy per se), as long as they fulfill the definition of an AE or serious AE (SAE)

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Events NOT Meeting the AE Definition
• Situations in which an untoward medical occurrence did not occur (eg, preplanned or elective surgery[a]) • Presence or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen[b] • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Cases of overdose with any medication without manifested side effects[c]

[a] Preplanned and elective surgeries are defined as those that were scheduled prior to signing of the ICF. See exceptions in Section 10.3.3.1. While these procedures are not considered AEs, they should be documented in the subjects source documents as described in Section 8.1.3.
[b] Pre-existing conditions (present at the time of signing of ICF) are considered concurrent medical conditions and should NOT be recorded as AEs. Likewise, baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as AEs unless they are related to study procedures.
[c] Overdoses should be documented in the subject's source documents.

10.3.2 Definition of Serious Adverse Event

SAEs are events that meet BOTH the AE criteria described in Section 10.3.1 AND the criteria for seriousness below.

SAE Definition
An SAE is defined as any untoward medical occurrence that meets 1 or more of the criteria listed:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills

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SAE Definition
any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: • Is an important medical event • May require intervention to prevent one of the outcomes listed above • May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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10.3.3 Additional Considerations in Identifying and Defining Adverse Events

10.3.3.1 *Defining Discrete Adverse Events*

Each reported AE should represent a single diagnosis, if the diagnosis is known. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs UNLESS the diagnosis is unknown. Specific examples are as follows:

Laboratory values and ECG findings:

- 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 should be reported as the AE.

Worsening of a condition:

If the subject experiences a worsening or complication of a medical condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…"). This includes:

- Pre-existing conditions present at the time of signing of ICF.
- Pre-existing episodic concurrent medical conditions (eg, asthma, epilepsy): An episode should only be recorded as an AE if the condition becomes more frequent, serious, or severe in nature.
- A degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis): Worsening of the condition should only be recorded as an AE if it occurs to a greater extent than expected.
- Worsening or complication of an AE after any change in study drug: The worsening or complication should be recorded as a new AE.

Complications associated with preplanned procedures:

- Changes in plan and surgical complications associated with preplanned or elective surgeries, therapies, or procedures should be recorded as AEs.
- 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 an elective surgery should be recorded as AEs.

Changes in intensity of AEs:

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

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10.3.3.2 *Adverse Events of Special Interest*

An AE of special interest (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation to characterize and understand them.

10.3.4 Recording and Follow-up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording
When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information. Each event must be categorized in terms of the attributes below, over the entire course of the event, including the start and stop dates. It is **not** acceptable for the investigator to send photocopies of the subject's source documents to the sponsor in lieu of completion of the required form. There may be instances when copies of source documents for certain cases are requested by the sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the source documents before submission to the sponsor. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.1 *Frequency*

Assessment of Frequency
The investigator should assess and record the frequency of the event. Episodic AEs/pretreatment events (eg, vomiting) or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

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10.3.4.2 *Intensity*

Assessment of Intensity

The investigator will assess the intensity for each AE and SAE (including any laboratory abnormality) reported during the study and assign it to 1 of the following categories:

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 or higher. AEs not listed by the NCI CTCAE will be graded as displayed in Table 10.b.

Table 10.b NCI CTCAE

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the subject.

ADL: activities of daily living; AE: adverse event; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events.

Please note: Intensity and seriousness are separate concepts. The terms "severe" and "serious" are not synonymous. Because serious events usually pose a threat to a subject's life or ability to function, seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.3.4.3 *Causality/Relatedness*

Assessment of Causality

The investigator must assess the relationship between the study drug(s) and each occurrence of each AE/SAE based on the criteria below:

Related:	An AE that follows a reasonable temporal sequence from administration of the study 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.

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Assessment of Causality	
	A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of the study drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

The investigator will also consult the IB and/or product information, for marketed products, in their assessment.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.3.4.4 *Action Taken*

Action Taken Concerning Study Drug

The investigator must make note of the action taken concerning the study drug:

- Dose not changed
- Drug interrupted
- Drug withdrawn
- Dose delayed
- Unknown
- 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).

For any AE that was ongoing at the time of a subject's death, the study intervention action should reflect the most recent action that had been taken at the time of death (eg, drug interrupted, reduced, withdrawn). If the subject had never received the study intervention, the action taken should be recorded as "dose not changed" or "not applicable." The study intervention action of "withdrawn" should not be selected solely as a result of the subject's death.

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10.3.4.5 *Outcome*

Outcome
The investigator must make note of the outcome of any AEs that occur during the course of the study: • Recovered/resolved: The subject returned to first assessment status with respect to the AE. • Recovered/resolved with sequelae: The subject recovered from an acute AE but was left with permanent/significant impairment. • Recovering/resolving: The intensity has decreased by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value has improved, but has not returned to the normal range or to baseline; the subject died from a cause *other than* this particular AE. • 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 is now worse than when it started; is an irreversible congenital anomaly; the subject died from another cause. • Fatal: The AE is considered to be the cause of death or contributed to the subject's death. • Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.3.4.6 *Follow-up*

Follow-up of AEs and SAEs
If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested. All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.4.7 *Reference Safety Information*

The reference safety information (RSI) for this study is the IB, and to date, no adverse drug reactions (ADRs) are considered expected by the sponsor.

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10.3.4.8 *Unexpected Adverse Events*

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the RSI. "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but will not be based on what might be anticipated based on the pharmacological properties of a product.

10.3.4.9 *Treatment-emergent Adverse Events*

As described in Section 1.3, all AEs will be collected from the time when the ICF is signed. For reporting purposes in the study, a TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with a study intervention or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the study intervention or medicinal product.

10.3.5 Expedited Reporting of Serious Adverse Events and Selected Adverse Events

This section describes the expedited reporting required for certain types of events:

- Sites must report SAEs immediately, and in no case in more than 24 hours.

Site must report SAEs and SAEs of Special Interest (AESIs) immediately via Electronic Data Capture (EDC) in no case in more than 24 hours. Pregnancy cases should also be reported within the same timeframe, using the paper form provided by the sponsor.

The following is a supplementary explanation for dealing in Japan, when transmission of an EDC is not feasible.

- When reporting SAEs, serious AESIs or pregnancy, SAE report form or pregnancy report form that are provided by the sponsor must be used.
- After the initial information of SAEs is reported to the Sponsor, the initial SAE report form (original wet-ink) must be submitted to the Sponsor in Japan. Also, if applicable, copy of related documents should be submitted to the sponsor as soon as possible, once they are available. The investigator should report detailed information without delay after notification of initial information. Additional detailed follow-up data surrounding the SAEs that become available following the initial report should be communicated through the same channels as outlined above.
- An operator of the Emergency Center for Safety Information is available for contact 24 hours a day and 365 days a year.

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Emergency Center for Safety Information (available 24 hours 365 days)

[redacted]

10.3.5.1 *Reporting of Abnormal Liver-Associated Test Results*

For any subject with AST or ALT ≥3× ULN **and** total bilirubin ≥2× ULN **or** INR >1.5× ULN, report the event as an SAE, irrespective of an alternative etiology being identified, contact the medical monitor and Takeda study clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Section 10.5.

10.3.5.2 *Safety Reporting to Investigators, Institutional Review Boards, and Regulatory Authorities*

The sponsor will be responsible for identifying and reporting all SUSARs and any other applicable SAEs to regulatory authorities including investigators, and IRB in accordance with national regulations in Japan. Adverse events that are already classified as expected (and therefore are not SUSARs) are listed in the RSI (see Section 10.3.4.7 for the location of the RSI).

- SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, relative to the first awareness of an event by/or further provision to the sponsor or sponsor's designee, unless otherwise required by national regulations.
- The sponsor will prepare an expedited report for other safety issues that 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 study.

The study site will forward a copy of all expedited reports to its IRB in accordance with regulations.

10.4 Contraceptive and Barrier Guidance

10.4.1 Definitions

For the purposes of this study, reproductive status is defined as follows:

- **Nonpregnant:** Negative urine and/or serum beta human chorionic gonadotropin (β-hCG) pregnancy test result

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- An individual previously of childbearing potential who **is <u>not</u> of childbearing potential**:
  - Surgically sterile for at least 6 weeks at screening (defined as having undergone one of the following procedures: hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
  - Postmenopausal at screening (defined as age ≥60 with absence of menses for ≥12 months with no alternative medical cause) or age <60 with absence of menses for ≥12 months AND follicle-stimulating hormone (FSH) >40 IU/L. Note, in the absence of 12 months of amenorrhea, an FSH measurement is insufficient to confirm postmenopausal state for the purposes of this study.
- An individual who ***is* of childbearing potential**: following menarche and until becoming postmenopausal unless permanently sterile by the definition above.

10.4.2 Contraception Guidance

In this study, the use of a highly effective contraception is required for subjects of childbearing potential who are sexually active with a nonsterilized male partner for the duration of the study and for 10 days thereafter. The use of effective contraception is not required for male subjects. In addition, contraceptive use should be consistent with regulation regarding the use of contraceptive methods for subjects in clinical studies.

The failure rates of contraceptives that are used consistently and correctly may differ in typical use. Therefore, when study participation requires any of these methods of contraception to be used, subjects must commit to using them:

- consistently throughout the required period
- correctly, as described below and in any labeling associated with the method

Contraception requirements depend in part on the reproductive status of the subject and the subject's partner.

Acceptable and unacceptable contraception methods are presented in Table 10.c, Table 10.d, and Table 10.e.

Note: TAK-279 may decrease the efficacy of oral hormonal contraception; please see additional guidance in Table 10.c.

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Table 10.c Acceptable Contraception Methods for This Study

Highly Effective Contraceptives; Failure rate of <1% per year when used consistently and correctly
User Dependent
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. [a, b] – Oral. • Sexual abstinence. [c]
Low User Dependency
• IUD. • IUS. • Bilateral tubal ligation/tubal occlusion. • Vasectomy; vasectomized partner. [d, e]

For subjects of childbearing potential who are sexually active with a nonsterilized male partner.
IUD: intrauterine device; IUS: intrauterine hormone-releasing system
[a] Combined estrogen and progestogen contraception (type of birth control pill) must be started 35 days prior to first dose of study drug.
[b] Oral hormonal contraception may be susceptible to interaction with TAK-279 which may reduce the efficacy of the contraceptive method. Therefore, if subject is on a form of combined hormonal oral contraception, a second highly effective or effective method of contraception should be used during the treatment period and for at least 10 days after the last dose of study treatment. A barrier method is recommended, preferably a male condom. Of note, an effective contraception method is only permitted in the case that hormonal contraception is used as the primary highly effective method of contraception. Effective method of contraception is listed in Table 10.d.
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.
[d] A vasectomy is a highly effective contraceptive method *only if* the absence of sperm has been confirmed.
[e] For subjects of childbearing ability, having a vasectomized partner is a highly effective contraception method provided that the partner is the subject's sole partner and that the absence of sperm has been confirmed.

Table 10.d Effective Contraception Methods for This Study

For use only as second method of contraception if primary highly effective method is hormonal contraception, see Table 10.c footnote b
Effective Contraceptives: Failure rate of >1% per year when used consistently and correctly
User Dependent
• Male condom without spermicide.

For subjects of childbearing potential who are sexually active with a nonsterilized male partner.

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Table 10.e Unacceptable Contraception Methods

Methods that are unacceptable in *any* study requiring contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (*coitus interruptus*) • Spermicides only • Lactational amenorrhea method (LAM) • Use of both female condom and male condom together at the same time

Source: CTFG version 1.1 (21/09/2020)

10.4.3 Pregnancy and Breastfeeding

Details about all pregnancies in subjects or their partners will be collected after the start of study intervention and for the entire pregnancy. Collection of pregnancy data from a subject's partner requires the partner's informed consent.

To the extent possible, the investigator will collect follow-up information on the outcome of the pregnancy and the neonate, and the information will be forwarded to the sponsor.

If a female subject becomes pregnant or donates ova (eggs) after dosing on Day 1, during the study, and up to 10 days after the end of the study, or if a female partner of a male subject becomes pregnant after male subject dosing on Day 1, during the study, and up to 10 days after the end of the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be permanently discontinued from the study treatment, if this occurs before the end of dosing period. The investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and report it to the sponsor within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting), and to the ethics committee, when applicable.

Pregnancy is not itself an AE or SAE; however, AEs or SAEs associated with pregnancy must be reported as such, including:

- Any pregnancy complication or elective termination of a pregnancy for medical reasons (to be reported as an AE or SAE).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital abnormalities, ectopic pregnancy) to be reported as SAEs.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3.5.2. Although the investigator is not obligated to actively seek poststudy pregnancy-related SAE information from former study subjects or their partners, he or she may learn of an SAE through spontaneous reporting.

Subjects should not breastfeed during the study and for 10 days after end of treatment.

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10.5 Abnormal Liver-Associated Test Result Monitoring and Follow-Up Assessments

Investigators must be vigilant for abnormal liver-associated test results in subjects during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical study subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver-associated test results in clinical study subjects who had no known liver disease and had either normal or near normal baseline liver test results (ie, AST or ALT <2× upper limit of normal [ULN], total bilirubin <1.5× ULN, and alkaline phosphatase [ALP] <1.5× ULN) at the time of enrollment.

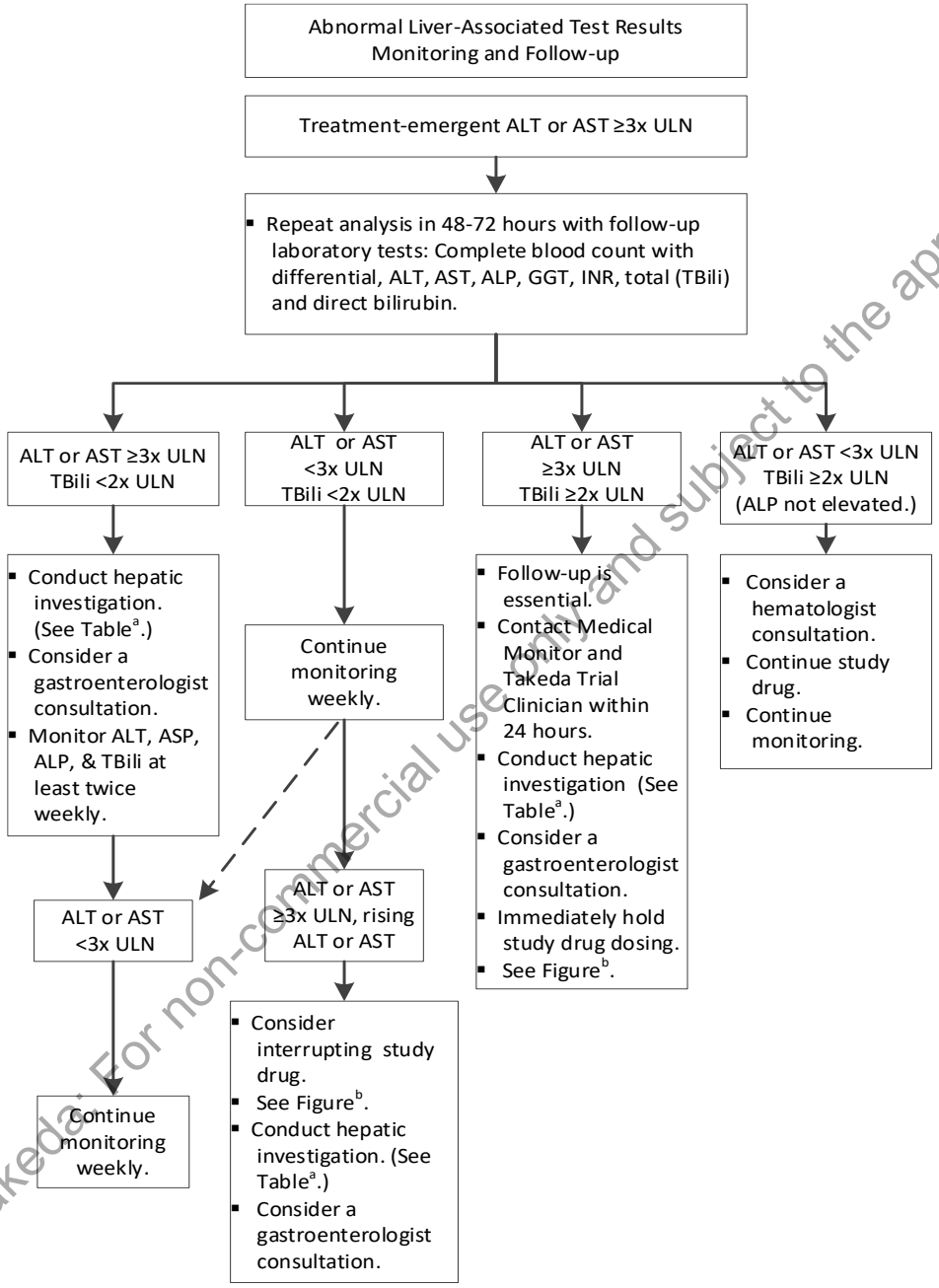
In evaluating study subjects with abnormal liver-associated test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver-associated test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 10.a. Suggested hepatic investigations are listed in Table 10.f. Criteria for considering discontinuation of study drug are shown in Figure 10.b.

Subjects with Combined Elevations in Aminotransferase(s) and Bilirubin

If a subject has elevated AST or ALT ≥3× ULN with **concurrent** elevated Tbili ≥2× ULN **or** elevated international normalized ratio (INR) >1.5, the investigator must contact the medical monitor and Takeda study clinician within 24 hours. Hepatic investigations as suggested in Table 10.f should be initiated. Any event of elevated AST or ALT ≥3× ULN with concurrent elevated Tbili ≥2× ULN or elevated INR >1.5 must be reported as an SAE, irrespective of an alternative etiology being identified.

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Figure 10.a Abnormal Liver-associated Test Results: Monitoring and Follow-up



ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; INR: international normalized ratio; Tbili: total bilirubin; ULN: upper limit of normal.
Source: Guidance for industry drug-induced liver injury: premarketing clinical evaluation, 2009
[a] Refer to Table 10.f.
[b] Refer to Figure 10.b.

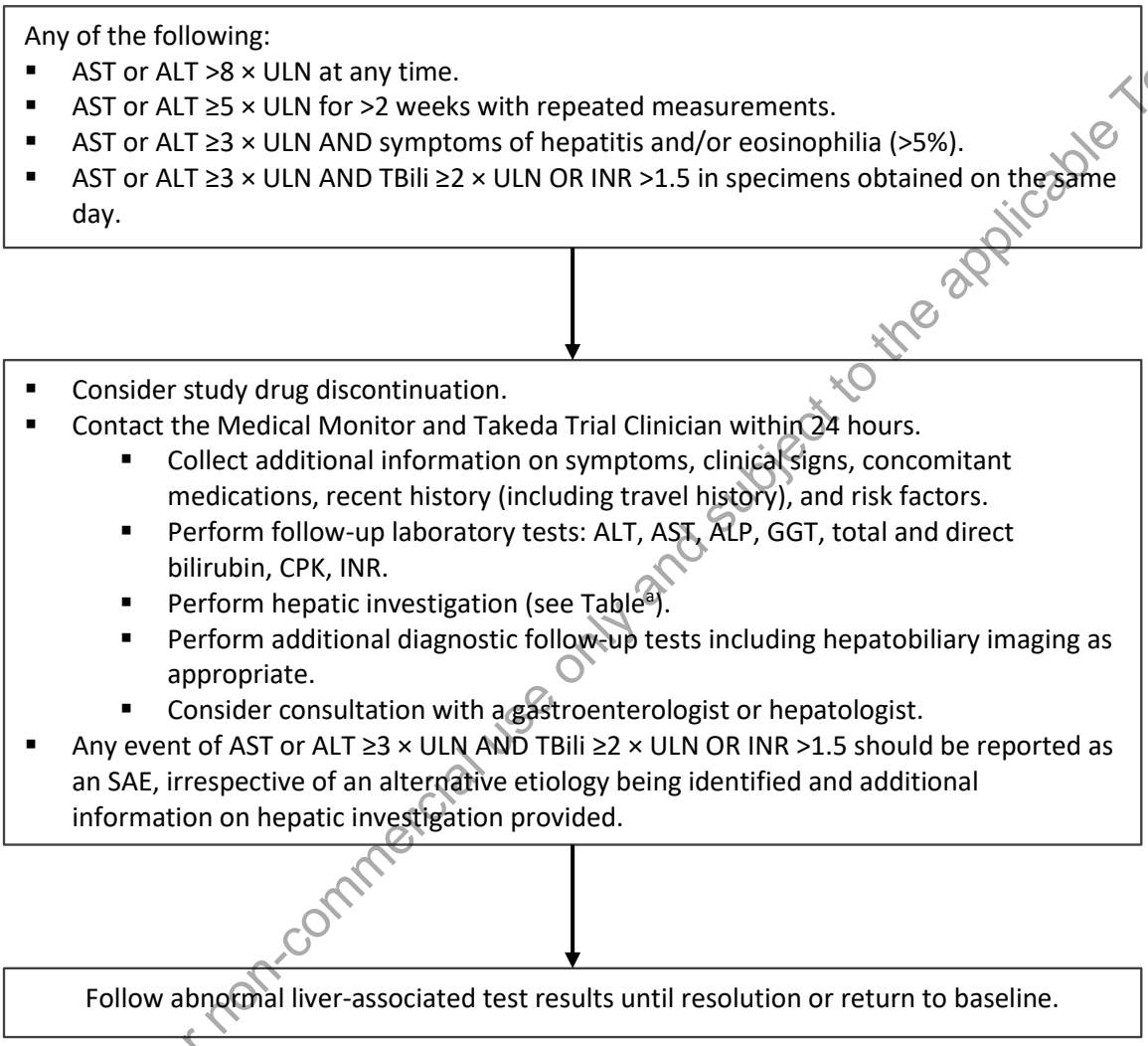
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Table 10.f Hepatic Investigation

Medical history	• Concomitant medications (including over-the-counter medications, such as acetaminophen, and herbal supplements) • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis) • Alcohol intake • Hepatobiliary disorder • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia) • Travel history
Physical examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting • Right upper quadrant pain or tenderness, fever, jaundice, rash • Eosinophilia >5%
Hepatic/hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging)
Viral hepatitis serology	• Hepatitis A antibody (total and immunoglobulin [Ig] M) • Hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (total anti-HBc and anti-HBc IgM), hepatitis C antibodies (anti-HCV) • Hepatitis E (IgG and IgM) • Consider polymerase chain reaction for hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen <VCA> nuclear antigen <EBNA>, early antigen <EA>) • Consider cytomegalovirus serology (IgG and IgM)
Autoimmune hepatitis serology	• Antinuclear antibody (ANA) • Antismooth muscle antibody (ASMA) • Anti–liver-kidney microsomal antibody (anti-LKM)

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Figure 10.b Abnormal Liver-associated Test Results: Considerations for Study Drug Discontinuation



ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; GGT: gamma glutamyl transferase; INR: international normalized ratio; SAE: serious adverse event; Tbili: total bilirubin; ULN: upper limit of normal.
[a] Refer to Table 10.f

10.6 Country-Specific Requirements

Not applicable.

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10.7 Abbreviations and Definitions

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
β-hCG	beta-human chorionic gonadotropin
BSA	body surface area
COA	clinical outcome assessments
COVID-19	coronavirus disease-2019
CPK	creatinine phosphokinase
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CRP	c reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLQI	dermatology life quality index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
EP	erythrodermic psoriasis
ET	early termination
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	good clinical practice
GPP	generalized pustular psoriasis
HBsAg	hepatitis B surface antigen

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HCV	hepatitis C virus
Hgb	hemoglobin
IB	investigator's brochure
ICE	intercurrent events
ICF	informed consent form
ICH	international council for harmonisation
ID	identification
IFN	interferon
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
JAK	janus kinase
LTBI	latent tuberculosis infection
MACE	major adverse cardiovascular events
MedDRA	medical dictionary for regulatory activities
NA	not applicable
NAPSI	nail psoriasis severity index
NCI	national cancer institute
NMSC	nonmelanoma skin cancer
PASI	psoriasis area and severity index
PASI-75	75% improvement from baseline in psoriasis area and severity index
PASI-90	90% improvement from baseline in psoriasis area and severity index
PASI-100	100% improvement from baseline in psoriasis area and severity index
PBPK	physiologically based pharmacokinetic
PGA	physician's global assessment
PHQ-8	8-item patient health questionnaire
PK	pharmacokinetic(s)
PPS	per-protocol set
PRO	patient-reported outcome
PsA	psoriatic arthritis
PUVA	psoralen and ultraviolet A
QD	once daily
RSI	reference safety information

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SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	system organ class
sPGA	static physician's global assessment
ssPGA	scalp-specific physician's global assessment
SSR	special situation reporting
STAT	signal transducers and activators of transcription
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UV	ultraviolet

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10.8 Protocol Amendment History

Date	Document	Global/Country/Site Specific
08 October 2024	Amendment 5	Japan
10 July 2024	Amendment 4	Japan
22 March 2024	Amendment 3	Japan
26 January 2024	Amendment 2	Japan
16 November 2023	Amendment 1	Japan
18 October 2023	Original Protocol	Japan

Summary of Changes Since the Last Version of the Approved Protocol			
Protocol Amendment 4			
Amendment Date: 10 July 2024			**Japan**
Overall Reason for the Amendment The reasons for this protocol update are to address recommendations received during regulatory agency review, to update pertinent safety language in line with the TAK-279 Investigator's Brochure Edition 7.0, and to update the content based on site feedback and/or clarification.			
Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of Change(s)**	**Rationale for Change(s)**	**Section**
1	Removed language indicating TAK-279 has the potential to be efficacious in humans.	Updated for clarity.	Section 1.1 Synopsis Section 2.4.4 Risk Benefit Conclusions
2	Changed cardiovascular adjudication committee name from Cardiac Adjudication Committee to Major Adverse Cardiovascular Events (MACE) adjudication committee.	Clarification to align with the naming convention used in the adjudication committee charter.	Section 1.1 Synopsis Section 4.1.2 Treatment Period Section 10.1.5.1 MACE Adjudication Committee
3	Updated language regarding birth control, reproductive status, and documentation of sex at birth.	Updated language to be inclusive/gender neutral.	Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 5.1 Inclusion Criteria Section 10.4.1 Definitions
4	Clarified that it is not necessary to perform T-SPOT on subjects who have a diagnosis of LTBI. Added clarification that x-ray must be obtained regardless of T-SPOT results unless the subject had a normal chest imaging in the 6 months prior to screening.	Clarification.	Section 1.1 Synopsis Section 1.3 Schedule of Activities Section 5.2 Exclusion Criteria
5	Corrected 'herpes simplex virus' to 'herpes zoster.'	Correction.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria

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6	Clarified exclusion criterion to indicate positive results for HIV are by serology, regardless of viral load.	Clarification regarding positive HIV serology results.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
7	Clarified that replacement of an infected prosthesis must have occurred at least 60 days prior to Day 1 to meet the eligibility.	Clarification.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
8	Clarified exclusion criteria for subjects with cardiovascular disease.	Regulatory agency feedback.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
9	Added information regarding the washout period for prohibited psoriasis treatments and other prohibited concomitant medications to the exclusion criteria.	Regulatory agency feedback.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria Section 6.7.2 Excluded Procedures and Treatments
10	Clarified that all prior TYK2 exposure is exclusionary, including participation in a trial involving a TYK2 inhibitor, unless assigned arm is known after unblinding.	Clarification of criteria to be met to ensure eligibility for study.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
11	Added to laboratory exclusion criteria creatine phosphokinase (CPK) screening laboratory criterion.	Added to allow flexibility regarding repeat CPK value and assessment for modulation factor.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
12	Changed ‘major’ protocol deviations to ‘important’ protocol deviations.	Updated based on regulatory guidance.	Section 1.1 Synopsis Section 9.2 Analysis Sets
13	Clarified that CTCAE versions higher than 5.0 can be used.	Clarification.	Section 10.3.4.2 Intensity
14	Addition of section clarifying potential drug interactions.	Regulatory agency feedback.	Section 2.3 Drug Interactions
15	Change in language to the potential risks and proposed risk mitigation strategy for an accurate depiction of clinical data.	Clarification and updates that align with currently available clinical data.	Section 2.4.2 Potential Risks Section 2.4.3 Proposed Risk Mitigation Strategy
16	Clarification on the definitions of EOT and EOS.	Clarification.	Section 4.4.1 EOT Section 4.4.2 EOS
17	Clarification regarding permitted use of medication during the study. Added no rescue medications are permitted during the study.	Clarification.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria Table 6.c Prohibited Therapies or Procedures Section 6.7.3 Permitted Concomitant Medications and Procedures
18	Removed mention of study diary when discussing how to record daily dosing.	Correction.	Section 6.1 Study Interventions Administered
19	Clarification that lifetime GPP/EP medication history will be collected at screening.	Clarification.	Section 6.7 Prior and Concomitant Therapy

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20	Updated the language for subject withdrawal reason recording, AE documentation, and expedited reporting.	Clarification.	Section 7.1 Discontinuation of Study Drug Section 8.3.8.3 Follow-up of AEs and SAEs Section 10.3.5 Expedited Reporting of SAEs and Selected AEs
21	Removed reason for temporary study drug interruption due to redundancy with abnormal liver-associated test result monitoring.	Clarification.	Section 7.1.1 Temporary Interruption of Study Drug
22	Addition of rhabdomyolysis for permanent discontinuation of study drug.	Clarification.	Section 7.1.2 Permanent Discontinuation of Study Drug
23	Added a medical records section.	Clarification regarding medical records related eligibility requirements.	Section 8.1.2.1 Medical Records
24	Removed safety follow-up collection window for pregnancy testing results.	Clarification.	Section 8.3.5 Pregnancy Testing
25	Revised the safety follow-up for subjects who discontinue study drug prematurely to have a safety follow-up visit (at minimum) 4 weeks after the last dose.	Clarification.	Section 8.3.8.1 Time Period for Collecting AE and SAE Information
26	Updated figures to add details for monitoring for subjects with ALT or AST elevation of ≥3 × ULN and total bilirubin ≥2. Clarified subjects with combined elevations in aminotransferase(s) and bilirubin must be reported as an SAE, irrespective of an alternative etiology being identified.	Clarification/regulatory agency feedback.	Section 8.3.8.4.1 Reporting of Abnormal Liver-Associated Test Results Section 10.3.5.1 Reporting of Abnormal Liver-Associated Test Results Section 10.5 Abnormal Liver Associated Test Result Monitoring and Follow-up Assessments Figure 10.a Abnormal Liver Associated Test Results: Monitoring and Follow-up Figure 10.b Abnormal Liver Associated Test Results: Considerations for Study Drug Discontinuation
27	Updated AESI section to include cytopenias, renal dysfunction, and hypersensitivity reaction; and renaming of liver injury to abnormal liver function tests.	Regulatory agency feedback. Clarification for accurate depiction of clinical data.	Section 8.3.8.7 Adverse Events of Special Interest
28	Clarified that 'bilateral tubal ligation' is also a highly effective method of contraception.	Clarification.	Table 10.c Acceptable Contraception Methods for This Study
29	Updated CTFG version.	Updated version for accuracy from 2014 to recent version 1.1 (21/09/2020).	Table 10.e Unacceptable Contraception Methods

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30	Added donation of eggs to the pregnancy and breastfeeding section, as a reason to notify the study site for AE and SAE reporting.	Clarification.	Section 10.4.3 Pregnancy and Breastfeeding
31	Replaced Appendices with a watermarked version and updated versions.	Updated for clarity to ensure that these appendices are used for reference only.	Appendix 4 Appendix 5 Appendix 6 Appendix 7 Appendix 8 Appendix 12 Appendix 13 (updated version) Appendix 14 Appendix 15 Appendix 16 Appendix 17

Summary of Changes Since the Last Version of the Approved Protocol			
Protocol Amendment 3			
Amendment Date: 22 March 2024			**Japan**
Overall Reason for the Amendment The immediate reason for this protocol update is to address recommendations for psoriasis studies received during Regulatory Agency review.			
Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of Change(s)**	**Rationale for Change(s)**	**Section**
1	Revised to add “highly” effective method of contraception.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section1.1 Synopsis Section 5.1 Inclusion Criteria Section 10.4.2 Contraception Guidance
2	Revised exclusion criteria for HBV.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria Table 10.f
3	Revised exclusion criteria for subjects with a history of cancer.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
4	Revised exclusion criteria for subjects with cardiovascular disease history.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
5	Revised exclusion criteria 31 and 32.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 1.1 Synopsis Section 5.2 Exclusion Criteria

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6	Revised the language to clarify the details of temporary drug interruption and permanent drug discontinuation.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 7.1.1 Temporary Interruption of Study Drug Section 7.1.2 Permanent Discontinuation of Study Drug
7	Added reference to Section 10.1.12 for more detailed list of safety parameters for site or study early termination.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 10.1.9.2 Study/Site Termination
8	Added table of AE subtypes and reporting.	For consistency with the amended protocol based on regulatory feedback in TAK-279 studies for psoriasis.	Section 10.3, Table 10.a

Summary of Changes Since the Last Version of the Approved Protocol

Protocol Amendment 2

Amendment Date: 26 January 2024 **Japan**

Overall Reason for the Amendment

The immediate reason for this protocol update is to add clinical test for safety evaluation.

In this amendment, minor grammatical, editorial, formatting, and administrative changes are included for clarification and administrative purposes only. These changes do not affect the conduct of this study; thus, they are not listed below.

Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of Change(s)**	**Rationale for Change(s)**	**Section**
1	Correction of the timepoint to JDA severity score assessment for GPP eligibility	Consistency with the selection criteria of conducting JDA severity score assessment at screening	Section 1.1 Synopsis Overall Design and Methodology Section 4.1 Overall Design
2	Clarify the criteria for drugs for immune-related diseases during clinical trials	Clarify the criteria for drugs for immune-related diseases during clinical trials	Section 1.1 Synopsis Section 5.2 Exclusion Criteria
3	Tuberculosis testing methods changed to T-SPOT	Tuberculosis testing changed to a method based on actual clinical	Section 1.1 Synopsis Section 1.3 Schedule of Activities (SoA) Section 5.2 Exclusion Criteria Section 8.3.4 Clinical Safety Laboratory Tests Table 8.a
4	Addition of C reactive protein (CRP) to clinical laboratory tests	Clarify that CRP specified in the JDA severity score should be conducted as one of the clinical safety laboratory tests in this study, including the timepoints	Section 1.3 Schedule of Activities (SoA) Table 1.a Section 8.3.4 Clinical Safety Laboratory Tests Table 8.a
5	Addition of scheduled date for Serology test, and table footnote for fasting lipid panel and GPPGA	Clarify the scheduled date of Serology test, and the description of fasting lipid panel and GPPGA	Section 1.3 Schedule of Activities (SoA) Table 1.a

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6	Correction to the timepoint	Clarify the timepoint at which information is observed	Section 5.4.2 Rescreening
7	Addition of alcohol use	Add alcohol use as the demographic information	Section 8.1.1 Demographics
8	Correction of the references	Clarify the reference for reporting procedures for SAEs or AESI	Section 8.3.4 Clinical Safety Laboratory Tests
9	Correction of reporting deadline	Clarify reporting deadline as within 24 hours	Section 8.3.8.7 Adverse Events of Special Interest
10	Addition of GPP and EP	Clarify the definition of psoriasis	Section 9.4.1.3 Strategy for Addressing Intercurrent Events Section 9.8 Other Analyses
11	Addition of PASI and GPPASI	Add the endpoints for secondary efficacy assessment	Section 9.4.2 Secondary Efficacy Endpoints
12	Update of abnormal liver test result monitoring and follow up assessments to include changes related to potential hepatic toxicity with parameter for elevation of aspartate aminotransferase (AST).	To update potential hepatic toxicity parameter consistent with drug-induced liver injury guidance	Section 10.5, Abnormal Liver Associated Test Result Monitoring and Follow-up Assessments; Figure 10.b
13	Revision to specify Abnormal Liver-Associated Test Results: Considerations for "Discontinuation" of Study Drug rather than "Temporary Hold" for consistency.	To be consistent in Section 10.5 and clearly specify that subjects presenting with findings suggestive of potential severe hepatic injury should be discontinued from investigational product	Section 10.5, Abnormal Liver-Associated Test Result Monitoring and Follow-up Assessments, Figure 10.b
14	Revision of SAE reporting language for subjects with combined elevations of aminotransferase(s) and bilirubin to remove "irrespective of an alternative etiology has not been identified"	To clarify that any event of elevated AST or ALT ≥3× ULN with concurrent elevated total bilirubin >2× ULN or elevated INR >1.5 must be reported as an SAE, irrespective of an alternative etiology being identified	Section 8.3.8.4.1, Reporting of Abnormal Liver-Associated Test Results; Section 10.3.5.1 Reporting of Abnormal Liver Associated Test Results; Section 10.5, Abnormal Liver Associated Test Result Monitoring and Follow-Up Assessments
15	Revision of figure to specify laboratory testing is to be repeated within "48-72 hours" rather than 3-5 days for subjects with significant elevations of aminotransferases that do not meet the individual stopping criteria (eg, isolated ALT or AST >3× ULN).	To comply with regulatory agency guidance for drug-induced liver injury	Section 10.5, Abnormal Liver Associated Test Result Monitoring and Follow-up Assessments, Figure 10.a
16	Correction of the laboratory location for the HBV DNA test and addition of table for the schedule	Clarify that the HBV DNA test will be conducted at central laboratory, and the scheduled timepoints	Appendix 2 Exclusion Criteria for Hepatitis B

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Protocol Amendment 1			
Amendment Date: 16 November 2023			**Japan**
Overall Reason for the Amendment The immediate reason for this protocol update is to incorporate regulatory feedback from the Pharmaceuticals and Medical Devices Agency. In addition, changes due to the establishment of the Cardiovascular Adjudication Committee were added. The following table summarizes these changes. In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only and are not captured in the following table.			
Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of Change(s)**	**Rationale for Change(s)**	**Section**
1	Exclusion criterion #5, Tuberculosis c) (2) Subject remains eligible if prophylaxis (appropriate in duration and type per current guidelines) was initiated at least 3 weeks prior to Day 1.	Corrected according to guidance for latent tuberculosis infection.	1.1 Synopsis 5.2 Exclusion Criteria
2	For eligible subjects who were negative for HBV-DNA at Screening test and are of the #3 and #5 types in Appendix 2, the timing of HBV DNA testing after initiation of study treatment was modified to be performed once per month for the first 6 months and every 3 months thereafter.	Corrected according to guideline for the management of Hepatitis B.	Table 1.a Schedule of Activities footnote 2.3.3 Proposed Risk Mitigation Strategy 8.3.4 Clinical Safety Laboratory Tests Appendix 2 Exclusion Criteria for Hepatitis B
3	The composition of TAK-279 tablet is described in Table 6.a. In addition, reference was added to Exclusion Criterion #28.	Provided additional information on the study drug.	1.1 Synopsis 5.2 Exclusion Criteria 6.1 Study Intervention(s) Administered
4	The establishment of the Cardiovascular Adjudication Committee (CAC) and the details of its adjudicate were described.	Additions due to establishment of CAC.	1.1 Synopsis 2.3.3 Proposed Risk Mitigation Strategy 4.1.2 Treatment Period 7.1.1 Temporary Interruption of Study Drug 10.1.5.1 Cardiovascular Adjudication Committee
5	Added detailed description of unscheduled visits.	Addition regarding unscheduled visits.	1.3 Schedule of Activities (SoA)
6	Removed exploratory objectives #3 and #4.	Correcting incorrect descriptions.	3.1.4 Exploratory Objectives

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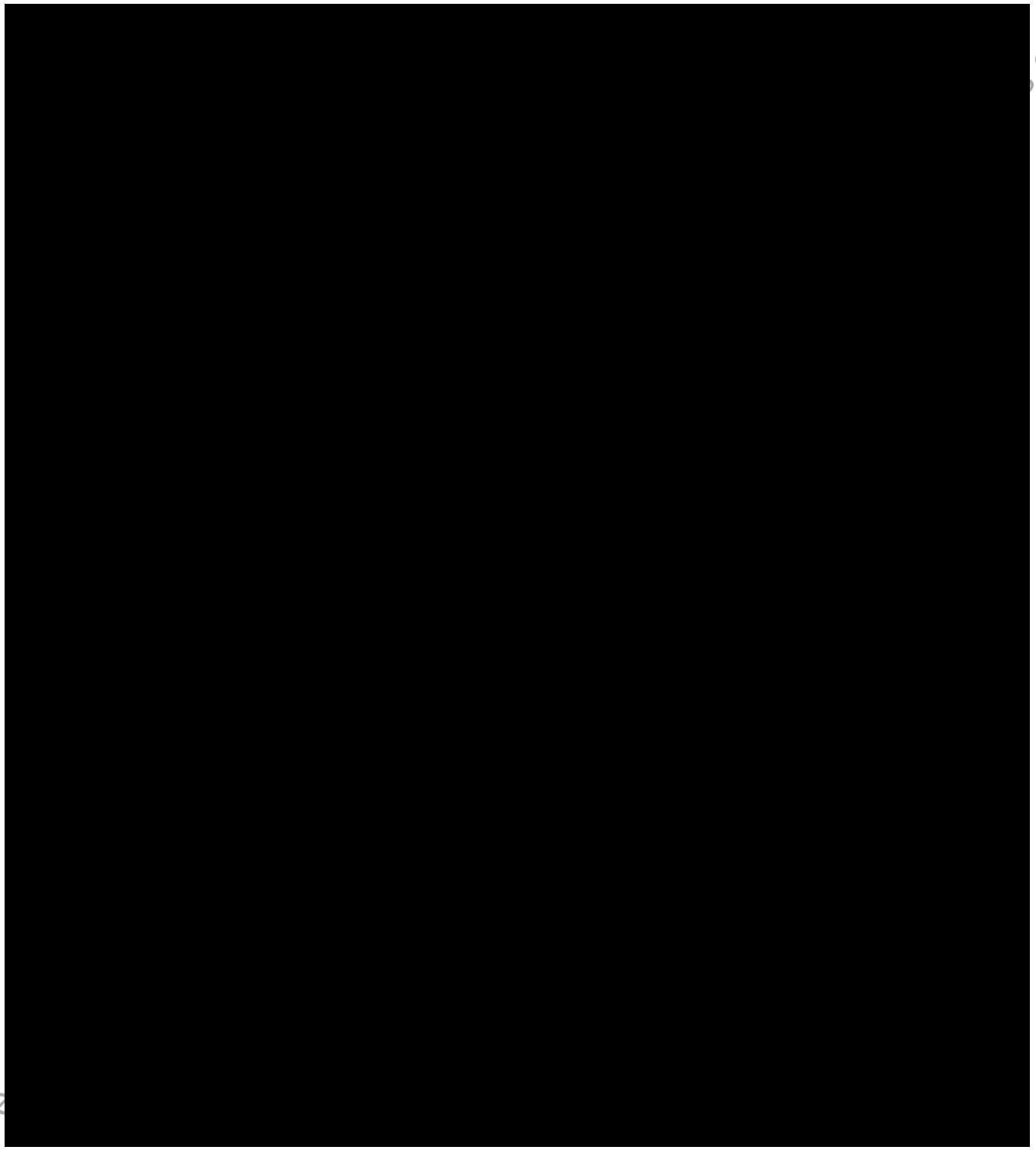
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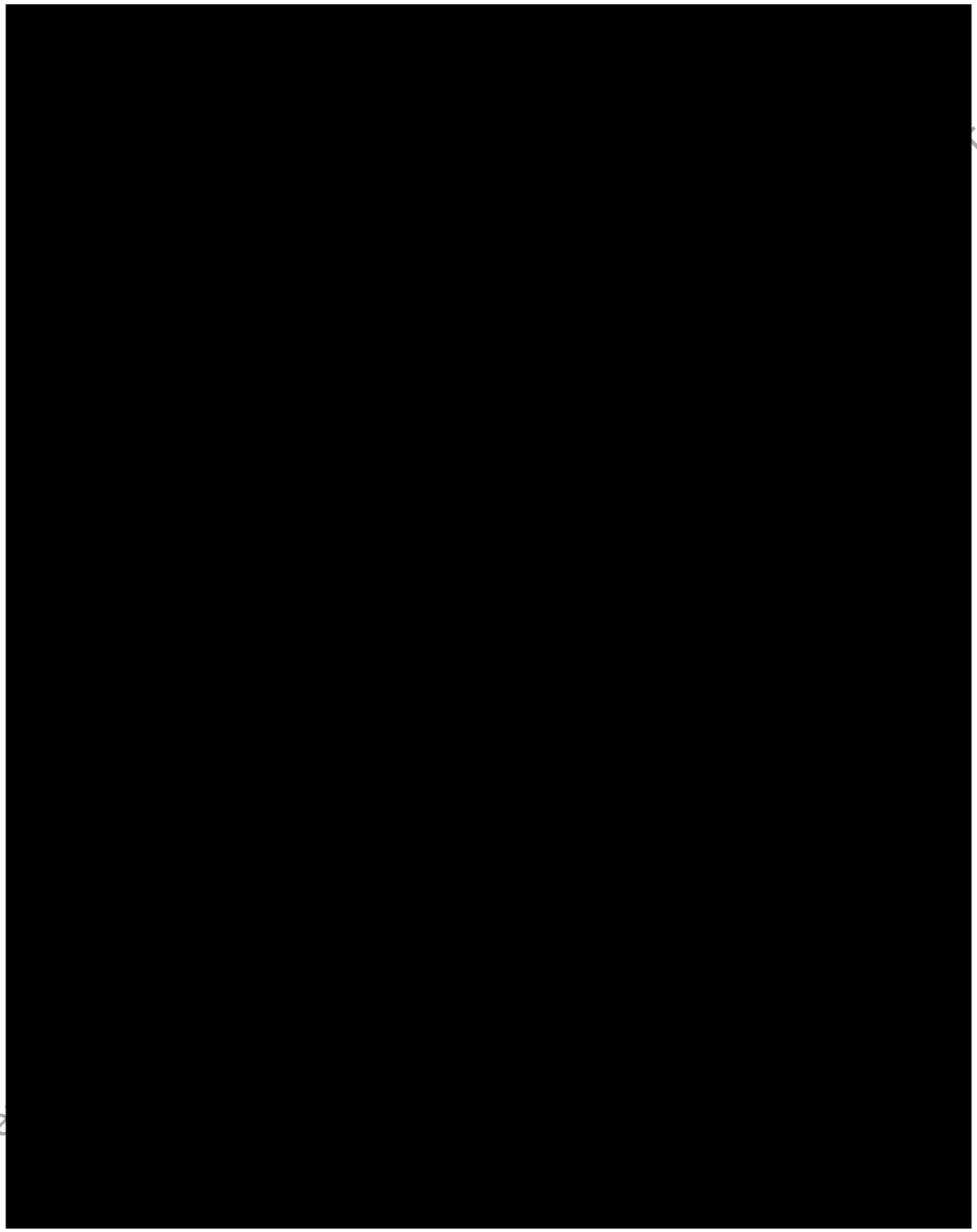
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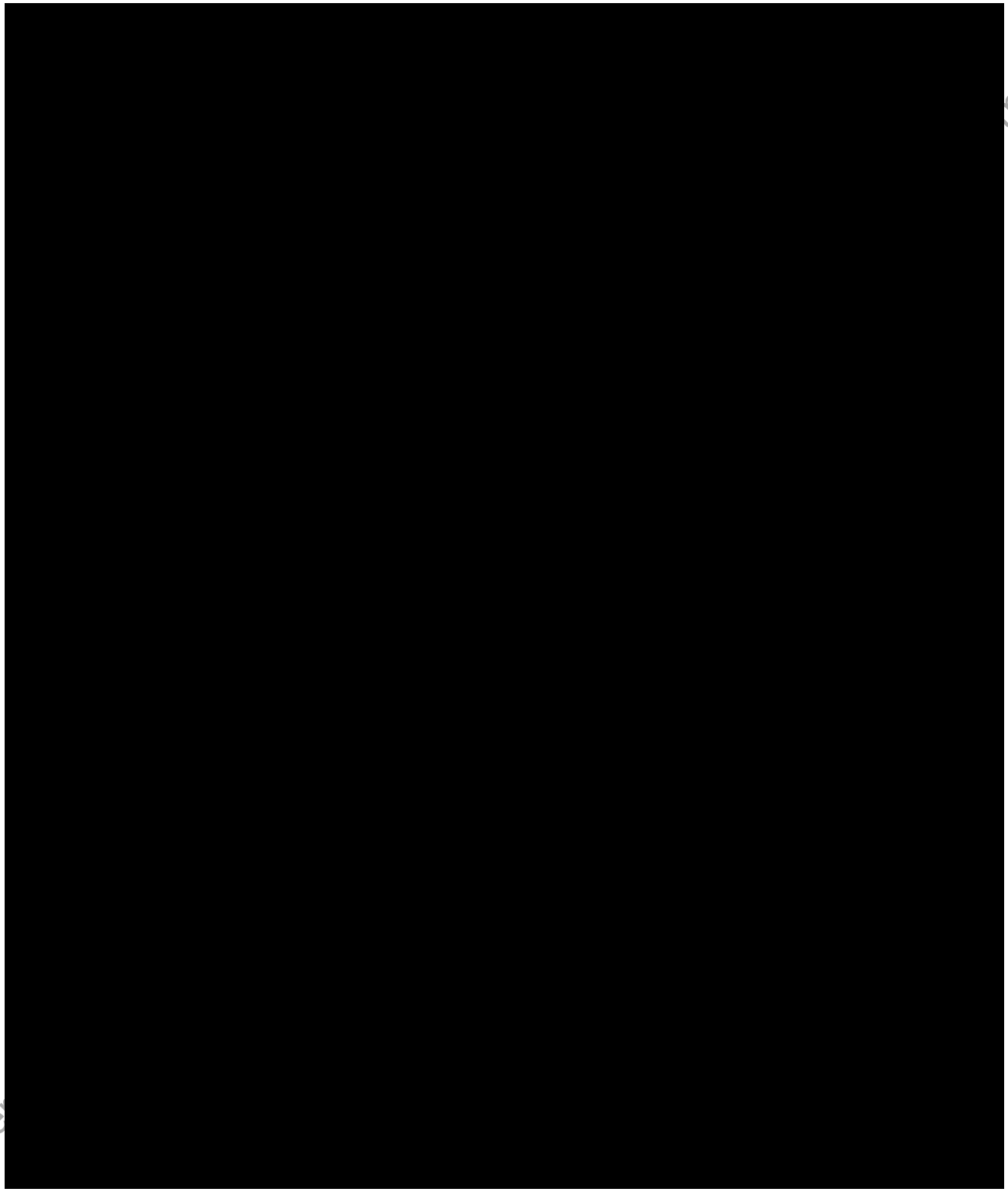
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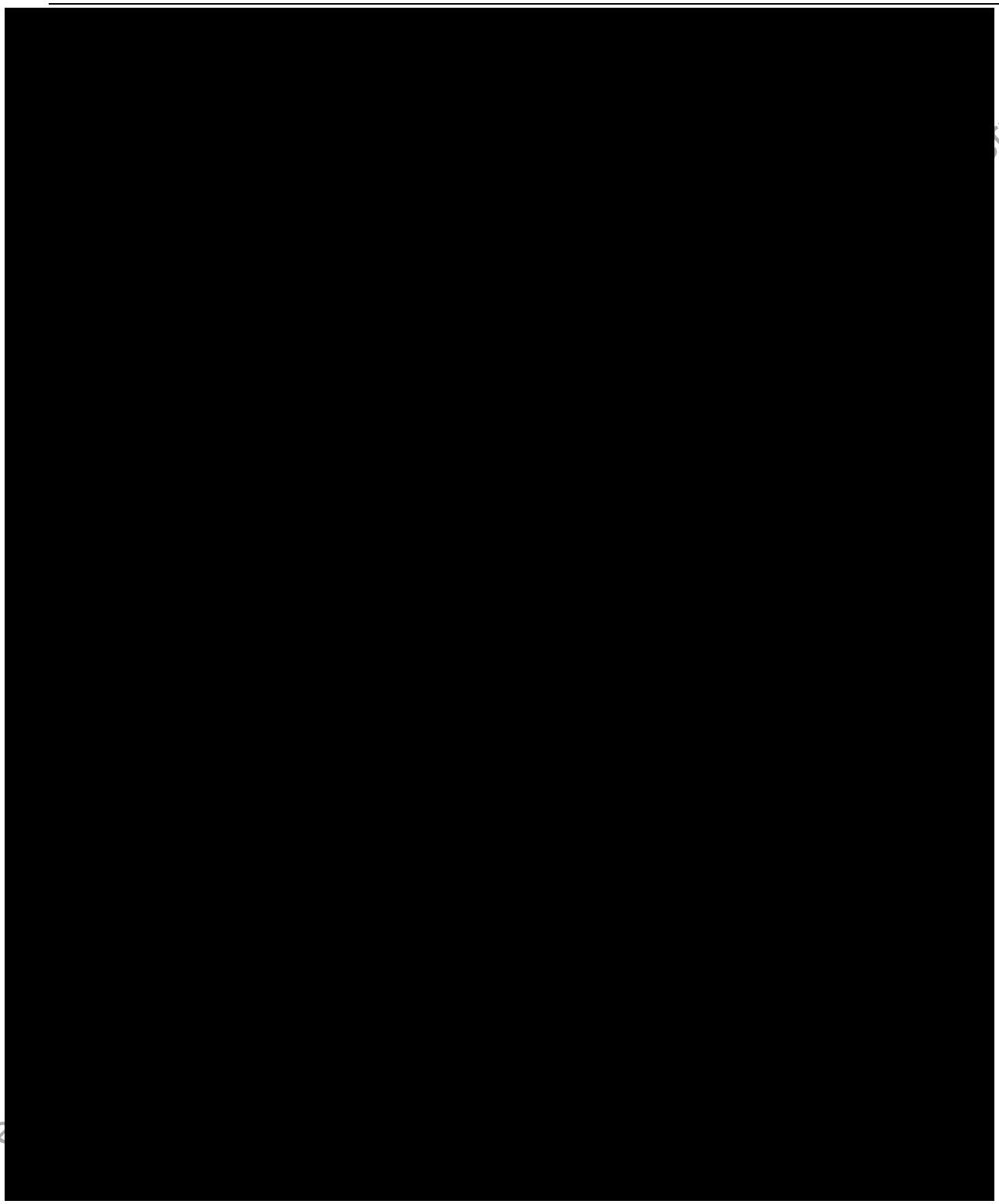
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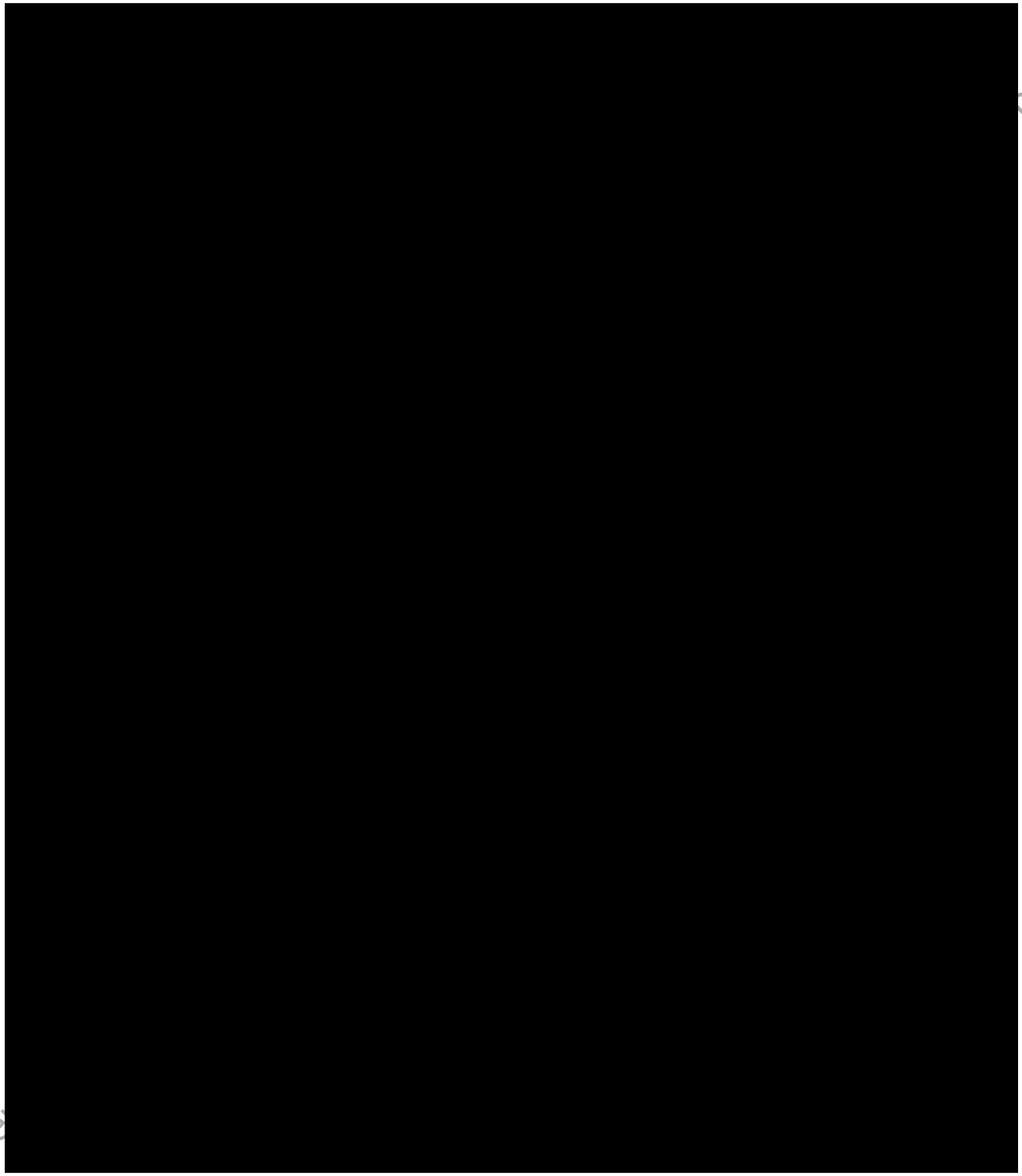


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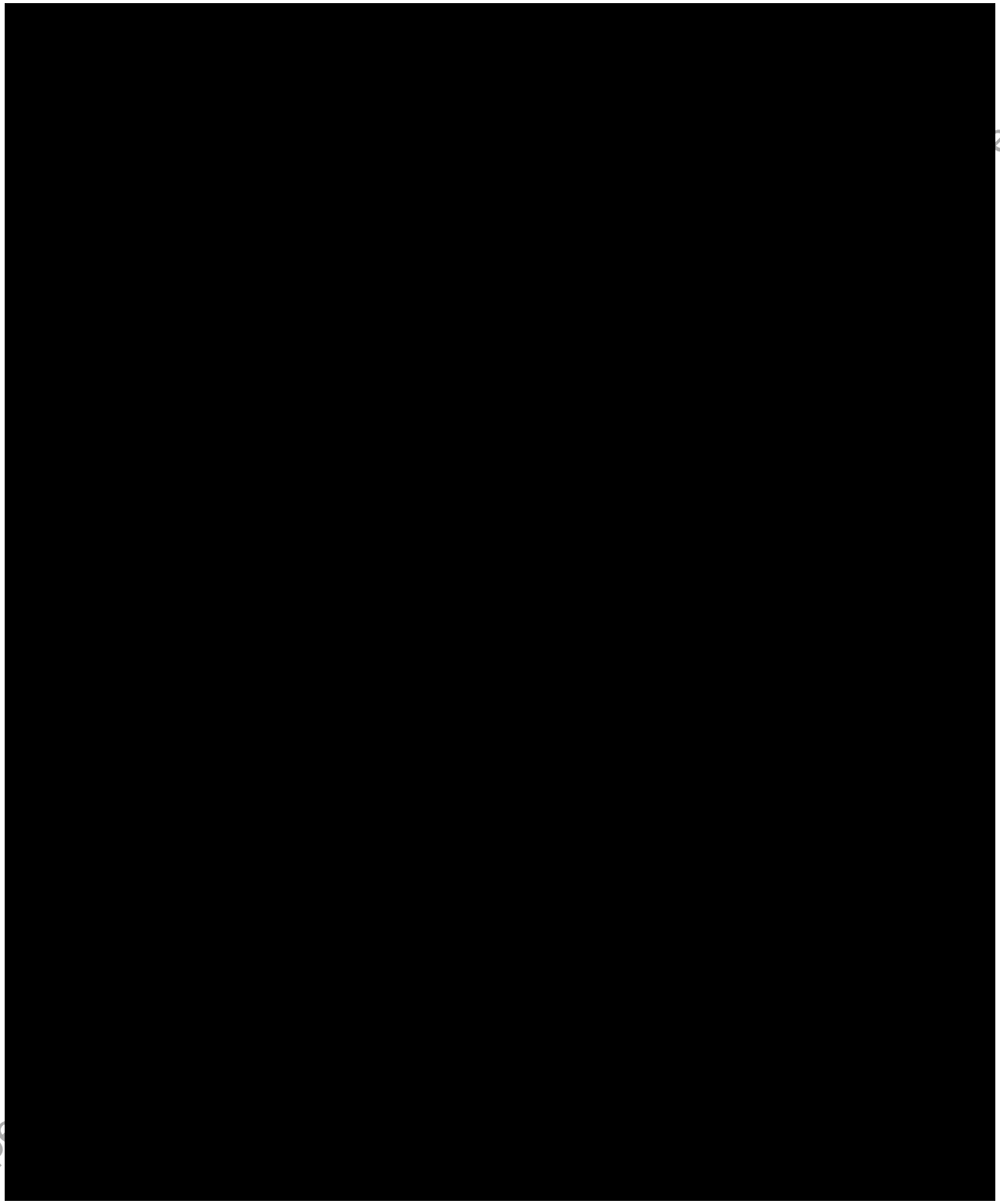


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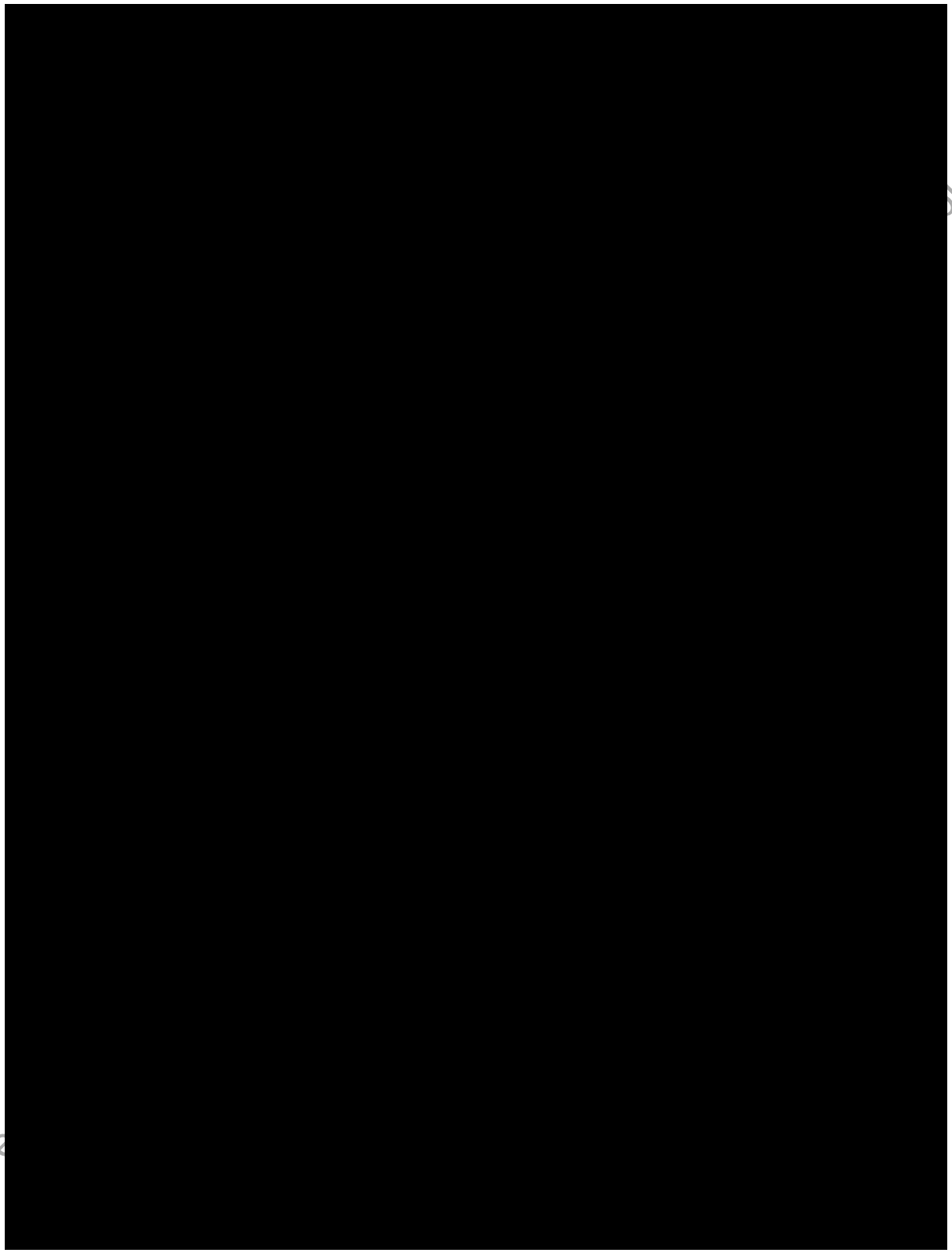


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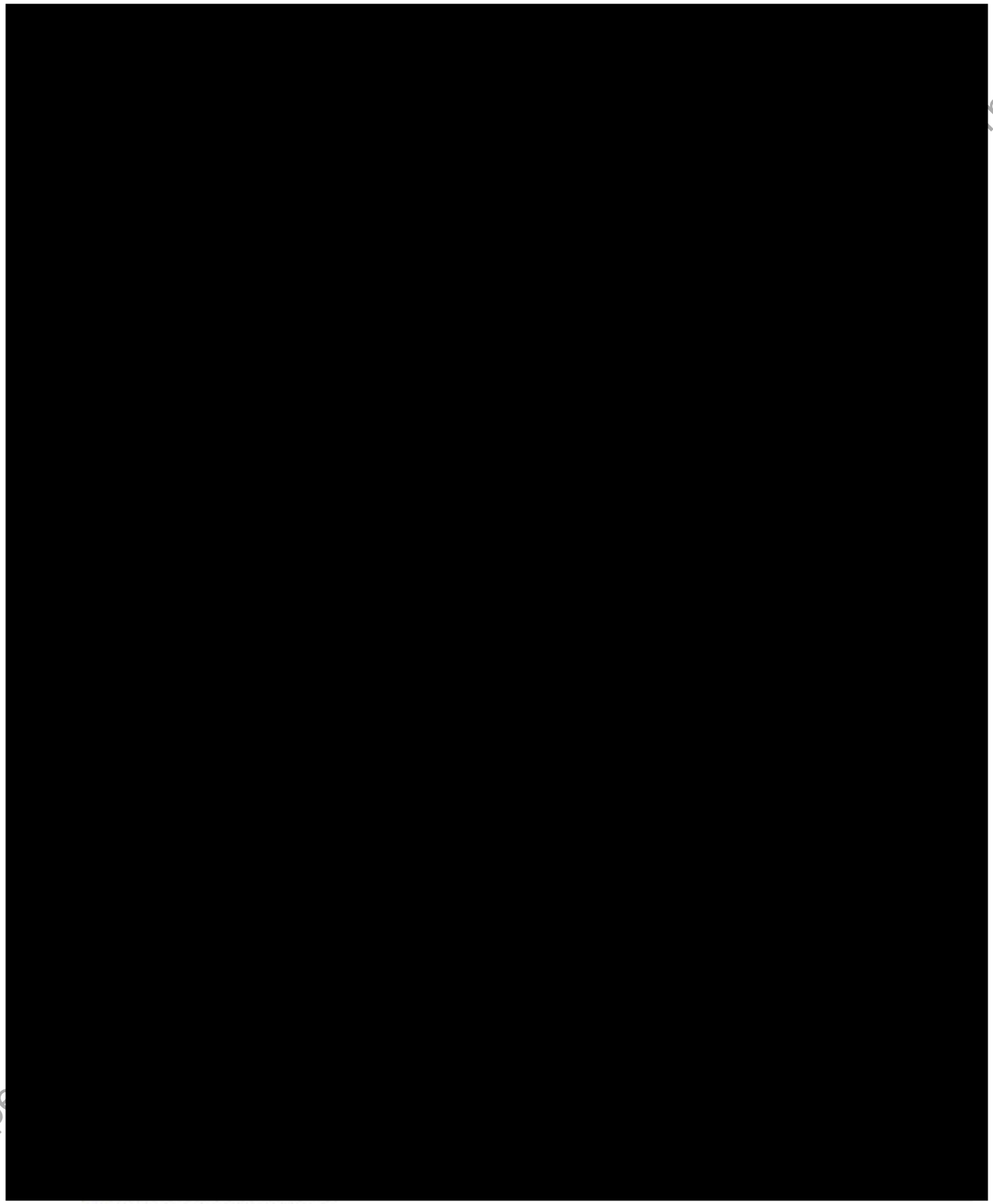


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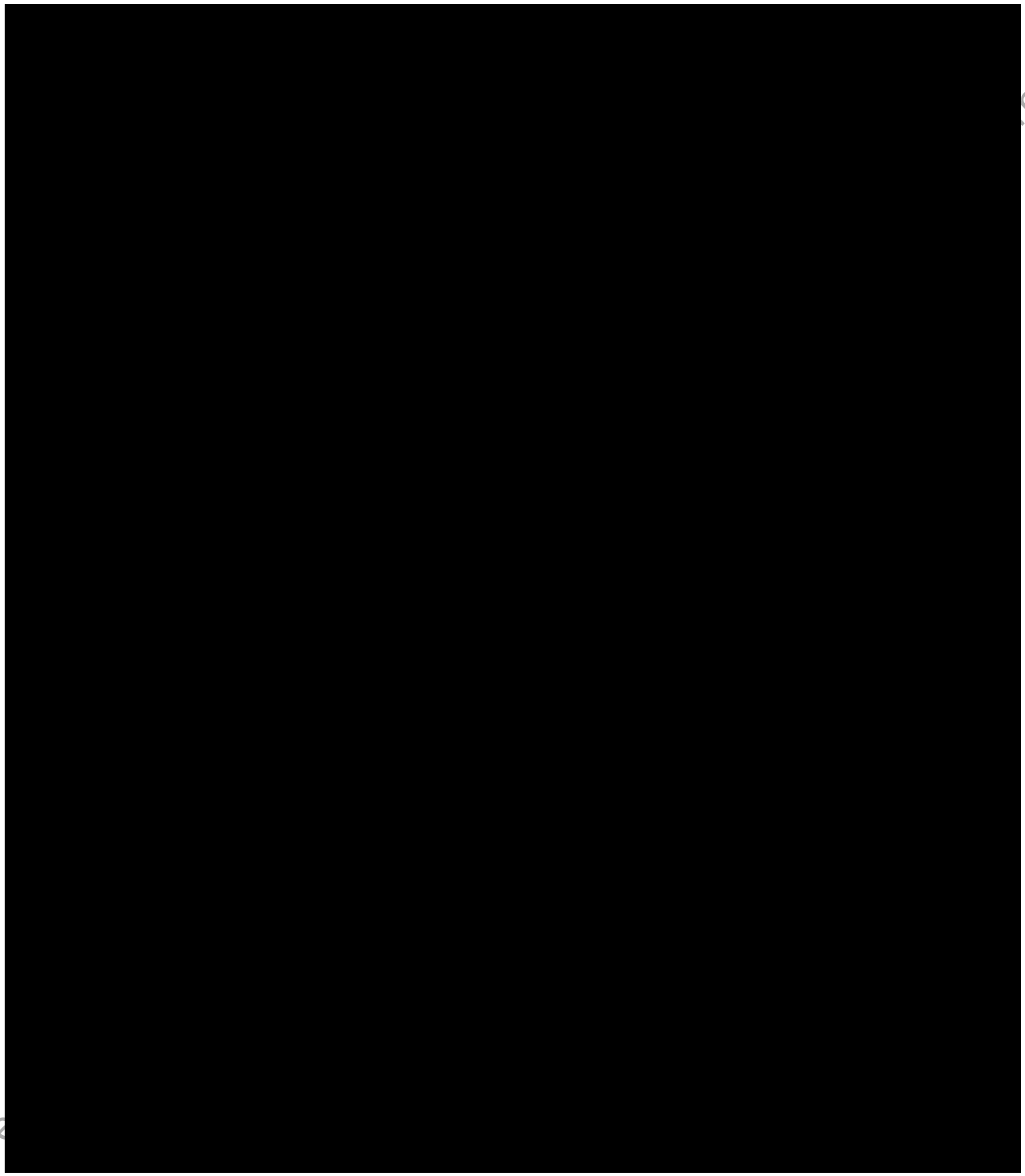


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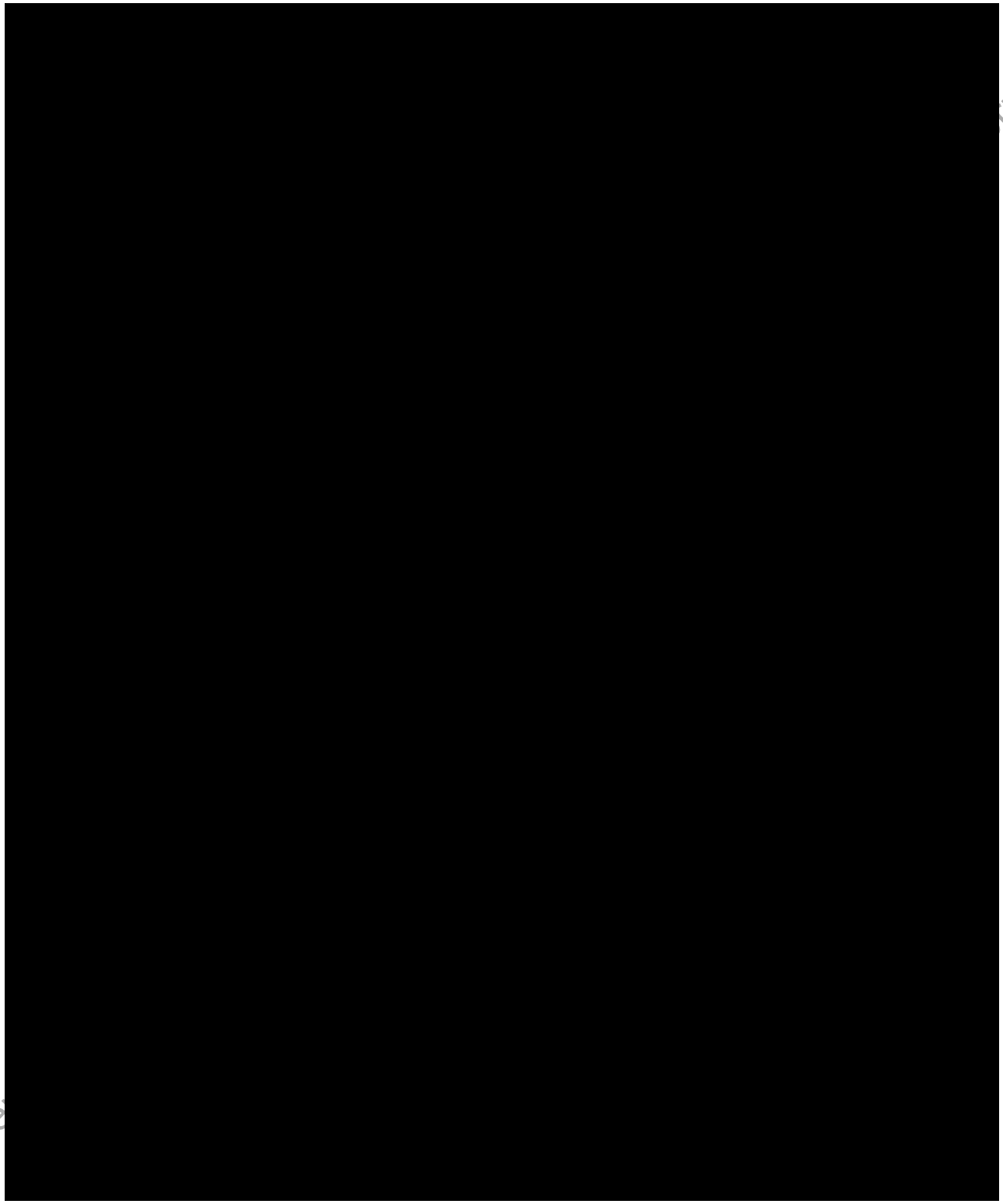
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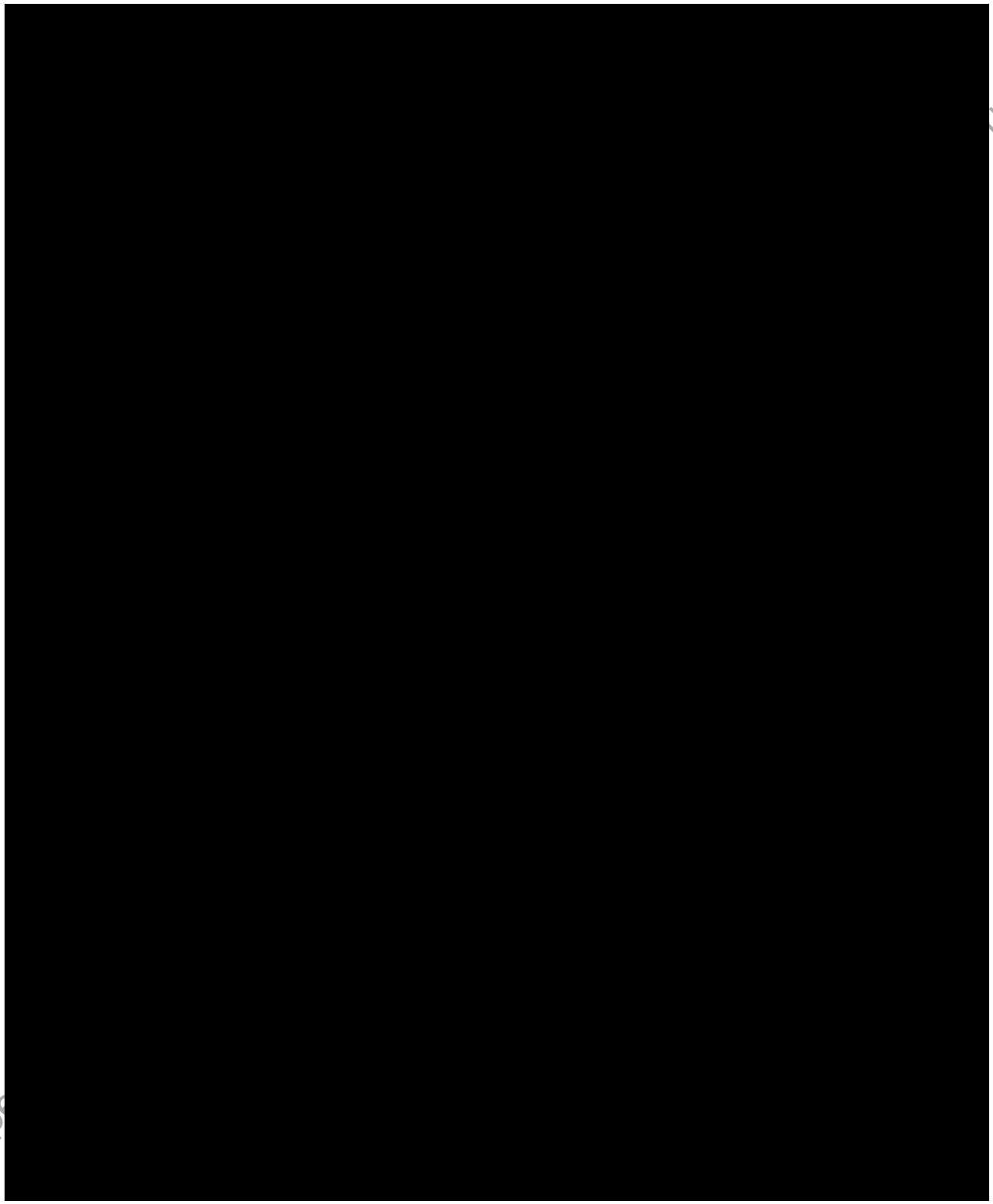
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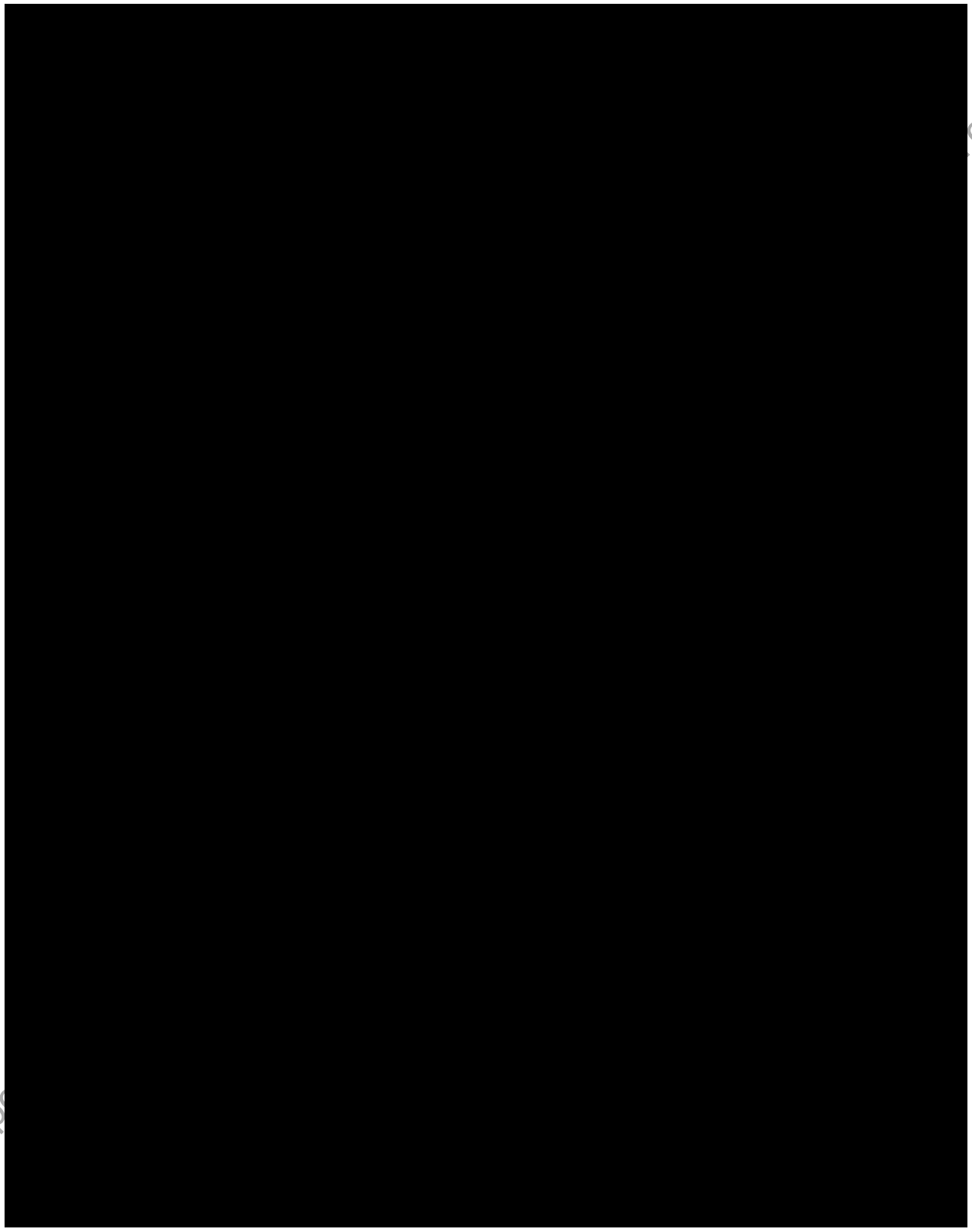


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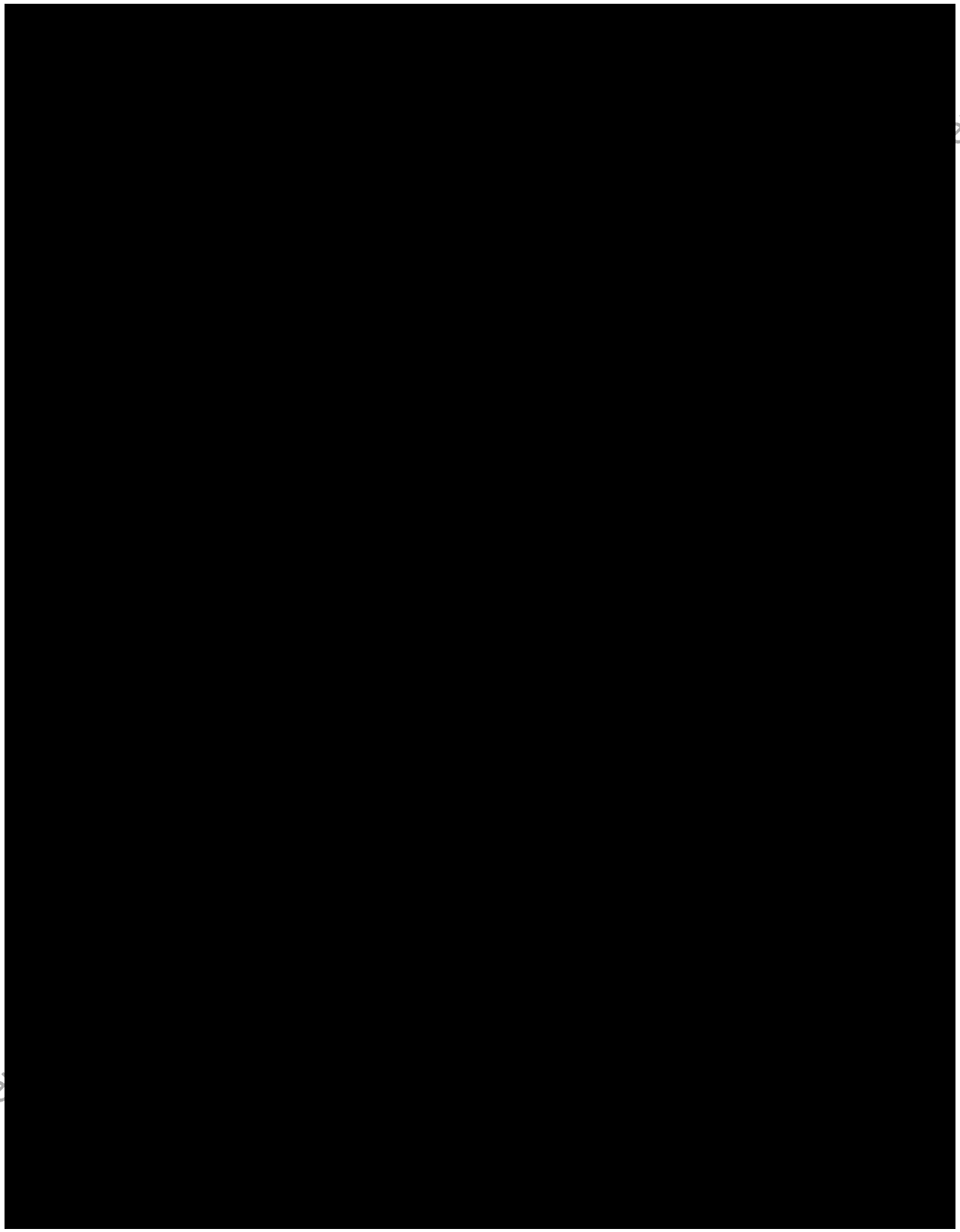


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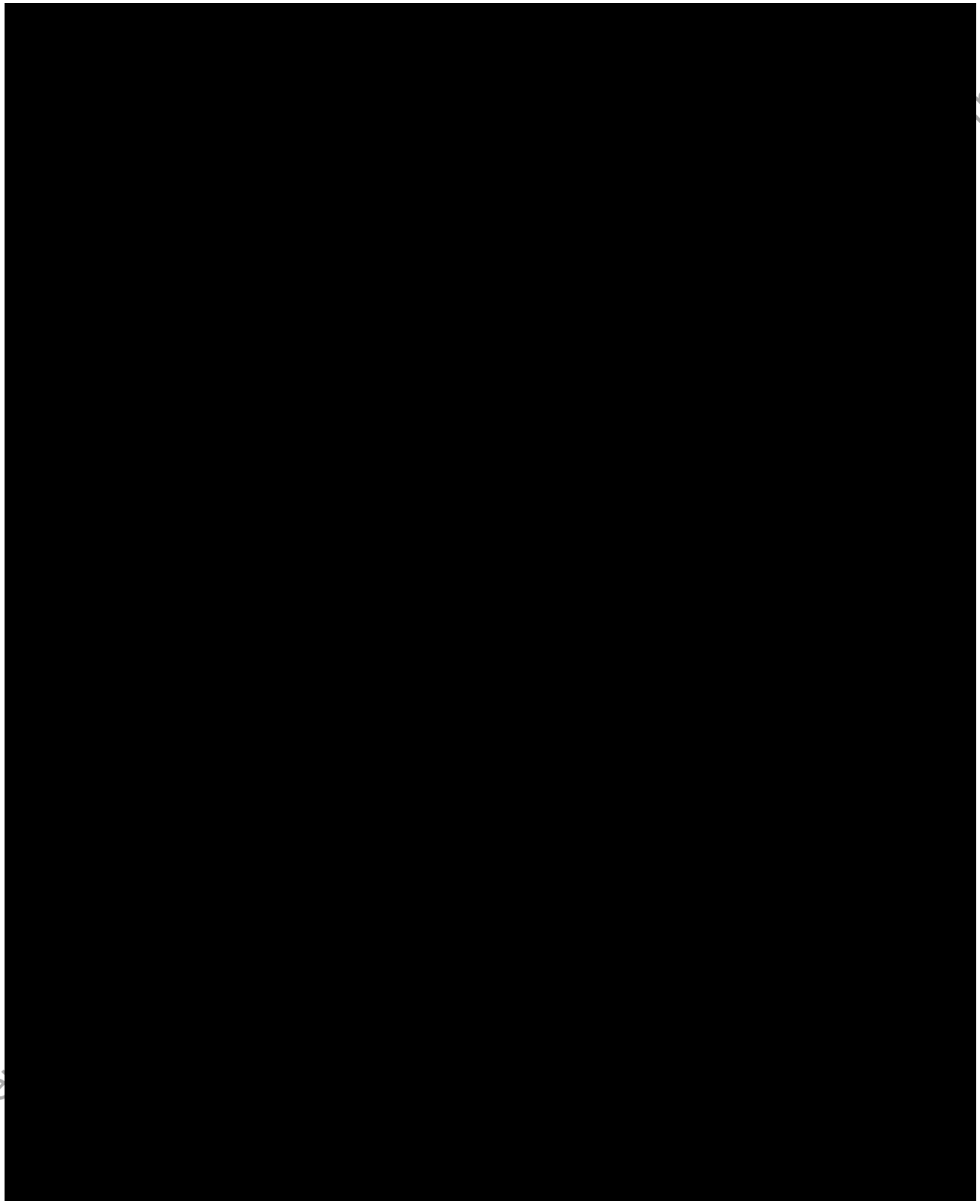


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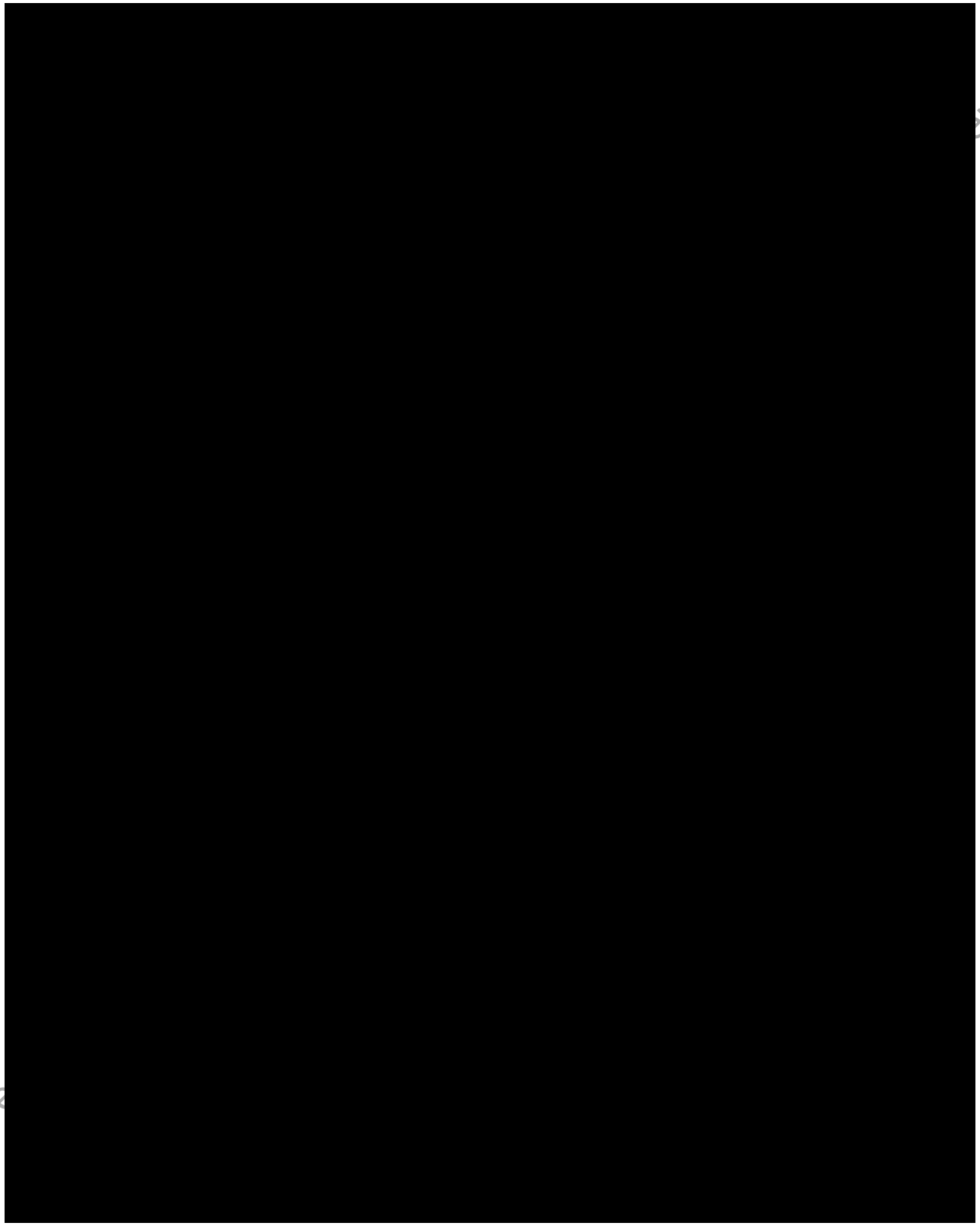


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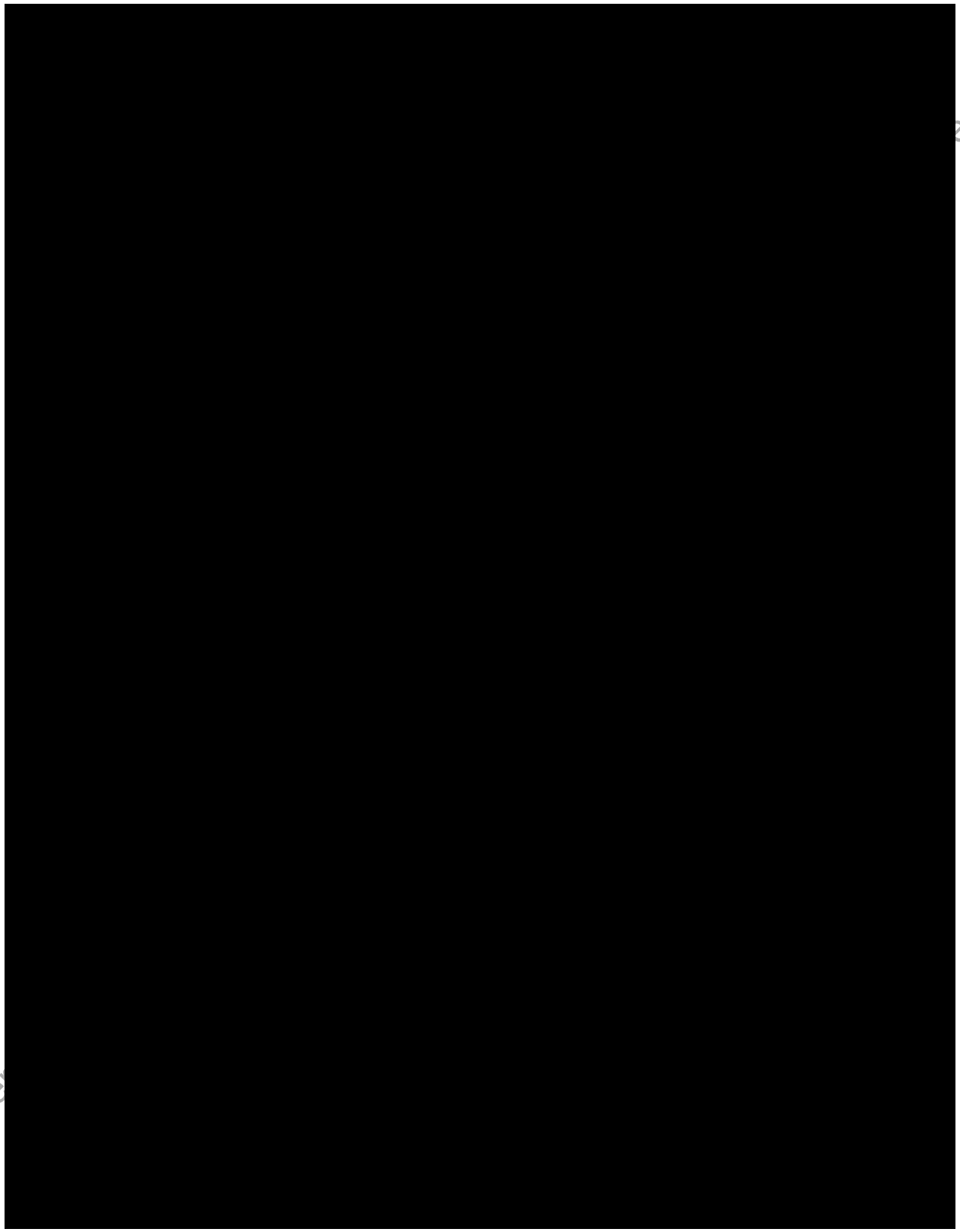


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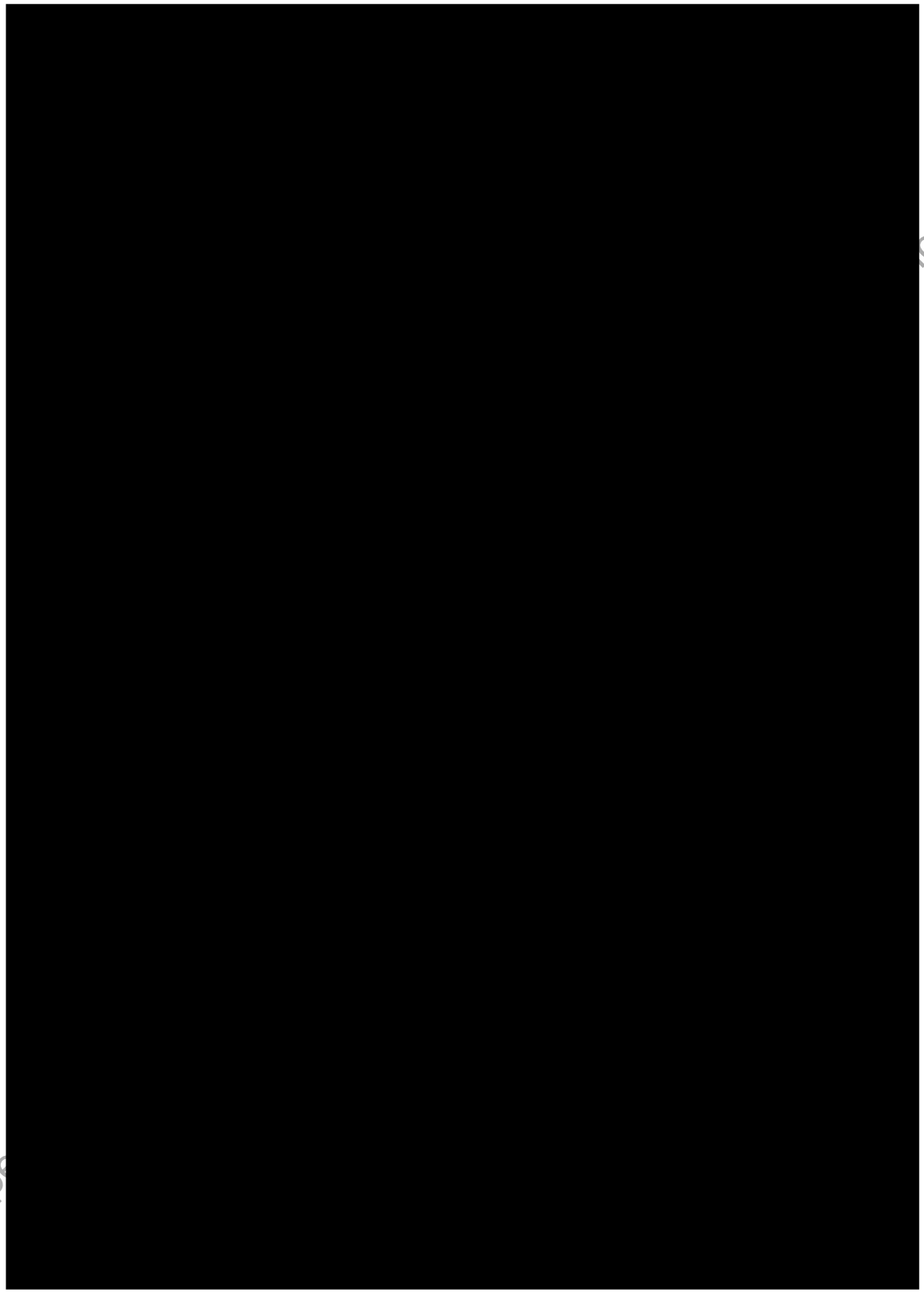


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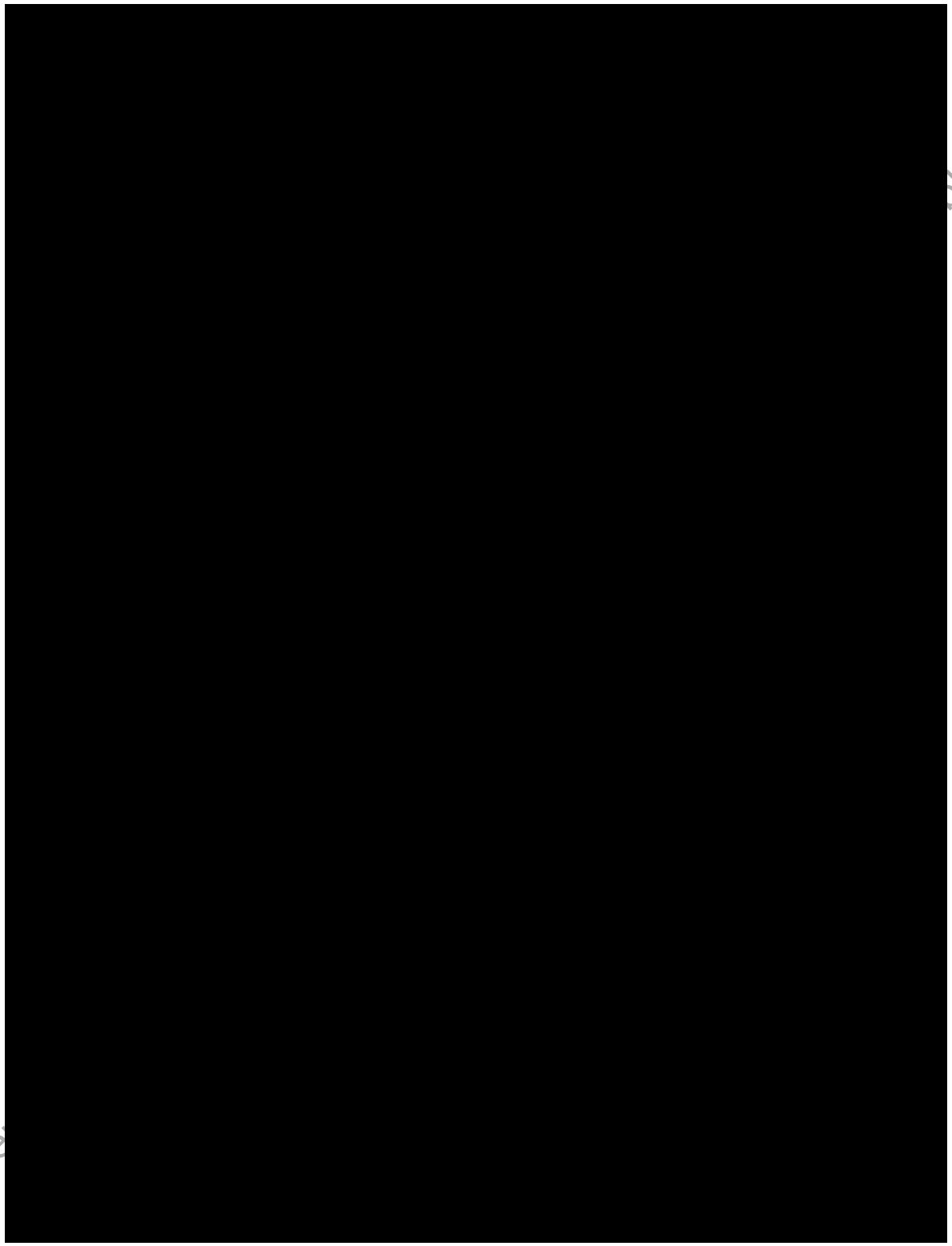
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