TRIAL STATISTICAL ANALYSIS PLAN

c37761029-02

BI Trial No.:	1368-0024
Title:	Trial Statistical Analysis Plan An open-label, single arm, long term trial of Spesolimab treatment in patients with Palmoplantar Pustulosis (PPP) who have completed previous BI Spesolimab trials [c29867818-02]
Investigational Product(s):	Spesolimab, BI 655130
Responsible trial statistician(s):	[redacted] Tel.: [redacted], Fax: [redacted] [redacted] Tel.: [redacted], Fax: [redacted]
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADAs	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BI	Boehringer Ingelheim
BIcMQ	Boehringer Ingelheim customized MedDRA Query
BMI	Body mass index
RPM	Report planning meeting
CARE	Clinical data analysis and reporting environment
CRF	Case report form
CTA	Clinical trial authorizations
CTP	Clinical trial protocol
CTR	Clinical trial report
DBLM	Database lock meeting
[redacted]	[redacted]
DMC	Data monitor committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDISH	Evaluation of drug-induced serious hepatotoxicity
EMA	European medicines agency
EOS	End of study
EOT	End of treatment
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
IB	Investigator's brochure
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use

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Term	Definition / description
iPD	important protocol deviation
ISF	Investigator site file
LD	Day of last treatment received
MAA/BLA	Market Authorization Application/Biologics Licence Application
MACE	Major adverse cardiovascular event
MedDRA	Medical dictionary for regulatory activities
MQRM	Medical quality review meeting
Nab	Neutralizing antibody
NMSC	Non-melanoma skin cancer
NRI	No response imputation
OC	observed cases excluding values after any use of rescue medication or 6 weeks following last drug administration if patient early discontinued treatment
OC-IR	Observed cases including values after rescue therapy or treatment discontinuation
OLE	Open label extension
OR	Original results
PD	Protocol deviation
PGA	Physician global assessment
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
[redacted]	[redacted]
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RCTC	Rheumatology common toxicity criteria
REP	Residual effect period
[redacted]	[redacted]
RPM	Report plan meeting
s.c.	subcutaneous
SAE	Serious adverse event

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Term	Definition / description
SAF	Safety analysis set
SAF-MT	Safety analysis set for maintenance treatment
SAP	Statistical analysis plan
SAS™	Statistical analysis software ™
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SMQ	Standardised MedDRA query
SOC	System organ class
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TS	Treated set
TS-MT	Treated set for maintenance treatment
TSAP	Trial statistical analysis plan
UDAEC	User-defined adverse event categories
ULN	Upper limit of normal range
[redacted]	[redacted]
WHO-DD	World health organisation – drug dictionary
WOCBP	Women of childbearing potential

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3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the clinical trial protocol (CTP) and its amendments, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the CTP and its amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, and planning of sample size.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

[redacted]

Since the primary aim of this study is to collect long-term safety and efficacy data on the use of Spesolimab (BI 655130) in patients with PPP who have completed their treatment in previous Spesolimab trials, multiple interim analyses will be done over the 5-year conduct phase of this trial in order to support, for example, regulatory interactions, Clinical Trial Authorizations (CTA), and MAA/BLA submissions, and also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to the investigators via IB updates and publications. Any data cut-off to be used for the reporting of trial data at interim will be presented in either a separate data cleaning plan, or in an appendix to this TSAP.

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4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In the CTP, only one patient population will be analysed in this trial: the treated set for maintenance treatment (TS-MT). In the TSAP, the enrolled set (ES) is added for analysis of patient disposition, and the word "treated set" is changed to "safety analysis set (SAF)" for the consistency with other trials of the study compound.

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5. ENDPOINTS(S)

For the summary of all efficacy data, only those observations which were collected during the on-treatment period will be used.

For estimand and handling of missing data and the occurrence of inter-current events, unless otherwise specified, see Section 6.3 and Section 6.6.

Regarding the analyses of the change from baseline by visit or compared to baseline by visit for efficacy endpoints, unless otherwise specified, the baseline in parent trial is used, which refers to the last measurement collected prior to initiation of treatment in parent trials.

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to week 260 of maintenance treatment.

Please refer to Section 7.8.1 for the description of the calculation of exposure-adjusted adverse event incidence rates.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable. No key secondary endpoints have been specified in the CTP.

5.2.2 Secondary endpoint(s)

Secondary endpoints are defined as described below. Note that for the secondary endpoints, any data collected after use of any rescue therapy or after 6 weeks following discontinuation of treatment (to allow for incorporation of the continuing maximum treatment effect period) in current trial are censored for the purpose of the primary estimand. This approach is in line with parent trial 1368.16.

- Percent change in PPP ASI from baseline in parent trial at week 48, 96, 144, 192, 240 and 260
- Proportion of patients with PPP ASI50 compared to baseline in parent trial at week 48, 96, 144, 192, 240 and 260
- Proportion of patients with PPP PGA of 0 (clear) or 1 (almost clear) at week 48, 96, 144, 192, 240 and 260

Derivations of PPP ASI related endpoints and PPP PGA related endpoints are described in Section 10.1.1 and Section 10.1.2.

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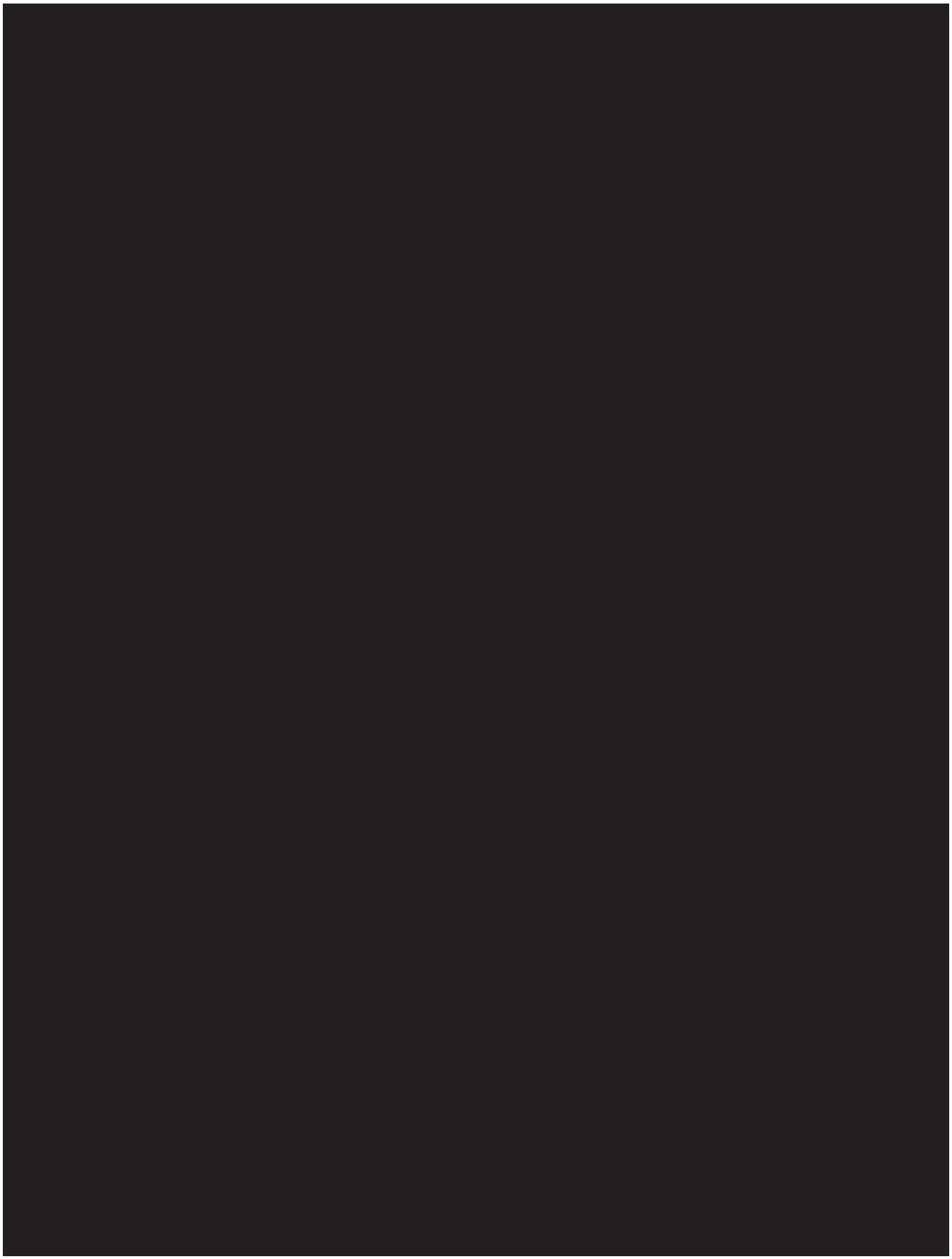

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[redacted]

5.4 OTHER VARIABLE(S)

5.4.1 Safety endpoints

Intensity of adverse events is assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0.

Safety is assessed based on:

- Adverse events
- Safety laboratory values

  Tests are listed in CTP Table 5.2.3: 1.

  Lab tests are planned to be performed at the central laboratory service provider.
- Physical examination (documentation as baseline condition or AE)
- Vital signs, including
  - body temperature
  - pulse rate
  - systolic blood pressure
  - diastolic blood pressure
  - respiratory rate
- Relevant findings in 12-lead ECG (documentation as baseline condition or AE)
- Local tolerability

  Local tolerability will be assessed by the investigator according to ‘swelling’, ‘induration’, ‘heat’, ‘redness’, ‘pain’, or other findings.
- ADA (anti-drug antibody), as detailed in the lab manual

5.4.2 Demographic and other baseline characteristics

Standard demographic data and baseline characteristics are used as recorded in the eCRF. These include sex, weight, height, BMI, race, ethnicity, age, site region and smoking history.

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BMI will be calculated as weight [kg] / height $[m]^2$ (based on the last available weight measurement prior to the first dose of Spesolimab of extension trial).

Age [years] will be determined as the difference between year of birth and year of informed consent of current study.

Details of smoking history and changes for current extension trial will be summarized in an additional output based on treated patients.

Disease characteristics of PPP will describe time since first diagnosis [years] of PPP based on treated patients.

Disease characteristics of plaque psoriasis will describe time since first diagnosis [years]. Only treated patients who showed signs of chronic plaque psoriasis at baseline in parent trial will be included.

Time since first diagnosis/tonsillectomy [years] will be calculated as the difference between date of first diagnosis and date of informed consent of current study, divided by 365.25. For calculation in the context of incomplete information on the date of first diagnosis, cf. Section 6.6.6.

5.4.4 Treatment compliance and treatment exposure

Treatment exposure will be assessed as the total dose of maintenance treatment [mg] administered. Per CTP Section 4.1.1, the investigational product is provided in prefilled syringes of either 1 mL or 2 mL (PFS-1 or PFS-2) volume, and the unit strength of the investigational product is 150 mg in 1 mL solution, the amount of Spesolimab within each syringe is 150 mg in 1mL prefilled syringe and 300 mg in 2 mL prefilled syringe. The total dose of maintenance treatment [mg] actually received will be calculated as the number of PFS-1 syringes actually injected multiplied by 150 mg plus the number of PFS-2 syringes actually injected multiplied by the 300 mg, which is:

Actual total dose [mg] =

$$\text{Actual number of PFS-1 injected} \times 150\ \text{mg} + \text{Actual number of PFS-2 injected} \times 300\ \text{mg}$$

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The total duration of exposure will be calculated as the date of last administration of trial treatment minus the date of first administration of trial treatment + 1 day.

The treatment compliance per subject (as a % of planned) is defined as the actual total dose injected, divided by the total dose that patient should have received, times 100, which is

$$Treatment\ compliance\ (\%) = \frac{Actual\ total\ dose\ [mg]}{Planned\ total\ dose\ [mg]}$$
$$= \frac{\text{Actual number of PFS-1 injected} \times 150\ \text{mg} + \text{Actual number of PFS-2 injected} \times 300\ \text{mg}}{\text{number of planned visits} \times 600\ \text{mg}}$$
$$\times 100.$$

For the patients who discontinued the study treatment prematurely only the visits on or before premature discontinuation will be used for the calculation of overall compliance.

[redacted]

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6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

The following maintenance treatment is planned in this study:

Spesolimab 600 mg q4w s.c. for up to 5 years for patients who have completed and clinically responded to the treatment with study drug (Spesolimab) in previous trials.

The following study phases are defined:

Table 6.1: 1 Flow chart of analysis phases of the study

Study analysis phase	Description	Start (included)	End (included)
Screening phase	Screening	Earliest of i) Date of informed consent, ii) First screening procedure	Date/time of start of injection for maintenance study drug minus 1 second
Maintenance treatment phase & Residual effect period	Maintenance on-treatment period	Date/time of start of injection of first maintenance study drug (Day 1 for maintenance)	Earliest of: i) Date of injection of last maintenance study drug + 112 days at 23:59, ii) cut-off for interim analysis if applicable.
Follow-up[1] phase	Off-treatment period	Date of injection of last maintenance study drug + 113 days at 12:00 a m.	Latest of: i) Date of EOS visit (Week 276 visit); ii) Last contact date on End of Study page at 11:59 p m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.

[1] The follow-up phase only exists if the date of EOS visit or the last contact date is after the date of injection/infusion of last study drug + 112 days.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., enrolled patients). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations will be provided to be discussed at the RPM/DBLM/MQRM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be queried in the clinical database. Each protocol deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM/MQRM minutes via an accompanying Excel spreadsheet (3). The following table contains the categories which are considered to be iPDs in this trial. If the data show other iPDs, for example, based on monitor visits to the sites, then this table will be supplemented accordingly by the time of the RPM/DBLM/MQRM. Not all iPDs will lead to

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exclusion from analysis sets. IPDs leading to exclusion from analysis sets are indicated as such in Table 6.2: 1.

As this is an open label, long term safety trial, all analyses will be performed based on the treated population only. Since no confirmatory efficacy testing is planned, no efficacy related iPDs leading to exclusion from analysis set are defined.

Table 6.2: 1 Important protocol deviations

Category/ Code	Description	Comments	Excluded from
A	**Entrance criteria violated**		
A1	**Inclusion criteria not met**		
A1.01	Have not completed treatment period in the parent trial LABEL: No completion of treatment period in parent trial	Inclusion criterion 2	None
A1.02	Have not obtained an individual health benefit, per investigator judgement (e.g. PPP PGA of 0 (clear) or 1 (almost clear) or other clinical improvement), from treatment in the parent trial LABEL: No individual health benefit from parent trial	Inclusion criterion 3	None
A1.03	Women of childbearing potential (WOCBP) who do not use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly LABEL: Contraception methods not used for WOCBP	Inclusion criterion 4	None
A2	**Exclusion criteria met**		
A2.01	Be pregnant, nursing, or plan to become pregnant while in the trial LABEL: Pregnant or nursing	Exclusion criterion 1	None

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Table 6.2: 1 Important protocol deviations (continued)

Category/ Code	Description	Comments	Excluded from
A2.02	Have experienced study treatment-limiting adverse events during parent trial LABEL: Treatment-limiting AE during parent trial	Exclusion criterion 2	None
A2.03	Congestive heart disease, as assess by the investigator LABEL: Congestive heart disease	Exclusion criterion 4	None
A2.04	Known history of lymphoproliferative disease LABEL: Lymphoproliferative disease	Exclusion criterion 6	None
A2.05	Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening in parent trial, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix LABEL: Malignancy	Exclusion criterion 7	None
A2.06	Have developed active or severe infective disease and opportunistic infections/infective diseases LABEL: Infective disease Exception: Patients with latent TB during preceding trial are allowed to be included in the extension study, provided they have received and/or receive currently appropriate treatment according to local guidelines.	Exclusion criterion 8	None
A2.07	Any restricted medication as specified in CTP or any drug considered by investigator likely to interfere with the safe conduct of the study since the last visit of parent trial and during screening period for current trial [#] LABEL: Restricted medication interfering safety	Exclusion criterion 9	None

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Table 6.2: 1 Important protocol deviations (continued)

Category/ Code	Description	Comments	Excluded from
A2.08	History of allergy/hypersensitivity to a systemically administered trial medication agent or its excipients LABEL: Allergy/hypersensitivity to trial medication	Exclusion criterion 11	None
A2.09	Presence of acute demyelinating neuropathy LABEL: Acute demyelinating neuropathy	Exclusion criterion 18	None
B	**Informed consent**		
B1	Informed consent not available/not done LABEL: IC not available	Date of informed consent missing or no signature on patient's "Declaration of Informed Consent"	All analyses
B2	Informed consent too late LABEL: IC too late	Date of informed consent not obtained prior to any study related procedure. Minimum requirement for initial informed consent <= date of Visit 1/date of any study procedure; a late signature but subject was fully informed and gave their consent verbally before or a new informed consent version signed late but subject's rights, safety or wellbeing were not impacted. If this is documented later on and signed by the subject, such cases do not qualify as iPD.	None
C	**Trial medication**		
C1	Incorrect treatment medication dose received by patients LABEL: Incorrect medication dose administration	Treatment dose > 1200 mg within 4 weeks.	None

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Table 6.2: 1 Important protocol deviations (continued)

Category/ Code	Description	Comments	Excluded from
D	**Concomitant medication**		
D1a	Use of not allowed medication or non-drug therapies as per protocol for other reason before last drug administration # LABEL: Restricted medication for other reason		None
D1b	Use of not allowed medication or non-drug therapies as per protocol for Covid-19 before last drug administration # LABEL: Restricted medication for Covid-19		None
D1c	Use of rescue medication and not discontinued from the trial treatment LABEL: Rescue medication and not trial treatment discontinuation		None
G	**Pregnancy test**		
G1	Pregnancy test not done for woman of childbearing potential per CTP flowchart # LABEL: Pregnancy test not done	Urine pregnancy test not done at any visit where such is scheduled, and serum pregnancy test not done when urine pregnancy test showed positive results.	None

PD will be detected manually;

6.3 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial:

Enrolled set (ES)
This patient set includes all patients who signed informed consent. It will be used for display of patient disposition.

Safety analysis set for maintenance treatment (SAF-MT)
This patient set includes all patients who received at least one dose of the maintenance treatment. This set will be used for presentation of iPDs, patient listings, safety and efficacy during the maintenance part of the extension trial.

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Table 6.3: 1 illustrates the data sets which are to be used for each category class of endpoints, and the approaches used with regard to missing data. For explanation of the different methods of handling missing data, cf. Section 6.6.

Table 6.3: 1 Subject sets analysed

Class of endpoint	Subject set	
	ES	**SAF-MT**
Disposition	OR	
Compliance and exposure		OR
iPD		OR
Baseline conditions/medical history		OR
Concomitant medications Concomitant non-drug therapies		OR
Demographics Baseline characteristics		OR
Primary endpoint		OR
Secondary endpoints		OC: for continuous efficacy endpoints OC-NRI: for binary efficacy endpoints
Further endpoints		OC: for continuous efficacy endpoints OC-NRI: for binary efficacy endpoints
AE		OR
Lab data, vital signs		OR OC-IR
[redacted]		[redacted]

NRI = Non Response Imputation, cf. Section 6.6.2.
OC = observed cases excluding values after any use of rescue medication or 6 weeks following last drug administration if patient early discontinued treatment, OC-IR = observed cases including also values after any rescue medication or treatment discontinuation, OR = original results.

[redacted]

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6.5 POOLING OF CENTRES

All patients from all centres will be pooled for descriptive analyses.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.3 of the CTP describes the handling of missing data.

The original results (OR) approach implies the presentation of data exactly as observed (not using time windows).

OR analysis will be performed on parameters and endpoints that are either not affected by patients' rescue therapy use (e.g. plasma concentration level of Spesolimab, rescue therapy use itself), or, if it is not meaningful to apply any imputation rule for the replacement of missing values.

6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

6.6.2 Efficacy data

Based on the different reasons for patients' data missing for different endpoints, various approaches will be used to assess the impact of missing data on the efficacy endpoints of this

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trial, depending upon the type of the endpoint (cf. Table 6.3: 1). Approaches to be applied are described below.

Continuous efficacy endpoints

For efficacy endpoints which are continuous in nature, the following imputation strategy will be applied to display the continuous efficacy data.

- Observed cases (OC) approach will include all collected data, with no imputation performed on the missing data. Such an OC approach will exclude all values measured after intake of a rescue therapy or after 6 weeks following last drug administration if a patient discontinued treatment early.

- Observed cases including all observed data (OC-IR) will be used as a sensitivity method for data display and is an extension of the OC approach which includes additionally all values which were measured after rescue therapy or treatment discontinuation.

Binary efficacy endpoints

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), the following will be performed as the primary imputation approach (analysis type: No Response Imputation [NRI]):

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success (independent of whether the preceding and following observations were selected for analysis based on time windows described in Section 6.7 and no rescue treatment has been given during this period);

- Otherwise, impute as a failure to achieve a response;

- Only patients continuing at this visit per analysis time window will be included in the denominator, excluding also ongoing patients before achieving this visit due to interim cut-off.

6.6.3 Safety data

From CTP Section 7.3: *For the safety data, including the primary endpoint, no missing data imputations are planned.*

For safety data that are not displayed by visit such as AE and possibly clinically significant laboratory abnormality, the following describes the approach to be used for the descriptive reporting:

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- Original results (OR).

For safety data that are displayed by time point (or visit) of measurement, the following approach is to be used for the descriptive reporting:

- Observed cases (OC-IR) approach will be used, with no imputation for any missing data, which will include values after any rescue medication or treatment discontinuation (see Section 6.3).

The only exceptions where imputation might be necessary for safety evaluation are AE dates and start and stop dates for concomitant medications. Missing or incomplete AE dates are imputed according to BI standards (4).

Partial start and stop dates for concomitant medications, rescue and historical medication for PPP will be imputed to enable subsequent calculation (but not for display) by the following "worst case" approach:

- If the day of the end date is missing, then the end date is set to last day of the month (or to the patient's trial completion date, if it is earlier than the last day of the month).
- If the day and month of the end date are missing then the end date is set to 31st of December of the year (or to the patient's trial completion date, if it is earlier than the 31st of December of the year).
- If the day of the start date is missing the start date is set to first day of the month (except for rescue therapy, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing then the start date is set to 1st January of the year (except for rescue therapy, where the first dosing day/month of study medication will be used if first dosing happened in the same year).
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

If a concomitant medication was ticked to be ongoing, it is expected that the end date is missing and will not be imputed for display purposes.

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6.6.6 Time since first diagnosis/tonsillectomy

Time since first diagnosis is derived as specified in Section 5.4.2. The handling of missingness will follow the rule implemented in the parent trial described as below.

For incomplete information on the date of first diagnosis, time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, time since first diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, time since first diagnosis will be calculated as if diagnosed on the 30th June of that year.
- If only the day of the first diagnosis is unknown, time since first diagnosis will be calculated as if diagnosed on the 15th of that month.

Time since tonsillectomy will be imputed in the same way.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Measurements reported with date and time and taken prior to start of administration of trial treatment will be considered pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment will also be considered pre-treatment values. These pre-treatment values will be assigned to visits according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

Baseline, unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment.

Baseline for “change from baseline” or “compared to baseline” types of efficacy endpoints , unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment in the parent trial. Baseline for time to event endpoints, is defined as the last measurement collected prior to the start of administration of the trial treatment in the current extension trial.

Measurements taken after start of administration of trial treatment will be considered either on- or off-treatment values based on the definition in Section 6.1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, potentially clinically significant abnormal laboratory values, concomitant medication, or non-drug therapies, as well as use of rescue therapy will not be based on visits. Frequency tables for these data will be using on-treatment data and categorized based on their occurring/starting dates. Therefore, no assignment to time windows will be necessary for such data.

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The derivation of the last value, minimum value and maximum value of laboratory and vital signs data will consider all on-treatment values (whether or not selected in any time window; see Table 6.1: 1 for definition of the on-treatment period) within the period of interest; these will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (whether or not selected in any time window) within the on-treatment period will be considered.

All other safety, efficacy [redacted] measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first trial treatment (which is scheduled for Visit V2).

The extended time windows for vital signs are defined in Table 6.7: 1 and the extended time windows for efficacy, safety lab, [redacted] measurements are defined in Table 6.7: 2.

Table 6.7: 1 Time windows for assignment of vital signs to visits for statistical analysis

Visit number /name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1*	Screening	-28 to -1	n/a				
V2*	Day 1	Day 1	+/-0	1 [A]	1 [A]	≤1 [A]	1 [A]
Planned On-Treatment Data							
V3	Week 4	Day 29	+/-7	22	36	2	43
V4	Week 8	Day 57	+/-7	50	64	44	71
V5	Week 12	Day 85	+/-7	78	92	72	99
V6	Week 16	Day 113	+/-7	106	120	100	127
…	…	…	…	Planned date-7	Planned date+7	End of extended window of last visit+1	Midpoint of planned days between current visit and next visit
V67/ EOT	Week 260/ EoT	Day 1821	+/-7	1814	1828	End of extended window of last visit+1	LD[B] +112
Planned Off-Treatment Data							
EOS	Week 276/ EoS	Day 1933	+7	1933	1940	LD[B] +113	Day of last f-up value

Days are counted relative to the day of first s.c. treatment in maintenance period, which is defined as Day 1 for maintenance.
* For the patients who enter OLE trial, V1 is strongly recommended to be performed during the EOT of the preceding parent trial, and the maximum days allowed between EOT of parent trial and V1 is 28 days (may be extended on a case by case basis); V2 is considered as/identical to the EOS of parent trial.
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of infusion of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B] LD=Day of last maintenance treatment received.

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Table 6.7: 2 Time windows for assignment of efficacy, safety lab, [redacted] measurements to visits for statistical analysis

Visit number /name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1*	Screening	-28 to -1	n/a				
V2*	Day 1	Day 1	+/-0	1 [A]	1 [A]	≤1 [A]	1 [A]
Planned On-Treatment Data							
M1	Week 16	Day 113	+/-7	106	120	2	169
M2	Week 32	Day 225	+/-7	218	232	170	281
M3	Week 48	Day 337	+/-7	330	344	282	393
M4	Week 64	Day 449	+/-7	442	456	394	505
…	…	…	…	Planned date-7	Planned date+7	End of extended window of last visit+1	Midpoint of planned days between current visit and next visit
M16	Week 256	Day 1793	+/-7	1786	1800	1738	1807
M17/ EOT	Week 260/ EoT	Day 1821	+/-7	1814	1828	End of extended window of last visit+1	LD[B] +112
Planned Off-Treatment Data							
EOS	Week 276/ EoS	Day 1933	+7	1933	1940	LD[B] +113	Day of last f-up value

Days are counted relative to the day of first s.c. treatment in maintenance period, which is defined as Day 1 for maintenance.
* For the patients who enter OLE trial, V1 is strongly recommended to be performed during the EOT of the preceding parent trial, and the maximum days allowed between EOT of parent trial and V1 is 28 days (may be extended on a case by case basis); V2 is considered as/identical to the EOS of parent trial.
[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of infusion of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B] LD=Day of last maintenance treatment received.

Repeated and unscheduled efficacy, safety [redacted] measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement.

Only one observation per time window will be selected for statistical analysis at a particular visit – the value which is closest to the protocol planned visit day will be selected. If there are two observations which have the same difference in days to the planned day, the later value will be selected. If there are two observations on the same day, the worst value will be selected.

Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data after the implement of estimand concepts. For example, for the

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OC method, values after rescue therapy intake or 6 weeks following last treatment in case of discontinuation should be censored first before assignment of efficacy endpoints.

For visits without an assigned value based on time windows, a value will thereafter be imputed (if needed) as defined in Section 6.6. Imputation of efficacy endpoints, when applicable, will be performed based on all available observations meeting the imputation rules, irrespective of whether the observation was selected in any time window.

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7. PLANNED ANALYSIS

Final trial analysis is planned to be performed at the end of the study once all patients have completed the study (including any follow-up period) if applicable. As specified in CTP Section 7.2.7, multiple interim analyses may be done over the 5-year conduct phase of this trial. The corresponding snapshot will be taken for the interim analysis and data only up to the cut-off will be included into the analysis.

General Remarks

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (10) [redacted]

The individual values of all patients will be listed, including those collected during the off-treatment period. Listings will generally be sorted by country, centre number, patient number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N:	number of non-missing observations
Mean:	arithmetic mean
SD:	standard deviation
Min:	minimum
Q1:	lower quartile
Median:	median
Q3:	upper quartile
Max:	maximum

[redacted]

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (10).

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Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treated patient set. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actual missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not if there is no other particular specification.

Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients enrolled, treated, enrolled but not treated, who completed all doses of trial medication as planned, who completed the trial (EOS), who were prematurely discontinued study treatment, by reason and who withdrew from the trial, by reason. The frequency of patients with iPDs will be presented; the iPDs will be listed per patient.

To better illustrate the long-term disposition of entire maintenance treatment (cf. Section 6.1), a summary table regarding patient status over time will be added. The cumulative frequency of patients for the following categories will be displayed based on 16-week intervals:

- Ongoing on study medication, i.e., without early treatment discontinuation by the time point
    - Intake of rescue medication
- Pre-maturely stopped study medication, i.e., discontinued study medication by the time point
    - Intake of rescue medication
    - Death
    - Any of the above
- Ongoing but not achieved the visit
    - Intake of rescue medication

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Descriptive statistics will be presented for baseline characteristics for overall population and patients with plaque psoriasis ongoing at the baseline of extension trial.

For demographic variables listed in Section 6.4, they will be presented by the number and percentage of patients in the categories defined in Section 6.4.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

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Concomitant diseases (i.e. baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organisation – Drug Dictionary (WHO-DD).

Concomitant diseases which are present at start of the study will be descriptively summarized.

A medication/non-drug therapy will be considered concomitant to treatment, if it

- is ongoing at the start of current extension trial treatment or
- starts within the on-treatment period (see Section 6.1 for the definition).

A medication/non-drug therapy will be considered as prior medication/non-drug therapy, if the end date of the medication/therapy is at any time prior to the start of trial treatment.

Concomitant medication use (excluding rescue therapy) taken any time during the on-treatment period (cf. Section 6.1) will be summarized with frequency and percentage of patients by Anatomical Therapeutic Chemical 3 (ATC3) class and preferred name.

Concomitant use of non-drug therapies (excluding rescue therapy) taken any time during the on-treatment period (cf. Section 6.1) will be summarized with frequency and percentage of patients.

Use of rescue therapy will be summarized separately (see Section 7.6.3).

7.3 TREATMENT COMPLIANCE

Treatment compliance (see Section 5.4.4 for the definition and calculation) will be summarized for the SAF-MT using descriptive statistics (N, mean, SD, minimum, median, maximum).

The number and percentage of patients with the following overall compliance categories will be presented:

- "< 80% of planned",
- "80 to 120% of planned" and
- "> 120% of planned".

7.4 PRIMARY ENDPOINT(S)

Refer to Section 7.8.1 for the description for adverse events including the primary endpoint.

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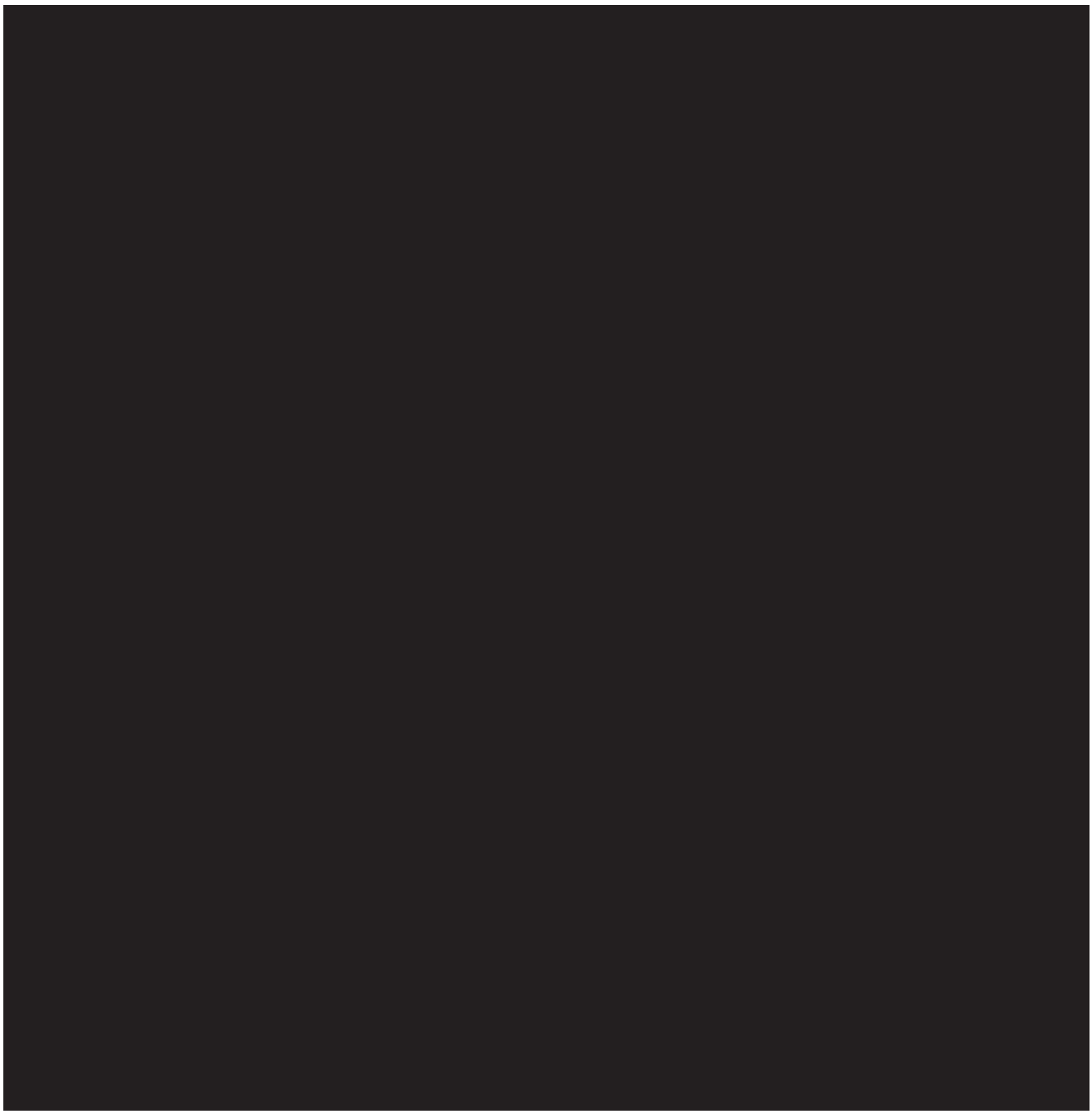
7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary endpoints

Descriptive summaries and graphical displays (line plots) will be produced using OC method for continuous secondary endpoints and OC-NRI method for binary secondary endpoints respectively.



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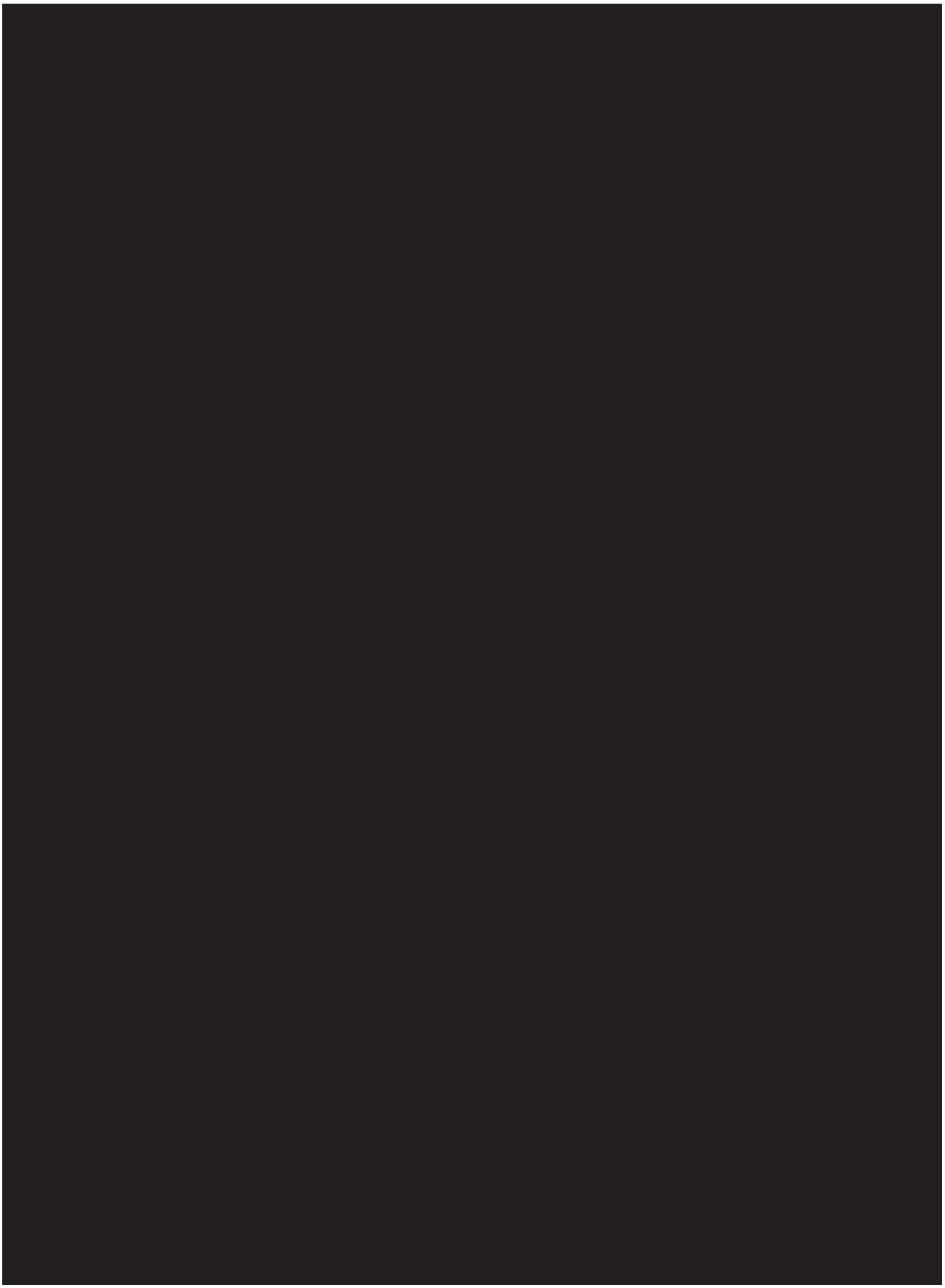

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[redacted]

7.7 EXTENT OF EXPOSURE

An overall table will be summarized for the entire maintenance treatment period. The number of subjects who received a dose of trial drug will be tabulated. The amount of treatment received [mg] will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum). The total duration of exposure [days] will also be displayed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed for the SAF-MT following BI standards. No hypothesis testing is planned.

For the overall maintenance treatment period, the AE data and possibly clinically significant laboratory abnormalities will be analysed under OR estimand concept (as defined in Section 6.6.3); the safety data by visit, i.e., laboratory, vital signs and local tolerability, will be analysed under OC-IR estimand concept (as defined in Section 6.6.3).

As the onset time of an AE will not be collected in the trial, any AE which occurs on the same day as a treatment dose will be assigned to the “post treatment”. For safety assessments by visits, if time is not collected, data on the same day of a treatment dose will be treated to be “prior treatment” except for scheduled local tolerability and post-dose vital signs assessments.

Off-treatment data will be listed only.

7.8.1 Adverse Events

AEs will be coded with the most recent version of MedDRA.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA, preferred terms (if applicable) will be sorted by total frequency (within system organ class).

For details on summarization of AE data, please refer to "Analysis and Presentation of Adverse Event data from Clinical Trials " (6), "Analysis and Presentation of Adverse Event data from Clinical Trials – Display Template" (7) and "Handling of missing and incomplete AE dates" (4).

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening period, maintenance period (i.e. maintenance treatment phase plus REP) or off-treatment period (i.e. follow up) as defined in Section 6.1. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first Spesolimab administration will be assigned to the on-treatment phase.

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Exposure-adjusted adverse event incidence rates for TEAE will be calculated using the following approach:

1) The exposure adjusted incidence rate (per 100 subject years) of a selected treatment emergent adverse event is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk to contribute the event to the analysis multiplied by 100 (per 100 subject years), where:

   Time at risk [subject years] = (date of onset of AE – first treatment start date+ 1) / 365.25

2) If, for a subject, the selected treatment emergent adverse event didn't occur, then the time at risk will be censored at min (date of death, last contact date per EoS page, cut-off date for the interim analysis, or the end of on-treatment period). For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

   Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with TEAE / Total TEAE-specific time at risk [subject years].

An overall summary of AEs will be presented. This overall summary will include summary statistics for the class of other significant AEs (sponsor definition based on ICH E3) and for the class of AESIs.

Based on the specification provided in ICH E3 (8), the sponsor has defined AEs which are to be classified as 'other significant'. For the current trial, these will include those non-serious AEs which were reported with 'action taken = Drug withdrawn' or 'action taken = Dose reduced'.

The following is considered an AESI in this trial (see Section 5.2.6.1.4 in CTP):

- Systemic hypersensitivity reactions including anaphylactic reaction
- Severe infections (according to RCTC grading in CTP Appendix 10.3)
- Opportunistic and mycobacterium tuberculosis infections
- Hepatic injury

  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

  - *an elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or*
  - *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.*

- Peripheral Neuropathy

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

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In addition, user defined adverse event concepts (UDAEC) identified through specific search criteria will be reported separately (see Table 7.8.1: 1).

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts

User-defined AE category		
	Label	Description
Infections (serious/severe, opportunistic)	Infections ALL	Combined search strategy based on the individual UDAECs described below; the UDAEC "severe infections (investigator-defined) will be disregarded for this search
	Opportunistic infections	Narrow SMQ "Opportunistic infections"
	Tuberculosis infections	BIcMQ "Infections": Narrow sub-search 8.2 "Tuberculosis related terms"
	Serious infections	all serious events in SOC "Infections and infestations"
	Severe infections	all events in SOC "Infections and infestations" of at least severe RCTC grade, by HLGT
Hypersensitivity	Hypersensitivity ALL	Combined search strategy based on the three individual UDAECs described below
	Anaphylactic reaction	Narrow SMQ "Anaphylactic reaction"
	Angioedema	Narrow SMQ "Angioedema"
	Hypersensitivity	Narrow SMQ "Hypersensitivity"
Malignancies	Malignant tumours	Narrow Sub-SMQ "Malignant tumours" Narrow Sub-SMQ "Haematological malignant tumours" Narrow Sub-SMQ "Non-Haematological malignant tumours"
	Malignant skin tumours	Broad Sub-SMQ "Skin malignant tumours"
	Skin melanomas	HLT Skin melanomas (excl. Ocular)
	Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ "Skin malignant tumours" excluding HLT Skin melanomas (excl. Ocular)
	Malignancies excluding NMSC	Sub-SMQ "Malignant tumours" excluding NMSC, whereas NMSC is defined above
3-point MACE	3-point MACE	BIcMQ "Major Adverse Cardiovascular Events" with Narrow sub-search 1.1 "3-Point MACE (part 1/2)" Narrow sub-search 1.2 "3-Point MACE (part 2/2)" *

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Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts (continued)

	Label	Description
Torsades de Pointes	Torsades de Pointes	Broad sub-SMQ “Torsade de pointes/QT prolongation”
DRESS	DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), broad	Algorithmic SMQ on "Drug reaction with eosinophilia and systemic symptoms syndrome", broad Algorithm: A or (B and C and D) or (B and C and E) or (B and D and E)
	DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), narrow	SMQ “Drug reaction with eosinophilia and systemic symptoms syndrome”, narrow
Peripheral neuropathy	Peripheral neuropathy	SMQ “Guillain-Barre syndrome”, narrow; SMQ “Demyelination”, narrow; SMQ “Peripheral neuropathy”, narrow

* this is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BIcMQ search ID 32019093) or subsearch 2 (BIcMQ serach ID 32019094

The exposure-adjusted incidence rate and frequency of patients with AEs will be summarized by primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for patients with SAEs, patients with AESIs, patients with AE leading to discontinuation of the trial medication, and patients with other significant AEs (as described previously) and User-defined Adverse Event Concepts (UDAEC) (See Table 7.8.1: 1). AEs will also be summarized by maximum intensity based on the RCTC measure (see Section 5.4.1).

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by primary system organ class and preferred term. The frequency of patients with SAEs and drug related SAEs will also be summarised respectively.

For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (9). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

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For continuous safety laboratory parameters, normalized values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (9). All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline will be calculated. For all outputs, the last assessment before the first treatment at Day 1 is chosen as the baseline value.

Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. All individual laboratory data will be listed. Values outside the reference range will be flagged.

For derivation of the last value, the minimum value, and the maximum value, all values during the on-treatment period will be considered under OR estimand concept. These will be derived for analysis of laboratory, vital signs and local tolerability data. For identification of potentially clinically significant abnormal laboratory values, all values during on-treatment period will also be considered under OR.

Descriptive statistics of laboratory values over time and for the difference from baseline on-treatment (see Section 6.7) will be based upon normalized values and provided by visit (including follow up) under OC-IR estimand concept, including summaries of the last value on treatment, the minimum value on treatment and the maximum value on treatment. Graphical displays via box plots will be produced for the change from baseline, over tie, for each continuous laboratory endpoint.

Laboratory values will be compared to their reference ranges; shift tables will be provided for the number of patients with a specific RCTC grade at baseline versus the grade at the last measurement on treatment, as well as the worst grade on treatment. These analyses will be based on standardized laboratory values.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted lab values, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Patients having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values; for each functional lab group all patient's lab values will be listed, if there exists at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN combined with a total bilirubin ≥ 2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin

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elevations). The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values.

A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed or total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, body temperature, respiratory rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided, including the last value, the minimum value and the maximum value during on-treatment period.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

No separate listing or analysis of ECG data will be prepared.

7.8.5 Local tolerability

Local tolerability will be summarized by visit under OC-IR estimand concept, with the frequency and percentage of patients who experienced any symptoms by severity/intensity.

7.8.6 Immunogenicity

The ADA status and titer as well as frequency of patients with ADA to Spesolimab will be presented by visit. Descriptive statistics of ADA titer (for ADA positive patients, when available) will be provided by visit. The number of subjects with ADA status positive/negative at any time will also be presented. ADA parameters (e.g. treatment-induced ADA positive subjects, transient ADA response and persistent ADA response) will also be

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presented by visit and cumulatively for the overall study duration. Further exploratory assessments of the ADA data will be performed once data is available and these will be described, if done, in the CTR.

7.9 ANALYSIS OF COVID-19 IMPACT

There is currently an outbreak of respiratory disease, COVID-19 worldwide which has impacted the conduct of this trial. This public health emergency has raised more difficulties for patients to meet protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. Site personnel or trial subjects are also under the risk to get infection with COVID-19.

The start date for the COVID-19 disruption is defined as March 17th, 2020, which is prior to trial initiation, and the end date will be updated in future revision. Consequently, there are unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public and individual health control measures. To assess the impact on patients' safety and drug efficacy in this trial, the following analyses are planned:

Disposition and iPD:

Frequency of the patients with missed relevant visits or prematurely discontinued from study treatment due to COVID-19 and related non-important and important protocol deviations will be listed.

AE related to COVID-19:

If there is any case, AE related to COVID-19 infection will be reported separately.

7.10 HANDLING OF DMC ANALYSES

A fully external DMC, independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A separate DMC SAP which describes the analyses required for assessment by the DMC will be produced. Further details are provided in a DMC charter.

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8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Due to the open-label nature of current trial, the treatment information will be loaded into the trial database at trial initiation.

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9. REFERENCES

1.	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-40-413*: "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON.
3.	*KM Asset BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", current version, KMED.
4.	*KM Asset BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version, KMED.
5.	[redacted]
6.	*KM Asset BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, KMED.
7.	*KM Asset BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version, KMED.
8.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
9.	*KM Asset BI-KMED-BDS-HTG-0042*: " Handling, Display and Analysis of Laboratory Data", current version, KMED.
10.	*KM Asset BI-KMED-BDS-HTG-0045*: "Standards for Reporting Clinical Trials and Project Summaries", current version, KMED.
11.	[redacted]
12.	[redacted]
13.	[redacted]

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14.	[redacted]

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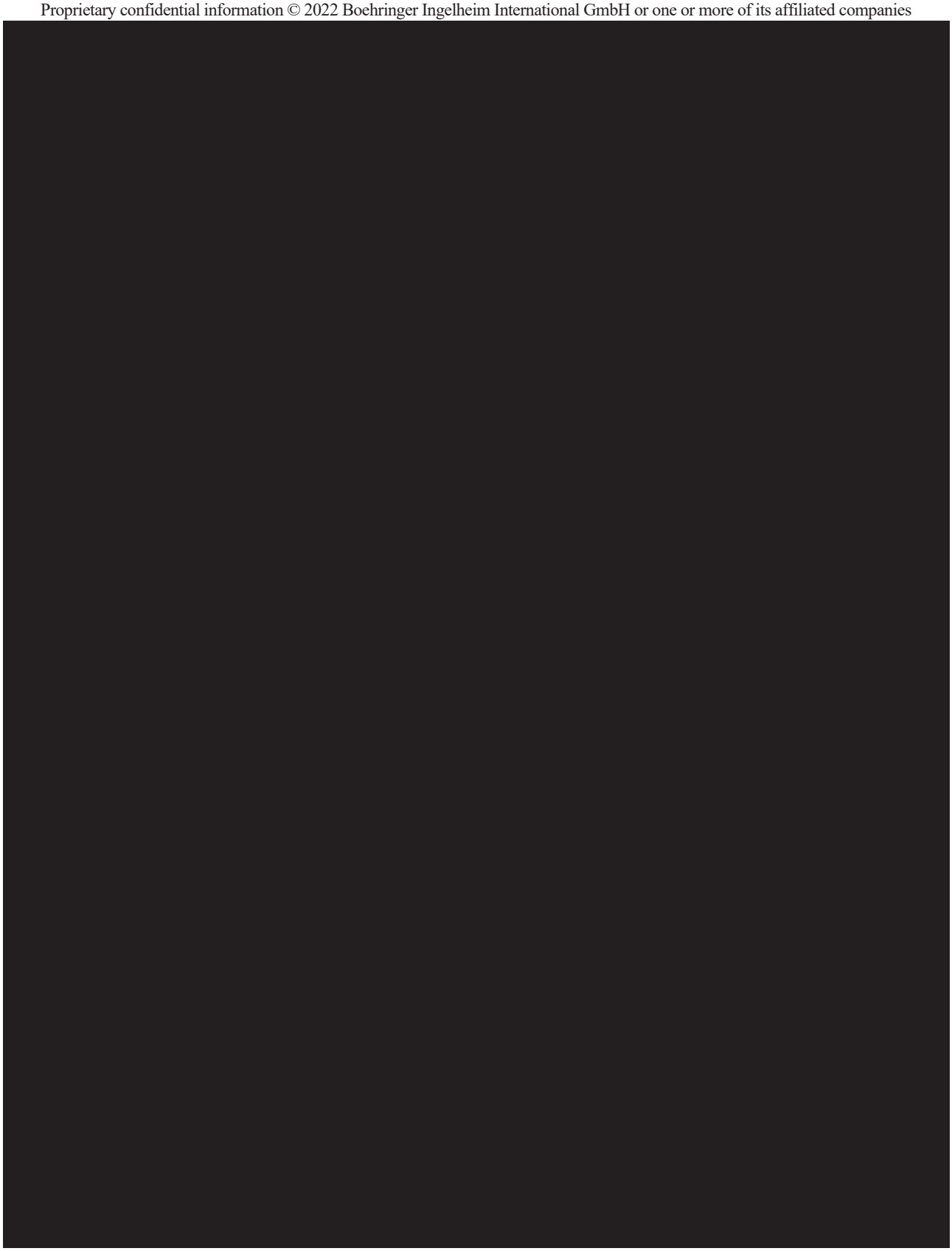

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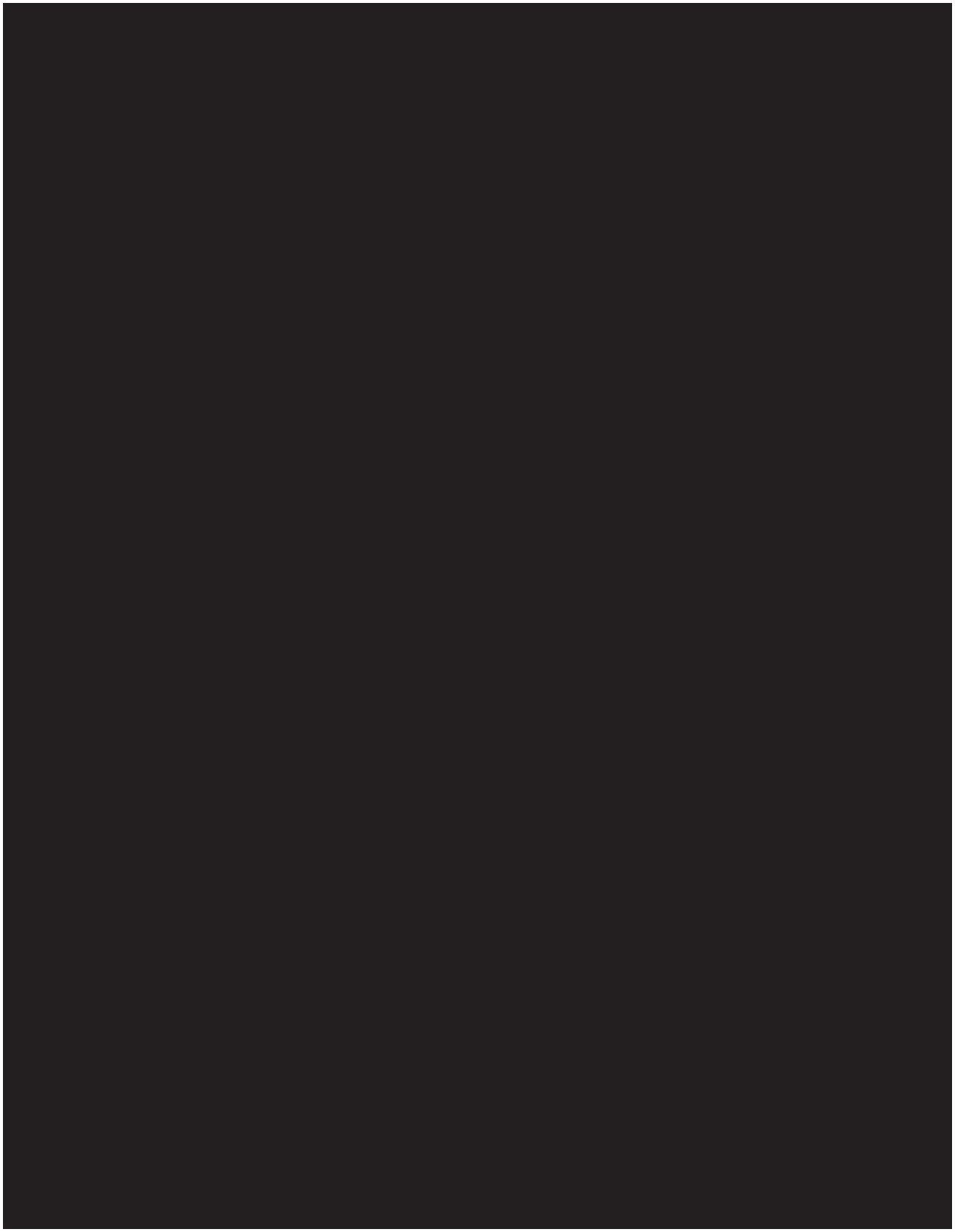

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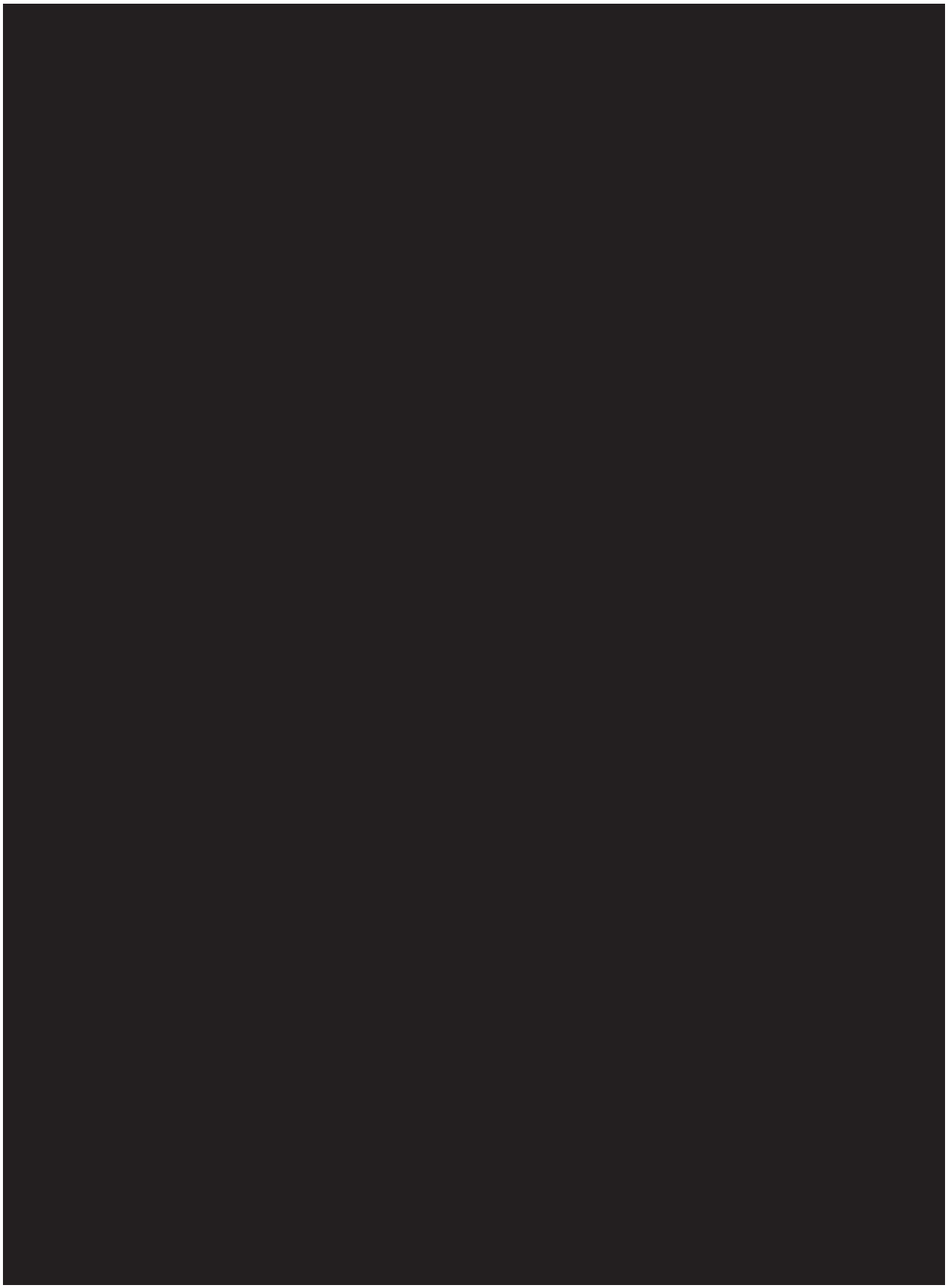

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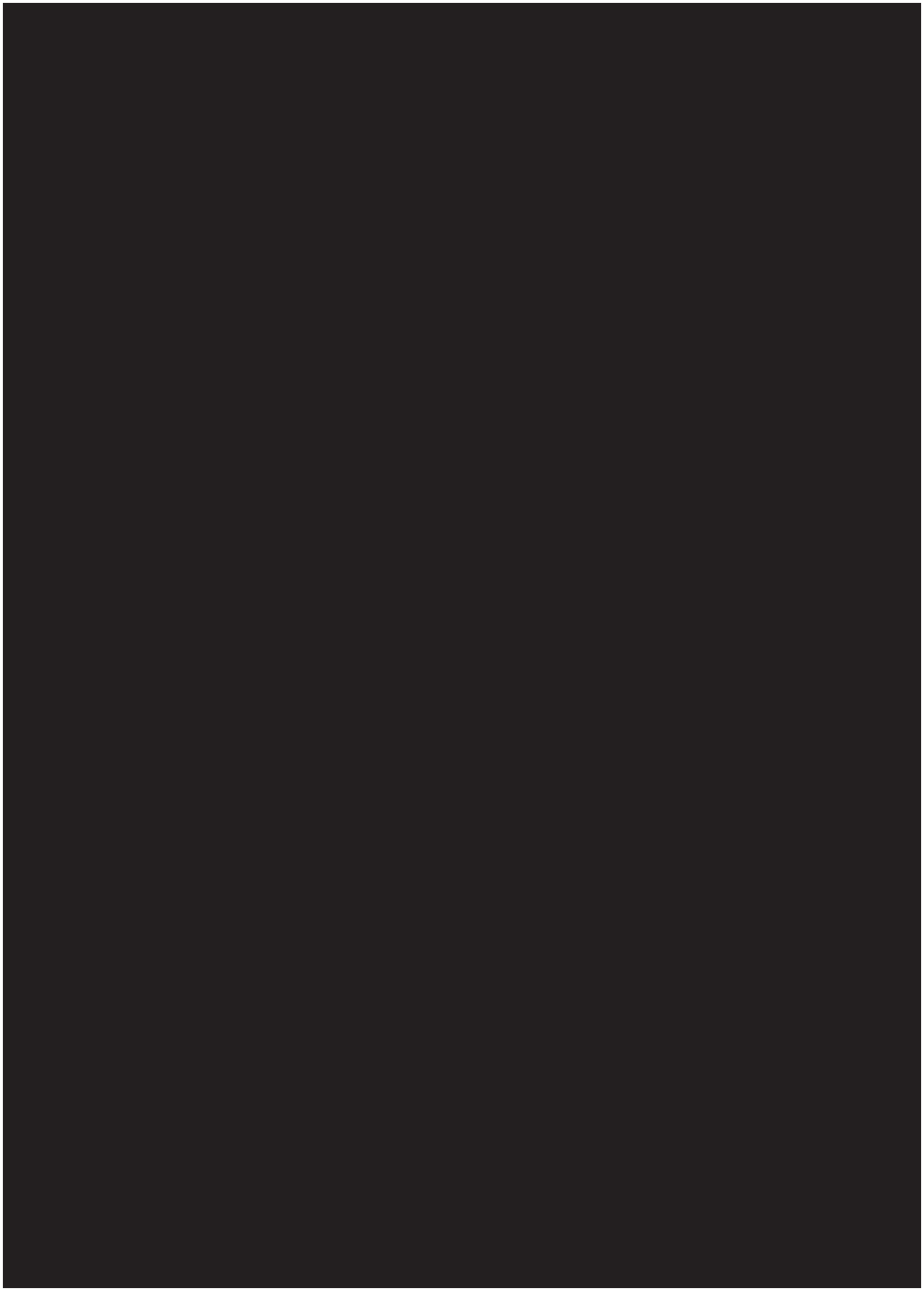

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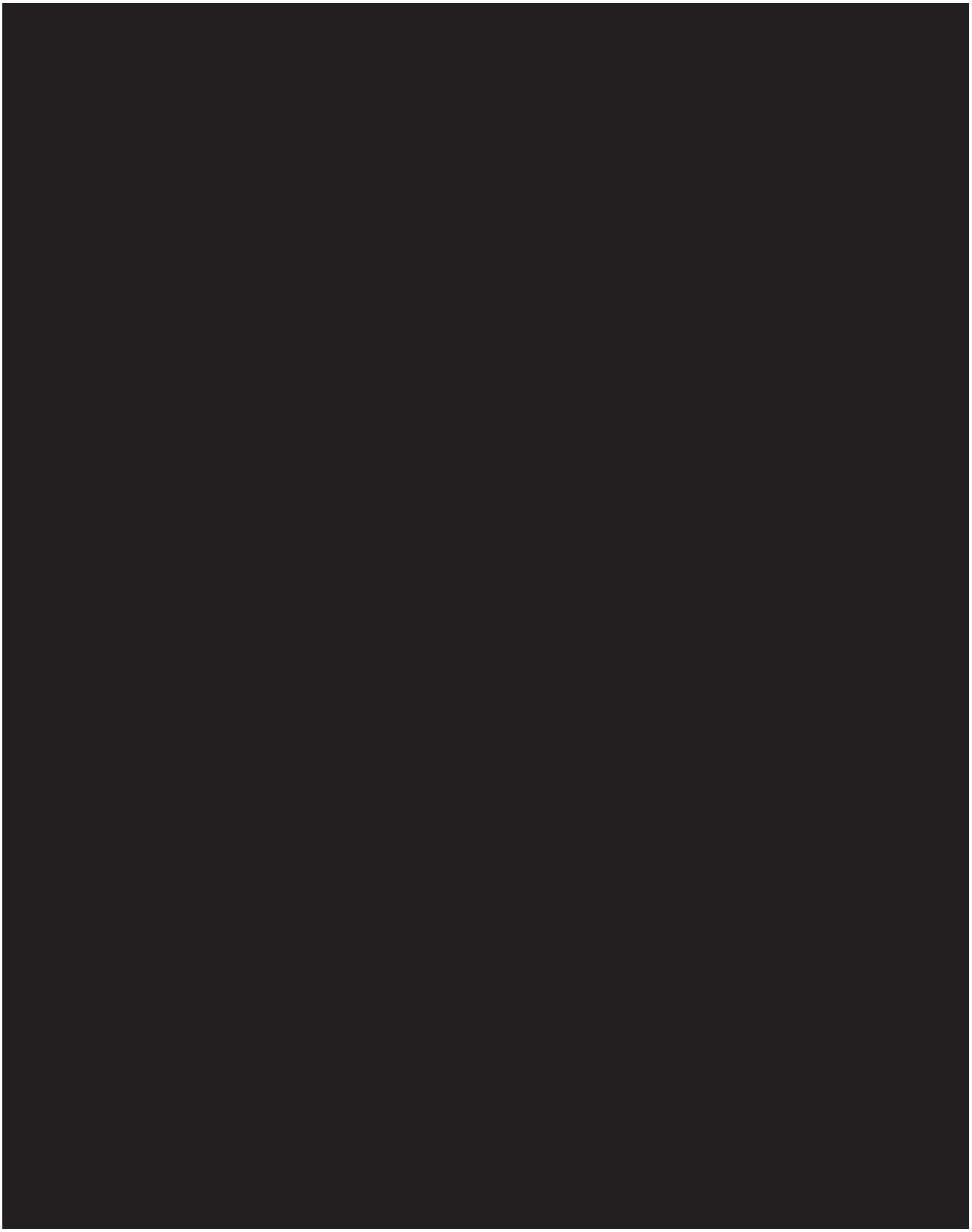

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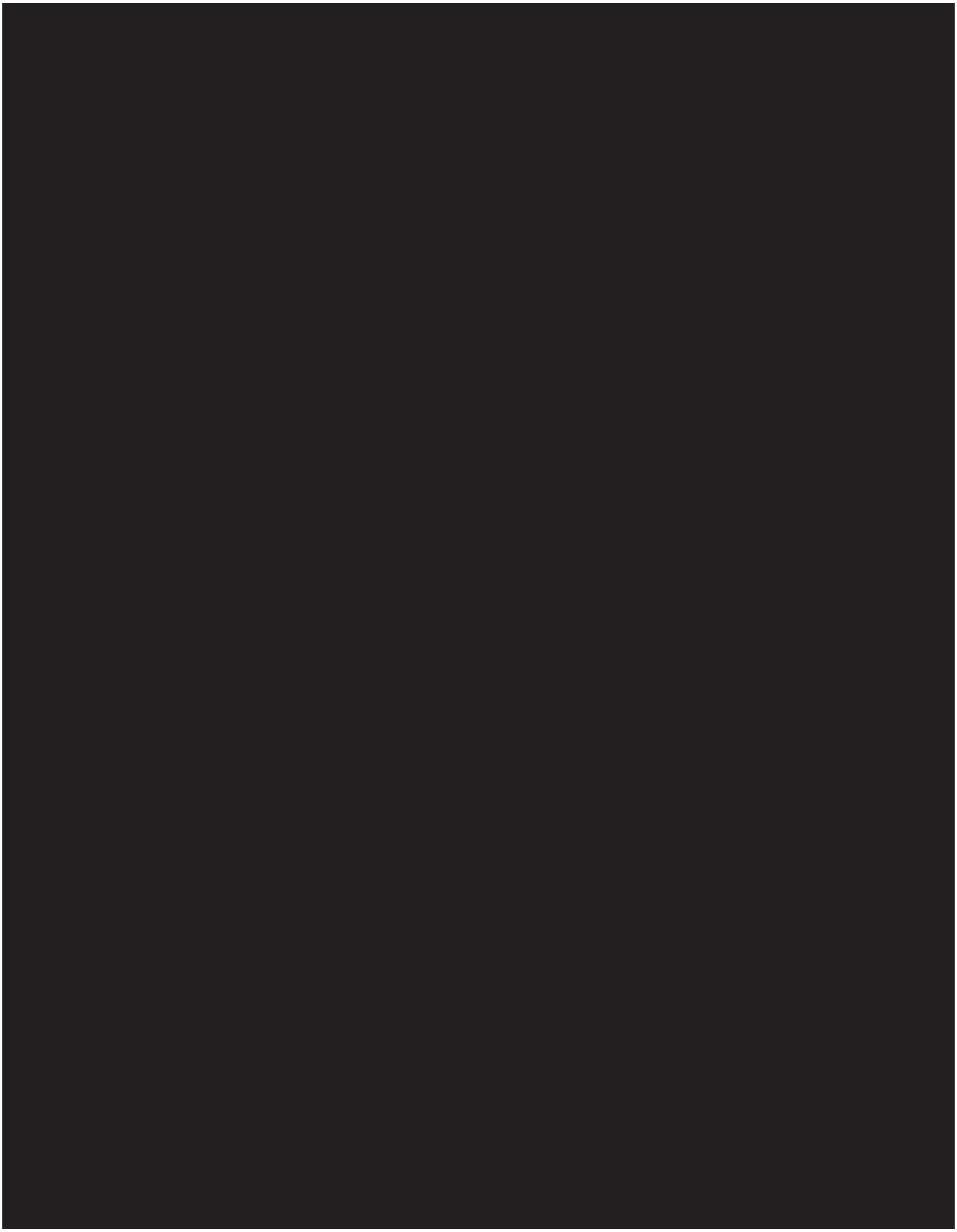

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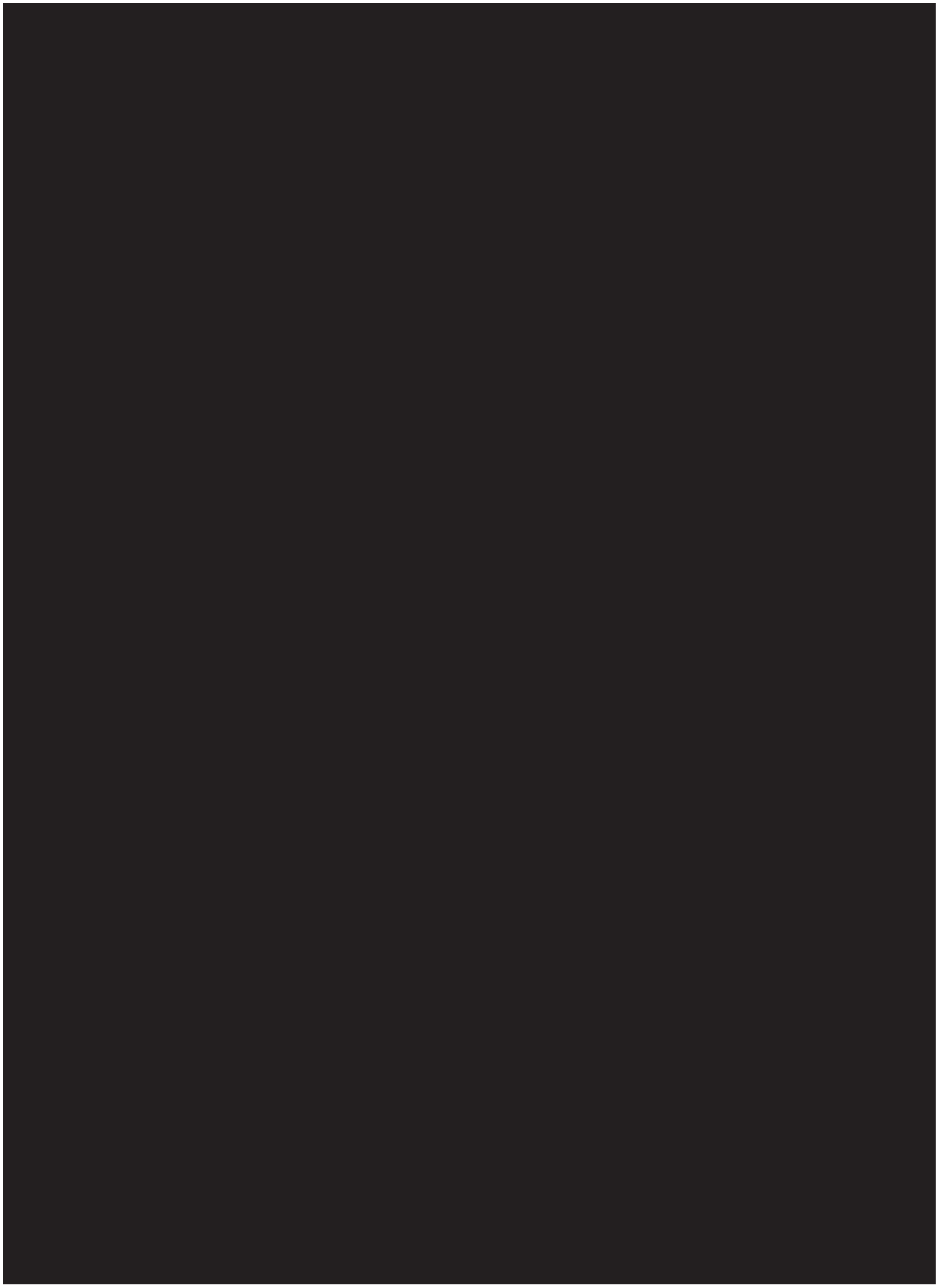

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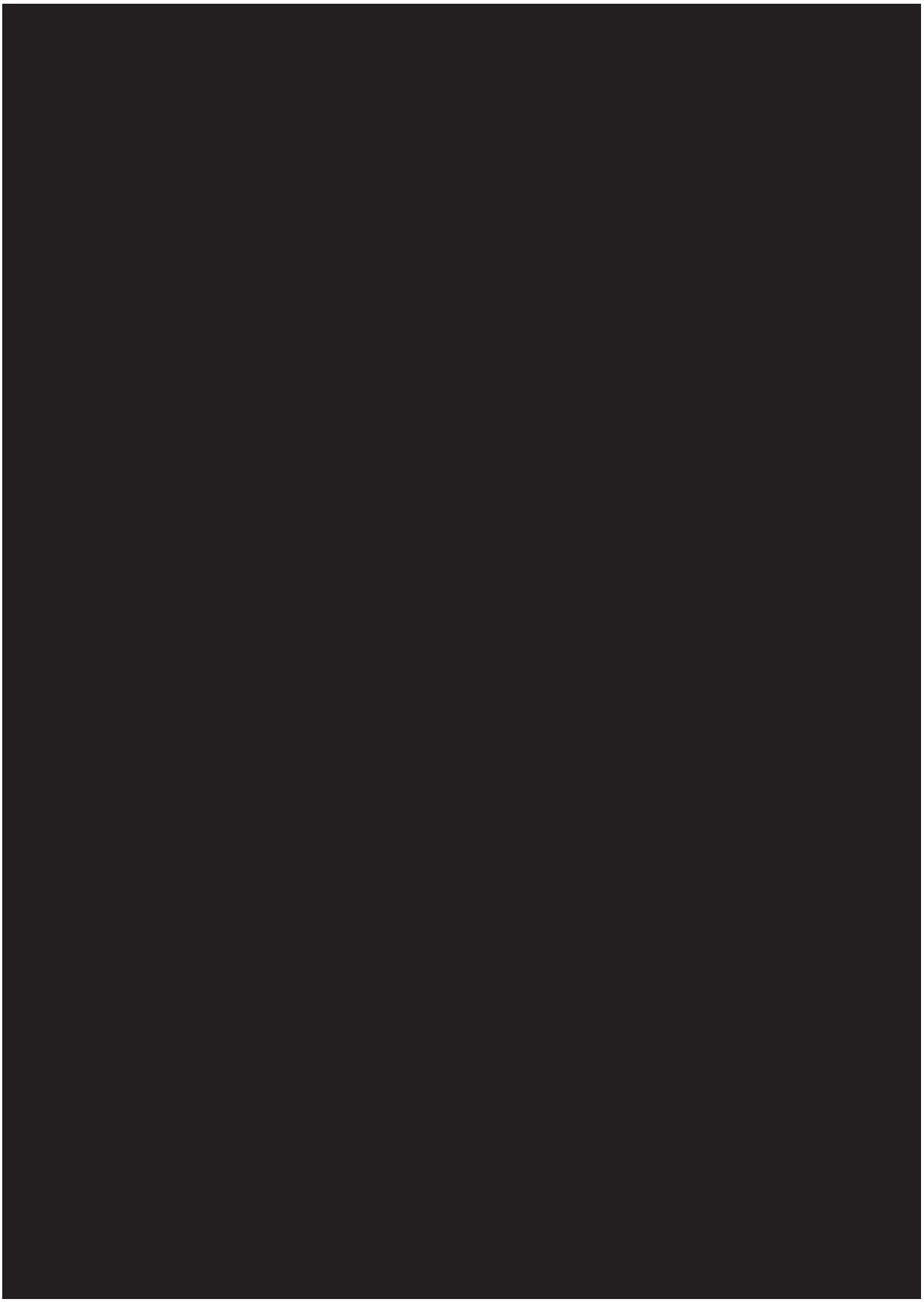

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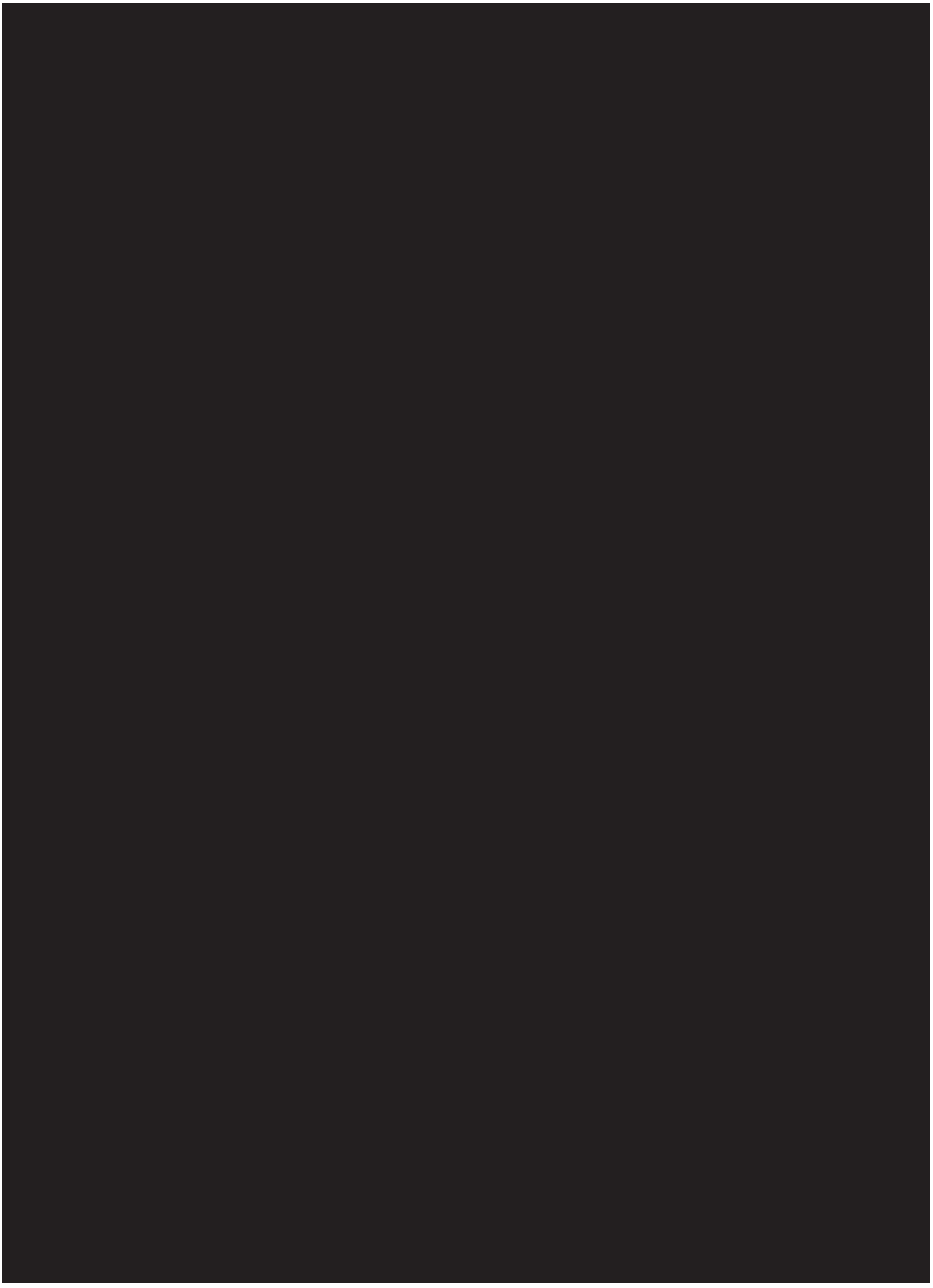

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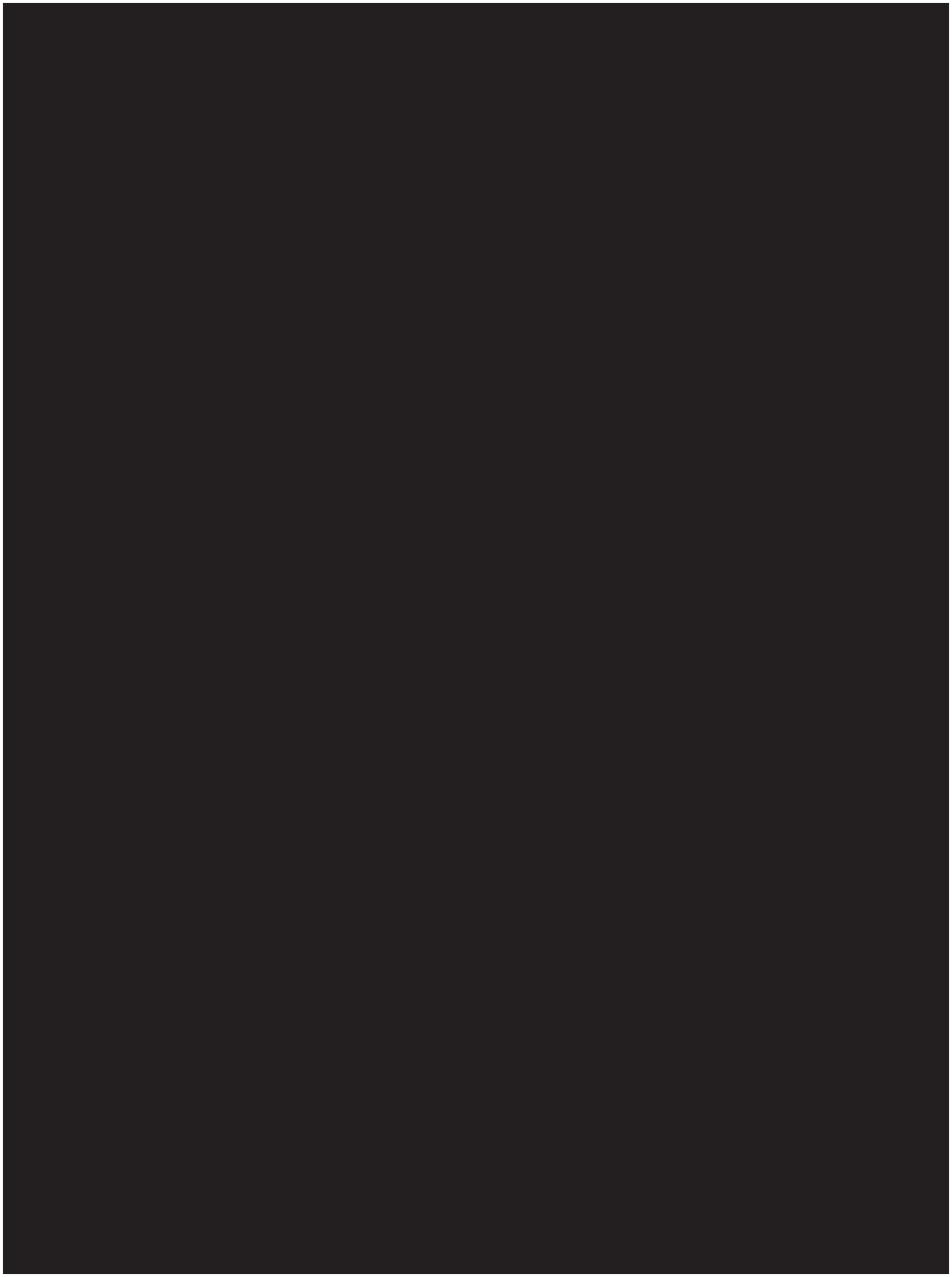

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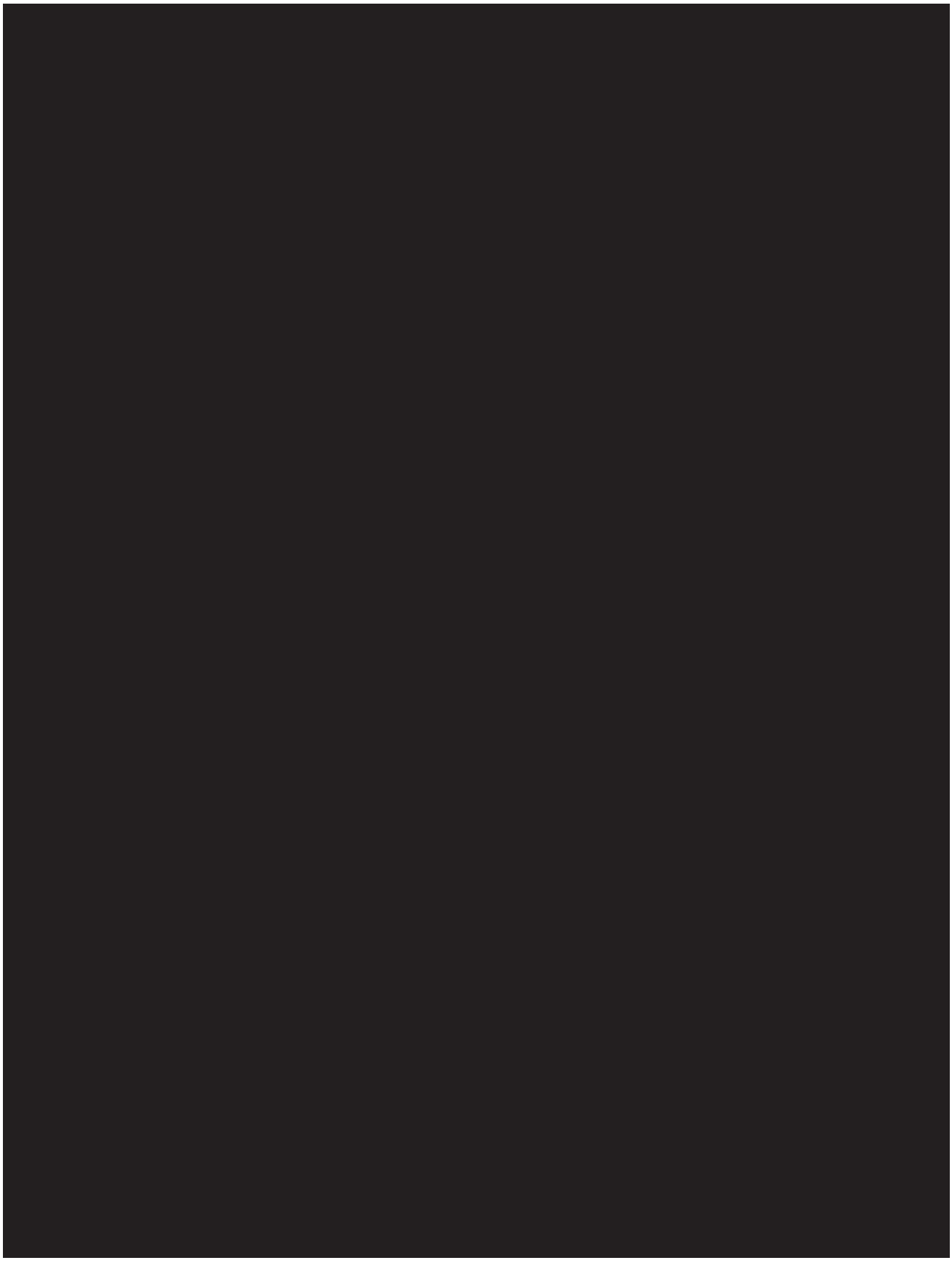

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11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**21-DEC-21**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct.
2.0	**13-SEP-22**		Section 5.4.3	The definition of rescue therapy was updated based on amended protocol. "Rescue therapy is defined as both the use of medication such as topical corticosteroids or other topical treatment applied on the affected palms and/or soles, systemic immunomodulating treatments or biologics and therapy such as tonsillectomy, for the treatment of worsening of PPP." was changed to: "Rescue therapy is defined as the use of topical corticosteroids or other topical treatment, systemic immunomodulating treatments or biologics and therapy such as tonsillectomy, for the treatment of worsening of PPP."
2.0	**13-SEP-22**		Section 6.2	In table 6.2:1, A2.09 - 'Presence of acute demyelinating neuropathy, LABEL: Acute demyelinating neuropathy' was added as iPD based on exclusion 18 in amended protocol.
2.0	**13-SEP-22**		Section 6.2	In table 6.2:1, D1c – "Use of rescue medication and not discontinued from the trial treatment, LABEL: Rescue medication and not trial treatment discontinuation" was added as iPD, based on updates "Patients who need to take rescue medication must be discontinued from the trial" in amended protocol.
2.0	**13-SEP-22**		Section 6.7	In table 6.7:1, time window of EOS visit was updated based on amended protocol.
2.0	**13-SEP-22**		Section 6.7	In table 6.7:2, time window of EOS visit was updated based on amended protocol.
2.0	**13-SEP-22**		Section 7.8.1	Peripheral neuropathy was added as one of AESIs based on amended protocol.
2.0	**13-SEP-22**		Section 7.8.1	In table 7.8.7:1, peripheral neuropathy was added as one of UDAEC in project level.