TRIAL STATISTICAL ANALYSIS PLAN

c32614118-01

BI Trial No.:	1368-0016
Title:	Multi-center, double-blind, randomised, placebo-controlled, phase IIb dose-finding study to evaluate efficacy and safety of different subcutaneous doses of BI 655130 in patients with moderate to severe Palmoplantar Pustulosis (PPP) [c18863881-01]
Investigational Product:	Spesolimab (BI 655130)
Responsible trial statisticians:	[redacted] Tel.: [redacted] Fax:
Date of statistical analysis plan:	22 Jul 2020 SIGNED
Version:	1.0 Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALQ	Above limit of quantification
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BM-SAP	Biomarker Statistical Analysis Plan
BMI	Body mass index
BRAVE	BI RAVE®
BRPM	Blinded Report Planning Meeting
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CI	Confidence interval
CRF	Case report form
CRP	C-reactive protein
CTC	Common Terminology Criteria
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBL	Database lock
DILI	Drug Induced Liver Injury
[redacted]	
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form

Term	Definition / description
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOT	End of trial
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
FAS	Full analysis set
F/U	Follow-up
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	Immunohistochemistry
IL	Interleukin
IPD	Important protocol deviation
IRT	Interactive response technology
kg	Kilogram
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
mQC	Medical quality control
MQRM	Medical quality review meeting
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NRI	No response imputation
OC	Observed cases
OC-IR	Observed cases including values after rescue therapy or treatment discontinuation
OR	Original results
PD	Pharmacodynamic(s), protocol deviation
PG	Pharmacogenomic(s)
PGA	Physician Global Assessment

Term	Definition / description
[redacted]	
PPP	Palmoplantar Pustulosis
PPP PGA	Palmoplantar Pustulosis Physicians Global Assessment
PPP ASI	Palmoplantar Pustular Psoriasis Area and Severity Index
PPS	Per protocol set
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual effect period
RS	Randomized set
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SMQ	Standardised MedDRA query
SOC	System Organ Class
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal range
ULOQ	Upper limit of quantification
VAS	Visual analogue scale

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 analyses described in the CTP and its amendments, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol 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, planning of sample size, and randomization.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), 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]

This TSAP will document the features of the primary analysis for week 16 (to be performed once all randomized patients have completed through the week 16 of trial), as well as the final analysis (to be performed once all patients have completed the trial).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses stated in the CTP (latest version) will be performed as planned with the following adaptations.

In the CTP, MMRM model for % change in PPP ASI from baseline will include baseline visits, visits 6, 7, 8 and 9. In TSAP, the visits 3, 4 and 5 are also included.

In the CTP, for the continuous secondary endpoint of percent change in PPP ASI from baseline at Week 52, the following maintenance treatment comparisons will be performed using an MMRM (incorporating weeks 4, 12, 20, 28, 36, 44, and 52). In TSAP, the visits including week 28, 40 and 52 will be included in addition to the visits included for primary analysis at week 16.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT(S)

The % change in PPP ASI at Week 16 from baseline is the primary endpoint of efficacy in this trial.

Derivation of % change in PPP ASI is described in Section 9.1.1.

Any data collected after use of any rescue therapy or after 6 weeks following last drug administration if a patient discontinued treatment early (to allow for incorporation of the continuing maximum treatment effect period) are censored for the purpose of the primary estimand (EC).

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

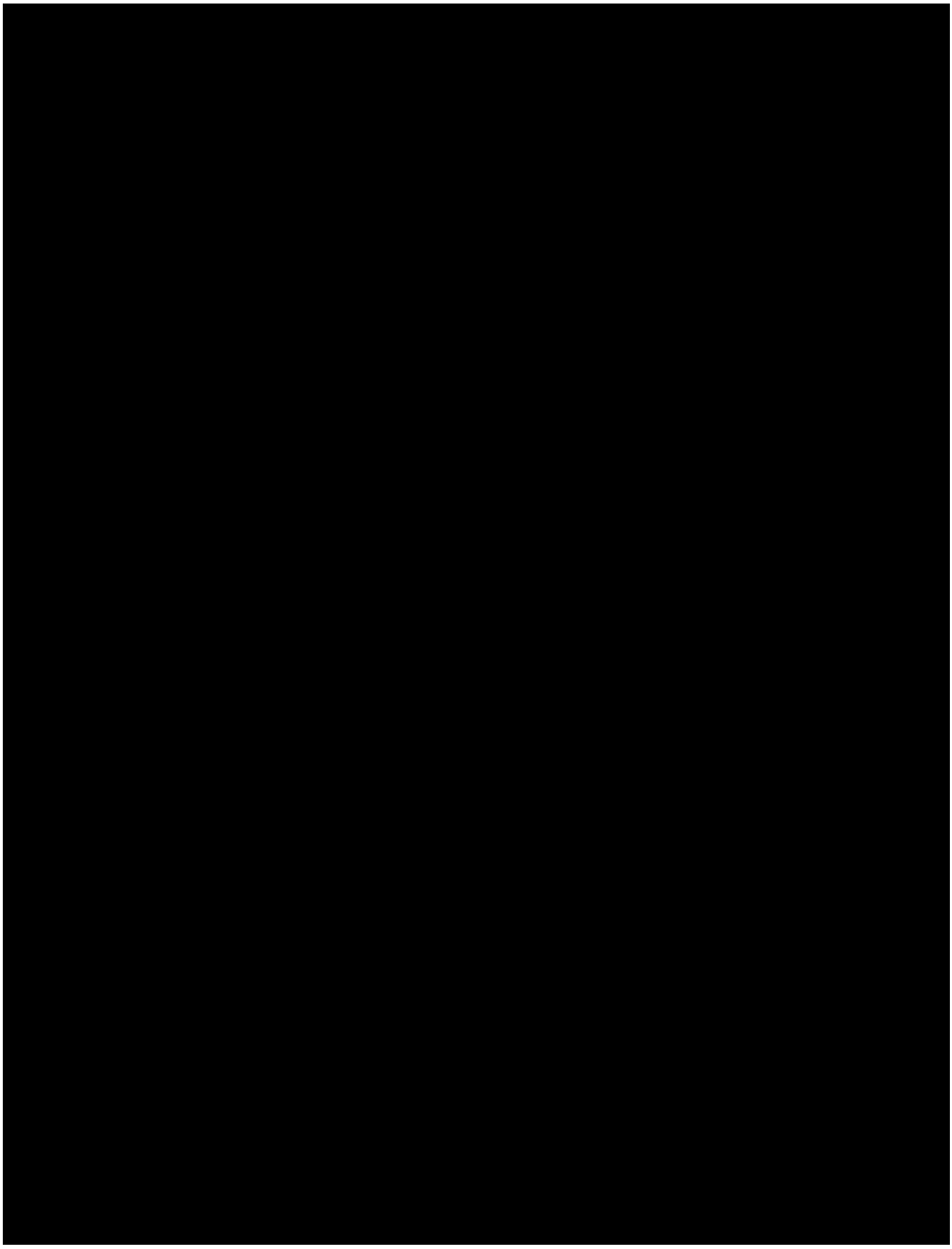
Secondary endpoints are defined as described below:

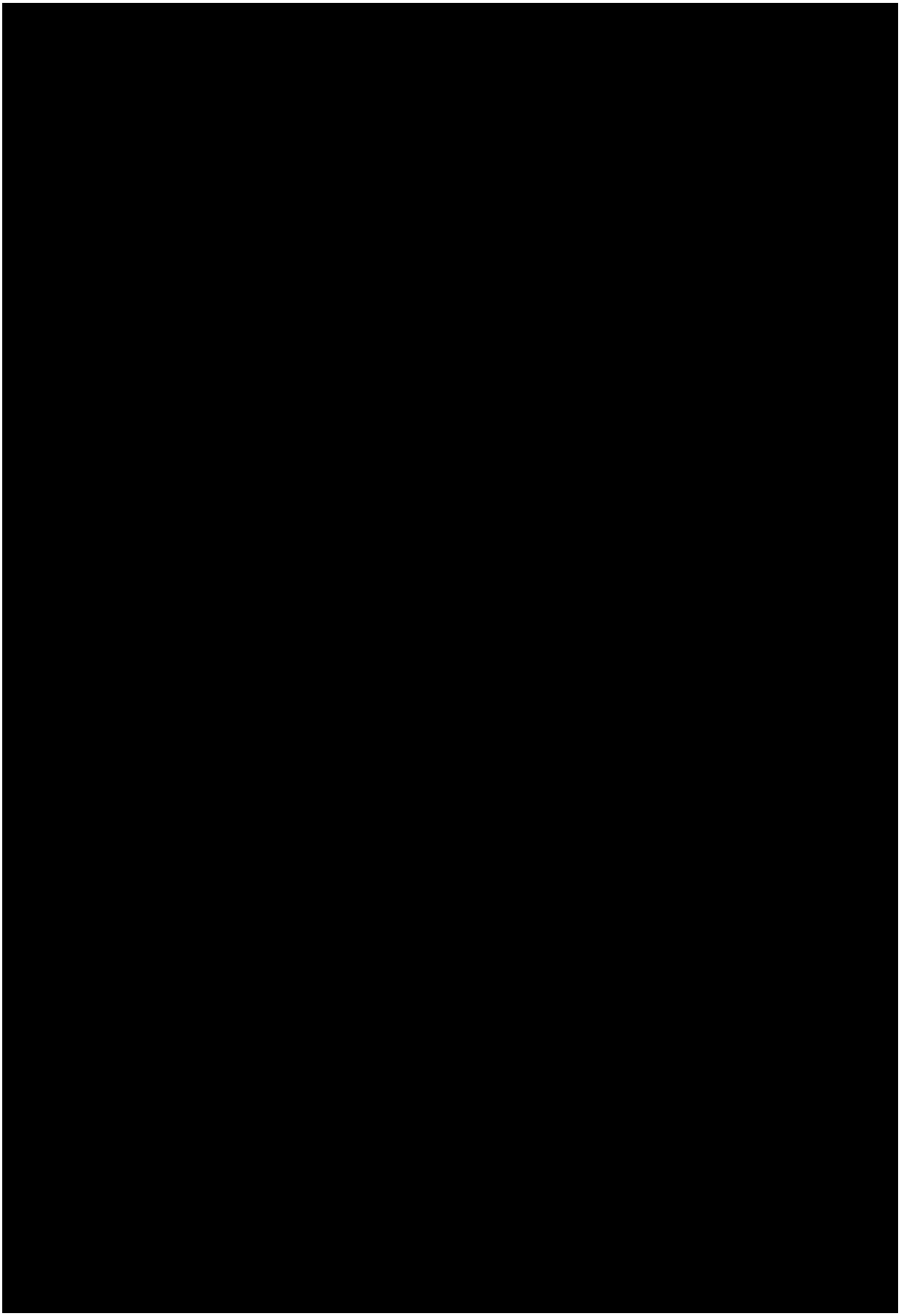
- Change from baseline in PPP Pain Visual Analog Scale (VAS) score at Week 4 and 16
- PPP SI change from baseline at Week 16
- PPP ASI50 at Week 16
- PPP ASI75 at Week 16
- PPP PGA clear/almost clear (0 or 1) at Week 16
- PPP PGA pustules clear/almost clear (0 or 1) at Week 16
- Percent change in PPP ASI from baseline at Week 52.

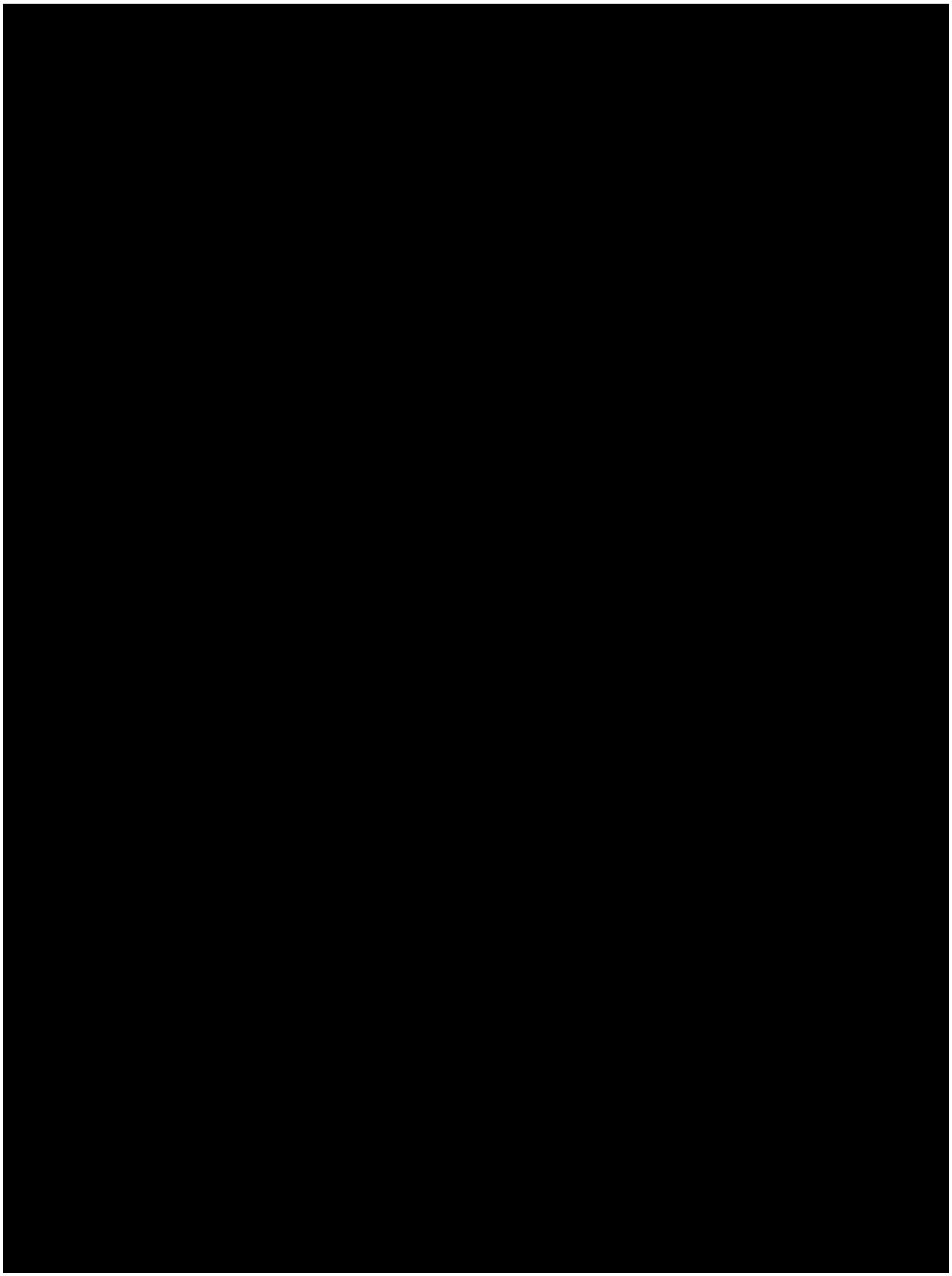
Derivations of PPP ASI related endpoints and PPP SI are described in Section 9.1.1.
Derivation of PPP PGA related endpoints is described in Section 9.1.2.

Note that for the secondary endpoints, any data collected after use of any rescue therapy or 6 weeks following last drug administration if a patient discontinued treatment early (to allow for incorporation of the continuing maximum treatment effect period) are censored for the purpose of the primary estimand (EC).

- The occurrence of Treatment Emergent Adverse Events (TEAEs)







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For more details of study information on the treatment to be administered, assignment to treatment, and selection of dose, refer to Section 4 of the CTP.

The following study phases are defined:

Table 6.1: 1 Flow chart of analysis phases

Study analysis phase	Description	Start (included)	End (included)
Screening phase	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of start of the first study dose minus 1 minute.
Loading treatment phase	On-treatment period	Date/time of start of the first study loading dose (Day 1)	Earlier of: i) Date/time of start of the first maintenance dose; or, ii) Date of end of last loading dose + 112 days at 11:59 p.m. if patient early discontinued study treatment before the first maintenance dose
Maintenance treatment phase (primary analysis at week 16)		Date/time of start of the first study maintenance dose (if applicable)	Earlier of : i) Date/time of start of the first maintenance dose at or after week 16; or, ii) Date of end of last maintenance dose + 112 days at 11:59 p.m. if patient early discontinued study treatment before week 16
Maintenance treatment phase (post primary analysis at week 16)		Date/time of start of the first maintenance dose at or after week 16 (if applicable)	Earlier of: i) Date/time of start of first dose in OLE 1368.24 trial; or, ii) Date of end of last study maintenance dose + 112 days at 11:59 p.m.
Follow-up[1] phase (if applicable)	Off-treatment period (if applicable)	Date of end of last study dose + 113 days at 0:00 a.m.	Latest of: i) Date of EOS visit; ii) end date on trial termination page at 11:59 p.m. iii) Date/time of start of first dose in OLE 1368.24 trial;

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 off-treatment period (i.e. Follow-up phase) only exists if the trial completion date is after the date of end of last administration + 112 days.

The primary analysis is planned to be performed once all patients have completed through the planned first 16 weeks of trial or early discontinued. The primary analysis will focus on individual patient's data up to treatment at week 16. If a patient early discontinued from treatment before week 16 or missed visit at week 16 but was still ongoing beyond week 16, all on-treatment data up to Day 127 which is the right limit of the week 16 extended time window (see Table 6.7: 1) will be included. In addition, for patients who missed visit at week

16 but was still ongoing beyond week 16, PPP Pain VAS, PPP ASI and PPP PGA assessments up to the first maintenance treatment after Week 16 (if available at time of primary analysis) will be included. They will not be reported in any outputs for primary analysis but might be used for imputation of endpoints related to PPP Pain VAS, PPP ASI and PPP PGA. See Section 6.6.2 for the details of imputation methods.

The final trial analysis is planned to be performed at the end of the study once all randomized patients have completed the study (including any applicable follow-up period). The final trial analysis will include all trial data.

Treatment groups for the analysis of Arm 1-4 will be labelled and sorted as follows:

- **"Speso Low":** (i.e., Arm 4)
- **"Speso Medium-low":** (i.e., Arm 3)
- **"Speso Medium-high":** (i.e., Arm 2)
- **"Speso High":** (i.e., Arm 1)
- **“Speso Total”** (i.e., Arm 1, 2, 3 and 4), where appropriate for analysis up to Week 16

Treatment groups for Arm 5 will be labelled differently based on the data included in the analysis:

- **"Placebo & Speso":** (i.e., Arm 5 if all trial data reported)
- **"Placebo":** (i.e., Arm 5 if only data prior to the first Spesolimab treatment reported)
- **"Speso post placebo":** (i.e., Arm 5 if only data post the first Spesolimab treatment reported)

If needed, Arm 1-5 could be pooled using the following label:

- **“Overall Total”:** (i.e., Arm 1, 2, 3, 4 and 5), where appropriate

For the analysis on safety data post Week 16, the following treatments will be added in addition to original treatments as follows (see Section 7.8):

- **"Speso** [redacted] (i.e., Arm 1 + Arm 3 + Arm 5)

For the additional analysis on efficacy and safety data within loading stage, treatments will be re-grouped as follows (see Section 7.6.4 and Section 7.8):

- **"Placebo":** (i.e., Arm 5)
- **"Speso** [redacted] (i.e., Arm 3 + Arm 4)
- **"Speso** [redacted] (i.e., Arm 1 + Arm 2)

For the additional analysis on efficacy data post Week 16, treatments will be regrouped as follows (see Section 7.5.3):

- **"Speso** [redacted] (i.e., Arm 4)
- **"Speso** [redacted] (i.e., Arm 2)
- **"Speso** [redacted] (i.e., Arm 1 + Arm 3 + Arm 5)

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

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 exclusion from analysis sets. IPDs leading to exclusion from analysis sets are indicated as such in Table 6.2: 1. IPDs will be summarised and listed for the randomized set.

IPDs will be summarized and listed for the randomized set.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]
A		**Entrance criteria violated**		
A1		**Inclusion criteria not met**		
	A1.01	Palmoplantar Pustulosis defined as presence of primary, persistent (>3 months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis elsewhere on the body. LABEL: No presence of PPP.	IC02 Also check versus PPP ASI that pustule severity > 0 on at least one region	PPS
	A1.02	Presence of white or yellow pustules on palms and/or soles at screening and baseline LABEL: No presence of white or yellow pustules on palms/soles.	IC03	PPS
	A1.03	Pustular severity score ≥2 in at least one region and ≥10 well-demarcated pustules (white or yellow pustules) across all regions at screening and baseline LABEL: No pustular severity score ≥2 in any region or <10 well-demarcated pustules	IC04 Also check versus PPP ASI that pustule severity ≥2 on at least one region	PPS
	A1.04	PPP PGA of at least moderate severity (≥3) at screening and baseline. LABEL: PPP PGA not at least moderate severity	IC05. Also check versus reported PPP PGA at baseline.	PPS
	A1.05	A minimum PPP ASI score of 12 at screening and baseline LABEL: PPP ASI < 12	IC06. Also check versus derived PPP ASI at baseline.	PPS

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]
	A1.06	Male or female patients. Women of childbearing potential (WOCBP) must be ready and able to 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.	IC07	None
A2		**Exclusion criteria violated** ***General Exclusion Criteria***		
	A2.01	Reduction in PPP ASI total score ≥ 5 from screening visit (Visit 1) to baseline (randomisation visit, Visit 2). LABEL: Reduction in PPP ASI total score ≥ 5 from V1 to V2	EC01 Also check versus PPP ASI at V1 and V2.	PPS
	A2.02	Patients with plaque psoriasis with worsening of plaque psoriasis within the last 3 months prior to screening. LABEL: Worsening of plaque psoriasis within the last 3 months	EC02	PPS
	A2.03	Skin conditions that affect ability to score area and severity of PPP components LABEL: No ability to score are and severity of PPP components	EC03	PPS
	A2.04	Women who are pregnant, nursing, or who plan to become pregnant while in the trial. LABEL: Pregnant or nursing.	EC04	None

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code	Description	Comments	Excluded from[1]
A2.05	Severe, progressive, or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof. LABEL: Severe or uncontrolled disease.	EC05	None
A2.06	Presence or known history of anti-TNF-induced PPP-like disease. LABEL: Anti-TNF-induced PPP-like disease.	EC06	PPS
A2.07	Patient with a transplanted organ or who have ever received stem cell therapy LABLE: A transplanted organ or a stem cell therapy	EC07	None
A2.08	Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly. LABEL: Lymphoproliferative disease.	EC08	None
A2.09	Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. LABEL: Malignancy within last 5 years.	EC09	None

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code	Description	Comments	Excluded from[1]
A2.10	Use of any restricted medication as specified in CTP Table 4.2.2.1: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator LABEL: Use of restricted medication interfering safety	EC10 – based on tick box only.	PPS
A2.11	Administration of live vaccines during the study period or within 6 weeks prior to randomisation. LABEL: Live vaccine within last 6 weeks.	EC11	None
A2.12	History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients. LABEL: History of allergy/hypersensitivity.	EC12	None
A2.13	Active systemic infections during the last 2 weeks (exception: common cold) prior to randomisation, as assessed by the investigator. LABEL: Systemic infections within last 2 weeks.	EC13	None
A2.14	Chronic or relevant acute infections including human immunodeficiency virus (HIV), viral hepatitis and (or) active or latent tuberculosis (TB): LABEL: Chronic or relevant acute infections.	EC14	None
A2.15	Major surgery performed within 12 weeks prior to randomisation or planned within 52 weeks after randomisation, as assessed by the investigator. LABEL: Recent or planned major surgery.	EC15	None

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code	Description	Comments	Excluded from[1]
A2.16	Patient has received surgical treatment of focal infection (e.g. tonsillectomy or dental therapy) within 6 months of randomisation. LABEL: Surgical treatment of focal infection	EC16	None
A2.17	Total white blood count (WBC) < 3,000/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL, or hemoglobin <8.5 g/dL at screening. LABEL: WBC, PLAT, NEU, HGB below limit.	EC17 Also check versus screen Lab values	None
A2.18	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal, or total bilirubin > 1.5x the upper limit of normal (patients with Gilbert's syndrome are not excluded) at screening. LABEL: AST/ALT/TBIL above limits.	EC18 Also check versus screen Lab values (medical review for Gilbert Syndrome)	None
A2.19	Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s). LABEL: Recent enrollment in other study.	EC19	PPS

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]	
	A2.20	Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to complete the trial. LABEL: Alcohol or drug abuse.	EC20	PPS	
	A2.21	Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled. LABEL: No expectation to comply with the CTP or complete the trial.	EC21	PPS	
	A2.22	Previous randomisation in this trial. LABEL: Previous randomisation in this trial.	EC22	PPS	
B		**Informed consent**			
	B1	Informed consent not available LABEL: IC not available.	IC01 Date of informed consent missing or no signature on patient's "Declaration of Informed Consent" In this case: Patient's data will not be used at all.	All	#
	B2	Informed consent too late LABEL: IC too late.	IC01 Informed consent date was after Visit 1	None	

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]	
C		**Trial medication and randomisation**			
C1		**Incorrect trial medication**			
	C1.01	Study drug medication not taken at all LABEL: Study drug medication not taken at all.		All except for ES and RS	
	C1.02a	Patient skipped an intermediate dose prior to Week 16 for other reason (all injections at one planned visit) LABEL: Patient skipped an intermediate dose prior to Week 16 for other reason.	Patient missing a dose at an intermediate visit when dose at a later scheduled visit has been taken due to other reason.	PPS	
	C1.02b	Patient skipped an intermediate dose prior to Week 16 due to COVID 19 (all injections at one planned visit) LABEL: Patient skipped an intermediate dose prior to Week 16 due to COVID 19.	Patient missing a dose at an intermediate visit when dose at a later scheduled visit has been taken due to COVID 19.	PPS	#
	C1.03a	Patient skipped an intermediate dose at or after Week 16 for other reason (all injections at one planned visit) LABEL: Patient skipped an intermediate dose at or after Week 16 for other reason.	Patient missing a dose at an intermediate visit when dose at a later scheduled visit has been taken due to other reason.	None	
	C1.03b	Patient skipped an intermediate dose at or after Week 16 due to COVID 19 (all injections at one planned visit) LABEL: Patient skipped an intermediate dose at or after Week 16 due to COVID 19.	Patient missing a dose at an intermediate visit when dose at a later scheduled visit has been taken due to COVID 19.	None	#

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]	
C2		**Incorrect Dosing**			
	C2.01	Incorrect medication received prior to Week 16 LABEL: Incorrect dose received prior to Week 16	Randomized patient who didn't receive correct planned total dose at any scheduled visit prior to Week 16. Can only be finally judged after DBL since unblinding information is required	PPS	
	C2.02	Incorrect medication received at or after Week 16 LABEL: Incorrect dose received at or after Week 16	Randomized patient who didn't receive correct planned total dose at any scheduled visit at or after Week 16 Can only be finally judged after DBL since unblinding information is required	None	
C3		**Randomization not followed**			
	C3.01	Treated without randomisation LABEL: Treated without randomisation.	Patient treated according to eCRF, but not randomised according to IVRS.	All	
	C3.02	Randomization order not followed LABEL: Stratification error	Stratification error Programming check and also manual review after DBL	None	#
C4		**Medication code broken**			
	C4.01	Medication code broken before week 16 without just cause LABEL: Code broken early without just cause.	Medication code was broken prior to DBL for the week 16 analysis for no valid reason. Final decision at the DBL meeting for the Week 16 analysis based on medical judgment.	PPS	#

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]	
	C4.02	Medication code broken after week 16 without just cause LABEL: Code broken late without just cause.	Medication code was broken after DBL for the week 16 analysis for no valid reason. Final decision at final DBL based on medical judgment.	None	#
D		**Concomitant medication**			
D1		**Previous medication**			
	D1.01	Washout of previous medication too short LABEL: Washout too short.		PPS	#
D2		**Prohibited medication use**			
	D2.01a	Use of restricted medication as per CTP Table 4.2.2.1: 1 on or after Screening or during the on-treatment period - when not provided as a rescue therapy to treat a worsening disease condition – prior to Week 16 primary analysis for other reason LABEL:# Restricted medication prior to week 16 primary analysis for other reason.		PPS	#
	D2.01b	Use of restricted medication as per CTP Table 4.2.2.1: 1 on or after Screening or during the on-treatment period - when not provided as a rescue therapy to treat a worsening disease condition – prior to Week 16 primary analysis due to COVID 19 LABEL: Restricted medication prior to week 16 primary analysis for COVID 19.		PPS	#

Table 6.2: 1 (cont'd) Important protocol deviations

Category / Code		Description	Comments	Excluded from[1]	
	D2.02a	Use of restricted medication as per CTP Table 4.2.2.1: 1 on or after Screening or during the on-treatment period - when not provided as a rescue therapy to treat a worsening disease condition – after Week 16 primary analysis for other reason LABEL: Restricted medication after week 16 primary analysis for other reason.		None	#
	D2.02b	Use of restricted medication as per CTP Table 4.2.2.1: 1 on or after Screening or during the on-treatment period - when not provided as a rescue therapy to treat a worsening disease condition – after Week 16 primary analysis due to COVID 19 LABEL: Restricted medication after week 16 primary analysis due to COVID 19.		None	#
E		**Missing data**	<not specified>		
F		**Study specific analysis**	<not specified>		
G		**Other safety related deviations**			
	G1.01	Pregnancy test not done for woman of child bearing potential before IMP administration LABEL: Pregnancy test not done.	Pregnancy test not done at any visit before IMP was given.	None	#

PD will be detected manually;
Source: BI reference document ' Identify and Manage Important Protocol Deviations (iPD)' [001-MCS-50-413] (2,6).
[1] See Section 6.3 for population definitions

6.3 PATIENT 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.

Randomized set (RS)
This patient set includes all patients who were randomized in the trial. Treatment assignment will be as randomised. It will be used for display of disposition, IPD and etc.

Safety analysis set (SAF)
This patient set includes all patients who were randomised and received at least one dose of study drug. It will be the main analysis set for presentation of safety data. Patients will be analyzed according to the actual treatment.

Safety analysis set – Post Week 16 (SAF-post 16)
This patient set includes all patients in SAF who received at least one dose of study drug after, and including, Week 16. It will be the main analysis set for presentation of safety data after Week 16 only. Patients will be analyzed according to the actual treatment after week 16.

Full Analysis Set (FAS)
This patient set includes all patients who were randomised, received at least one dose of study drug and had a baseline for the primary endpoint. Treatment assignment will be as randomised. This is the main analysis set for presentation of efficacy data.

Full Analysis Set – Post Week 16 (FAS-post 16)
This patient set includes all patients in the FAS and had received at least one dose of study drug after, and including Week 16. Treatment assignment will be as randomised. This is the set for additional analysis of efficacy data post Week 16.

Per-Protocol Set (PPS)
This patient set includes all patients in the FAS set who adhered to the CTP without any iPDs which are flagged for exclusion from the PPS in the table above. The PPS will be used for sensitivity analysis on the primary efficacy endpoint.

Modified FAS set (m-FAS)
This patient set includes all patients in the FAS set excluding pre-identified questionable cases (mild cases) based on mQC (medical quality control) review where the severity of PPP could not be clarified and confirmed based on the descriptive review and quality control of the photo documentation. The m-FAS will be used for sensitivity analysis on the primary efficacy endpoint and selected secondary endpoints.

Handling of Treatment Misallocations in Analysis Sets

If a patient is randomized but not treated, they will not be included into efficacy or safety analysis according to FAS (including FAS-post 16), m-FAS, PPS and SAF (including SAF-post 16).

If a patient is treated but not randomized, they will be excluded from both efficacy analysis and safety analysis by definition. However, patients under such circumstances will be described separately in the final clinical trial report.

If a patient is randomized but took incorrect treatment during the study, then:

- For efficacy analyses according to FAS (including FAS-post 16), m-FAS and PPS, they will be reported under their randomized treatment groups.

- For safety analyses using the SAF,

    - For Arm1-4: If a patient is planned to receive multiple dose administrations of Spesolimab, then patients will be reported under their randomized treatment group for safety analysis because the overall safety profile is expected to be driven by the amount of Spesolimab received in totality over the entire treatment duration. It is not expected that the safety profile will deviate from the planned treatment regimen if the subject receives only a few vials of the incorrect medication at only some dosing occasions.

    - For Arm 5: If a patient is planned to receive multiple dose administrations of placebo (prior to Week 16 only), then patients will be reported under their randomized treatment group for safety analysis if the patient receives no dose of randomized Spesolimab during this treatment period (i.e., prior to Week 16). If the patient receives ≥1 syringe of randomized Spesolimab during this treatment period, then the patient will be assigned to Arm 4 (lowest dose of Spesolimab planned in the trial before week 16).

- For safety analyses using the SAF-post 16,

    - For Arm1-5: If a patient is planned to receive multiple dose administrations of Spesolimab, then patients will be reported under their randomized treatment group for safety analysis because the overall safety profile is expected to be driven by the amount of Spesolimab received in totality over the entire treatment duration. It is not expected that the safety profile will deviate from the planned treatment regimen if the subject receives only a few vials of the incorrect medication at only some dosing occasions.

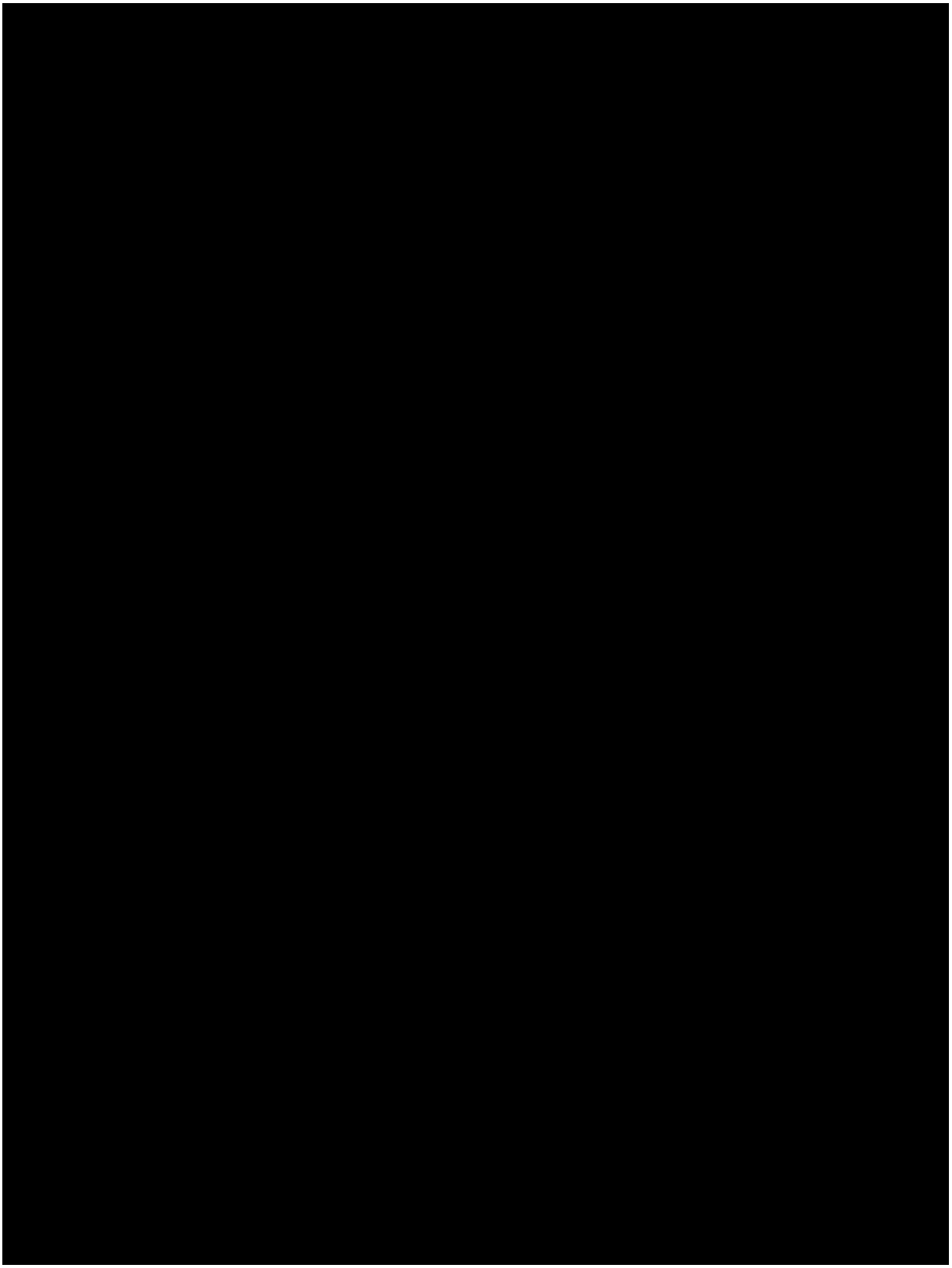
Table 6.3: 1 illustrates the data sets which are to be used for each category class of endpoints, and the approaches used with regard to missing data. For explanation of the different methods of handling missing data, cf. Section 6.6.

Table 6.3: 1 Patient sets analysed

Class of endpoint	Patient set					
	ES	RS	SAF (including SAF-post 16)	FAS (including FAS-post 16, m-FAS)	PPS	[redacted]
Disposition	OR	OR				
Compliance and exposure			OR			
iPD		OR				
Demographic/baseline characteristics			OR	OR		
CM			OR			
Primary efficacy endpoint				EC-MMRM, EC-MMRM[1] EC-EP-MMRM[1] EC-E19-MMRM[1] EC-ID-MMRM[1] EC-MI[1], OC[2], OC-IR[2]	EC-MMRM[1]	
Secondary efficacy endpoints (Binary)				EC-NRI, EC-NRI[1,3] EC-EP-NRI[1,3] EC-E19-NRI[1,3] EC-ID-NRI[1,3] EC-BRI[1,3] OC[2], OC-IR[2]		
Secondary efficacy endpoints (Continuous)				EC-MMRM, EC-MMRM[1,3] OC[2], OC-IR[2]		
[redacted]						
[redacted] ADA/Nab						OR
[redacted]						

[1] sensitivity analysis or subgroup analysis
[2] descriptive display only
[3] selected endpoints.

EC: Primary estimand for binary and continuous efficacy endpoints. Any data collected after use of any rescue therapy or after 6 weeks following last drug administration if patient early discontinued treatment (to allow for incorporation of the continuing maximum treatment effect period) are censored.
EC-EP: Alternative estimand for binary and continuous efficacy endpoints. Any data collected after use of any rescue therapy or restricted therapy for other purpose or after 6 weeks following last drug administration if patient early discontinued treatment (to allow for incorporation of the continuing maximum treatment effect period) are censored.
EC-E19: Alternative estimand for binary and continuous efficacy endpoints. Any data collected after use of any rescue therapy or after the first visit with missing treatment due to COVID-19 or after 6 weeks following last treatment before or at discontinuation (to allow for incorporation of the continuing maximum treatment effect period) are censored.
EC-ID: Alternative estimand for binary and continuous efficacy endpoints. Any data collected after use of any rescue therapy are censored.
"NRI", "MMRM" and "MI" represent analyses involving imputed data, 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.



6.5 POOLING OF CENTRES

There is no plan to perform statistical analysis by pooling centers.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.5 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 trial, depending upon the type of the endpoint (cf. Table 6.3: 1). Approaches to be applied are described below.

Missing data imputations of PPP Pain VAS, PPP PGA and PPP ASI related endpoints at the primary analysis of the trial may be performed using all data up to the first maintenance dose at or after week 16 if available. Missing data imputations of other endpoints at the primary analysis will be performed using all data up week 16.

Continuous efficacy endpoints

For efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach as the primary method, if applicable, will ensure that missing data are handled implicitly, via a missing at random (MAR) assumption, by the statistical model.

In order to check the robustness of MMRM method to missing data, a sensitivity analysis will be performed using Multiple imputation with jump to reference method (only for primary analysis at week 16):

As the first step, the non-monotone missing data of PPP ASI total score will be imputed using Markov Chain Monte Carlo (MCMC) simulation and standard techniques. 100 imputations will be performed to ensure adequate efficiency and stability of the estimation for missing data. In a second step, for each imputation, the monotone missing data of patients that were still ongoing in the trial will be imputed once by standard sequential linear regression MI including treatment as categorical covariate and PPP ASI from baseline up to week 16 as

continuous covariates (other missing values will also be imputed as a by-product but subsequently deleted).

In a third step, the monotone missing data of patients who early discontinued study treatment before week 16 will be imputed using a residual-based jump to reference method. The implicit assumption underlying this step is that patients in the active treatment groups are assumed to lose any treatment effect if they early discontinued from the trial treatment. Covariate-adjusted differences between each treatment arm and placebo (i.e. 0 for those in the placebo arm) will be calculated for each visit of each imputed data set using ANCOVA (with treatment as categorical covariate and baseline PPP ASI as continuous covariates). The relevant treatment effects are then deducted from the measurements in each data set, i.e. the expected effects of treatment are removed. Sequential linear MI is then performed once per modified imputed data set, but only including patients in the placebo arm and those that require imputation at the visit being imputed, i.e. imputation will be solely based on the placebo distribution. The imputation model will include PPP ASI values at previous time points (including baseline) as covariates. After this imputation, all originally-observed values will be restored. All monotone missing data will therefore follow the distribution of the placebo arm, jumping from one arm's distribution to the placebo's at the point of start of the missingness, while still accounting for the past within-treatment performance (the residuals).

For each imputed complete dataset, an ANCOVA (Analysis of Covariance) model for Week 16 data analogous to the primary MMRM model will be used for the analysis. The results will be pooled using Rubin's rules across the 100 imputations and the primary MCPMod analysis will be repeated on the summarized outcomes.

The following additional methods will be used to display the continuous 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

Other imputation scheme will be also considered for analysis of the secondary binary efficacy endpoints.

- Best response imputation (BRI): impute all missing values based on the best response observed for the patient at visits prior to withdrawal/occurrence of missing data (independent of whether the observations were selected for analysis based on time windows described in Section 6.7). If there is no non-missing data available (including baseline), then the missing value will be imputed as a failure.

OC and OC-IR methods will be also used to display the binary data.

6.6.3 Safety data

With respect to safety evaluations, it is not planned to impute missing values. For safety data that are displayed by time point (or visit) of measurement, the OC-IR approach will be used. For safety data that are not displayed by visit such as AE and possibly clinically significant laboratory abnormality, OR will be used.

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.

[redacted]

[redacted]

6.6.7 Time since first diagnosis/tonsillectomy

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.

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.

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.

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). These extended time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital [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 - 14					
V2	Day 1	Day 1		1 [A]	1	1 [A]	1
V3	Week 1	Day 8	+/- 2	6	10	2	11
V4	Week 2	Day 15	+/- 2	13	17	12	18
V5	Week 3	Day 22	+/- 2	20	24	19	25
V6	Week 4	Day 29	+/- 2	27	31	26	43
V7	Week 8	Day 57	+/- 7	50	64	44	71
V8[C]	Week 12	Day 85	+/- 7	78	92	72	99
V9	Week 16	Day 113	+/- 7	106	120	100	127
V10	Week 20	Day 141	+/- 7	134	148	128	155
V11	Week 24	Day 169	+/- 7	162	176	156	183
V12	Week 28	Day 197	+/- 7	192	204	184	211
V13	Week 32	Day 225	+/- 7	218	232	212	239
V14	Week 36	Day 253	+/- 7	246	260	240	267
V15	Week 40	Day 281	+/- 7	274	288	268	295
V16[C]	Week 44	Day 309	+/- 7	302	316	296	323
V17	Week 48	Day 337	+/- 7	330	344	324	351
V18[D]	Week 52 (EoT)	Day 365	+/- 7	358	372	352	393
V19	Week 60	Day 421	+/- 7	414	428	394	449
V20	Week 68 (EoS)	Day 477	+/- 7	470	484	450	491
For patients who discontinue the treatment early and are not willing to follow the whole visit schedule:							
-	EoS	LD[B]+112	-	-	-		

Days are counted relative to the day of first treatment, which is defined as Day 1.
[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=Last dose.
[C] Data within the extended time window of Week 8/16 but after the actual dose at Week 8/16 will not be selected to represent Week 8/16 except for local tolerability and post-dose vital sign assessments.
[D] For the patients who enter OLE trial, the EOT will be the last visit (i.e., V19 and V20 are not required). The EOS (=individual end of the study) will be the first administration of the trial drug in OLE trial.

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.

Note that data within the extended time window of Week 8/16 but after the actual dose at Week 8/16 will not be selected to represent Week 8/16 except for local tolerability and post-dose vital sign assessments.

Assignment of 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 EC and OC methods, 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 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.

7. PLANNED ANALYSIS

The following analyses of this trial protocol are planned:

Primary Analysis (Week 16)

This primary analysis will be performed when all patients have completed 16 weeks of the study or early discontinued and a database lock will be performed.

Each patient's available data up to the earlier time point of treatment at week 16 or Day 127, (i.e., the right limit of week 16 extended time window) will be considered in the primary analysis.

The primary analysis will be performed by the sponsor. The selected project and trial team members will be un-blinded for this analysis. Since the study is planned to continue after the primary analysis in a blinded manner at sites (for investigators and patients), a logistics (and access) plan will be developed in order to describe the processes to be implemented in order to protect the integrity of the ongoing trial through the final analysis.

[redacted]

Final analysis

The analysis of the entire efficacy, safety, [redacted] data collected will be performed once all randomized patients have completed the trial; at that time point, a final database lock will be done and all results of the trial will be reported.

A formal clinical trial report is planned for the primary analysis, and a separate clinical trial report will be prepared for the final analysis.

General Remarks

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (10) [redacted] (5).

[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 treatment (see Section 7.8.1 below for details).

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 "Reporting of clinical trials and project summaries" (10).

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 treatment. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are 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.

Note that for the analysis of all data in this trial, the primary approach is to report only those data that fall within the on-treatment period. Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients screened, randomized, treated, who completed the PE visit, who were prematurely discontinued study treatment before PE visit, by reason, who withdrew from the trial before PE visit, by reason (only for primary analysis), who completed all doses of treatment as planned (only for final analysis), who were prematurely discontinued study treatment, by reason (only for final analysis), who completed the trial (only for final analysis), and who withdrew from the trial, by reason (only for final analysis).

The frequency of patients with IPDs will be presented for the RS by treatment. The IPDs will be listed per patient indicating whether or not the IPD led to exclusion from patient sets analyzed.

The frequency of patients in each of the different analysis sets will also be presented by treatment.

[redacted]

[redacted]

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Descriptive statistics will be presented by treatment for demographic parameters and baseline characteristics, based on the SAF and FAS respectively.

For the continuous variables described below, categories are defined in Table 7.1: 1. These variables will be presented according to the number and percentage of patients in each category.

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories
Age	< 50 years 50 to < 65 years ≥ 65 years < 65 years ≥ 65 years
Weight	≤70 kg >70 to ≤80 kg >80 to ≤ 90 kg >90 kg
BMI	< 25 kg/m^2 25 to < 30 kg/m^2 ≥ 30 kg/m^2
Time since first diagnosis	≤ 1 year > 1 to ≤ 5 years > 5 to ≤ 10 years > 10 years

[redacted]

7.2 CONCOMITANT DISEASE AND MEDICATION

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

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

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

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

- is ongoing at the start of randomized trial treatment or
- starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases).

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 randomized trial treatment.

Concomitant medication use (excluding rescue therapy) will be summarised with frequency and percentage of patients by ATC3 class and preferred name. Summaries will be presented for

- concomitant medication starting any time prior to Day 1 (the day of start of trial treatment)
- concomitant medication starting any time during the on-treatment period (cf. Section 6.1).

Concomitant use of non-drug therapies (excluding rescue therapy) will be summarized with frequency and percentage. Summaries will be presented for

- concomitant non-drug therapies starting any time prior to Day 1 (the day of start of trial treatment)

- concomitant non-drug therapies starting any time during the on-treatment period (cf. Section 6.1).

For primary analysis of the trial, concomitant therapies/non-drug therapies starting up to the earlier time point of 1) Day 127 or 2) treatment at week 16 will be reported based on SAF.

For final analysis of the trial, concomitant therapies/non-drug therapies starting up to the first maintenance treatment at or after week 16 based on SAF (if applicable) and starting post the first maintenance at or after week 16 based on SAF-post 16 will be reported separately.

The frequency and percentage of patients with historical medication for PPP will be displayed, including presentation by type of historical medication (preferred name), and by reason for discontinuation.

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

7.3 TREATMENT COMPLIANCE

Treatment compliance will be summarised up to week 16, post week 16 (for final analysis only), and overall (for final analysis only) for the SAF (as a % of planned) using descriptive statistics (N, mean, SD, minimum, median, maximum). The volume injected (as a % of planned) is defined as the number of syringes injected at a visit (as recorded in the eCRF), divided by number of syringes that patient should have received, 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.

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

For the primary endpoint analysis, first a mixed effect model for repeated measurements (MMRM) is calculated to estimate the treatment effects and the corresponding covariance matrix. Using the MCPMod approach (11, 12), these estimates are then further used to (1) test for a non-flat dose response curve and (2) to identify suitable dose-response shapes out of a selection of candidate models. The final model will then be calculated by averaging over all significant model shapes.

Details on both the specification of the MMRM and the MCPMod approach are given in the CTP Section 7.2.2. Sample size calculations are described in CTP Section 7.5.

The primary analysis of primary endpoint will be based on the FAS. Any data collected after use of any rescue therapy or after 6 weeks following last drug administration if a patient

discontinued treatment early will be censored as the primary estimand (EC).

MMRM analysis

The % change in PPP ASI from baseline (Visit 2), at Visits 3, 4, 5, 6, 7, 8 and 9 (Weeks 1, 2, 3, 4, 8, 12 and 16) will be evaluated using an MMRM accounting for the following sources of variation: 'baseline' as a continuous covariate, and 'visit', 'treatment', 'region' (stratification according to Japan vs. non-Japan), 'visit*treatment' and 'visit*baseline' interaction as fixed effects as well as the random 'subject' effect. The unstructured covariance structure will be used to model the within patient measurements. To estimate denominator degrees of freedom the Kenward-Roger approximation will be used.

In the event of model non-convergence, the methods described in Section 9.3 will be utilized to resolve this.

SAS code for MMRM:

The following SAS code will be used to calculate the MMRM.

```
PROC MIXED DATA=alldat cl method=reml;
  CLASS visit trt stratum subject;
  MODEL ept = stratum visit*trt base*visit / ddfm=kr s CL;
  REPEATED visit / subject= subject type=un r rcorr;
  LSMEANS visit*trt / pdiff=all om cl alpha=0.05 slice=visit;
RUN;
```

Results of the MMRM (N, mean, SE and 95% CI per dose group and timepoint) will be presented in tables and displayed graphically.

MCPMod Analysis

For the primary analysis the dose-response relationship will be modeled using the total doses. Here, the total is the sum of all doses administered to the patient prior to the week 16 visit including both loading and maintenance phase. Thereby, it is assumed that the cumulative concentrations over time (AUC) and thus the cumulative total dose is the key driver of the efficacy response in the modelling part of MCPMod. Table 7.4: 1 shows the calculated total doses per treatment arm.

Table 7.4: 1 Total dose per treatment arm.

High dose regime (Arm 1)	[redacted]
Medium-high dose regime (Arm 2)	
Medium-low dose regime (Arm 3)	
Low dose regime (Arm 4)	
Placebo (Arm 5)	

W: Week.

The multiple comparison procedure will then be implemented using optimal contrast tests which control the family-wise type I error rate at a one-sided $\alpha = 0.05$. For the MCPMod test, the optimal contrasts of each candidate model are calculated using the R-function `optCont` using weights (`w`) proportional to the sample size of each dose group, respectively, and are shown in Table 7.4: 2.

Table 7.4: 2 Contrast coefficient.

	Contrast coefficients for (total) dose				
Model	Placebo	Low dose: [redacted]	Medium-low dose: [redacted]	Medium-high dose: [redacted]	High dose: [redacted]
Linear	0.783	0.049	-0.049	-0.196	-0.587
Emax	0.869	-0.112	-0.151	-0.190	-0.416
Exponential	0.574	0.194	0.118	-0.106	-0.780
Logistic	0.706	0.220	-0.036	-0.279	-0.612
Sigmoid Emax	0.638	0.247	0.052	-0.256	-0.681

BI: Spesolimab total dose, [redacted] administered before week 16.

For the final evaluation, these contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix extracted from the MMRM model. The updated contrast coefficients will be reported in the CTR.

Once the significance of a dose-response signal is established, the dose-response profile and the target dose can be estimated using a model averaging approach. Here, the final model is

derived as a weighted average over all significant model shapes. Here, the weights for each significant model (M_k) are given by

$$w(M_k) = \frac{\exp(0.5 \cdot AIC(M_k))}{\sum_{i=1}^{K} \exp(0.5 \cdot AIC(M_i))},$$

where $AIC(M_k)$ is the Akaike Information Criterion (AIC) of model M_k.

Estimates for each dose group will be calculated and will be based on the final dose-response model. The choice of the target dose to be investigated in Phase 3 will be based upon efficacy as well as considering safety and other relevant information.

R code to perform the evaluations is available in Section 9.4.

The following displays are planned.

- Table of the updated contrast coefficients per dose group and candidate model, together with the MCPMod test statistics and p-values for each model and the critical value
- For averaging model, figure of the dose-response curve
- For all significant model shapes, figures of the dose-response curve plus 95% confidence band (of the predicated shape) and 95% CI per dose (estimated from MMRM)
- For all significant model shapes, figure with the placebo corrected dose-response curve plus 95% confidence band (of the predicated shape).

R code is also available in Section 9.4.1.

Descriptive statistics

Descriptive displays of percentage change from baseline in PPP ASI (with 95% CI) will be presented by treatment using OC and OC-IR methods respectively. The method to provide confidence intervals for each arm and unadjusted differences to placebo is derived from the Student's t-distribution.

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

Continuous secondary endpoints
Continuous secondary endpoints up to week 16 will be evaluated using MMRM model and MCP-Mod in the same way as for the primary endpoint.

For percent change in PPP ASI from baseline at Week 52, a similar setting to that described for the primary endpoint MMRM model (in Section 7.4) will be applied with the inclusion of the additional visits of Week 28, 40 and 52.

[redacted]

Binary secondary endpoints
For each of the binary secondary endpoints at Week 16, a logistic regression and MCPMod model will be used to evaluate the treatment effect of multiple doses of Spesolimab vs. placebo. This method will be implemented for MCPMod in a binary setting.

The primary analysis of binary secondary endpoints will be based on the FAS. Any data collected after use of any rescue therapy or after 6 weeks following last drug administration if a patient discontinued treatment early will be censored as the primary estimand (EC).

Logistic regression analysis
For binary endpoints, the difference in the proportion of patients with a response between Spesolimab and placebo will be analysed, for the FAS, using a logistic regression approach with a logit link via PROC LOGISTIC in SAS®. Fixed classification effects will include treatment and region (Japan vs. Non-Japan). In case 0 event is observed in any of the combination of dose group and strata a penalized regression based on the Firth's bias reduction method (19, 20) will be used.

The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale. Odds ratio will be also reported between each Spesolimab arm vs placebo

Confidence intervals will be calculated using the cumulative distribution function method of Reeve (14). More specifically, as suggested in Reeve (14), a numerical search algorithm will be employed to find the quantiles x_A of the cumulative distribution function, $F_{\widehat{\Delta p}}$, such that $F_{\widehat{\Delta p}}(x_A) = A$, where A = 2.5% and A = 97.5% and $F_{\widehat{\Delta p}}$ is given by equation (10) in Reeve (14). R code that will be used to implement this is provided in Section 9.2.

MCP-MOD analysis

The estimate of response rate from each dose group obtained via logistic regression or penalized regression based on the Firth's bias reduction method (as described above) without intercept will be used as basis for the MCPMod analysis of the binary secondary endpoints. The subsequent MCP-Mod analyses are based on the response rates on the logit scale.

The multiple comparison procedure will be implemented using optimal contrast tests which control the family-wise type I error rate at a one-sided $\alpha = 0.05$. The same candidate models as for the primary endpoint will be used for all secondary binary endpoints. For the MCPMod test, the optimal contrasts of each candidate model are calculated using the R-function `optCont` using weights (`w`) proportional to the sample size of each dose group, respectively, and are shown in Table 7.5.2: 1. These contrasts will be recalculated using the actual sample size of the dose groups (in case this differs from the planned numbers). The final contrasts will be presented in the CTR.

Table 7.5.2: 1 Contrast coefficient

	Contrast coefficients for (total) dose				
Model	Placebo	Low dose: [redacted]	Medium-low dose: [redacted]	Medium-high dose: [redacted]	High dose: [redacted]
Linear	-0.783	-0.049	0.049	0.196	0.587
Emax	-0.869	0.112	0.151	0.190	0.416
Exponential	-0.574	-0.194	-0.118	0.106	0.780
Logistic	-0.706	-0.220	0.036	0.279	0.612
Sigmoid Emax	-0.638	-0.247	-0.052	0.256	0.681

BI: Spesolimab total dose, [redacted] administered before week 16.

The MCP-Mod test will be applied using these fixed contrasts. R code is also available in Section 9.4.2.

All significant dose-response models will be re-fitted to the data without any parameter assumptions to generate a set of new estimates of the model parameters from the data. The final model is derived as a weighted average over all significant model shapes obtained via the same averaging procedure as described for the primary endpoint.

The following displays are planned.

- Table of the contrast coefficients per dose group and candidate model, together with the MCPMod test statistics and p-values for each model and the critical value
- For the average model, figure of the dose-response curve
- For all significant model shapes, figures of the dose-response curve plus 95% confidence band (of the predicted shape)

Descriptive statistics

Descriptive statistics and graphical displays (line plots) of the response on each binary endpoint will be produced using EC-NRI, OC and OC-IR methods respectively. The method to provide confidence intervals for single proportions will be based on Wilson (16). The method to provide confidence intervals for risk differences is derived from the Wilson method by Newcombe (17).

[redacted]

[redacted]

[redacted]

7.5.3 Analysis of % change in PPP ASI from week 16

Analysis regarding the % change in PPP ASI will be performed, using the FAS-post 16 set, which focuses on the maintenance treatment period post primary endpoint (Week 16). Data starting from the first dose administered at Week 16 will be evaluated using the MMRM model where week 16 data will be used as baseline and visits at week 28, 40 and 52 will be included. Patients who didn't receive treatment at week 16 will be excluded from this analysis.

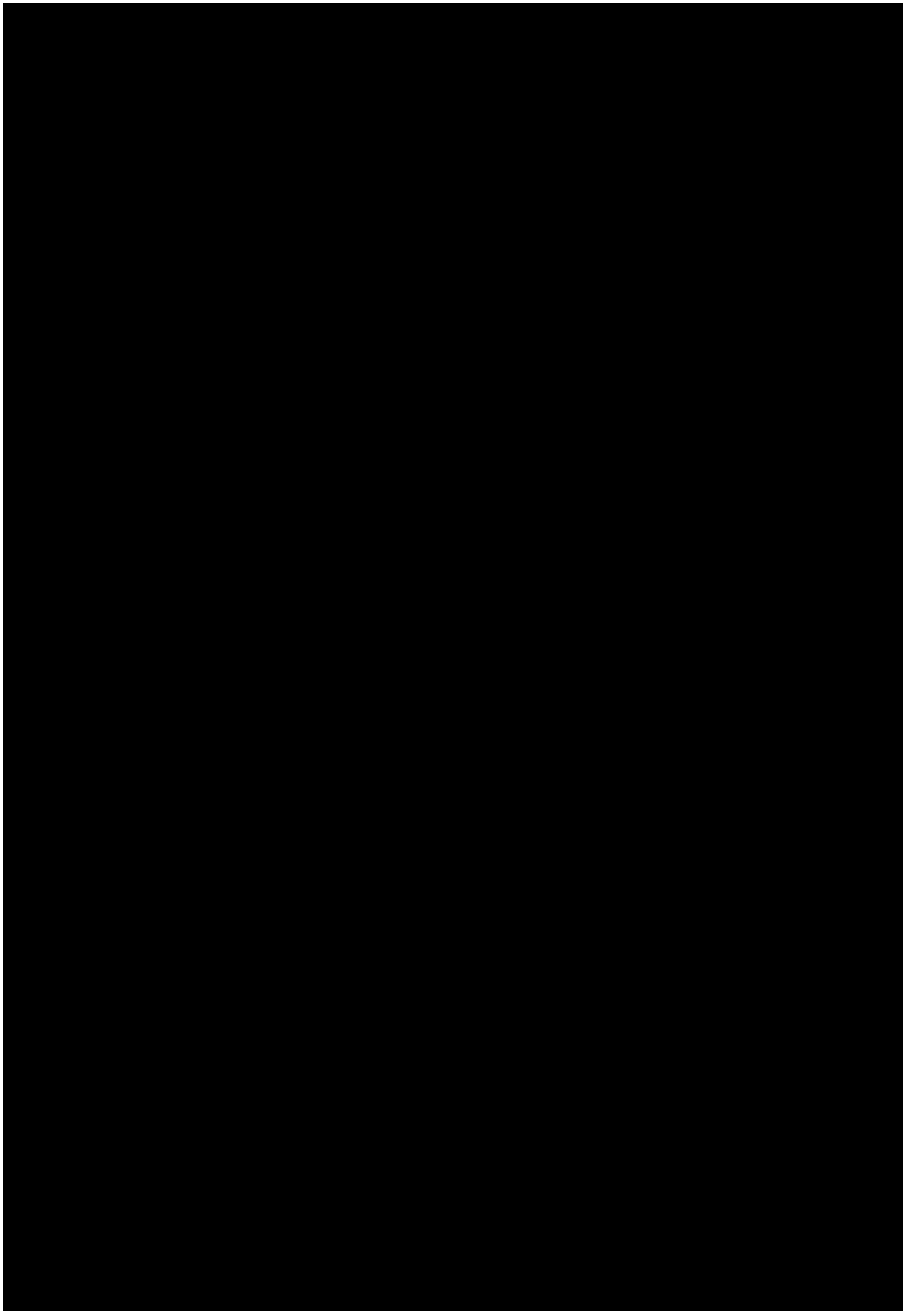
MMRM model accounts for the following sources of variation: 'baseline' (week 16) as a continuous covariate, and 'visit', 'dose group', 'region' (stratification according to Japan vs. non-Japan), 'dose group*visit' and 'visit*baseline' (week 16) interaction as fixed effects as well as the random 'subject' effect.

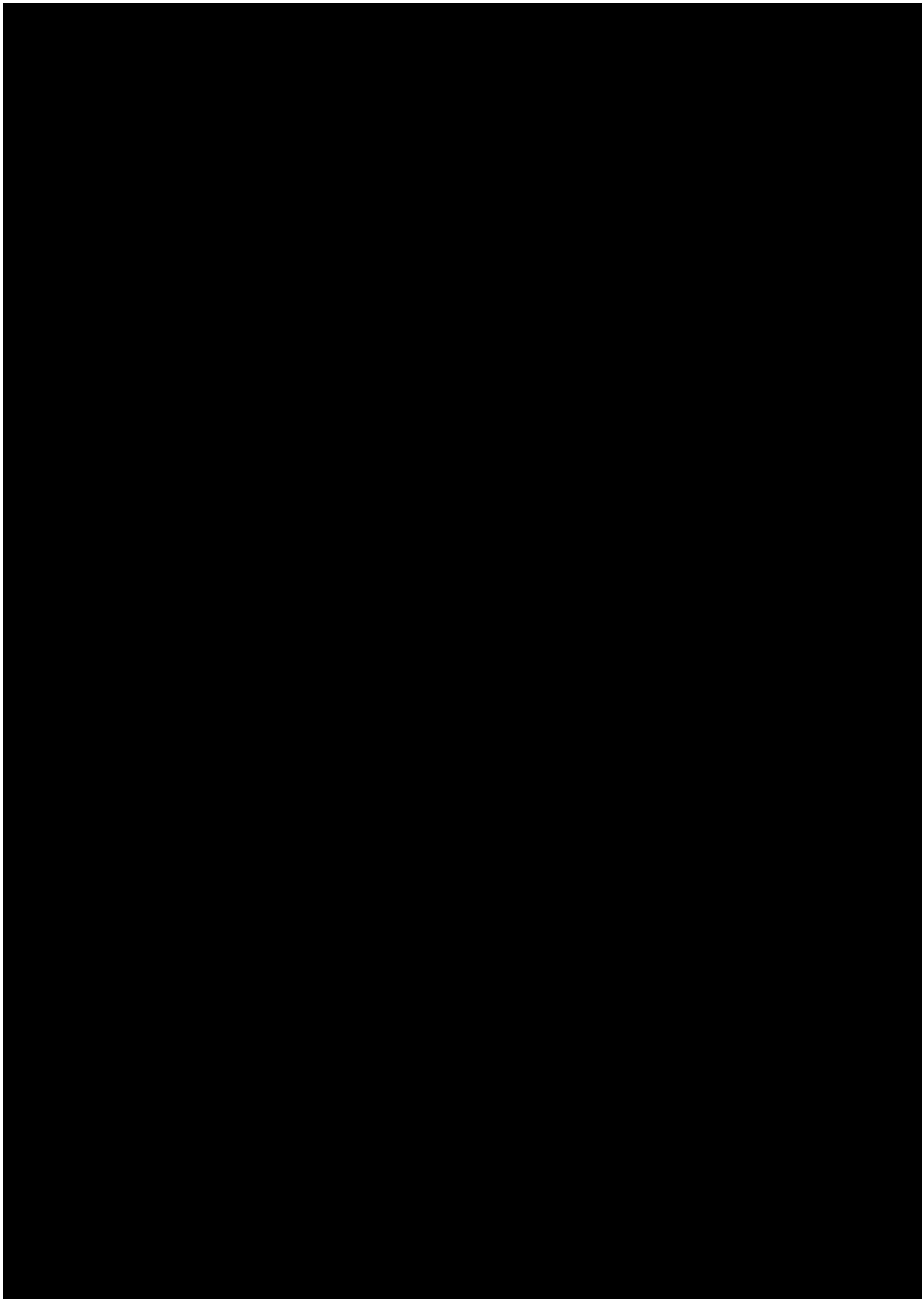
In the event of model non-convergence, the methods described for the primary endpoint analysis in Section 9.3 will be repeated except that ANCOVA model at week 52 and not at week 16 will be instead performed.

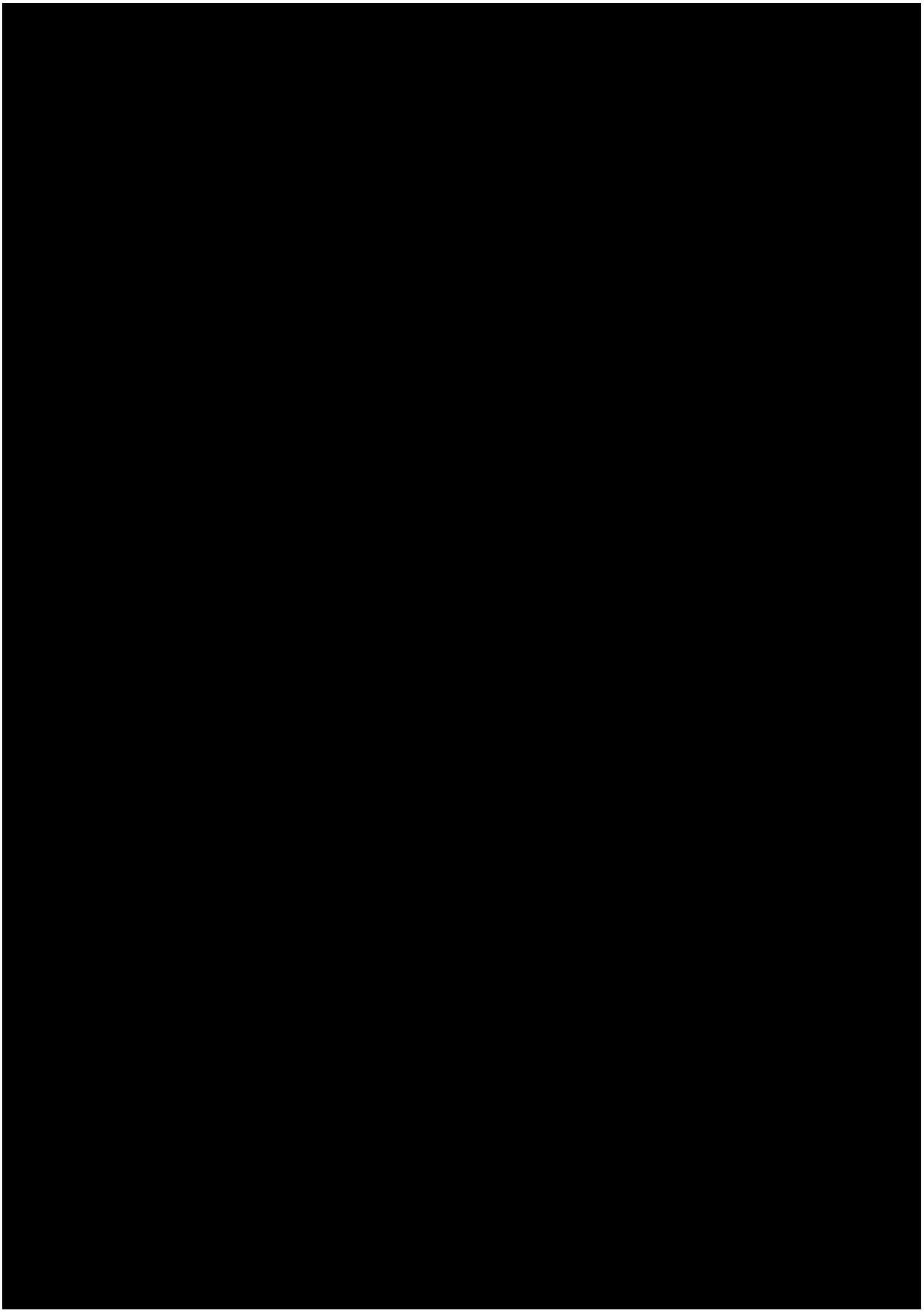
Dose groups will be presented per the dose regimen administered post primary endpoint (Week 16) as follows:

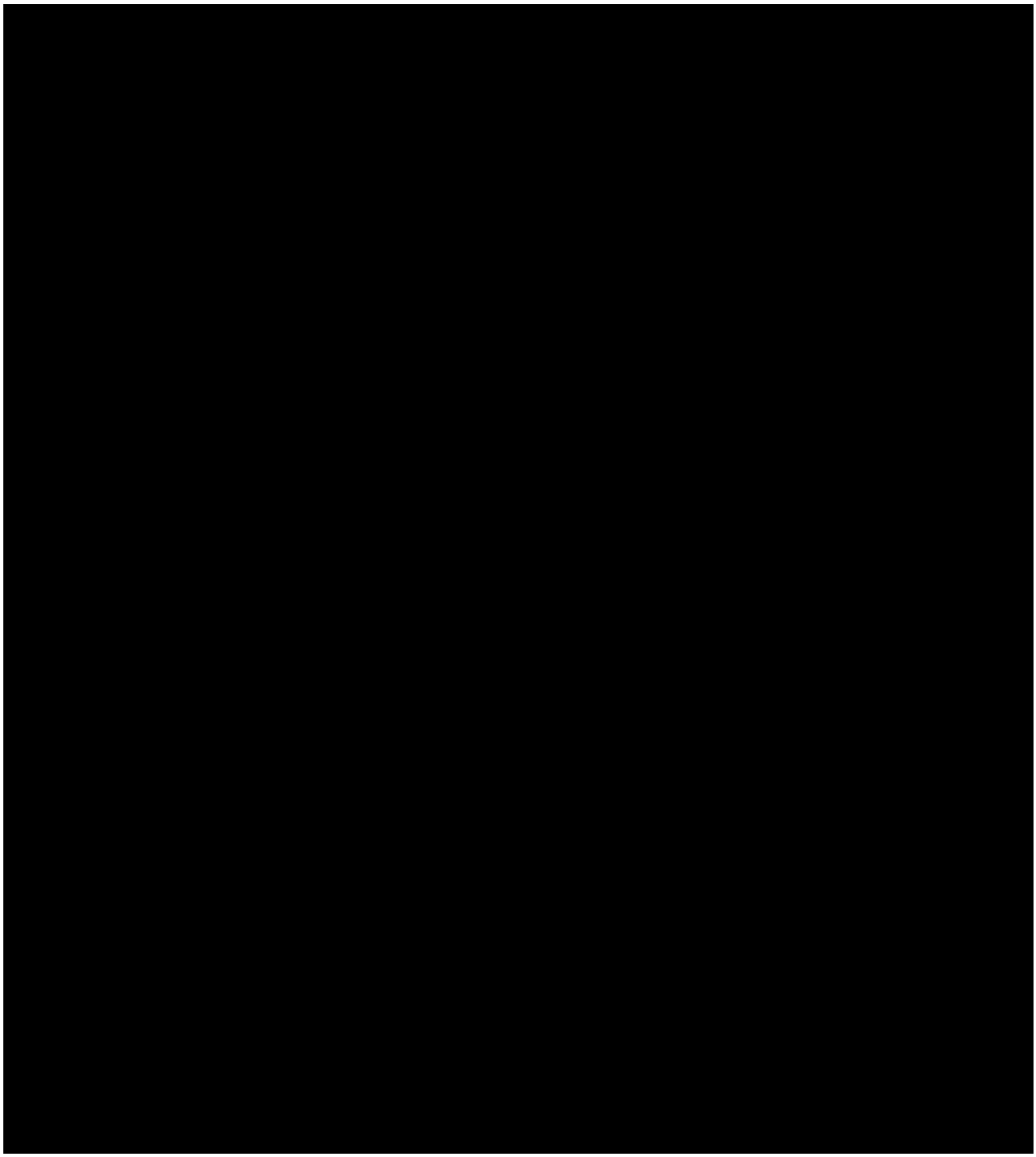
- [redacted] (i.e., Arm 4)
- [redacted] (i.e., Arm 2)
- [redacted] (i.e., Arm 1 + Arm 3 + Arm 5)

Results of the MMRM (N, adjusted mean, SE and 95% CI per dose groups and timepoint) will be presented in tables and displayed graphically. No statistical comparisons will be performed. Note that the results from this analysis need to be interpreted with caution as the efficacy outcomes post week 16 may also be impacted by treatments administered before week 16 and FAS-post 16 could not represent all population of the trial.









7.7 EXTENT OF EXPOSURE

The number of subjects who received a dose of trial drug will be tabulated. The amount of treatment received as well as the amount injected [% of planned] will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum) for the loading stage, the maintenance stage up to week 16, overall up to week 16 (primary analysis only), and the maintenance stage post week 16 (final analysis only), as well as the overall dose across all stages (final analysis only).

7.8 SAFETY ANALYSIS

All safety analyses will be performed following BI standards. No hypothesis testing is planned. OC-IR and OR methods will be used for safety reporting.

In primary analysis, AE and possibly clinically significant laboratory abnormalities up to week 16 will be analyzed. In final analysis, AE and possibly clinically significant laboratory abnormalities up to and post the first maintenance treatment at or after week 16 will be analyzed separately.

Primary analysis: AE and possibly clinically significant laboratory abnormalities up to week 16
The analysis will include all on-treatment events up to the treatment at week 16 based on SAF. If patient early discontinued from treatment prior to week 16 or missed week 16 treatment, then the on-treatment events up to Day 127 (the right limit of the extended week 16 visit window) will be included.

Final analysis: AE and possibly clinically significant laboratory abnormalities prior to the first maintenance at or after week 16
The analysis will include on-treatment events up to the first maintenance treatment at or after week 16 based on SAF. If a patient early discontinued from treatment prior to week 16, then the patient's events up to the end of REP of the last treatment will be included.

One additional group will be reported for AE and possibly clinically significant laboratory abnormalities, which is the combination of Arm 1, 2, 3 and 4 ("Speso Total").

Final analysis: AE and possibly clinically significant laboratory abnormalities post the first maintenance at or after week 16
The analysis will include on-treatment events post the first maintenance treatment at or after week 16 based on SAF-post 16. Only patients who have received at least one dose of treatment at or after week 16 will be included.

For AE and possibly clinically significant laboratory abnormalities, except for 5 treatment arms of the trial, one additional group will be reported which is the combination of Arm 1, 3 and 5 [redacted]

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

Additional analyses on AE will be also included:

AE within loading stage
For AE, the additional safety tables for loading dose stage will be produced by re-grouping patients based on their loading doses [redacted] using SAF. The outputs

will include on-treatment data up to the first maintenance dose at week 8. If patient early discontinued from treatment prior to week 8 or missed treatment at week 8, then the safety data up to Day 71 (the right limit of the extended time window of week 8) will be included:

- Overview on TEAE
- TEAE by SOC, preferred term
- Serious TEAE
- All AESI
- UDAEC

AE over on-treatment period
In the final analysis, the additional selected tables for the overall period will be produced based on SAF to report AE occurring during whole treatment period from Day 1. Note that only Arm 1-4 will be reported:

- Overview on TEAE
- TEAE by SOC, preferred term
- Serious TEAE
- All AESI
- UDAEC

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) across all treatment arms, or, if a total column across all arms is not foreseen in the table, by total frequency (within system organ class) across the BI arms.

For details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (7) and "Handling of missing and incomplete AE dates" (4).

The analysis of AEs will be based on the concept of treatment emergent AEs. 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.

An overall summary of AEs will be presented by treatment. 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 (9), 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:

Systemic hypersensitivity reactions including anaphylactic reaction

Severe infections (according to RCTC grading in CTP Appendix 10.2)

Opportunistic and mycobacterium tuberculosis infections

Hepatic injury

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

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 Concepts	**Categories**
Infusion/Systemic hypersensitivity reactions including anaphylactic reactions	Narrow SMQ "Anaphylactic reaction" Narrow SMQ "Angioedema" Narrow SMQ "Hypersensitivity"
Opportunistic infections	Narrow SMQ "Opportunistic infections":
Tuberculosis infections	BIcMQ Narrow sub-search 8.2 "Tuberculosis related terms"
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-BIcMQ "Skin Malignancies excluding melanomas"
Malignancies excluding NMSC	*Sub-SMQ "Malignant tumours" excluding broad sub-BIcMQ "Skin Malignancies excluding melanomas"*
3-point MACE	BIcMQ 3-MACE with subsearch 1.1 narrow and subsearch 1.2 narrow *"
Torsades de pointes	Broad SMQ "Torsades de pointes/QT prolongation"
Severe infections (according to RCTC grading)	SOC Infections and infestations of at least severe RCTC grade, by HLGT

* 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 frequency of patients with AEs will be summarised by treatment, 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). AEs will also be summarized by maximum intensity.

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 treatment, 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 (8). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

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 (8). 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 randomized 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.

Descriptive statistics of laboratory values and for the difference from baseline on-treatment (see Section 6.7) will be based upon standardized values and provided by visit. In primary analysis, all visits up to week 16 will be reported including summaries of the last value, the minimum value and the maximum value up to week 16 based on SAF. In final analysis, all visits will be reported including summaries of the last value, the minimum value and the maximum value on treatment period for Arm 1-4 and, up to and post the first treatment at or after week 16 respectively for Arm 5 based on SAF.

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, as well as the worst grade. In particular, for shift tables in final analysis, the last measurement and the worst graded will be counted by the period up to and post the first treatment at or after week 16 respectively for Arm 5.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on normalized 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 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 analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate), body temperature, and body weight will be descriptive in nature. In primary analysis, descriptive statistics of vital signs and for the difference from baseline (see Section 6.7) up to week 16 will be provided based on SAF, including the last value, the minimum value and the maximum value up to week 16. In final analysis, descriptive statistics of vital signs and for the difference from baseline (see Section 6.7) for all visits will be provided based on SAF, including the last value, the minimum value and the maximum value on treatment for Arm 1-4 and, up to and post the first treatment at or after week 16 respectively for Arm 5.

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, with the frequency and percentage of patients who experienced any symptoms by severity/intensity.

[redacted]

[redacted]

[redacted]

7.9 ANALYSIS OF COVID19 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.

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 patient with missed relevant visits or early discontinued from study treatment due to COVID-19 and related iPDs will be listed.

Efficacy endpoints:

To evaluate the impact of COVID-19 on efficacy analysis, the following estimand is implemented.

- Alternative estimand (EC-E19) whereby any data collected after use of any rescue therapy or after the first visit with missing treatment due to COVID-19 or after 6 weeks following last treatment before or at discontinuation (to allow for incorporation of the continuing maximum treatment effect period) are censored.

For the percent change in PPP ASI, a similar MMRM model to that used in the primary analysis will be performed.

For PPP ASI50, PPP ASI75 and PPP PGA clear/almost, descriptive statistics will be displayed.

AE based on the periods of COVID-19 disruption

To assess whether there was any potential change in AE assessment during the COVID-19 disruption, AEs prior the disruption, during the disruption and post the disruption (for final analysis only) will be reported separately. It will include the following AE tables,

- Overview on TEAE
- TEAE by SOC, preferred term
- Serious TEAE

The start date for the COVID-19 disruption is chosen to be 1st March 2020 and the end date will be updated in future revision for final analysis.

In addition, 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.

8. 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 *BI-KMED-COPS-TMP-0001:* "Important Protocol Deviation (iPD) log", current version; IDEA for CON

4 *BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON

5 *001-MCS-36-472_RD-01:* "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON

6 *001-MCS-40-413_RD-00:* "List of References to SOP Identify and Mange Important Protocol Deviations (iPD)", current version; IDEA for CON

7 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON

8 *BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON

9 *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

10 *BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.

11 *Pinheiro J, Bornkamp B, Bretz F.* Design and analysis of dose-finding studies combining multiple comparisons and modelling procedures. J Biopharm Stat 16 (5), 639-656 (2006). [R10-1424]

12 *Pinheiro J, Bornkamp B, Glimm E, Bretz F.* Model-based dose finding under model uncertainty using general parametric models. Stat Med 33 (10), 1646 – 1661 (2014). [R15-4293]

14 *Reeve R.* Confidence interval of difference in proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research: 27 issue: 2, 451-465, 2016. [R16-4414]

15 SAS/STAT(R) 9.2 User's Guide, Second Edition. http://support.sas.com/documentation/cdl/en/statug/63033/HTML/default/viewer.htm#statug_lifetest_a0000000260.htm (retrieved 16-May-2018)

16 *Brown LD, Cai TT, DasGupta A*. Confidence intervals for a binomial proportion and asymptotic expansions. Ann Statistics 30, 160-201, 2002 [R12-3710]

17 *Newcombe R.G.* Interval estimation for the difference between independent proportions: Comparison of eleven methods. Stat Methods Med Res 17, 873-890 1998.

18 *Carpenter, James R., James H. Roger, and Michael G. Kenward.* "Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation." Journal of biopharmaceutical statistics 23.6 (2013): 1352-1371.

19 *Heinze G, Schemper M*. A solution to the problem of separation in logistic regression. Statistics in Medicine 21: 2409-2419 (2002).

20 *Firth D*. Bias reduction of maximum likelihood estimates. *Biometrika* 80, 27−38 (1993)

21 *Hawker GA, Mian S, Kendzerska T, French M.* Measures of Adult Pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res. 2011. 63: S240-S252.

22 *Rentz AM, Skalicky AM, Burslem K, Becker K, Kaschinski D, Esser D, et.al*. The content validity of the PSS in patients with plaque psoriasis. J Patient Rep Outcomes. 2017. 1: 4.

[redacted]

24 *Langley RGB, Feldman SR, Nyirady J, Kerkhof P van de, Papavassilis C.* The 5-point Investigator`s Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatol Treat. 2015. 26(1): 23-31.

25 *Farley E, Masrour S, McKey J, Menter A.* Palmoplantar psoriasis: A phenotypical and clinical review with introduction of a new quality-of-life assessment tool. J Am Acad Dermatol. 2009. 60(6): 1024-1031.

26 *Augustin M, Radtke MA, Zschocke I, Blome C, Behechtnejad J, Schäfer I, et.al.* The patient benefit index: a novel approach in patient-defined outcomes measurement for skin diseases. Arch Dermatol Res. 2009. 301: 561-571.

27 *Ware JE, Snow KK, Kosinski M, Gandek B.* SF-36 Health Survey: Manual and Interpretation Guide. Boston: The Health Institute, New England Medical Center. 1993.

28 *Ware JE.* SF-36 Health Survey Update. Spine. 2000. 25(24): 3130-3139.

29 *Frendl DM, Ware JE.* Patient-reported Functional Health and Well-Being Outcomes with Drug Therapy: A Systematic Review of Randomized Trials Using the SF-36 Health Survey. Medical Care. 2014. 52(5): 439-445.

[redacted]

9. ADDITIONAL SECTIONS

[redacted]

9.1.1 PPP ASI and related endpoints

The Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPP ASI) is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. The adaptation from PASI, an established measure of severity and area of psoriatic lesions in patients with psoriasis, will be used in this trial (Table 9.1.1: 1).

This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 to 72. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation).

Table 9.1.1: 1 Palmoplantar Pustulosis Psoriasis Area and Severity Index

Score	0	1	2	3	4	5	6
Erythema (E)	None	Slight	Moderate	Severe	Very severe		
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe		
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe		
Area affected (in%)* (A)	0	<10	10<30	30<50	50<70	70<90	90 - 100

* where area assessed is glabrous skin on the palms/ soles

The Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPP ASI)

The PPP ASI is calculated as follows as a weighted sum of the scores obtained for E, P, D and A in Table 9.1.1: 1:

PPP ASI = [(E+P+D) x A x 0.2 (right palm)]

+ [(E+P+D) x A x 0.2 (left palm)]

+ [(E+P+D) x A x 0.3 (right sole)]

+ [(E+P+D) x A x 0.3 (left sole)]

Missing values for severity or area of involvement will not be imputed. If at least one of these values is missing, then the PPP ASI score will also be considered to be missing. However, individual items and subscores may be presented as applicable.

Achievement of Decrease in PPP ASI ≥ xx% (PPP ASIxx)

Achieving a response of xx% or larger decrease from baseline in PPP ASI score is denoted as PPP ASIxx. The PPP ASIxx represents a binary variable with values of 0 (= non-response) or 1 (=response).

It is calculated based on the following approach (with xx typically taking a value of 50, 75 or 90):

If $$\left\{\frac{PPP\ ASI\ (BL) - PPP\ ASI\ (current)}{PPP\ ASI\ (BL)} \times 100\right\} \geq xx$$

then PPP ASIxx = 1,

else PPP ASIxx = 0.

PPP ASI severity (by component)

Within each component (E, P or D), the mean severity across all body areas (both palms and both soles) is calculated and presented for each component separately. For example, for Erythema, present $(E_{right\ palm} + E_{left\ palm} + E_{right\ sole} + E_{left\ sole})/4$.

Within a component, a missing value in one body area leads to a missing value for the component.

Present the results separately "(by component)".

PPP ASI severity (by palms or soles)

Among the two palms only, calculate the PPP ASI (palms) score via the components E, P, or D as well as the area (A) but replacing the region factor of 0.2 with a factor of 0.5 (total range combining both palms of 0 to 72):

$$PPP\ ASI\ (palms) = 0.5 * \{ [(E_{right\ palm}+P_{right\ palm}+D_{right\ palm}) \times A_{right\ palm}] + [(E_{left\ palm}+P_{left\ palm}+D_{left\ palm}) \times A_{left\ palm}] \}$$

If at least one of the two palms has a missing value, then the PPP ASI (palms) score will be missing.

Repeat for the PPP ASI (soles) score but replacing the region factor of 0.3 with a factor of 0.5.

Present results separately for each of "(palms or soles)".

Palmoplantar Pustulosis Severity Index (PPP SI)

PPP SI will be based on severity scores of individual components of PPP ASI assessments. The most severely affected area based on pustules is identified by the investigator at baseline and the same area is assessed in all subsequent visits.

Table 9.1.1: 2 Palmoplantar Pustulosis Severity Index (PPP SI)

Score	0	1	2	3	4
Erythema (E)	None	Slight	Moderate	Severe	Very severe
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe

PPP SI total score = E+P+D

Missing values for any subscore will not be imputed. If at least one of these values is missing, then the PPP SI score will also be considered to be missing. However, individual subscores may be presented as applicable.

The sum score for the worst area represents the PPP SI (range 0-12).

9.1.2 PPP PGA

The Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) relies on clinical assessment of the patient's skin presentation on the palms and soles. The investigator scores the individual components (erythema, pustules and scaling/crusting) from 0 to 4 as clear, almost clear, mild, moderate or severe.

PPP PGA is using severity scores for erythema, pustules, and scaling. The PPP PGA will be analyzed as PPP PGA total score including erythema, pustules and scaling, and as PPP PGA pustules score for pustules only. Further details and practical guidance will be available in the ISF.

The PPP PGA total score is derived as the mean of all individual components:

0 = If mean=0 for all three components
1 = If 0 < mean <1.5
2 = If (1.5 <= mean <2.5)
3 = If 2.5 <= mean <3.5
4 = If mean >=3.5

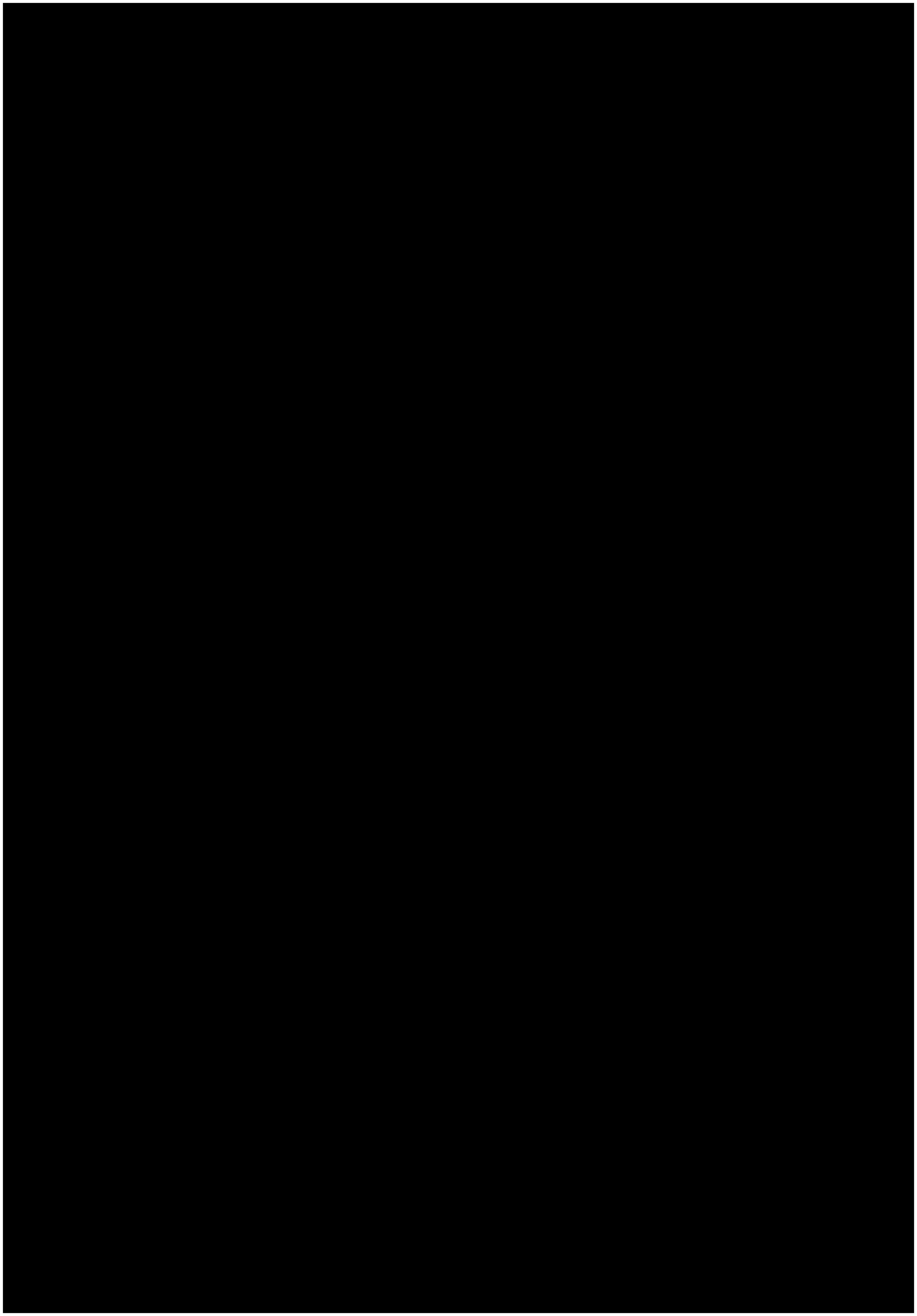
Missing component scores on erythema, pustules, scaling/crusting will not be imputed and the PPP PGA total score will be considered to be missing for a patient. Individual component scores may be presented, as applicable.

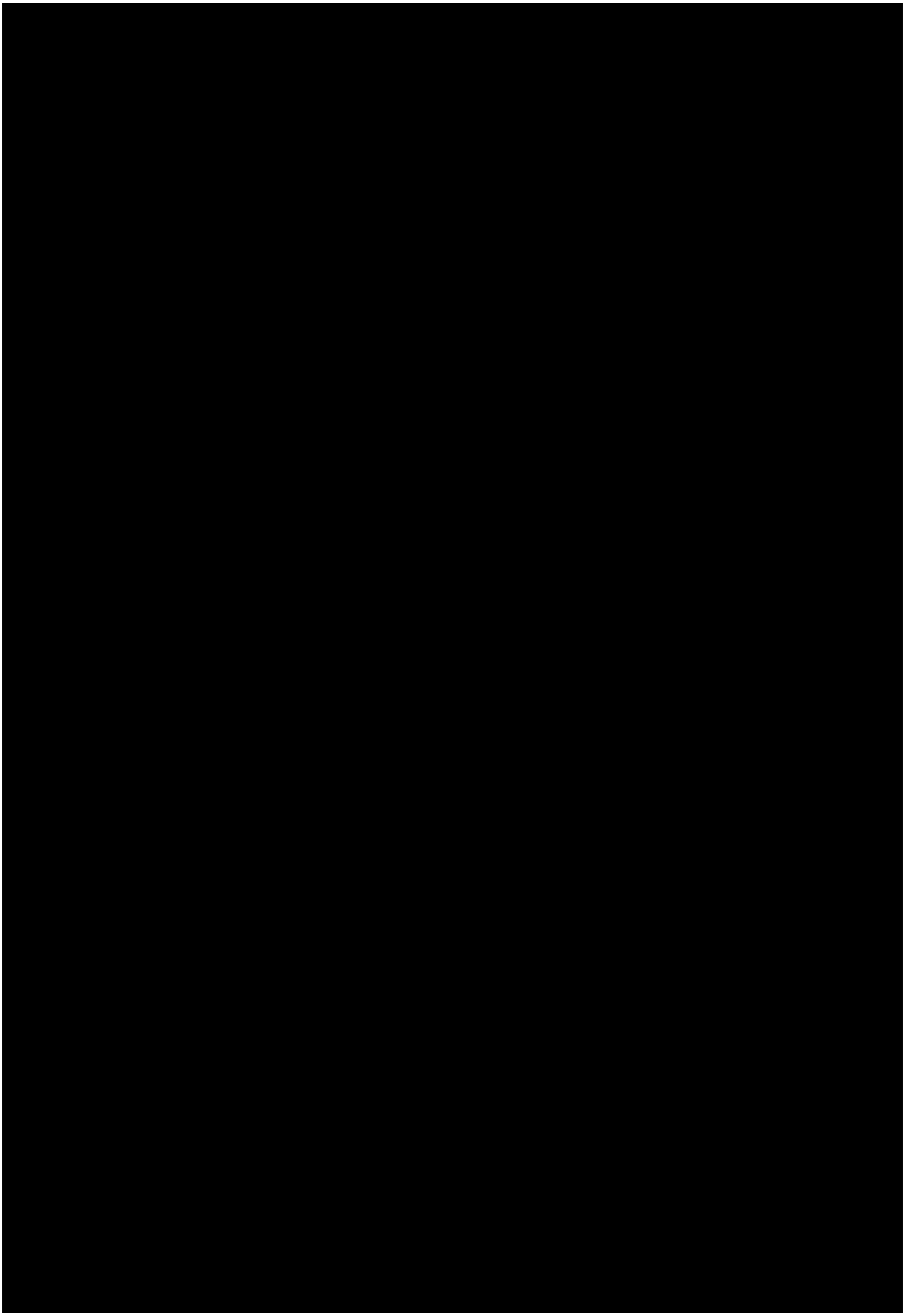
A lower PPP PGA score indicates a lesser severity, with 0 being clear and 1 being almost clear.

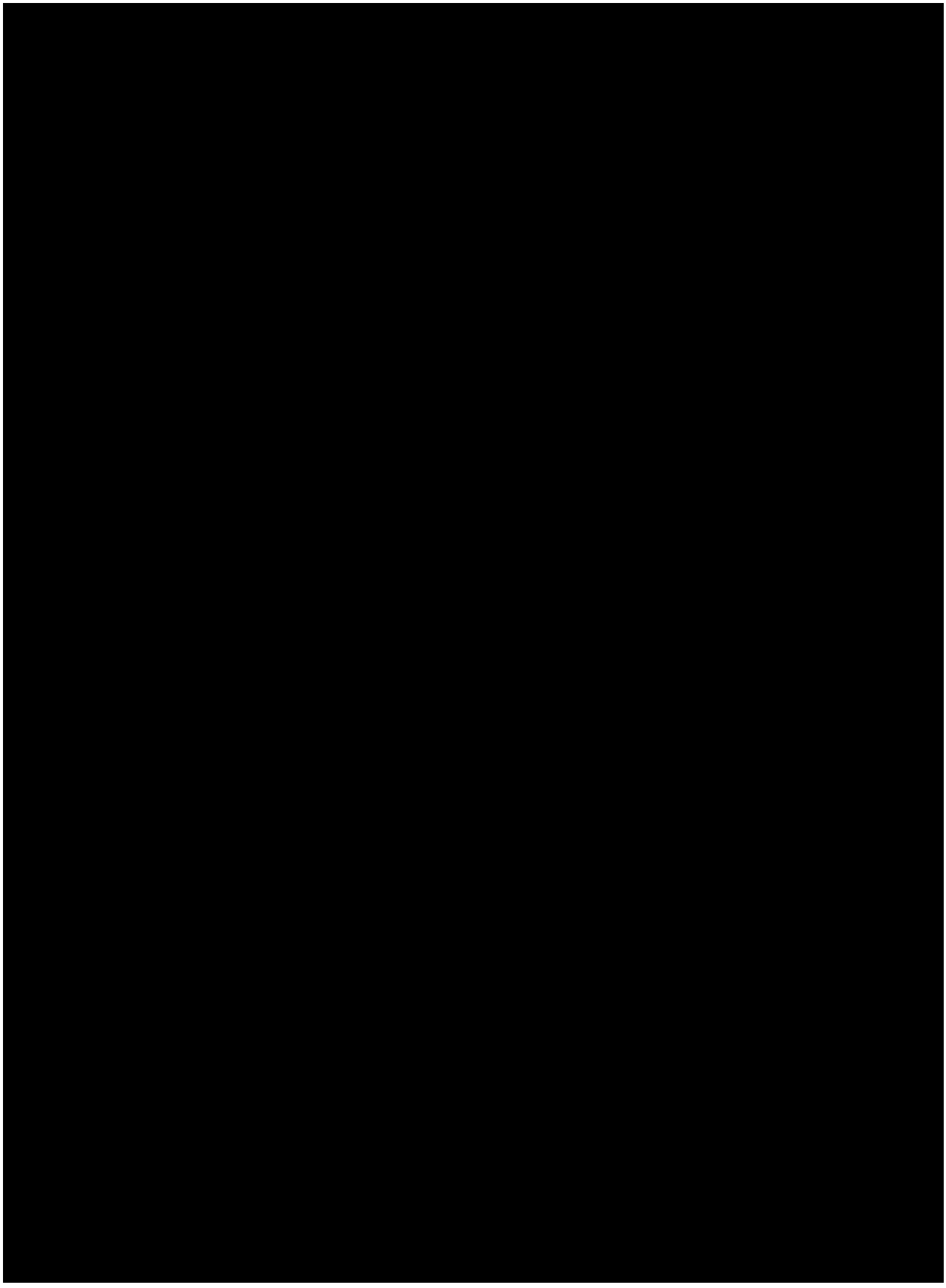
9.1.3 Pain VAS score

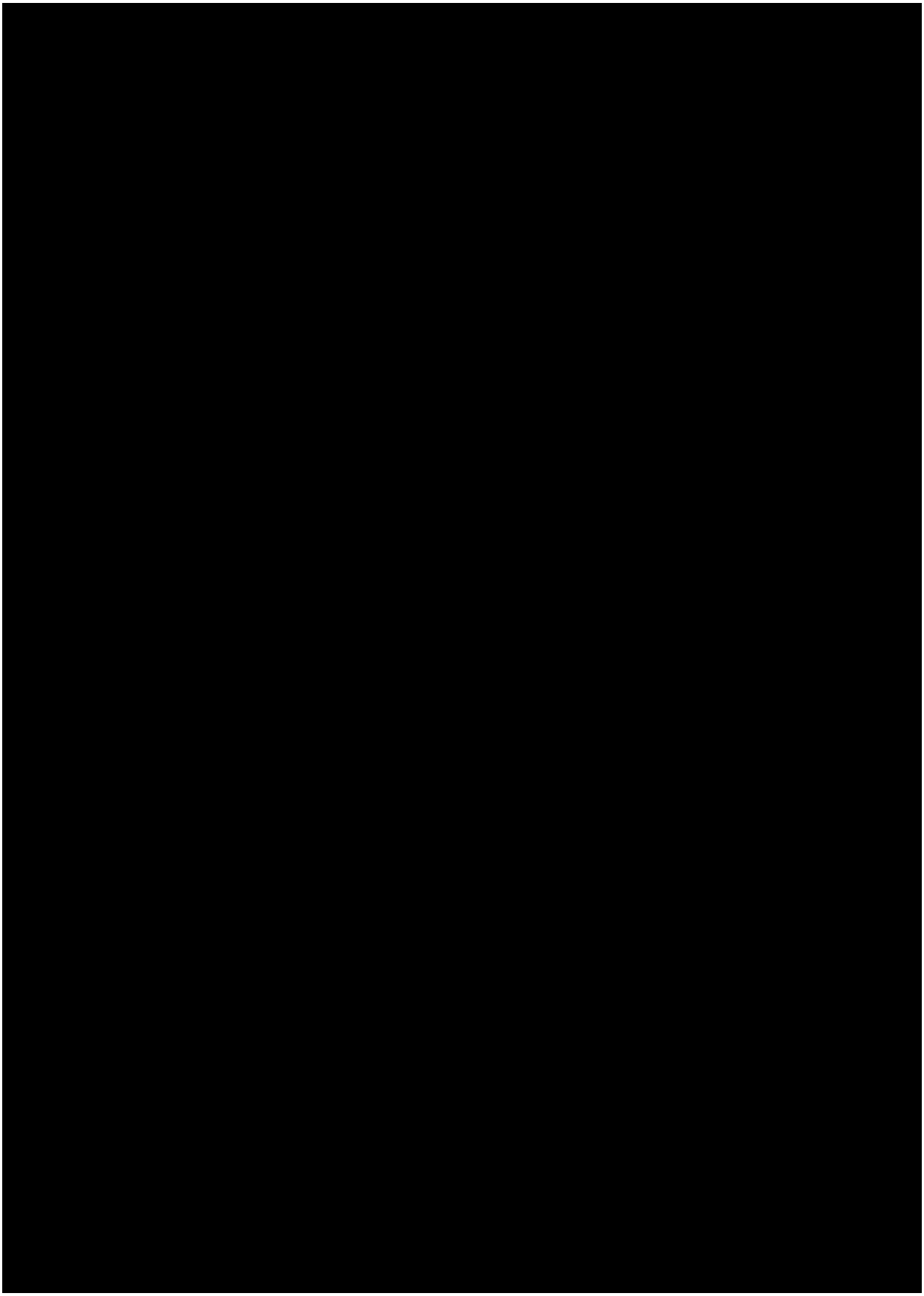
There will be two pain VAS questionnaires, one specifically asking for pain on palms and/or soles (PPP Pain VAS) and one for muscular and joint pain.

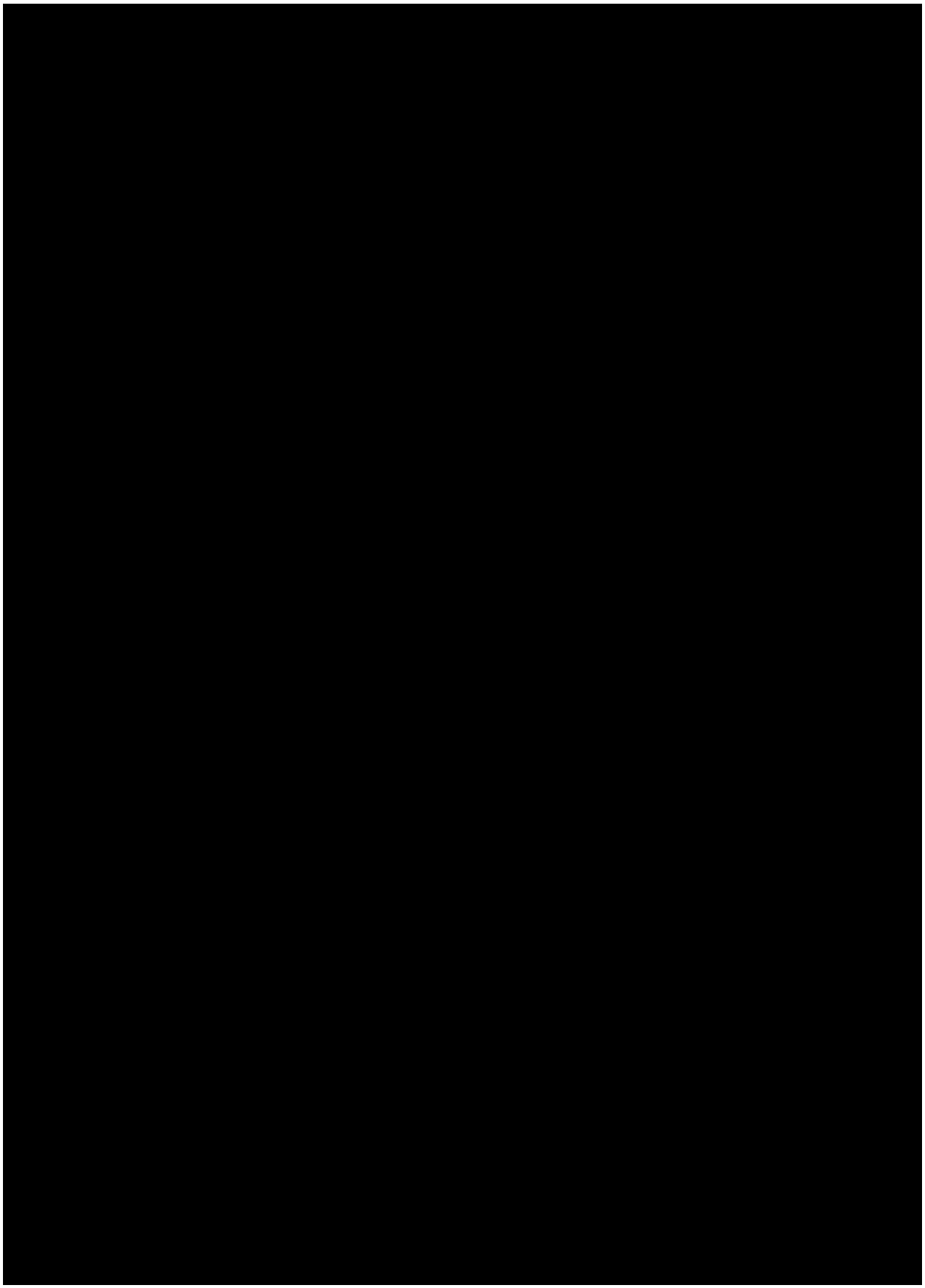
The pain VAS is a unidimensional measure of pain intensity (21). It is a continuous scale comprised of a horizontal or vertical line, usually 10 centimeters (100 mm) in length, anchored by word descriptors at each end (“no pain”, “very severe pain”). The pain VAS is self-completed by the patient. The patient is asked to place a vertical (|) mark on the horizontal line to indicate the severity of the pain. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the “no pain” anchor and the patient's mark, providing a range of scores from 0–100. A higher score indicates greater pain intensity.

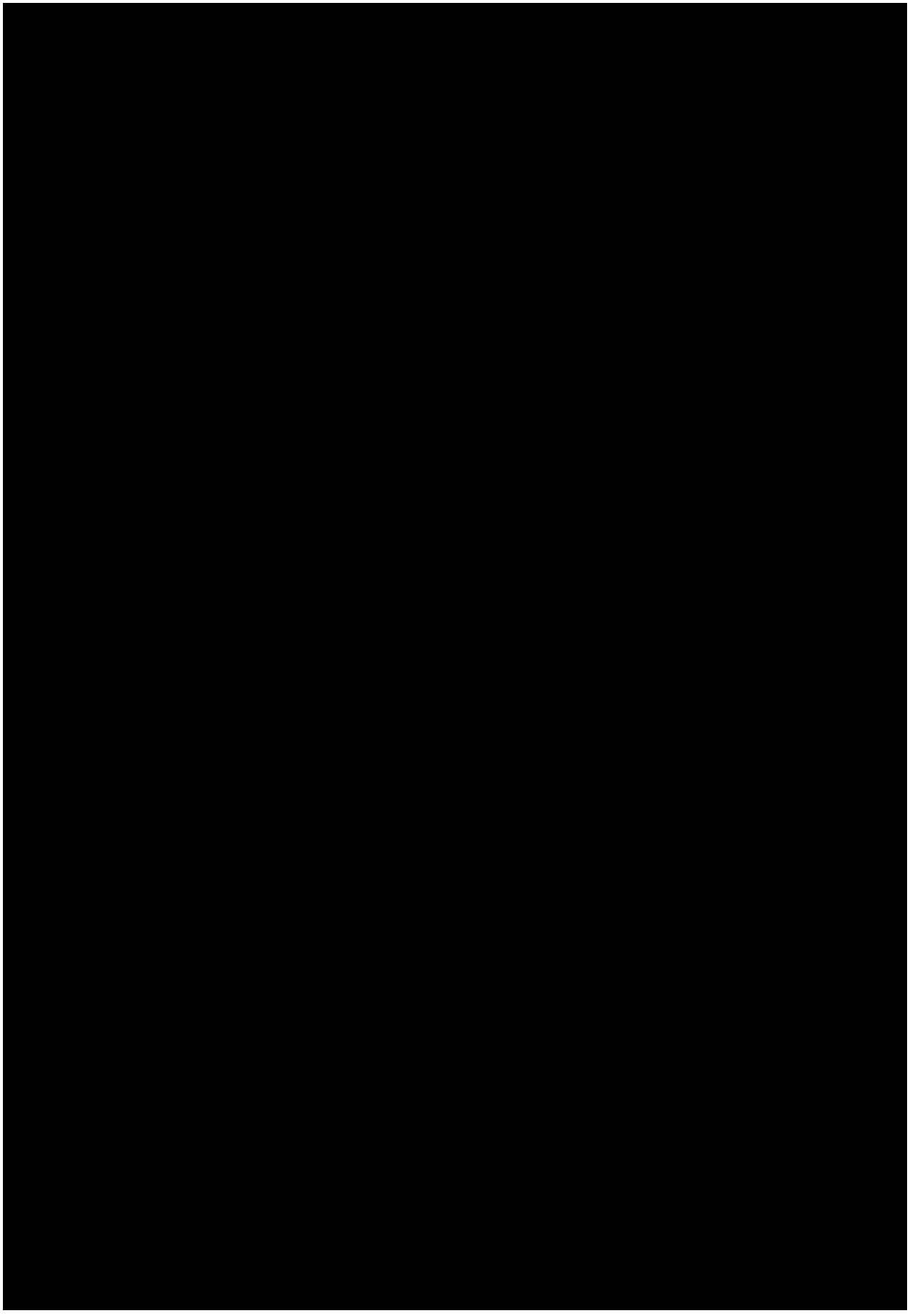


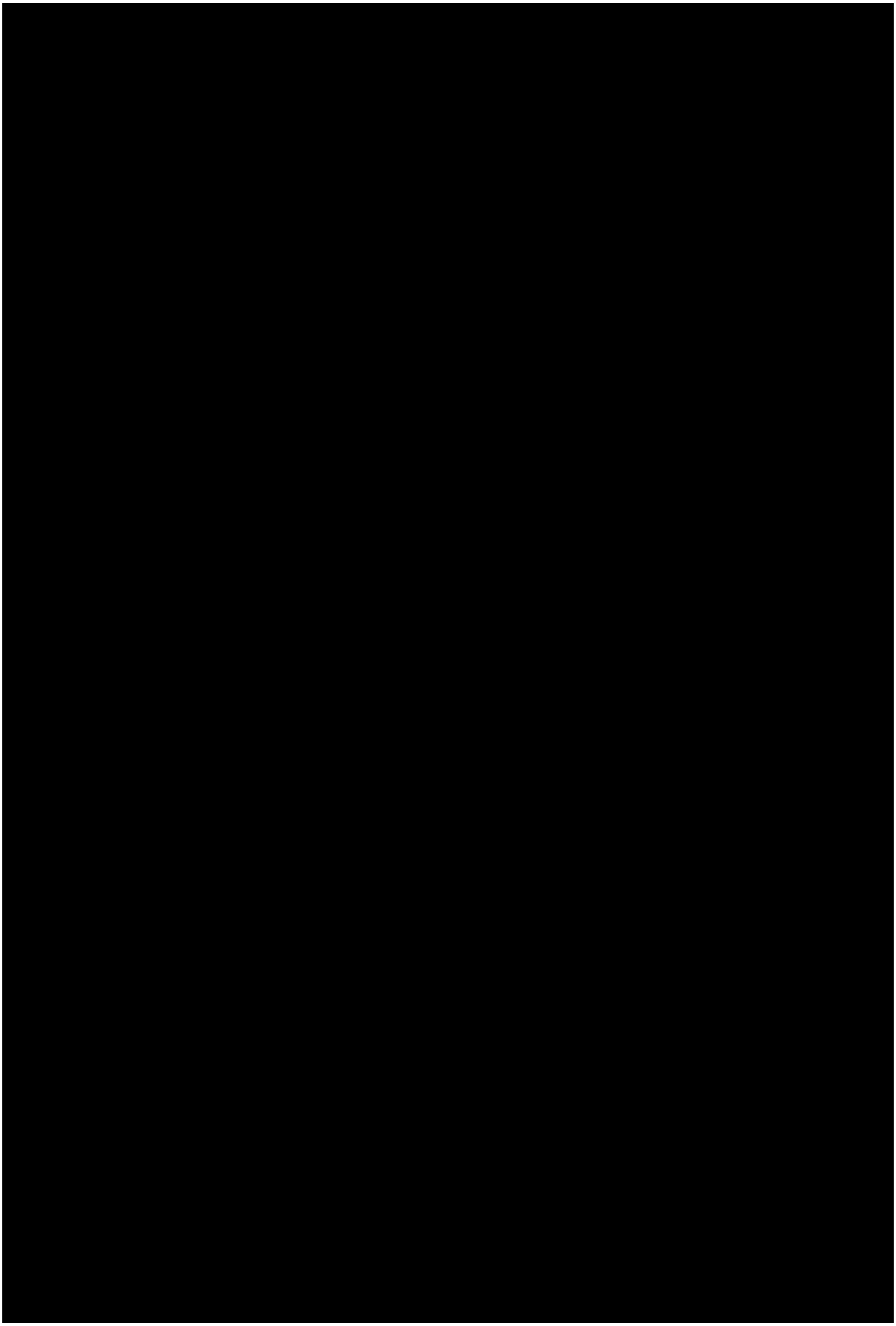


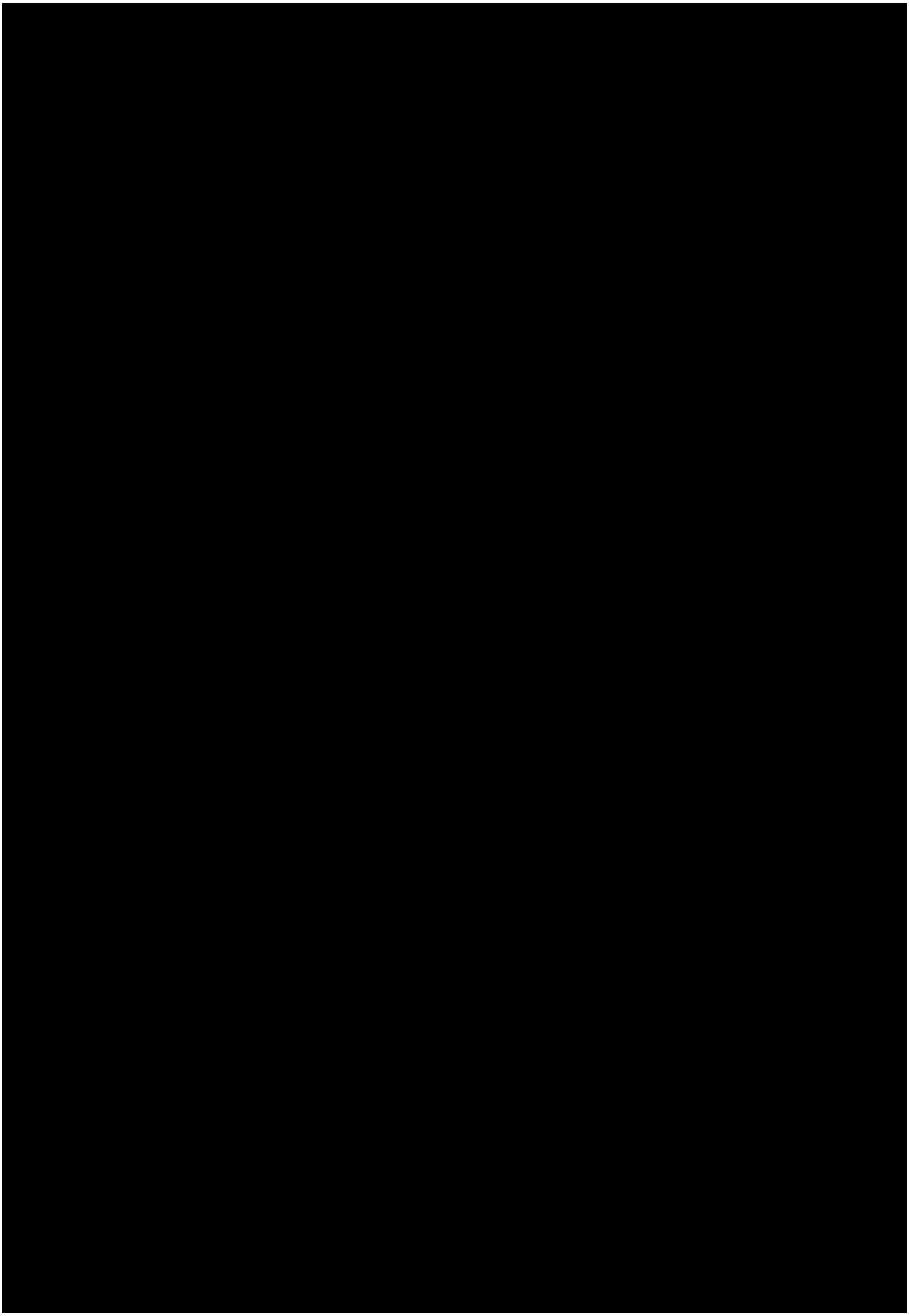


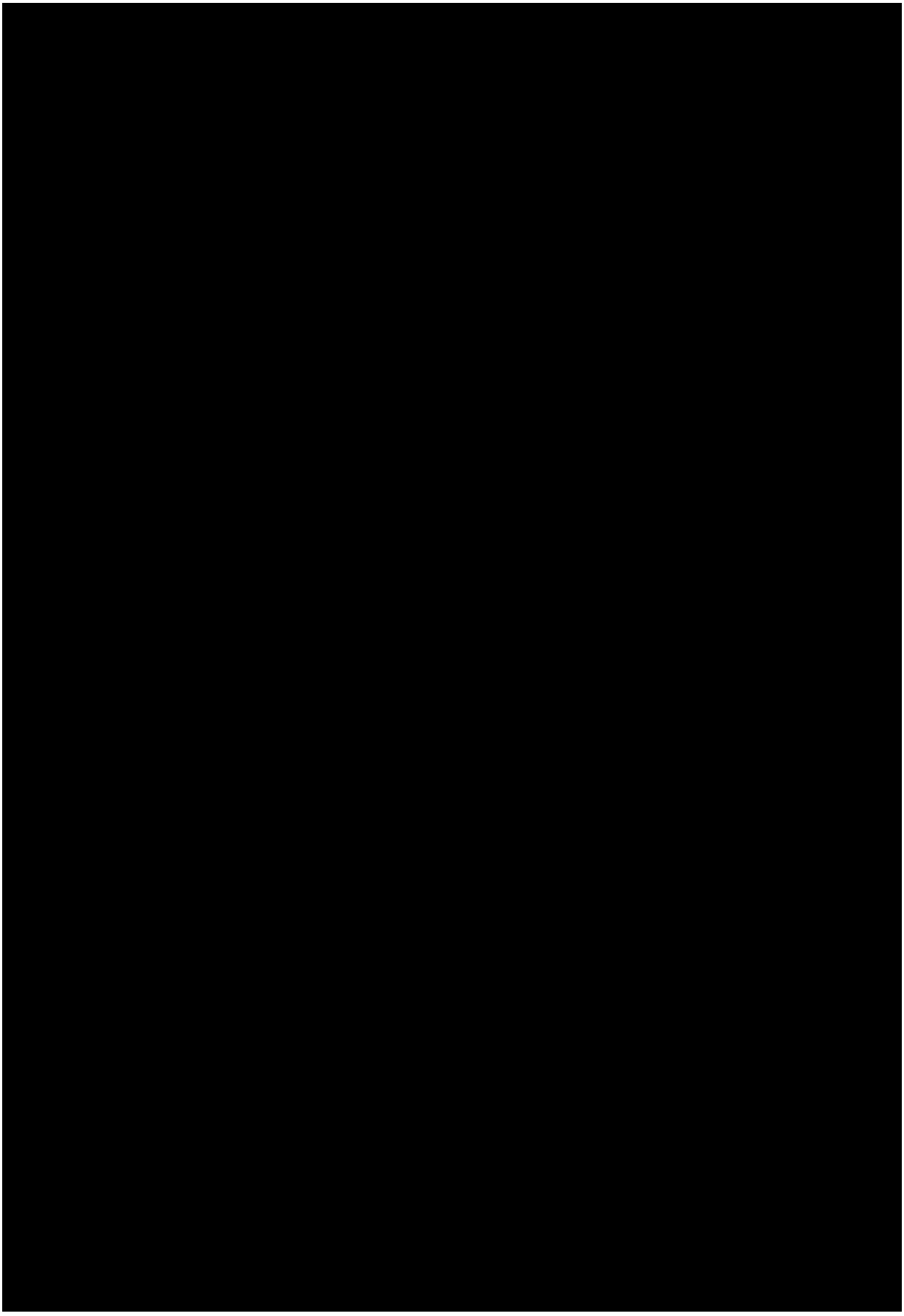


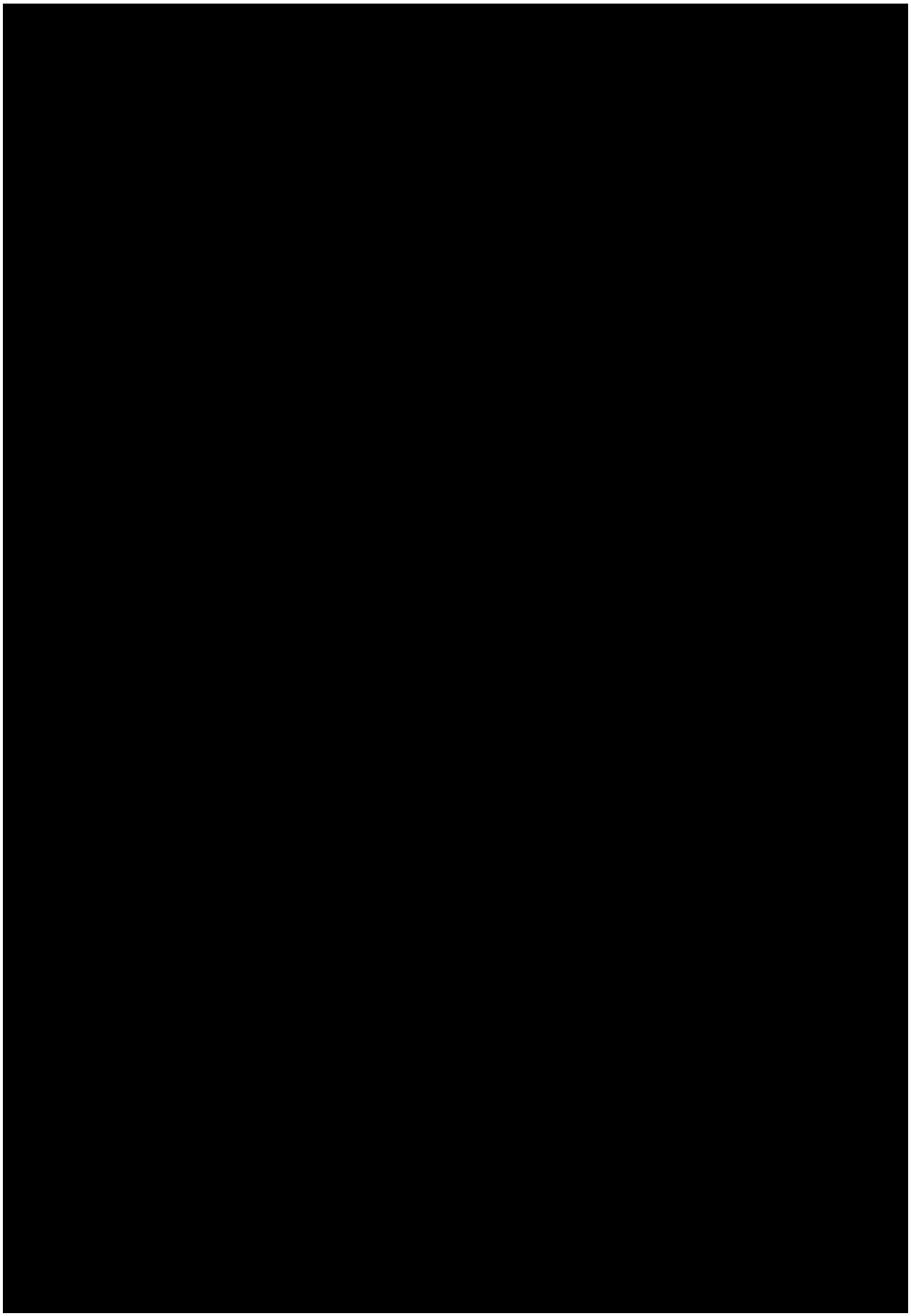












10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**22-JUL-20**	[redacted]	None	This is the final TSAP