TRIAL STATISTICAL ANALYSIS PLAN

c35110764-01

BI Trial No.:	1368-0052
Title:	Randomized, double-blind, placebo-controlled, study of Spesolimab in patients with moderate to severe hidradenitis suppurativa (HS). Including Protocol Amendment 1 [include c32824792-02]
Investigational Product(s):	Spesolimab (BI 655130)
Responsible trial statistician(s):	[redacted] Tel.: [redacted] Fax: [redacted]
Date of statistical analysis plan:	28 DEC 2021
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above the upper limit of quantification
ALT	Alanine aminotransferase
AN	Abscess and inflammatory nodule
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CGI	Clinical Global Impression
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid
EC	Estimand concept
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
FACIT	Functional Assessment of Chronic Illness Therapy

Term	Definition / description
FUP	Follow-up
gCV	Geometric coefficient of variation
GCP	Good Clinical Practice
gMean	Geometric mean
GPP	Generalized pustular psoriasis
HASI	HS Area and Severity Index
HS	Hidradenitis suppurativa
HS-PGA	HS Physician Global Assessment
HiSCR	Hidradenitis suppurativa clinical response
HS-CRP	High-Sensitivity C-Reactive Protein
IHS4	International Hidradenitis Suppurativa Severity Score System
IL-36	Interleukin 36
IL-36R	Interleukin 36 Receptor
NRS	numerical rating scale
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
HiS-QoL	Hidradenitis suppurativa quality of life
iPD	Important protocol deviation
ICEs	Intercurrent events
MAP	Meta-Analytic Predictive
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
DLQI	Dermatology Life Quality Index
NRI	No response imputation
OC	Observed cases
OR	Original results
OLE	Open Label Extension
PD	Pharmacodynamic(s), protocol deviation
PE	Primary endpoint
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPS	Per protocol set
PT	Preferred term

Term	Definition / description
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
REP	Residual effect period
RNA	Ribonucleic acid
RPM	Report planning meeting
RS	Randomized set
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan
UDAEC	User-defined Adverse Event Category
ULN	Upper limit of normal range
VAS	Visual analogue scale
MCMC	Markov Chain Monte Carlo

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 [redacted], and a number of SAS™-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

Study data will be stored in a trial database within the BRAVE system.

Analyses of the biomarker and gene expression data are described in a separate biomarker SAP, unless otherwise specified in this document.

This is a multicenter, randomized, double-blind, placebo-controlled Phase IIa study with Spesolimab/placebo in patients with moderate to severe HS. In total, approximately 45 patients will be randomized to receive Spesolimab/ placebo (2:1). Study medication (1200 mg Spesolimab or matching Placebo) is administered intravenously at Baseline, Week 1 and 2 and then subcutaneously every two weeks at Weeks 4, 6, 8, and 10. Patients completing Week 12 of the study, will roll-over to an extension study if they agree and meet the eligibility criteria of the extension trial. (see Flow Chart of CTP).

The primary and secondary efficacy endpoints of the trial will be evaluated at Week 12. This TSAP fully specifies the analyses of the trial.

[redacted]

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint of the study is:

- Percent change from baseline in total abscess and inflammatory nodule (AN) count at Week 12.

See Section 10.1.1 for further details on the derivation of the abscess and inflammatory nodule count.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

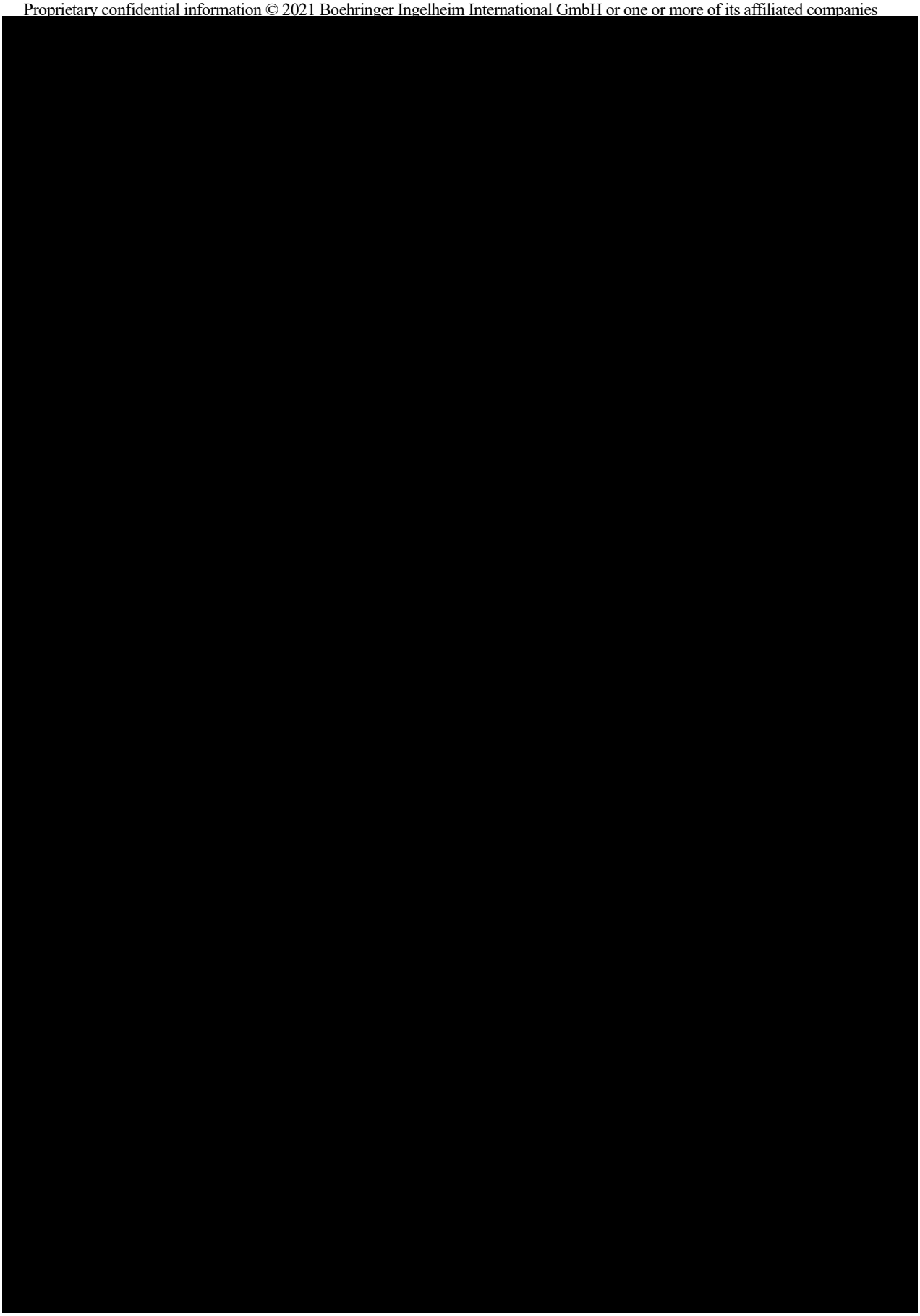
Secondary Endpoints at Week 12 are defined as described below:

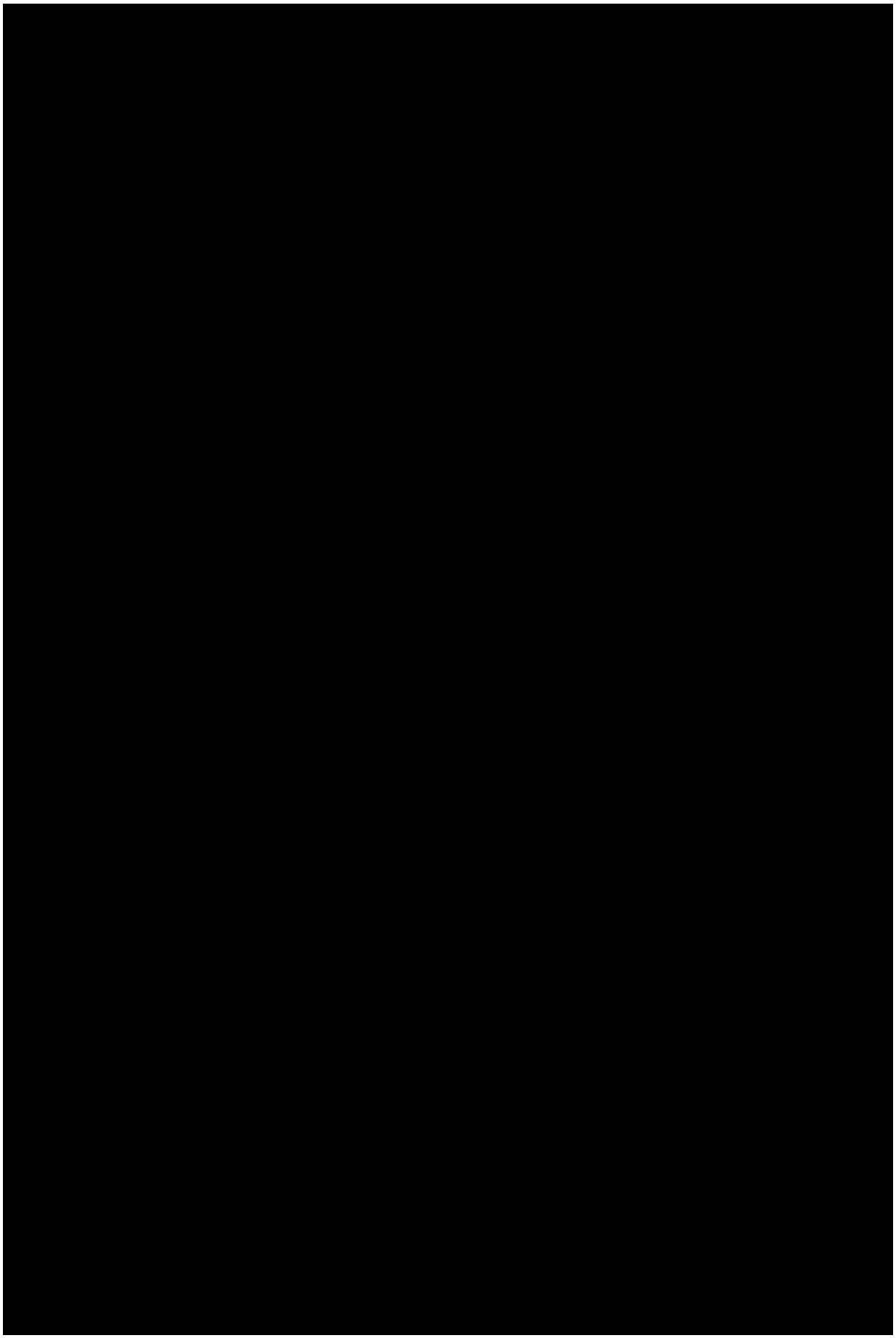
- Percent change from baseline in draining fistula count at Week 12
  (Only patients with at least one draining fistula at baseline will be used for analysis).
- Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline.
- Absolute change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value at Week 12
- Absolute change from baseline in HASI score at Week 12
- Achievement of PGA score of 0 or 1 at Week 12
- Achievement of at least 30% reduction from baseline in Numerical rating scale (NRS30) in Patient's Global Assessment of HS Pain at Week 12
- Occurrence of complete elimination of draining fistulas at Week 12
  (Only patients with at least one draining fistula at baseline will be used for analysis).
- Occurrence of at least one flare (defined as at least 25 % increase in AN count with a minimum increase of 2 relative to baseline) up to Week 12
- Absolute change from baseline in DLQI Score at Week 12
- Absolute change from baseline in HiS-QoL Total Score at Week 12

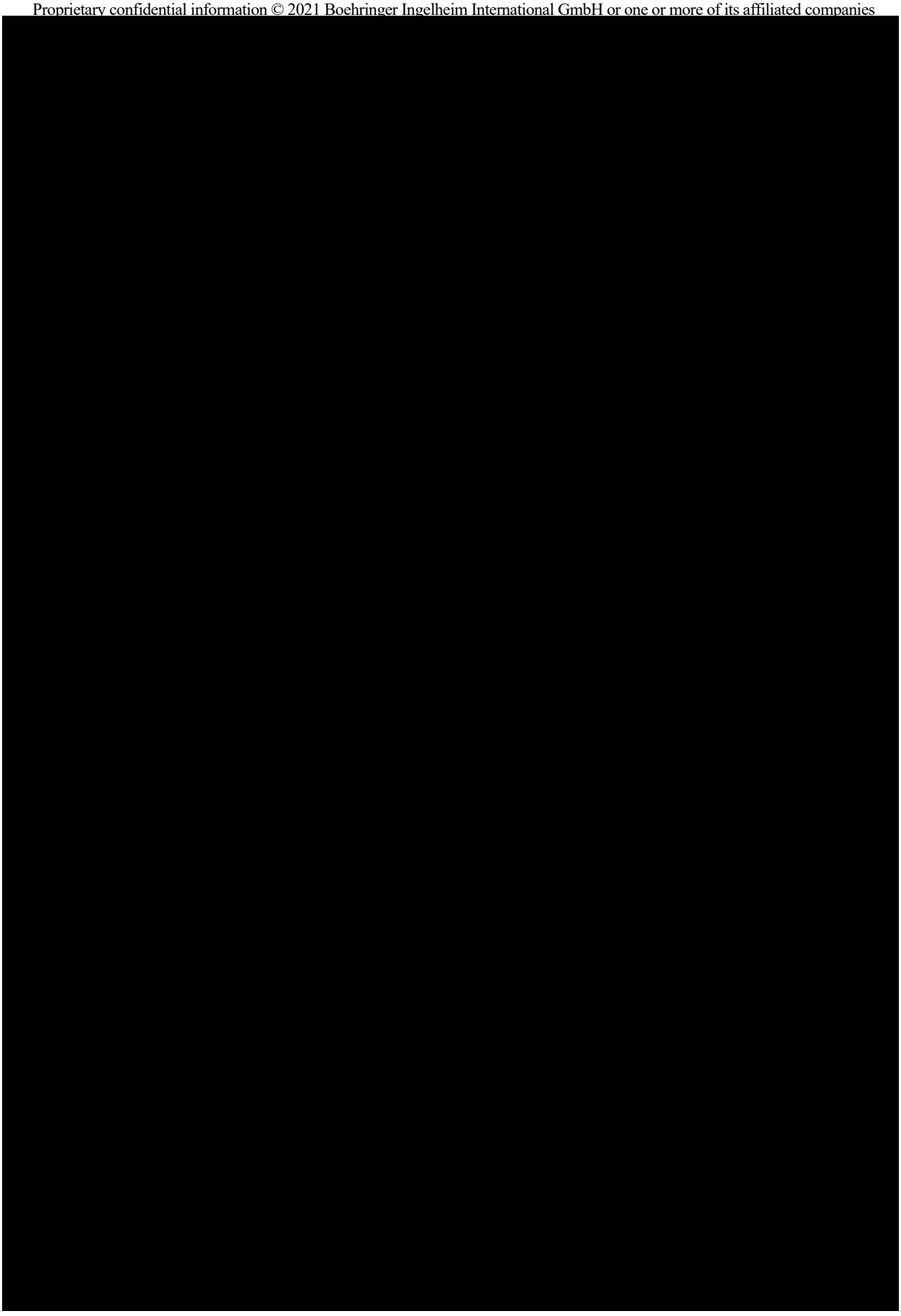
See Section 10.1 for further details regarding endpoint definition and derivation.

The following safety endpoint is also defined:

- The occurrence of Treatment Emergent Adverse Events (TEAEs)







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, assignment to treatment, and selection of dose, cf. Section 4 of the CTP.

The study phases are defined relative to randomized dose at Day 1 as below:

Table 6.1: 1 Flow chart of analysis phases of the study according to randomized treatment

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 minus 1 minute; 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 12)		Date/time of start of the first study maintenance dose (if applicable)	Earlier of : i) Date/time of start of the first dose in the extension trial 1368.67; or, ii) Date of end of last maintenance dose + 112 days at 11:59 p.m, iii) cut-off date for primary analysis.
Follow-up phase[1] (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) last contact date on trial termination page at 11:59 p.m. iii) Date/time of start of first dose in the extension trial 1368.67;

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 date of EoS visit or the last contact date is after the date of end of last administration + 112 days.

Treatment groups for the analysis phases according to the randomized/actual treatment on Day 1 (see Table 6.1: 1) will be labelled as follows:

- **"Placebo"** (i.e. randomized to receive /actual received Placebo)
- **"Speso"** (i.e. randomized to receive /actual received Spesolimab)
- **"Overall Total"**(across treatments), where appropriate.

"Overall Total" is applicable in disposition, demographics and baseline characteristics, compliance summaries, AE, clinically significant abnormal lab values and others if needed. Where applicable, output columns should be arranged in the order as given above.

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 deviations of time windows) and a list of protocol deviations will be provided to be discussed at the RPM/DBLM. 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). These categories are described below in order to ensure that those iPD which lead to exclusion from the PPS are suitably documented before unblinding and locking of data.

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)". (8)

If any patients fulfil the iPD categories, then they are to be summarized and will be captured in the RPM/DBLM 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 site(s), then this table will be supplemented accordingly by the time of the RPM/DBLM. 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 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	Male or female adult patients, 18 years of age or older LABEL: Age not met	IC01 Also require programmatic check	PPS

A1.02	Moderate to severe HS, based on IHS4 criteria, for at least 1 year prior to the baseline visit LABEL: medical history of HS not met based on IHS4	IC03	PPS
A1.03	HS lesions in at least 2 distinct anatomic areas LABEL: HS lesions in less than 2 anatomic areas	IC04	PPS
A1.04	Biologic naïve or TNFi-failure for HS LABEL: Not Biologic naïve or TNFi-failure for HS	IC05	PPS
A1.05	Inadequate response to an adequate course of appropriate oral antibiotics for treatment of HS in the last 1 year, for TNFi biologic naïve patients LABEL: Inadequate response to oral antibiotics for HS for TNFi naïve patients	IC06	PPS
A1.06	Total abscess and inflammatory nodule (AN) count of greater than or equal to 5 LABEL: AN count<5	IC07	PPS
A1.07	Total draining fistula count of less than or equal to 20 LABEL: Draining fistula count>20	IC08	PPS
A1.08	Women of childbearing potential must be ready and able to use highly effective methods of birth control, for the duration of the trial and 16 weeks after last administration. LABEL: Women not use birth control	IC09	None
A2	**Exclusion criteria violated**		
	General Exclusion Criteria		

A2.01	Presence of active skin lesions other than HS that interferes with the assessment of HS LABEL: Presence of active skin lesions other than HS	EC01	PPS
A2.02	Use of restricted/prohibited medication per protocol LABEL: use of restricted/prohibited medication	EC02 See the further list in section 4.2.2 in CTP	PPS
A2.03	Prior exposure to any immunosuppressive biologic other than TNFi for HS LABEL: Prior exposure to any immunosuppressive biologic other than TNFi for HS	EC03	PPS
A2.04	Prior exposure to IL-36R inhibitors including Spesolimab LABEL: Prior exposure to IL-36R inhibitors	EC04	PPS
A2.05	Treatment with any investigational device or investigational drug of chemical or biologic nature within of 30 days or 5 half-lives of the drug, whichever is longer, prior to visit 2 LABEL: Treatment with any investigational device or investigational drug of chemical or biologic nature	EC05	PPS
A2.06	Women who are pregnant, nursing, or who plan to become pregnant while in the trial. LABEL: Pregnant or nursing	EC06	None

A2.07	History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients LABEL: History of allergy/hypersensitivity	EC07	PPS
A2.08	Patient with a transplanted organ (with exception of a corneal transplant >12 weeks prior to screening) or who have ever received stem cell therapy LABEL: patient with transplanted organ or stem cell therapy	EC08	None
A2.09	Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix LABEL: Active or suspected malignancy	EC09	None
A2.10	Active or latent TB: LABEL: Active or latent TB	EC10	None
A2.11	Active systemic infection within 2 weeks of visit 2. Patients can be re-screened after treatment of the acute infection LABEL: Active systemic infection	EC11	PPS
A2.12	Relevant chronic infections as determined by the investigator, including human immunodeficiency virus (HIV) or viral hepatitis.	EC12	None

A2.13	Major surgery performed within 12 weeks prior to first study drug administration or planned during the study LABEL: Major surgery performed or planned during the study	EC13	None
A2.14	Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, and >2-fold ULN elevation in the total bilirubin LABEL: Severe, progressive, or uncontrolled hepatic disease	EC14 Also check versus screen Lab values	None
A2.15	Evidence of a current or previous disease, medical condition other than HS, surgical procedure, psychiatric or social problems, medical examination finding, or laboratory value at the screening outside the reference range that would compromise the safety of the patient or compromise the quality of the data, make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial. LABEL: Relevant conditions with concern on adherence or compliance	EC15	None
A2. 16	Planned use of laser or other hair removal procedures over HS-affected areas during the trial period LABEL: Planned use of laser or other hair removal procedures	EC16	PPS
A2.17	Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 12 months LABEL: Any suicidal ideation of type 4 or 5 on the C-SSRS	EC17	None

A2.18	Any suicide behaviour in the past 2 years LABEL: Any suicide behaviour in the past 2 years	EC18	PPS
A2.19	Previous enrolment in this trial except for patients re-screened. LABEL: Previous enrolment in this trial except for patients re-screened	EC19	PPS
B	**Informed consent**		
B1	Informed consent not available LABEL: No IC form	IC02 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.	IC02 Informed consent date was after Visit 1	None
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.		PPS, SAF
C1.02#	Patient skipped an intermediate dose without proper reason LABEL: Patient skipped an intermediate dose without proper reason.	Patient missing a dose at an intermediate visit without proper reason when dose at a later scheduled visit has been taken. Decision based on medical judgment.	PPS

C1.03#	Patient skipped an intermediate dose due to COVID 19 LABEL: Patient skipped an intermediate dose 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 Decision based on medical judgment.	PPS
C2	**Incorrect Dosing**		
C2.01	Incorrect medication received prior to Week 12 LABEL: Incorrect dose received prior to Week 12	Randomized patient who received or miss one or more incorrect syringes of treatment not as planned at any scheduled visit prior to Week 12 Can only be finally judged after DBL since unblinding information is required	PPS
C3	**Randomization not followed**		
C3.01	Treated without randomisation LABEL: Treated without randomisation.	Patient treated according to eCRF, but not randomised according to IVRS.	RS, SAF, PPS
C3.02	Randomization order of stratification not followed LABEL: Stratification error	Stratification error regarding TNFi naïve and TNFi-failure Programming check and manual review after DBL	PPS
C4	**Medication code broken**		
C4.01	Medication code broken before week 12 inappropriately LABEL: Code broken early without valid reason.	Medication code was broken prior to DBL for no valid reason. Final decision at the DBL meeting based on medical judgment.	PPS
D	**Concomitant medication**		
D1	**Previous medication**		
D1.01#	Washout of previous medication too short LABEL: Washout too short.	Washout period too short – See Table 4.2.2.1:1 in CTP	PPS
D2	**Prohibited medication use**		

D2.01#	Use of restricted medication (other than systemic antibiotics) for HS (with potential influence of efficacy data) prior to or up to week 12 Label: Use of restricted medication other than systemic antibiotics for HS	See the list of restricted medication in section 4.2.2 of CTP, manual assessment at MQRM/RPM/DBLM	PPS
D2.02#	Use of antibiotic before week 4 for HS LABEL: Use of antibiotic before week 4 for HS	See section 3.3.4.1 of CTP for details, manual assessment at MQRM/RPM/DBLM	PPS
D2.03#	Inappropriate use of Systemic antibiotics for HS disease worsening at/after week4. LABEL: Inappropriate use of Systemic antibiotics for HS disease worsening at/after week4	Including usage 1) without meeting criteria for HS disease worsening, or 2) longer duration than allowed See section 4.2.2 of CTP for details, manual assessment at MQRM/RPM/DBLM	PPS
E	**Missing data**	<not specified>	
F	**Study specific analysis**	<not specified>	
G	**Other safety related violations**		
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 when it is scheduled and the patient did not yet complete follow-up.	None

PV will be detected manually
Source: BI reference document 'Identify and Manage Important Protocol Deviations (iPD)' [001-MCS-50-413] (8,12).
[1] See Section 6.3 for population definitions

6.3 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial:

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

Randomized Set (RS):
This patient set includes all randomized patients. Treatment assignment will be as randomized.

Safety Analysis Set (SAF):
This patient set includes all patients who were randomized and received at least one dose of study drug. This is the main analysis set for efficacy and safety. Patients will be analyzed according to the actual treatment received.

Per-Protocol Set (PPS):
This patient set includes all patients in the randomized 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 endpoint.

The discussion of all exceptional cases and problems and the decisions on the allocation of patients to populations will be made at latest at the RPM/DBLM.

Handling of Treatment Misallocations in Analysis Sets

If a patient is randomized but not treated, they will not be reported under their randomized treatment group for efficacy and safety analysis according to PPS, and SAF.

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

If a subject is randomized but takes incorrect treatment during the study, then:

- For efficacy and safety analyses using the SAF which are based on actual treatment:
    - If a subject is planned to receive administration of Spesolimab (randomized to Speso), then they will be reported under the Spesolimab group if the subject receives at least 1 vial of randomized Spesolimab.
    - If a subject is planned to receive placebo treatment, then they will be reported under the placebo arm if they are treated and receive no vial of randomized Spesolimab. If the subject receives >= 1 vial of randomized Spesolimab, then the patient will be handled differently for efficacy analysis and safety analysis. It will keep as placebo for efficacy reporting. For safety, then the patient will be reported as treated with Spesolimab treatment group.

Table 6.3: 1 Overview of use of patient analysis sets by class of endpoint and handling of estimand and missing data

Class of Endpoints	**ES**	**RS**	**SAF**	**PKS**	**PPS**
Disposition	OR	OR			
Compliance and exposure			OR		
iPD		OR			
Demographic/baseline characteristics		OR	OR		
Concomitant medication		OR			
Primary endpoint			EC-H-MMRM EC-H-MMRM[1] EC-H-MMRM[4] EC-S-MMRM[1] OC[2], OC-IR[2]		EC-H-MMRM[1]
Secondary binary efficacy endpoints			EC-H-NRI, EC-H-NRI[1] EC-H-NRI[4] OC[2] EC-H-MI[3]		
Secondary continuous efficacy endpoints			EC-H-MMRM EC-H-MMRM[1] EC-H-MMRM[4] EC-S-MMRM[3] OC[2]		
Further efficacy endpoints			Binary: EC-H-NRI Continuous: EC-H-MMRM[1] All: OC[2],		
Concentration & ADA			OR	OR	
Safety data			**OR** **OC-IR**		

[1] sensitivity/further analysis
[2] descriptive display only
[3] selected endpoints.
[4] subgroup analysis
For explanation of the different approaches with regard to missing data see Section 6.6.
EC-H: Hybrid strategy by implementing estimand concept. Any data post rescue medication use will be censored.
EC-S: Supplementary strategy by implementing estimand concept. Any data collected after use of any rescue therapy or restricted medication are censored.
OC = observed cases excluding values after any use of rescue medication.
OC-IR = observed cases including also values after any use of rescue medication.
OR = original results.

[redacted]

6.5 POOLING OF CENTRES

No analysis is planned to explore the effect of individual centres; all centres will be pooled for analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

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

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 itself), or 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 will be performed using all available on-treatment data observed up to the respective analysis cut-off date, if applicable.

Some efficacy endpoints are defined with a particular binary outcome, i.e. Achievement of PGA score of 0 or 1. Then imputation is planned to take place only at the binary level, i.e., the PGA score itself as a ordinal variable will not be imputed, but the binary endpoints derived based on these scores will be imputed, unless otherwise specified.

Continuous efficacy endpoints

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

In addition, the efficacy endpoints during randomized treatment period may be displayed descriptively using following methods:

- Observed cases (OC) approach will include all collected data, without imputation for any missing data. Such an OC approach will exclude all values measured after intake of a rescue therapy.
- Observed cases (OC-IR) approach will include all collected data, without imputation for any missing data. Such approach 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. Will also include all values measured after any use of investigator prescribed SoC.

Binary efficacy endpoints

Primary Imputation Approach – No Response Imputation [NRI]:
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):

- 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.

Other Imputation Approaches:
- OC method will be also used to display the binary data.

- Multiple Imputation (MI) approach:
  For selected secondary binary endpoint, i.e., achievement of HiSCR at Week 12, multiple imputation (MI) will be used to handle missing data as a sensitivity analysis. Use baseline and on-treatment data only and impute HiSCR as binary variables with values 0, 1. The

imputation will be done using OC data as the input dataset, and will follow the steps outlined below:

1. *Multiple Imputation of Missing data:* use SAS procedure PROC MI with the Fully Conditional Specification (FCS) method and corresponding options/statements (SAS manual). Discriminant function method is used to impute missing values by using the ordering of the class level in each variable.

   PROC MI DATA= hiscr_mi2 seed= 136852 nimpute=100 out=mi_fcs;
   CLASS HiSCR_base- HiSCR_12 trt stratum;
   VAR HiSCR_base- HiSCR_12 trt stratum;
   FCS DISCRIM (HiSCR_base- HiSCR_12 trt stratum /CLASSEFFECTS=include);
   RUN;

   Note that the seed 136852 will be used throughout. If a second seed is required, 136853 will be used, and so on as necessary.

2. *Analysis of Completed Datasets*: The imputed complete dataset will be used to calculate the response rate for each arm. The risk difference will be also calculated together with the standard error based on the normal approximation.

3. *Combine Results*: Separate approach will be applied to the combination of the response rate for each arm and the difference between them.
   - For the response rate of each arm, the distributions are not expected to be approximately normal, so Rubin's rules (13) should not be used. Instead, the point estimate will be calculated as the mean of individual imputations and the 95% confidence interval for each arm will implement the MIWilson(14) approach.
   - For the risk difference, the distribution is approximately normal, so Rubin's rules can be used. Accordingly, PROC MIANALYZE is used to combine the analysis results from step 2 and generate valid statistical inferences by accounting for the variability introduced by the MI process.

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 HS 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 then 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 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.

6.6.4 PK data

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

6.6.5 Biomarker data

The handling of other biomarkers e.g. RNA expression will be specified in a separate document.

6.6.6 Time since first diagnosis

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.

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 and biomarker 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 2). These extended time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs and biomarker to visits for statistical analysis

Visit number	Visit label	Planned day	Time window				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
1	screening	-28 to-1					
2	Week0	Day1	none	1 [A]	1	1 [A]	1
3	Week1	Day 8	+-1	7	9	2	11
4	Week2	Day15	+-1	14	16	12	22
5	Week4	Day29	+-3	26	32	23	36
6	Week6	Day43	+-3	40	46	37	50
7	Week8	Day57	+-3	54	60	51	64
8	Week10	Day71	+-3	68	74	65	78
9[C]	Week12 (EoT)	Day85	+-3	82	88	79	92
10	Week20 (FUP1)	Day141	+-7	134	148	93	169
11	Week 28 (EOS)	Day197	+-7	190	204	170	211
For patients who discontinue the treatment early and are not willing to follow the whole visit schedule:							
-	EOS	LD [B] +112	-	-	-		

All days are counted relative to the day of randomized 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 trial treatment) via assessment on date & time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B]LD= Last dose.
[C] For the patients who enter extension trial, the EOT will be the last visit (i.e., V10 and V11 are not required). The EOS (=individual end of the study) will be the first administration of the trial drug in extension trial.

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

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

Assignment of observations to visits based on time windows will be based on the non-imputed (observed) data after the implement of estimand concept. For example, for EC and OC methods, values after rescue therapy intake 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
The primary analysis will be performed once all patients have either 1) completed the 12 weeks treatment period or 2) have reached the 12 weeks after starting of treatment if early discontinued the trial treatment; for this assessment a first database lock (before the final database lock) will be performed.

The primary analysis will be performed by the sponsor. The project and trial team members will be un-blinded for treatment information and this analysis.

Note that biomarker data may be reported in a separate biomarker report at this time. If applicable, details of these analyses will be provided in a separate Biomarker Statistical Analysis Plan.

Final analysis
Final trial analysis will be performed once all randomized patients have completed the trial; at that time point, a final database lock will be done.

If separate primary analysis and final analysis, comprehensive analysis will be performed in the primary analysis. All data up to the cut-off date will be included for analysis. In final analysis, only concomitant medication/therapy and safety listings will be provided for these ongoing patients before trial completion at the time of database lock for primary analysis. A final clinical trial report will be written for all data from primary analysis and final analysis.

The primary analysis and final analysis may be performed as a single analysis (at the time of trial completion), if insufficient time interval between the two planned analysis and agreement by the trial team not to perform two separate analyses before the time of the primary analysis. For example, majority of patients enter the extension study and no patient is ongoing under REP at time of DBL of primary analysis.

The decision will be described and documented in final CTR.

General Remarks
The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries " (*BI-KMED-BDS-HTG-0045*) (10) and those generated for PK are based on 001-MCS-36-472 (5).

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

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

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

For PK analyte concentrations, the following descriptive statistics will additionally be calculated: variables:

CV:	arithmetic coefficient of variation
gMean:	geometric mean
gCV:	geometric coefficient of variation

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations.

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

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.

Disposition of the patient population participating in the trial will be summarized by the presentation of the frequency of patients screened, randomized, screened but not randomized, randomized but not treated, randomized and treated, who completed randomized medication, who withdrew from the trial before EOT visit, by reason, who were prematurely discontinued from trial medication, by reason, who received rescue therapy for HS worsening and who entered the extension trial 1368.67.

The frequency of patients with iPDs, also summarized by whether or not the iPD led to exclusion from the PPS, will be presented.

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

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 RS.

For the continuous variables described below, the following categories will be defined in Table 7.1: 1, and 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	< 30 years 30 to < 65 years ≥ 65 years
Weight	≤60 kg >60 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 year > 5 to ≤ 10 years > 10 years

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Analyses of concomitant diseases and medication will be based on the RS.

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 summarized with frequency and percentage of patients by 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) taken any time during the on-treatment period (cf. Section 6.1) 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).

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

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

7.3 TREATMENT COMPLIANCE

Treatment compliance (see Section 5.4.4 for the definition and calculation) will be summarized for the SAF using descriptive statistics (N, mean, SD, minimum, median, maximum). The number and percentage of patients with the following overall compliance categories will be presented:

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

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary analysis will implement the Hybrid strategy (EC-H) of handing intercurrent event defined in Section 5.4.6. Any data collected after the intercurrent event will be censored for the timepoint afterwards, i.e., only data prior to the ICE will be considered.

For the primary endpoint analysis, a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) is calculated to compare the adjusted relevant difference between the two arms.

MMRM analysis
The % change in total abscess and inflammatory nodule count from baseline (Visit 2), at Visits 3, 4, 5, 6, 7, 8 and 9 (Weeks 1, 2, 4, 6, 8, 10 and 12) will be evaluated using an MMRM accounting for the following sources of variation: fixed, categorical effects of treatment at each visit, the effect of stratum (stratification according to TNFi-naive population vs. TNFi-failure population) and the fixed continuous effects of baseline at each visit. 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 10.2 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.

7.4.2 Sensitivity analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

Sensitivity analysis

As one sensitivity analysis for the primary endpoint, the observed data will be augmented with historical data. The 1368.52 placebo group will be combined with prior historical data for the placebo group from Humira Pioneer I and Pioneer II trials to derive the respective posterior distribution of the primary endpoint. A comparable population according to inclusion criteria in the current trial is obtained by trimming the historical data to patients with baseline total AN count no less than 5 and baseline total draining fistula count no larger than 20. A meta-analytic predictive (MAP) prior will be derived from the trimmed data. Similarly, the observed data of spesolimab group will be combined with a non-informative prior to derive the respective posterior distribution for spesolimab treatment. These posterior distributions will be used to evaluate the posterior treatment difference in primary endpoint between spesolimab and placebo. The posterior median and 95% credible intervals will be reported.

Furthermore, as the historical placebo data is from TNFi-naïve population, an additional sensitivity analysis will only consider the combination of the historical data with the observed data from TNFi-naïve patients in the placebo arm of the current study to derive the respective posterior distribution. The observed data from TNFi-failure patients in the placebo arm of the current study will be combined with a non-informative prior to derive the corresponding posterior distribution. The information from the strata will be weighted per sample size to obtain an overall estimate.

The MAP prior derivations for placebo arm obtained from Humira Pioneer I and Pioneer II trials, as well as posterior distribution for the treatment difference will be implemented following Section 10.3.1.

In addition, the following sensitivity analysis for MMRM may be done:

- Sensitivity analyses utilizing MMRM model on different patients sets (such as the PPS)

Supplementary analysis

The analysis based on supplementary strategy (EC-S) of handling intercurrent event defined in Section 5.4.5 may be done if the interested event occurs. Any data collected after the intercurrent event will be censored for the timepoint afterwards.

Subgroup analysis

Subgroup analysis will use similar MMRM model as described for primary analysis of primary endpoint. A single MMRM model will be fitted involving all terms from the primary analysis model except replacing the treatment-by-visit term by the treatment-by-subgroup-by-visit term. Considering the exploratory nature of the study with small sample size, no test will be carried out to compare the treatment effect between spesolimab and placebo within subpopulation. The variables used for subgroup analysis is defined in Section 6.4. If the model cannot converge, the level with smallest sample size will be excluded.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

For each of the secondary endpoint described below, hybrid strategy will be used to handle intercurrent events which lead to data censoring as described for the primary endpoint.

Continuous secondary endpoints

The continuous secondary endpoints up to Week 12 will be analysed using a MMRM approach based upon the model specification as described for the primary endpoint.

Additionally, subgroup analysis will be performed for variables as described in Section 6.4.

Binary secondary endpoints

The binary secondary endpoints will be evaluated descriptively by treatment arm via frequency tables (with 95% confidence interval based on the Wilson score for each group and based on the Chan and Zhang method for risk difference). As in the case of the primary estimand, any binary data collected after use of any rescue therapy will be censored and then imputed using the NRI method as described in CTP section 7.3 “Handling of Missing Data”.

Example SAS code for CI of proportion difference by Chan and Zhang method is as follows:

```
PROC FREQ DATA=data;
<WHERE treat IN (’Treatment_1’,’Treatment_2’) ;>
TABLES treat*endpoint_bin / RELRISK RISKDIFF.
EXACT RELRISK (METHOD=SCORE column=2) RISKDIFF (METHOD=SCORE
column=2);
RUN;
```

For selected binary endpoint, e.g., achievement of HiSCR at Week 12, following additional analyses are planned.

Logistic regression analysis

The difference in the proportion of patients with a response between Spesolimab and placebo will be analysed using predictive margins in a binary logistic model via %Margins in SAS®. Fixed classification effects will include treatment and stratification factor (TNFi-naive population versus TNFi-failure population).

Example SAS code:

```
%Margins(data= data,
class    = treat stratum,
response = endpoint_bin,
roptions = event='1',
dist     = binomial,
model    = treat stratum,
margins  = treat,
options  = cl diff)
```

Stratified risk difference

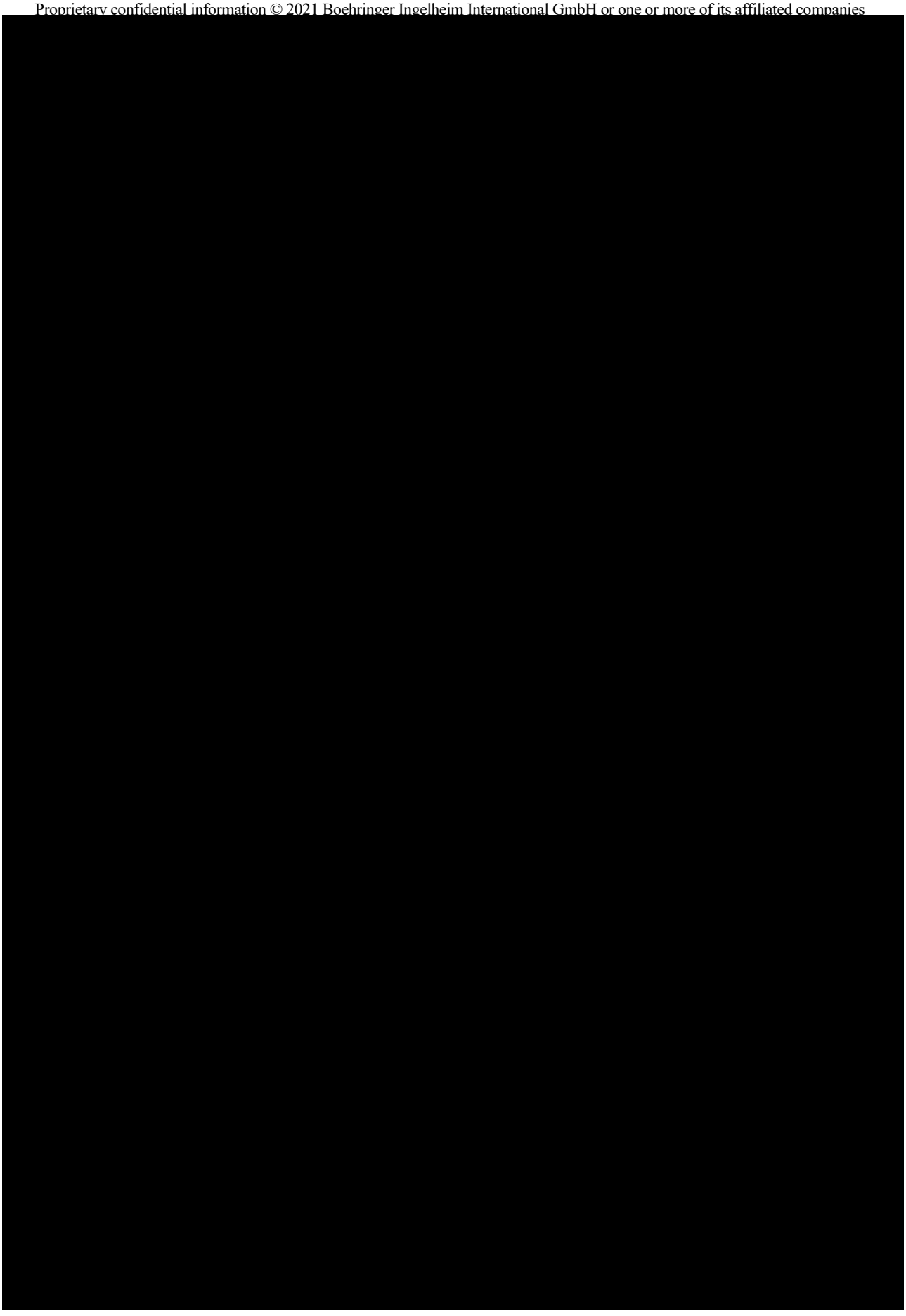
A Mantel-Haenszel type weighted average of differences will be implemented with corresponding Wald confidence intervals based on the variance formula provided by Sato.

Example SAS code:

```
Proc freq data=data;
tables stratum*treat*endpoint_bin/cmh commonriskdiff(cl=mh);
quit;
```

In addition, sensitivity analyses utilizing MAP Bayesian method for achievement of HiSCR at Week 12, will be considered. For the process, please refer to section 7.4.2 as described for the primary endpoint. The MAP prior derivations for placebo arm obtained from Humira Pioneer I and Pioneer II trials, as well as posterior distribution for the treatment difference will be implemented following Section 10.3.2.

Please refer to Section 7.8.1 for the analysis of safety endpoint as a secondary endpoint, which is defined as the occurrence of Treatment Emergent Adverse Events (TEAEs).



7.7 EXTENT OF EXPOSURE

An overall table will be summarized for the entire maintenance treatment period. The number of subjects who received a dose of trial drug will be tabulated. Treatment exposure will be assessed as the total dose of randomized treatment [mg] administrated for the loading stage, the maintenance stage, as well as the overall dose across the two stages, which will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum). The total duration of exposure [days] will also be displayed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the safety analysis set.

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. All safety analysis will be performed for on-treatment period.

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

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

Off-treatment data will be listed only.

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 grouping patients based on their loading doses (1200 mg, Placebo) using SAF. The outputs will include on-treatment data up to the first maintenance dose at or post week 4. If patients discontinued from treatment prior to receiving first maintenance dose, then the safety data up to the date of last loading dose + 112 days will be included.

7.8.1 Adverse Events

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

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

For details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (15) and "Handling of missing and incomplete AE dates" (4).

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

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.

The following is considered an AESI in this trial:

Systemic hypersensitivity including infusion reaction and anaphylactic reaction

Severe infections (according to RCTC grading)

Opportunistic and mycobacterium tuberculosis infections

Hepatic injury

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

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other
  OR
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

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

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

User-defined AE category		
	Label	Description
Hypersensitivity	Hypersensitivity ALL	Combined search strategy based on the three individual UDAECs described below
	Anaphylactic reaction, narrow	Narrow SMQ “Anaphylactic reaction”
	Angioedema, narrow	Narrow SMQ “Angioedema”
	Hypersensitivity, narrow	Narrow SMQ “Hypersensitivity”
Infections (serious/severe, opportunistic)	Infections 'ALL'	terms from combined search with sort order # in (20, 30, 40, 21, 22) Sort order if applicable to project or trial
	Opportunistic infections	SMQ "Opportunistic infections", narrow
	Tuberculosis infections	sub-BIcMQ “Tuberculosis related terms”, narrow BIcMQ "Infections", sub-search 8.2 “Tuberculosis related terms” narrow
	Severe infections	SOC "Infections and infestations" with AETOXGR >= 3 OR AESEV = 'Severe'. Not derived for studies where both severity variables are collected. SOC "Infections and infestations" of at least severe RCTC grade (>= 3) or any severe events
	Serious infections	SOC “Infections and infestations” with [AECOND: AESER = 1] SOC “Infections and infestations” with "intensity= serious"
Malignancies	Malignant tumours	sub-SMQ “Haematological malignant tumours”, narrow, sub-SMQ “Non-Haematological malignant tumours”, narrow
	Malignancies excluding NMSC	sub-SMQ “Malignant tumours” excluding terms from search with sort order #=340 Sub-SMQ “Malignant tumours” excluding NMSC, where NMSC is defined above
Torsades de Pointes	Torsades de Pointes	Broad sub-SMQ “Torsade de pointes/QT prolongation”

Depression	Depression	sub-SMQ "Depression (excl suicide and self-injury)", broad
Suicidal ideation and behavior (SIB)	sub-SMQ "Suicide/self-injury"	
DRESS	DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), broad	SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome", broad Algorithm: A or (B and C and D) or (B and C and E) or (B and D and E)
	DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), narrow	SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome", narrow Only category A

* 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 (16). 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 (16). All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline will be calculated. For all outputs, the last assessment before the first treatment at Day 1 is chosen as the baseline value.

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

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

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

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

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

The frequency of patients with AST or ALT elevations ≥ 3xULN, ≥ 5xULN, ≥ 10xULN, and ≥ 20xULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥ 3xULN combined with a total bilirubin ≥ 2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin 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, AST 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, respiratory rate) and body weight will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided, including the last value, the minimum value and the maximum value during on-treatment period.

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

7.8.4 ECG

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

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

7.8.5 Local tolerability

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

7.8.6 Others

Not applicable.

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 missing visits or early discontinuation due to COVID-19 will be listed. iPDs related to COVID-19 will be also listed if any.

Identification of SARS-CoV-2 infections

If patients get SARS-CoV-2 infection while on treatment with study drug, AE frequency analysis for subgroup of subjects with SARS-CoV-2 infection while on treatment with study drug will be provided, based on the narrow BIcMQ SARS-CoV-2 infections..

AE based on the periods of COVID-19 disruption

- Overall summary of AEs
- AEs by SOC and PT
- AEs leading to d/c by SOC and PT
- SAEs by SOC and PT

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.

7.11 OTHERS

7.11.1 Biomarkers

The following biomarkers will be analysed and reported as a part of the CTR:

- HS-CRP

Results on other biomarkers (e.g. RNA expression, serum and plasma biomarkers) may or may not be reported in the CTR, depending e.g. on the availability of the data. In case they are reported outside the CTR the analysis will be defined in a separate document (otherwise the analysis will be described in the CTR).

For the analysis of biomarkers, log transformed data will be used where deemed necessary.

7.11.2 Immunogenicity

The ADA status and titer as well as frequency of patients with ADA to Spesolimab will be presented by visit. Descriptive statistics of ADA titer (for ADA positive patients, when available) will be provided by visit. The number of subjects with ADA status positive/negative at any time will also be presented. ADA parameters (e.g. treatment-induced ADA positive subjects, transient ADA response and persistent ADA response) will also be presented by visit and cumulatively for the overall study duration. Further exploratory assessments of the ADA data will be performed once data is available and these will be described, if done, in the CTR.

Further analyses based on ADA data may be performed such as

- efficacy-based subgroup analysis as described in Section 7.4.2 for the 2 groups
    - ADA positive and ADA negative subjects (at Week 12), or

- NAb positive and NAb negative subjects (at Week 12)

- Safety-based subgroup analysis (using e.g. hypersensitivity safety events) for the 2 groups

  - ADA positive and ADA negative subjects (at any time), or

  - NAb positive and NAb negative subjects (at any time), or before ADA development (including subjects with events either before their first ADA positive sample or without ADA positive sample throughout) and after ADA development (including subjects with events from the time point of their first ADA positive sample onwards). This approach takes into account the time when ADA actually developed and when the safety event occurred in relationship to ADA.

7.11.3 Pharmacokinetics

No PK parameters will be calculated.

The descriptive analysis of Spesolimab plasma concentrations will be based on the SAF.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains columnvariables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’ the value will be excluded from half-life calculation only; the value is included for all other analyses.

Further details are given in (5).

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed. Any further exploratory analyses, if done, will be described in the CTR or in a separate report.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

As the discussion in Section 7, if the primary analysis and the final analysis are planned to be performed separately, then a database lock for the primary analysis will be done and treatment will be unblinded to trial and project team members.

Then we will follow Fast-track approach: *Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for analysis.*
The data collection for the off-treatment residual effect period until the End-of-Study (EoS)/ Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.

After the release of treatment information, it is expected that only trial data related to the off-treatment residual effect period will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to the End-of-Treatment (EoT) visit will be documented and summarized in the CTR.

If the primary analysis and final analysis are combined as a single analysis (at the time of trial completion), if insufficient time interval between the two planned analysis and agreement by the trial team not to perform two separate analyses before the time of the primary analysis.

Then we will follow Standard approach: *The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form.*

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCS-50-415_RD-03:* "Clinical Trial Analysis Decision Log (template) Decision Log", current version, Group "Biostatistics & Data Sciences", 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-40-106_RD-03:* "Clinical Trial Protocol general template for Phase I-IV", current version, Group "Clinical Operations", IDEA for CON.
7.	*001-MCS-80-60*6: "Management of Non-Compliances", current version, Group "Quality Medicine", IDEA for CON.
8.	*001-MCS-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", IDEA for CON.
9.	*001-MCS-40-135_RD-01:* "Integrated Quality and Risk Management Plan", current version, Group "Clinical Operations", IDEA for CON.
10.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
11.	*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, EMA webpage.
12.	001-MCS-40-413_RD-00: "List of References to SOP Identify and Mange Important Protocol Deviations (iPD)", current version; IDEA for CON
13.	Rubin, D. B. (1976), "Inference and Missing data" (with discussion), Biometrika, 63, 581–592.[109]
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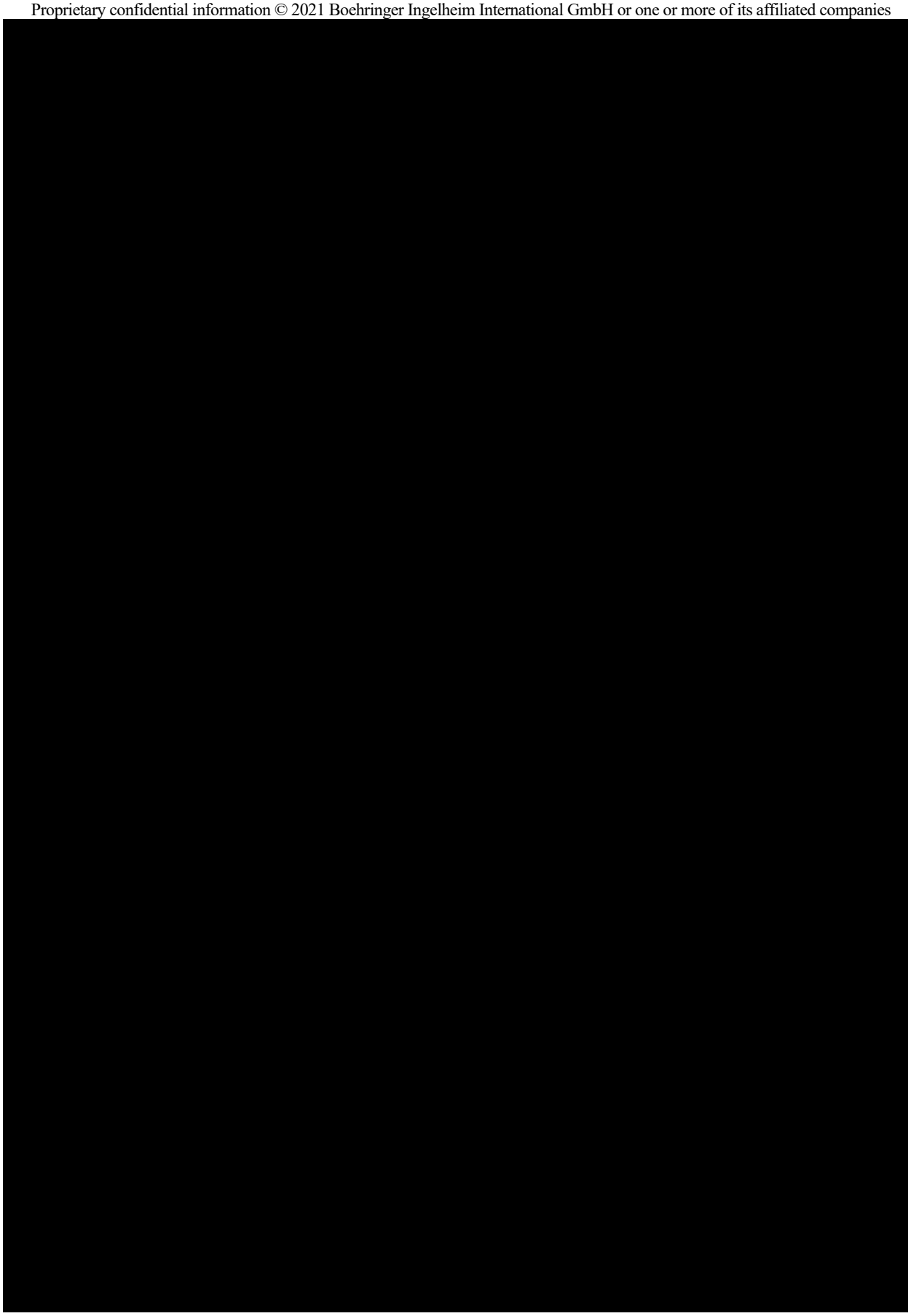
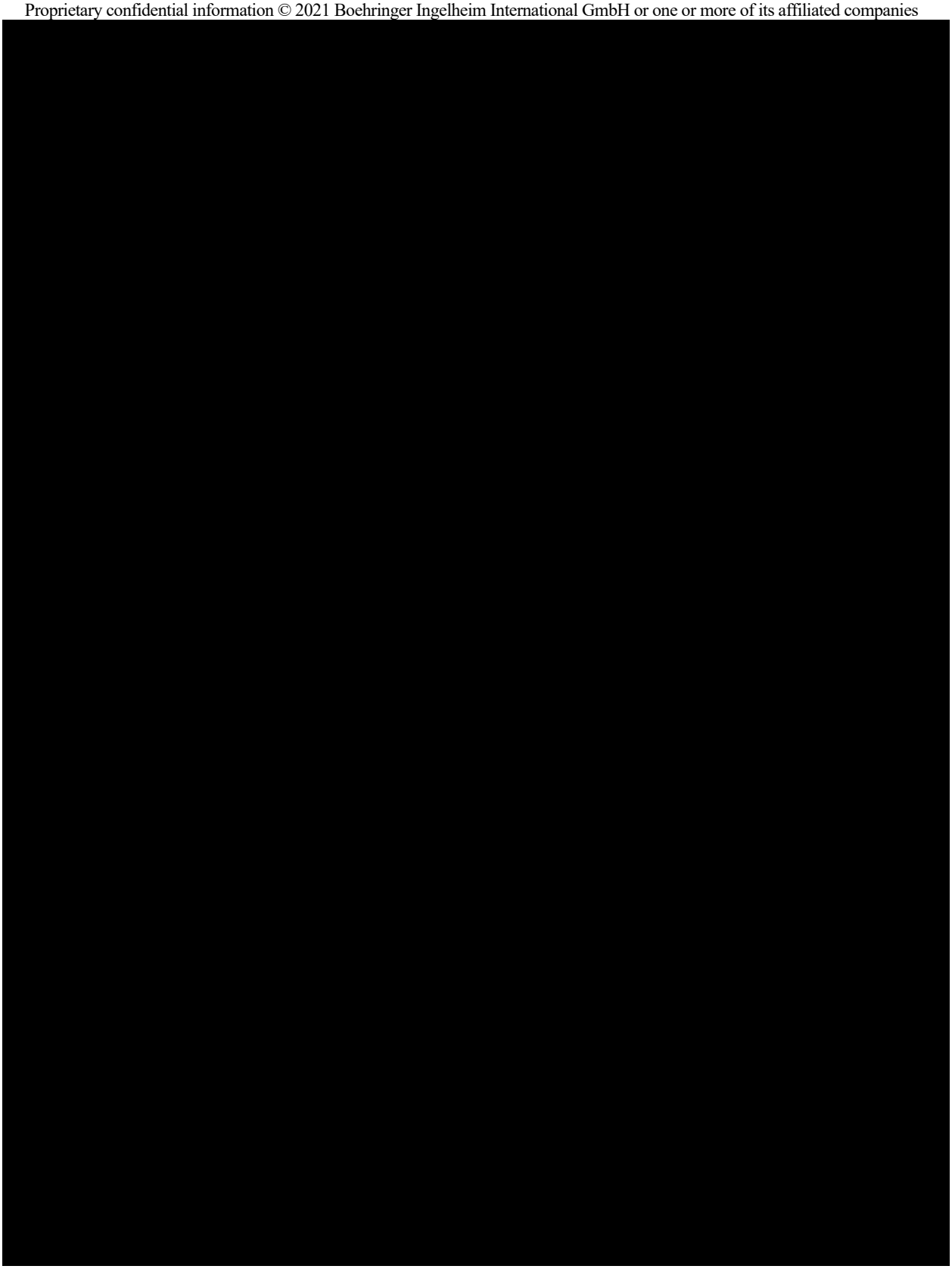
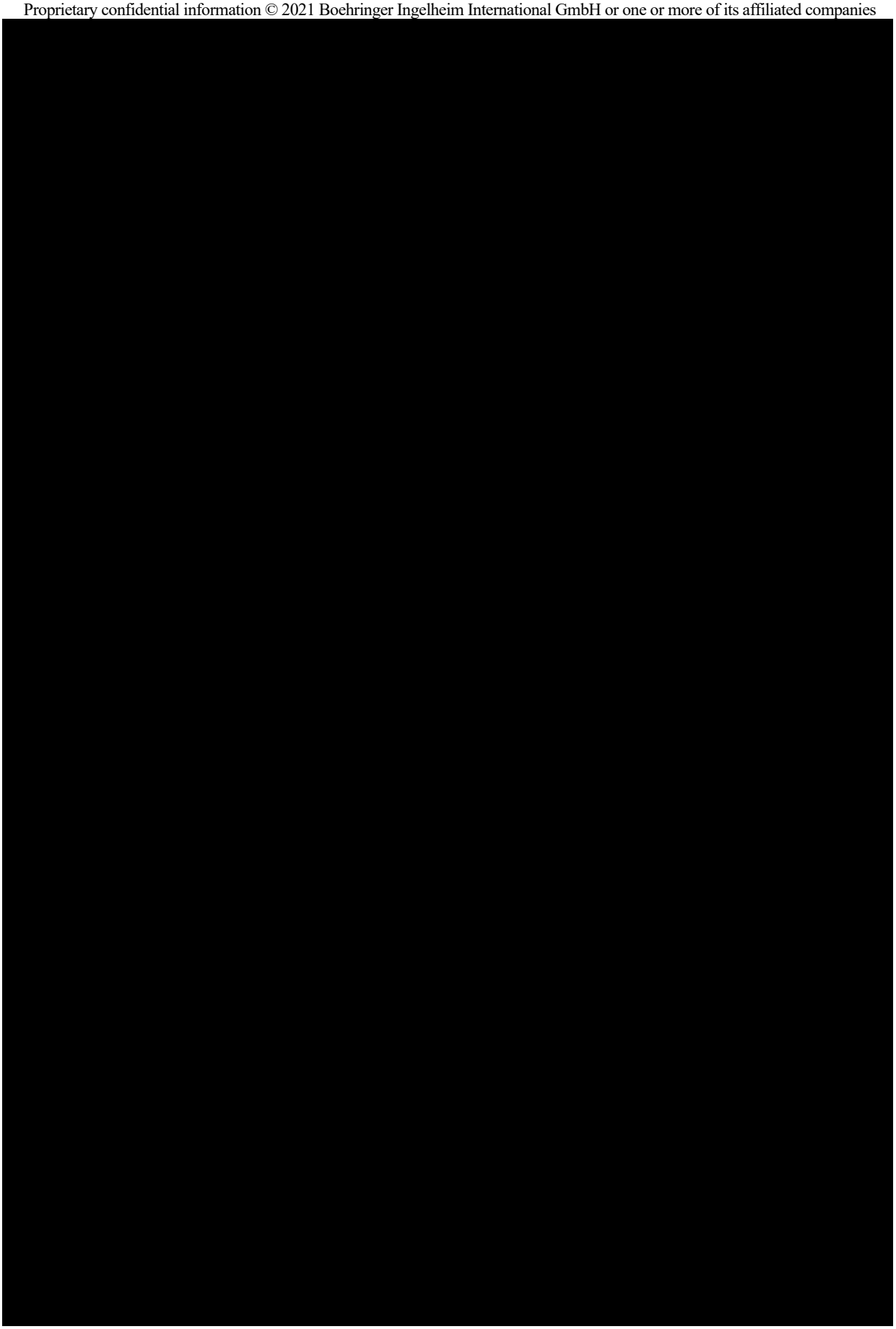
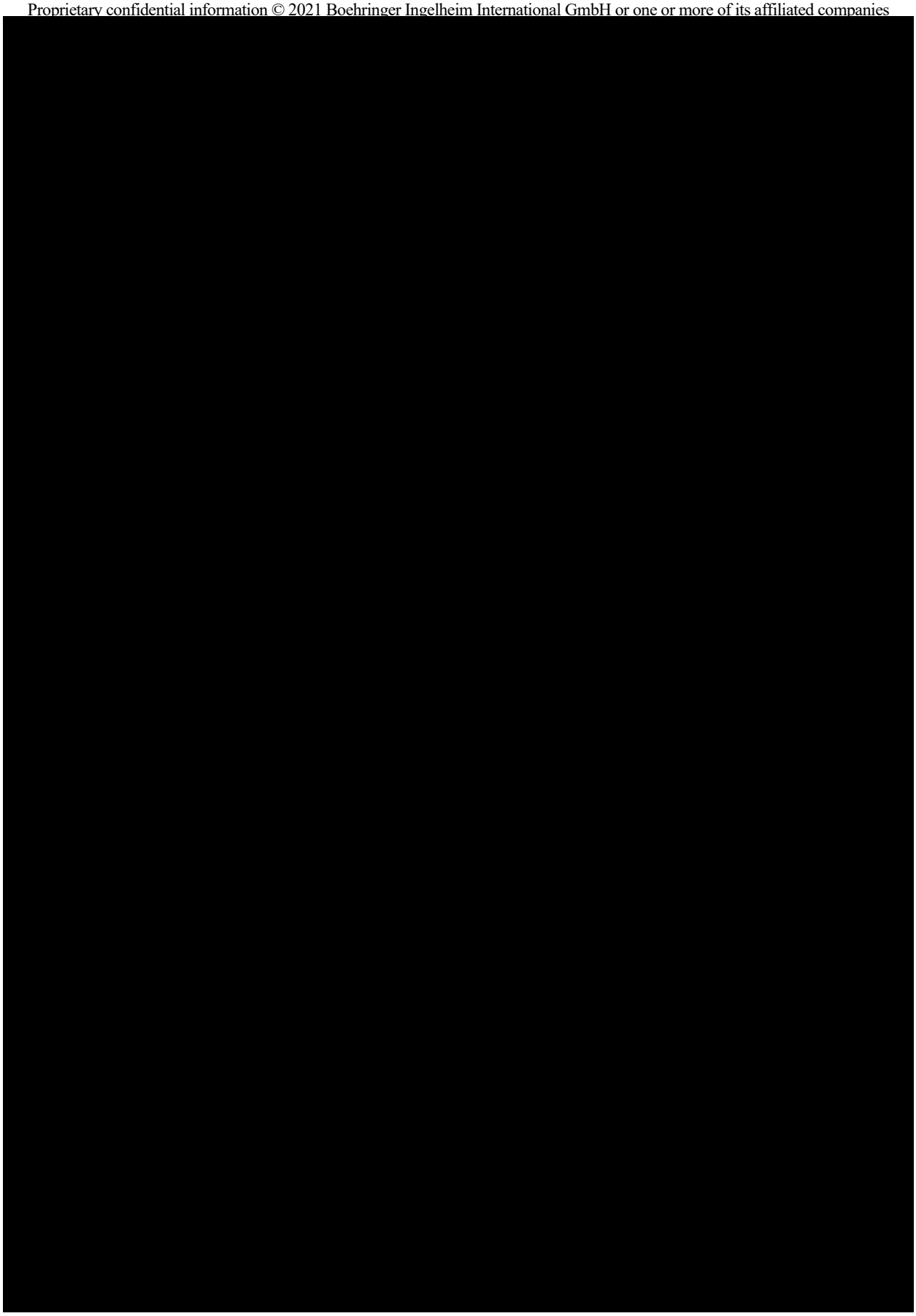
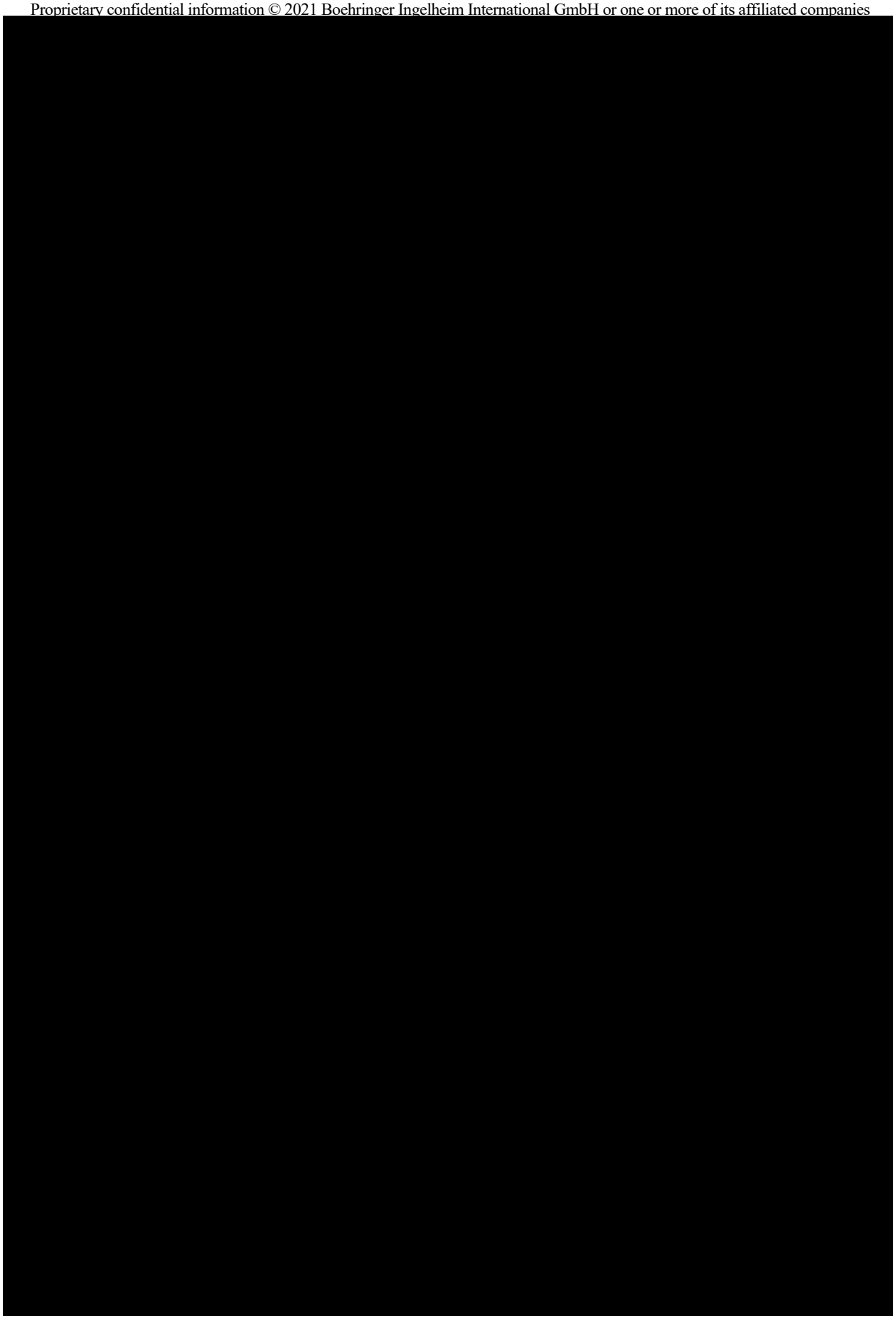
16.	BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON
17.	Kirby et al. The Hidradenitis Suppurativa Quality of Life (HiSQoL) score: development and validation of a measure for clinical trials. British Journal of Dermatology (2020) 183, pp340–348
18.	Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Joint Ann Mtg of the British Association of Dermatologists and the Canadian Dermatology Association, Oxford, 6 - 10 Jul 1993. Clin Exp Dermatol 1994; 19; 210-216.

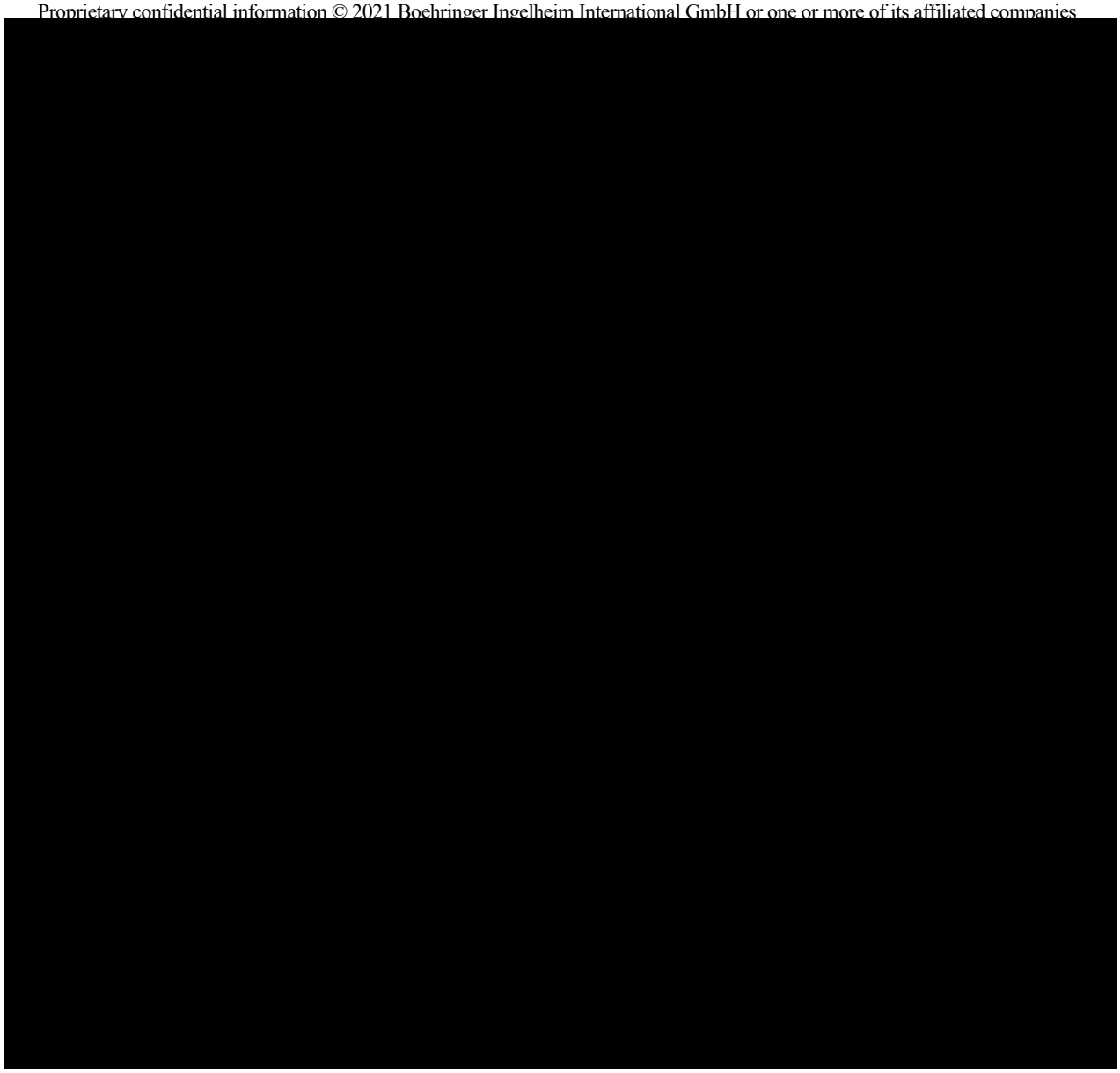


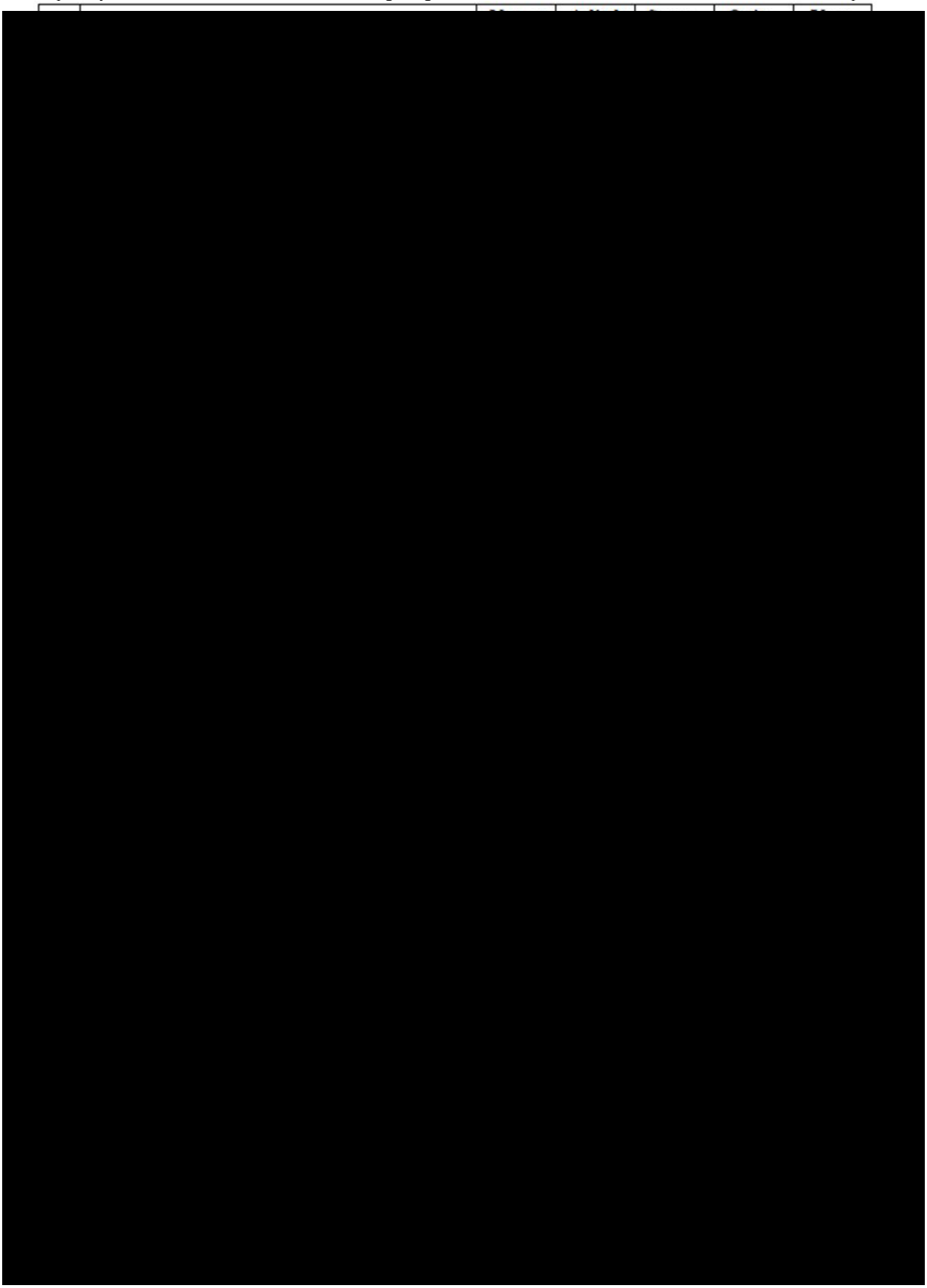


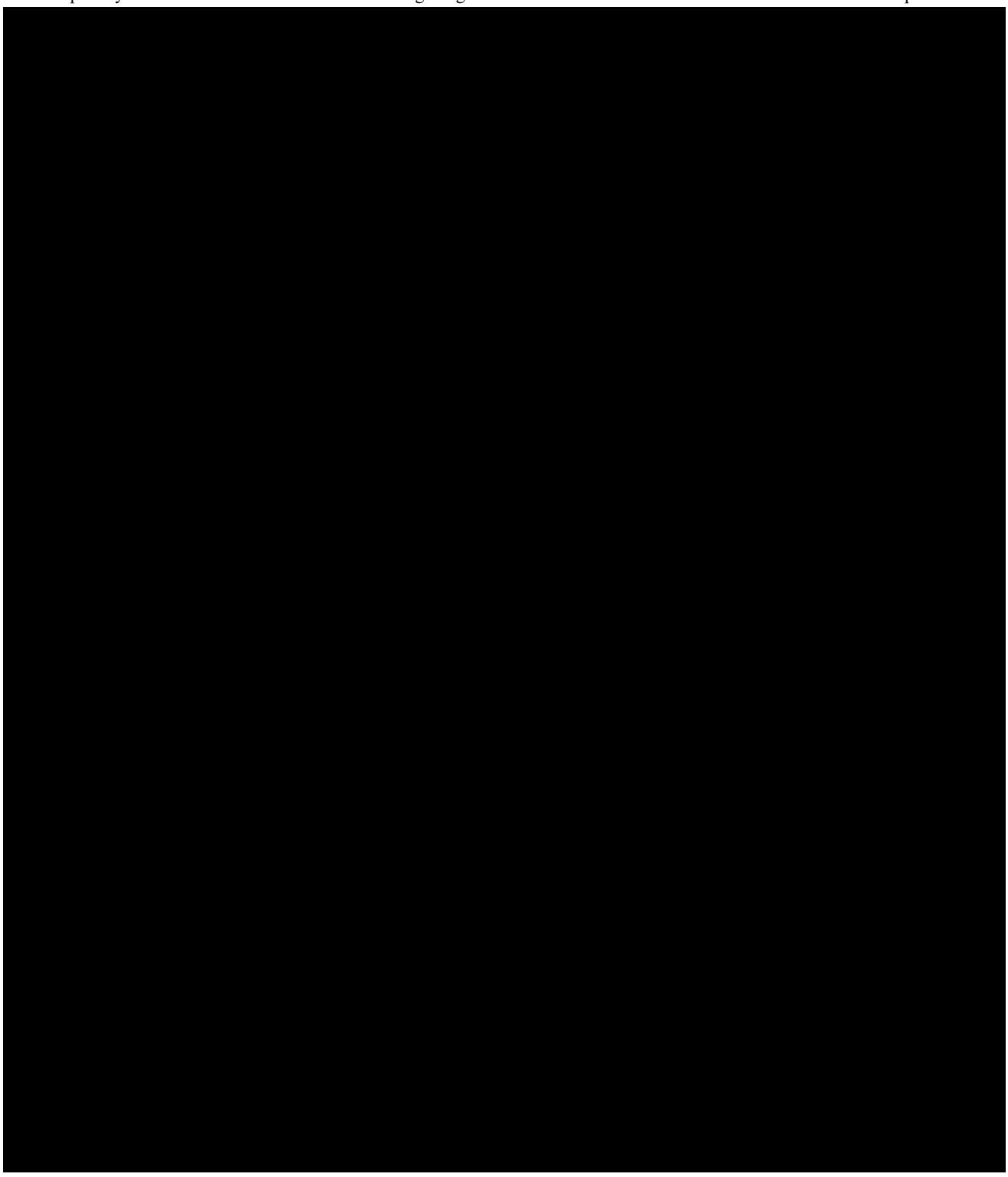


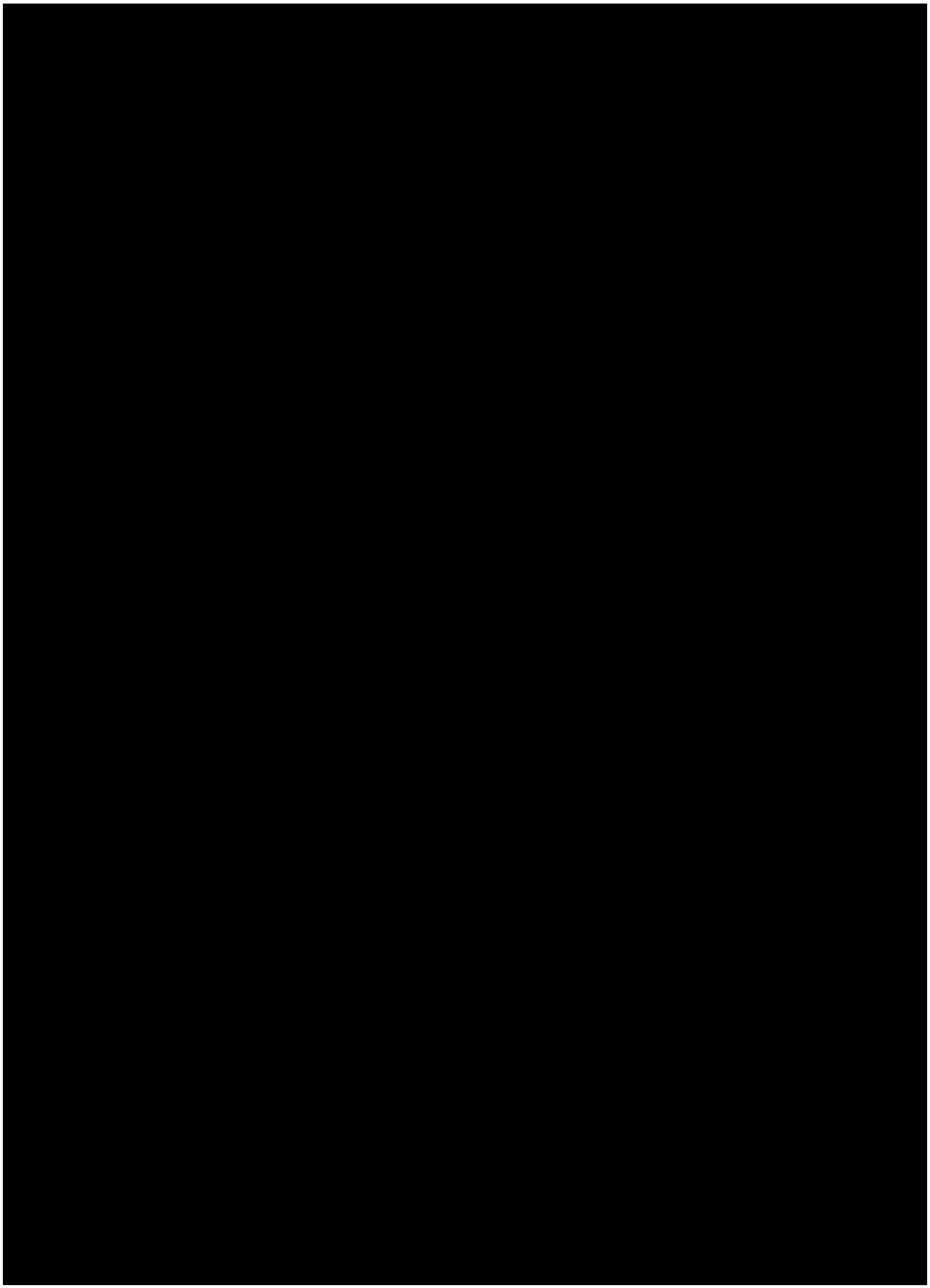


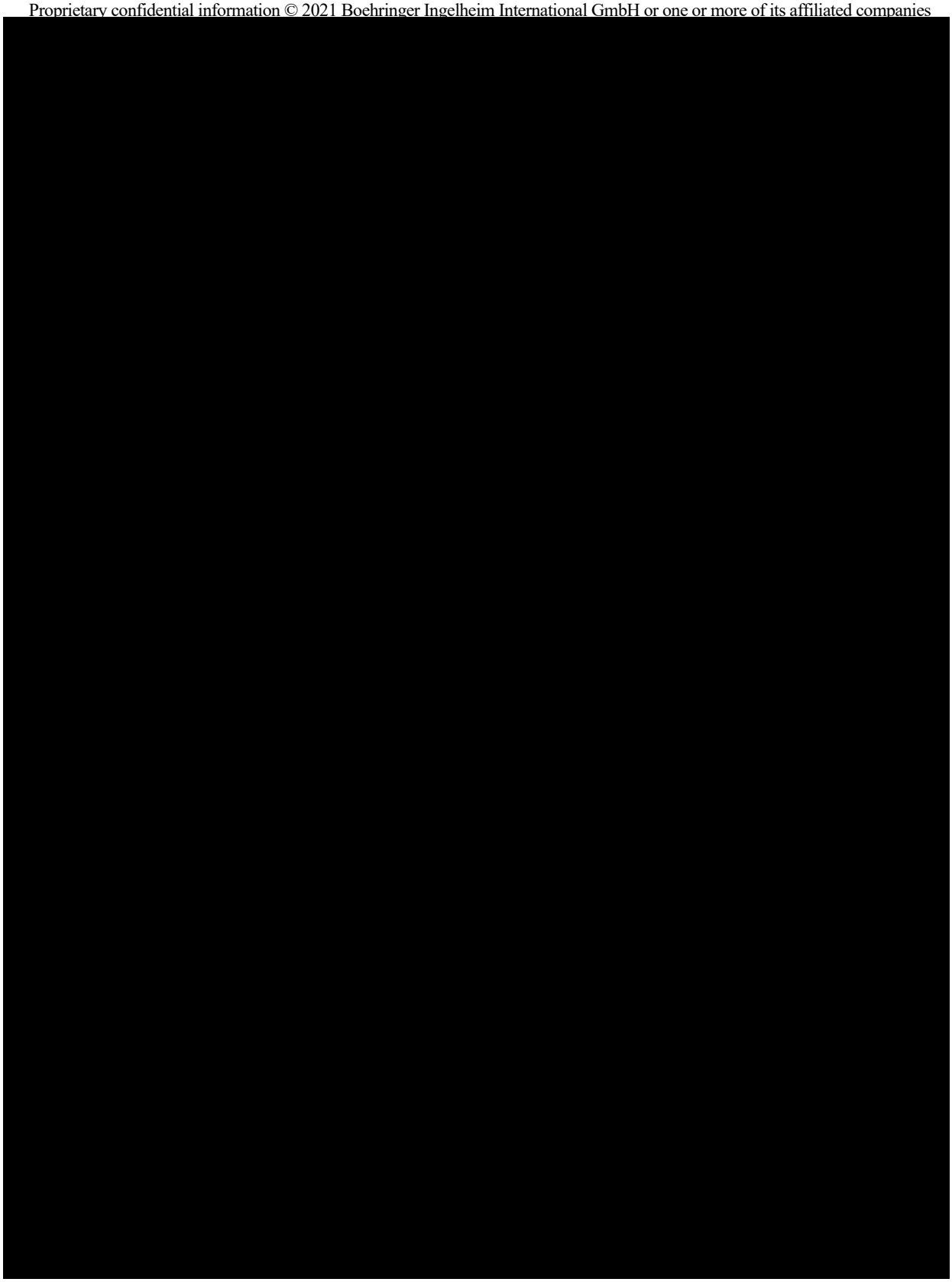












[redacted]

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**28-DEC-21**	[redacted]	None	This is the final TSAP.