TRIAL STATISTICAL ANALYSIS PLAN

c36061687-01

BI Trial No.:	1305-0013
Title:	A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally. (Including Protocol Amendment 1, 2, 3 [c29492723-04])
Investigational Product(s):	BI 1015550
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	08 OCT 2021 SIGNED
Version:	1

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[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Antifibrotic
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BMI	Body Mass Index
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
[redacted]	[redacted]
ECG	Electrocardiogram
ECGS	ECG set
eCRF	Electronic Case Report Form
EoT	End of Treatment
EoTrial	End of Trial
ES	Entered Set
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
HR	Heart Rate
HRCT	High Resolution Computed Tomography Scan
ICH	International Council on Harmonisation
iPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
[redacted]	[redacted]

LPF	Living with Pulmonary Fibrosis
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
[redacted]	[redacted]
[redacted]	[redacted]
PoC	Proof of Concept
PPS	Per Protocol Set
PR interval	ECG interval from the onset of the P wave to the beginning of the QRS complex
[redacted]	[redacted]
[redacted]	[redacted]
QRS duration	Combination of the Q, R, and S waves
QT interval	ECG interval from the beginning of the QRS complex to the end of the T wave
QTcB	QT interval, heart rate corrected using Bazett's formula
QTcF	QT interval, heart rate corrected using Fridericia's formula
RA	Regulatory Authority
REP	Residual Effect Period
RMP	Risk Management Program
RS	Randomised Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
t_{max}	Timepoint of Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Events
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
UIP	usual interstitial pneumonia
[redacted]	[redacted]

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, 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, randomization.

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

The following adaptations, which do not affect the planned analysis, have been done:

In Section 7.2.1 of the CTP the following was defined: *Specifications of important protocol deviations leading to exclusion will be provided in the trial Integrated Quality and Risk Management Plan (IQRMP) and all decisions concerning IPDs will be made before un-blinding.* Due to SOP changes, the IPD categories are no longer available in the IQRM plan but included in an IPD specification file (2). The IPD categories originally defined in the IQRM plan were transferred to this IPD specification file. Minor changes regarding the IPD categories were performed.

The priors for placebo and BI treatment presented in Section 7.2.2.1 of the CTP have been slightly changed in the TSAP (see Section 7.4.1) by using the same set of historical trial data, same R programming codes, but with an updated version of the RBesT package (v.1.6.1). This is an stable package version that guarantees replicability of the prior derivations.

Further binary efficacy endpoints have been added based on the relative change in FVC (mL and %predicted) from baseline to week 12, using cut-offs 3%, 5%, and 10%. The binary FVC endpoint based on 3% cut-off will be analysed by a logistic regression model.

Further ECG endpoints have been added for safety analysis, and the respective ECG set has been defined in the TSAP.

The Entered Set will be renamed to Enrolled Set (ES) in the CTR Tables.

It has been clarified that patients will be analyzed based on the trial medication they have actually received, except for the Enrolled set and Randomised set.

Time to onset of adverse event diarrhoea has been added for Safety analysis.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP: *The primary endpoint is the change from baseline in FVC at 12 weeks (in mL).*

Section 7.2.2. of the CTP:
The main analysis for the primary endpoint will be conducted separately for patients not on antifibrotic treatment and for patients on antifibrotic treatment at baseline […]

The primary estimand of interest is the treatment effect assuming all patients took randomized treatment for the duration of the trial using a hypothetical approach, i.e. trial drug is taken as directed. The primary analysis of the primary endpoint will include all data collected while on treatment. Any data collected at the follow up will not be included in the primary analysis. The resulting missing data will be assumed to be missing at random (MAR). Patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

The expected intercurrent events of interest and handling strategies in this trial are as follows:

Table 5.1: 1 Summary of intercurrent events and handling strategy

	While on treatment: Use data while on-treatment until week 12, and before occurrence of the intercurrent event.	Treatment policy: Use all data collected until week 12, regardless of whether or not the intercurrent event occurs.
Intercurrent events		
Treatment discontinuation	x	x
Start use of restricted medication, different from AF treatment (nintedanib / pirfenidone)		x
Switch of non-AF baseline treatment to AF treatment		x

Table 5.1: 2 Summary and description of intercurrent event handling in the analysis

Intercurrent event	Strategy (primary analysis)	Strategy (sensitivity analysis)
Treatment discontinuation [a]	use data until date of treatment discontinuation	include available follow-up data until week 12.
Start use of restricted medication [b], different from AF treatment (nintedanib / pirfenidone)	include data after starting use of restricted medication.	include data after starting use of restricted medication.
Switch of non-AF baseline treatment [c] to AF treatment	include data after switching from non-AF baseline treatment to AF treatment. Keep patient in the non-AF baseline stratum.	include data after switching from non-AF baseline treatment to AF treatment. Keep patient in the non-AF baseline stratum.

[a] Data of REP (7 days) after last medication intake should be included.
[b] Only restricted medications leading to important protocol deviations will be considered as intercurrent events.
[c] Wrong assignment of a patient to a AF baseline stratum is not considered an intercurrent event. In this case the patient will simply be re-assigned to the right stratum.

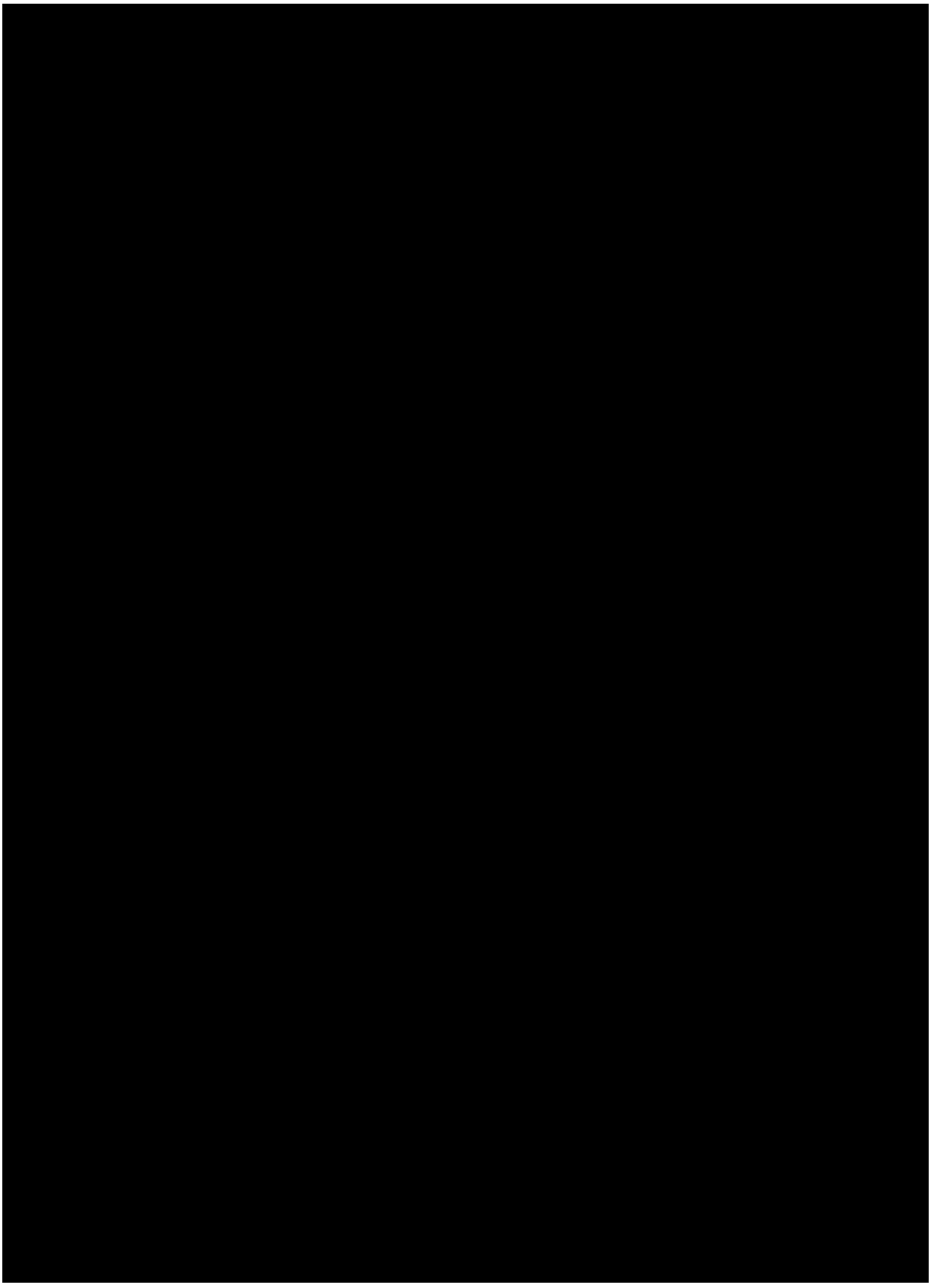
5.2 SECONDARY ENDPOINT(S)

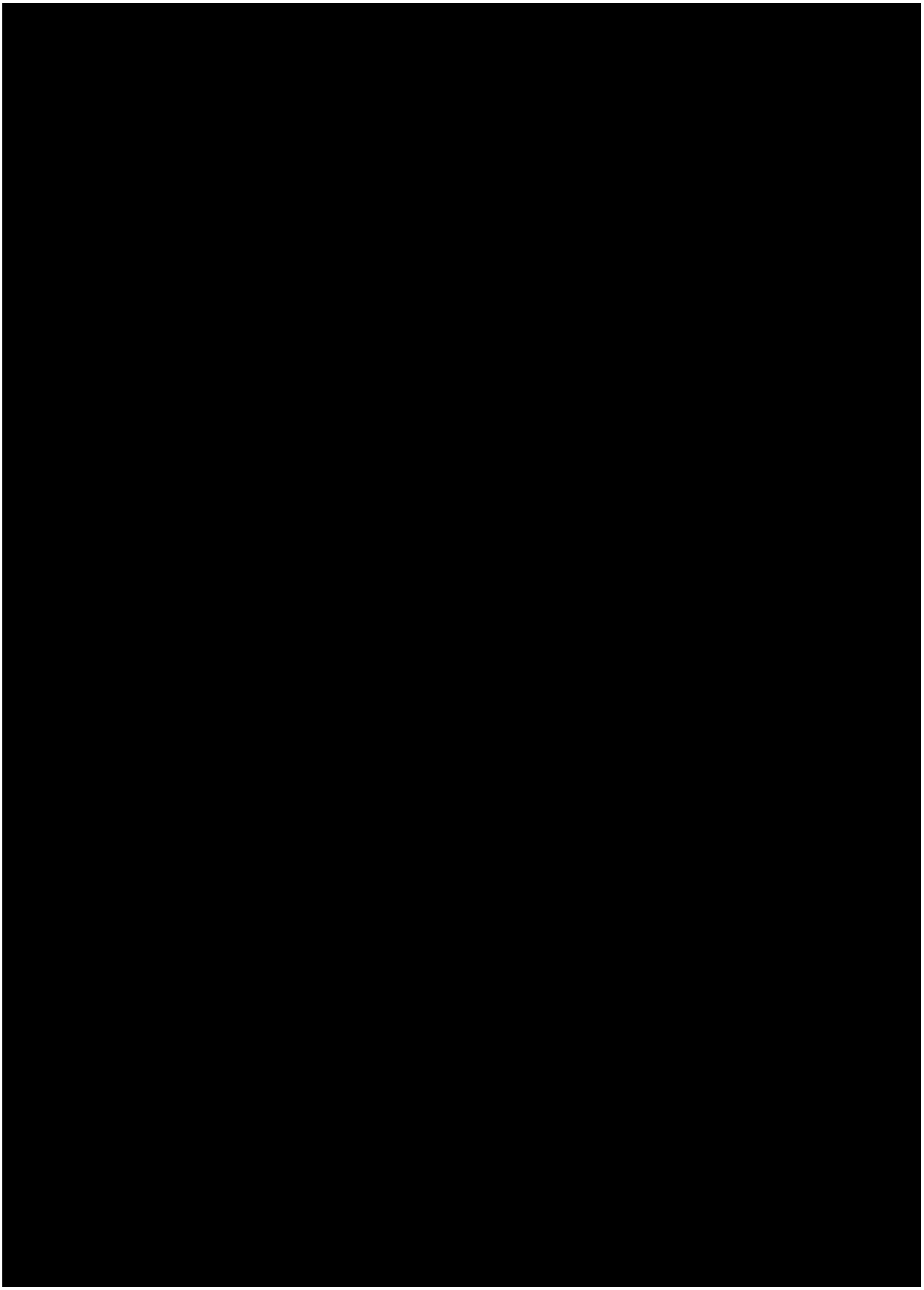
5.2.1 Key secondary endpoint(s)

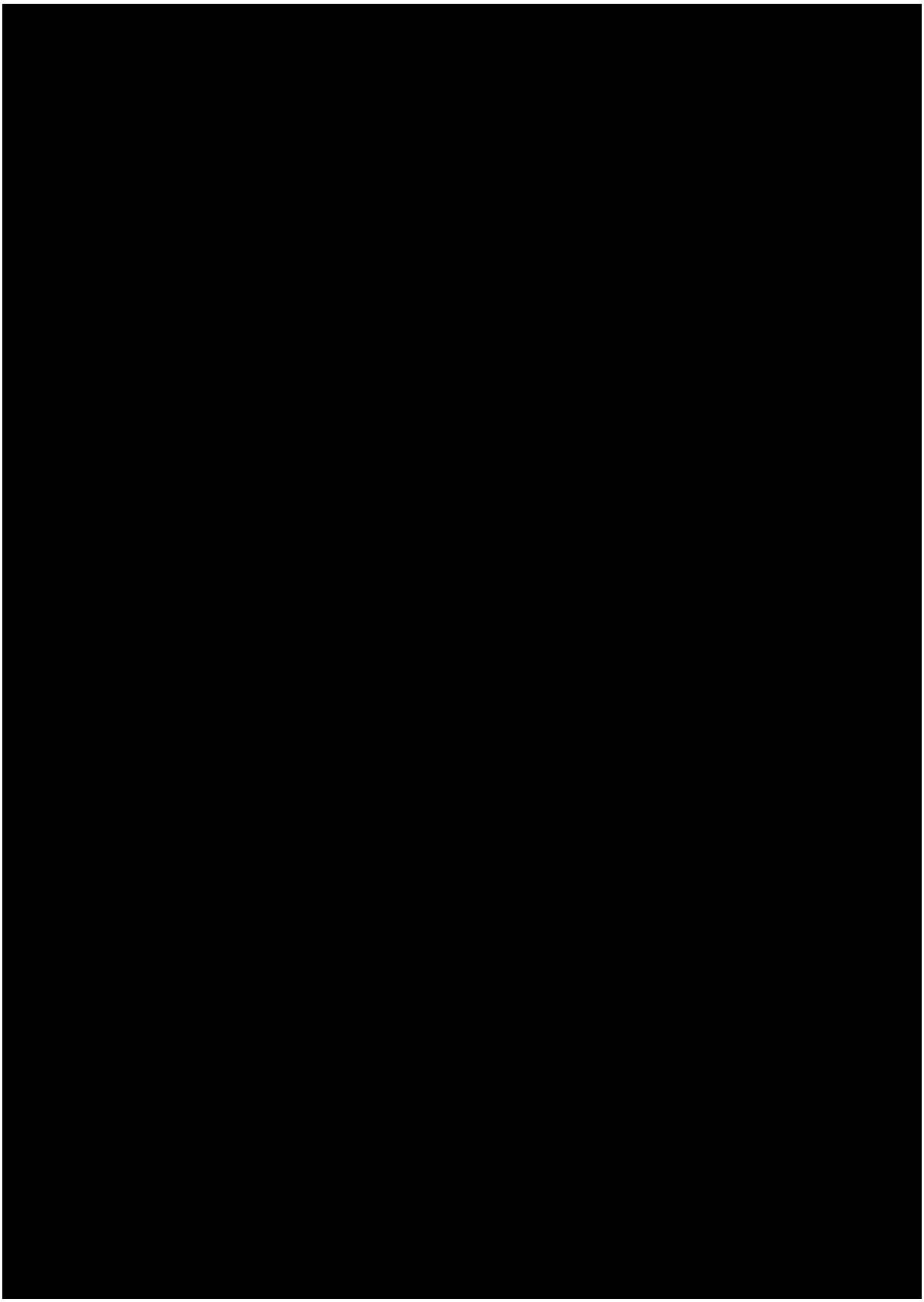
Not applicable.

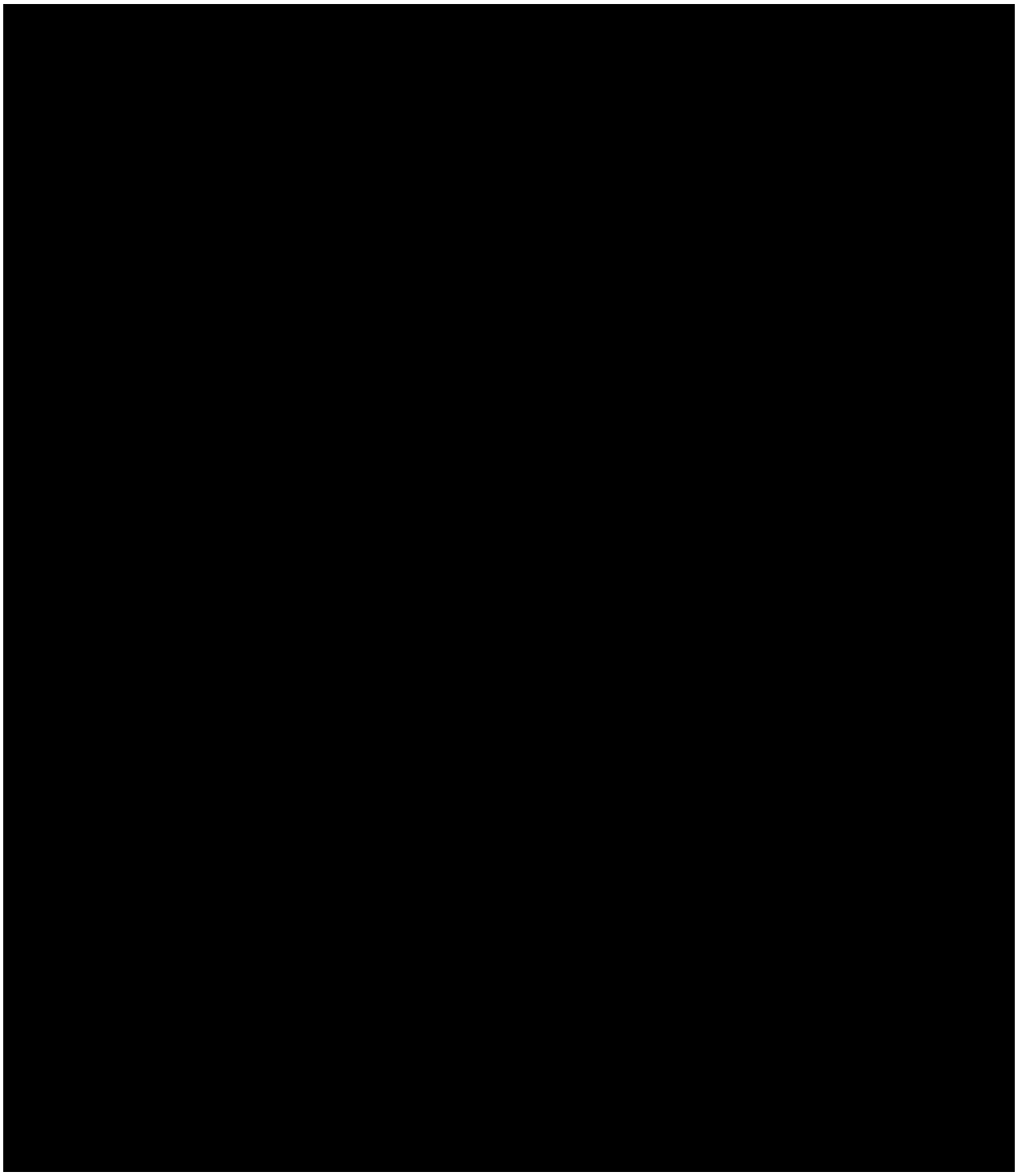
5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP: *The percentage N (%) of patients with Treatment Emergent Adverse Events (TEAE).*









6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatment to be administered, assignment of treatment groups, and selection of doses, refer to CTP Sections 3 and 4. This phase II trial will be performed as a double-blind, placebo-controlled comparison of BI 1015550 18 mg b.i.d over 12 weeks in IPF patients treated with antifibrotic treatment or not treated with antifibrotic treatment at baseline.

Eligible patients will be randomised in the trial in a 2:1 ratio (BI 1015550 18 mg b.i.d/ placebo b.i.d) and will be treated for 12 weeks. The randomization will be stratified by background of antifibrotic treatment. After the patients have terminated their treatment period, they will enter a 1-week follow-up period. Follow up visit will be the End of Trial.

It is planned to randomize a maximum of 150 patients, with at least 60 patients in each stratum with/without antifibrotic treatment at baseline.

Section 1.2.4 of CTP: *The Residual Effect Period (REP) of BI 1015550 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.*

Section 7.2.5 of the CTP: *The analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.*

For the analysis of adverse events (AEs), the following study phases are defined:

Table 6.1: 1 Flow chart of analysis phases

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**Pbo**, **18 mg BI**, respectively	Date/time of first administration of study drug	12:00 a.m. on the day after last administration of study drug + REP (7 days) or 12:00 a.m. on the day after patient's trial termination date, whichever occurs earlier
Follow-up[1]	**F/U Pbo**, **F/U 18 mg BI**, respectively	12:00 a.m. on the day after last administration of study drug + REP (7 days)	12:00 a.m. on the day after patient's trial termination date

[1] Follow-up phases might not exist, e.g. if the patient's trial termination date is within 7 days after last administration of BI 1015550.

For treatment interruptions, the occurrence of AEs between the start of interruption and re-start of treatment will be assigned to the randomized treatment. These cases will be flagged in the safety listings as occurring during the off-treatment period.

Reporting of AEs will be stratified by background of antifibrotic treatment and combined for the two strata.

AEs will be displayed by study treatment (BI 18 mg b.i.d and Placebo), and will be provided in the report:

Section 15.3 and Appendix 16.1.13.1.8 (for ClinicalTrials.gov and EudraCT) of the CTR displays. In addition, the total over all on-treatment phase included in this analysis (**"Total"**) will be provided.

In Section 15.4 and Appendix 16.2 (Listings) of the CTR displays, screening and follow-up periods will be included and no totals will be provided.

Tables of vital signs, laboratory values and other safety-relevant data will present results of on treatment phase.

For the efficacy analyses (Section 7.4 and Section 7.6) the on treatment phase will be considered taking into account the intercurrent events (see Section 5.1). Efficacy endpoints measured later than end of treatment + REP (7 days) will be discussed at MQRM/BRPM. The analyses is planned to be performed once all patients have completed the study or early discontinued.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of violations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the MQRM, at the Trial Oversight Meeting prior to DBL or at the BRPM. At these meetings, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected 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 "Identify and Manage Important Protocol Deviations (iPD) (3).

If any iPDs are identified, they are to be summarised into categories and will be captured in the MQRM/BRPM minutes or the TOM minutes and additionally via an accompanying Excel spreadsheet. The iPDs may lead to exclusion of subjects from analysis sets (e.g. the Per Protocol Set). The documentation of the iPD categories and how to handle iPDs in the analysis is included in the DV domain specifications and stored within the TMF in EDMS. If the data show other iPDs, this domain will be supplemented accordingly.

Non-important COVID-19 related PDs will only be listed.

A summary of iPD decisions will be provided in the decision log.

6.3 SUBJECT SETS ANALYSED

The subject sets for statistical analysis will be used as defined in the CTP, Section 7.2.1. Patients will be analyzed based on the trial medication they have actually received, except for the ES and RS.

Additionally, the ECG set is defined.

ECG Set (ECGS): This patient set includes all patients in the TS who do not have artificial cardiac pacemakers and have at least one on-treatment value for at least one ECG endpoint.

Table 6.3: 1 Subject sets analysed

	Patient set						
Class of endpoint	ES	RS	TS	ECGS	FAS	PPS	PKS
Disposition		X					
Exposure			X				
IPDs	X						
Demographic/baseline			X				
Primary endpoint					X	X	
Secondary endpoint			X				
Other safety/tolerability			X				
ECG endpoints				X			
[redacted]							
[redacted]							

ES: Enrolled set, RS: Randomised set, TS: Treated set, ECGS: ECG set, FAS: Full analysis set, PPS: Per-protocol set, PKS: PK set.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Withdrawals

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

6.6.2 Efficacy data

6.6.2.1 Primary efficacy endpoint

Missing data for primary analysis (continuous endpoint) will not be imputed. The MMRM approach used for primary analysis (see Section 7.4.1) allows for missing data, assuming they are missing at random. Even patients with only one post-baseline assessment can be included in the model and can therefore participate in variance estimation. The statistical model assumes that patients who dropout would have behaved similarly to those who remained in the study. Hence, the primary analysis will be performed using the while on treatment strategy (see Section 5.1).

Sensitivity analyses will be conducted to investigate the potential effect of missing data on the results of the primary analysis. The analysis will be performed using the treatment policy strategy for handling intercurrent events (see Section 5.1).

Details about implementation into the statistical analysis are described in Section 7.4.3.

6.6.3 Safety data

Missing values of safety related data will not be imputed. The only planned imputation is related to AE dates, and start/stop dates of concomitant medication.

Missing or incomplete AE dates are imputed according to BI standards (4).

Concomitant therapies: In case of (partially) missing start and end dates of concomitant medication, the dates will be imputed to enable subsequent calculation (but not for display) by the "worst case" approach, so that the extent of exposure to the concomitant therapy is maximal, i.e. the first day (month) of the month (year) for incomplete start dates and the last day (month) of the month (year) for incomplete end dates.

ECG

If single cardiac cycles of an ECG are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

If baseline is missing, a QTcF/QT interval > 500 msec at any time on treatment will be a notable finding.

The handling of missing values regarding the overall ECG interpretation is described in additional Section 10.4.2.

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as data collected at visit 2 prior to administration of first dose of study medication (BI 1015550 or Placebo), or screening data if visit 2 data are missing. For laboratory safety measurements, the last assessments / measurements taken prior to start of treatment will be considered as baseline.

Measurements taken after start of administration of trial treatment will be considered on-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. 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 and efficacy 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: 2, Table 6.7: 3.

Repeated and unscheduled efficacy and safety measurements (except for laboratory data) will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement. For handling of laboratory measurements see also Section 7.8.2.

Only one observation per time window will be selected for statistical analysis at a particular visit. For non-PFT measurements, 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. For PFT measurements, the scheduled PFT measurement that is closest to the protocol planned visit day will be selected for analysis. If a scheduled measurement is not available, a measurement from unscheduled visits will be selected for analysis (e.g. the value which is closest to the protocol planned visit day). Other rules mentioned for the non-PFT measurements also applies here. In addition, for ECG measurements, the value for analysis will be selected in the same way as for the PFT measurements.

Table 6.7: 1 Time window for assignment of efficacy, safety lab, and vital signs measurements to visits for statistical analysis of the double-blind treatment period

Visit number/ name	Visit label	Planned day	Time window (Days)				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
V1/V2	Baseline	Day 1	n/a	n/a[1]	1	n/a[1]	1
V3	Week 2	Day 15	+/- 3	12	18	2	19
V4	Week 4	Day 29	+/- 7	22	36	20	42
V5	Week 8	Day 57	+/- 7	50	64	43	70
V6 End of Treatment (EoT)	Week 12	Day 85	- 7/+4	78	89	71	EoT_{end} [2]
V7 End of Trial	EoT + 1 week	EoT + 7 days	+ 3	EoT + 7 days	EoT + 10 days	EoT_{end} + 1 day	End of Trial visit date

Days are counted relative to the day of first treatment, which is defined as Day 1.
[1] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of administration 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.
[2] The end of time window equals:
maximum[day 89, last treatment day +1], for patients who completed the trial medication.
maximum[day 89, End of Treatment visit day +1], for patients early discontinued from the trial medication.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI standards "Standards for reporting of clinical trials and project summaries" (6), [redacted]

The individual values of all patients will be listed, sorted by antifibrotic stratum (AF/non-AF), study treatment (placebo/BI 1015550), patient number and visit (if visit is applicable in the respective listing). AE listings will be sorted by antifibrotic stratum and study treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 of the CTR.

For end-of-text tables, the set of summary statistics of continuous variables ([redacted] is:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

[redacted]

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 (%). 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.

Units of variables should be given in the titles or column/row descriptors in square brackets (e.g. [mg]).

In addition to the standard disposition tables subject enrolment and study conduct will be analysed relative to COVID-19 disruption.

The primary analysis will not consider country level evaluations due to small number of patients per participating centers and countries.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS. The data will be summarised by antifibrotic stratum and study treatment, and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the CTR, based on the TS.

Concomitant diseases and concomitant non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary. The coding version number will be displayed as a footnote in the respective output.

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 will be summarized with frequency and percentage of patients by ATC3 class and preferred name. Summaries will be presented for concomitant medication starting any time prior to start of trial treatment and starting any time during the on-treatment period (cf. Section 6.1).

Concomitant use of non-drug therapies will be summarized with frequency and percentage. Summaries will be presented for concomitant non-drug therapies starting any time prior to start of trial treatment and starting any time during the on-treatment period (cf. Section 6.1).

Restrictions regarding concomitant treatment at the study periods are defined in Section 4.2.2.1 of the CTP.

The relevance of the concomitant therapies to the evaluation of PK will be decided no later than at the BRPM.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned according to percentage of patients meeting the compliance target, %compliance, and categories of %compliance. Descriptives will be provided per visits and overall (see Section 5.4.2).

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint

The primary endpoint will be analysed in combination with 'while on treatment' strategy of handling intercurrent events (see Section 5.1).

Refer to Section 7.2.2 of the CTP for a description of the statistical analysis for the change from baseline in FVC at 12 weeks (in mL).

The adjusted mean FVC [ml] change from baseline at 12 weeks and its standard deviation will be obtained from MMRM for the placebo and treatment groups. The estimate of the placebo group will be combined with prior historical data for placebo group to derive its respective posterior distribution. Similarly, the estimates of the BI 1015550 treatment group will be combined with a vaguely-informative prior to derive the respective posterior distribution for BI 1015550 treatment group. These posterior distributions will be used to evaluate the posterior FVC [ml] difference change from baseline between BI treatment and placebo.

SAS code for the MMRM model will be based on the following structure:

```
PROC MIXED DATA=alldat cl method=reml;
  CLASS visit trt subject;
  MODEL chg =  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;
```

In the event of model non-convergence, the methods described in Section 10.5 will be attempted (in order) to overcome it.

The prior derivations for placebo and BI treatment were obtained separately for antifibrotic and non-antifibrotic strata (cf. Section 7.2.2.1 of the CTP) by using RBesT package version 1.6.1, and R Software version 4.0.1, as follows:

- for the placebo group of patients (mixture normal distributed prior with 3 informative and 1 vaguely informative components)
  - non-antifibrotic stratum:

$$\mu_{P,nAF} \sim 0.26\mathrm{N}(-73.8, 15.5) + 0.19N(-71.7, 38.8) + 0.05N(-72.5, 83.8) + 0.5N(-73.0, 315.7)$$

- antifibrotic stratum:

$$\mu_{P,AF} \sim 0.26\mathrm{N}(-19.7, 15.7) + 0.22N(-17.0, 40.2) + 0.02N(-13.5, 103.4) + 0.5N(-19.0, 385.7)$$

- for the BI 1015550 treatment group (vaguely-informative prior, this prior does not consist of a mixture of priors)
  - non-antifibrotic stratum: $\mu_{BI,nBTX} \sim \mathrm{N}(-73.0, 315.7)$
  - antifibrotic stratum: $\mu_{BI,BTX} \sim \mathrm{N}(-19.0, 385.7)$

The posterior distributions for the FVC [ml] difference in change from baseline between BI treatment and placebo will be implemented following derivations in additional Section 10.6. The posterior median and 95% credible intervals will be reported. The posterior probabilities that the difference is higher than a range of boundary values, e.g. 0, 10, 20, 30, 35, 40, 50, 60, 70 ml will be evaluated.

[redacted]

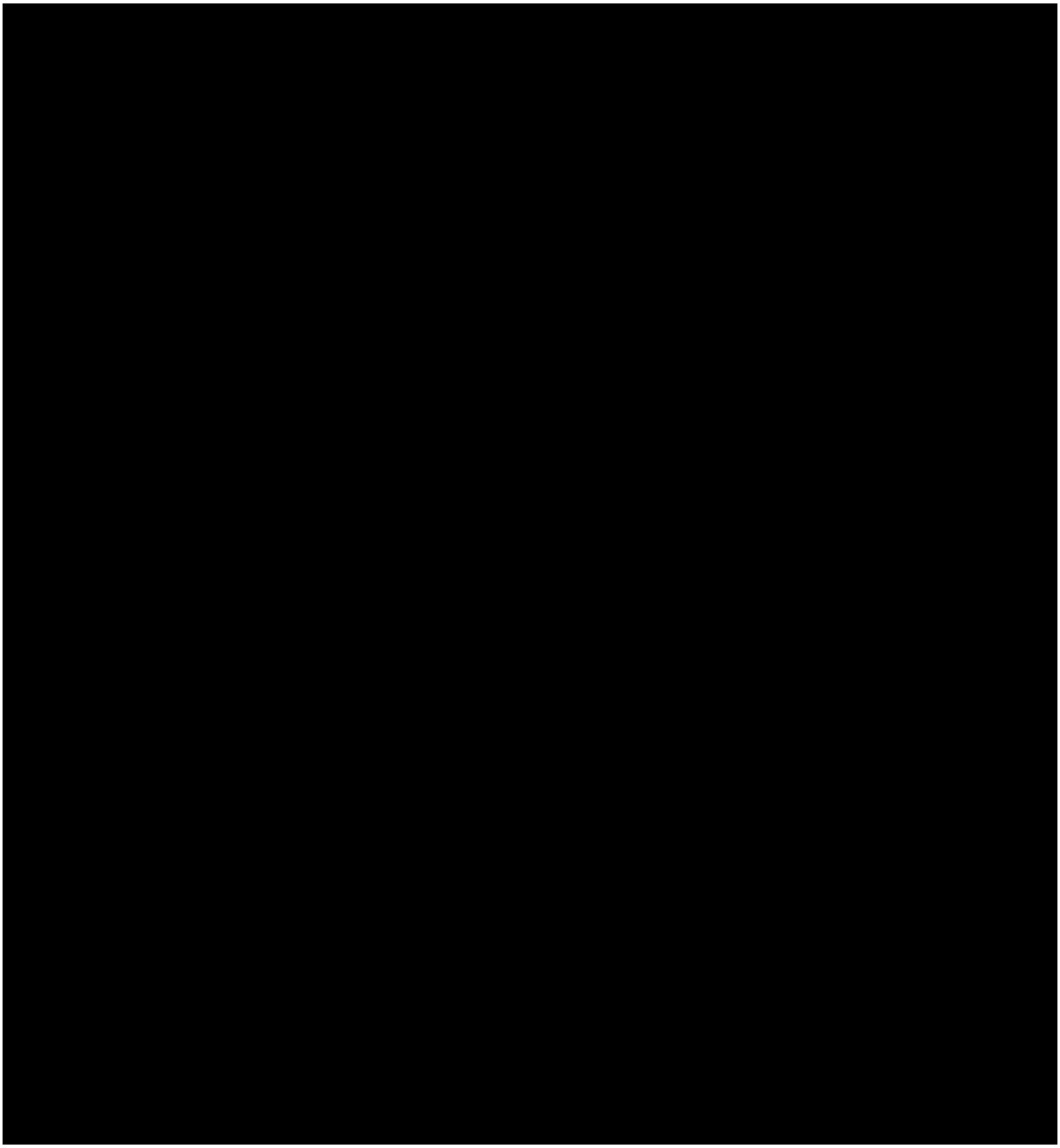
7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 Secondary endpoint(s)

The analysis of the secondary endpoint percentage N (%) of patients with Treatment Emergent Adverse Events (TEAE) is described in Section 7.2.5 of the CTP.



7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of each drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS following BI standards. No hypothesis testing is planned. All safety analysis will be performed on treatment phase.

7.8.1 Adverse Events

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

Statistical analysis and reporting of adverse events will be conducted separately for the patients on antifibrotic treatment and the patients not on antifibrotic treatment and combined for the two strata.

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.

For further details on summarization of AE data, please refer to "Analysis and presentation of adverse event data from Clinical Trials" (9) and "Handling of missing and incomplete AE dates" (4).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 7 days after last drug intake will be assigned to the randomised treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + 7 days will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

If only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first BI 1015550 administration will be assigned to the on-treatment phase.

An overall summary of AEs will be presented by antifibrotic stratum and study treatment, and in total. This overall summary will comprise summary statistics for the class of AESIs.

CTP: *The following are considered as AESIs:*

- *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*
  - *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.*

- *Vasculitis*

  In this trial protocol vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad).

The investigator had to classify on the eCRF whether an observed AE was an AESI or not. Only those AEs that are indicated by the investigator as AESI in the eCRF will be analysed in this category.

According to ICH E3 (10), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation).

The frequency of patients with AEs will be summarised in total, and by antifibrotic stratum, study treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with serious AEs, patients with Acute IPF exacerbations, patients with AESIs, patients with fatal AEs, patients with discontinuations due to AEs. Separate tables will also be provided by safety topics (overall AEs, fatal AEs, and serious AEs), see list of safety topics in additional Section 10.9.

In addition, the patients with AEs will be summarised by treatment, worst intensity, causal relationship, primary system organ class (SOC) and preferred term (PT).

The SOCs and PTs will be sorted by descending frequency (within SOC). The MedDRA version number will be displayed as a footnote in the respective output.

The frequency of patients with AEs such as Suicidal Risk (assessed by C-SSRS) or self-injurious behavior will also be summarised.

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 will also be summarised.

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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (11). Note that data from the central Laboratory will be used for all displays described below, unless otherwise specified.

The analysis of continuous laboratory parameters will be based on normalised values, which means transforming to a standard unit and to a standard reference range. The last assessment before the first randomized treatment at visit 2 is chosen as the baseline value.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be based upon normalised values and provided by visit, including summaries of the last value on treatment, the minimum and maximum value on treatment.

Laboratory values will be compared to their reference ranges; a shift table will be provided for the number of patients within and outside the reference range at baseline and at the last measurement on treatment. This analysis will be based on standardized laboratory values.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted values and converted reference ranges using SI lab 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.

All individual laboratory data will be listed. Values outside the reference range will be flagged. In addition, potentially clinically significant values will be flagged in the listing.

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, and the frequency of patients with AST and/or ALT ≥ 10xULN, will be displayed. This analysis will be based on standardized laboratory values. A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed or total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥ 3xULN and total bilirubin < 2xULN).

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

Results from the pregnancy test will only be listed.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse 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.

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

12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

The evaluation of ECG data will be based on the ECGS. The ECG analysis will be conducted separately for the patients on antifibrotic treatment and the patients not on antifibrotic treatment and combined for the two strata.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. For QTcB and RR, only listings will be provided. Occurrences of values above thresholds (refer to the ECG endpoint description in Section 5.3) will be flagged.

Categorical Endpoints

For the categorical endpoints, frequency tables will be provided. Frequencies of the increases in QTcF and QT intervals above thresholds (refer to Section 5.3) such as 450 msec, 480 msec, and 500 msec between baseline and on-treatment values will be displayed in two-way shift tables by antifibrotic strata and per treatment.

Categorical endpoints will also include morphological findings that might be attributable to treatment. In particular, new onsets of findings not present at baseline will be explored. A morphological finding observed on treatment that was not reported at baseline will be categorized as a 'new onset' of this finding.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding values will be presented graphically.

Patients in the TS who have notable findings but are excluded from the ECG Set will be listed in separate listings which will be presented in Section 15 of the CTR.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, HR, QT, PR and QRS by antifibrotic strata, per treatment and time point. The mean and SD for the absolute values and changes from baseline will also be displayed graphically.

7.8.5 Others

7.8.5.1 Physical examination incl. body weight

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE (if they occurred on treatment) and will be summarised as such.

Special emphasis is given to body weight once at each study visit. Statistical analysis will be in line with the analysis applied for vital signs: Descriptive statistics including change from baseline and percent change from baseline will be calculated by study treatment and by planned time point. Time profiles of mean and SD will be provided and displayed graphically by study treatment. Tables and figures will be provided based on the TS. Listings of patients with weight loss categories <5%, 5-10%, > 10%, and any weight increase, will be provided.

For findings in further parameters of the physical examination, no separate listing or analysis will be prepared.

7.8.5.2 C-SSRS category types

All C-SSRS reports of suicidal ideation type 1, 2, 3, 4 and 5, and group type 1-3 and 4-5, will be summarized at each study visit. Shift tables of type 1-3 to 4-5 per visit will be provided.

7.8.5.3 Time to first onset of adverse event diarrhoea

Descriptive statistics for the time to first onset [days] of AE diarrhoea will be obtained using the Kaplan-Meier approach. Frequency for categories of time to onset will also be provided with cut-off days: 31, 61, and 91.

Number and duration of AE episodes of diarrhoea will also be presented.

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, PD and iPD:

Frequency of the patient with missing visits or early discontinuation due to COVID-19 will be listed. PDs and iPDs related to COVID-19 will be also listed if any.

In addition, if there is any case, COVID-19 infection will be reported.

This study started after the COVID-19 disruption (start date chosen to be 1st March 2020). Therefore, evaluations of efficacy or adverse event assessments by prior versus post disruption are not applicable in this trial.

7.10 HANDLING OF DMC ANALYSES

An external DMC, independent of the trial and project teams, was set-up to review all available safety data as well as selected efficacy data in an unblinded manner at regular intervals following first-patient-in. A separate DMC SAP which describes the analyses required for assessment by the DMC was produced. Further details were provided in a DMC charter.

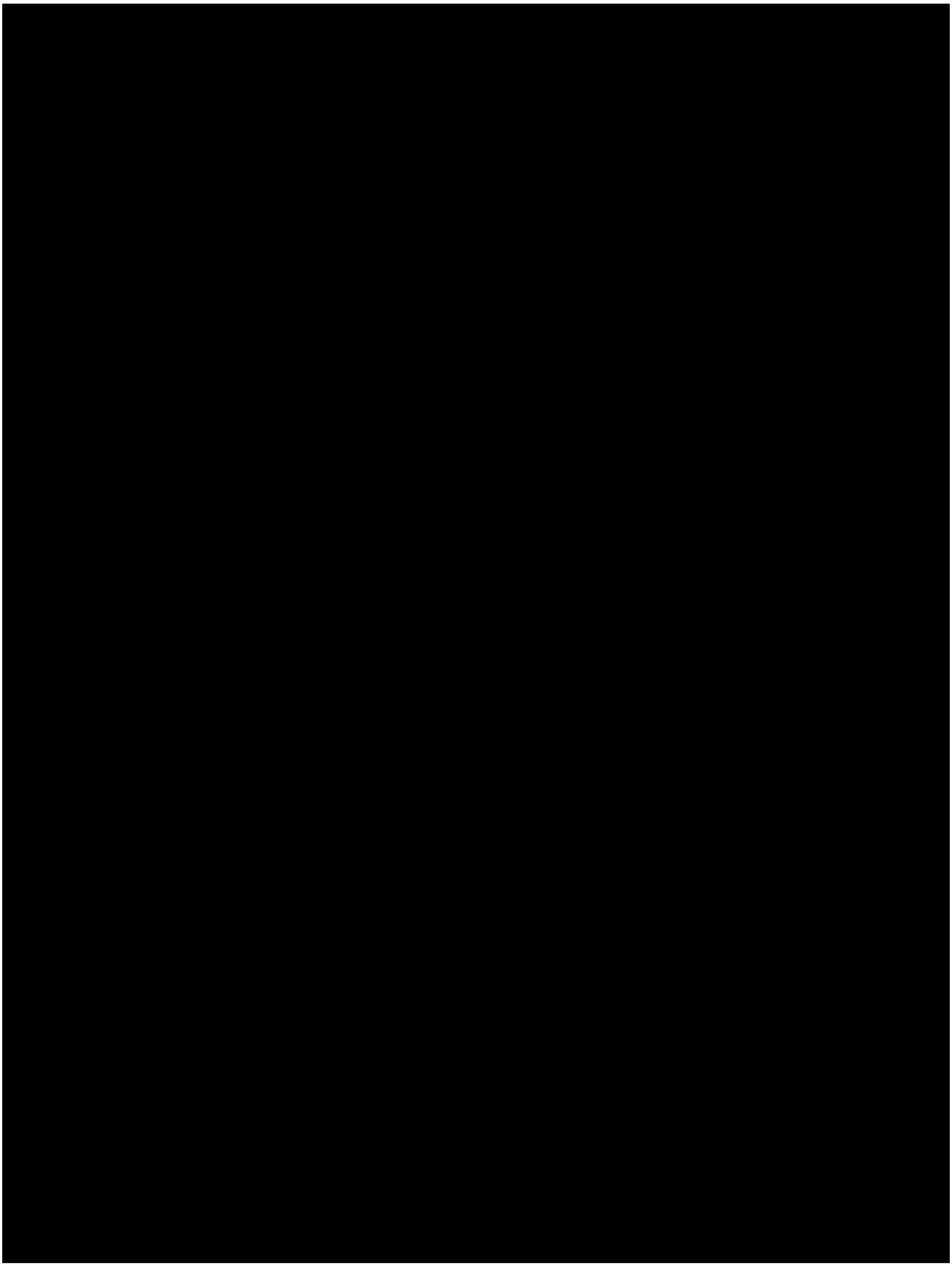
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

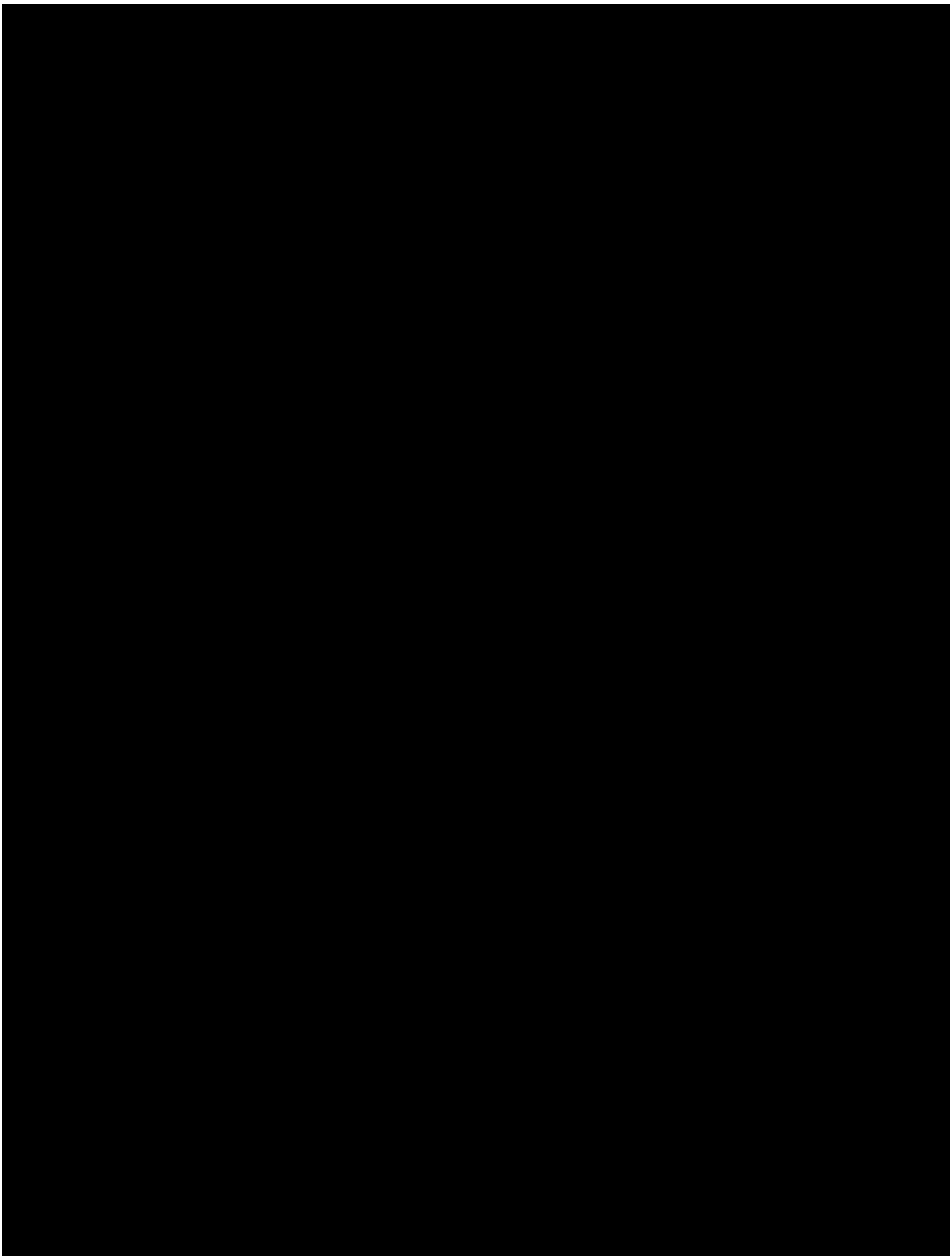
Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure 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.

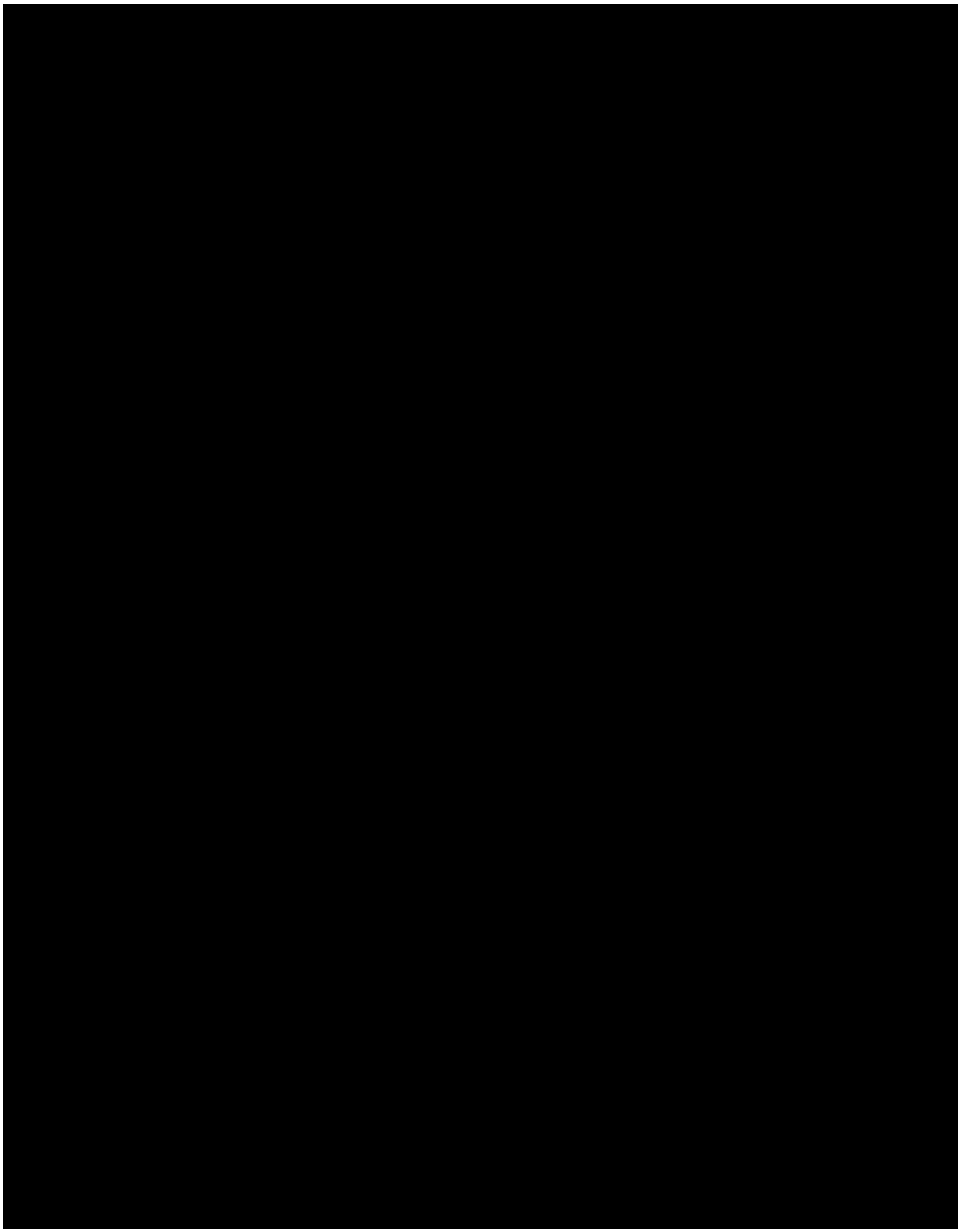
The treatment information will be released to produce key efficacy and safety results at the time of preliminary DBL. The access to the data will not be restricted to the project and trial team members after preliminary DBL, and therefore no logistic and access plan is needed.

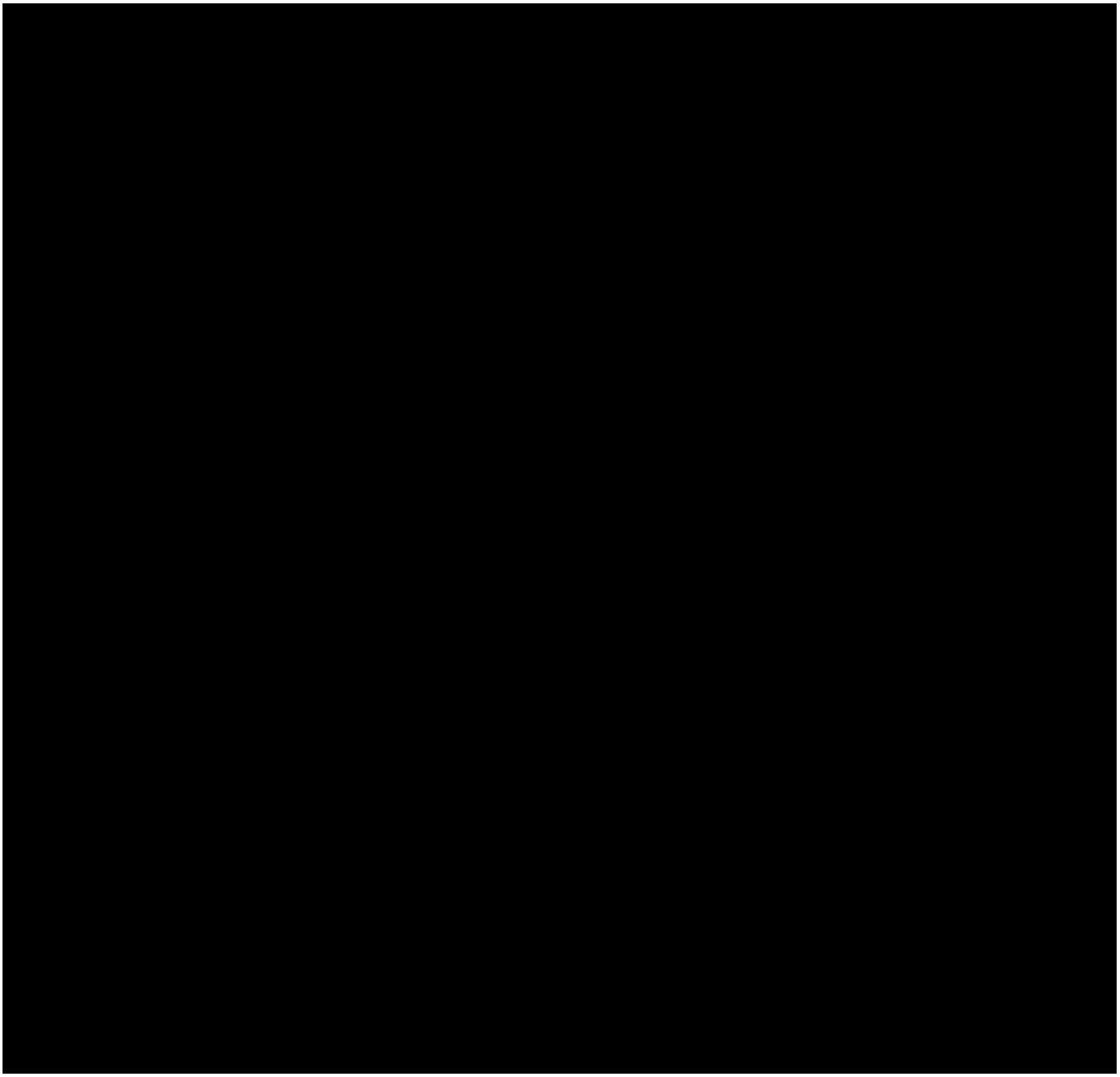
9. REFERENCES

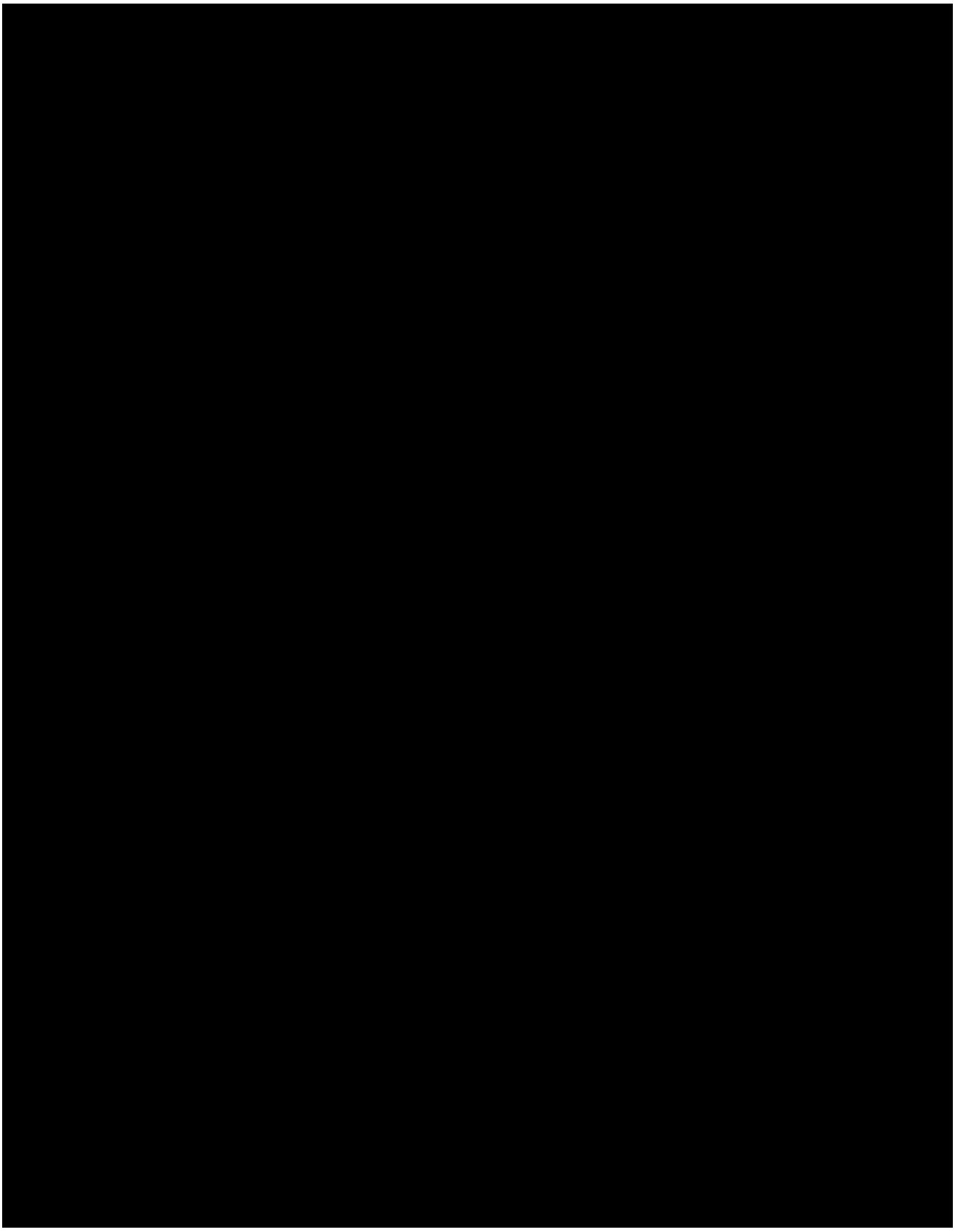
1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, KMED.
3.	*001-MCS-40-413:*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

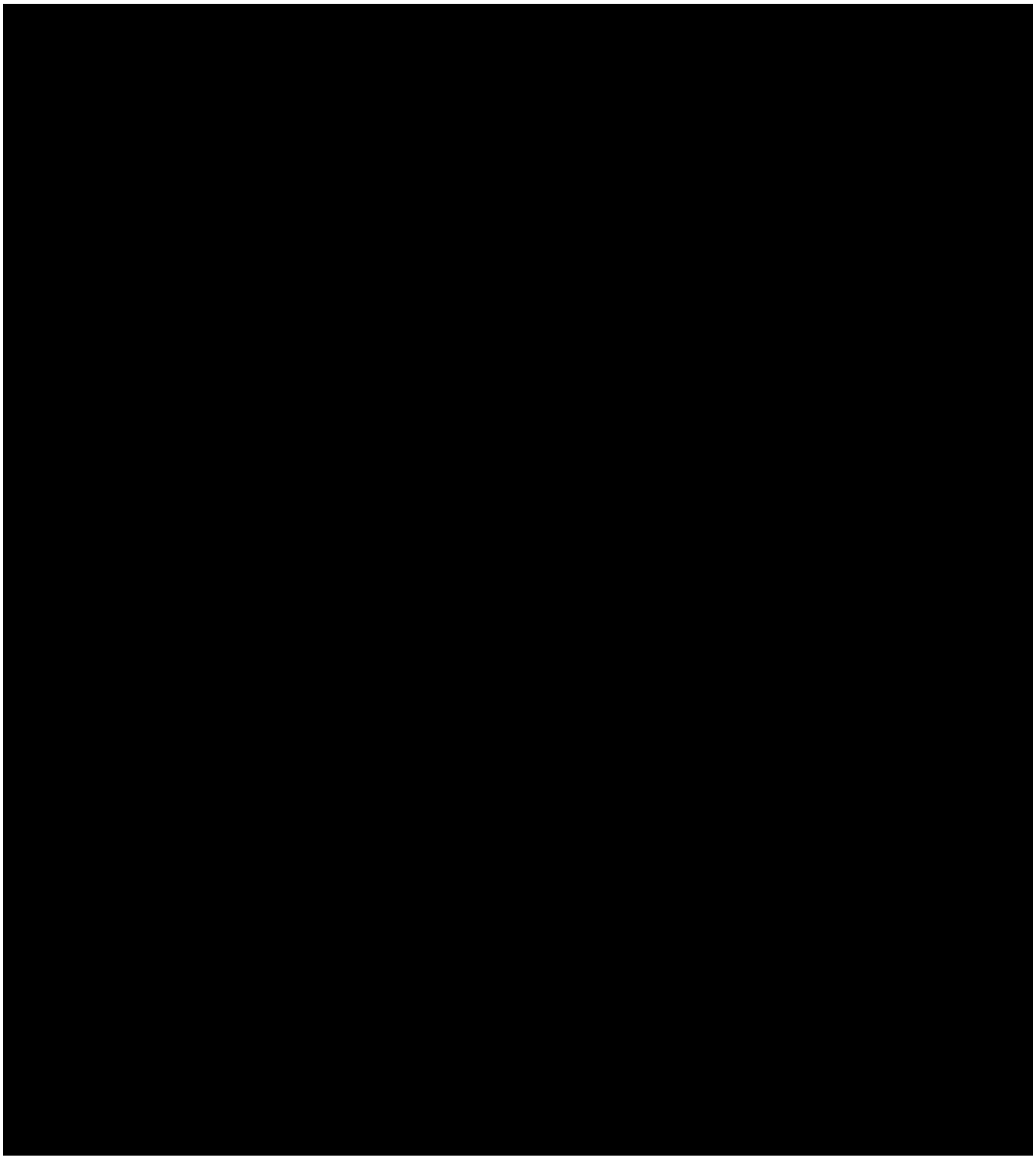












11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	08-OCT-2021	[redacted]	None	This is the final TSAP