Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

c35421742-01

BI Trial No.:	1434-0009
Title:	BI 764198 efficacy and safety in prevention/progression of ARDS and ARDS-related complications secondary to COVID-19 (ACTION ON COVID-19)
BI Investigational Product(s):	BI 764198
Responsible trial statistician(s):	[redacted] Fax:
Date of statistical analysis plan:	08 APR 2021
Version:	1

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
BRPM	Blinded Report Planning Meeting
BES	Biopsy Evaluable Set
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DM&SM	Boehringer Ingelheim Data Management And Statistics Manual
DRA	Drug Regulatory Affairs
DM	Diabetes mellitus
DMG	Dictionary Maintenance Group
EDC	Electronic Data Capture
EMEA	European Agency For The Evaluation Of Medicinal Products
FAS	Full Analysis Set
HPT	Hypertension
ICH	International Conference On Harmonisation
IPD	Important Protocol Deviation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary For Regulatory Activities
MCPMod	Multiple Comparison Procedure and Modelling
MQRM	Medical Quality Review Meeting
MMRM	Mixed Effect Model Repeated Measurement
PASI	Psoriasis Area Severity Index
PCR	Pol$_{y\,m}$ erase Chain Reaction
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
PV	Protocol Violation
QI	Lower Quartile

Term	Definition / description
Q3	Upper Quartile
REP	Residual Effect Period
RS	Randomised Set
SA	Statistical Analysis
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
sPGA	Static Physician's Global Assessment
TOM	Trial Oversight Meeting
ToC	Table of Contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9 i11, 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 trial data is stored in the BI Rave (BRAVE) database system.

S A S® Version 9.4 will be used for analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This section is not applicable as no change has been made.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Please refer to protocol.

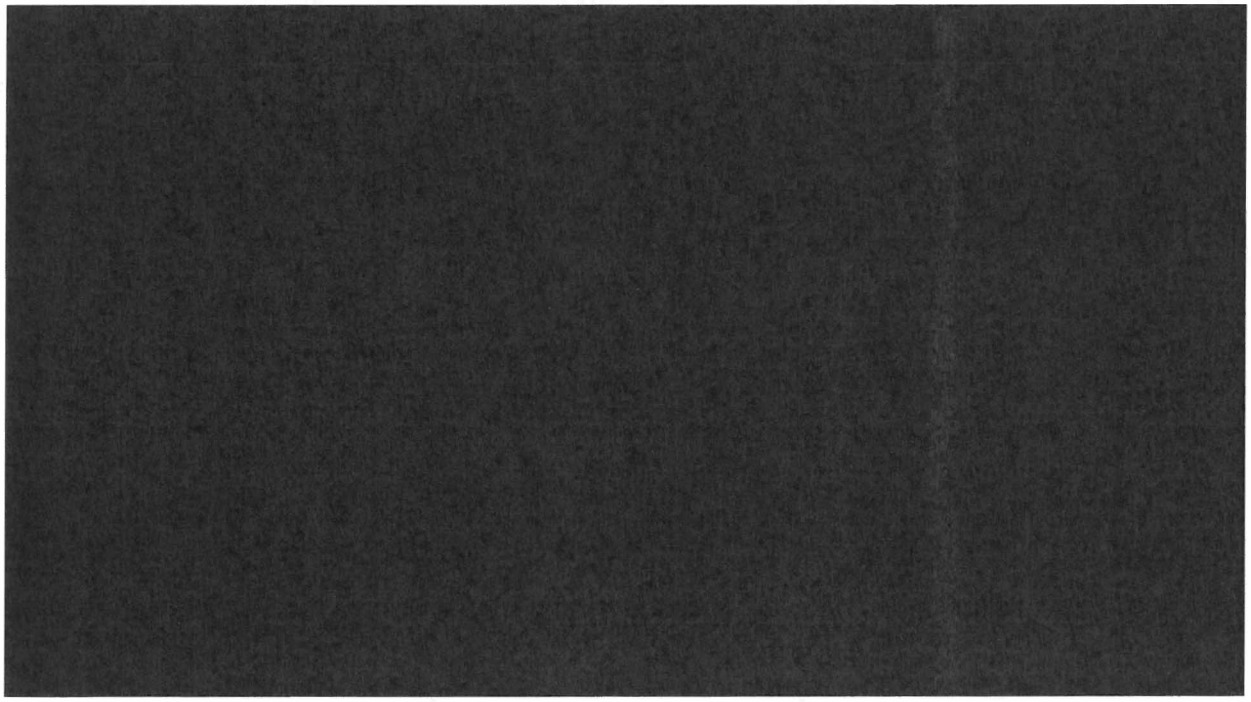
5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 Secondary endpoints

Please refer to CTP.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Patients will be randomised 1: 1 to BI 764198 treatment group or placebo.

The assignment of treatment groups will be based on randomization for randomized patient set as defined in Section 6.3.

The following study periods based on actual start and stop dates of study treatment administration are defined:

Table 6.1: 1 Definition of treatment periods

Analysing Treatment Period	Start Date (including)	Stop Date (including)
Screening	Day of informed consent	Date of first administration of study medication -1 day (It could be the same day of informed consent)
On-treatment period	Day of first administration of study medication	[redacted]
Post-treatment	[redacted]	Last contact date

For detailed rules for assigning AEs to these time periods, please refer to Section 7.8. 1.

6.2 IMPORTANT PROTOCOL DEVIATION

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. Patients with important PDs that could potentially impact the evaluation of the primary endpoint(s) will be excluded from PPS, if applicable.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. Important PDs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviations will be discussed at the Blinded Report Planning Meetings (BRPMs).

If the data show other important PDs, this table will be supplemented accordingly at BRPMs or through team review of the manual PD log. The decision whether a subject will

be excluded from the analysis will be made at the final BRPM prior to Database Lock (DBL).

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 SUBJECT SETS ANALYSED

There are 4 patient sets defined in this trial:

- Screened Set (SCR)

This set includes all patients with signed informed consent. The screened set will be used for disposition summaries.

- Randomised Set (RS)

The RS includes all patients who signed the informed consent form and were also randomised, regardless whether the patient was treated with trial medication or not. The randomized set will be used for analysis of important protocol deviations (IPDs).

- Full Analysis Set (FAS)

The FAS includes all patients in the RS who received at least 1 dose of trial medication. The FAS is used for efficacy and safety analyses.

- Per Protocol Set (PPS)

The PPS includes all patients from the FAS without IPDs leading to exclusion from per protocol analysis. The PPS is used for efficacy sensitivity analyses only if the number of patients with IPDs is> 10% of total number of patients in FAS.

Analyses will be performed as outlined in Table 6.3: 1.

Table 6.3: 1 Patient sets analysed

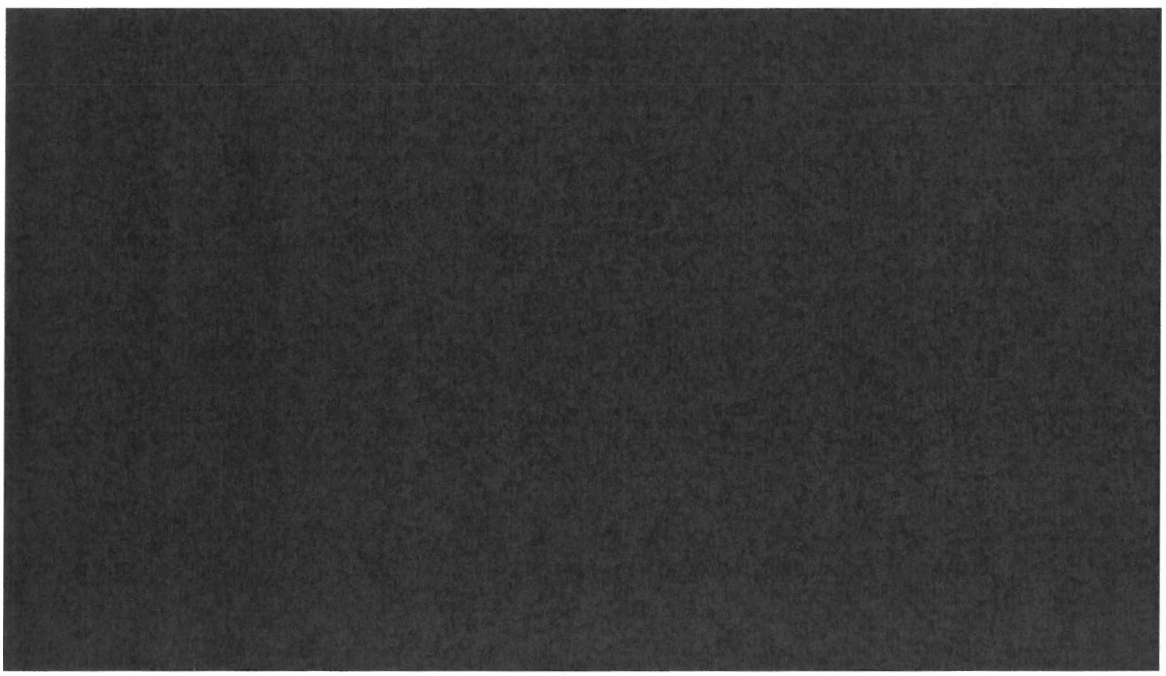
	Patient set			
Class of endpoint	Screened set	Full analysis set	Randomised set	Per Protocol Set
Efficacy analysis		**X**	si	02
Safety analysis		**X**		
Patients disposition	**X**			

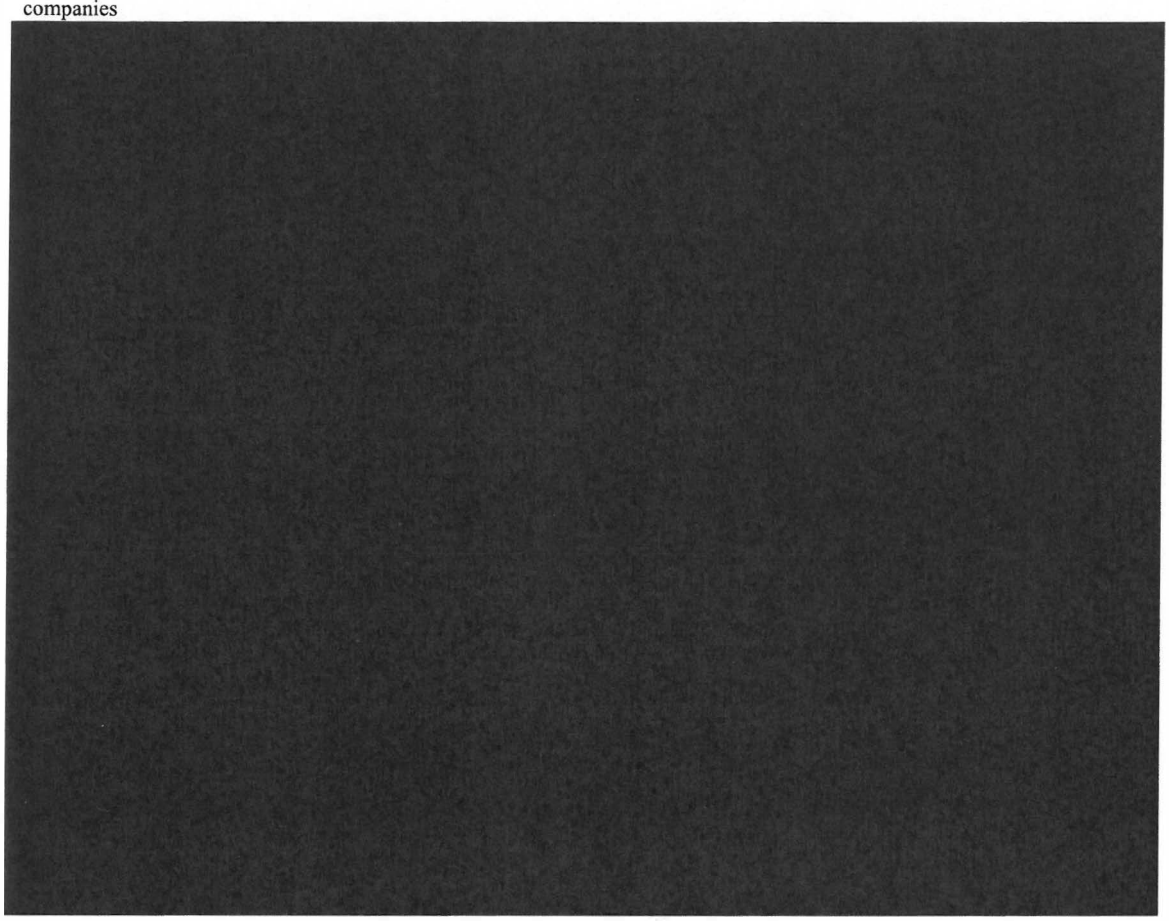
[1] S = Sensitivity analyses

[2] 0 : Optional

The FAS will be used for the efficacy analyses following the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e., efficacy analyses will be analysed as randomised using the FAS.

If a patient receives incorrect medication for the entire treatment period, efficacy will be analysed as randomized and safety will be analysed as treated. If a patient receives incorrect medication for part of the treatment period, such cases will be discussed in the RPM.





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

All patients will be followed to collect necessary efficacy and safety information, even if patients discontinue study medication prematurely.

For patients who miss WHO clinical progression scales, imputation will be performed using data from other sources if available, e.g., oxygen use, ventilation use, etc.

For patients who miss start date and/or end data of hospitalisation, ventilator use and oxygen use, data will be imputed based on available information on the eCRF page of WHO Clinical Progression Scales.

If a patient dies while hospitalised, the number of days of hospitalisation will be imputed until day 29 (i.e, 28 days of hospitalisation). If a patient dies while in ICU, the duration of ICU stay will be imputed until day 29. For patients who die before day 29, WHO progression scale will be imputed as 10 for all remaining visits: in addition, duration of oxygen (or ventilation) use will be imputed until day 29.

For patients who are discharged before day 29, WHO progression scale will be imputed using the last available observation if no additional data is available after discharge.

For patients who discontinue treatment early, if the patient is on oxygen/ventilation before discontinuation, the number of days on oxygen/ventilation will be imputed until day 29. If the patient is not on mechanical ventilator at the last observed assessment, the number of ventilator free days will be imputed until day 29.

For missing or incomplete AE dates, BI internal procedures and guidelines will be followed Q,]J_. The same philosophy will be applied to missing concomitant medication dates (where applicable), and dates of study medication discontinuation, and trial completion date.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For efficacy endpoints, baseline is defined as the pre-treatment observation at Visit 2. If Visit 2 is missing, then Visit 1 will be used for baseline.

For laboratory safety measurements, the last measurements taken prior to the treatment start will be considered as baseline.

The visit schedule with accompanying details can be found in Flow Chart 1 in CTP. Measurements taken after start of treatment will be considered either on- or off-treatment values based on definition in Table 6.1: 1.

7. PLANNED ANALYSIS

Descriptive statistics for continuous variables will be N (number of patients with non-missing values), mean, standard deviation (SD), minimum, median, and maximum. In general, means, medians, SDs, will be presented to one more decimal place than the raw data. Minimums and maximums will be presented to the same number of decimal places as the raw data.

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 group. Percentages will be rounded to one decimal place. The category "missing" will be displayed only if there are actually missing values. Percentages will be based on all patients in the respective patient set no matter whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic parameters collected and to be presented include, but are not limited to, the following:

- Sex (Male, Female)
- Race and ethnicity (as defined in the eCRF)
- Region
- Age [years]
- Height [cm]
- Weight [kg] (continuous)
- Body mass index [kg/m^2] (defined as weight [kg]/(height [cm]/ 100)^2)
- Smoking history (Never-smoked, Former-smoker, Currently smokes)
- Alcohol History (Never drink, Former-drinker, Currently drinker)
- COVID-19 Symptom
- SARS-CoV-2 Seropositive at baseline
- WHO clinical progression scale at baseline
- Clinical Frailty Scale
- Blood type
- Cardiac disease disease (Yes, No)
- Hypertension (Yes, No)
- Respiratory disease (Yes, no)
- Diabetes mellitus (Yes, No)
- Kidney disease (Yes, No)
- Coagulation parameters (Normal, Abnormal)
- Infection date to admission (< 7 days, 7 days)

- Time to drug intake from hospitalization(< 24 hours, 24 hours)
- Duration of symptoms before hospitalization

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be summarised descriptively. The frequency [N (%)] of patients with different concomitant diseases (baseline conditions) will be presented. The concomitant medications taken at baseline and those taken while on treatment will be coded using the World Health Organization (WHO) Drug coding dictionary. These will then be summarized by standardized drug grouping and listed by patient with each medication taken.

Concomitant non-Drug Therapies will also be summarized descriptively.

7.3 TREATMENT COMPLIANCE

This section is not applicable because study medication is not dispensed directly to patients and instead is administered to hospitalized patients by a site staff member. Any missed doses are recorded in the eCRFs.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary Analysis

The primary objective is to evaluate the difference in proportions of patients alive and free of mechanical ventilation at Day 29 with BI 764198 and placebo. The primary analysis of the primary efficacy endpoint will be performed on the full analysis set (FAS) following the treatment policy, i.e., patients who initiate other therapies during the treatment period or patients who terminate the study medication prematurely will be followed up for data collection until the time point of interest and all these data will be included in the analysis.

A logistic regression model will be used including covariates of treatment, WHO clinical progression scale at baseline, age, creatinine at baseline, and duration of symptoms before hospitalization. The point estimate, standard error and confidence interval for the risk difference in proportions will be derived based on the estimates from the logistic regression model. The fitted logistic regression model will be used to predict the probability of response for every subject in the study as if they had received treatment or placebo, and the average in the difference of response probabilities between treatment and placebo will be calculated. For primary analysis, nominal p-value for the risk difference will be provided.

With a data set of n subjects, define a binary response vector for n patients alive and free of mechanical ventilation at Day 29 as $Y = (y_1, y_2, \cdots, y_n)^T$, and covariate matrix $X = [x_1, x_2, \cdots, x_n]^T$, where x_i indicates a covariate vector that consists of treatment, severity grade at baseline, age, creatinine at baseline, and duration of symptoms before hospitalization for ith subject. A logistic regression model assumes $\log \frac{P(y_i=1 \mid x_i)}{1-P(y_i=1 \mid x_i)} = \beta^T x_i$. Define b as the maximum likelihood estimate of β, and its estimated variance-covariance matrix is V. To estimate the proportions of responders in both treatment and placebo arms, and their difference:

1. Create the new covariate matrix X_t from X by adjusting the column corresponding to treatment assignment such that all subjects are in the treatment group. Then calculate the vector of estimated probabilities of response to treatment, P_t, from X_t and b, $P_t = \text{logit}^{-1}(X_t b)$.

2. Similarly, assume each subject is assigned to placebo and repeat the step 1 to get X_c and P_c for placebo group.

3. The estimated difference in proportions is $d = \frac{1}{n}\sum_{i=1}^{n}(\hat{P}_{ti} - \hat{P}_{ci})$, where $\hat{P}_{ti}$ and $\hat{P}_{ci}$ are the ith elements of P_t and P_c, respectively. Define A_t as a vector with elements $A_{ti} = P_{ti}(1 - P_{ti})$ and $A_{ci} = P_{ci}(1 - P_{ci})$. Then, the standard errors of these estimators are derived as follows:

$$d_t = \frac{A_t' X_t}{n}$$

$$d_c = \frac{A_c' X_c}{n}$$

$$SE(d) = \sqrt{d_t V d_t' + d_c V d_c' - 2 d_c V d_t'}$$

The confidence interval of the estimation is $d \pm Z_{1-\frac{\alpha}{2}} \cdot SE(d)$. The details of logistic regression analysis and SAS code are provided in Section 10.1.1 and Ge, et al. (2011) ffi

In addition to the primary analysis, an analysis using composite strategy will be conducted to handle intercurrent events. The expected intercurrent events of interest in this trial are treatment discontinuation, death, and use of new therapies which are SoC for COVID-19 including Remdexivir and Dexamethasone. This analysis strategy considers patients with intercurrent events as treatment failure.

Sensitivity analyses will be conducted on the primary endpoint as follows:

- A logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, D-dimer at baseline, and duration of symptoms before hospitalisation in FAS.

- A logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, and time from first symptoms to start medication in FAS.
- A logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, and time from screening of patient to first drug in mouth in FAS.
- A logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, and time from hospitalization to first drug in FAS.
- A logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, and duration of symptoms before hospitalization on PPS. This analysis will be performed only if number of patients with IPDs excluded from PPS is greater than 10% of total number of randomised patients.
- A Cochran-Mantel-Haenszel type weighted average of differences with weights by severity grade at baseline on FAS. The details of Cochran-Mantel-Haenszel test and SAS code are provided in Section 10.1.2.
- To deal with patients who stop treatment due to sponsor's request, a logistic regression model including covariates of treatment, severity grade at baseline, age, creatinine at baseline, and duration of symptoms before hospitalization by defining a hypothetical estimand: treating these patients as non-responders (i.e. neither alive nor free of mechanical ventilation).
- A logistic regression model including covariates of treatment, severity grade at baseline, and age in FAS

7.4.2 Subgroup analysis

Analyses for subgroups specified in Section 6.4 will be performed for the primary endpoint using the logistic regression model to evaluate treatment-by-subgroup interactions.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 (Other) Secondary endpoints

Secondary endpoints will be analyzed on the FAS using treatment policy estimand.

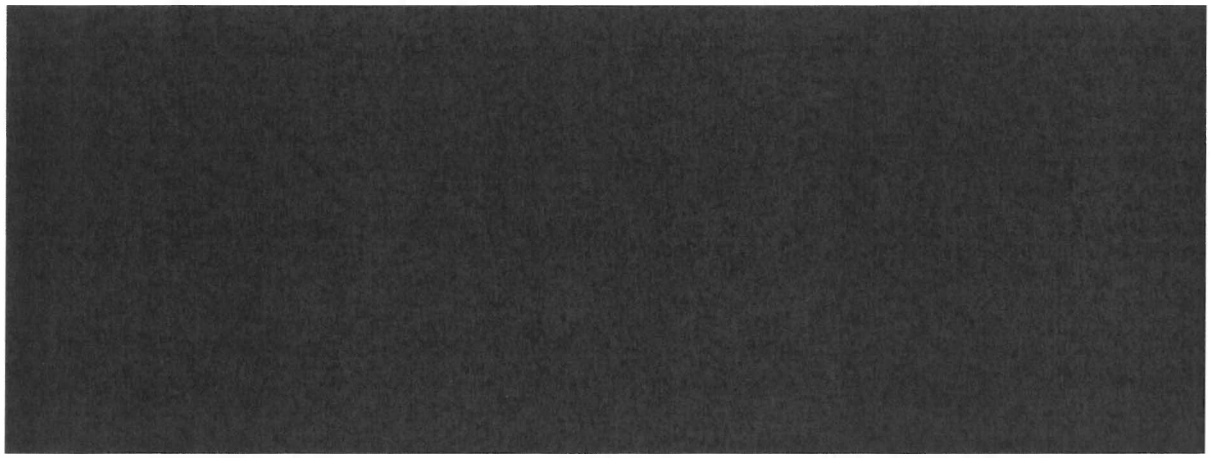
- Analysis of patients alive and discharged free of oxygen at Day 29 will be conducted using the same model as for the primary endpoint, to assess the difference in proportions of patients with BI 764198 and placebo.

- Analysis of patients with occurrence of any component of composite: In-hospital mortality or intensive care unit (ICU) admission or mechanical ventilation at Day 29, will be conducted using the same model used as the primary endpoint, to assess the difference in proportions of patients with BI 764198 and placebo.

- Time to response, defined as clinical improvement of at least 2 points (from randomisation) on the World Health Organization Clinical Progression Scale, discharge from the hospital, or considered fit for discharge (a score of 0, 1, 2, or 3 on the Clinical Progression Scale), whichever comes first, by Day 29, will be analysed using the Cox proportional-hazards model adjusting for treatment, age, creatinine at baseline, and duration of symptoms before hospitalisation. Hazard ratio and Kaplan-Meier curves with 95% confidence interval will be provided. Patients who do not respond will be censored at Day 29. Patients who prematurely discontinued from the treatment or lost to follow-up will be censored at the time of their last observed assessment. Patients who die prior to observing response will be censored at Day 29.

- The number of ventilator free days will be analysed using an ANCOVA model including treatment, age, creatinine at baseline, and duration of symptoms before hospitalisation. WHO progression scale below 7 are defined as ventilator free. Hence, ventilator free days can be counted as number of days with WHO progression scale below 7 from the day of randomization to day 29. A sensitivity analysis excluding patients who died during treatment period will be conducted.

- Analysis of mortality at Day 15, 29, 60 and 90 will be conducted using the same model as for the primary endpoint, to assess the difference in proportions of patients with BI 764198 and placebo.



[redacted]

7.7 EXTENT OF EXPOSURE

Exposure will be presented as categorized period o[redacted] based on dose received for total study medication intake. Only descriptive statistics are planned for this section of the report. Summaries will be provided on FAS during treatment period. Total exposure (in days) is defined as date of last administration of study medication - date of first administration of study medication+ 1, ignoring the temporary interruptions, i.e. intermittent off-treatment periods were considered in the extent of exposure.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the FAS during on-treatment period.

7.8.1 Adverse events

Analyses of adverse events 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.

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- 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- will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

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 or dose reduced or interrupted).

For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' ill:

An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and PT (mention MedDRA levels to be displayed in the tables). Separate tables will be provided for subjects with SAEs, AEs leading to treatment discontinuation, AEs of at least moderate severity and related AEs. with significant non-serious adverse events

The system organ classes will be sorted by default alphabetically, PTs will be sorted by frequency (within SOC). Customized sorting orders may also be used based on trial needs, e.g. SOC sorted by frequency.

The following are considered as protocol-specified AESI:

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) 23 fold ULN combined with an elevation of total bilirubin 22 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations 2:10 fold ULN.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards, 001-MCG-157: "Display and Analysis of Laboratory Data", current version, IDEA for CON. ill

7.8.3 Vital signs

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

7.8.4 ECG

ECGs will be evaluated locally by eCRF. Summary statistics will be displayed. Additional summaries will be produced for patients who have abnormal ECG findings at baseline or during the study period: patients with confirmed QT prolongation of QTc interval to greater than 450 ms in males or 470 ms in females.

7.8.5 Others

Frequency of patients with extrapulmonary organ failure (based on reported AEs) will be summarized descriptively by treatment group and organ class: cardiovascular failure, CNS failure, renal failure, hepatic failure, and coagulation abnormalities.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

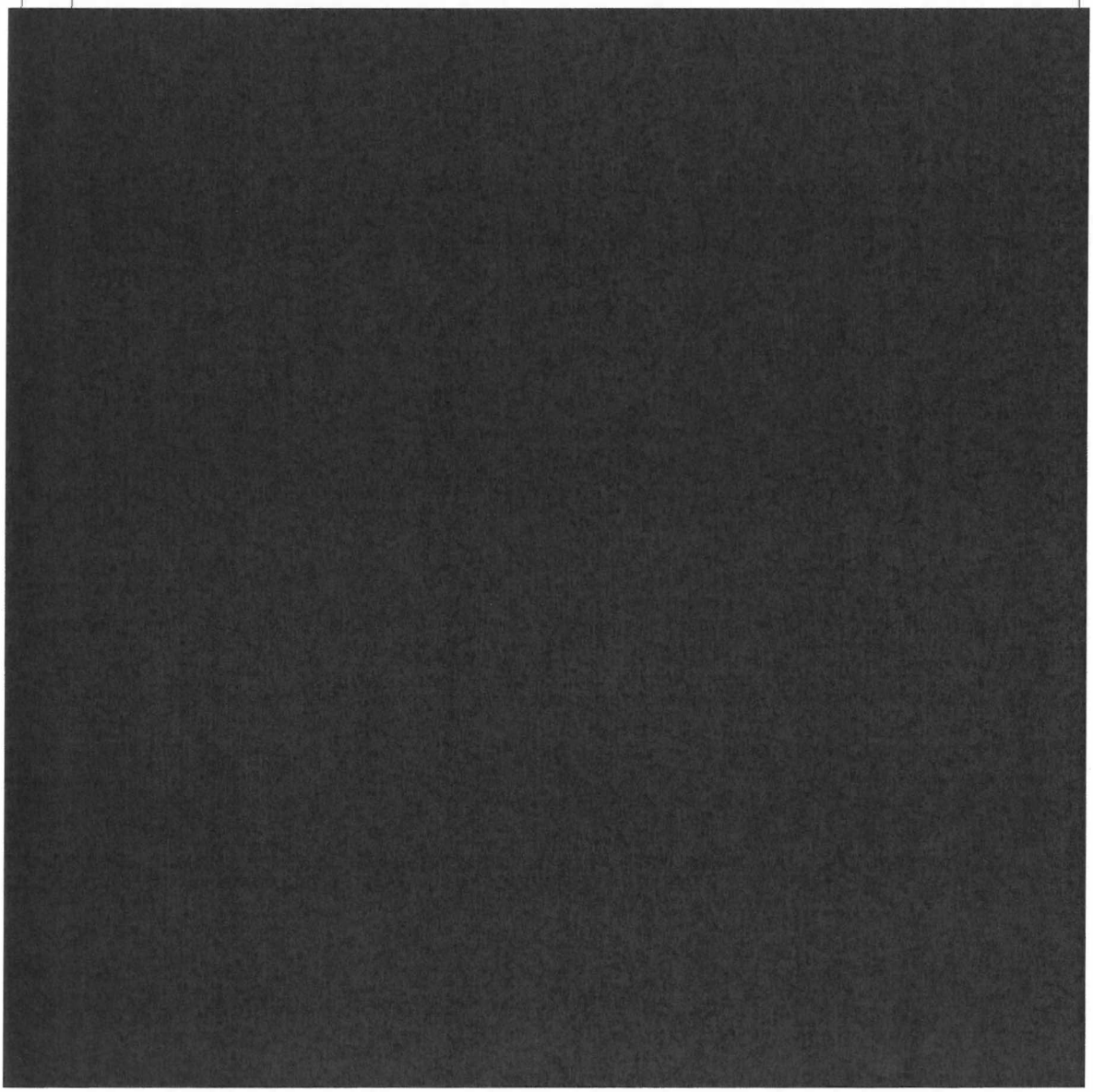
Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Snapshot will be at EOT or any time after once thresholds are met (including Day 29 data thresholds). Then the treatment information will be released for analysis.

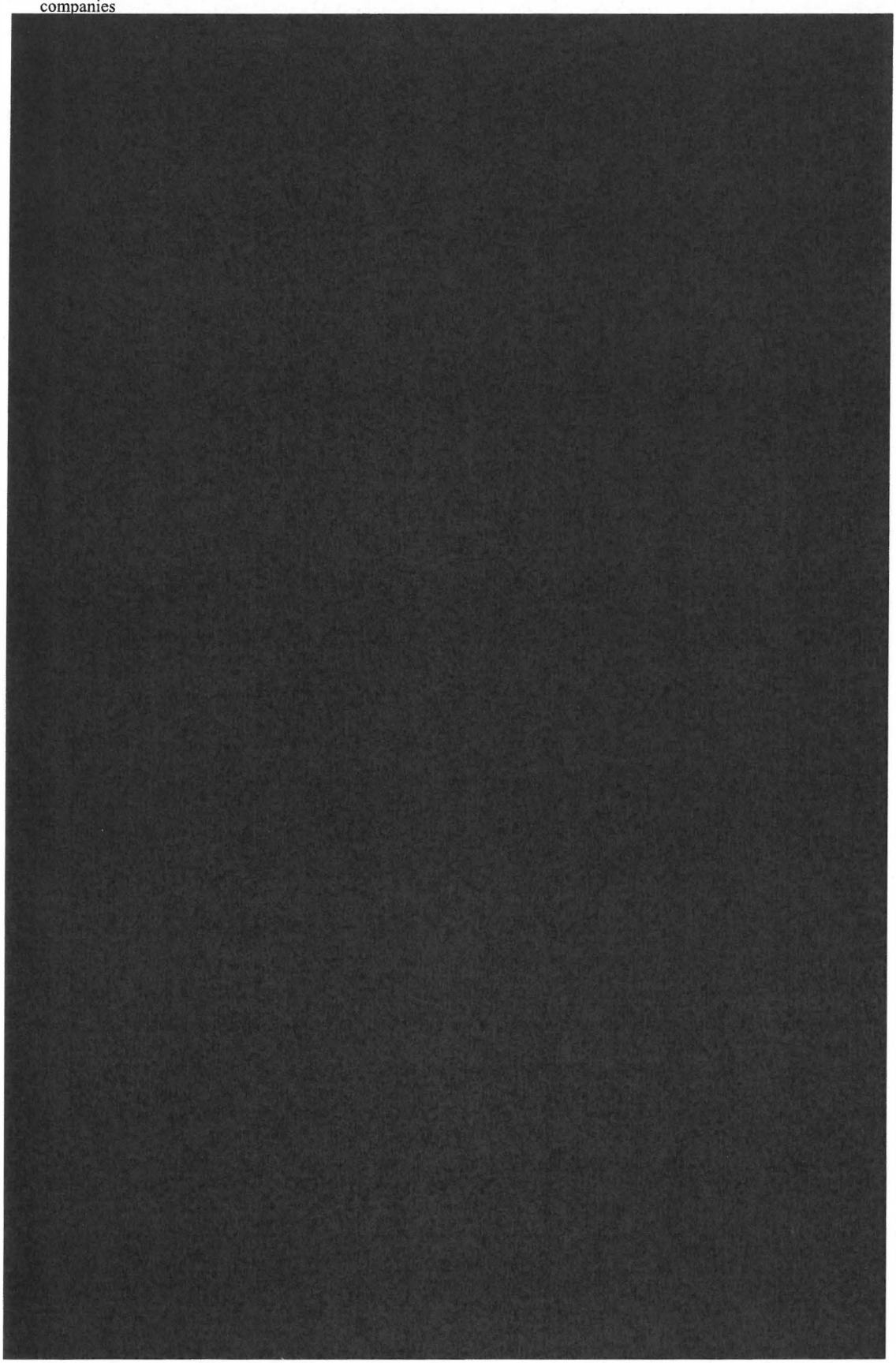
The data collection for the off-treatment residual effect period until the End-of-Study (EoS)/ Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.

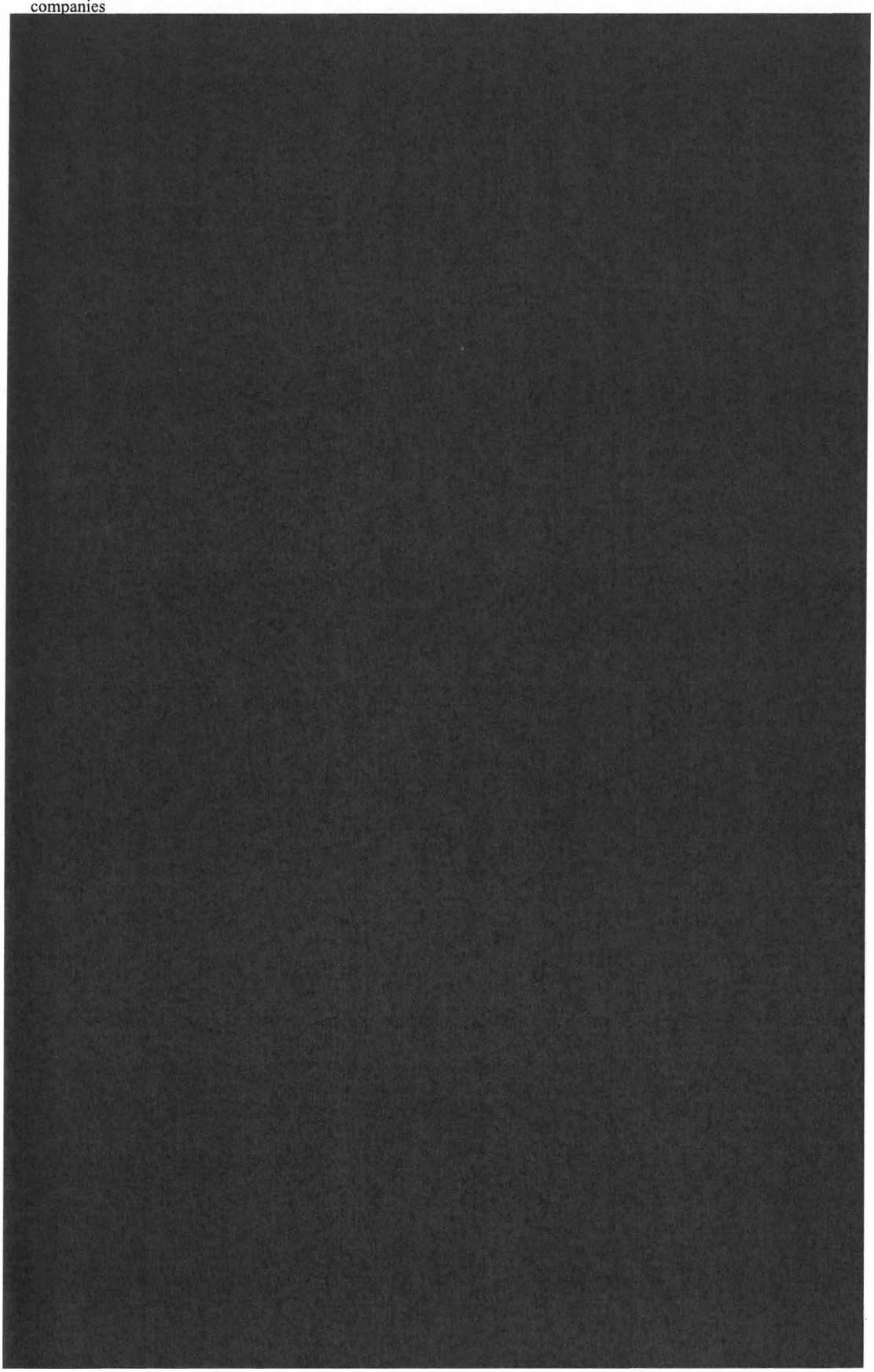
After the release of treatment information, it is expected that only trial data related to the off-treatment residual effect period will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to the End-of-Treatment (EoT) visit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

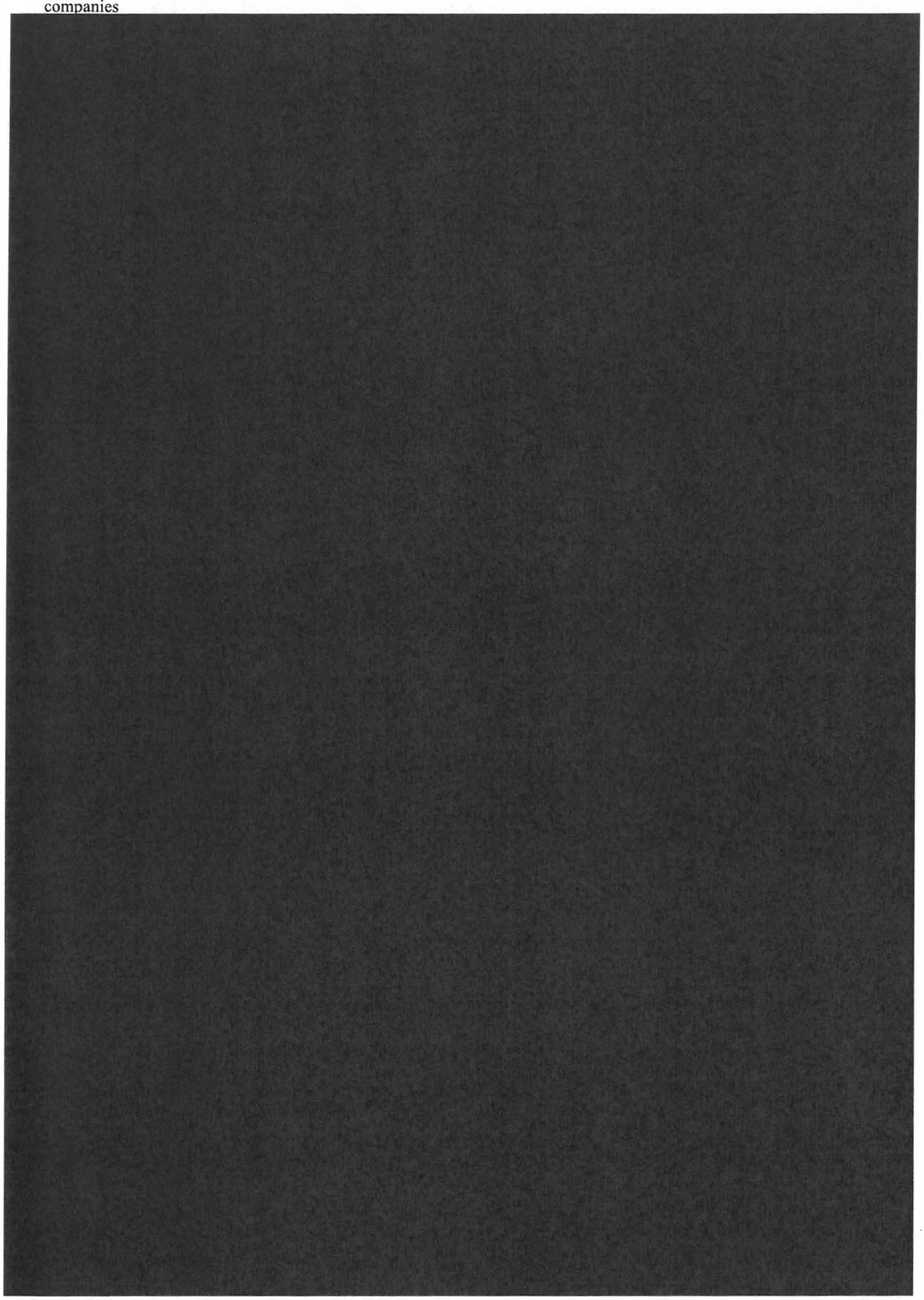
9. REFERENCES

1.	*CPMPIICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCG-156:* "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
3.	*001-MCG-157:* "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
4.	Ge, M., Durham, L. K., Meyer, R. D., Xie, W., & Thomas, N. (2011). Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug information journal: DIJ/Drug Information Association, 45(4), 481-493.
5.	Greenland Sand Robin JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985;41 :55-68 [R09-1299]









11. HISTORY TABLE

Table 11: 1 History table

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

Boehringer
Ingelheim

APPROVAL/ SIGNATURE PAGE

Document Number: c35421742 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core

Title: BI 764198 efficacy and safety in prevention/progression of ARDS

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Project Statistician	[redacted]	08 Apr 2021 07:50 CEST
Author-Trial Medical Writer		08 Apr 2021 10:06 CEST
Approval-Clinical Trial Leader		08 Apr 2021 17:36 CEST
Approval-Team Member Medicine		08 Apr 2021 18:44 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed