Trial Statistical Analysis Plan

c05079948-01

BI Trial No.:	1237.19
Title:	A randomised, double-blind, active-controlled parallel group study to evaluate the effect of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination compared with tiotropium on Chronic Obstructive Pulmonary Disease (COPD) exacerbation in patients with severe to very severe COPD. [DYNAGITO] Including Protocol Amendment 01 1237.19-protocol-amendment-01 [c02247259-03]
Investigational Product(s):	Tiotropium + olodaterol fixed dose combination inhalation solution-RESPIMAT®
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	15 NOV 2016 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
ANCOVA	Analysis of Covariance
AUC	Area under the curve
BI	Boehringer Ingelheim
BMI	Body Mass Index
BRPM	Blinded report planning meeting
COPD	Chronic Obstructive Pulmonary Disease
[redacted]	[redacted]
CI	Confidence interval
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CT	Concomitant Therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database lock
EC	Exclusion Criterion
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of treatment
EoT	End-of-text
FDC	Fixed dose combination
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good clinical practice
GOLD	Global Initiative on Chronic Obstructive Lung Disease
H	Hypothesis
IC	Inclusion Criterion
ICF	Informed Consent form
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroids
(I)PV	(Important) Protocol violation

Term	Definition / description
IRT	Interactive Response Technology
[redacted]	[redacted]
LABA	Long Acting Beta Agonists
LOCF	Last observation carried forward
LLT	Lowest level term
Max	Maximum
MI	Myocardial Infarction
Min	Minimum
MMRM	Mixed Model for Repeated Measures
MQRM	Medical Quality Review Meeting
N	Number
NYHA	New York Heart Association
PFT	Pulmonary Function Test
PH	Proportional Hazards
PT	Preferred term
PV	Protocol violation
REML	Restricted maximum likelihood
RR	Rate ratio
RS	Randomized Set
S	Survival distribution
SAS®	Statistical Analysis Software®
SD	Standard deviation
[redacted]	[redacted]
SOC	System organ class
[redacted]	[redacted]
T+O	Tiotropium bromide and Olodaterol
TIA	Transient Ischemic Attack
Tio	Tiotropium bromide
TS	Treated Set
TSAP	Trial statistical analysis plan
UN(1)	Banded Main Diagonal
AE	Adverse event

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.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint will be used as defined in the revised CTP, Section 5.1.1:

- Annualized rate of moderate to severe COPD exacerbations during the actual treatment period.

The actual treatment period is defined as the interval from first in-take of study medication until 1 day after last in-take of study medication (see section 6.1).

The definition of a moderate to severe COPD exacerbation is given in Section 5.1.2 of the revised CTP.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

The key secondary endpoint in this study is defined in the revised CTP, Section 5.1.:

- Time to first moderate to severe COPD exacerbation during the actual treatment period.

5.2.2 Secondary endpoints

Secondary endpoints are defined in the revised CTP, Section 5.1. They are:

- Annualized rate of exacerbation leading to hospitalization during the actual treatment period.
- Time to first COPD exacerbation leading to hospitalization during the actual treatment period.
- Time to all-cause mortality occurring during the actual treatment period.

All deaths are adjudicated by a blinded and independent adjudication panel to determine the primary cause of death.

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

As described in Section 4 of the revised CTP, patients will be randomized in equal allocation to one of two treatment groups delivered by the Respimat® inhaler:

- Tiotropium + olodaterol fixed dose combination (FDC) (5µg / 5µg) inhalation solution once daily
- Tiotropium (5 µg) inhalation solution once daily.

Table 6.1: 1 Treatments and their labels

Treatment	**Short label**
Tiotropium + olodaterol FDC (5 µg / 5 µg) inhalation solution	T+O 5/5
Tiotropium (5 µg) inhalation solution	Tio 5

The trial consists of a 360 days of treatment followed by a 21 day residual effect period.

For analysis purposes the following periods are defined:

- Planned study period
  The planned study period is defined as 360 days of treatment + 21 days of follow up after the administration of the first dose of trial medication according to the CTP flow chart.

- Planned treatment period
  The planned treatment phase is defined as 360 days of treatment + 1 day for wash-out according to the CTP flow chart.

- Actual treatment period
  The actual treatment period is defined as the interval from first in-take of study medication until 1 day after last in-take of study medication.

- On-treatment period
  The on-treatment period is defined as the interval from first in-take of study medication until 21 days after last in-take of study medication.

Patients that discontinue early will be monitored for exacerbations and vital status until they have reached the end of their planned study period.

Table 6.1:2 Analyses performed within each period

Types of Analyses to be performed	Periods			
	Actual treatment period (Treatment +1 day wash-out)	Planned treatment period (includes 1 day wash-out)	Planned study period (includes residual effect period of 21 days)	On-treatment period (includes residual effect period of 21 days after last drug intake)
Primary Exacerbation analysis	✓			
Sensitivity primary exacerbation analysis		✓		
Key secondary exacerbation analysis	✓			
[redacted]				
AE safety analysis				✓

Patients will be analyzed according to the treatment group of the first treatment received. Potential treatment switcher scenarios caused by treatment misallocation will be discussed at the Blinded Report Planning Meeting (BRPM). After database lock (DBL) patients who fall into these discussed scenarios will be analyzed according to meeting decisions.

For the main safety analysis, data occurring during the on-treatment period (as described above) will be assigned to the respective treatment. Adverse events (AEs) occurring before first drug intake will be assigned to 'screening'. AEs occurring after the 21 day residual effect period will be assigned to the follow-up period (not to any of the treatment arms).

6.2 IMPORTANT PROTOCOL VIOLATIONS

A patient's deviation from the trial protocol is considered "important" if it can be expected that the deviation had a distorting influence on the assessment of the treatment effect on the primary endpoint of the trial or could affect the patient's safety/rights.

If the Interactive Response Technology (IRT)-assigned randomized medication is not available at the site at the first visit, a forced randomization will occur, and the IRT will assign a treatment that is available at the site. That patient will be assigned within the IRT system to receive that same treatment for the remainder of the trial. Forced randomizations

are part of the study plan and are not classified as important protocol violations. The number of forced randomizations will be closely monitored and described in the clinical trial report.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from	Automatic /Manual
A		**Entrance criteria not met**			
	A1	**Inclusion criteria not met**	IC 3, 4, 5, 7, 8, 2, 6,	None	Automatic and manual
	A2	**Exclusion criteria not met**	EC 3, 7, 9, 10, 11, 13, 14, 15, 17, 23, 5, 6, 1, 4, 8, 2, 12, 16, 18, 19, 20, 21, 22	Excluded from TS: EC 22 Excluded from none: EC 1-21, 23	Automatic
B		**Informed consent**			
	B1	Informed consent to study not available/not done*		All	Manual
	B2	Informed consent too late**		None	Manual
C		**Trial medication and randomization**			
	C1	Incorrect trial medication taken		None	Manual
	C2	Randomization order not followed	Date of first trial drug intake prior to randomization date	None	Automatic
	C3***	Serious non-compliance with study medication as reported in monitoring report	Decision at BRPM/MQRM.	None	Manual
	C4	Medication code broken inappropriately		None	Manual
D		**Concomitant medication**			
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	D2	Prohibited medication use during study	Refer to Table 4.2.2.1: 1 in revised CTP.	None	Manual
Z		**Other**			
	Z1	Serious Good Clinical Practice (GCP) non-compliance	Manual PVs reported by CML/CRA or in the GEM system.	None	Manual
	Z2	Other PV affecting efficacy and possibly safety		None	Manual

* Informed consent date missing; no signature on ICF.
** Applies to all informed consents. Date of informed consent was after the date of any study-related procedure.
*** "Serious non-compliance with study medication" is defined by compliance >=200% (twice the dose or more).

Note: The following IPVs are not programmed and should therefore be identified at site level on the manual PV log: B1, B2, C1, C3, C4, D1, D2, Z1, and Z2.

6.3 PATIENT SETS ANALYZED

Randomized set (RS)
This patient set includes all patients that were assigned a randomization number within the IRT system.

Treated set (TS)
This patient set includes all randomized patients who were documented to have taken at least one dose of study medication.

[redacted]

The treated set will be used in all planned analyses [redacted]

No per-protocol set is defined and no analysis is planned.

[redacted]

6.5 POOLING OF CENTRES

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

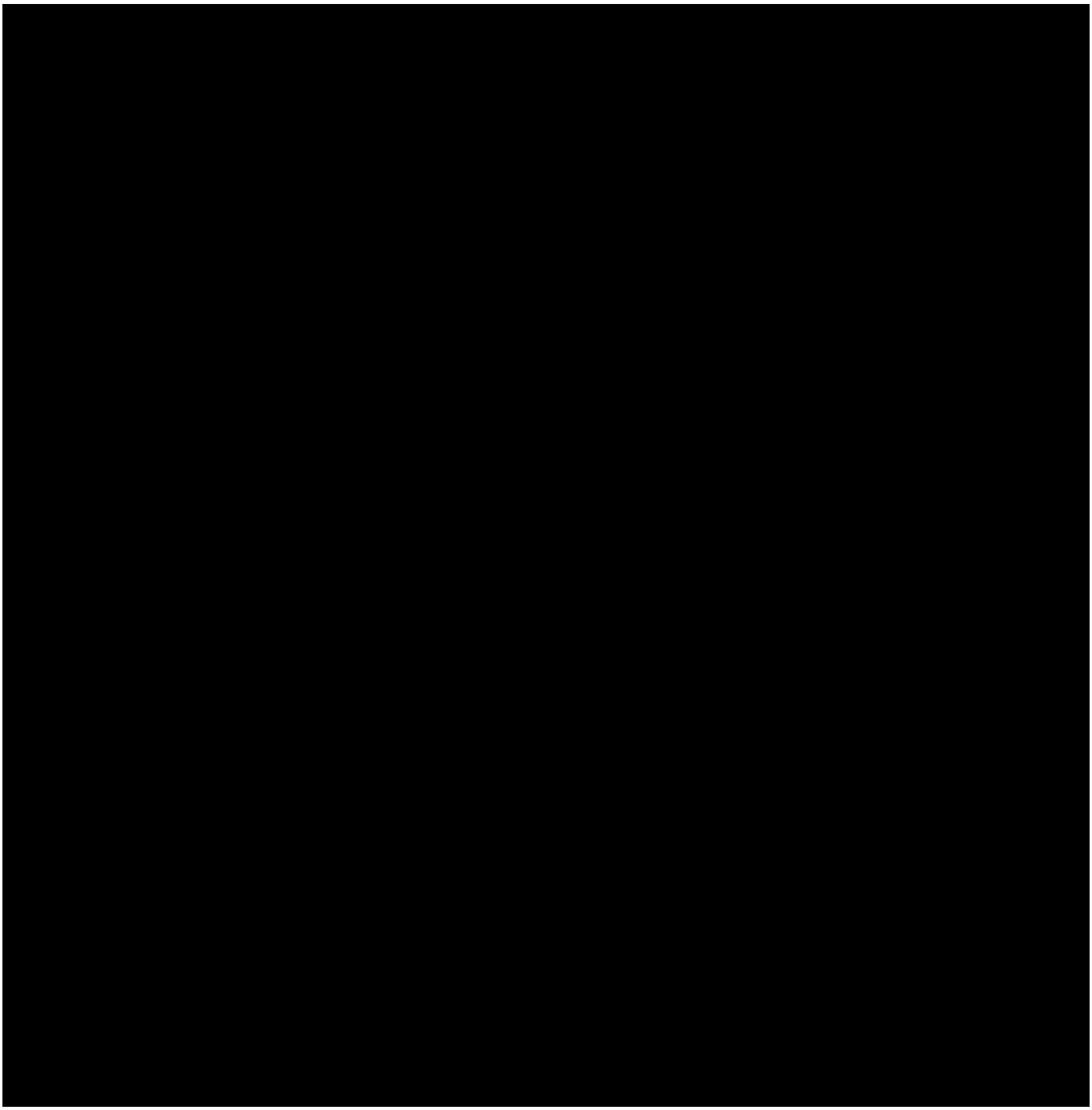
6.6 HANDLING OF MISSING DATA AND OUTLIERS

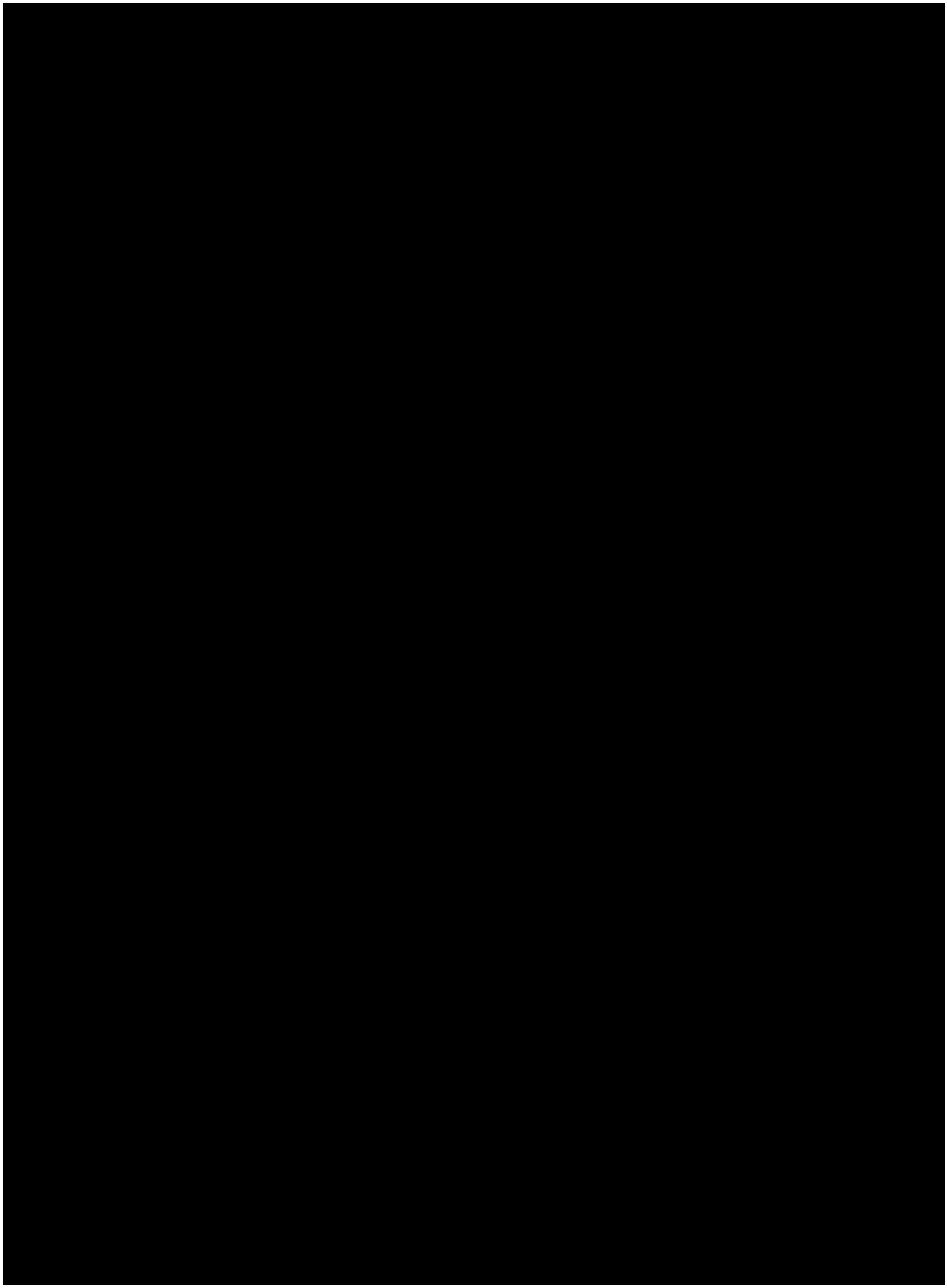
Exacerbations and vital status data

Patients will be followed up for exacerbation and vital status. Missing data for these endpoints will not be imputed. For each time to event analysis, patients who do not have a particular outcome will be censored (for details see section 7.5.2).

AE data

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates" (2).





[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The study's treatment period is planned to have a duration of 360 days and includes 5 clinic visits, conducted every 3 months, interspersed with a telephone contact call 6 weeks between clinic visits. Twenty-one (21) days after the end-of-treatment (EOT) visit a follow-up visit will be performed.

Time windows will not be used. Variables that are collected at clinic visits will be analyzed by planned visit (e.g. for trough FEV_1 in the sub-study). Exacerbation and time-to-event analyses are collected in real-time.

With regard to all efficacy assessments, the term "baseline" refers to the last observation obtained at visit 2.

For all other data, including relevant medical history, concomitant therapies, AEs, lab values, and vital signs, visit 1 will be classed as "baseline".

[redacted]

6.8 CALCULATION OF TIME TO EVENT

The calculation of the time-to-event and the time that patients without an event were in the study (at risk) is described here.

Day 1
The date of first administration of treatment is the reference for all time-related analyses.

Date of event
In the exacerbation analyses, where a patient can have multiple events, the onset date of the first event will be used.

For death, the adverse event end date reported on the eCRF will be used as the final date of death.

Last known date alive
The date of last known day alive is determined as the latest date among: the final vital status date (defined as the assessment date if alive, or date last known alive if 'unknown'), the date of first dose of study medication, the date of last drug administration, all the visit dates (including phone contact dates in which the patient was reached and follow-up contact dates) and start or stop dates of events reported on the adverse event forms.

If a patient dies, the date of death is the last date known alive.

Survival time calculations:

A. *Actual treatment event analysis:* Events (death or exacerbation) are counted in the actual treatment time to event analysis whenever they occur between the first dose of randomized treatment and one day after treatment discontinuation (i.e. during the actual treatment period) (see section 6.1).

Patients with no event observed during the actual treatment period will be censored at date of last dose of randomized study drug administration (i.e. treatment discontinuation) +1 day.

Time at risk:

- *Patients with event counted*: (<date of event> – <date of first drug administration> +1).

- *Patients without event counted*: (<date of last dose of study drug> – <date of first drug administration > +1) + 1 day wash-out

[redacted]

6.9 CALCULATION OF ANNUALIZED RATE

In all analyses of annualized* rate of event, the length of the event will be subtracted from the extent of exposure or the length of the observation period because an additional event cannot occur during an event.

For the on-treatment analysis total exposure is calculated as follows:

$$total\ exposure\ in\ patient\ years\ = \frac{\sum \text{all patients}'\text{exposure}}{365}$$

$$observed\ rate\ of\ event = \frac{\sum \text{number of events}}{\sum \text{all patients}'\text{exposure} - \sum \text{duration of events}}$$

[redacted]

7. PLANNED ANALYSIS

For End-of-Text (EoT) tables, the set of summary statistics for descriptive statistics of continuous variables displays is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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 (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category ‘missing’ will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics by treatment group (and total) for the treated set are planned for this section of the report.

[redacted]

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases and medication are collected by checkbox and will be summarized by treatment using descriptive statistics. For medical history, displays will be created for each: past, ongoing or recurring events as recorded at baseline. The following concomitant diseases and medications will be included:

- Medical history [N (%)] (Metabolic disorders [diabetes mellitus, hyper-/dyslipidaemia], psychiatric disorders [anxiety, depression], renal and urinary disorders [prostatic disorder, urinary retention, urinary tract infection, renal impairment (renal failure)], cancer [treated basal cell carcinoma, squamous cell skin cancer], cardiac arrhythmia [supraventricular tachyarrhythmia, atrial fibrillation/flutter, ventricular tachyarrhythmia, palpitations, bradyarrhythmia, QT prolongation], cerebrovascular disorders/stroke [haemorrhagic cerebrovascular conditions, ischaemic cerebrovascular conditions, transient cerebrovascular event (TIA)], other cardiovascular disease [hypertension, hypotension, aneurysm, syncope, myocardial infarction (MI), other ischaemic heart disease (non-infarction, angina pectoris), cardiac arrest, cardiac failure class (New York Heart Association (NYHA) failure classification)], including number of COPD exacerbations or worsening episodes in the last year that were treated with steroids or antibiotics, number of COPD exacerbations in the last year that were associated with hospitalization, CAT

- Concomitant therapy (CT) at baseline [N,(%)]
    - Pulmonary classes (as specified on case report form)
    - Cardiac classes (as specified on case report form)
    - Metabolic disease, psychiatric disease (as specified on case report form)

- CT during treatment period [N (%)], if indicated to have been used for one day during randomized treatment period (Visit 2 through termination of trial medication will be summarized together. A separate display will be generated summarizing from the end of treatment until the 21 day follow-up visit.)

7.3 TREATMENT COMPLIANCE

Treatment compliance will only be assessed whether or not it is in the recommended range of between 80% and 100%. Compliance % is based on doses used during the maximum possible treatment period.

7.4 PRIMARY ENDPOINT

Primary Analysis
As stated in section 7.3.1 in the revised CTP: “The annualized rate of moderate to severe COPD exacerbation will be analyzed using a negative binomial model including the fixed, category effect of treatment as well as the logarithm of the treatment exposure as an offset. […] Moderate to severe COPD exacerbations occurring within 1 day (24 hours) after the last drug administration date, are included in the primary analysis”.

See section 6.9 for calculation of observed rate.

Annualized rates of moderate to severe COPD exacerbations will be tested for equivalence between the two treatment groups T+O 5/5 and Tio 5. The hypothesis (H) test is:

$$\mathbf{H_{10}}: \text{RR} = 1$$
vs.
$$\mathbf{H_{11}}: \text{RR} \neq 1,$$

where $RR = \frac{\lambda(\text{T+O})}{\lambda(\text{Tio})}$ and λ_{Tio} is the annualized rate for the patients in the Tio 5 group and $\lambda_{\text{T+O}}$ is the annualized rate for the patients in the T+O 5/5 group and RR is the rate ratio between the two groups.

The hypothesis test will be evaluated using a two-sided α=0.01. Ninety-nine (99)% confidence intervals will be obtained. Type III sums of squares will be produced.

The following SAS® code for the negative binomial model will be used:

```
proc genmod data=exac_negbin;
      class trt;
      model evtnum=trt/noint dist=negbin  link=log offset=logdurs type3
      alpha=0.01;
      lsmeans trt/cl diff exp alpha=0.01;
    run;
```

where TRT=treatment group and LOGDURS=log(exposure) as described in section 6.9. The OFFSET=LOGDURS is used to account for different exposure, or observation periods per subject.

The primary analysis will be an actual treatment analysis performed on the treated set (TS) (see section 6.3). The exacerbation events will be only counted in this analysis if they occurred during the actual treatment period (see section 6.1).

Section 9.1 details additional rules applied to the analysis of the primary endpoint.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Time to first moderate to severe COPD exacerbation is the key secondary endpoint and will be assessed sequentially after the testing of the primary hypothesis (section 7.4), thereby protecting the overall type I error (at the 2-sided 0.01 level).

As stated in the revised CTP (section 7.2), the hypotheses for this test of equivalence between T+O and Tio, are:

$$\mathbf{H_{20}}: S_{T+O} = S_{Tio}$$
vs.
$$\mathbf{H_{21}}: S_{T+O} \neq S_{Tio}$$

where S = survival distribution.

The key secondary analysis will be performed on the TS and will include events that have occurred during the actual treatment period.

A Cox proportional hazards model will be used to estimate the hazard ratio and the corresponding 99% CI, while log-rank test statistics will be used to obtain the p-value for testing the survival curves. Accompanying plots of cumulative hazard over time by treatment will also be presented.

The SAS® code for the Cox proportional hazards model is as follows:

```
proc phreg data=exac_surv;
      class trt (ref='control');
      model time*event(1)=trt / RL; *ADEXAC spec:0 is "not censored", 1 is
                                    "censored";
      hazardratio trt / diff=ref cl=wald alpha=0.01;
      ods output hazardratios=hazard;
run;
```

Patients who discontinue medication early (i.e. prior to the planned end of the treatment period, see section 6.1) will be censored at the time they discontinue medication + 1 day.

[redacted]

The proportional hazards assumption will be checked prior to running the analysis. This will be done by conducting a Cox PH test for proportionality and examining the log(-log) versus log(survival time) plot.

The SAS® code for the Cox proportional hazards test for proportionality is as follows:

```
proc phreg data=testProp;
        class trt(ref='control');
        model time*event(1) = trt ttreat/ RL;
        id ptno;
```

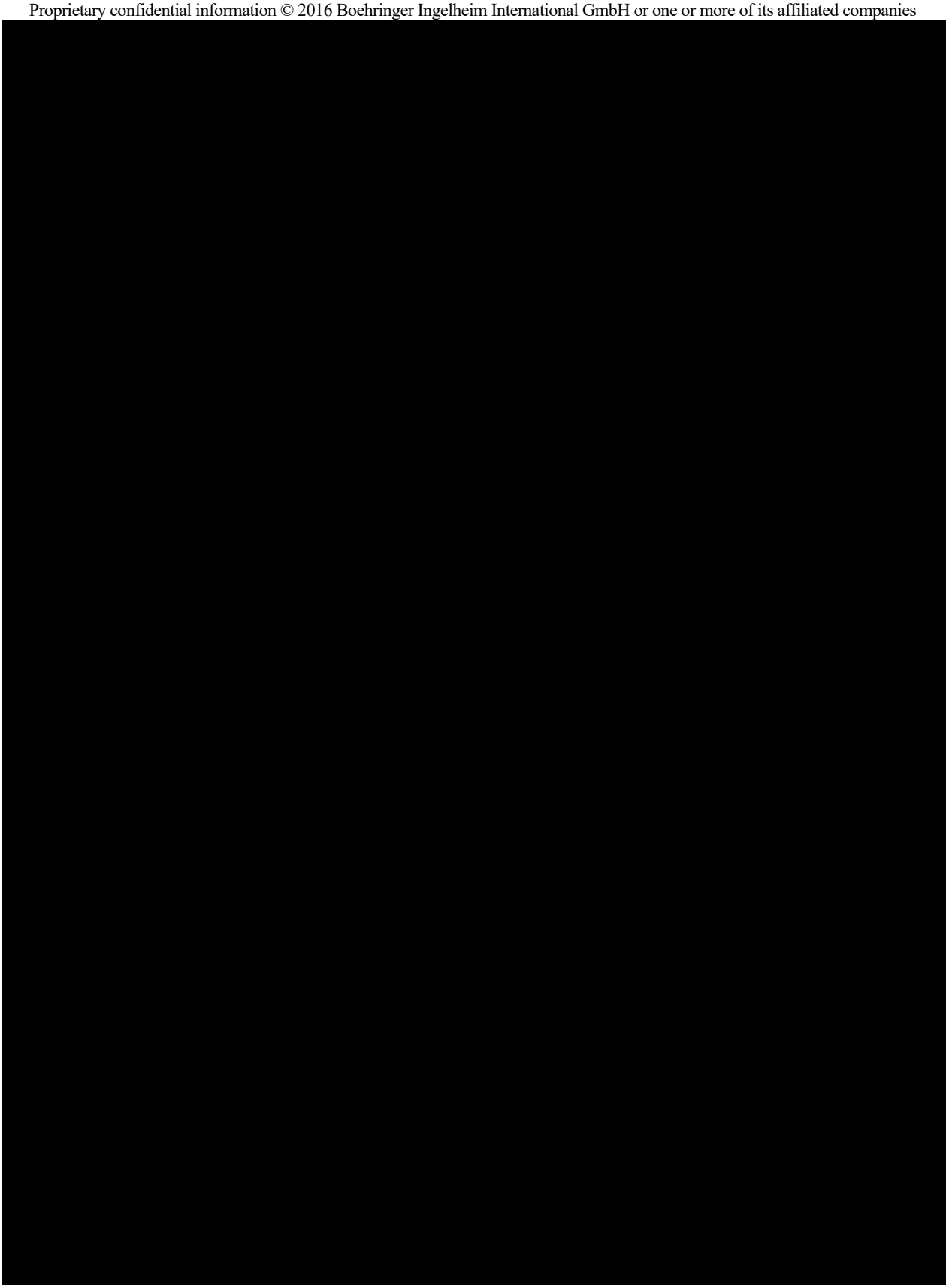
```
        ttreat=trt*log(time);
        proportionality_test: test ttreat;
run;
```

7.5.2 Secondary endpoints

Secondary endpoints are:

- Annualized rate of COPD exacerbations leading to hospitalization during the actual treatment period.
- Time to first COPD exacerbation leading to hospitalization during the actual treatment period.
- Time to all-cause mortality occurring during the actual treatment period

Annualized rate endpoints will be analyzed using a negative binomial model, as described in section 7.4. Time to event endpoints will be analyzed using a Cox model as described in section 7.5.1.



7.7 EXTENT OF EXPOSURE

Extent of exposure to trial medication within the study will be displayed by treatment for the TS. Treatment exposure will be calculated as drug stop date - drug start date + 1 day. Both descriptive statistics and categorization by exposure intervals (e.g. <=90 days, 91-180 days, 181-270 days, 271-360 days, >=361 days) will be used.

The extent of observation time will be summarized similarly. The time intervals will be similar except for an additional category to account for the full follow-up period (i.e. 360 – 381 days and >=382 days).

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS. Adverse events (AE) were actively collected during the on-treatment phase, which for AEs includes the time period from first dose of study drug until the last dose of study drug + 21 days (see section 6.1).

AEs that were voluntarily reported during the vital status and exacerbation follow-up period for early discontinuations will be listed within the study report in a separate table.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AE 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 the analysis, multiple AE occurrence data on the eCRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (lowest level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (2), (3).

The analysis of AE will be based on the concept of treatment-emergent adverse events. That means that all AE occurring between first drug intake through last drug intake + residual effect period will be assigned to the randomised treatment. All AE occurring before first drug intake will be assigned to ‘screening’ and all AE occurring after the residual effect period will be assigned to ‘follow-up’ (for listings only). For details on the treatment definition, see section 6.1.

According to ICH E3 (4), AEs classified as ‘other significant’ need to be reported and will include those non-serious and non-significant AE with
(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or

(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting (MQRM).

An overall summary of AE will be presented.

The frequency of patients with AE will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with other significant AE according to ICH E3 (4) as well as for patients with serious AE and for patients with AEs leading to death.

The SOCs will be sorted alphabetically and PTs will be sorted by frequency (within SOC).

7.8.2 Mortality

All deaths are adjudicated by a blinded and independent adjudication panel to determine the primary cause of death. For each death, the cause as determined by both investigator and adjudication will be listed. Frequency tables summarizing AEs leading to death will be displaying adjudicated causes of death.
Fatal AE SOC shifts (if applicable) from investigator determined SOC to adjudicator determined SOC will be displayed.

7.8.3 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). Appendix 16.1.9.2 and Appendix 16.2 displays to be included are as follows (table/listing numbers refer to the standard lab table/listing types).

End-of-text

- Frequency of patients [N (%)] with transitions relative to reference range (TCTCCHG)
- Frequency of patients [N (%)] with possible clinically significant abnormalities (TPCSAF)
- Descriptive statistics for baseline, last value on treatment, and difference from baseline (normalized values) (TDSTATBE)
- Hy's Law figure (HYLAW)

Appendix 16.1.9.2

- Descriptive statistics for normalized values
- Descriptive statistics for baseline, last value on treatment, and difference from baseline (normalized values) (TDSTATBE)

Appendix 16.2

- Criteria for clinically significant abnormalities based on normalized laboratory values (Listing CRITPCSA – "normalized")
- Laboratory values (normalized values) by functional group, sorted by centre, treatment, and patient (Listing LBNGRP)
- Investigator comments for original values (Listing COMMENTS)
- Peak values of ALT/Bilirubin in relation to their upper limit of the reference range (PEAKLIST)

7.8.4 Vital signs

Only descriptive statistics and change from baseline are planned for this section of the report.

7.8.5 ECG

Only baseline data (screening) were collected. Abnormal findings will be summarized within the medical history display.

8. REFERENCES

1	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
4	*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
5	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

9. ADDITIONAL SECTIONS

9.1 DETAILED DESCRIPTION OF ENDPOINT: COPD EXACERBATION

Detailed definition of an exacerbation is provided in the revised CTP section 5.1.2.1. The following additional rules will be applied in the analysis:

Collapsing rules
The revised CTP states that the end date of a COPD exacerbation is decided by the investigator. If, however a second exacerbation occurs within 7 days of the determined end date of a previous exacerbation, these two events will be collapsed and counted as one in the analysis with an onset date as the date of the beginning of the first event.
Severity rules:

- If a milder event is collapsed with one that is more severe, the collapsed event will be classified according to the more severe event.

Fatal COPD exacerbation event
As defined in the revised CTP, an exacerbation will meet the definition if, among other factors listed, the duration is of three days or more. However, in cases where the primary cause of death has been determined by the investigator to be due to a COPD exacerbation, but the duration until death was less than 3 days, the COPD exacerbation event will be counted within the COPD exacerbation analysis as a severe exacerbation.

Analysis of COPD exacerbation leading to hospitalization
Only COPD exacerbations that have been marked on the eCRF as being associated with "admission to hospital" will be included in this analysis.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**15-Nov-16**	[redacted]	None	This is the final TSAP without any modification