Trial Statistical Analysis Plan

c03567142-01

BI Trial No.:	1311.14
Title:	A phase IIa, randomized, double-blind, placebo controlled, parallel group study to assess the safety and efficacy of subcutaneously administered BI 655066/ABBV-066 (risankizumab) as add-on therapy over 24 weeks in patients with severe persistent asthma. Including Protocol Amendment 5 [c03185695-07].
Investigational Product(s):	BI 655066
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	26 OCT 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse event
ALQ	Above the assay limit of quantification
ANCOVA	Analysis of Covariance
BLQ	Below the assay limit of quantification
BMI	Body mass index
BRPM	Blinded report planning meeting
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CRF	Case report form
CTP	Clinical Trial Protocol
DBL	Database lock
DCC	Differential Cell Counts
EMEA	European Agency for the Evaluation of Medicinal Products
EoT	End-of-Text
FAS	Full analysis set
ICH	International Council for Harmonisation
GCP	Good clinical practice
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NGAL	Neutrophil gelatinase-associated lipocalin
PFT	Pulmonary function test
PT	Preferred term
PV	Protocol violation
RS	Randomised set
SD	Standard deviation

Term	Definition / description
SOC	System organ class
TSAP	Trial statistical analysis plan
VEGF	Vascular endothelial growth factor

3. INTRODUCTION

As per ICH E9, 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, and randomization.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In section 7.3 of CTP, it indicates that a 95% confidence interval for annualized rate of asthma worsening will be presented, however since the sample size calculation is based on a 1-sided type-I error $\alpha = 0.1$, an 80% confidence interval will be presented instead.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT

The primary endpoint of this study is time to first asthma worsening (in days) during the planned 24-week treatment period as defined in section 5.2 of CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the protocol.

5.2.2 (Other) Secondary endpoints

The secondary endpoints are defined in section 5.1.2 of CTP.

5.4 OTHER VARIABLES

Demographics and other baseline characteristics

- Age, weight, height, race, ethnicity, gender, BMI, smoking history, smoking pack years
- History of asthma
- Concomitant asthma medication
- Asthma background characteristics
- Sputum cell counts (absolute and differential) at baseline
- Asthma phenotype
- Asthma endotype
- Lung function measurements at screening and baseline
- E-diary measurements at baseline

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Patients will be randomised at a ratio of 1:1 to one of the following treatment groups:

1. 90 mg BI 655066 administered SC every 4 weeks, up to a total duration of 20 weeks.
2. Placebo administered SC every 4 weeks, up to a total duration of 20 weeks.

The following treatment period will be defined:

- Screening period: from the date of informed consent to the date of randomisation -1 day.
- Planned on-treatment period: 24 weeks from the date of randomisation
- Planned study period: 40 weeks from the date of randomisation
- Actual on-treatment period

- Post-treatment period

- Post-study period: from 20 weeks + 1 day after last dose onwards

6.2 IMPORTANT PROTOCOL VIOLATIONS

A PV is important if it affects the rights or safety of the study subjects or if can potentially influence the primary outcome measurement(s) for the respective subjects in a way that is neither negligible nor in accordance with the study objectives.

The following table defines the different categories of important PVs. They will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically based on data accumulated during the trial. A list of protocol deviations and of unresolved discrepancies will be discussed at the Blinded Report Planning Meetings (BRPMs). The decision whether the protocol deviation is an important PV will be made at the final BRPM prior to database lock (DBL).

Table 6.2: 1 Important protocol violations

Category/Code		Description	Example/Comment	Excluded from	Automatic / Manual
A		**Entrance criteria not met**			
	A1.1	Age < 18 or >75	Inclusion criteria 2	None	Automatic
	A1.2	Pre-bronchodilator FEV_1 not met at Visit 1B or Visit 2	Inclusion criteria 3	None	Automatic
	A1.3	History of asthma , or FEV_1 reversibility not met at visit 1B	Inclusion criteria 4	None	Automatic
	A1.4	Previous asthma therapy not met	Inclusion criteria 5	None	Automatic
	A1.5	History of severe asthma exacerbation not met	Inclusion criteria 6	None	Automatic
	A1.6	Current smoker; ex-smoker who stopped smoking within one year prior to screening or have a smoking history >=10 pack years	Inclusion criteria 7	None	Automatic
	A1.7	Not able to perform all trial related procedures	Inclusion criteria 8	None	Automatic
	A2.1	Not able to produce sputum, or sputum samples of insufficient quality	Exclusion criteria 4	None	Automatic
	A2.2	Oral corticosteroids use criteria not met	Exclusion criteria 10; Systemic corticosteroids CRF	None	Automatic
	A2.3	Other exclusion criteria not met	Other exclusion criteria not met as specified in the protocol	None	Automatic
B		**Informed consent**			
	B1	Informed consent not available/not done	Informed consent date missing; no signature on ICF	All	Automatic and Manual
	B2	Informed consent too late	Applies to all informed consents. Date of informed consent was after the date of any study-related procedure, i.e., after visit 1A. If patient signed the wrong version of ICF and then signed	None	Automatic and Manual

Category/Code		Description	Example/Comment	Excluded from	Automatic / Manual
			the correct version of ICF with date after randomisation, such cases will be discussed at MQRM/BRPM/DBL meetings.		
C		**Trial medication and randomisation**			
	C1.1	Incorrect trial medication taken at randomisation	Medication kit assigned not matching IVRS assignment at randomisation visit (Visit 2)	None	Automatic and Manual
	C1.2	Incorrect trial medication taken after randomisation	Medication kit assigned not matching IVRS assignment after randomisation visit (Visit 3 and onwards)	None	Automatic and Manual
	C2	Non-compliance			
	C2.1	Interval of two infusions of study medications <14 days	Patient did not meet minimum interval required for two consecutive infusions	None	Automatic
	C2.2	E-diary non-compliance at baseline	Baseline E-diary compliance < 75% or < 2 ACQ_5 sessions available	None	Automatic
	C2.3	Missing administration of study drug	Patients missing doses due to any reason	None	Automatic
	C3	Medication code broken inappropriately	To be discussed and decided during MQRM/BRPM	None	Manual
D		Concomitant medication			
	D1	Restricted medication use	Refer to Table 4.2.2.1: 1 in CTP.	None	Manual
Z		Other			
	Z1	Serious GCP non-compliance	Manual PVs reported by CML/CRA. Decision to be made during MQRM/BRPM	None	Manual
	Z2	Other PV affecting efficacy and possibly safety	Additional PV identified through monitoring which impacts the primary analysis and possibly patient's rights or safety, e.g., patients on non-stable dose To be discussed during MQRM/BRPM	None	Manual
	Z3	Other PV affecting safety only		None	Manual

6.3 PATIENT SETS ANALYSED

- Randomised set (RS):
  This patient set includes all randomised patients, whether treated or not.

- Full analysis set (FAS):
  This patient set includes all patients in the randomised set who receive at least one dose of investigational treatment.

The RS will be used for patient disposition, demographic, and baseline characteristics.
The FAS will be used for the primary efficacy evaluation and all safety evaluations.

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

E-diary data

The 24-hour rescue medication use (AM + PM) will be calculated for each day by adding the AM and PM puffs. An interval (AM or PM) that is missing leads to a missing 24-hour total and will be used as missing when calculating the weekly mean.

In-clinic pulmonary function testing data

If a patient takes rescue medication at a clinic visit before pre-bronchodilator pulmonary function tests (PFT), any measurements taken on and after the time of the rescue medication use will be set to missing. If the time of rescue medication use is unknown, data for the entire visit will be set to missing. If a patient takes rescue medication at a clinic visit after pre-bronchodilator PFTs, the measurements taken on and after the time of rescue medication use will be used.

Concomitant medication dates

The imputation rules will be described in the technical TSAP.

AE dates

Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”). (1)

Sputum cell counts

Missing sputum cell count data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The definition of baseline values is defined in Section 7.1 of the CTP.

7. PLANNED ANALYSIS

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

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 are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

A table of the number (%) of patients with concomitant diagnoses by system organ class (SOC) and preferred term (PT) will be included along with a supporting listing. Concomitant diagnoses will be coded with the most recent version of MedDRA in effect at database lock.

Frequency tables (%) will be presented for medical history of interest and asthma background characteristics.

Pulmonary medication will be summarized as the number (%) of patients taking pulmonary medications at baseline. The number (%) of patients who have dose reduction in maintenance therapy will also be summarized.

7.3 TREATMENT COMPLIANCE

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

Treatment compliance (%) = number of drug administrations / [(date of last drug administration – date of first drug administration) / 28 + 1] * 100%

E-diary compliance (%) for PEF = (number of PEF sessions / 2) / (date of discontinuation from the study – date of randomisation + 1) * 100%

E-diary compliance (%) for rescue medication = (number of rescue medication record / 2) / (date of discontinuation from the study – date of randomisation + 1) * 100%

E-diary compliance (%) for ACQ_5 = number of ACQ_5 record / [(date of discontinuation from the study – date of first drug administration) / 7 + 1] * 100%

7.4 PRIMARY ENDPOINT(S)

The analyses of primary endpoint will be performed as described in section 7.3.1 of CTP.

7.5 SECONDARY AND FURTHER 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

The analyses of secondary endpoints will be performed as described in section 7.3.2 of CTP.

7.7 EXTENT OF EXPOSURE

Extent of exposure, including days on treatment, follow-up time and observation time, will be summarized using descriptive statistics for days of exposure as well as number (%) of patients whose exposure falls in the categories with 4-week intervals.

On treatment (days) = drug stop date – drug start date + 28
Follow-up time (days) = max(0, date of discontinuation from the study – drug stop date – 28)
Observation time (days) = date of discontinuation from the study – drug start date + 1

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the FAS.

7.8.1 Adverse events

Unless otherwise specified, the 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.

Furthermore, for analysis of AE attributes such as duration, severity, etc., multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- 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)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

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' (3) [001-MCG-156].

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake till 130 days

after last drug intake will be assigned to the randomised treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after last drug intake + 130 days will be assigned to 'post-treatment' (for listings only). For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary SOC and PT. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (4), and for patients with serious adverse events.

The SOCs will be sorted according to the standard sort order specified by EMEA, PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5).

7.8.3 Vital signs

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

7.8.4 ECG

ECGs were collected with an adverse event recorded if the readout was associated with any clinical finding.

7.8.5 Others

Not applicable, there are no other safety analyses.

8. REFERENCES

1 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

3 *001-MCG-156*: "Handling and summarisation 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*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	**Date (DD-Mmm-YY)**	**Author**	**Sections changed**	**Brief description of change**
Final	**26-Oct-17**		None	This is the final TSAP without any modification