Boehringer Ingelheim

Trial Statistical Analysis Plan

BI Trial No.:	1200.205
Title:	GIDEON: GIOTRIF® in the first-line treatment of advanced NSCLC with EGFR activating mutations
Investigational Product(s):	GIOTRIF®
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	05DEC2017
Version:	Final 1.0

Signature Page

This Statistical Analysis Plan has been reviewed and accepted by:

19-12-2017
Date

Trial Clinical Monitor

12-12-2017
Date

Local Clinical Monitor

18-12-2017
Date

Trial Member Medicine

21-12-2017
Date

Trial Statistician (

12/11/2017
Date

Oversight Statistician

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
BI	Boehringer Ingelheim Pharma GmbH&Co. KG
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CTP	Clinical Trial Protocol
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
MedDRA	Medical Dictionary for Drug Regulatory Activities
NC	No change
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIS	Non-interventional study
NSCLC	Non-Small Cell Lung Cancer
OS	Overall survival
PFS	Progression free survival
PR	Partial Response
QLQ	Quality of Life Questionnaire
SAE	Serious Adverse event
SmPC	Summary of product characteristics
TEAE	Treatment-emergent AE
TS	Treated Set
TSAP	Technical Statistical Analysis Plan

3. INTRODUCTION

The purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the observational plan, 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 6 "Statistical Analysis". 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 9.3 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

None.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

- Progression-free survival rate after 12 months

5.2 SECONDARY ENDPOINT(S)

- Objective response rate (CR+PR)
- Tumor control rate (CR + PR + SD)
- Progression-free survival
- PFS of patients from start of treatment with Giotrif® until PD under osimertinib (Tagrisso®)
- PFS of patients from start of treatment with osimertinib (Tagrisso®) until PD under osimertinib (Tagrisso®)
- Safety
- Frequency and severity of diarrhoea, skin reactions, stomatitis and paronychia
- Treatment duration, interruptions and dose modifications
- Symptom control (cough, dyspnoea and pain) through EORTC questionnaire QLQ-C30/LC13

5.4 OTHER VARIABLE(S)

Other variables will be baseline characteristics and patient's characteristics such as age, gender, height and weight. Additionally information about concomitant medication, diagnosis, therapy data, starting dose of Giotrif®, dose adjustments, further therapies and comorbidities will be collected. Moreover, Charlson Score will be displayed.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In the presented study, treatment with GIOTRIF® will be according to SmPC.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.2	IC 2- Age >=18 years	Not met as specified in the protocol	None
	A1.3	IC 3- EGFR-TKI-naïve women and men with pathological confirmed NSCLC, stadium IV with EGFR activating mutations (Exon 18-21)	Exclusion criteria not met as specified in the protocol	None
	A1.4	IC 4- No diagnostic or therapeutic measures necessary, which go beyond clinical routine	Not met as specified in the protocol	None
	A2	Exclusion criteria not met	Not met as specified in the protocol	None
B		**Informed consent**		
	B1	Informed consent not available/not done (Inclusion criterion 1)	IC 01 not met as specified in the protocol or informed consent date missing	All

6.3 PATIENT SETS ANALYSED

Enrolled set (ES): All patients who gave their informed consent and for whom at least baseline data were documented

Treated set (TS): All patients who gave their informed consent and have at least one documented administration of GIOTRIF®.

Table 6.3: 1 Patient sets analysed

	Patient set	
Class of endpoint	ES	TS
Primary and secondary endpoints		X
Safety endpoints		X
Demographic/baseline	X	

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

In context of EORTC QLQ-C30 questionnaire, missing scale items can be replaced by the average of the answered items, if at least half of the items from the corresponding scale have been answered. Otherwise no scale score will be calculated. Regarding the dyspnea scale of the EORTC QLQ-LC13, no items will be replaced and the scale score will be set to missing, if one item is missing. No other missing data will be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline will include general patient data, information about anamnesis, pre-treatment, EGFR-mutations as well as registration and initial examination. Treatment with GIOTRIF® will be documented during the therapy. After 12 and 24 months follow up information's, like survival status and further therapies, will be documented.

Baseline: last value before first dose of Gideon or screening value

Treatment: values between first and last dose of Gideon

Follow up: values after last dose of Gideon

The EORTC questionnaires (QLQ-C30 and LC13) will be completed by the patient before the start of therapy and during the therapy every 8 weeks (=2 therapy months).

7. PLANNED ANALYSIS

All analyses in this study are descriptive; results are to be interpreted in an explorative manner.

For categorical variables summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. Percentages will be rounded to two decimal places. For continuous variables number of values, mean, standard deviation, minimum, Q1 (25% quantile), median, Q3 (75% quantile), maximum and number of missing values will be presented. 95% CI will be given when appropriate.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. All baseline analyses will be done for the enrolled and treated set, respectively.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. All analyses will be done for the treated set.

7.3 PRIMARY ENDPOINT(S)

For the PFS rate the Kaplan-Meier survival rate with double-side 95% CI after 12 months will be shown. For the calculation of the confidence intervals the Greenwood's variance estimator will be used. Subgroups will be compared by using log-rank test.

7.4 SECONDARY ENDPOINT(S)

All analyses will be descriptive. The exact 95% confidence interval will be calculated for the objective response rate and the tumor control rate. The PFS will be estimated by the Kaplan-Meier and 95% confidence intervals will be displayed. For the treatment duration and modifications regimens, duration of treatment and treatment interruptions will be shown. The number of patients with no/ one/ two or more dose modifications will be calculated. For the symptom control the duration to worsening of the symptoms (cough, dyspnoea and pain) will be analysed through the QLQ questionnaires and estimated by Kaplan-Meier. Subgroups will be compared by using log-rank test for time to event analysis, by χ^2-Test for categorical variables and by Wilcoxon Rank-Sum Test/Kruskal-Wallis Test for continuous variables when appropriate

7.6 EXTENT OF EXPOSURE

See secondary endpoints, i.e. treatment duration and dose modifications as well as survival.

7.7 SAFETY ANALYSIS

All patients who received at least one dose of Giotrif® will be included in the safety analysis. All analyses of adverse events will be descriptive and conducted according to Boehringer Ingelheim standards. AE's will be divided by CTCAE version 4.3. The main focus will be on treatment emergent events. All AE that occurred between start of treatment and 30 days after permanently discontinuation of therapy or end of study will be considered as treatment emergent and will be displayed in frequency tables. Non treatment-emergent events will be assigned to "screening" or "post-treatment" and only be displayed in listings. All analyses will be based on the treated set.

Furthermore the adverse events leading to dose reduction and those leading to therapy interruption will be shown.

Frequency, severity and causality of treatment-emergent AEs will be tabulated according to MedDRA-SOC and PT. Treatment-emergent SAEs will be tabulated as well as adverse events leading to treatment discontinuation. Additionally the safety analysis includes frequency, severity and causality of diarrhea, skin reactions, stomatitis and paronychia.

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.

An overall summary of adverse events will be presented.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with serious adverse events.

The system organ classes will be sorted alphabetically, preferred terms will be sorted by frequency (within system organ class).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE event provided that all of the following applies:

- All AE attributes are identical (PT, NCI-CTC grade, 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 classification into TEAE or Non-TEAE, the first documented start of event will be used.

8. REFERENCES

See Protocol (Version 5, 01.08.2015) as well as the underlying Boehringer Ingelheim guidelines, which are displayed in the following

1	*001-MCG-159_RD-03:* "Standard table shells for inferential and descriptive End-of-Text tables (EoT-Catalogue)", current version; IDEA for CON.
2	*001-MCG-410*: "Structure, Derivation, and Documentation of Analysis Data Sets", current version; IDEA for CON.
3	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
4	*001-MCG-741*: "Clinical subgroup analyses for local and regional Populations in Asia - Clinical Bridging Study Waiver (BSW) and Descriptive Subgroup Analysis (SGA) Reports" , current version; IDEA for CON.
5	*001-MCP-090:* "BI Style Guide", current version; IDEA for CON.
6	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
7	*001-MCS-50-413*: "Handling of Protocol Violations in Clinical Trials and Projects", current version; group: Study Conduct; IDEA for CON.
8	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON. *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", version 5; IDEA for CON.
9	*001-MCG-159*: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
10	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
11	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
12	*001-MCG-157*: "Handling, 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
Draft v1.0	**24-AUG-2016**		None	This is the first Draft-Version of TSAP without any modification
Draft v0.2	**25-SEP-2017**		3	ICH deleted, "protocol" replaced by "observational plan"
			5.2	Adaption of secondary endpoints
			5.4	Starting dose and dose modifications added
			6.1	"product information" replaced by "SmPC"
			6.2	A1.1 deleted, A1.2 adapted to correct age
Draft v0.3	**18-OCT-2017**		2	SmPC added
			6.3	Demographic/baseline analyses only for ES
			6.7	Time windows added
			10	History adapted