SIGNATURE INFORMATION

Document: 1200-0038--tsap

Document No.: T11-1081-01

Title Phase I, open label trial to explore safety of combining BIBW 2992 and Radiotherapy with or without Temozolomide in newly diagnosed GBM

SIGNATURES (ELECTRONICALLY OBTAINED)

Meaning of Signature:	Signed by:	Date signed: (GMT)
Author-Trial Statistician	[redacted]	12/1/2011 10:01:36
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Author-Trial Clinical Monitor		12/1/2011 11:09:50
Verify Paper Signature Completion		12/1/2011 14:25:56
Approval-Project Statistician		12/1/2011 15:22:51

SIGNATURE INFORMATION (continued)

Document 1200-0038--tsap

Document No.: T11-1081-01

Title Phase I, open label trial to explore safety of combining BIBW 2992 and Radiotherapy with or without Temozolomide in newly diagnosed GBM

SIGNATURES (ELECTRONICALLY OBTAINED)
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Meaning of Signature:	**Signed by:**	**Date signed: (GMT)**

Boehringer Ingelheim

Trial Statistical Analysis Plan

T11-1081-01

BI Trial No.:	1200.38
Title:	Phase I, open label trial to explore safety of combining BIBW 2992 and Radiotherapy with or without Temozolomide in newly diagnosed GBM (Including Protocol Amendment 1 [U09-1323-01-AM1], Protocol Amendment 2 [U09-1323-01-AM2], Protocol Amendment 3 [U09-1323-01-AM3])
Test substance:	Tomtovok ®, afatinib (BIBW 2992)
Responsible trial statistician:	[redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	01 December 2011 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
BI	Boehringer Ingelheim
BIBW 2992	Afatinib
BMI	Body mass index
BSA	Body surface area
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DLT	Dose limiting toxicity
EMA	European Medicines Agency
ICH	International Conference on Harmonisation
IPV	Important protocol violation
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O^6-methylguanine-DNA methyltransferase
NCI	National Cancer Institute
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RT	Radiotherapy
SAE	Serious adverse event
SD	Standard deviation
SIAE	Significant adverse event
SOC	System Organ Class
TMZ	Temozolomide
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per International Conference on Harmonisation (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 Trial Statistical Analysis Plan (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, randomisation.

SAS® Version 9.2 (or later version) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

See statistical changes described in:

- Protocol amendment 3, dated 07 February 2011 (1).

In addition the following changes were not documented in CTP amendments.

Section 7.3.3 of the CTP states:

> *In-depth analyses will describe the onset, CTCAE grades, duration and clinical consequences of:*
>
> - *Diarrhoea;*
> - *Nausea and vomiting;*
> - *Rash and acne;*
> - *Worsening of cardiac left ventricular function;*
> - *Worsening of laboratory abnormalities;*
> - *Other AEs that occur with sufficient overall frequency (>10%).*

However project defined special grouped-term search categories have not been identified for either worsening of cardiac left ventricular function or laboratory abnormalities as reported adverse events (AEs), therefore in-depth analyses will not be performed as described above. Instead, descriptive statistics are planned for left ventricular ejection fraction which will include worst value on treatment and change from baseline. Furthermore, clinically significant laboratory abnormalities will be analysed according to Boehringer Ingelheim (BI) standards. Also, dependent on the final sample size, it is possible that all AEs will occur with frequency >10%; thus the other AEs that will be analysed in-depth will be determined pragmatically by the trial team.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Investigator defined dose limiting toxicity during concomitant treatment period:

At least one AE meeting the criteria for dose limiting toxicity (DLT; as determined by the investigator and defined in Section 5.2.3 of the CTP) with onset during the 42 day concomitant treatment period when trial medication is given concomitantly with radiotherapy (RT).

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 CTP.

5.2.3 (Other) Secondary endpoints

Adverse events:

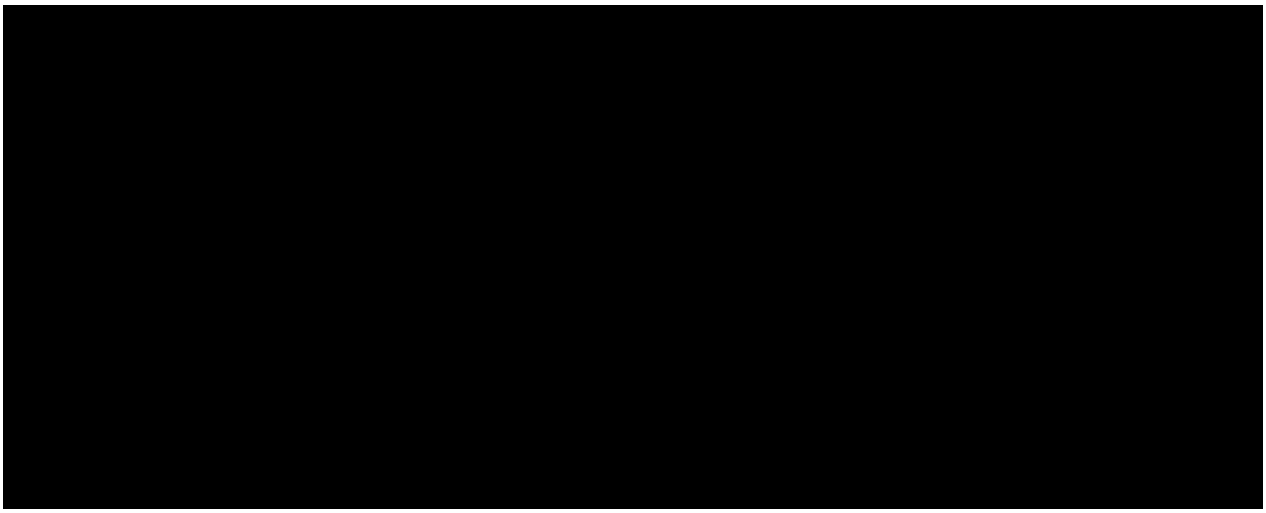
Maximum grade (severity) of AEs according to the United States National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Objective response:

Best overall response of complete response (CR) or partial response (PR), where best overall response is the best overall response to trial medication (without clinical disease assessment) according to the Macdonald criteria (defined in Section 5.1.3 of the CTP) recorded since first administration of trial medication and until disease progression or start of further anti-cancer treatment.

Pharmacokinetic (PK) parameters:

The derivation of standard PK parameters is performed according to BI standards. (2)



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For safety analyses, data up to and including 28 days after last treatment intake will be considered as on-treatment.

Patients will be analysed according to the treatment group initially assigned. All planned analysis will be presented by this treatment group. Handling of patients where treatment group assignment has not been followed will be handled on a case-by-case basis, to be agreed at report planning meetings.

Analyses for Regimen M and Regimen U will be presented separately.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Important protocol violations (IPVs) are defined according to BI standards (3) and are specified in Table 6.2: 1 of this document. A per protocol set will not be defined for the analysis of this trial but IPVs will be described for patients in the treated set (as defined in Section 6.3 of this document).

Table 6.2: 1 Important Protocol Violations

Category / Code		**Description**	**Comment/Example**
A		Entrance criteria not met	
	A1	Diagnosis of trial disease questionable	Inclusion criteria IN1 not met. or Trial diagnosis is not histologically-confirmed WHO Grade IV newly diagnosed malignant glioma.
	A2	MGMT testing	
	A2.1	Methylated MGMT status not proven (Regimen M only)	For patients in Regimen M enrolled before implementation of CTP amendment 3 only: Inclusion criteria IN2 not met. or MGMT test result is not methylated. or Date of MGMT test is missing.
	A2.2	Unmethylated MGMT status not proven (Regimen U only)	For patients in Regimen U enrolled before implementation of CTP amendment 3 only: Inclusion criteria IN2 not met. or MGMT test result is not un-methylated. or Date of MGMT test is missing.
	A2.3	Tumour material not available for MGMT testing or MGMT test results not available	For patients in Regimen M enrolled after implementation of CTP amendment 3 only: Inclusion criteria IN2 not met. or Both of the following: MGMT test result not already available. and Date of MGMT test is missing.
	A3	Safety exclusion criteria met	
	A3.1	Prohibited baseline condition or diagnosis	At least one of exclusion criteria EX6-E11is met. or At least one baseline condition meeting exclusion criteria (defined in Section 3.3.2 of the CTP).
	A3.2	LVEF assessment indicating inadequate cardiac function	Exclusion criteria EX12 is met. or Screening left ventricular ejection fraction (LVEF) both missing or < 50%.
	A3.3	Laboratory result indicating inadequate organ function	At least one of exclusion criteria EX13-E17 is met. or Screening and baseline laboratory results both missing or meeting exclusion criteria (defined in Section 3.3.2 of the CTP).
	A3.4	Negative pregnancy test result not obtained	Exclusion criteria EX19 is met. or For female patient with reproductive potential, screening pregnancy test is positive or not done.
	A3.5	Hypersensitivity to trial medication	Exclusion criteria EX22 is met.

Table 6.2: 1 Important Protocol Violations (continued)

Category / Code		Description	Comment/Example
	A3.6	Requirement for treatment with P-gp inhibitors or P-gp inducers	For patients enrolled after implementation of CTP amendment 2 only: Exclusion criteria EX23 is met.
B		Informed consent	
	B1	Informed consent not given	
	B1.1	Informed consent 1 not given	For patients enrolled before implementation of CTP amendment 3 and who do not already have an MGMT test result only: Inclusion criteria IN7 is not met. or Date of informed consent 1 is missing.
	B1.2	Informed consent 2/3 not given	Inclusion criteria IN7 is not met. or Date of informed consent 2/3 is missing.
	B2	Informed consent given too late	
	B2.1	Informed consent 1 given too late	For patients enrolled before implementation of CTP amendment 3 and who do not already have an MGMT test result only: Date of any study specific procedures before date of informed consent 1.
	B2.2	Informed consent 2/3 given too late	Date of any study specific procedures before date of informed consent 2/3.
C		Trial medication and randomisation	
	C1	Incorrect trial medication taken	
	C1.1	Incorrect TMZ dosing during concomitant treatment period (Regimen M only)	For patients in Regimen M only: At least one TMZ dose during concomitant treatment period not according to the dose described in Section 4.1.4.2 of the CTP.
	C2	Treatment group assignment not followed	
	C2.1	Afatinib treatment during concomitant treatment period in discordance with treatment group assignment	Initial dose of afatinib does not correspond to treatment group assignment. or Afatinib dose changes during concomitant treatment period not according to the dose reduction scheme described in Section 4.1.4.1.2 of the CTP.
	C2.2	TMZ treatment during concomitant treatment period in discordance with treatment group assignment	For patients in Regimen M only: No dose of TMZ during concomitant period. or For patients in Regimen U only: At least one dose of TMZ during concomitant treatment period.
	C3	Non-compliance	
	C3.1	Afatinib non-compliance during concomitant treatment period	Total number of doses of afatinib missed for reasons other than AE is more than 8 during concomitant treatment period. or Number of consecutive doses of afatinib missed for non-AE reasons is more than 5 during concomitant treatment period.

Table 6.2: 1 Important Protocol Violations (continued)

Category / Code		Description	Comment/Example
	C3.2	TMZ non-compliance during concomitant treatment period (Regimen M only)	For patients in Regimen M only: Total number of doses of TMZ missed for reasons other than AE is more than 8 during concomitant treatment period.
	C4	Trial specific PVs related to trial medication	
	C4.1	Dose reduction scheme for afatinib not followed	Regardless of treatment period, incidence of DLT without subsequent adherence to the dose reduction scheme described in Section 4.1.4.1.2 of the CTP.
	C4.2	TMZ treatment continued but re-treatment criteria not met (Regimen M only)	For patients in Regimen M only: Following the concomitant treatment period, TMZ not terminated despite re-treatment criteria described in Section 4.1.4.2 of CTP not met.
D		Concomitant medication	
	D1	Prohibited concomitant medication	
	D1.1	Prohibited medication use before the start of study treatment period	Inclusion criteria IN6 is not met. or At least one of exclusion criteria EX1-EX5 is met. or Prohibited concomitant therapy use before start of study treatment (defined in Sections 3.3.1 and 3.3.2 of the CTP).
	D1.2	Prohibited medication use during study treatment period	Prohibited concomitant therapy use during study treatment (defined in Section 4.2.2 of the CTP).
	D2	Mandatory medication not taken	
	D2.1	Incorrect dose of radiotherapy administered during the concomitant treatment period	Radiotherapy total dose not equal to 60 Gy.
	D2.2	Pneumocytis pneumonia prophylaxis not taken during concomitant treatment period (Regimen M only)	For patients in Regimen M only: Concomitant therapy use during concomitant treatment period does not include appropriate prophylaxis.
G		Trial specific protocol violations	
	G1	Non-adherence to safety withdrawal criteria	Trial medication continued despite withdrawal criteria in Section 6.3 of the CTP met.
	G2	Other protocol violations affecting patient rights or safety	Any other protocol violation that affects the rights or safety of trial patients.

6.3 PATIENT SETS ANALYSED

Treated set:

This patient set includes all patients who were dispensed trial medication and were documented to have taken at least one dose of investigational treatment. The treated set is to be used for all planned analysis.

[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

PK parameters:

Missing data and outliers of PK data are handled according to BI standards. (2)

Time from first histological diagnosis:

If day of first histological diagnosis is missing it will be imputed using 15.

If both day and month of first histological diagnosis is missing they will be imputed using 1st July.

Adverse events:

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline:

The measurement observed immediately preceding start of trial medication will be assigned to baseline; note that for some trial procedures (vital signs, mini mental state examination and laboratory tests) this may be the value measured on the same day trial medication was started.

7. PLANNED ANALYSIS

For end of text tables, unless otherwise specified, the set of summary statistics is: N, mean, standard deviation (SD), minimum, median 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. Percentages will be given in whole numbers. The category missing will be displayed only if there are actually missing values. Unless otherwise specified, percentages will be based on all patients in the respective patient set 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.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINTS

DLT during concomitant treatment period:

The analysis of the primary endpoint will summarise DLT using descriptive statistics with the aim of determining the maximum tolerated dose (defined in Section 5.2.4 of the CTP) of:

- Afatinib in combination with TMZ when given concomitantly with RT (Regimen M);
- Afatinib when given concomitantly with RT (Regimen U).

An overall summary of AE occurrences with onset during the concomitant treatment period, which were defined to be DLTs by the investigator, will be presented. This will include the following AE attributes:

- Preferred term,
- Maximum CTCAE grade,
- Outcome,
- Time to first occurence (relative to start of trial medication; see Section 9.2 of this document).

Any AE meeting the criteria for DLT, regardless of date of onset, will be considered a significant adverse event (SIAE). The analysis of non-serious SIAEs and serious adverse events (SAEs) is described in Section 7.8.1 of this document.

DLTs with onset after the concomitant treatment period will be listed separately.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 (Other) Secondary endpoints

Adverse events:

See Section 7.8.1 of this document.

Objective response:

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

PK parameters:

The analysis of standard PK parameters is performed according to BI standards. (2)

[redacted]

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). For this purpose, AE data will be combined in a 2-step procedure into AE records.

In a first step, AE occurrences, i.e. AE entries on the case report form, will be collapsed into AE episodes provided that all of the following applies:

- The same Medical Dictionary for Regulatory Activities (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.

In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are

assigned to the same treatment. For further details on summarisation of AE data, please refer to BI standards for AEs. (5)

CTCAE grade and investigator-defined DLT will be included as additional AE attributes. For the purposes of collapsing, additional deterioration rules will be defined for both attributes. In addition, in this trial, the standard AE attribute 'action taken with trial drug' is separated for afatinib and TMZ; the standard condensing rules will be applied for both.

The analysis of AEs will be based on the concept of treatment emergent adverse events. That means that all AEs occurring between first administration of trial medication until 28 days after last administration of trial medication will be assigned to trial medication. All AEs occurring before first administration of trial medication will be assigned to ‘screening’ and all AEs occurring after last administration of trial medication + 28 days will be assigned to ‘post-study’.

Any AE meeting the criteria for DLT (defined in Section 5.2.2 of the CTP), regardless of date of onset, will be considered an SAE or SIAE.

According to ICH E3 (6), AEs classified as ‘other significant’ will include those non-serious and non-significant AEs:
(i) with ‘action taken = discontinuation’ or ‘action taken = reduced’, or
(ii) with marked haematological and other lab abnormalities or which lead to significant concomitant therapy as identified by the Trial Clinical Monitor/Investigator at a report planning meeting.

An overall summary of AEs will be presented, this will include the additional AE attributes maximum CTCAE grade and investigator defined DLT.

The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with other significant AEs according to ICH E3 (5), for patients with non-serious SIAEs, for patients with SAEs, for patients with investigator defined DLTs and for patients with related AEs. An additional table will be produced of AEs stratified by the attribute maximum CTCAE grade.

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

7.8.1.1 Adverse events of special interest

The following AEs are considered of special interest for this trial:

- Diarrhoea,
  To be identified by the PT ‘Diarrhoea’;
- Nausea and vomiting,
  To be identified by the PTs ‘Nausea’ and ‘Vomiting’;
- Rash and acne,
  To be defined by the PTs contained within the project-defined special grouped-term category 'RASH/ACNE';

- Other AEs that occur with sufficient overall frequency,
  To be determined by the trial team at the report planning meeting prior to database lock.

An overall summary of each of these AEs of special interest will be presented. This will include the additional AE attributes 'Patients with investigator-defined DLTs', 'Maximum CTCAE grade' and 'Time to first occurrence' (see Section 9.2 of this document).

In addition, the frequency of patients with AEs will be summarised by treatment and project-defined special grouped-term category or preferred term. Where applicable, AE PTs will be re-categorised into one of the following grouped-term categories:

- Fatigue (FATIGUE);
- Nail effect (NAILS);
- Ocular effect (OCULAR);
- Rash and acne (RASH/ACNE);
- Stomatitis (STOMA).

Otherwise, AEs will be categorised according to MedDRA PT. Further tables will be provided for patients with related AEs for AEs stratified by the attribute maximum CTCAE grade.

The PTs identified within each of the project-defined special grouped-term categories will be listed.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards. (7)

7.8.3 Vital signs

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

7.8.4 ECG

This section is not applicable because only limited ECG data are collected. Clinically relevant ECG findings will be reported as AEs.

7.8.5 Others

Left ventricular ejection fraction:

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

Karnofsky performance scale:

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

Mini mental state examination:

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

8. REFERENCES

1 *U09-1323-01-AM3*: [redacted] Phase I, open label trial to explore safety of combining BIBW 2992 and Radiotherapy with or without Temozolomide in newly diagnosed GBM (trial 1200.38) 07 February 2011.

2 *029-DCP-102*: "Noncompartmental Pharmacokinetic Analyses of Clinical Studies", current version; IDEA for CON.

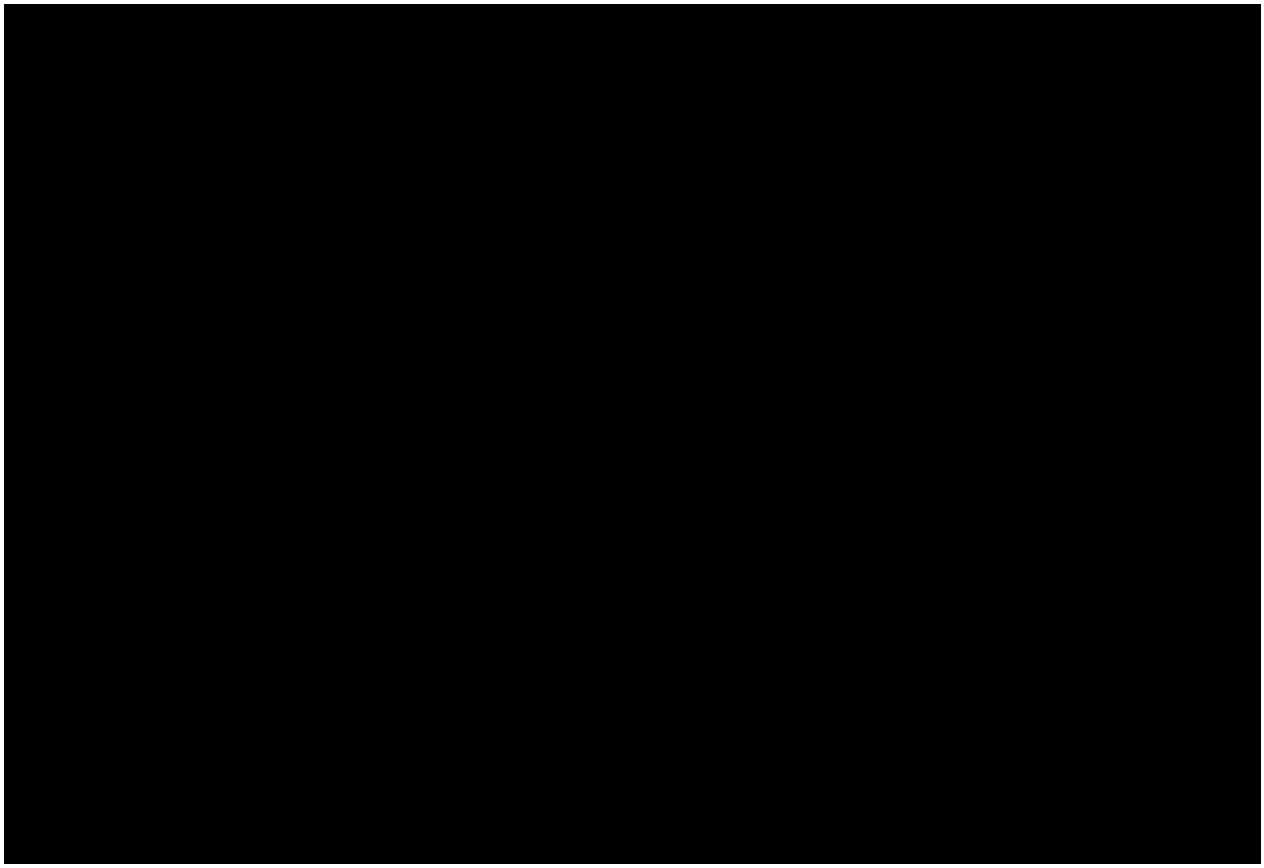
3 *001-MCG-158*: “Handling of Protocol Violations ", current version, IDEA for CON.

4 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

5 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

6 *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.

7 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.



10. HISTORY TABLE

Version No.	Date (dd Mmm yyyy)	Author	Sections changed	Brief description of change