NOVARTIS

Clinical Development

AMG334/Erenumab/Aimovig®

CAMG334ADE03 / NCT04084314

Assessment of Prolonged safety and tOLerability of erenumab in migraine patients in a Long-term OpeN-label study (APOLLON)

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
CRF	Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
IA	Interim Analyses
IAS	Interim Analysis Set
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analysis according to Section 12 of the study protocol v01 for AMG 334 Study CAMG334ADE03 dated April 30, 2020. The scope of this plan includes the primary, secondary [redacted] analyses which will be executed by the CRO ([redacted]).

1.1 Study design

This is an open-label, multi center, single arm study with flexible dosing allowing both dose adjustment and one drug holiday per patient.

The study design consists of 3 parts:

• **Screening Epoch** (0 - 2 weeks): required for all patients to assess initial eligibility.

• **Open-label Treatment Epoch** (128 weeks): Individual patients are treated for 128 weeks in the open-label treatment phase. During this open-label Treatment Epoch the erenumab dose may be adjusted from 70 mg to 140 mg or vice versa by discretion of the physician at any scheduled study visit. Additionally, a voluntary single treatment interruption (‘drug holiday’) of up to 24 weeks (approximately six months) may be introduced after at least 12 weeks of treatment in the open-label Treatment Epoch.

• **Follow-up Epoch** (4 weeks): A Follow-Up Visit 4 weeks after the last regular study visit (8 weeks after last IMP application) will be required as part of routine safety monitoring.

End of trial will occur when the last patient completes last visit (LPLV).

This 128-week open-label study will provide further treatment to patients still blinded for the randomization of the study CAMG334ADE01. In general, the 750 subjects randomized for clinical trial CAMG334ADE01 will be eligible for participation in the open-label study. It is estimated that approximately 75% to 85% of the study population meaning 563~638 subjects will enroll in the open-label study.

This is a single arm study. All patients will receive Erenumab. No randomization is required.

[redacted]

1.2 Study objectives, endpoints and estimands

The purpose of this study is to determine the long-term safety, efficacy and quality of life data of erenumab in patients with episodic or chronic migraine.

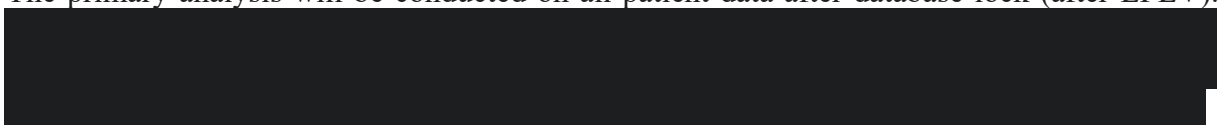
Primary Objective • To evaluate the long-term safety of 70 and 140 mg erenumab in patients with episodic or chronic migraine.	**Endpoint for primary objective** • Exposure adjusted incidence rate of AE during Open-label Treatment Epoch per 100 subject years
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**

• To evaluate the long-term tolerability of 70 and 140 mg erenumab in patients with episodic or chronic migraine.	• Proportion of patients discontinuing open-label Treatment Epoch due to AE • Proportion of patients discontinuing open-label Treatment Epoch due to non-AE reasons

2 Statistical methods

2.1 Data analysis general information

The primary analysis will be conducted on all patient data after database lock (after LPLV).



Analyses will be performed by [redacted]. SAS Version 9.4 will be used for all analyses. Tables and lists will be produced by the SAS Output delivery system (ODS) as rtf document which is transferred into docx-Format to reduce size.

General descriptive statistical rules:

Categorical data will be presented as frequencies and percentages. In general, missing values are not considered for calculation of percentages (i.e., adjusted percentages are calculated) if not otherwise specified.

For continuous data, mean, standard deviation, median, minimum and maximum will be presented.

General information on decimal places and other output-related information will be specified in tables, figures and listing (TFLs) shells accompanying this analysis plan. A separate TFL document will be prepared for each of the interim and final analysis.

2.1.1 General definitions

Study treatment erenumab

Novartis will supply the market sourced investigational medicinal product (IMP) erenumab in pre-filled autoinjectors containing 70 mg or 140 mg erenumab. When not specifically specified, "erenumab" refers to the individual erenumab dose of 70 mg or 140 mg.

Migraine-specific medication

Medication belonging to the triptan or ergotamine family.

2.1.1.1 Study dates

First IMP Dose Date

The first IMP dose date is the date on which a subject is administered the first dose of erenumab following screening. For subjects who are screened but no dose administration is documented, first IMP Dose Date is considered missing.

Last IMP Dose Date

The last IMP dose date for each subject is defined as the latest date of a dose administration.

Time under treatment

Time under treatment is defined as (Last IMP Dose Date + 28 – First IMP Dose Date) - Duration of treatment interruption due to drug holiday (if applicable).

Exposure-adjusted incidence rate of AE

Exposure-adjusted patient incidence rate of AE is defined as the total number of patients who reported an AE in a given time period of follow up divided by total patient-years of exposure in that period.

Total patient-years of exposure is defined as the sum of the duration of exposure from first IMP dose to the earliest of end-of-study date, end-of-OLTP date, or first report of event across all patients during the OLTP.

Study Day

Study Day 1 is defined as the first IMP dose date. For patients who are screened but not dosed after inclusion, Study Day 1 is defined as the date of screening visit.

Study Day is defined as the number of days from Study Day 1.

Before Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1)

On or after Study Day 1:

Study Day = (Date of Interest – Date of Study Day 1) + 1

Therefore the day prior to Study Day 1 is Day -1.

Drug holiday

Drug holiday is defined as a voluntary single treatment interruption of up to 24 weeks introduced after at least 12 weeks of treatment in the open-label Treatment Epoch.

After the "Planned date of last dose before drug holiday" starts a 28 day drug holiday initiation period, followed by the actual drug holiday period (see definitions below).

Drug holiday planned

Drug holiday is defined as planned if in the eCRF "Planned date of last dose before drug holiday" is not missing.

Drug holiday started

Drug holiday is defined as started if in the eCRF "Planned date of last dose before drug holiday" is not missing and lies at least 4 weeks before the cut-off date (regarding the interim analysis) resp. end of study date and up to day 28 after the "Planned date of last dose before drug holiday" no IMP application is documented.

Return to treatment after drug holiday

Patients are defined as returned after drug holiday if in the eCRF "Date of first dose after drug holiday" is not missing.

Completion of drug holiday

Patients are defined to have completed their drug holiday if they either returned after drug holiday (see below) or if they discontinued study treatment, i.e. date of first dose after drug holiday or date of discontinuation of study treatment or date of study completion/discontinuation is given.

Drug holiday initiation period

The drug holiday initiation period [redacted] is defined as the 28 days-interval after start of the drug holiday initiation period.

Start of drug holiday initiation period

The start date of drug holiday initiation period is defined as date of "planned date of last dose before drug holiday" from the eCRF + 1.

Start of actual drug holiday period

The start date of the actual drug holiday period is defined as date of "planned date of last dose before drug holiday" + 28.

Patient-level End of Study (EoS) Date

The end of study (EoS) date for each subject is defined as the last date on which the subject participated in the study. The date will be recorded on the Treatment / study Completion eCRF page (Date of study completion/discontinuation).

On-treatment period

The on-treatment period lasts from the date of first administration of study treatment to 84 days after the date of the last actual administration of study treatment.

2.1.1.2 Visit and analysis window

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to a study visit.

The nearest study day window will be utilized to define study visit for lab, vital signs, ECG and PROs collected during office visits [redacted] before dose is administered.

2.1.1.3 Demographics and other baseline characteristics

Patient demographic and baseline characteristic data have been collected on all patients including: age, sex, race, relevant medical history/current medical condition present before signing informed consent for trial CAMG334ADE01 (HER-MES). These data from HER-MES trial will also be included in the analyses described in this SAP.

Prior headache characteristics and previous headache medication history prior to treatment in trial CAMG334ADE01 (HER-MES), including information on the suitability for migraine prophylactics will be collected as part of baseline characteristics.

Relevant medical history/current medical conditions present before signing the Informed consent for trial CAMG334ADE03 (APOLLON) will be recorded on the 'Medical History' eCRF page. Medical history and adverse events from the HER-MES trial represent medical history in APOLLON trial.

Prior and concomitant medication in APOLLON trial will be recorded on the 'Prior/concomitant medication/non-drug therapies' eCRF page. Ongoing medication from HER-MES will be taken over on the APOLLON eCRF page 'Ongoing concomitant medication/non-drug therapies from HER-MES'. All concomitant medication from the HER-MES trial will be taken over as prior resp. concomitant medication. A comparison between the data records takes place to filter out duplicate entries.

2.1.1.4 Safety endpoints

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Discontinuation of treatment due to AE during the Treatment Epoch

Discontinuation of treatment due to AE during the Treatment Epoch is determined by the flag on the Treatment Completion eCRF page. "Death" as a reason for treatment discontinuation will be also included in AEs leading to treatment discontinuation.

Treatment-Emergent Adverse Event (TEAE)

Treatment emergent adverse events are defined as AEs occurred on or after the first dose of study treatment. AEs registered prior and after the first dose of study treatment are considered as treatment emergent if they have increased severity based on preferred term any time after the first dose of study treatment.

In case of missing data on a day of AE start date, the AE is considered as treatment emergent if *date of first dose of study treatment* $\leqslant$ *latest possible start date*

Please, see section 5.1.2 AE date imputation for "latest possible start date" definition.

Serious Adverse Event (SAE)

SAEs are determined by the flag on the Adverse Events eCRF page.

Treatment-Related Adverse Event

Treatment-emergent adverse event is defined as treatment-related, if investigator considered it as having a reasonable possibility to be related to study treatment, which is reflected in the eCRF with a corresponding flag.

Adverse Event leading to dose adjustment

Adverse event is defined as leading to dose adjustment if at least one of the following actions was taken with the study treatment due to AE:

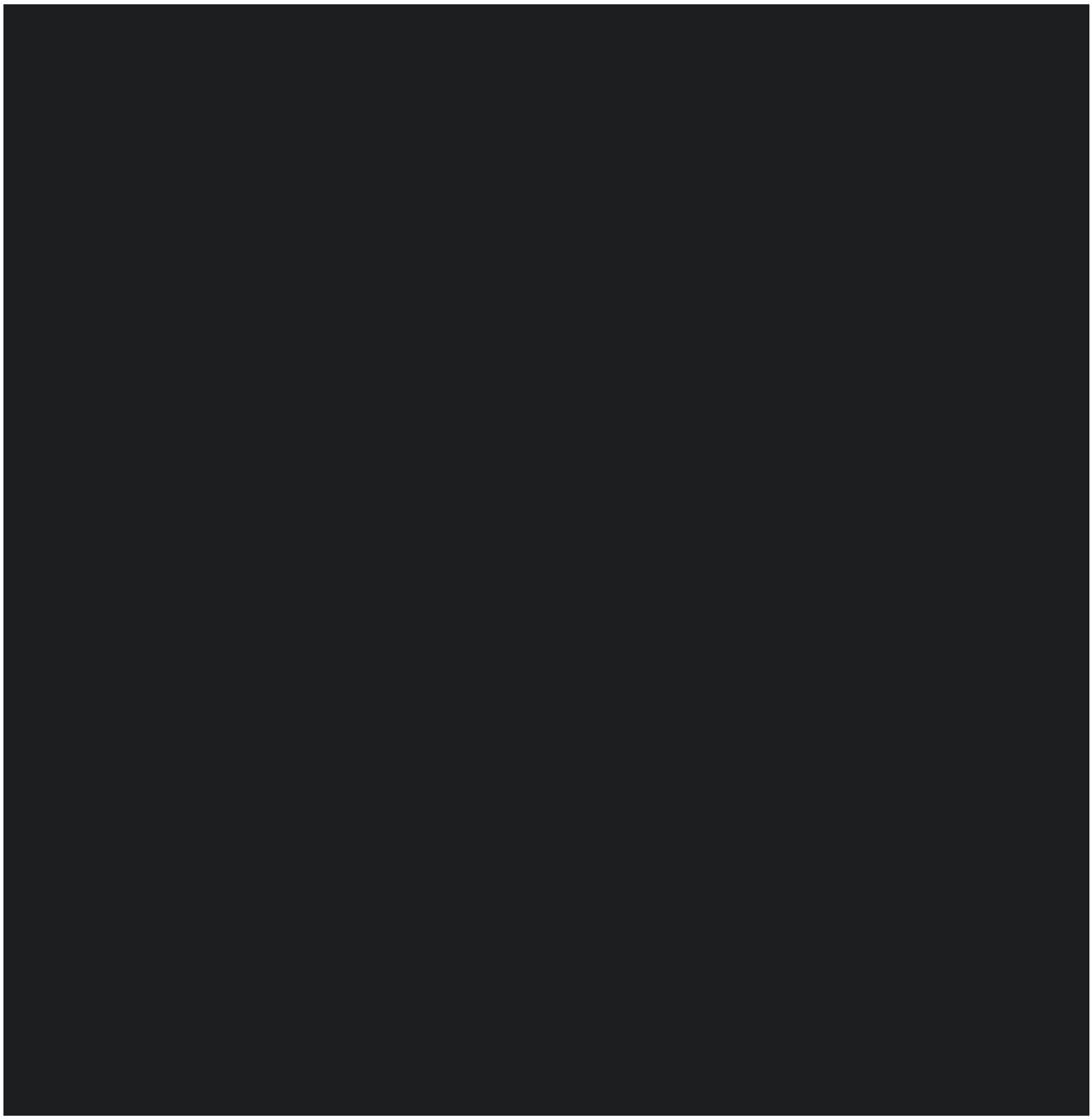
- dose increased
- dose reduced
- drug interrupted
- drug withdrawn

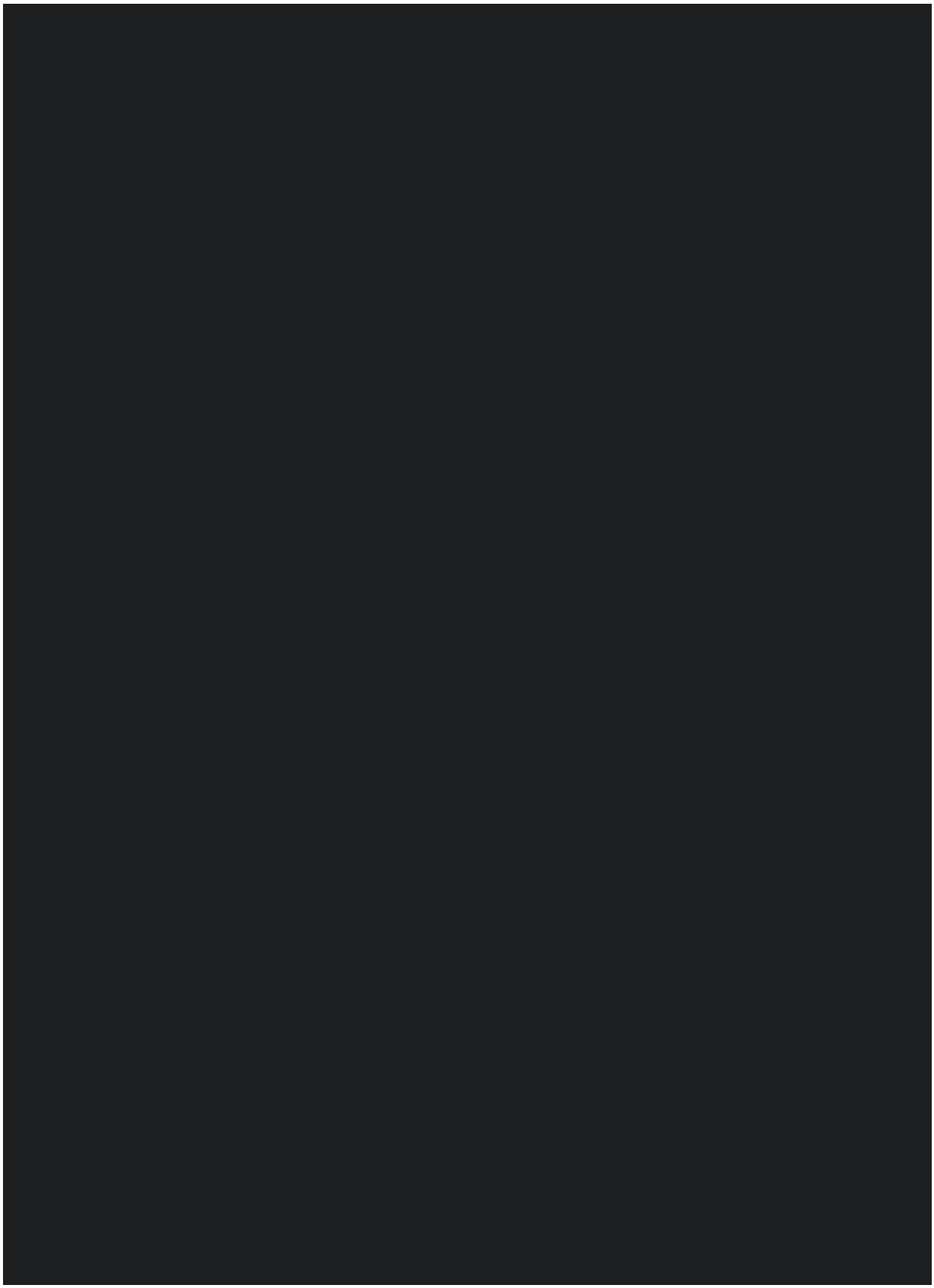
Duration of exposure to IMP

For all calculations of exposure, dose date refers to receiving dose > 0. The duration of exposure to IMP is computed as min (last IMP dose date + 27, EoS date) – first IMP dose date + 1 either including the time of drug holiday or excluding the time of drug holiday.

Subject Incidence

The subject incidence for a given event in a given period is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who entered that period. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.





2.2 Analysis sets

The **Safety Set (SAF)** comprises all subjects who received at least one dose of study treatment in the open-label treatment epoch of CAMG334ADE03.

The **Full Analysis Set (FAS)** is equivalent to the safety set.

The **Interim Analysis Set (IAS)** consists of all Patients from FAS with planned or conducted drug holiday documented up to cut-off date for interim analysis.

The **Drug Holiday Analysis Set (DHAS)** consists of all Patients from FAS with planned or conducted drug holiday.

2.2.1 Subgroup of interest

Subgroup analyses are planned only for the primary endpoint (see section 2.5.4 Sensitivity analyses).

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be based on all screened patients data.

A patient disposition summary will include number and percentage of patients, concerning

- Screening: A patient is defined as screened if signed informed consent is available
- Screening failure: A patient is defined as screening failure if he was screened but did not enter the treatment epoch

The number of patients within each of the analysis sets (FAS, SAF, IAS, DHAS) used in the study will be given.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data collected in trial CAMG334ADE01 (HER-MES) will be summarized descriptively for all subjects using the FAS.

Patient demographic data includes age (years), sex, race, weight (kg), height (cm), BMI (kg/m2), aura and disease duration.

Baseline disease characteristics contain following information assessed at baseline (see section 2.1.1 General definitions for baseline definition):

- Monthly migraine days
- Monthly headache days
- Acute headache medication (none vs. migraine-specific vs. non migraine-specific)
- Prior prophylactic treatment failure status (naïve vs. prior prophylactic treatment failure)

2.3.3 Medical history

Relevant medical history/current medical conditions present before signing the Informed consent will be recorded on the 'Medical History' eCRF page. Medical history and adverse events from the HER-MES trial will be taken over as medical history.

General medical history data includes medical history term, which will be summarized by system organ class and preferred term in the MedDRA dictionary.

Medical history possibly contributing to liver dysfunction data includes medical history term, which will be summarized by system organ class and preferred term in the MedDRA dictionary.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The analysis of study treatment data will be based on the SAF.

A data listing and a summary of erenumab administered will be provided. The summary will include

- duration of exposure summarized descriptively, patients assigned to 70 mg or 140 mg erenumab dose will be analyzed together under one treatment arm erenumab
- number and percentage of patients with starting dose of 70 mg or 140 mg
- number and percentage of patients with dose reduction or dose increase and the corresponding reason

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medication will be recorded on the 'Prior/concomitant medication/non-drug therapies' eCRF page. Ongoing medication from HER-MES will be recorded on the eCRF page 'Ongoing concomitant medication/non-drug therapies from HER-MES'. All concomitant medication from the HER-MES trial will be taken over as prior or concomitant medication.

The number and percentage of patients receiving rescue medications will be reported. The number and percentage of patients receiving concomitant medications and significant non-drug therapy will be summarized by ATC level 1 and preferred name (coded by WHO Anatomic Therapeutic Chemical classification [ATC]) and by treatment group.

The use of concomitant medications and significant non-drug therapy during the follow-up period will be summarized in the same way, in a separate table.

Data listings of rescue medications and concomitant medications and significant non-drug therapy will be provided.

2.5 Analysis supporting primary objective(s)

The primary aim of the study is to evaluate the long-term safety of 70 and 140 mg erenumab in patients with episodic or chronic migraine.

Analysis on primary endpoint should be done based on the Safety Set (SAF).

2.5.1 Primary endpoint(s)

The primary endpoint variable is the exposure adjusted incidence rate of AEs during the open-label treatment epoch per 100 subject years.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analyses will be conducted dividing the number of AEs by the time under treatment and standardizing it per 100 person-years. Exact Pearson-Clopper confidence intervals for single proportions will be calculated in order to evaluate the precision of the estimated parameter. No formal hypotheses testing will be conducted.

2.5.3 Handling of missing values/censoring/discontinuation

Missing data will not be imputed for primary endpoints.

For every patient, it can be determined whether he/she discontinued for AE-related reasons. Non-AE-related discontinuations or losses to follow up will not be counted as AE-related discontinuations. AE-related discontinuations are counted as events, discontinuation due to other reasons are not counted as events.

2.5.4 Sensitivity analyses

The primary analysis will also be conducted within the subgroups defined by sex, disease severity (MMD/MHD) at baseline and prior prophylactic treatment failure status (naïve vs. prior treatment failures).

2.5.5 Supplementary analyses

Not applicable

2.6 Analysis supporting secondary objectives

The secondary objective of the study is to evaluate the long-term tolerability of 70 and 140 mg erenumab in patients with episodic or chronic migraine.

2.6.1 Secondary endpoint(s)

The secondary endpoints are the proportion of patients discontinuing open-label treatment epoch due to AE and the proportion of patients discontinuing open-label treatment epoch due to non-AE reasons.

2.6.2 Statistical hypothesis, model, and method of analysis

Summary statistics for the proportion of patients discontinuing open-label treatment epoch due to AE and the proportion of patients discontinuing open-label treatment epoch due to non-AE reasons will be presented.

2.6.3 Handling of missing values/censoring/discontinuation

For every patient, it can be determined whether he/she discontinued for AE-related reasons. AE-related discontinuations are counted as events. Discontinuation due to the other reasons as non-AE-related treatment discontinuations or losses to follow up should not be counted as event.

2.6.4 Sensitivity analyses

The secondary analysis will also be repeated for all-cause treatment discontinuations (instead of AE-related).

2.6.5 Supplementary analyses

Not applicable

[redacted]

2.8 Safety analyses

Safety analyses will be based on safety data set (SAF).

Missing data will not be imputed for safety endpoints.

2.8.1 Adverse events (AEs)

In the frame of safety analysis the following treatment-emergent AE types will be considered:

- Any AE
- Study treatment related AE
- AE leading to study treatment discontinuation
- AE leading to dose adjustment (including study treatment discontinuation)
- Serious AE (SAE)
- Study treatment related SAE
- SAE leading to study treatment discontinuation
- Death

The Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later will be used to code all adverse events (AE) to a system organ class (SOC) and a preferred term (PT).

The SOCs will be presented in the alphabetic order and PTs will be ordered within the SOCs by decreasing order of frequency.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by primary system organ class and preferred term.
- by primary system organ class, preferred term and maximum severity
- by Standardized MedDRA Query (SMQ) and preferred term

If a patient reported more than one adverse event with the same PT, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The overview of adverse events occurring during treatment will additionally be presented by starting dose (70mg/140mg).

All AEs, deaths (see see section 2.8.2 Deaths for details), SAEs and AEs leading to permanent study drug discontinuation will be listed separately.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable

2.8.2 Deaths

Deaths will be listed including the start date of the study treatment, the last date on study treatment, the death date and the reason for death.

2.8.3 Laboratory data

Summary statistics of laboratory hematology and blood chemistry results will be presented as absolute values as well as change from baseline by visit and laboratory test category. Change from baseline will be summarized for each time point and only for patients with both, baseline and post-baseline assessment. Shift tables will be used to compare baseline to the worst on-treatment value.

All laboratory data with clinically notable values will be listed by subject and visit. Abnormal values will be marked according to the definitions of the central laboratory (see section 5.8 Abnormal laboratory value definitions).

2.8.4 Other safety data

2.8.4.1 12-lead ECG

For the numeric ECG measurements

- ECG Mean Heart Rate

- PR Interval
- QRS Duration
- QT Interval
- QTcF Interval
- RR Interval

summary statistics will be presented by visit. Descriptive summary statistics for the change from baseline will be calculated for patients with available ECG data at both time points.

All ECG data will be listed by subject and visit.

2.8.4.2 Vital signs

Assessed vital signs include:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate
- Temperature

Patient's values on blood pressure will be calculated as a mean of three readings. Readings with missing values will be ignored.

Descriptive summary statistics presented by type of measurement will contain vital signs measurements for each study visit as well as change from baseline.

All vital signs data will be listed by subject and visit.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

Not applicable

[redacted]

2.12 Biomarkers

Not applicable

[redacted]

3 Sample size calculation

In general, the 750 subjects randomized for clinical trial CAMG334ADE01 will be eligible for participation in the open-label study. It is estimated that approximately 75% to 85% of the study population meaning 563~638 subjects will enroll in the open-label study thus allowing the collection of long-term safety, efficacy and quality of life data of a large group of patients.

In the three-year open-label phase II study 20120178 the proportion of patients reporting at least one AE was 87%. Based on this finding event rates and precisions were calculated for the proposed 128-week trial for the primary endpoint. In conclusion a study population of at least 500 patients was found to be sufficient for the primary endpoint with an adequate range in precision.

The calculation of effect size and precision for the secondary endpoints is based on the proportion of study discontinuation rates in the three-year open-label phase II study 2012017. 4.2% of 383 patients discontinued this trial due to adverse events. Effect size and precision for the proposed study with at least 500 patients were calculated. In conclusion a study population of at least 500 patients was found to be sufficient for the secondary endpoints with an adequate range in precision.

4 Change to protocol specified analyses

Contrary to what was stated in the protocol, an interim analysis will be conducted. For details please refer to section 2.14 Interim analysis.

5 Appendix

5.1 Imputation rules

No imputation will be done for missing endpoints.

5.1.1 Study drug

In case of missing or partial start date of the first study drug application, the start date should be shifted to the earliest possible date, but not earlier than screening visit.

5.1.2 AE date imputation

Incomplete day

Incomplete start day will be imputed as MAX(date of study day 1, *earliest possible start date*).

Incomplete end day will be imputed as MIN(EoS, *latest possible end date*).

Earliest possible start/end date is calculated on the eCRF page and refers to the first day of the corresponding month. *Latest possible start/end date* is calculated on the eCRF page and refers to the last day of the corresponding month.

Incomplete day/month

Incomplete start day/month will be imputed as MAX(date of study day 1, 1st January of the year entered).

Incomplete end day/month will be imputed as MIN(EoS, 31th December of the year entered).

Incomplete day/month/year

Incomplete day/months/year will not be imputed.

5.1.3 Concomitant medication date imputation

Incomplete day

Incomplete start day will be imputed as MAX(date of study day 1, *earliest possible start date*).

Incomplete end day will be imputed as MIN(EoS, *latest possible end date*).

Earliest possible start/end date is calculated on the eCRF page and refers to the first day of the corresponding month. *Latest possible start/end date* is calculated on the eCRF page and refers to the last day of the corresponding month.

Incomplete day/month

Incomplete start day/month will be imputed as MAX(date of study day 1, 1st January of the year entered).

Incomplete end day/month will be imputed as MIN(EoS, 31th December of the year entered).

Incomplete day/month/year

Incomplete day/months/year will not be imputed.

5.1.4 Prior therapies date imputation

Incomplete day

Incomplete start day will be imputed as *earliest possible start date*.

Incomplete end day will be imputed as MIN (date of the day prior to study day 1, *latest possible end date*).

Incomplete day/month

Incomplete start day/month will be imputed as 1st January of the year entered.

Incomplete end day/month will be imputed as MIN(31th December of the year entered, date of the day prior to study day 1).

Incomplete day/month/year

Incomplete start date will be imputed as very early date

Incomplete end date will be imputed as a date of the day prior to study day 1.

5.1.5 Post therapies date imputation

Not applicable

5.1.6 Other imputations

[redacted]

5.1.6.2 Aura

The presence of aura in patient demographics is defined as at least one day with aura during baseline epoch in the HER-MES trial.

5.1.6.3 Disease duration

Disase duration at baseline will be calculated from *derived age* at informed consent for the HER-MES trial and *age at migraine onset* documented in headache and migraine frequency history form in HER-MES trial.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. Already coded terms will not be recoded in case of MedDRA version changes.

Severity of adverse events is graded by investigator (mild, moderate, severe) and reflected in the eCRF.

5.3 Laboratory parameters derivations

Not applicable

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

See section 2.5 Analysis supporting primary objective(s).

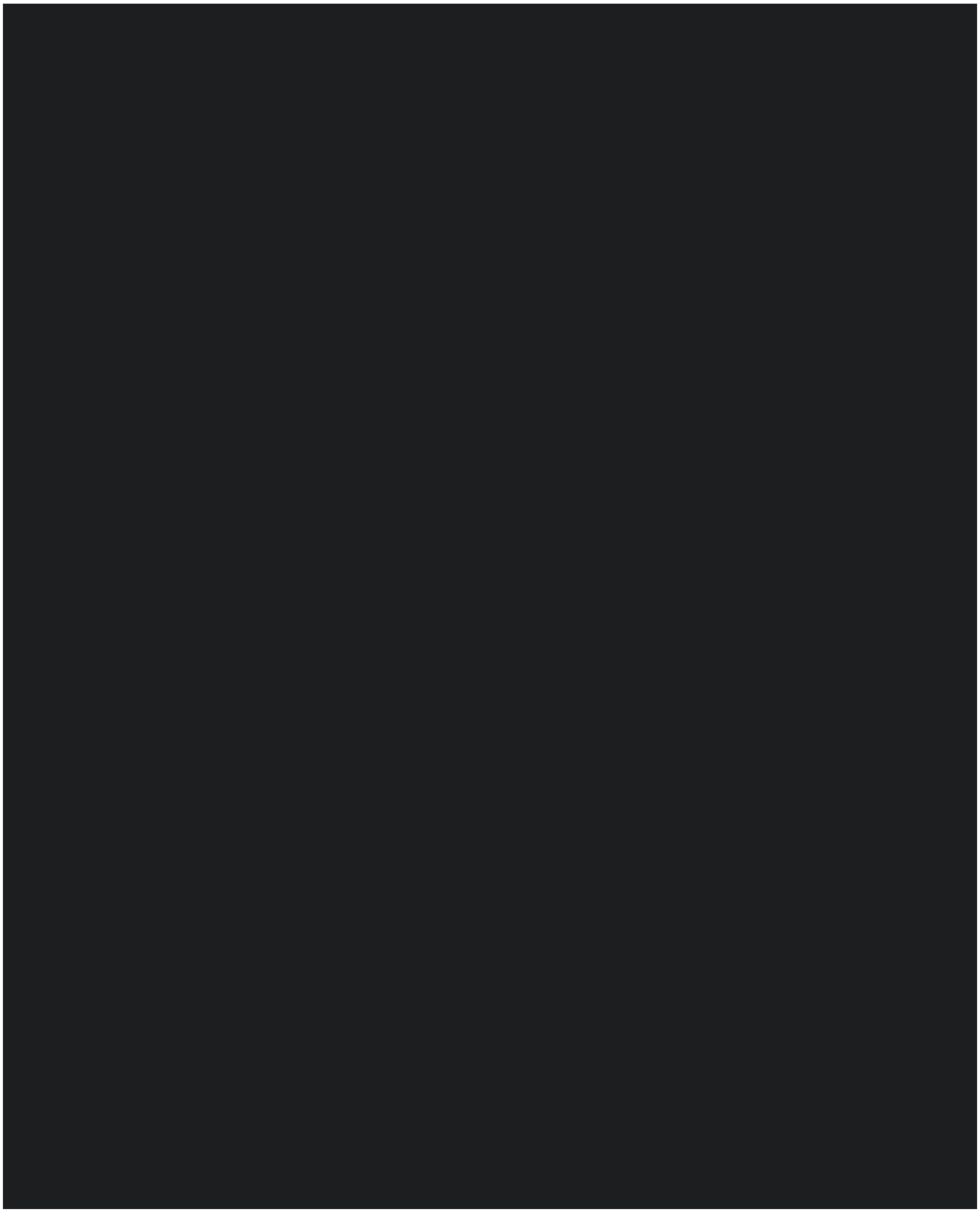
5.4.2 Analysis supporting secondary objective(s)

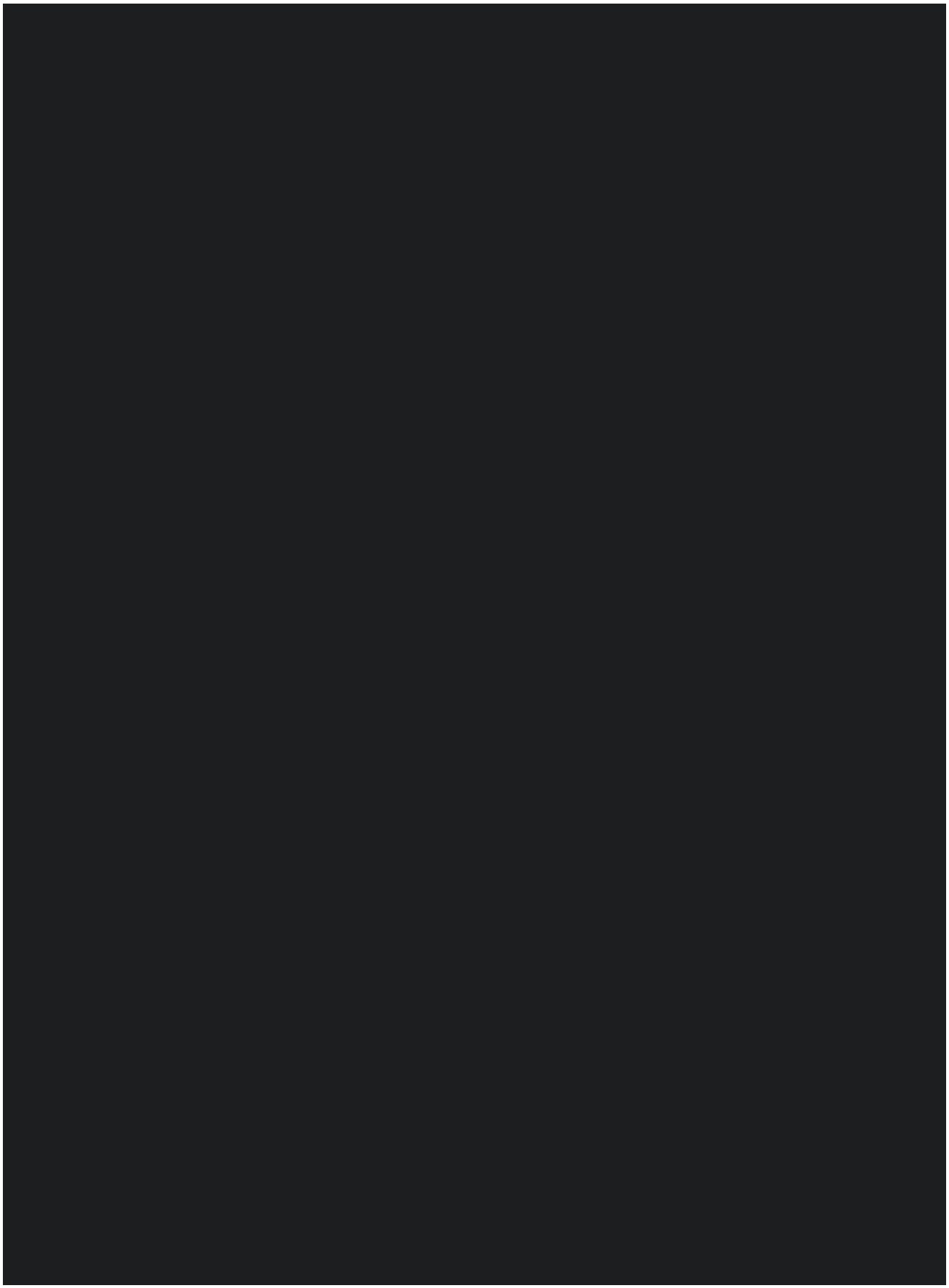
See section 2.6 Analysis supporting secondary objectives.

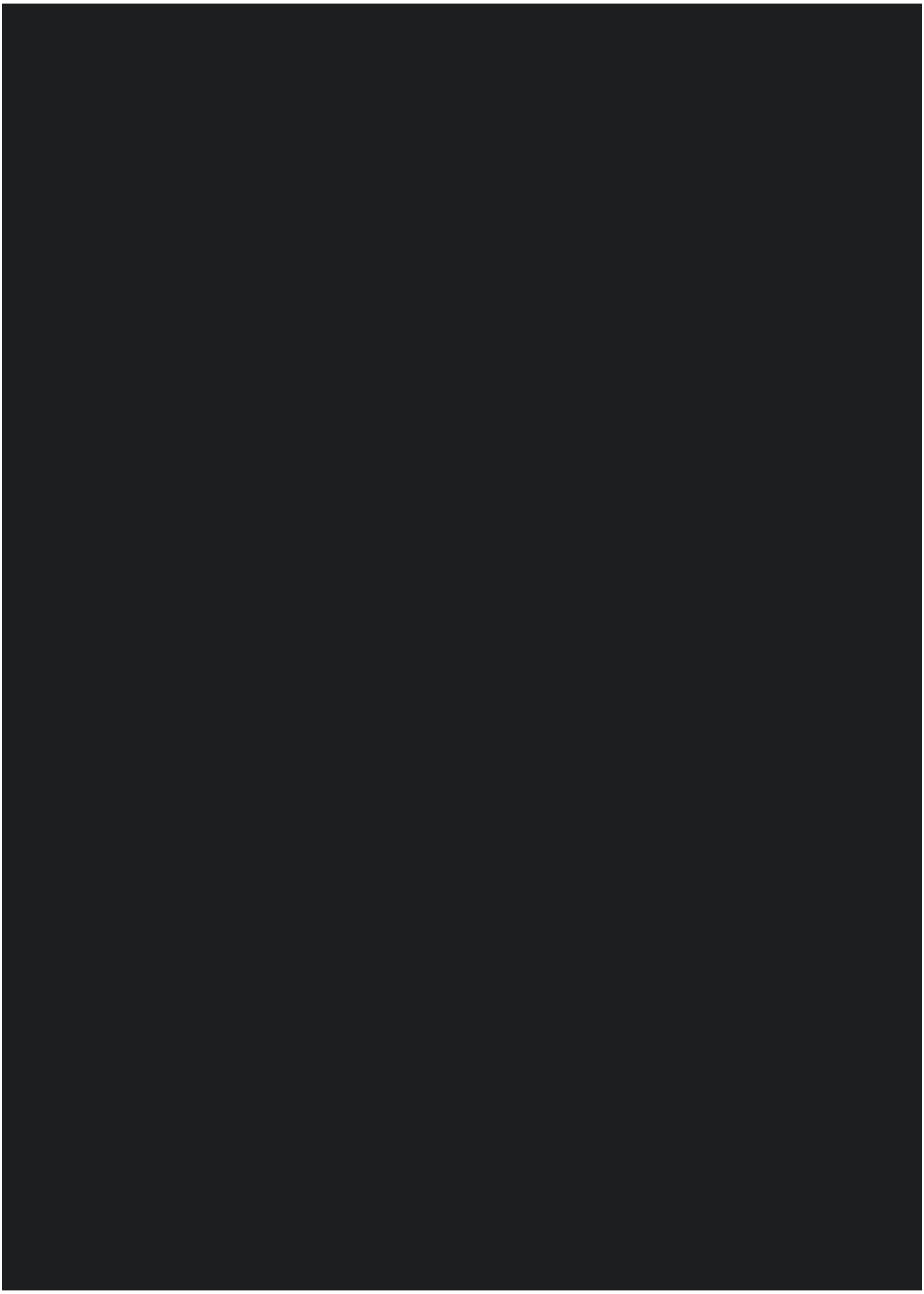
5.5 Rule of exclusion criteria of analysis sets

Exclusion criteria of analysis sets are complementary to those used for corresponding analysis set definitions (see section 2.2 Analysis sets).

[redacted]







5.8 Abnormal laboratory value definitions

5.8.1 Liver event and laboratory trigger definitions

The following table defines the threshold for laboratory triggers and liver events. Abnormal laboratory values are listed and the violated threshold is indicated.

						Medical alerts					
Parameter	Labcode	TP	Age	Gender	Unit	- - -	- -	-	+	+ +	+ + +
Haemoglobin	HB		16	F	g/dl	8.5	9.5	12.0	16.0	18.5	23.0
			16	F	mmol/l	5.3	5.9	7.4	9.9	11.5	14.3
			16	M	g/dl	8.5	9.5	14.0	18.0	18.5	23.0
			16	M	mmol/l	5.3	5.9	8.7	11.2	11.5	14.3
Haematocrit	HK		17	F	%	25.0	30.0	35.0	45.0	54.0	60.0
			17	F	l/l	0.25	0.30	0.35	0.45	0.54	0.60
			17	M	%	25.0	30.0	39.0	50.0	54.0	60.0
			17	M	l/l	0.25	0.30	0.39	0.50	0.54	0.60
Red Blood Cells	ERY		17	F	Mio/cmm	2.00	3.60	4.00	5.10	5.80	7.50
			17	F	Tpt/l	2.00	3.60	4.00	5.10	5.80	7.50
			17	M	Mio/cmm	2.00	3.80	4.50	5.90	6.20	7.50
			17	M	Tpt/l	2.00	3.80	4.50	5.90	6.20	7.50
White Blood Cells	LEUK		19		/cmm	2000	3000	4000	10000	12000	20000
			19		Gpt/l	2.0	3.0	4.0	10.0	12.0	20.0
			13		/cmm	1000		4500	10500		35000
			13		Gpt/l	1.0		4.5	10.5		35.0
Basophils	BASO				%				2.0	4.0	10.0
					l/l				0.020	0.040	0.100
Basophils, abs.	BASOAB				/cmm				100	200	500
					Gpt/l				0.100	0.200	0.500
Eosinophils	EOS				%				5.0	8.0	15.0
					l/l				0.050	0.080	0.150
Eosinophils, abs.	EOSAB				/cmm				500	800	1500
					Gpt/l				0.500	0.800	1.500
Lymphocytes	LYMP		3		%	10.0	15.0	20.0	55.0	65.0	70.0
			3		l/l	0.100	0.150	0.200	0.550	0.650	0.700

Parameter	Labcode	TP	Age	Gender	Unit	Medical alerts ---	--	-	+	++	+++
Lymphocytes, abs.	LYMPAB				/cmm	800	900	1000	3500	3800	4200
					Gpt/l	0.800	0.900	1.000	3.500	3.800	4.200
Monocytes	MONO				%			1.0	12.0	15.0	18.0
					l/l			0.010	0.120	0.150	0.180
Monocytes, abs.	MONOAB				/cmm			200	800	1100	1400
					Gpt/l			0.200	0.800	1.100	1.400
Neutrophils	NEUT		3		%	25.0	30.0	36.0	75.0	80.0	85.0
			3		l/l	0.25	0.30	0.36	0.75	0.80	0.85
Neutrophils, abs.	NEUTAB				/cmm	1000	1500	2000	7500	8000	9000
					Gpt/l	1.000	1.500	2.000	7.500	8.000	9.000
Platelets	THROM				T/cmm	50	120	140	440	500	600
					Gpt/l	50	120	140	440	500	600
Serum albumin, chem.	ALB		19		g/dl	2.00	3.00	3.50	5.20	5.70	6.00
			19		g/l	20.0	30.0	35.0	52.0	57.0	60.0
			15		g/dl	2.00	2.60	3.20	4.50	5.30	6.00
			15		g/l	20.0	26.0	32.0	45.0	53.0	60.0
Alk. Phosphatase	AP		19	F	U/l			35	104	300	700
			19	F	µmol/sl			0.58	1.74	5.01	11.69
			19	M	U/l			40	129	300	700
			19	M	µmol/sl			0.67	2.15	5.01	11.69
			17	F	U/l			45	87	750	800
			17	F	µmol/sl			0.75	1.45	12.53	13.36
			17	M	U/l			55	149	750	800
			17	M	µmol/sl			0.92	2.49	12.53	13.36

Parameter	Labcode	TP	Age	Gender	Unit	Medical alerts ---	--	-	+	++	+++
ALT (SGPT)	GPT		18	F	U/l			10	35	100	800
			18	F	µmol/sl			0.17	0.58	1.67	13.36
			18	M	U/l			10	50	100	800
			18	M	µmol/sl			0.17	0.84	1.67	13.36
AST (SGOT)	GOT		18	F	U/l			10	35	100	800
			18	F	µmol/sl			0.17	0.58	1.67	13.36
			18	M	U/l			10	50	100	800
			18	M	µmol/sl			0.17	0.84	1.67	13.36
gGT	GGT		20	F	U/l			6	42	100	600
			20	F	µmol/sl			0.10	0.70	1.67	10.02
			20	M	U/l			10	71	100	600
			20	M	µmol/sl			0.17	1.19	1.67	10.02
			14	F	U/l			6	23	100	600
			14	F	µmol/sl			0.10	0.38	1.67	10.02
			14	M	U/l			6	30	100	600
			14	M	µmol/sl			0.10	0.50	1.67	10.02
LDH	LDH		16	F	U/l			135	214	350	600
			16	F	µmol/sl			2.25	3.57	5.85	10.02
			16	M	U/l			135	225	350	600
			16	M	µmol/sl			2.25	3.76	5.85	10.02

Parameter	Labcode	TP	Age	Gender	Unit	Medical alerts ---	--	-	+	++	+++
Calcium	CA		91	F	mmol/l	1.70	1.85	2.09	2.62	2.80	2.90
			91	F	mg/dl	6.8	7.4	8.4	10.5	11.2	11.6
			91	M	mmol/l	1.70	1.85	2.12	2.47	2.80	2.90
			91	M	mg/dl	6.8	7.4	8.5	9.9	11.2	11.6
			61	F	mmol/l	1.70	1.85	2.14	2.61	2.80	2.90
			61	F	mg/dl	6.8	7.4	8.6	10.4	11.2	11.6
			61	M	mmol/l	1.70	1.85	2.13	2.57	2.80	2.90
			61	M	mg/dl	6.8	7.4	8.5	10.3	11.2	11.6
			19	F	mmol/l	1.70	1.85	2.16	2.58	2.80	2.90
			19	F	mg/dl	6.8	7.4	8.6	10.3	11.2	11.6
			19	M	mmol/l	1.70	1.85	2.19	2.60	2.80	2.90
			19	M	mg/dl	6.8	7.4	8.8	10.4	11.2	11.6
			13	F	mmol/l	1.70	1.85	2.26	2.58	2.80	2.90
			13	F	mg/dl	6.8	7.4	9.0	10.3	11.2	11.6
			13	M	mmol/l	1.70	1.85	2.27	2.61	2.80	2.90
			13	M	mg/dl	6.8	7.4	9.1	10.4	11.2	11.6
Magnesium	MGLG		91		mmol/l	0.50	0.60	0.70	0.95	1.10	1.80
			91		mg/dl	1.22	1.46	1.70	2.31	2.67	4.38
			60		mmol/l	0.50	0.60	0.66	0.99	1.10	1.80
			60		mg/dl	1.22	1.46	1.60	2.41	2.67	4.38
			21		mmol/l	0.50	0.60	0.66	1.07	1.10	1.80
			21		mg/dl	1.22	1.46	1.60	2.60	2.67	4.38
			13		mmol/l	0.50	0.60	0.70	0.91	1.10	1.80
			13		mg/dl	1.22	1.46	1.70	2.21	2.67	4.38

Parameter	Labcode	TP	Age	Gender	Unit	Medical alerts ---	--	-	+	++	+++
Phosphate	PO4		19		mg/dl	1.9	2.3	2.5	4.5	6.8	8.7
			19		mmol/l	0.60	0.75	0.81	1.45	2.20	2.80
			16	F	mg/dl	1.9	2.3	2.5	4.8	6.8	8.7
			16	F	mmol/l	0.60	0.75	0.80	1.55	2.20	2.80
			16	M	mg/dl	1.9	2.3	2.6	5.0	6.8	8.7
			16	M	mmol/l	0.60	0.75	0.85	1.60	2.20	2.80
Sodium	NA		18		mmol/l	125	130	136	145	150	155
			18		mg/dl	287	299	313	333	345	356
Potassium	K		18		mmol/l	2.90	3.00	3.50	5.10	5.60	6.10
			18		mg/dl	11.3	11.7	13.7	19.9	21.9	23.9
Creatinine, Jaffé	KREA		16	F	mg/dl			0.50	0.90	1.50	2.80
			16	F	µmol/l			44	80	133	248
			16	M	mg/dl			0.70	1.20	1.80	3.00
			16	M	µmol/l			62	106	159	265
CK	CK		19	F	U/l				170	280	400
			19	F	µmol/sl				2.84	4.68	6.68
			19	M	U/l				190	280	400
			19	M	µmol/sl				3.17	4.68	6.68
			15	F	U/l		23	34	147	250	400
			15	F	µmol/sl		0.38	0.57	2.45	4.18	6.68
			15	M	U/l		23	28	142	250	400
			15	M	µmol/sl		0.38	0.47	2.37	4.18	6.68
Direct Bilirubin	BILD				mg/dl				0.30	1.00	3.00
					µmol/l				5.13	17.10	51.30
Indirect Bilirubin	BILIN				mg/dl				0.90	1.80	5.00
					µmol/l				15.39	30.78	85.50

Parameter	Labcode	TP	Age	Gender	Unit	Medical alerts ---	--	-	+	++	+++
Total Bilirubin	BIL		19		mg/dl				1.20	2.00	6.00
			19		µmol/l				20.52	34.20	102.60
			1		mg/dl				1.00	2.00	6.00
			1		µmol/l				17.10	34.20	102.60
Blood urea nitrogen	HN		61		mg/dl			8.0	23.0	32.0	46.0
			61		mmol/l			2.85	8.19	11.40	16.38
			18		mg/dl			6.0	20.0	32.0	46.0
			18		mmol/l			2.14	7.12	11.40	16.38
INR	INRP								1.3	1.4	1.5
APTT	PTTP		18		s	10.4	15.6	25.9	36.6	46.7	62.2

Legend: TP time point + / - out of normal range + + / - - pathologic value + + + / - - - extremely pathologic value

6 Reference

Not applicable

7 Approval signatures

This Statistical Analysis Plan was subject to critical review and has been approved after review by:

[redacted]
Digitally signed by [redacted]
DN: dc=com, dc=novartis, ou=people, ou=PH, serialNumber=2503830, cn=[redacted]
Date: 2022.11.16 13:33:52 +01'00'

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Signature Date

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Date: 2022.12.01 13:23:13 +01'00'

Trial Statistician Signature Date

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CRO Statistician Signature Date

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CRO Statistician Signature Date