NOVARTIS

Clinical Development

Dabrafenib (DRB436)

BRF116013 (CDRB436A2102) / NCT01677741

Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Patients with Advanced BRAF V600-Mutation Positive Solid Tumors

Statistical Analysis Plan (SAP) – Final Analysis

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Document type: SAP Documentation

Document status: Final v1.0

Release date: 13-Nov-2020

Number of pages: 18

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-Sep-2017	Prior to DB lock	Creation of first version	N/A – First version	NA
[redacted]				
09-Mar-2020	Prior to DB lock	As per client comment	[redacted] [2] Added the references	Section 2.11 updated

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
22-Sep-2020	Prior to DB Lock	As per comment	[1] To include Protcol deviations related to COVID-19 [redacted] [3] To include New RANO criteria assessments by independent reviewer [4] To include concordance analysis between Old and New RANO assessments by independent reviewer [5] Added ORR analysis for New RANO (2017) criteria. [6] Added Concordance analysis between investigator and independent reviewer using Old and New RANO criteria [7] Updated minor edits in SAP.	Section 2.3.2 , 2.10, 2.11 and 2.6.1
13-Nov-2020	Prior to DBL	Novartis comments	1) Minor typos corrected 2) Response-evaluable population definition updated 3) Key secondary endpoint corrected to match original GSK SAP 4) Corrected PFS definition 5) Updated DOR definition	 Section 2.2.5 Section 2.6.1 Section 2.11.2 Section 2.11.3

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
COVID-19	Coronavirus Disease-2019
CRF	Case Report Form
DLT	Dose Limiting Toxicity
DRL	Drug Reference Listing
ECG	Electrocardiogram
HGG	High grade gliomas
HR	Heart Rate
LCH	Langerhans cell histiocytosis
LGG	Low-grade gliomas
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
QTcB	QT duration corrected for heart rate by Bazett's formula
RANO	Response Assessment in Neuro-oncology
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) details the planned analysis for the final CSR of the study. This is a 2-part, phase I/IIa study to evaluate the safety, tolerability and pharmacokinetics of oral dabrafenib in pediatric patients with advanced BRAF V600-mutation positive solid tumors.

The contents are based on the previous SAP Interim I, the GSK CSR SAP and the study protocol 11.0 and this SAP will only describe the changes/additions from the previous analyses conducted/planned. All outputs detailed in the previous SAP are required for this final analysis. The TFL shell document will list all of the outputs in the previous SAP for this final analysis as well as providing shells for the new or modified outputs.

For a more detailed statistical analysis plan for the study please refer to the first version of the SAP – CDRB436A2102_SAP_CSR_1_final (GSK template)_amendment 01.docx stored in CREDI under the location DRB436A2102/Administrative files (study level)/RAP and RAMP Meeting. Hereafter this document will be referred as GSK SAP.

The previous interim analysis SAP is also stored in the above mentioned location.

1.1 Study design

For information on the study design, see the GSK SAP.

1.2 Study objectives and endpoints

For information on the study objectives and endpoints, see the GSK SAP.

2 Statistical methods

For information on the statistical hypotheses, see the GSK SAP.

2.1 Data analysis general information

Prior anti-cancer therapy and anti-neoplastic therapy's medications will be coded using World Health Organization (WHO) Drug Reference Listing (DRL) dictionary; anti-neoplastic surgery will be coded using Medical Dictionary for Regulatory Affairs (MedDRA). Concomitant medications will be coded using the WHO DRL dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

Refer to the study GSK SAP for more information.

For final CSR analysis, in addition to the analysis performed by study parts, to understand disease specific reporting, pooled analysis will also be performed by combining all the patient data from part 1 and part 2 of the study based on disease specific cohorts. This pooled analysis will be carried out for four disease cohorts; i.e. LGG BRAF V600 Mutant, HGG BRAF V600 Mutant, LCH BRAF V600 Mutant and other tumor.

The disease specific cohorts from Part 1 will be identified based on their tumor type data collected in the Regimen form of eCRF.

For example, if tumor type is High Grade Glioma then disease cohort will be "HGG, BRAF V600 Mutant" and if tumor type is Low Grade Glioma then disease cohort will be "LGG, BRAF V600 Mutant". Similary, if tumor type is Langerhans Cell Histiocytosis (LCH) then disease cohort will be "LCH, BRAF V600 Mutant" and if tumor type is Other/Solid tumor then disease cohort will be "Other".

For part 2 expansion, the disease cohort will be similar to the enrollment cohort.

2.1.1 General definitions

For more information, see the GSK SAP.

2.2 Analysis sets

2.2.1 All Treated Population

The All Treated population is defined as all patients who receive at least one dose of study treatment. An incorrect treatment schedule or drug administration or an early termination of treatment will not result in exclusion of patients from this population.

2.2.2 Safety Population

The Safety population consists of all patients who received at least one dose of study treatment. All safety data will be analysed using the Safety population.

In this study, the All Treated population and Safety population are identical.

2.2.3 Dose Limiting Toxicity Evaluable Population

The Dose Limiting Toxicity (DLT) Evaluable population is defined as those Part 1 patients fulfilling the All Treated population criteria, and having received an adequate treatment for the first 28 days to enable an appropriate evaluation of study drug related DLTs. Adequate exposure during the first 28 days will be defined as having received > 75% of planned study drug doses, exclusive of missed doses due to treatment-related toxicity. Patients who are either withdrawn or dose reduced due to toxicity during the first 28 days will be included in the DLT evaluable population. Any patient from Part 1 in the 'All Treated' population who experiences a DLT, as defined in section 3.3 of the protocol, will also be included in the DLT evaluable population regardless of exposure.

2.2.4 Pharmacokinetic Population

The Pharmacokinetic (PK) population is defined as those patients fulfilling the All Treated population criteria and for whom pharmacokinetic sample(s) are obtained and analysed. This population will be used for the primary, secondary PK endpoints, [redacted] analyses.

Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. Specific time points might be removed from the analysis set if technical issues with the sample are reported (e.g. sampling issues, missing information) or if LLOQ sample is observed in between measurable concentrations. These patients and concentration data points will be identified at the time of analysis.

2.2.5 Response-evaluable Population

The Response-evaluable population is defined as those patients fulfilling the All Treated population criteria with a pre-dose and at least 1 post–dose disease efficacy assessment. In addition, for patients evaluated by RANO criteria, their disease must be 'measurable' at baseline to be included in the Response-evaluable population. This population will be used for sensitivity analysis on the efficacy endpoints.

2.2.6 Subgroup of interest

There are no formal plans for examining subgroups.

2.3 Patient disposition, demographics and other baseline characteristics

Age (years, months or days) will be collected in CRF based on the derivation in the table below. There will be 2 age variables calculated in ADS, age in years, and derived age: age in years, months and days.

AGE in years =round ((AGEY*365.25+AGEM*30.4375+AGED)/365.25, 0.1)

where AGEY for age in years; AGEM for age in months; AGED for age in days.

If Age in years > 0, then AAGE = floor(Age in years);
Else if Age in months > 0, then AAGE = floor(Age in months);
Else if Age in days > 0, then AAGE = floor(Age in days).

Listing will include the birth year and age as collected.

For details, refer to section 10.3 of GSK SAP.

In addition to the analysis mentioned in section 10.3 of GSK SAP , the similar summary of subject demographics, baseline characterstics, disease history, prior anti-cancer treatments and change from baseline in Karnofsky and Lansky performance status will be carried out by pooled disease cohort (as defined in section 2.1).

2.3.1 Patient disposition

For details, refer to study GSK SAP.

Additionally, the similar anlysis will be carried out for subject disposition by pooled disease cohort (as defined in section 2.1).

2.3.2 Protocol deviation

The number and percentage of patients in the All Treated population with any major protocol deviation will be tabulated by deviation category (as specified in the study protocol deviation plan).

Similarly, a separate table and listing will be provided for protocol deviations related to COVID-19.

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

Refer to GSK SAP for more information.

For pooled disease cohort, similar summary of treatment exposure will be carried out for overall duration of exposure and also for dose reductions/interruptions.

Dose intensity and relative dose intensity will be summarized by age categories (<12 years and >=12 years

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

Refer to study GSK SAP.

2.5.2 Statistical hypothesis, model, and method of analysis

There are no formal tests of hypotheses planned for this trial. With respect to the primary objectives and endpoints, the primary focus will be on determining the maximum tolerated dose (or recommended dose based on available safety, PK, and response data), the safety profile, and PK/PD relationship of dabrafenib in pediatric patients with advanced BRAF V600-mutation positive solid tumors. Most analyses will be descriptive or exploratory.

2.5.3 Handling of missing values/censoring/discontinuations

Refer to study GSK SAP.

Supportive analyses Refer to study GSK SAP.

2.6 Analysis of the key secondary objective

2.6.1 Secondary endpoint

The All Treated population will be used for all efficacy analyses.

Overall response rates along with 95% confidence intervals will be separately calculated for all the disease cohorts including the LGG, HGG, LCH and Other disease cohorts.

Efficacy assessments are based on RANO criteria for LGG and HGG patients. In addtion, for LGG patients, the updated RANO criteria will be used for independent review. For LCH patients, the response assessment criteria are described in Appendix 2 of the protocol. For patients with other solid tumor, efficacy assessments are based on RECIST 1.1.

Refer to study GSK SAP for additional details.

2.6.2 Handling of missing values/censoring/discontinuations

Refer to study GSK SAP.

[redacted]

2.8 Safety analyses

The Safety population will be used for all safety analyses.

Refer to study GSK SAP for additional details.

2.8.1 Adverse events (AEs)

AEs will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the MedDRA dictionary. The latest available MedDRA version at the time of the analyses will be used. The MedDRA version used for reporting will be specified as a footnote in the applicable tables/listings.

For more details, refer to study GSK SAP.

Similar summary of overview of AEs for pooled disease cohorts will be generated. Moreover, summary of AEs regardless of relationship by preferred term and maximum grade and summary of AEs suspected to be related to study drug by preferred term will also be carried out by pooled disease cohort.

In addition, For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Seriouse Adverse events

For SAEs, in a similar way as of AEs, summary by preferred term regardless of relationship to study drug and also summary for suspected study drug related SAEs by preferred term will be carried out by pooled disease cohorts.

Refer to study GSK SAP for additional details.

2.8.3 Deaths

Refer to study GSK SAP for additional details.

2.8.4 Laboratory data

Refer to study GSK SAP for additional details.

Summary of shift from baseline, based on CTC grade will be carried out for Hematology and Biochemistry laboratory parameters by pooled disease cohorts instead of treatment.

2.8.5 Other safety data

Refer to study GSK SAP for additional details.

2.8.5.1 ECG and cardiac imaging data

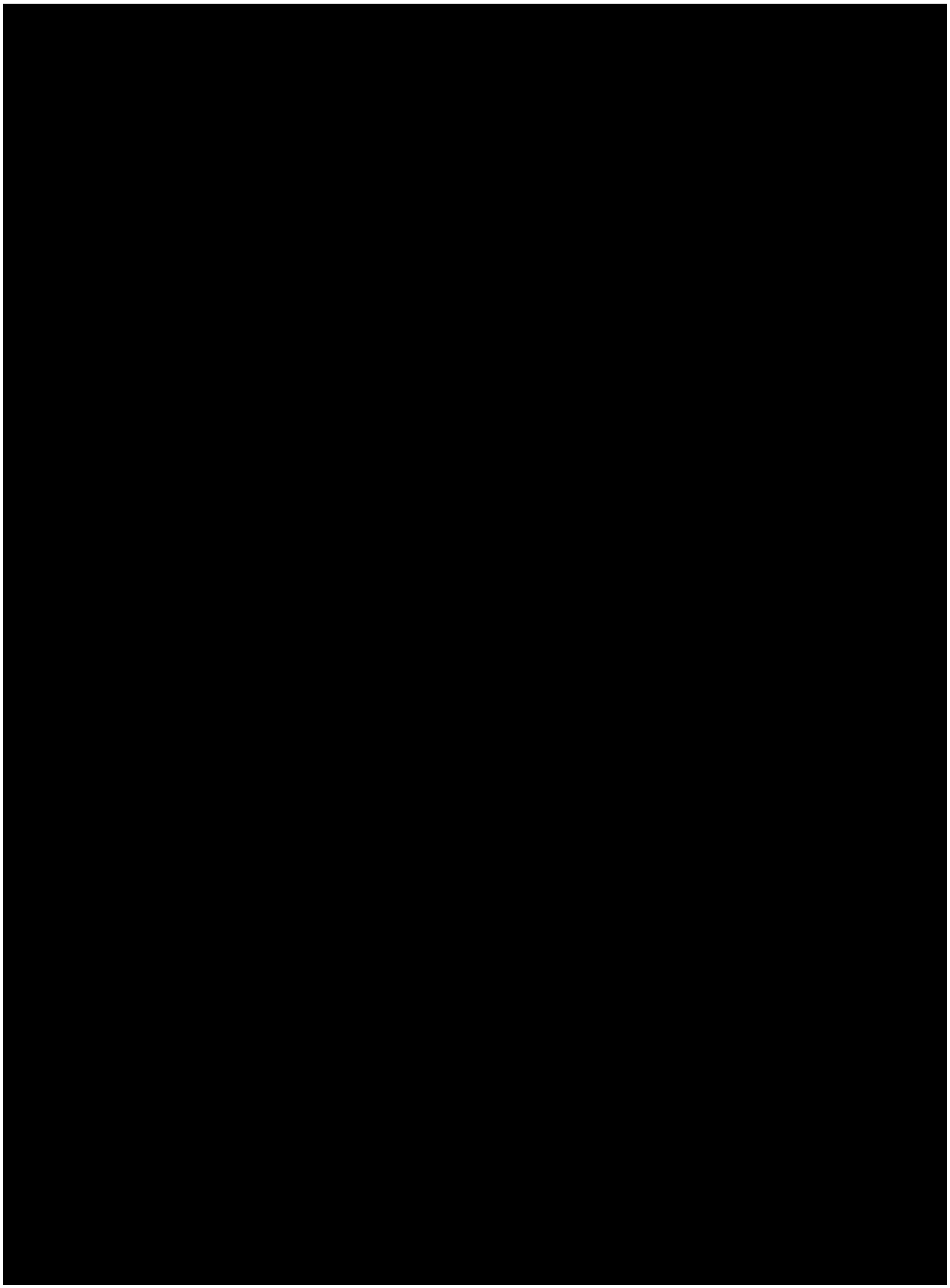
The corrected QT duration for heart rate (QTcB) will be manually calculated using Bazett's formula if the data is not available. See Appendix 5.1.

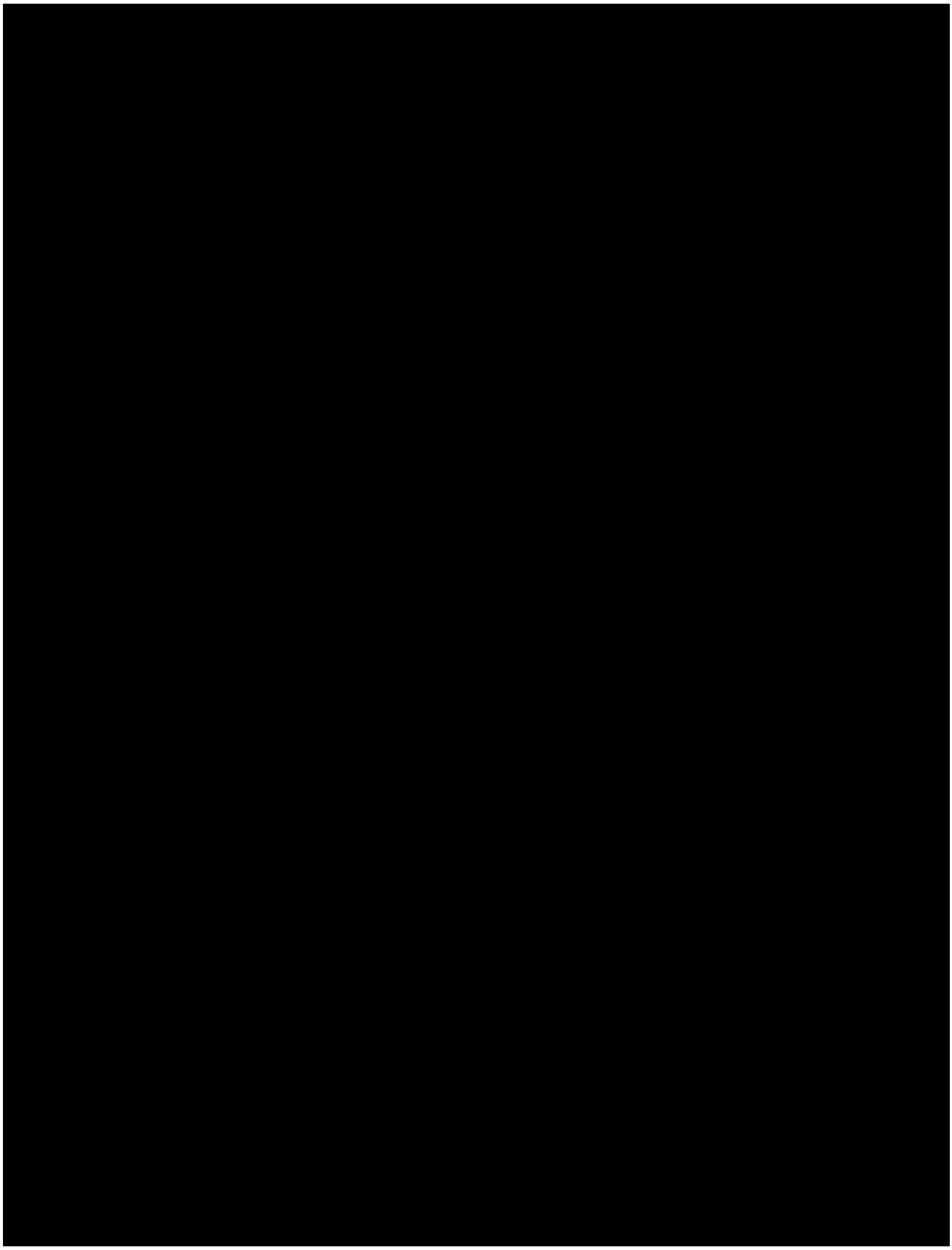
2.8.5.2 Vital signs

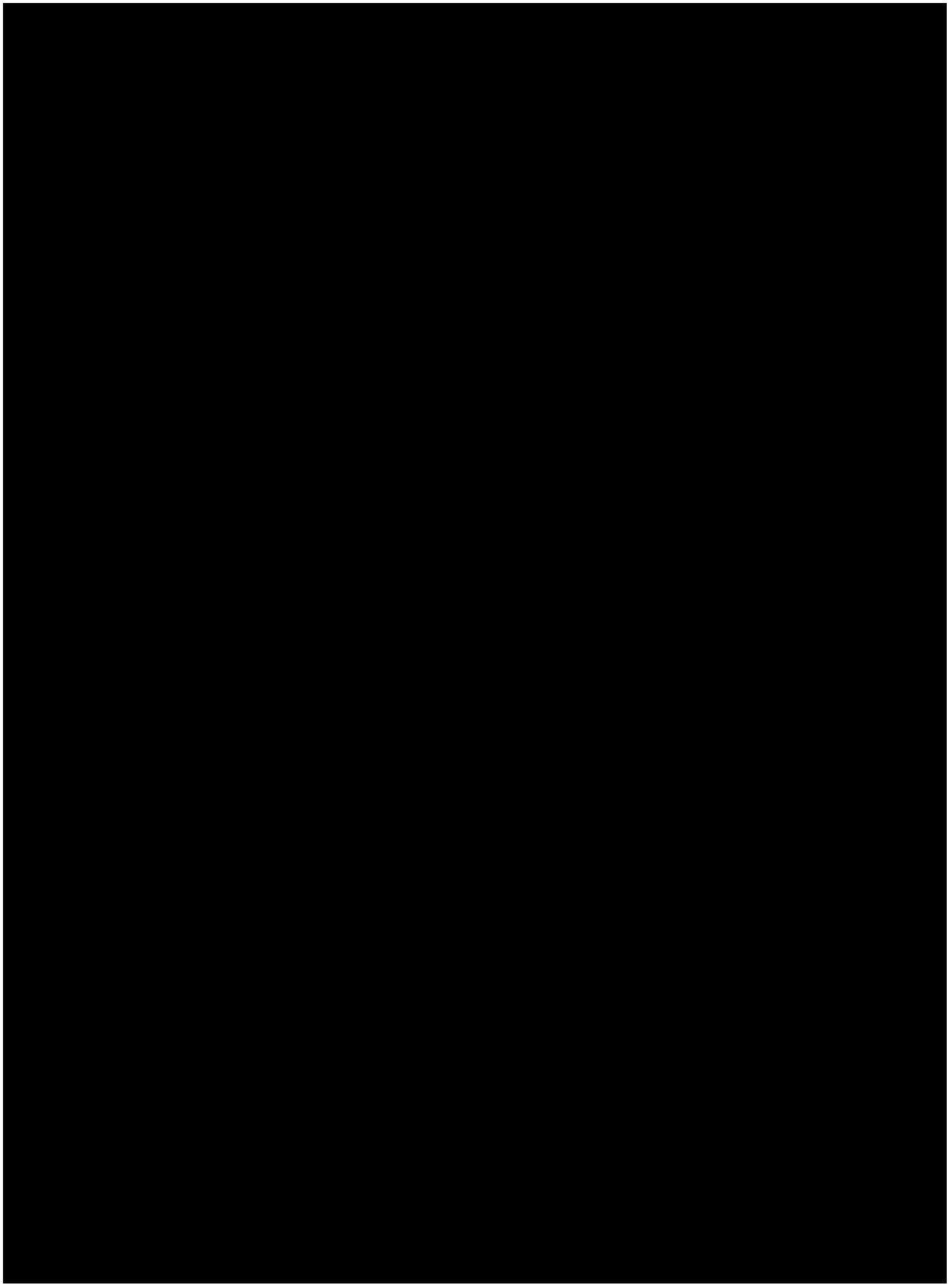
Refer to study GSK SAP.

2.9 Pharmacokinetic endpoints

Refer to study GSK SAP.







[redacted]

2.12 Interim analysis

A number of previous interim analyses have been performed for Health Authority interactions, or when a specified minimum follow up was reached in certain cohorts. These interim analyses are documented in separate CSRs.

No efficacy or futility conclusions were made based on these interim analyses.

3 Sample size calculation

Refer to study GSK SAP; Section 5.

4 Change to protocol specified analyses

No change from protocol specified analysis except [redacted] reporting of protocol deviations related to COVID-19.

5 Appendix

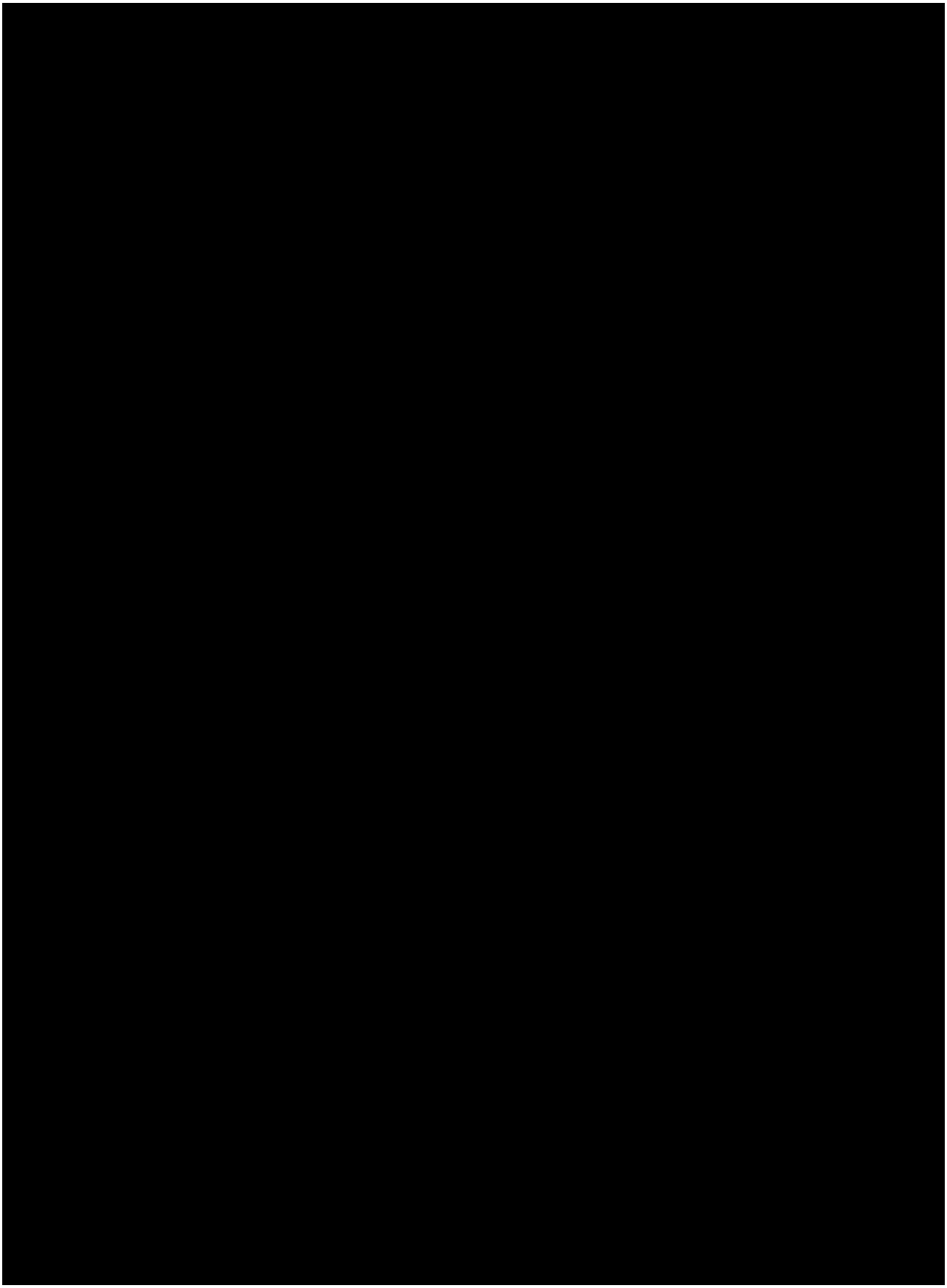
5.1 Laboratory parameters derivations

Bazett's formula is as follows:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

where QTcB is the QT interval corrected for heart rate, QT is the measured QT interval and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex (all measurements in seconds). RR is often derived from the heart rate (HR) as 60/HR. QT interval is collected in milliseconds on the CRF and will be displayed in milliseconds in the outputs.

[redacted]



[redacted]

[redacted]

6 Reference

Refer to the study GSK SAP.