NOVARTIS

INC280A/capmatinib/Tabrecta®

CINC280A2301 / NCT04427072

A phase III, randomized, controlled, open-label, multicenter, global study of capmatinib versus SoC docetaxel chemotherapy in previously treated patients with EGFR wt, ALK negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation (METΔex14)

Statistical Analysis Plan (SAP)
Final analysis
Addendum 1

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
06-Oct-2023	Prior to DB lock for final analysis	Creation of final version	N/A - First version	NA
29-Nov-2023	Prior to DB lock for final analysis	Amendment 1: Need for update of the derivation of censoring reasons for duration of response	Participants who move to capmatinib treatment outside of the trial are presented with the correct reason for censoring	2.6.1 Secondary efficacy endpoint 5.1 Determination of missing adequate tumor assessments
			Abbreviations not used in the document were removed	List of abbreviations
		Addition of analyses for 3 efficacy endpoints because late updated data have an impact on these endpoints	Analyses for secondary endpoints overall response rate, disease control rate, and time to response by investigator assessment were added back. Paragraphs for ORR/DCR and TTR were added to the subsection 2.7.1.	2.6 Analysis supporting secondary objectives 2.7.1 Secondary efficacy endpoints
dd-Jan-2024	After DB lock	Addendum 1: Addition of outputs to fulfill a HA request	Analyses for main efficacy endpoints performed in the primary analysis (not planned for re-analysis with the final data (PFS, ORR, DCR, TTR, OS, [redacted]) were added (excluding sensitivity and supportive analyses). Estimand-related text parts were removed as they are related to the primary analysis.	1 Introduction 1.2.1 Primary estimand 1.2.2 Secondary estimand 2.5 Analysis supporting primary objective(s) 2.6 Analysis of the key secondary objective 2.7 Analysis supporting secondary objectives [redacted] 5 Appendix 5.2 Statistical models 6.1 Published

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				literature General: correction of typos and minor wording updates

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BILI	Total Bilirubin
BIRC	Blinded Independent Review Committee
BOR	Best Overall Response
CI	Confidence Interval
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DCR	Disease Control Rate
DNA	Deoxyribonucleic Acid
DOIR	Duration Of Intracranial Response
DOR	Duration Of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor; also known as ErbB1
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
ET	Extension Treatment
FAS	Full Analysis Set
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IDCR	Intracranial disease control rate
MedDRA	Medical Dictionary for Drug Regulatory Affairs
METΔex14	MET exon 14 skipping
NCI	National Cancer Institute
[redacted]	[redacted]
NSCLC	Non-Small Cell Lung Cancer
OIRR	Overall intracranial response rate
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
[redacted]	[redacted]
PK	Pharmacokinetics

PT	Preferred Term
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
QTcF	Corrected QT interval using Fridericia correction
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TTIR	Time to Intracranial Response
TTR	Time to Response
WHO	World Health Organization
wt	Wild type

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the final Clinical Study Report (CSR) of the study CINC280A2301, a randomized, controlled, open-label, multicenter, global phase III study of capmatinib versus SoC docetaxel chemotherapy in previously treated patients with EGFR wt, ALK negative, locally advanced or metastatic (stage IIIB/IIIC or IV) NSCLC harboring MET exon 14 skipping mutation (METΔex14).

The content of this SAP is based on the protocol version 02 and the statistical analysis plan for the primary analysis, amendment 2, referred to as "primary analysis SAP" (CINC280A2301_SAP_CSR_1_primary_amendment2, dated 22-Mar-2023). All decisions regarding the final analysis, as defined in the SAP, have been made prior to database lock.

Due to changes in the treatment landscape which have heavily impacted the enrollment of new participants into the study, Novartis has taken the decision to permanently halt recruitment of participants in September 2022. Based on the primary analysis results of all randomized participants available in April 2023 (cut-off date 15-Feb-2023), the decision to stop the study prematurely was taken in May 2023. Last participant last visit was achieved on 31-Oct-2023.

This abbreviated SAP describes the planned analyses for the final CSR and the posting of results in registries.

Baseline data will not be summarized again unless data changes after the interim database lock necessitate an update. Based on a Heath Authority request to provide the updated results for the main efficacy endpoints, the corresponding analyses were added in this SAP addendum 1. They had not been planned before because no significant changes were expected.

1.1 Study design

This is a multicenter, open-label, randomized, active-controlled, global phase III study that will enroll adult participants with EGFR wt, ALK rearrangement negative, NSCLC harboring METΔex14 skipping mutations who have progressed on one or two prior lines of systemic therapy for locally advanced or metastatic stage and are candidates for docetaxel.

The study will randomize approximately 90 participants globally. Participants eligible for the study will be randomized in a 2:1 ratio to one of the two treatment arms: capmatinib (investigational therapy) or docetaxel. The randomization will be stratified by prior lines of systemic therapy received for advanced/metastatic disease (one line vs. two lines).

Participants randomized to docetaxel treatment will be eligible to crossover to receive capmatinib treatment after BIRC-confirmed, RECIST 1.1-defined progressive disease (PD) and after meeting the eligibility criteria outlined in the study protocol.

For all participants, the respective treatment (either with capmatinib or docetaxel) may be continued beyond initial disease progression as per RECIST 1.1 (as assessed by the investigator and confirmed by BIRC) if, in the judgment of the investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment.

After treatment discontinuation, all participants will be followed for safety evaluations during the safety follow-up period, and the participant's status will be collected every 12 weeks as part of the survival follow-up.

The primary analysis was performed after enrollment had been closed with 22 randomized participants.

1.2 Study objectives, endpoints and estimands

For all detailed objectives and endpoints as well as the primary and secondary estimands of the study refer to primary analysis SAP. The following Table 1-1 shows the objectives and related endpoints in scope for this final SAP.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary Objective	**Endpoint for primary objective**
To compare the efficacy of capmatinib versus docetaxel	Progression-free survival (PFS) by BIRC as per RECIST 1.1
Key secondary objective	**Endpoints for key secondary objective**
To compare the overall response rate (ORR) of capmatinib and docetaxel	ORR calculated per RECIST 1.1 by BIRC
Secondary Objectives	**Endpoints for secondary objectives**
To assess the antitumor activity of capmatinib versus docetaxel	All calculated per RECIST 1.1, both by BIRC and investigator: • Duration of response (DOR) • Time to response (TTR) • Disease control rate (DCR) All calculated per RECIST 1.1, by investigator: • ORR • PFS
To evaluate overall survival (OS) in participants treated with capmatinib versus docetaxel	Overall survival
To evaluate the safety profile of capmatinib versus docetaxel	Incidence of adverse events and serious adverse events, change in vital signs, laboratory results and ECG
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures, and listings.

Data included in the analysis

Data from all participants who signed the main informed consent for this study will be used in the analysis. Data collected after participants' withdrawal of informed consent for further participation in the study will not be reported (except for death date, if it is obtained from public records).

The analysis cut-off date for the final analysis of study data will be established at the end of the study. All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will, be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing.' The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to the expected small number of participants enrolled at each center, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment arm; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (e.g., mean, standard deviation, median, percentiles, minimum, and maximum) by treatment arm.

2.1.1 General definitions

For general definitions regarding investigational drug and study treatment, date of first/last administration of study treatment, last date of exposure to study treatment, baseline, on-treatment assessments/events and observation period, windows for multiple assessments, last contact date, and other specifications please refer to the primary analysis SAP.

2.2 Analysis sets

Participants are considered to be enrolled into the study if they have signed the main informed consent. Only participants who have signed the main informed consent will be included in the analysis data sets.

Participants who signed a molecular pre-screening informed consent form but failed to meet pre-screening criteria, as well as participants who signed the main informed consent form and were subsequently found to be ineligible prior to randomization will be considered screen failures. The set of All Screened Participants comprises all those who have signed the main informed consent.

Analysis sets will be summarized by treatment arm and stratum.

Full analysis set

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned by randomization, regardless of whether or not the treatment was administered. According to the intent to treat principle, participants will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

Unless otherwise specified the FAS will be the default analysis set used for all efficacy analyses.

Safety set

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment, if the participant took at least one dose of that treatment, or the first treatment received if the randomized treatment was never received.

All safety data will be analyzed using the Safety Set.

Crossover analysis set

The crossover analysis set (CAS) consists of participants randomized to the docetaxel arm who crossed over to receive at least one dose of capmatinib. This analysis set will be used for all analyses pertaining to safety evaluations collected after participants crossed over in the extension treatment phase.

2.3 Patient disposition, demographics, and other baseline characteristics

The FAS will be used for all participant demographic and baseline characteristic summaries and listings.

2.3.1 Patient disposition

The following information will be presented by treatment arm:

Participants randomized:

- Number (%) of participants treated
- Number (%) of participants not treated
- Reasons for not being treated

Related to the treatment phase (participants randomized):

- Number (%) of participants who are still on-treatment;
- Number (%) of participants who discontinued treatment;
- Reasons for study treatment discontinuation;

Related to the post-treatment follow-up phase (participants who discontinued from randomized treatment):

- Number (%) of participants who did not enter the post-treatment follow-up phase;
- Number (%) of participants who entered the post-treatment follow-up phase and discontinued;
- Reasons for discontinuation from the post-treatment follow-up phase;

Related to the extension treatment (ET) phase (participants who crossed over to capmatinib):

- Number (%) of participants who entered the ET phase;
- Number (%) of participants who discontinued from the ET phase;
- Reasons for discontinuation from the ET phase;

Related to the ET safety follow-up (participants who discontinued from the ET phase):

- Number (%) of participants who entered ET safety follow-up and discontinued;
- Reasons for discontinuation from the ET safety follow-up;

The information will be derived from the applicable 'Subject status' and 'Disposition' eCRFs.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm.

The following age categories will be presented: 18–< 65, ≥ 65–< 85, ≥ 85 years. Categories with zero counts will not be included.

Diagnosis and extent of cancer

Summary statistics were prepared in the primary analysis. Data on diagnosis and extent of cancer will be listed.

Protocol deviations

Frequency counts and percentages of participants in the FAS with any important protocol deviations (eligibility, withdrawal, concomitant medication, study treatment, other) will be tabulated by the deviation category by treatment arm. All protocol deviations will be listed.

In addition to the study PD terms, Novartis has defined 6 new protocol deviations related to the COVID-19 pandemic and the corresponding relationship (health status related vs. site lockdown, patient concerns, drug supply issue, etc.) in line with "FDA Guidance on Conduct

of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (FDA 2021) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (EMA 2022). One additional study specific PD is also defined to capture treatment delay/interruption due to COVID-19. The deviations related to the COVID-19 pandemic were summarized separately in the primary analysis. Any potential new PDs will be included in the main PD summary and listing.

2.4 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for all medication data summaries and listings unless otherwise specified.

2.4.1 Study treatment / compliance

The exposure related analyses will be presented separately for the investigational drug and the control drug, if applicable.

Duration of exposure to study treatment, actual cumulative dose, dose intensity (DI), and relative dose intensity (RDI) will be summarized. In addition, a categorical summary of RDI will be presented in the respective summaries. The duration of exposure will be categorized into time intervals (< 6, ≥ 6–< 12, ≥ 12–< 18, ≥ 18–< 24, ≥ 24–< 36, ≥ 36–< 48, ≥ 48–< 60, ≥ 60–< 72, ≥ 72–< 84, ≥ 84–< 96, ≥ 96 weeks, or as appropriate); frequency counts and percentages will be presented for the number (%) of participants in each interval. The number (%) of participants who have dose reductions or interruptions, and the reasons, will be summarized.

Participant level listings of all doses administered on treatment along with dose change reasons will be produced. Participants who continue treatment beyond disease progression will be listed.

Definitions related to the duration of exposure and dose intensity for investigational drug as well as for the control drug are specified in the primary analysis SAP.

2.4.2 Prior, concomitant and post therapies

Prior anticancer therapy and concomitant antineoplastic radiotherapy

Prior antineoplastic medications, and radiotherapies were summarized in the primary analysis and did not change. Prior antineoplastic surgeries will be listed based on the FAS.

There was no additional data collected on concomitant radiotherapy, therefore no new analysis will be done.

Concomitant therapy

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments, and blood transfusions), surgeries or procedures (including physical therapy) administered in the study and are recorded on the eCRFs for Concomitant Medications and Prior or Concomitant non-drug therapies/procedures, respectively.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Surgeries or procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. All summaries will be tabulated using frequency counts and percentages.

Concomitant therapies will be summarized by ATC class, preferred term, and treatment arm. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries during the on-treatment period will include: 1) medications starting on or after the start of study treatment but starting no later than 30 days after last dose of study treatment and 2) medications starting prior to the start of study treatment but continuing after the start of study treatment.

All concomitant therapies will be listed by treatment arm. Any concomitant therapies starting more than 30 days after the last date of study treatment and collected in the extension-treatment phase will be flagged in the listings. The safety set will be used for all concomitant medication tables and listings.

Antineoplastic therapy after discontinuation of study treatment

The FAS will be used for listings and summaries of antineoplastic therapies initiated after discontinuation of study treatment. Summaries will be tabulated using frequency counts and percentages by treatment arm.

Antineoplastic medications initiated after discontinuation of study treatment will be summarized and listed by Anatomical Therapeutic Chemical (ATC) class, preferred term, and treatment arm.

Antineoplastic radiotherapy since discontinuation of study treatment will be listed. Antineoplastic surgeries since discontinuation of study treatment did not change, therefore no new analysis will be performed.

2.5 Analysis supporting primary objective(s)

The primary objective is to evaluate whether capmatinib prolongs PFS by BIRC according to RECIST 1.1 compared to docetaxel. This objective was evaluated in the primary analysis as planned in the study protocol and median PFS was reached. No significant change is expected. However, to fulfill a HA request, a descriptive summary of the PFS endpoint will be provided in the final analysis.

2.5.1 Primary endpoint

Progression-free survival (PFS) based on BIRC assessment as per RECIST 1.1 is the primary efficacy endpoint. The analysis will be based on the FAS and will include all data observed up-to the cut-off date. Censoring conventions are defined in Section 2.5.3.

PFS is defined as the time from the date of randomization to the date of the first documented disease progression based on BIRC assessment as per RECIST 1.1 or date of death due to any cause, whichever occurs first.

The analysis of PFS will be based on the central radiological assessments done until the cut-off date defined in Section 2.1. The analysis will use the default censoring and event date options from table 16-5 of the [Study Protocol Appendix 16.1] based on options A(1), B(1), C1(1), C2(1), D(1), E(1), and F(1); option G is not applicable. In particular, PFS will not be censored if a new antineoplastic therapy is started; instead, an Intent to treat (ITT) approach will be used and this new antineoplastic therapy will be ignored for the purposes of PFS derivation (and tumor assessments will continue), i.e., option F(1) in Table 16-5 of the [Study Protocol Appendix 16.1] will be used. Discontinuation of study treatment (for any reason before a PFS event [radiological progression or death]) will not be considered as a reason for censoring. Tumor assessment data collected after discontinuation of study treatment or occurrence of any unforeseen intercurrent event (e.g., due to COVID-19 pandemic) but before the PFS event will be used for PFS.

2.5.2 Statistical hypothesis, model, and method of analysis

The confirmatory part of the objective was evaluated in the primary analysis. For the update based on final data, the hypothesis test as well as the supportive and sensitivity analyses will not be repeated.

The distribution of PFS will be estimated using the Kaplan-Meier method. The results will be depicted graphically by treatment arm. The median PFS, 25th and 75th percentiles, and PFS rate at different timepoints (e.g., 3, 6, 9, 12, 15 months) along with 95% confidence intervals (CIs) will be presented by treatment arm. A Cox regression model stratified by the randomization stratification factor will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI based on the Wald test.

2.5.3 Handling of missing values

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment performed on or before the cut-off date, if no PFS event (radiological progression or death) is observed prior to the analysis cut-off date. Clinical deterioration will not be considered as documented disease progression. PFS events will be included in the analysis if they occur after one missing assessment.

Radiological progression or death observed after 2 or more missing tumor assessments (including missed assessments due to the COVID-19 pandemic) will not be included in the derivation of the time to event for PFS, and the observation will be censored at the time of the last adequate tumor assessment prior to the first missing assessment. Participants without a post-baseline tumor assessment (and without death) will be censored at the time of randomization.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD or non-CR/non-PD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of randomization will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "not evaluable (NE)." The rule to determine the number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-1 for censoring and event date options and outcomes for PFS and Section 5.1 for details regarding missing adequate tumor assessments.

Table 2-1 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of randomization[1]	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to "Disease progression" without documented progression, i.e., clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Progressed

[1] The rare exceptions to this are

(1) if the participant dies no later than the time of the second scheduled assessment as defined in the protocol, in which case this is a PFS event at the date of death,

(2) if baseline target or non-target lesion assessments are unknown or missing, but a new lesion is identified post-baseline with overall response of PD, this is a PFS event at the date of PD assessment.

Other supportive analyses

Censoring pattern of PFS

The number of participants with a PFS event and number of participants censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided by treatment arm based on the following reasons:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available

- Event after ≥ 2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate tumor assessment date and the earliest of the following dates is smaller or equal to the interval of 2 missing tumor assessments

1. Analysis cut-off date,
2. Date of consent withdrawal,
3. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up,

then the PFS censoring reason will be

1. "Ongoing"
2. "Withdrew consent"
3. "Lost to follow-up", respectively

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed, then the PFS censoring reason will always default to "Adequate assessment no longer available". If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments, then the censoring reason will be "Event documented after two or more missing tumor assessments".

These summaries on censoring reasons will be produced for PFS by investigator assessment and by BIRC assessment.

2.6 Analysis of the key secondary objective

The key secondary objective is to compare the ORR of capmatinib and docetaxel. This objective was evaluated in the primary analysis as planned in the study protocol. No significant change in the ORR is expected. However, to fulfill a HA request, a descriptive summary of the ORR endpoint will be provided in the final analysis.

2.6.1 Key secondary endpoint

ORR based on BIRC assessment as per RECIST 1.1 is the key secondary efficacy endpoint. The analysis will be based on the FAS.

The BOR will be determined from response assessments undertaken while on treatment. In addition, only tumor assessments performed before the start of any further anti-neoplastic therapy will be considered in the assessment of BOR. Localized palliative radiotherapy for pre-existing, painful bone and/or liver metastases is permitted. Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture is permitted when not delivered to a target lesion. Tumor assessment data collected after occurrence of any unforeseen intercurrent event (e.g., due to COVID-19 pandemic) will be included in the BOR assessment.

BOR for each participant is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.

- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).
- Non-CR/non-PD* = at least one Non-CR/non-PD assessment > 5 weeks after start of treatment (and not qualifying for CR).
- PD = progression ≤ 13 weeks after randomization (and not qualifying for CR, PR, or SD)
- NE = all other cases (i.e., not qualifying for confirmed CR or PR and without SD after more than 5 weeks or early progression within the first 13 weeks).

* For participants with only non-measurable disease present at baseline. A non-CR/non-PD response is considered equivalent to an SD response for the ORR determination and participants will be considered "non-responders."

Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

The NE BOR status can be due to the following reasons (and was presented in the primary CSR):

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response NE
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early (≤ 5 weeks after randomization date)
- PD too late (> 13 weeks after randomization date)

Note 1: An SD is considered as "SD too early"' if the SD is documented within the first 5 weeks after randomization date.

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 13 weeks after the randomization date with no qualifying CR, PR, or SD in between.

Note 3: Special (and rare) cases where BOR is "NE" due to both too early SD and too late PD will be classified as "SD too early".

2.6.2 Statistical hypothesis, model, and method of analysis

A descriptive summary of the ORR by treatment arm will be provided in the final analysis (including 2-sided exact 95% confidence intervals (Clopper and Pearson 1934)).

2.6.3 Handling of missing values

The determination of the BOR incorporates missing values including cases of participants with no valid post-baseline assessments.

2.7 Analysis supporting secondary objectives

Further secondary efficacy objectives, see Table 1-1, were evaluated in the primary analysis. There were only 4 participants ongoing on treatment at that time (including 1 participant ongoing post BIRC-confirmed progression). Based on the additional data from these participants up to the cut-off date (LPLV) at the final database lock, no or only minimal changes in the results were expected, except for duration of response, in which some improvement might be observed. However, to fulfill a HA request, the RECIST-based secondary efficacy analyses, as well as overall survival, will be repeated in the final analysis.

2.7.1 Secondary efficacy endpoints

The secondary efficacy endpoints will be assessed using the FAS. The following analyses will be performed based on both local investigator assessment and BIRC per RECIST 1.1 (see [Study Protocol Appendix 16.1]).

For analyses of the secondary endpoints there will be no multiplicity adjustment. All results will be considered as exploratory.

Overall response rate

ORR per local investigator assessment will be analyzed using the same method as for ORR by BIRC, see Section 2.6.

Construction of waterfall graphs

Waterfall graphs will be used to depict the anti-tumor activity based on local investigator or based on BIRC assessment. For details please refer to the primary analysis SAP.

Disease control rate

DCR is defined as the proportion of participants with BOR of CR, PR, or SD.

DCR will be estimated and the 95% exact confidence interval (Clopper and Pearson 1934) will be provided by treatment arm. These analyses will be performed separately based on investigator assessment and based on BIRC assessment.

Duration of response

Among participants with a confirmed response (PR or CR), DOR is defined as the time from the first documented response (PR or CR) to the date of the first documented PD or death due to any cause. If a participant has not had an event, DOR is censored at the date of last adequate tumor assessment using the censoring rules described in Table 2-21. Refer to Section 5.1 for details regarding missing adequate tumor assessments.

Please note that the rules to derive the reason for censoring have been adjusted to the situation in this early terminated study. Participants who were still receiving study treatment and discontinued the study to continue with capmatinib treatment outside of the study could have their last visit much earlier than the LPLV due to different regulations and/or possibilities in their country. When their last imaging assessment is compared to the global LPLV it might

appear as if there were missing assessments. To avoid this, the cut-off date definition in Section 5.1 was updated to include study discontinuation due to "study terminated by sponsor".

Table 2-2 Outcome and event/censor dates for DOR analysis

Situation	Date	Outcome
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to "Disease progression" without documented progression, i.e., clinical progression based on investigator claim	Date of last adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed

The distribution function of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment arm. The DOR results will also be listed.

These analyses will be performed separately based on investigator assessment and based on BIRC assessment.

Time to response

TTR is defined as the time from the date of randomization to the first documented response of either CR or PR, which must be confirmed subsequently.

All participants in the FAS will be included in the TTR calculation. Participants without a confirmed PR or CR will be censored at

- the maximum follow-up time (i.e., FPFV − LPLV) for participants with a PFS event (i.e., disease progression or death due to any cause), or
- at the date of the last adequate tumor assessment date for participants without a PFS event.

TTR will be listed and summarized by treatment arm. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CIs will be presented by treatment arm.

An additional summary of time to response with descriptive statistics based on responders' results only will also be prepared.

These analyses will be performed separately based on investigator assessment and based on BIRC assessment.

Overall survival

OS is defined as the time from the date of randomization to the date of death due to any cause. If a participant is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to the data cut-off date.

The distribution of OS will be estimated using the Kaplan-Meier method. The median OS and 25th and 75th percentiles along with 95% CI will be presented by treatment arm. The results will also be presented graphically by treatment arm. The survival probabilities at specific time points and the associated 95% confidence intervals will be summarized by treatment arm.

Censoring pattern of OS

The pattern of censored data will be examined regarding reasons for censoring ('Alive' or 'Lost to follow-up'). In addition, survival status, reason for censoring, and cause of death will be listed.

Duration of follow-up

Study follow-up will be summarized using the following:

- Summary of duration between randomization and cut-off date, and follow-up times for PFS and OS, which are defined as follows:
  - Duration between randomization and data cut-off date = (cut-off date – date of randomization + 1) / 30.4375 (months). This item will be summarized overall.
  - Follow-up time = (date of event or censoring – date of randomization + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date for OS. This item will be summarized by treatment arm.

All summaries will be reported in months. The calculations for PFS will be based on the BIRC assessment. Date of censoring is the same as defined for the PFS and OS analysis.

2.8 Safety analyses

For all safety analyses, the safety set will be used unless otherwise specified. All listings and tables will be presented by treatment arm.

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 deaths 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). The definition of the pre-treatment, on-treatment, and post-treatment period as well as the crossover period is given in the primary analysis SAP (Section 2.1.1.8).

All data, regardless of observation period, will be listed and assessments collected in the post-treatment period will be flagged in all the listings. Data collected in the extension-treatment

phase (including those during and after crossover period) for participants in the crossover analysis set will be flagged with a different symbol.

2.8.1 Adverse events (AEs)

AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

AE summaries will include all AEs occurring during the on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g., relationship to study treatment, outcome, etc.

Treatment-emergent adverse events (events that started after the first administration of study treatment or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) and maximum grade. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the "All grades" column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically, and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational drug arm.

The following AE summaries will be produced:

- AEs regardless of study treatment relationship
- AEs suspected to be study treatment related
- On-treatment deaths, by primary system organ class and preferred term
- All deaths, by primary system organ class and preferred term
- SAEs regardless of study treatment relationship
- SAEs suspected to be study treatment related
- AEs leading to permanent discontinuation of study treatment regardless of study treatment relationship
- AEs leading to permanent discontinuation of study treatment suspected to be study treatment related
- AEs requiring dose adjustment and/or study treatment interruption regardless of study treatment relationship
- AEs requiring dose adjustment and/or study treatment interruption suspected to be study treatment related
- AEs excluding SAEs
- AEs leading to fatal outcome.

Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables will be provided by SOC and PT based on the safety set for randomized phase and extension treatment phases:

- On-treatment AEs which are not SAEs with an incidence greater than 5%
- On-treatment SAEs and SAEs suspected to be related to study treatment

If for the same participant, 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 AEs 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.

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to capmatinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

All AESI definitions or AE groupings are specified in the electronic Case Retrieval Strategy (eCRS). The latest version of the eCRS available at the time of the analysis will be used.

For each specified AESI, the number and percentage of participants with at least one event of the AESI occurring during the on-treatment period will be summarized. The summaries will present grade, SAE, relationship to study treatment, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death, etc. A listing of the MedDRA terms that define the AESIs will be generated.

2.8.2 Deaths

Separate summaries for on-treatment deaths and all deaths will be produced by treatment arm, system organ class and preferred term. All deaths will be listed, and post-treatment deaths will be flagged.

2.8.3 Laboratory data

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected in the pre-treatment (for baseline, if applicable) and on-treatment period. All laboratory assessments will be listed and those collected in the post-treatment period will be flagged in the listings.

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values (in SI units) only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low, normal, or high based on laboratory normal ranges.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment arm):

- Worst post-baseline CTC grade (regardless of the baseline status). Each participant will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value (hypo and hyper worst grade will be summarized separately, if applicable)
- For laboratory tests where CTC grades are not defined, shift tables using low, normal, high (as well as low and high combined) classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades, if applicable, and the classifications relative to the laboratory normal ranges.

All laboratory data will be listed by participant and visit/time, and if normal ranges are available, abnormalities will be flagged.

Liver function parameters

Liver function parameters of interest are total bilirubin, ALT, AST, and alkaline phosphatase. A listing of these parameters will be prepared and participants with combined post-baseline peak elevations of AST or ALT and Bilirubin (ALT or AST > 3× ULN and BILI > 2 × ULN) will be flagged.

A summary table and/or graph (eDISH plot) will only be prepared if there are new observations (after primary database lock) which fulfill the lab criteria of potential Hy's law events. Please refer to the primary analysis SAP for the categories in the summary table.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT, and QTcF intervals and heart rate will be obtained for each participant during the study. ECG data will be read and interpreted centrally. The

average of the ECG parameters at each assessment should be used in the analyses. ECGs collected during the on-treatment period will be summarized.

The number and percentage of participants with notable ECG values will be presented by treatment arm. Please refer to the primary analysis SAP regarding the categories.

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period and during the extension treatment period will be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: systolic and diastolic blood pressure (mmHg), pulse (beats per minute), body temperature (°C), weight (kg), and height (cm).

The number and percentage of participants with notable vital signs values will be presented by treatment arm based on the categories described in the primary analysis SAP.

A listing of all vital sign assessments will be produced, and notable values will be flagged. In the listing, the assessments collected during the post-treatment period and during the extension treatment period will be flagged.

2.8.4.3 ECOG performance status

ECOG performance status at each time point will be listed. Participants with brain metastases at baseline will have continued assessments after the end of treatment to assess intracranial response per RANO-BM criteria. Post-treatment assessments will be included in the listing and flagged (also identifying assessments in the extension treatment period).

The frequency table by timepoint as well as the analysis of definitive deterioration in ECOG performance status will not be repeated in the final analysis. The ECOG performance status scale is specified in the primary analysis SAP.

2.8.4.4 Safety evaluation after crossover

All participants who had crossed over from the docetaxel arm and received capmatinib had discontinued prior to the primary analysis. Their safety data has been reported in the primary CSR. No further analysis will be done except including the data in the clinical trial safety disclosure tables.

2.9 Pharmacokinetic endpoints

The PK lock at the primary analysis was considered the final lock. No further analysis of pharmacokinetic data will be performed.

2.10 PD and PK/PD analyses

No analyses are planned.

2.11 Patient-reported outcomes

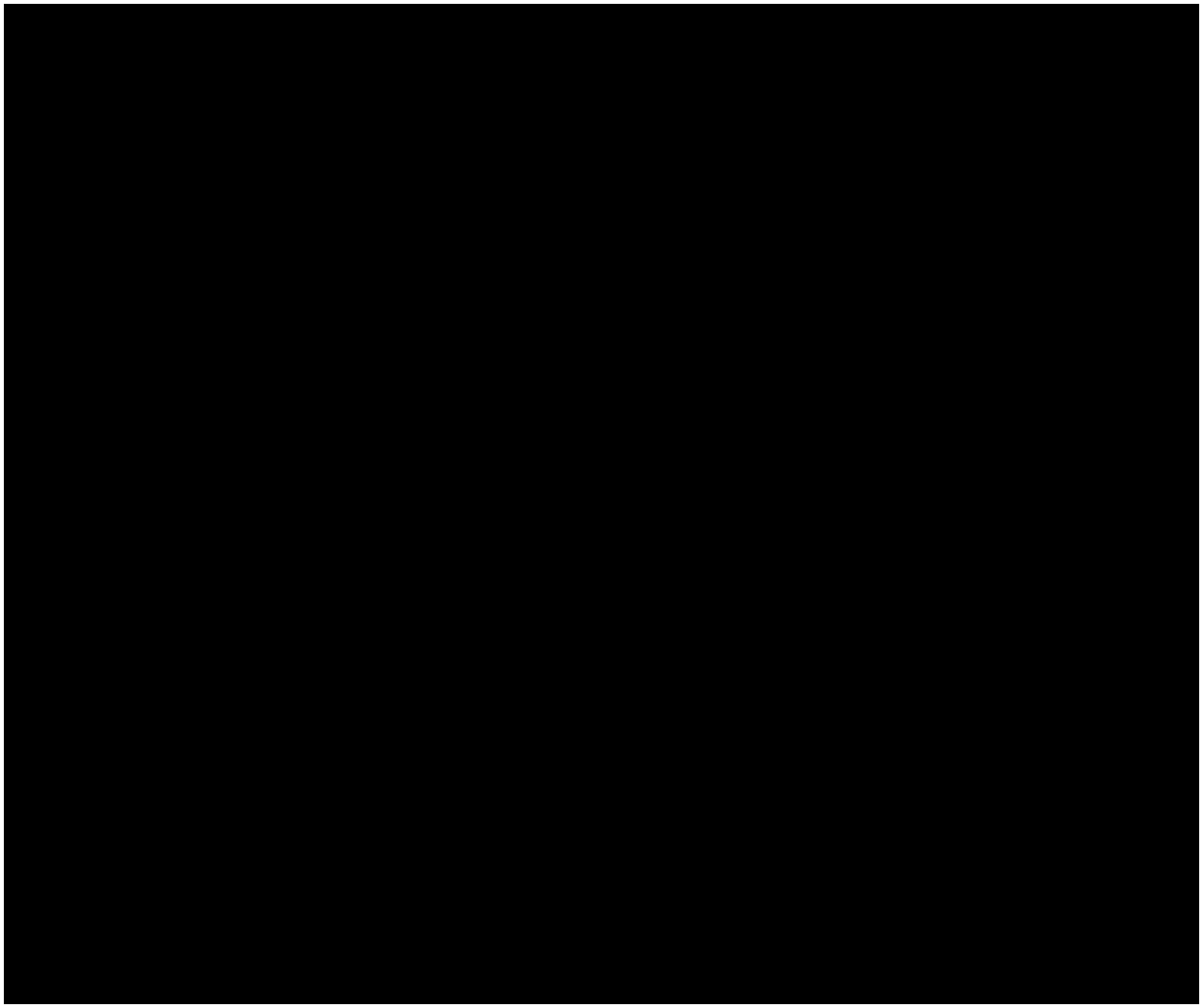
To assess the effect of capmatinib versus docetaxel on patient-reported disease-related symptoms, functioning, and health-related quality of life via patient-reported outcomes questionnaires is a secondary objective of the study.

The objective was evaluated in the primary analysis. Only minimal changes are expected from an analysis based on additional data. A reanalysis will therefore not be performed.

2.12 Biomarkers

Any analysis of biomarker data, if performed, will be outlined in a separate biomarker analysis plan with results described in a stand-alone biomarker report.

[redacted]



2.14 Interim analysis

Not applicable.

3 Sample size calculation

Please refer to the primary analysis SAP regarding the sample size calculation for the primary and key secondary endpoint.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

In general, please refer to the primary analysis SAP for the appendices. The following topics are covered in the primary analysis SAP appendices. Determination of missing adequate

tumor assessments and Statistical models (except the subsection for Patient-reported outcomes) are presented again in Section 5.1 and Section 5.2, respectively, below. Not all details in Section 5.2 are applicable to the final CSR analysis.

- Dose interruptions and dose changes
- Imputation rules
- AEs coding/grading
- Laboratory parameters derivations
- Determination of missing adequate tumor assessments
- Statistical models
- Novartis internal criteria for CTC grading of laboratory parameters (based on CTCAE v5 – Nov 2017)

5.1 Determination of missing adequate tumor assessments

As detailed in the [Study Protocol Appendix 16.1], the PFS and DOR censoring and event date options depend on the presence and the number of missing tumor assessments. For example, an event occurring after two or more missing assessments is censored in the analysis of PFS/DOR at the last adequate tumor assessment before the event date.

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date. If the distance is larger than threshold D_1 or D_2 then the analysis will assume one or two missing assessments, respectively. The threshold D_1 will be defined as the protocol- specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold D_2 is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. In this study, the protocol defined schedule of tumor assessment is every 6 weeks and each assessment is expected to be performed at the scheduled time point plus or minus 1 week, i.e., the window is 2 weeks, then any distance larger than $D_1 = 6 + 2 = 8$ weeks means one missing assessment and any distance larger than $D_2 = (2\times6) + 2 = 14$ weeks means two missing assessments.

The same definition of D_2 will be used to determine the PFS/DOR censoring reason.

Possible censoring reasons for PFS/DOR are:

1. Ongoing without event
2. Lost to follow-up
3. Withdrew consent
4. Adequate assessment no longer available
5. Event after ≥ 2 missing tumor assessments

The PFS/DOR censoring reason is then derived by the following sequence of rules.

- If the participant is considered to have a PFS event, then PFS/DOR censoring reason is set to missing.

- Else, if the participant has had no baseline assessment then PFS censoring reason = 4 (not applicable for DOR).
- Else, if the participant has a PFS event after two or more missing assessments [if (PFS event date ≤ censoring date and (PFS event date − date of last adequate tumor assessment (LATA) ≥ D_2)] then PFS/DOR censoring reason = 6.
- Else, if the participant has no PFS event, and the participant is censored at a date after two or more missing assessments ((censoring date − date of LATA) ≥ D_2) then PFS/DOR censoring reason = 4.
- Else, if the censoring date equals the date of discontinuation due to consent withdrawal then PFS/DOR censoring reason = 3.
- Else, if the censoring date equals the date of discontinuation due to loss to follow-up then PFS/DOR censoring reason = 2.
- Else, if the censoring date equals the analysis cut-off date and the time between LATA and the cut-off date is greater than D_2 days then PFS/DOR censoring reason = 4.
- Else, if the censoring date equals the analysis cut-off date and the time between LATA and the cut-off date is less than or equal to D_2 days then PFS/DOR censoring reason = 1

Where censoring date = min (analysis cut-off date, date of discontinuation due to consent withdrawal, date of discontinuation due to loss to follow-up, date of discontinuation due to study terminated by sponsor).

5.2 Statistical models

5.2.1 Primary analysis

The LIFETEST procedure in SAS with the TIME statement including a variable with survival times and a (right) censoring variable, and with a STRATA statement including variables of stratification factors, and with a GROUP option in the STRATA statement will be used for time-to-event endpoints.

Kaplan-Meier estimates

To analyze time-to-event variables, an estimate of the survival function in each treatment arm will be constructed using the Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with the METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG (complementary log-log transformation for derivation of CI).

Median survival for each treatment arm will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of Brookmeyer and Crowley 1982. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collett 1994).

Hazard ratio

The hazard ratio will be estimated by fitting the Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A stratified unadjusted Cox model will be used, i.e., the MODEL statement will include the treatment arm variable as the only covariate and the STRATA statement will include the stratification variable.

The hazard ratio with two-sided 95% confidence interval will be based on the Wald test.

Treatment of ties

The STRATA statement in the LIFETEST procedure will be used to analyze time to event data with ties. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

Checking proportionality of hazard assumption

Plots (SURVIVAL, LOGSURV, LOGLOGS) generated by the LIFETEST procedure in SAS will be used to provide visual checks of the proportional hazard assumption.

- SURVIVAL plots the estimated survivor functions. The shape of the curves should be basically the same if hazards are proportional.
- LOGSURV plots the cumulative hazard functions. The larger cumulative hazard should be a multiple of the smaller if hazards are proportional.
- LOGLOGS plots (cumulative hazard) will show parallel curves if the hazards are proportional.

5.2.2 Secondary [redacted] analysis

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100 \times (1 - \alpha)\%$ confidence interval using an exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for a one-way table; Clopper and Pearson 1934).

6 References

References are available upon request.

6.1 Published literature

Brookmeyer R and Crowley J (1982) A Confidence Interval for the Median Survival Time. Biometrics; 38:29-41.

Clopper C, Pearson ES (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika; 26(4):404–413.

Collet D (1994) Modelling survival data in medical research. London, Chapman & Hall.

Miettinen O, Nurminen M (1985) Comparative analysis of two rates. Stat Med; 4(2):213-226.

6.2 Health authority guidance

European Medicines Agency (2022) Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. Version 5.0 February 2022. Amsterdam, The Netherlands.

Food and Drug Administration (2021) FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic: Guidance for industry, investigators, and institutional review boards. August 2021. Silver Spring, MD.