NOVARTIS

Clinical Development

DRB436/dabrafenib/Tafinlar®, TMT212/trametinib/Mekinist®

CDRB436F2410 / NCT03551626

COMBI-APlus: Open-Label, phase IIIb study of dabrafenib in COMBInation with trametinib in Adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE management algorithm (Plus)

Statistical Analysis Plan (SAP) Addendum

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
	Prior to database lock	Incorporate changes as per protocol amendment 1 and 2	First version	NA
22 September 2020	Prior to database lock of primary analysis	Addition of analyses to describe and adjust for impact of COVID-19	Additional outputs added for analysis to describe and adjust for impact of COVID-19	
22 September 2020	Prior to database lock of primary analysis	Addition of analyses to support the pyrexia label update	Addition of analyses to support the pyrexia label update	
20 July 2021	Prior to the final database lock	Final output specifications		

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List of abbreviations

AEs	Adverse Events
AESIs	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Classification
AJCC	American Joint Committee on Cancer
BID	bis in diem/twice a day
CRS	Case Retrieval Strategy
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ECG	Electrocardiogram
EoT	End of Treatment visit
EoS	End of Study visit
FACT-M	Functional Assessment of Cancer Therapy–Melanoma
FAS	Full Analysis Set
IA	Interim analysis
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
RFS	Relapse-Free Survival
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
QD	Qua’que di’e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

2 Addendum details:

The purpose of this Statistical Analysis Plan (SAP) is to outline the statistical methods and document the outputs needed for the clinical study report (CSR) of the final analysis of study CDRB436F2410, a open-label, phase IIIb study of dabrafenib in combination with trametinib in the adjuvant treatment of stage III BRAF V600 mutation-positive melanoma after complete resection to evaluate the impact on pyrexia related outcomes of an adapted pyrexia AE-management algorothim.

The final analysis was planned to be performed at the end of the study defined as 24 months after last patient last visit.

The final analysis will be a re-run of all the analyses described in the primary analysis SAP, dated on Nov 4, 2020 (/CREDI Projects/D/DRB436F/CREDI Studies/DRB436F2410/Administrative Files (study level)/RAP or RAMP Meeting - SAP_CDRB2410_CSR_Primary_Analysis_SAP.docx https://webedi02.na.novartis.net:8443/webEDI02_non_SSO/drl/objectId/090095af8e1016b1).

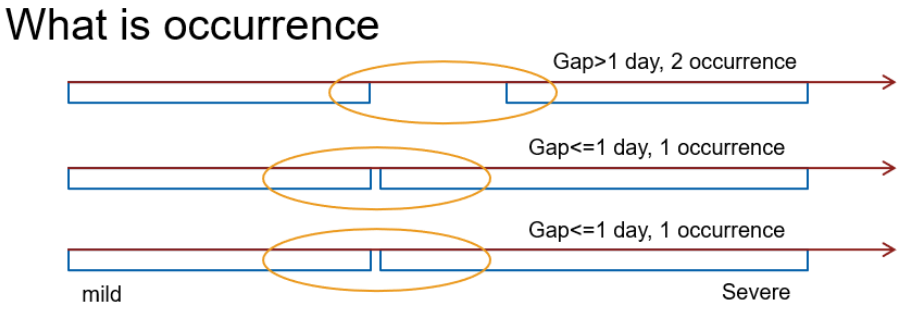
All the analyses, data rules will follow the rules described in the above SAP. The final analysis will not include the analyses described in section 2 to support label update (Section 4.2 in the primary analysis SAP). The content of this SAP is based on protocol CDRB436F2410 version 02 (Amendment 2).

The tables/listings/figures will follow the shells described in COMBI_Aplus_Final reported in

/CREDI Projects/D/DRB436F/CREDI Studies/DRB436F2410/Administrative Files (study level)/RAP or RAMP Meeting - SAP_CDRB436F2410_COMBI_Aplus_Final.docx

https://webedi02.na.novartis.net:8443/webEDI02_non_SSO/drl/objectId/090095af8b2267b8

For any occurrence , the following rules will be followed.



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

Specifically, the occurrence of AESI will follow the following rules.

To calculate the duration of AESI, the rule will be [max(end date of all below bullets)-[min(start date of all below bullets]+1.

For the first occurrence of AESI, when subsequent records AE start date is same as first occurrence start date or end date is earlier than first occurrence end date

For the first occurrence of AESI, when subsequent records start date is after first occurrence start date, but is earlier than first occurrence end date

For the first occurrence of AESI, when subsequent records start date is after first occurrence start date, but is earlier than (previous latest occurrence end date+7)

3 The changes from primary analysis to final analysis

The changes in the final analysis will be as of below:

1) Listing number changes

Previous Listing Number	Listing Name	New Listing Number
Listing 14.3.3-1.7	Adverse events of special interest (Safety set)	Listing 14.3.2-1.7

2) The tables not needed

Table Number	Table Name
Table 14.3.1-12.2	Summary of Concomitant Oral or IV Corticosteroids

Table 14.3.1-12.1	Summary of Pyrexia (Single Preferred Term) Complicated by Severe Chills, Hypotension, Dehydration, Syncope, or Renal Dysfunction
Table 14.3.1-12.3	Summary of Serious Pyrexia AESIs Requiring Hospitalization
Table 14.3.1-12.4	Summary of Occurrences and percentage of time for Pyrexia AESIs
Table 14.3.1-12.6	Event level Summary of Action Taken with Pyrexia AESI

4 Study design

This is an open-label Phase IIIb study of dabrafenib in combination with trametinib in the adjuvant treatment of melanoma after complete resection. Patients with completely resected, histologically confirmed, BRAF V600E/K mutation-positive, high-risk [AJCC ed. 8 Stage IIIA (lymph node metastasis >1 mm), IIIB, IIIC or IIID] cutaneous melanoma will be screened for eligibility. The main purpose of the study is to assess whether an adapted AE-management algorithm for pyrexia (Fever (> 38 °C)), will reduce the incidence of Grade 3/4 pyrexia, hospitalization due to pyrexia and permanent treatment discontinuation due to pyrexia. The effectiveness of dabrafenib and trametinib therapy in this setting will also be assessed based on RFS and OS.

As per the protocol amendent version dated 09-May-2019, approximately 600 subjects were planned to be enrolled to receive dabrafenib (150 mg BID) and tramatinib (2 mg once daily) combination therapy for 12 months. Due to global drug supply availibility, the enrollment of patients was slower than anticipated,resulting in the final sample of 556 enrolled patients in the study by the end of anticipated recruitment period. The final sample size is reasonably close to the planned target.

At enrollment, subjects will be instructed on the pyrexia management algorithm (refer to protocol Section 6.5.1.1). Doses of study treatment may be modified and/or interrupted for management of toxicities associated with study treatment.

Three analyses are planned for this study.

- The interim analysis (IA) based on primary endpoint and secondary endpoint conducted when 203 subjects were dosed for 6 months (either completed 6 months of treatment or discontinued earlier). The data cut-off date was 16 August, 2019.
- The primary analysis is planned to be performed at 12 months after the last patient first visit (LPFV). The data cut-off is planned on 26th September, 2020.

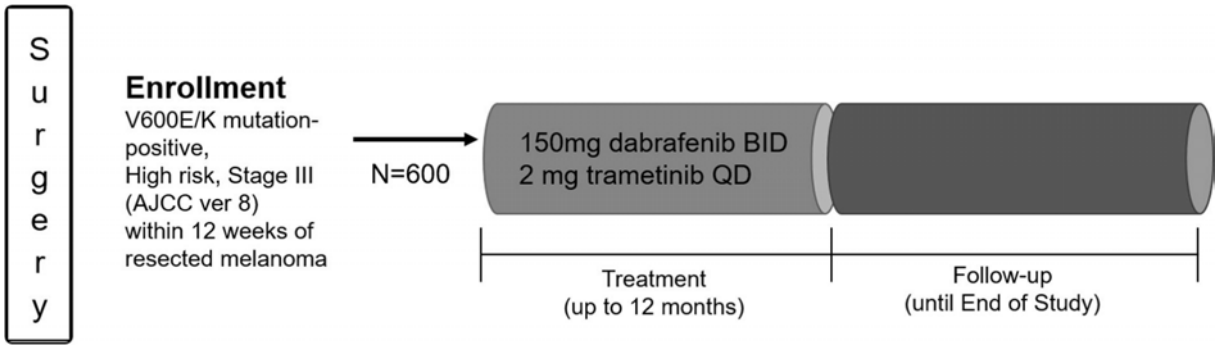
- The final analysis will be performed at the end of the study defined as 24 months after LPFV.

At the time of IA, an independent data monitoring committee (IDMC) recommended to continue the trial without any changes.

This study consists of two Periods for Enrolled subjects:

- Treatment Period – subjects will receive up to 12 months of treatment (refer to the schedule as noted in protocol Table 8-1).
- Follow-up Period – subjects will be followed from treatment discontinuation through 24 months from their first dose date for relapse; and will be followed for overall survival through withdrawal, lost to follow-up, death, or the end of study (see definition in protocol Section 9.2), whichever occurs first. Follow-up will start once: 1) treatment is completed; or 2) is prematurely discontinued and continue until withdrawal, lost to follow-up, death, or the end of study even if disease recurs. Follow-up contact prior to disease recurrence and through the 24 month assessment will include clinic visits (refer to the schedule as noted in protocol Table 8-2). Follow-up after disease recurrence and until EoS should follow the schedule as noted in protocol Table 8-3.

Figure 1.1 Study design



4.1 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**

• To assess whether an adapted AE-management algorithm for pyrexia will reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control	• The composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia by 12 months in overall treated subjects
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
Secondary Objectives	
• RFS rate at 12 and 24 months	• RFS is defined as the time from the first dose of the study medication to disease recurrence or death from any cause (whichever occurs first) at 12 and 24 months
• OS rate at 12 and 24 months	• OS is defined as the time from the first dose of study medication to date of death due to any cause at 12 and 24 months
Other Secondary Objectives	
• To evaluate the life quality: Health-Related Quality Of Life (HRQOL) measures assessed using FACT-M	• Changes in the HRQOL from baseline will be assessed using by FACT-M questionnaire
• To evaluate the overall AE rate leading to permanent treatment discontinuation by 12 months	• The proportion of subjects in the study who permanently discontinued treatment due to any adverse event by 12 months
• To evaluate pyrexia	• Frequency, number of episodes, duration, AE management (including concomitant medications and study treatment modifications) due to pyrexia
• To evaluate safety (AEs and SAEs)	• Safety will be assessed by the frequency and severity of adverse events (AEs), serious AEs (SAEs) and laboratory abnormalities

5 Statistical methods

5.1 Data analysis general information

All analysis will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The analysis cut-off date for the primary analysis will be September 26, 2020. This date will be changed based on whether all enrolled 556 patients will complete 12 months of treatment or will discontinued from the study.

All statistical analysis 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. 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 events, the end date will not be imputed and therefore will not appear in the listings.

The analysis cut-off date for the final analysis of study data will be established at the end of the study.

General analysis conventions

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

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

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

5.1.1 General definitions

Study treatment

The study treatment, used throughout the protocol and SAP, will refer to the combination of dabrafenib 150 mg twice a day (BID) and trametinib 2 mg once a day (QD). Study drug will refer to the each component (either dabrafenib or trametinib) of the study treatment.

Date of first/last administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as start date of study drug.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF. This date will also be referred to as last date of study drug.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the (e)CRF. (Example: if 1st dose of Dabrafenib is administered on 13-Jul-2013, and 1st dose of Trametinib is administered on 11-Jul-2013, then the date of first administration of study treatment is on 11-Jul-2013). The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per the (e)CRF. (Example: if the last dabrafenib dose is administered on 13-Jul-2014, and the last dose of trametinib is administered on 15-Jul-2014, then the date of last administration of study treatment is on 15-Jul-2014).

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date, etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, pk, etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (e.g. ECOG performance status and patient reported outcomes (PRO)) is the start of study treatment.

Time units

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as “baseline” assessment.

For cases where time of assessment and time of treatment start is captured (e.g. pre-dose ECG, laboratory assessments), the last available assessment before the treatment start date/time is used for baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: For ECGs or vital signs, the last value will be considered as baseline.

If patients have no value defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's sign informed consent to the day before first administration of study treatment.
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment: dabrafenib or trametinib (including start and stop date).
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

For cases where time of assessment and time of treatment start/stop is captured (e.g. ECG's laboratory assessments), the last available assessment before the treatment period start/stop date/time will be used.

If dates are incomplete in a way that clear assignment to pre-, on-, and post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period. Refer to section 5.1.1 for imputation rules concerning AE start and stop dates.

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).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize PRO measures, performance status (ECOG), physical exam, vital sign, ECG, ECHO, laboratory collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used.

If multiple assessmentson the same date then the worst case result will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window.

Time windows for PRO, ECOG assessments

Time window	Planned Visit Timing/Target date	Time Window Definition
On treatment		
Baseline	-28	<Day 1
Day 1	1	Day 1
Month 1	29	Day 2 to day 42
Month 2 (	57	Day 43 to day 70
Month 3	85	Day 71 to day 98
Month 4	113	Day 99 to day 126
Month k (k≥5)	d=k*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
Post treatment		
Follow-up Month 3	85	Day 2 to day 112
Follow-up Month k	d=k*28+1	d±28

Study Day 1 = drug administration date;

Time windows for laboratory assessments

Time window	Planned Visit Timing/Target date	Time Window Definition
On treatment		
Baseline	-28	< Day 1
Day 1	1	Day 1
Month 1	29	Day 2 to day 42
Month 2	57	Day 43 to day 70
Month 3	85	Day 71 to day 98
Month 4	113	Day 99 to day 126
Month k (k≥5)	d=k*28+1	Day d-14 to day d+13
End of Treatment		Assessment taken at the end of treatment visit
Post treatment		
30 day safety follow-up	Post treatment study day 30	Assessment taken at the 30-day safety follow-up visit

Study Day 1 = drug administration date;

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival Follow-up page	Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (CT or MRI scan) assessment date	Evaluation is marked as 'done'.
Laboratory	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

5.2 Analysis sets

Full analysis set and safety set

The full analysis set (FAS) as well as safety set includes same subjects. They comprise all subjecs who received at least one dose of any study treatment.

Patient classification

The patients who signed informed consents and received at least one dose of the study drug will be included in the analysis.

Withdrawal of informed consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

5.2.1 Subgroup of interest

Not applicable.

5.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless otherwise specified. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will summarized and listed. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, 25^{th} and 75^{th} percentiles, minimum and maximum). BMI (kg/m2) will be calculated as weight[kg] / (height[m2]) using weight at Baseline.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary tumor ulceration, stage at initial diagnosis, time since initial diagnosis of melanoma (in months) , stage at time of study entry (AJCC version 8) etc.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e) CRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version 24.1.0 used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline including will be listed as appropriate.

5.3.1 Patient disposition

Enrollment by country and center will be summarized for all screened patients. The number and percentage of patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the 'Treatment Disposition' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'Treatment Disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'Treatment Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on 'Subject Status' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'Subject Status page);
- Number (%) of patients who have entered the survival follow-up (based on the 'Subject Status' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category overall for the FAS. All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in section 2.2) will be summarized.

5.4 Treatments (study treatment, concomitant therapies, compliance)

5.4.1 Study treatment/compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized separately for each component of study treatment (dabrafenib and trametinib). The duration of exposure will also be presented for the study treatment of dabrafenib and trametinib combination therapy. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of subjects in each interval. The number (%) of subjects who have dose reductions, escalations or interruptions, and the reasons, will be summarized by dabrafenib and trametinib.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to dabrafenib and trametinib:

Duration of exposure to study treatment (*days*) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to dabrafenib or trametinib.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.).

Duration of exposure to dabrafenib and trametinib

Duration of exposure to dabrafenib (days) = (last date of exposure to dabrafenib) – (date of first administration of dabrafenib) + 1.

Duration of exposure to trametinib (days) = (last date of exposure to trametinib) – (date of first administration of trametinib) + 1.

Table 2-2 Definition of last date of exposure of study drug

Scenario	Definition of last date of exposure of study drug	Example
Daily administration of the study drug	Date of last administration of a non - zero dose of the study drug.	Example: A patient had a permanent discontinuation of the study drug 06Jan2013 after being put on a temporary interruption since 01Jan2013. In this case the last date of exposure is- 31Dec2012.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components.

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of study drug administration. The planned cumulative dose will not be summarized/listed. It will be used for relative dose intensity calculations.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration eCRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg / day) = Actual Cumulative dose (mg) / Duration of exposure to study treatment (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (mg / day) = Planned Cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg / day) / PDI (mg / day).

DI and RDI will be summarized separately for each of the study treatment components, but using the duration of exposure of each of the components.

Table 2-3 Examples of dabrafenib dose administration and exposure

DAR record number	Start/End date	Dose prescribed (mg), frequency	Dose administered (mg) [total daily]	Dose changes, dose interruption	Dose permanently discontinued	Reason
1	01Jan2016 /05Jan 2016	150mg BID	300	No	No	AE
2	6Jan2016/03 Feb 2016	150mg BID	200	Yes	No	
3	04Feb2016/ 25Feb2016	150mg BID	300	No	No	

Duration of exposure (days) = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 300*56 days = 16800 mg

Actual cumulative dose = 300*5 + 200*29 + 300*22 = 13900 mg

Dose intensity = 13900 mg / 56 days = 248.21 mg/day

Planned dose intensity = 16800 mg / 56 days = 300 mg/day

Relative dose intensity = DI / PDI = (248.21 mg/day) / (300 mg/day) = 83%

Table 2-4 Examples of trametinib dose administration and exposure

DAR record number	Start/End date	Dose prescribed (mg), frequency	Dose administered (mg) [total daily]	Dose changes, dose interruption	Dose permanently discontinued	Reason
1	01Jan2016 /10Jan 2016	2 QD	2	No	No	AE
2	11Jan2016/15 Jan 2016	2 QD	0	Yes	No	
3	16Jan2016/25 Feb2016	1 QD	1	No	No	

Duration of exposure = 25Feb2016 – 01Jan2016 + 1 = 56 days

Planned cumulative dose (for 56 days) = 2*56 days = 112 mg

Actual cumulative dose = 2*10 + 0*5 + 1*41 = 61 mg

Dose intensity = 61 mg / 56 days = 1.09 mg/day

Planned dose intensity = 112 mg / 56 days = 2 mg/day

Relative dose intensity = DI / PDI = (1.09 mg/day) / (2 mg/day) = 54%

Dose reductions, interruptions or permanent discontinuation

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

'Dose interrupted' and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction is defined as a dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

5.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic surgery will be summarized. For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic surgery.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term and by means of frequency counts and percentages using FAS. Note that biopsies will not be regarded as an anti-neoplastic surgery for the purpose of this analysis.

The number and percentage of patients who reported taking at least one anti-neoplastic therapy since discontinuation of study treatment by category (e.g immunotherapy, targeted therapy, chemotherapy, radiotherapy, etc.), the duration of treatment and the best response will be summarized.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (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. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

5.5 Analysis of the primary objective

The primary objective of the study is to assess whether an adapted AE-management algorithm for pyrexia will reduce the incidence of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia compared to historical control from COMBI-AD study.

5.5.1 Primary endpoint

The primary endpoint is defined as the composite rate of grade 3/4 pyrexia (single preferred term), hospitalizations due to pyrexia or permanent treatment discontinuation due to pyrexia up to 12 months of therapy among overall treated patients.

The rate of this composite primary endpoint is calculated as the total number of patients experiencing at least one of the three components of the composite endpoint (i.e., Grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent treatment discontinuation due to pyrexia), divided by the total number of patients in the FAS. The composite endpoint is assessed over a treatment period of 12 months; that is, any patient who experiences at least one of the components of the composite endpoint anytime within 12 month on-treatment will be included in the numerator for the calculation of the composite rate.

5.5.2 Statistical hypothesis, model and method of analysis

The primary analysis will be based on the calculation of the observed pyrexia event rate up to12 months of therapy (primary endpoint) using the FAS. The observed pyrexia event rate will be summarized using descriptive statistics (N, %) along with its two-sided exact 95% confidence interval (Clopper and Pearson 1934).

In the COMBI-AD study, 87 out of 435 subjects in the treatment arm (20%) developed either grade 3/4 pyrexia or hospitalization due to pyrexia or discontinued due to pyrexia. This rate of 20% will be used as the historical control rate for the assessment of pyrexia management algorithm in this study.

Evidence of treatment effect (improvement in pyrexia event rate using the AE-management algorithm) will be concluded, if the upper bound of the two-sided 95% confidence interval is less than 20%.

The exact 95% confidence intervals for various observed event rates at the primary analysis are shown in Table 2-5. This table has been updated from the protocol for the new sample size = 556 subjects.

If 92 (16.5%) out of 556 subjects are observed with pyrexia event, then the upper bound of the 95% confidence interval will be less than 20%.

Table 2-5 Exact 95% CI for different observed event rates at primary analysis

N	r	95% exact CI using n=600	N	r	Pyrexia event rate (%)	95% exact CI (%)* using n=556
600	92	12.5 - 18.5	556	92	16.5%	13.6 - 19.9
600	93	12.7 - 18.6	556	93	16.7%	13.7 - 20.1
600	100	13.8 – 19.9	556	100	18%	14.9 - 21.4
600	101	13.9 – 20.1	556	101	18.2%	15.0 - 21.6
600	102	14.1 – 20.2	556	102	18.3%	15.2 - 21.8
600	103	14.2 – 20.4	556	103	18.5%	15.4 - 22.0
600	104	14.4 – 20.6	556	104	18.7%	15.5 - 22.2
600	105	14.5 – 20.8	556	105	18.9%	15.7 - 22.4

N: Total numbers of subjects;

r: Number of subjects with pyrexia events at primary analysis

* Clopper and Pearson (1934)

In addition, the probability that the pyrexia event rate is below the threshold of 20% will be calculated from the posterior distribution. The pyrexia event rate will be assumed to be binary and the number of subjects with pyrexia events will be assumed to follow a binomial distribution. If Y represents the number of patients with composite pyrexia events then predictive distribution of Y conditional on the observed data at the primary is a beta-binomial distribution. A diffuse (highly non-informative) prior distribution of the composite rate with a skeptical expectation of 20%, namely Beta (0.25, 1) will be assumed. For illustration, as shown in Table 2-6, if 96 out of 556 subjects are observed with pyrexia events at primary analysis, then the posterior probability of observing an event rate of $< 20\%$ is 0.952 (probability ≥ 0.95). This table has been modified for sample size = 556 from the protocol.

Table 2-6 Posterior probability for a positive effect at primary analysis

r	Posterior* Pr (event rate<20%|data) N= 600	Posterior* Pr (event rate<20%|data) N= 556
92	0.999	0.982
96	0.994	0.952
100	0.983	0.890
101	0.977	0.868
102	0.971	0.843
103	0.963	0.816
104	0.954	0.786
105	0.943	0.753
110	0.854	0.559

r	Posterior* Pr (event rate<20%|data) N= 600	Posterior* Pr (event rate<20%|data) N= 556
115	0.703	0.352
120	0.508	0.183
125	0.313	0.078
130	0.161	0.027
135	0.068	0.007

N: Total numbers of subjects;

r: Number of subjects with pyrexia events at primary analysis

* A diffuse (highly non-informative) prior distribution of the composite rate with a skeptical expectation of 20%, namely Beta (0.25, 1) is assumed.

5.5.3 Handling of missing values/censoring/discontinuations

Only observed events will be summarized in the analysis; incomplete dates of events may be appropriately imputed. For the primary endpoint, patients who discontinued prematurely prior to 12 months without pyrexia will be counted as no event.

5.5.4 Supportive analyses

Time to first occurrence of pyrexia will be analysed using the Kaplan-Meier (KM) method. If a patient has not experienced an event by the time of analysis cut-off, the time will be censored at the lastest date of study treatment in which the patient is known to be at risk.

The components of the composite primary endpoint (grade ¾ pyrexia, hospitalizations due to pyrexia or permanent treatment discontinuation due to pyrexia) will also be analyzed individually by frequency counts in order to evaluate their contributions to the overall treatment effect.

5.6 Analysis of the key secondary objective

Not applicable.

5.7 Analysis of the secondary objective(s)

The secondary efficacy objectives are to

- Evaluate the relapse free survival (RFS) at 12 and 24 months.
- Evaluate overall survival (OS) rate at 12 and 24 months.
- Evaluate patients' quality of life with respect to patient reported outcomes (PROs) of functional assessment of cancer therapy–melanoma (FACT-M) melanoma subscales.

5.7.1 Secondary endpoints

Relapse free survival

RFS is defined as the time from the date of first dose of the study treatment to the date of the first documented disease recurrence or death due to any cause whichever comes first. Treatment emergent malignancies other than second melanomas will not be considered as events. The analysis will be based on FAS and will include all data observed up-to the cut-off date.

RFS will be censored if no RFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-cancer therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to data cut-off date/start of new anti-cancer therapy date (see Section 2.7.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment).

Overall survival

OS is defined as the time from start date of study treatment to date of death due to any cause. All deaths occurring on or before the cut-off date in the FAS will be used in the OS analysis.

If a patient is not known to have died, then OS will be censored at the last contact date when the patient was known to be alive (on or before the cut-off date) (see Section 2.1.1 for the derivation of the last contact date).

Functional assessment of cancer therapy-melanoma (FACT-M)

FACT-M will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms, treatment-related side effects, and global health status. The Melanoma Subscale of the FACT-M are recognized as reliable and valid measures (Cormier 2008) frequently used in clinical trials of patients with advanced or metastatic cancer.

The FACT-M quality of life questionnaire consists of the FACT-General (FACT-G) plus the Melanoma Subscale and the Melanoma Surgery Subscale, which complement the general scale with items specific to health-related quality of life (HRQOL) in melanoma. For the purpose of this study the 16 items that comprise the Melanoma Subscale (MS) of the FACT-M are used.

5.7.2 Statistical hypothesis, model and method of analysis

RFS and OS will be analyzed descriptively in the FAS population. The RFS and OS distribution will be estimated using the Kaplan-Meier method. The Kaplan-Meier estimates will be plotted graphically. The median, 25th and 75th percentiles of RFS and OS along with 95% confidence intervals [Brookmeyer and Crowley 1982] will be presented.

The survival probabilities at 12 and 24 months, and the associated 95% confidence intervals will be summarized. The percentage of surviving subjects who are alive and disease free 1 year intervals from the time of first treatment will be estimated from the Kaplan-Meier curves for the RFS. The probabilities will be calculated at 1 year and at 2 years. Approximate 95%

confidence intervals will be calculated, based on Greenwood's formula for the standard error (SE) of the Kaplan-Meier estimate. The similar analysis will be presented for the OS as well.

5.7.3 Handling of missing values/censoring/discontinuations

Censoring of RFS

If no event has occurred by the primary analysis cutoff, then RFS will be censored as the date of the last efficacy assessment (i.e. either radiological or non-radiological) prior to the analysis cutoff that shows no disease recurrence. Patient will be censored for RFS at the date of first treatment for any of the following situation:

- The censoring algorithm calls for the patient to be censored at the date of the last adequate assessment meeting a certain set of criteria (e.g. prior to subsequent anticancertherapy), but no such assessment exists.

RFS will be censored for extended loss to follow-up to account for missed efficacy assessments prior to relapse or death. Specifically, if there are two or more scheduled efficacy assessments which are missing during the first 12 months of the treatment period, two or more missing during the follow up period followed by an assessment of relapse or death (due to any cause), RFS will be censored at the last adequate assessment prior to relapse or death. If the time interval between the last adequate efficacy assessment date and the RFS event date is larger than the interval of 2 missing efficacy assessments (7 days for treatment phase and 14 days for follow-up phase, protocol-specified time window) then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments. For this type of censoring, the 'last adequate assessment' is defined as the date of the last MRI or CT assessment prior to the missing assessments that shows no disease recurrence.

For patients who receive subsequent anti-cancer therapy the following rules will apply.

- If such therapy is started without evidence of documented disease recurrence, then RFS will be censored at the date of the last efficacy) assessment before the date of initiation of anti-cancer therapy.
- If a patient has only a baseline visit or does not have an efficacy assessment before the date of initiation of anti-cancer therapy, RFS will be censored at the date of first treatment.

Table 2-7 below further describes the algorithm to determine whether a patient should be classified as RFS event or censored.

Table 2-7 Outcome and event/censor dates for RFS analysis

Situation	Date	Outcome
Recurrence documented between scheduled visits	Date of assessment of Recurrence	Event

Situation	Date	Outcome
No recurrence (or death)	Date of last efficacy assessment	Censored
New anti-cancer therapy (including surgery for melanoma) started prior to documented disease recurrence*	Date of last efficacy assessment on or prior to starting anti-cancer therapy	Censored
Death before recurrence assessment	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or recurrence after two or more missed scheduled efficacy assessments during study treatment period or after two or more missing during the follow up period	Date of last adequate assessment prior to missed assessments	Censored

*If relapse and new anti-cancer therapy occur on the same day then the relapse will be counted as event. If anticancer therapy is started prior to any adequate assessments, censoring date should be the date of first treatment.

Censoring of OS

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date when patient was alive, i.e., last contact date.

5.8 Safety analyses

All safety analyses will be based on safety set.

5.8.1 Adverse events (AEs)

Adverse events are coded using MedDRA terminology. The MedDRA 24.1 version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only

once in the respective AE category. A subject 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 SOC 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.

The following adverse event summaries will be produced: overview of adverse events and deaths, AEs by PT, SOC and PT, summarized by relationship to study treatment, seriousness, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term). Note that Adverse events leading to fatal outcomes with relationship is a EudraCT requirement.

The proportion of subjects in the study, who have permanently discontinued treatment due to any AE PT, will be estimated along with 95% confidence intervals using Clopper Pearson exact method.

5.8.1.1 Pyrexia

For pyrexia, other characteristics like number of episodes, duration, and AE management (including concomitant medications and study treatment modifications) due to pyrexia will be summarized..

The number (%) of patients who received medications for treatment of pyrexia will be summarized along with the type of medications.

5.8.1.2 Adverse events of special interest (AESI)/grouping of AEs

All AESI definitions or AE grouping for the clinical program need to be specified in the Compound Case Retrieval Strategy sheet (CRS) with one exception of pyrexia AESI with clear versioning and reference to the MedDRA version used. The CRS version will be included in a footnote of the AESI tables.

Pyrexia AESIs will be defined using the following list of PTs:

Pyrexia PT	PT Code
Body temperature increased	10005911
Cytokine release syndrome	10052015
Hyperpyrexia	10020741
Hyperthermia	10020843
Influenza like illness	10022004
Pyrexia	10037660
Sweating fever	10042666
Systemic inflammatory response syndrome	10051379
Tumour associated fever	10052243

Table 2-6 Adverse events of special interest by study treatment

	trametinib	dabrafenib	dabrafenib and trametinib combination
Hepatic disorders	x		x
Pneumonitis/Interstitial lung disease	x		x
Skin toxicities (e.g., rash, dermatitis acneiform)	x		x
Bleeding events	x		x
Hypersensitivity	x	x	x
Pancreatitis		x	x
Neutropenia			x
Pulmonary embolism, deep vein thrombosis	x		x
Pre-renal and intrinsic renal failure		x	x
New primary melanoma		x	x
Non-Cutaneous Treatment-Emergent Malignancies		x	x
Hyperglycemia		x	x
Cardiac related events	x		x
Complicated pyrexia and/or Grade 3 and Grade 4 pyrexia		x	x
Uveitis		x	x
Ocular events (e.g., retinal vein occlusion, retinal pigment epithelial detachment and uveitis)	x		x
Cutaneous squamous cell carcinoma including keratocanthoma		x	x
Hypertension	x		x

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to each components of study treatment, i.e. dabrafenib and trametinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A 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. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

Summaries of these AESIs will be provided, (specifying PTs, grade, serious adverse event (SAE), relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.).

5.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by SOC and PT.

All deaths will be listed for the Safety set, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

5.8.3 Laboratory data

On analyzing laboratory, data from all sources will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date.

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

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject 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
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of chemistry and hematology lab parameter values over time should be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities.

Liver parameters

Liver parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN

- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those patients with occurrence of AST or ALT > 3xULN and TBL > 2xULN, and ALP < 2xULN at initial presentation during the on-treatment period. Note that the criteria relating to combined elevations of AST (or ALT) and TBL are based on the peak values at any post-baseline time for a patient.

For patients with abnormal ALT or AST baseline values, a clinically significant liver safety signal corresponding to Hy's law is defined by : [ALT or AST > 3*baseline] OR [ALT or AST >8*ULN], whichever is lower, combined with [TBIL >2*baseline AND >2*ULN].

5.8.4 Other safety data

5.8.4.1 Electrocardiogram (ECG) and cardiac imaging data

Single standard 12-lead ECGs will be obtained using an ECG machine that automatically calculates heart rate (HR) and measures RR, PR, QRS, QT, and QTcF intervals. All ECG assessments will be performed in the supine position. All ECG assessments will be read and interpreted locally.

ECHO/MUGAs will be performed to assess cardiac ejection fraction. The same procedure (either ECHO or MUGA) should be performed at baseline and follow-up visits. All ECHO/MUGA assessments will be read and interpreted locally.

Data handling

In case of ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

The number and percentage of subjects with notable ECG values will be presented.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms

- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

The summaries will include all ECG assessments performed no later than 30 days after the last study treatment date.

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

For each of the ECG parameters, descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point will be summarized.

Patients with notable ECG interval values will be listed and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG values.

For left ventricular ejection fraction (LVEF), descriptive statistics at baseline, at each postbaseline time point and changes from baseline at each post-baseline time point will be summarized. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline

To identify LVEF values of potential clinical importance, the following table will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF Parameter Potential Clinical Importance (PCI) Range Unit	**Potential Clinical Importance (PCI) Range**	**Unit**

Absolute change from baseline LVEF	• No change or any increase
	• Any decrease
	  • >0-<10 decrease
	  • 10-19 decrease
	  • >=20 decrease
	  • >=10 decrease and >= LLN
		%

	• >=10 decrease and < LLN • >10 decrease and < LLN • >=20 decrease and >= LLN • o >=20 decrease and < LLN	

5.8.4.2 Vital signs

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

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-7 below.

Table 2-7 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > =10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented. Descriptive statistics will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure.

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

The ECOG performance status scale will be used to assess physical health of subjects and as described in Table 8-6 in the protocol. The scale ranges from 0 (fully active) to 5 (dead).

ECOG performance status will be summarized for each assessment time. Frequency counts and percentages of subjects in each score category will be provided by time point based on the windows defined in Section 2.1.1.

A supporting listing will also be provided.

5.8.4.3 Opthalmic examination

A listing of ophthalmic examinations at screening will be produced.

5.8.5 Additional analyses

Time to first occurrence

Time to first occurrence of an event is defined as time from start of study treatment to the date of first occurrence of this event (or first event within an AE grouping), i.e. time in days is calculated as (start date of first occurrence of event) – (start of study treatment) +1.

For Kaplan-Meier analyses of time to occurrence, in the absence of an event during the on-treatment period, the censoring date applied will be **the earliest** of the following dates:

- death date
- new anticancer antineoplastic therapy start date
- end date of on-treatment period
- data cut-off date
- withdrawal of informed consent date.

Failure curves (ascending Kaplan-Meier curves) will be constructed. Median together with 95% confidence interval as well as 25th percentile and 75th percentile will be presented.

In addition, the median time to occurrence for the subset of patients who experienced the event of interest will be calculated. Simple descriptive statistics, median, min and max as well as 25th percentile and 75th percentile, will be presented.

5.9 Pharmacokinetic endpoints

Not applicable.

5.10 PD and PK/PD analyses

Not applicable.

5.11 Patient reported outcomes (PRO)

5.11.1 General PRO analysis

The FAS will be used for analyzing PRO data

In this study, the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) questionnaire will be used to evaluate the quality of life in patients with melanoma. This questionnaire consists of "physical well-being (PWB)", "social/family well being (SWB)", "emotional well-being (EWB)", "functional well-being (FWB)", "Melanoma subscale (MS)". The total FACT-M score is calculated as PWB score+ SWB score+EWB score+FWB score+MS score. In this study, the 16 items that comprise MS of the FACT-M will be used.

The variables analysed will be by the summary score. The summary score will be summarized descriptively in tables and graphs for baseline, post-baseline on treatment assessments (including the EoT assessment, if collected within 30 days of last non-zero dose intake) and scheduled post-treatment time points, and change from baseline to visit for total FACT-M score. The time windows as described in Section 2.1.1 will be used.

The FACT-M is planned to be administered during baseline and at each scheduled post-baseline visit as per protocol through 24 months. The FACT-M will continue to be collected during the follow-up after the end of treatment. The baseline is defined as the last PRO assessment on or prior to first day of treatment.
No imputation procedures will be applied for missing items or missing assessments.

5.12 Biomarkers

Not applicable.

5.13 Other exploratory analysis

Not applicable.

5.14 Interim analysis

There was an interim analyses planned for this study when 203 patients completed 6 months of treatment or discontined earlier. The details of statistical analysis can be found in the SAP of interim analysis. DMC recommended to continue the trial based on interim analysis.

6 Sample size calculation

As per the protocol amendent version dated 09-May-2019, approximately 600 subjects were planned to be enrolled to receive dabrafenib (150 mg BID) and tramatinib (2 mg once daily) combination therapy for 12 months. Due to global drug supply availibility, the enrollment of patients was slower than anticipated,resulting in the final sample of 556 enrolled patients in the study by the end of anticipated recruitment period. The final sample size is reasonably close to

the planned target. The impact of the reduced sample size for the interim analyses has been discussed in detail in the Interim SAP (dated 21-Nov-2019) and DMC charter (17-Jan-2020). See Section 2.8 and Appendix B respectively for details.

The sample size calculation was based on the primary variable. The protocol amendement dated provided justification for the planned sample size of 600. However the current sample size of 556 demonstartes that the study operating characteristics comply with the requirement to have a highprobability (e.g. > 95%) for futility at IA if the true 12-month pyrexia event rate is > 20%, e.g., when the true pyrexia event rate is 27%, the probability is 95.5% for futility at interim analysis.

Detailed Operating characteristics are described below (see Table 2-8). For illustration, if the true 12-months pyrexia event rate is 30%, then there is a high chance (99.6%) of futility at the time of the interim, and the probability to continue the study and conclude success is lower than 0.001.

If the true pyrexia event rate is 20%, then the probability of observing a pyrexia event rate < 20% (i.e., study success for primary analysis) is 46.3%. If the true pyrexia event rate is lower (for example 18%), then there is 84.6% probability of declaring study success for primary analysis.

Table 2-8 Operating Characteristics

True 6 -month event rate	Probability to stop the study at IA	Probability of success at primary analysis (i.e., not stop at the IA and observe event rate < 20% at primary analysis)*
16%	0.016	0.980
17%	0.040	0.940
18%	0.086	0.846
19%	0.161	0.679
20%	0.265	0.463
21%	0.391	0.258
22%	0.528	0.115
25%	0.856	0.002
26%	0.917	<0.001
27%	0.955	<0.001
28%	0.978	<0.001
30%	0.996	<0.001

* Probabilities are calculated based on the exact binomial distribution.

7 Changed to protocol specified analyses

7.1 Impact of COVID-19

Due to pandemic COVID in year 2020, some extra analyses will be performed outside protocol specified.

Oprational impact: Specified protocol deviation categories will be assigned to important deviations related to COVID-19 (e.g., missing efficacy assessments and treatment interruptions) and these will be summarized and listed separately. A summary table of the COVID-19 related deviations by relationship category will be provided.

Safety: To help to evaluate the impact of the pandamic on safety, the incidence of COVID-19 related adverse event preferred terms will be presented incorporating (a) COVID-19 related adverse events with an onset date prior to the start of the outbreak (i.e., pre-2020, please refer the following paragraph for the definition) and (b) all COVID-19 related adverse events occuring before data cut-off. A listing of all COVID-related AEs will also be provided.

The Pre-COVID period is defined as before March 1, 2020 for Rest of the World and before Feb 23, 2020 for Italy patients. That means March 1 will play a data-cut off role. All the data before March 1 will be considered as pre-Covid period. The data from March 2, 2020 onwards will be considered as Post-Covid period.

The Post-COVID period is defined as after March 1, 2020 for Rest of the World and after Feb 23, 2020 for Italy patients.

Primary endpoint:

To help to evaluate the impact of the COVID-19 on the primary endpoint and on overall pyrexia, the following sensitivity analyses will be performed. The summary analyses will be performed if we have 10% total sample size in each of the caterogies. The KM plot will be performed only if we have more than 30 patients have pyrexia event in each of the categories.

1) Composite rate of grade ¾ pyrexia, hospitalization or permanent discontinue due to pyrexia by 12 months for Rest of the World (Full analysis set) Pre-Covid and post-Covid-period.
2) Composite rate of grade ¾ pyrexia, hospitalization or permanent discontinue to pyrexia by 12 months for Italy (Full analysis set) with data cut-off Feb 23, 2020 vs data after February 23, 2020.
3) Composite rate of grade ¾ pyrexia, hospitalization or permanent discontinue to pyrexia by 12 months with suspected and confirmed covid subjects using full analysis set.
4) Summary of pyrexia – Pre and post COVID period for rest of the world
5) Summary of pyrexia– Pre and post COVID period for Italy (Full analysis set)
6) Summary of pyrexia – confirmed and suspected covid subjects (Full analysis set)
7) Time to first pyrexia event - Pre and post COVID period for Rest of the World.

8) Time to first pyrexia event – Pre and post COVID period for Italy (Full analysis set).
9) Time to first pyrexia event – confirmed and suspected covid subjects (Full analysis set)
10) Kaplan-Meier plot time to first pyrexia event - Pre and post COVID period for Rest of the World.
11) Kaplan-Meier plot time to first pyrexia event – Pre and post COVID period for Italy (Full analysis set).
12) Kaplan-Meier plot time to first pyrexia event – confirmed and suspected covid subjects (Full analysis set)

7.2 Analyses to support label update

This section outlines additional safety analyses needed to evaluate the impact of the implementation of the new pyrexia management guideline used in COMBI-A+ study.

The current dabrafenib and trametinib labels reflect the pyrexia management guidance in COMBI-d/v and COMBI-AD protocols; to interrupt dabrafenib if the patients temperature is ≥38.5ºC and continue trametinib at the same dose. However, the increased incidence of pyrexia with combination compared to dabrafenib monotherapy, suggests that trametinib influences the dabrafenib -driven pyrexia process. Therefore, optimal guidance per current clinical consensus is to interrupt both dabrafenib + trametinib at the very first symptom of pyrexia or its associated prodrome (chills, rigors, night sweats or flu-like symptoms), as used in COMBI-i/COMBI-A+ protocols.

With a more proactive intervention for pyrexia, it is hypothesized that a cross-study comparison of pyrexia-related safety outcomes (e.g. incidence of grade ≥3 pyrexia, incidence of permanent discontinuations) in the metastatic melanoma setting (COMBI-d/v versus COMBI-i) and the adjuvant setting (COMBI-AD vs COMBI-A+) may support of a change to the dose modification section of the dabrafenib and trametinib labels. If warranted, the safety outputs defined in this SAP will be used to support the label update.

For the analyses related to complicated pyrexia and time spent in pyrexia, the following definitions will be used.

Complicated pyrexia events

Subjects who have pyrexia (single preferred term (PT)) and any of the following terms at any time while on-treatment will be considered as having complicated pyrexia: severe (≥ Grade 3) chills, hypotension, dehydration, syncope, or renal dysfunction.

Percentage of time spent in pyrexia

Percentage of time spent in pyrexia AESI will be calculated for each subject who experienced a pyrexia AESI as follows:

Total numbers of days in pyrexia AESI/ total duration of exposure in days *100.

The maximum duration of exposure to dabrefinb or trametinib will be used in the calculation.

The following tables will be required from this study. The tables generated outside protocol defined analyses, are flagged with (*) in the below list.

1) Demographics and disease characteristics
2) Disease History
3) Summary of exposure and dose of study drug received for dabrafenib and trametinib
4) Dose interruptions of trametinib
5) Dose interruptions of dabrafenib
6) Summary of Concomitant Oral or IV Corticosteroids (*)
7) Pyrexia AESIs leading to dose interruptions of trametinib (*)
8) Pyrexia AESIs leading to dose interruptions of dabrafenib (*)
9) Pyrexia AESIs leading to dose interruptions of both trametinib and dabrafenib (*)
10) Pyrexia AESIs leading to dose reductions of trametinib (*)
11) Pyrexia AESIs leading to dose reductions of dabrafenib (*)
12) Pyrexia AESIs leading to dose reductions of both trametinib and dabrafenib (*)
13) Summary of Pyrexia AESIs by maximum grade (*)
14) Summary of Characteristics of Pyrexia AESIs (*)
15) Time to onset and duration of first pyrexia AESI (*)
16) AE leading to treatment discontinuation of trametinib
17) AE leading to treatment discontinuation of dabrafenib
18) AE leading to treatment discontinuation of both trametinib and dabrafenib
19) Pyrexia AESI leading to treatment discontinuation of trametinib (*)
20) Pyrexia AESI leading to treatment discontinuation of dabrafenib (*)
21) Pyrexia AESI leading to treatment discontinuation of both dabrafenib and trametinib (*)
22) Summary of Pyrexia (Single Preferred Term) Complicated by Severe Chills, Hypotension, Dehydration, Syncope, or Renal Dysfunction (*)
23) Summary of Skin-toxicity AESIs by Maximum Grade
24) Summary of Serious Pyrexia AESIs Requiring Hospitalization (*)
25) Summary of Occurrences and percentage of time for Pyrexia AESIs (*)
26) Event level Summary of Action Taken with Pyrexia AESI (*)
27) Composite rate of grade 3/4 pyrexia, hospitalization or permanent treatment discontinuation due to pyrexia by 12 months

For all of the analyses mentioned in this SAP, pyrexia AESIs will be defined using the following list of PTs:

Pyrexia PT	PT Code
Body temperature increased	10005911
Cytokine release syndrome	10052015
Hyperpyrexia	10020741
Hyperthermia	10020843
Influenza like illness	10022004
Pyrexia	10037660
Sweating fever	10042666
Systemic inflammatory response syndrome	10051379
Tumour associated fever	10052243

For complicated pyrexia analyses, renal dysfunction will be defined using the following list of PTs:

Renal Dysfunction PT	PT Code
Prerenal failure	10072370
Acute kidney injury*	10069339
*PT Acute renal failure was replaced by Acute kidney injury in MedDRA 24.1 They are equivalent terms.	

8 Appendix

8.1 Imputation rules

8.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page, and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date. Scenario 1 should not be applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR.

Scenario 2: If the dose end date is completely or partially missing and theEOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

8.1.1 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawl of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

8.1.1.1 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

8.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest available MedDRA version at the time of the analyses should be used.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

8.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used (refer to Table 5-3 in the Novartis internal criteria for CTC grading of laboratory parameters). For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

8.4 Statistical models

8.4.1 Primary analysis of binary data

Pyrexia events will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated [Clopper and Pearson 1934]

SAS procedure FREQ will be used to estimate the proportion of subjects with pyrexia events (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI.

8.4.2 Secondary analysis

Kaplan-Meier estimates

An estimate of the survival function will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival 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].

9 Appendix for identification of corticosteroids

CMDECOD

ABIRATERONE ACETATE W/PREDNISOLONE
ADRENAL CORTICAL EXTRACT
BECLOMETASONE
BECLOMETASONE DIPROPIONATE
BECLOMETASONE DIPROPIONATE MONOHYDRATE
BETAMETHASONE
BETAMETHASONE ACETATE
BETAMETHASONE BENZOATE
BETAMETHASONE DIPROPIONATE
BETAMETHASONE PHOSPHATE
BETAMETHASONE SODIUM PHOSPHATE
BETAMETHASONE VALERATE
BETAPRON
BUDESONIDE
CELESTONA BIFAS
CLOPREDNOL
CORTIPAN
CORTISONE
CORTISONE ACETATE
CORTIVAZOL
DEFLAZACORT
DEHYDROCORTICOSTERON
DEXAMETHASONE
DEXAMETHASONE ACETATE
DEXAMETHASONE ACETATE MONOHYDRATE
DEXAMETHASONE BELOXIL
DEXAMETHASONE DIPROPIONATE
DEXAMETHASONE ISONICOTINATE
DEXAMETHASONE PALMITATE
DEXAMETHASONE PHOSPHATE
DEXAMETHASONE SODIUM METASULFOBENZOATE
DEXAMETHASONE SODIUM PHOSPHATE
DEXAMETHASONE SODIUM SUCCINATE
DEXAMETHASONE SODIUM SULFATE
DEXAMETHASONE TEBUTATE

DEXAMETHASONE VALERATE
DI-HYDROCORTISONE
DI-HYDROCORTISONE PHOSPHATE
DI-HYDROCORTISONE SODIUM PHOSPHATE
DIPROSPAN /00582101/
DUO DECADRON
EMORRIL /01757601/
FLUOCORTOLONE
FLUOCORTOLONE CAPROATE
FLUOCORTOLONE PIVALATE
FLUPAMESONE
FLUPREDNISOLONE
FLUPREDNISOLONE ACETATE
FLUPREDNISOLONE VALERATE
GLUCOCORTICOIDS
HALOPREDONE
HALOPREDONE ACETATE
HYDROCORTISONE
HYDROCORTISONE ACETATE
HYDROCORTISONE BUTYRATE
HYDROCORTISONE CIPIONATE
HYDROCORTISONE HYDROGEN SUCCINATE
HYDROCORTISONE IN EURAX
HYDROCORTISONE PROBUTAT
HYDROCORTISONE SODIUM PHOSPHATE
HYDROCORTISONE SODIUM SUCCINATE
HYDROCORTISONE VALERATE
LEDERSPAN CUM LIDOKAIN
MAZIPREDONE
MAZIPREDONE HYDROCHLORIDE
MEPREDNISONE
MEPREDNISONE SUCCINATE
METHYLPREDNISOLONE
METHYLPREDNISOLONE ACETATE
METHYLPREDNISOLONE HEMISUCCINATE

METHYLPREDNISOLONE SODIUM SUCCINATE
METHYLPREDNISOLONE SULEPTANATE
PARAMETHASONE
PARAMETHASONE ACETATE
PARAMETHASONE DISODIUM PHOSPHATE
PELONINE R
PREDNISOLON STREULI /06304501/
PREDNISOLONE
PREDNISOLONE ACETATE
PREDNISOLONE BUTYLACETATE
PREDNISOLONE FARNESYLATE
PREDNISOLONE HEMISUCCINATE
PREDNISOLONE METASULFOBENZOATE SODIUM
PREDNISOLONE PALMITATE
PREDNISOLONE PHOSPHATE
PREDNISOLONE PIVALATE
PREDNISOLONE SODIUM PHOSPHATE
PREDNISOLONE SODIUM SUCCINATE
PREDNISOLONE SODIUM SULFATE
PREDNISOLONE SODIUM TETRAHYDROPHTALATE
PREDNISOLONE STEAGLATE
PREDNISOLONE VALEROACETATE
PREDNISONE
PREDNISONE ACETATE
PREDNYLIDENE
PREGNENOLONE
PREGNENOLONE ACETATE
PREGNENOLONE SUCCINATE
RIMEXOLONE
SURELEN /00817601/
TRIAMCINOLONE
TRIAMCINOLONE ACETONIDE
TRIAMCINOLONE ACETONIDE DIPOTASSIUM PHOSPHATE
TRIAMCINOLONE ACETONIDE SODIUM PHOSPHATE
TRIAMCINOLONE DIACETATE

TRIAMCINOLONE HEXACETONIDE
TRINIOL
WACODEX
WACOMETASONA /03018901/
BETAMETHASONE W/CHLORPHENAMINE

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