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Description: This document details the analyses to support a post-marketing requirement to further report independently reviewed echocardiogram (ECHO) results for subjects treated with dabrafenib as monotherapy or in combination with other anti-cancer drugs to evaluate the incidence rate and natural history of cardiac valvular abnormalities.

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ABBREVIATIONS

DSUR	Developmental Safety Update Report
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
IDSL	Integrated Data Standards Library
PMR	Post Marketing Requirement
RAP	Reporting and Analysis Plan

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1. INTRODUCTION

This reporting and analysis plan details the analyses that support an FDA post-marketing requirement (PMR) to further investigate independently reviewed echocardiogram (ECHO) results for subjects treated with dabrafenib, either as monotherapy or in combination with other anti-cancer therapies on randomized controlled clinical trials. These analyses will evaluate the potential for cardiac valve abnormalities in patients treated with dabrafenib based on preclinical findings.

Interim reports will be generated within 6 months of the approval of the new drug application (NDA), one year after the first interim report, and every two years thereafter until 2020. The first interim report will be submitted in November 2013 and will only include data from BRF113683. Following the first interim report, analyses will include integrated data from randomized studies of dabrafenib as monotherapy or in combination with other anti-cancer therapies which have reached the study specific primary analysis reporting criteria.

Data from the following phase III randomized studies will be integrated:

- BRF113683, a Phase III study that evaluated efficacy and safety of dabrafenib compared to chemotherapy (dacarbazine/DTIC) in subjects with advanced or metastatic (unresectable stage III or Stage IV) BRAF V600 mutation-positive melanoma. Only data from the randomized phase will be used. The first interim report will include data as of 4 March 2012, the date the last DTIC subject was dosed. Subsequent reports will either include the final study data, if the criteria for study closure (i.e. 70% of subject die or are otherwise lost to follow-up) has been met, or data from the data cut off date for the Developmental Safety Update Report (DSUR).
- MEK115306 (COMBI-D) in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation positive cutaneous melanoma; double-blinded placebo-controlled; randomized; phase III; trametinib (2mg QD) plus dabrafenib (150 mg BID) vs. Placebo plus dabrafenib (150 mg BID). The data available at the time of the primary analysis will be used for purposes of data integration for the second interim reporting in 2014. Thereafter, data used for the Development Safety Update Report (DSUR) will be included each year until study closure, at which time the final data will be included.
- MEK116513 (COMBI-V) in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation positive cutaneous melanoma; open label; randomized; phase III; trametinib (2mg QD) plus dabrafenib (150 mg BID) versus vemurafenib. Data will not be included in any integration until the study has reached database freeze for the primary endpoint (anticipated for second quarter 2014). At database freeze these data will be integrated. Thereafter, data used for the Development Safety Update Report (DSUR) will be included each year until study closure, at which time the final data will be included.
- BRF115532 (COMBI-AD) in the adjuvant treatment of high risk BRAF V600 mutation-positive melanoma after surgical resection; double-blinded; randomized;

phase III; trametinib (2mg QD) plus dabrafenib (150 mg BID) versus two placebos. Data will not be included in any integration until the study has reached database freeze for the primary endpoint (anticipated for fourth quarter 2015). At database freeze these data will be integrated. Thereafter, data used for the Development Safety Update Report (DSUR) will be included each year until study closure, at which time the final data will be included.

Note: MEK116513 and BRF115532 are event-driven studies, so the timing of database freeze for each is only projected based on the study design and current event rates. If database freeze is achieved prior to the DSUR data cut off date for a given interim and final reporting year, the study will be included in that year's report. The rationale for requiring database freeze prior to the DSUR data cut off date is to allow the time necessary to integrate the data.

Any additional GSK sponsored randomized study of dabrafenib either as monotherapy or in combination with other anti-cancer agents, which reaches the primary analysis endpoint during the reporting time period for each interim and final report will also be integrated. The addition of other trials does not require amendments to this RAP unless additional analyses not specified here are required based on study specific data collection or modification in data collection based on evolving experience on currently ongoing studies.

The addition of studies as specified in the final bullet above will not require amendments to this RAP unless additional analyses not specified here are required based on study specific data collection or modification in data collection based on evolving experience on currently ongoing studies. All studies included in data integration and analyses will be detailed in the interim and final reports.

2. ANALYSIS OBJECTIVE

The objective of this analysis is to fully describe the results of the independently reviewed ECHO data of subjects treated with dabrafenib. .

3. OVERVIEW OF CENTRAL BLINDED REVIEW

GlaxoSmithKline has engaged Perceptive Informatics to manage the independent central review of echocardiograms for the BRF program. The independent safety review will comprise a central blinded assessment of medical imaging data by an independent cardiologist. A complete description of the independent review process, including methods used to perform the centralized blinded, independent review are provided in the Independent Cardiology Review Charter.

4. ANALYSIS POPULATION

All analyses of the independently reviewed ECHO data will use the Safety population (SAFETY), which comprises all randomized subjects who received at least one dose of study medication and will be based on the actual treatment received if this differed from that to which the subject was randomized.

5. TREATMENT COMPARISONS

All analyses will be presented by treatment arm (e.g., dabrafenib monotherapy, dabrafenib plus trametinib, DTIC).

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES

All programming will be performed using SAS* version 9.1.3 or greater and S-Plus version 7.0 or higher in a UNIX† environment.

All data analyses and tables, listings, and figures will use the formats in the Integrated Data Standards Library (IDSL), unless there is no standard for a particular analysis. Any non-standard data displays will follow the general format of the IDSL and Therapeutic Standards Team (TST) data displays to the extent possible.

Unless otherwise stated, continuous variables will be summarized with the descriptive statistics mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

Data from all assessments will be included in listings. Summaries of safety data will include data from unscheduled visits only in sections labelled “worst case on-therapy”.

If multiple measurements or evaluations are reported at the same assessment, the worst case rules will apply with the exception of laboratory data reported from both central and local laboratories for a given assessment. In this case, the central laboratory data will be used.

7. DATA HANDLING CONVENTIONS

7.1. Derived and Transformed Data

The following sections describe the derived and transformed variables that will be used to analyze the data. Separate dataset definition tables will provide full details on all data derivations and transformations including descriptions of standard integrated data standards library (IDSL) algorithms and standard Oncology algorithms.

7.2. Common Variables

The following common variables will be added to all analysis and reporting (A&R) datasets: INVID, CENTREID, USUBJID, AGE, RACE, RACECD, and SEX.

In addition, each dataset will contain variables for the randomized treatment group, the actual treatment group, and the treatment periods (where applicable).

7.3. Actual Treatment

Actual treatment as derived in the primary analysis for each study will be used. For example the rules that were used to derived actual treatment for BRF113683 are:

- • If a subject's actual treatment was the same as randomized treatment, then actual treatment is the randomized treatment.
- • If a subject received a study treatment that was different from the randomized treatment for the entire time of treatment in the randomized phase, then actual treatment is the different non-randomized treatment.

Similar rules are used in the Phase III combination studies (COMBI-D, COMBI-V, and COMBI-AD).

7.4. Reference Dates

There are two reference dates:

- Because age is an eligibility requirement, the reference date for age is the date of screening.
- The safety reference date is the treatment start date in the randomized phase, and will be used to calculate study day.

7.5. Study Day for Safety Measures

Study day for safety measures is calculated and stored on the datasets. If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs prior to the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There will be no safety study day 0. Note: It is possible that the safety study day 1 can be after the randomization day.

7.6. Baseline, change from baseline and worst-case

Baseline is defined as the most recent non-missing value before the first dose of study treatment. If there is no pre-treatment ECHO, then the baseline value is considered missing.

A derived worst-case on-therapy record will be created for each of the four parameters below and for LVEF for each subject. The worst-case record will be the subject's first on-therapy record for their worst grade for each parameter or worst LVEF value and will be copied into a new record with a new VISIT/VISITNUM assigned and DTYPE variable added. DTYPE (coded variable for the derivation type), is assigned 'WB' for the worst case change from baseline record when SCTESTCD=LVEF; otherwise it is assigned 'WC' for the worst case (i.e., the greatest) post baseline SCGRDCD/SCRESCD value.

If the SCRES (scan result) variable is not normal (that is, one of the results shown for Grade 0), then the SGCRD (scan grade) variable is derived based on the SCRES value.

Grades are based on American Society of Echocardiography (ASE) guidelines.

Grade assignments for ECHO results (SCRES or SCGRD):

Parameter Test (SCTEST)	Grade 0 (SCRES)	Grade 1 (SCGRD)	Grade 2 (SCGRD)	Grade 3 (SCGRD)	Grade 4 (SCGRD)
Excursion Reduced	No, not applicable		Mild	Moderate	Severe
Structure Appearance (Thickening)	Normal, not applicable		Mild	Moderate	Severe
Regurgitation	Not visualized, no insufficiency (SCGRD)	Trace	Mild	Moderate	Severe
Stenosis	Not applicable, not present		Mild	Moderate	Severe

An analysis flag will be created to indicate which records are to be used in the analyses. Only the baseline record (previously described), scheduled visits (defined programmatically as visitnum=int(visitnum)), and the worst-case derived records will be flagged.

7.7. Treatment Periods

For BRF113683:

Pre-therapy is defined for the randomized phase as before the date of the first dose. Measurements from clinical tests or assessments on Day 1 are pre-therapy.

On-therapy for the randomized phase is defined as the date of the first dose until the earliest of 28 days after the last dose of randomized treatment, date of first dose of dabrafenib (*only for subjects randomized to DTIC who received dabrafenib after initial progression*), last contact, or death. If an event occurs on the same date as first dose, then the event will be considered as occurring during the randomized phase.

Post-therapy for the randomized phase is defined as any time beyond the minimum of 28 days post last dose of study treatment until last contact or death for subjects randomized to dabrafenib and subjects randomized to DTIC who do not cross over to treatment with dabrafenib after progression. For subjects randomized to DTIC who crossed over to treatment with dabrafenib after progression, post-therapy for the randomized phase is defined as any time beyond 28 days post last dose of DTIC and prior to the first dose of dabrafenib.

For MEK115306, MEK116513, and BRF115532:

Pre-therapy is defined as before the date of the first dose. Measurements from clinical tests or assessments on Day 1 are pre-therapy.

On-therapy is defined as the date of the first dose until the earliest of 30 days after the last dose of randomized treatment, last contact, or death. If an event occurs on the same date as the first dose, then the event will be considered as on-therapy.

Post-therapy as any time beyond the minimum of 30 days post last dose of study treatment until last contact or death.

7.8. Treatment Arms

As the trials to be integrated are reported, the treatment arms to be used in analyses are as follows:

- Dabrafenib monotherapy (BREAK-3 + COMBI-D);
- MEK + Dabrafenib (COMBI-D+COMBI-V+COMBI-AD);
- DTIC (BREAK-3);
- Vemurafenib (COMBI-V); and
- Placebo (COMBI-AD).

8. STUDY POPULATION

8.1. Disposition of Subjects

A summary of the number and percentage of subjects in the Safety population by study treatment status, including reaching the study endpoint or discontinuing study treatment, will be provided. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. The summary will also include study treatment status (i.e., on study treatment or discontinued).

Subject status and the reasons for withdrawing from the study prematurely will be summarized using the number and percentage of subjects in the Safety population by status. The primary reasons for withdrawal will also be summarized for those subjects who have withdrawn prematurely from the trial.

8.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, ethnicity, sex, height, and body weight) will be summarized for the Safety population. Age will be summarized both as a continuous variable and categorized as < 65 and ≥ 65 years.

Disease history and characteristics (time since initial diagnosis in months, stage at initial diagnosis, date of initial diagnosis) at initial diagnosis and screening will be summarized and listed separately.

9. SAFETY ANALYSES

All analyses will be by treatment arm and will use the SAFETY Population. Summaries will include data from unscheduled visits only in sections labeled "worst case on-therapy".

9.1. Echocardiogram Results

The independently-reviewed results will be summarized by location (e.g. mitral valve, aortic valve, tricuspid valve) and test at each scheduled visit and by worst case overall. The summary will include the number of subjects with results for each test and visit, the result, and the number and percentage with each result by treatment arm. A listing of all results will also be provided.

A summary of grade change from baseline to final assessment will be produced. This summary will be by location (e.g. mitral valve, aortic valve, tricuspid valve) for each test. It will use the final on-therapy ECHO. The number and percentage of subjects with no increase in baseline grade, increasing to grade one, increasing to grade two, increasing to grade 3, and increasing to grade 4 will be shown for each treatment arm.

A summary of grade change from baseline to worst case on therapy will also be produced. This summary will be by location (e.g. mitral valve, aortic valve, tricuspid valve) for each test. The number and percentage of subjects with no increase in baseline grade, increasing to grade one, increasing to grade two, increasing to grade 3, and increasing to grade 4 will be shown for each treatment arm.

The joint distribution of the grade of the final and worst-case on-therapy ECHOs will be shown to explore the reversibility of valvular abnormalities. This will be a series of displays that show 5 grades (0 - 4) as the row and column headers. The number and percentage of subjects in each cell will be those subjects with that combination of final and worst-case on-therapy ECHO grades. This summary will be produced for each location (e.g. mitral valve, aortic valve, tricuspid valve) and test by treatment arm. A listing of the ECHO results by visit will be provided for all subjects with different final and worst-case ECHO grades.

9.2. Natural History of Valvular Abnormalities

The natural history of valvular abnormalities will be explored through patient narratives for subjects experiencing new abnormalities or progression of existing abnormalities. Narratives will include details such as time to onset, exposure, pre-existing abnormalities, and reversibility.

If a sufficient number of subjects have new abnormalities or progression of existing abnormalities, additional analyses (e.g., summaries of subject characteristics for subjects with and without treatment emergent abnormalities; logistic regression if appropriate) will be explored.

10. REFERENCES

Echocardiographic Assessment of Valve Stenosis: EAE/ASE Recommendations for Clinical Practice, JASE, January 2009.

GlaxoSmithKline Document Number UM2010/00166/03: BRF113683, A Phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. (November 3, 2010).

Recommendations for Evaluation of the Severity of Native Valvular Regurgitation with Two-Dimensional and Doppler Echocardiography, JASE, July 2003.

11. APPENDIX A: TABLES AND LISTINGS

Table Number	Table
6.1101	Summary of Subject Status and Reason for Study Withdrawal
6.1201	Summary of Study Treatment Status
6.2001	Summary of Demographic Characteristics
6.2101	Summary of Disease Characteristics at Screening
8.9001	Summary of Independently-Reviewed Echocardiogram Results
8.9002	Summary of Independently-Reviewed Echocardiogram Grade Changes from Baseline Grade to Worst Case On-Therapy
8.9003	Summary of Independently-Reviewed Echocardiogram Grade Changes from Baseline Grade to Final Assessment
8.9004	Summary of the Joint Distribution of Independently-Reviewed Echocardiogram Final and Worst-Case On-Therapy Grades

Listing Number	Listing
28.9001	Listing of Independently-Reviewed Echocardiogram Results
28.9002	Listing of Independently-Reviewed Echocardiogram Results for Subjects with Discordant Final and Worst-Case On-Therapy Grades
28.9003	Listing of Subject Numbers for Subjects with Final Independently-Reviewed Echocardiogram Grade Worse Than Baseline Grade