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Title:	Clinical Pharmacology Reporting and Analysis Plan for PKB115131: An Open Label Continuation Study of the Oral AKT Inhibitor GSK2110183 in Subjects with Solid Tumors and Hematologic Malignancies

Compound Number: GSK2110183

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Description:

The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol PKB115131 (CASB183X2X01B). This RAP is intended to describe the safety analyses required for the study. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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Subject: Afuresertib, GSK2110183, AKT inhibitor, hematologic malignancy, solid tumor, safety

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood pressure
BPM	Beat Per Minute
BUN	Blood urea nitrogen
CRF	Case Report Form
CBC	Complete blood count
CPSR	Clinical Pharmacology Study Report
DBP	Diastolic blood pressure
DDS	Drug Development Sciences
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GBMD	Global Brand Medical Director
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HR	Heart rate
IB	Investigator's Brochure
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
Kg	Kilogram
L	Liter
LVEF	Left Ventricular Ejection Fraction
µg	Microgram
µL	Microliter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
msec	Milliseconds
MTD	Maximum Tolerated Dose
MUGA	Multi Gated Acquisition Scan
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
PCI	Potential Clinical Importance Range
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula

RAP	Reporting and Analysis Plan
RBC	Red blood cells
SAE	Serious adverse event(s)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SOC	System Organ Class
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organization

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Pharmacology Study Report for Protocol PKB115131:

Revision Chronology:		
Document Number	**Date**	**Version**
2010N109478_00	2011-APR-29	Original
2010N109478_01	2011-JUN-24	Original-Republished
2010N109478_02	2011-NOV-10	Amendment 01
2010N109478_03	2014-SEP-30	Amendment 02
2014-002041-22	2016-MAR-31	Amendment 03 (Version 4.0)

All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze of the study data.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objectives

2.1.1. Primary Objective

- To provide treatment with afuresertib for subjects who have previously participated in an afuresertib study sponsored by GSK or another research organization working on behalf of GSK.

2.1.2. Secondary objective

- To collect safety data on continued treatment with afuresertib.

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Adverse Events

3. STUDY DESIGN

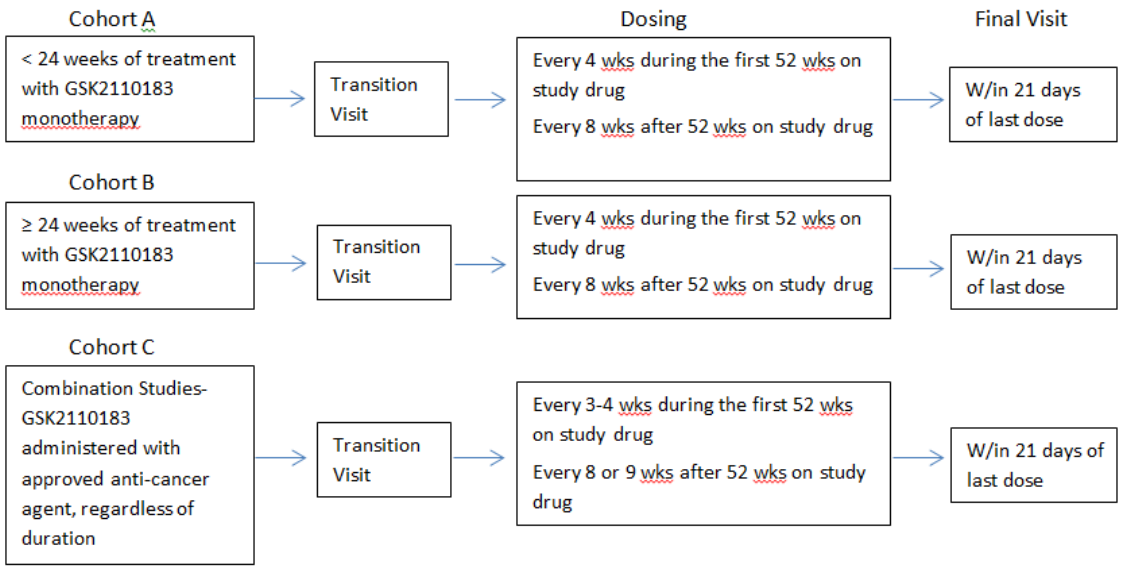
This multicenter, non-randomized, open-label, rollover study is designed to provide continued access to afuresertib to subjects who have previously participated in an afuresertib study. Approximately 200 subjects from approximately 60 investigative sites worldwide will be transitioned to this study from other afuresertib studies.

Subjects may enroll into Cohorts A and B based on the duration of treatment on a monotherapy in their parent study. Cohort C will enroll subjects who have participated in a combination study where afuresertib is given with an approved anti-cancer agent(s). The purpose of having separate cohorts is to be able to better report and define the safety profile for these treatment groups.

The dose of study treatment to be administered to subjects will be individualized based upon the dose/regimen received during their participation in the parent study at the time of transition to this rollover study. No dose of afuresertib above the maximumn tolerated dose (MTD) established in the parent study will be allowed in this study. In Cohorts A and B, subjects will receive afuresertib as an oral, daily dose up to 150 mg. In Cohort C, subjects who transition from a combination study may continue to receive afuresertib in combination with the approved anti-cancer agent defined by the parent study, or they may receive afuresertib as monotherapy.

The study will consist of a transition visit, continuous dosing treatment period and a final study visit, see the following figure for study design.

Figure 1 - Study Design



Safety assessments will be performed throughout the study: including physical examinations, vital sign measurements (blood pressure (BP), pulse rate, weight and

temperature), 12-lead electrocardiograms (ECGs), echocardiograms (ECHOs) or multiple-gated acquisition (MUGA) scans, clinical laboratory assessments and monitoring of adverse events (AEs). Disease assessments must be performed at least every 12 weeks or more frequently if the investigator decides that it is necessary.

Subjects may continue treatment in this rollover study until disease progression, unacceptable toxicity or withdrawal of consent occurs, or death. Study will be completed when the last subject has withdrawn from study treatment.

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal interim analyses are planned.

4.2. Final Analyses

The final planned analyses will be performed after all subjects have completed the study. See Sections 9 and 10 for all final planned analyses for this study. Given the low priority of this study and low enrolment of subjects, a short close-out CSR will be produced for the final analyses.

5. ANALYSIS POPULATIONS

All Treated Subjects Population:

The All Treated Subjects Population will consist of all subjects who receive at least one dose of afuresertib in this rollover study. Safety data will be evaluated based on this population if not otherwise stated.

6. HYPOTHESES AND TREATMENT COMPARISONS

No statistical hypotheses are being tested. Only descriptive methods will be used in analysis and summary of the data obtained from this study.

7. TREATMENT DESCRIPTIONS FOR DATA DISPLAYS

Given the low enrolment of subjects, summary of data will not be displayed by cohorts. All subjects will be used for summary of data.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Unless otherwise stated, continuous variables will be summarized with the statistics mean, median, standard deviation (SD), minimum and maximum. The mean and median will be presented to one decimal place beyond the precision with which the data were captured. The SD will be presented to two decimal places beyond the precision with

which the data were captured. The minimum and maximum will be presented to the precision with which the data were captured.

Categorical variables will be summarized with frequency counts and percentages. A percentage will not be presented when the corresponding count is zero in order to draw attention to the non-zero counts.

8.1. Reporting Conventions

- All data, including unscheduled assessments, will be listed by subject.
- Summaries will include data from scheduled assessments only. Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment(s)
- Clinical laboratory, Vital signs, will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied).
- If multiple assessments at any given time point (baseline or any post-baseline) exist, the most recent assessment within the assessment window for that time point will be used.
- AEs and concomitant medications terms will be coded using the Medical dictionary for Regulatory Activities (MedDRA) dictionary version 19.0 or later and an internal validated medication dictionary, GSK Drug.
- Missing data will not be imputed.
- Reporting and analyses are performed using the SAS/STAT® module of the SAS System, Version 9.2 or higher.
- [redacted] standard reporting template will be used.

8.2. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations defined in Section 5.

8.3. Baseline Definition

Baseline is defined as the last non-missing observed value before the first dose, which is generally the assessment performed on the day of transition visit.

8.4. Derived and Transformed Data

8.4.1. Change from Baseline

The results of any specified study assessments performed on the day of the Transition Visit will serve as the baseline value for said assessment. The change from baseline will be calculated by subtracting the baseline values from the individual post-Transition Visit values. If either the baseline or post-Transition Visit value is missing, the change from baseline is set to missing as well.

8.4.2. Study Day

Actual study day will be calculated using the first dose date (in continuous dosing treatment period after transition visit) as the reference date. In relevant datasets, if the date of assessment is not missing and the reference date is not missing then study day will be calculated as (date of assessment – reference date + 1) if the date of assessment is greater than or equal to the reference date, otherwise it is equal to (date of assessment – reference date).

9. STUDY POPULATION

All tables will use the "All Treated Subjects Population" unless otherwise specified.

9.1. Disposition of Subjects

The subject disposition, reasons for study treatment discontinuation and reasons for end of study will be listed and summarized.

9.2. Eligibility and Protocol Violation

As a short close-out CSR will be produced, data will not be listed or summarized.

9.3. Demography and Baseline Disease Assessment

Demographic characteristics consisting of age, sex, race, ethnicity, weight, height and body mass index (BMI) will be listed and summarized descriptively for total subjects.

As a short close-out CSR will be produced, baseline disease characteristics will not be summarized or listed.

9.4. Concomitant Medications

A listing of prior and concomitant medications will be presented. Prior medications are defined as medications with a stop date occurring before the first dose date (in continuous dosing treatment period after transition visit). Concomitant medications are defined as

medications with a stop date occurring on or after the first dose date. Medications with start and stop dates which bracket the first dose date will be classified as both prior and concomitant medications.

9.5. Medical History and Family History

All relevant medical histories will be presented in listing. Family histories will not be listed or summarized.

9.6. Information from Parent Study

A listing presenting subject-related data from parent study, including parent study protocol number, previous subject number assigned in parent study, treatment start and stop date of the parent study at time of transition to this study will be provided.

10. SAFETY ANALYSES

10.1. Study Compliance and Extent of Exposure

Duration of therapy, total amount of study drug taken and average daily dose (afuresertib) will be summarized. Details of dosing diary, including dosage volume, treatment start and stop date, treatment interruptions or dose reductions or dose escalations, for both afuresertib and other anti-cancer agents (in case of Cohort C) will be presented in listing.

Duration of therapy (day) = date of last study medication dose – date of first study medication dose + 1.

As a short close-out CSR will be produced, drug accountability data will not be listed or summarized.

10.2. Adverse Event

Adverse events (AEs) will be coded using MedDRA and grouped by system organ class and will be graded by the investigator according to the NCI-CTCAE (version 4.0 or later).

On treatment AEs is defined as any AEs collected from the time of first dose of study treatment until 30 days after last study treatment dose. AE summaries will include all on-treatment AEs.
Listing of all AEs, along with SAEs and AEs leading to permanent discontinuation of study treatment will be provided. AEs with start date outside of on-treatment period will be flagged in the listings.

Events will be summarized by maximum NCI-CTCAE grade and proportion of total subjects, by SOC and preferred term. At each level of summarization, a subject will be counted only once for each AE he/she experiences within that level. Only the maximum grade at each level will be summarized when summarizing by grade.

Separate summaries will be given for all AEs, drug-related AEs, serious AEs, non-serious AEs and AEs leading to study treatment discontinuation.

AEs leading to death and on-treatment Drug Related SAEs leading to death will be summarized by proportion of total subjects, by SOC and preferred term.

The complete list of outputs for AE is available in section 12.

10.3. Death

On-treatment death is defined as deaths occurred from the time of first dose of study treatment until 30 days after last study treatment dose. On-treatment death will be summarized by preferred term. Summary for all deaths will be produced by SOC and preferred term. All death will be listed.

Summary for on-treatment deaths and SAEs by SOC and preferred term will be produced in a separate table.

10.4. Clinical Laboratory Assessments

All haematology and clinical chemistry laboratory data will be listed for each subject and flagged high (H) or low (L) relative to their normal ranges where applicable.

10.5. Electrocardiograms

Results for all ECG parameters (PR, QRS, QT, and QTc intervals, RR and Heart Rate (HR)) and overall interpretation will not be summarized but listed.

10.6. Vital Signs

As a short close-out CSR will be produced, data will not be listed or summarized.

10.7. Disease Assessments

Disease assessments will be performed at regular intervals, at least every 12 weeks per local standard practice using criteria appropriate for the disease type and location. Results and disease response evaluation will not be summarized but listed.

10.8. Other Safety Data

10.8.1. ECHO/MUGA Scans

As a short close-out CSR will be produced, data will not be listed or summarized.

10.8.2. Performance Status

The performance status (0-5) assessment is based on the Eastern Cooperative Oncology Group (ECOG) scale. Data will not be summarized but listed.

10.8.3. Pregnancy

As a short close-out CSR will be produced, data will not be listed or summarized.

11. REFERENCES

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12. ATTACHMENTS

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12.1.2. Safety Tables

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14.3.1-1.2	All Treated	Summary of Drug Related Adverse Events by Preferred Term and Maximum Grade
14.3.1-1.3	All Treated	Summary of Serious Adverse Events by System Organ Class, Preferred Term and Maximum Grade
14.3.1-1.4	All Treated	Summary of Adverse Events Leading to Study Treatment Discontinuation by Preferred Term and Maximum Grade
14.3.1-1.5	All Treated	Summary of non-Serious Adverse Events by System Organ Class and Preferred Term
14.3.1-1.6	All Treated	On-Treatment Deaths and Serious Adverse Events by System Organ Class and Preferred Term
14.3.1-1.7	All Treated	On-Treatment Deaths by Preferred Term
14.3.1-1.8	All Treated	All Deaths by System Organ Class and Preferred Term

12.1.3. ICH Listings

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L14.3.2-1.1	All Treated	Listing of Death
L14.3.2-1.2	All Treated	All Adverse Events
L14.3.2-1.3	All Treated	All Serious Adverse Events
L14.3.2-1.4	All Treated	Adverse Events Leading to Permanent Discontinuation of Study Treatment
L14.3.4-1.1	All Treated	Haematology
L14.3.4-1.2	All Treated	Chemistry
L16.2.1-1.1	All Treated	Disposition
L16.2.4-1.1	All Treated	Demographics
L16.2.4-1.2	All Treated	Medical Conditions
L16.2.4-1.3	All Treated	Subject Related Information from Parent Study
L16.2.4-1.4	All Treated	Prior and Concomitant Medications
L16.2.5-1.1	All Treated	Study Treatment Administration – Afuresertib
L16.2.5-1.2	All Treated	Study Treatment Administration – Non-Afuresertib
L16.2.6-1.1	All Treated	Disease Response Evaluation
L16.2.9-1.1	All Treated	ECG Values
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12.1.4. In-text Tables

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