

Clinical Development

GSK2110183/Afuresertib

Protocol PKB115131 / NCT01531894

**An Open Label Continuation Study of the Oral AKT
Inhibitor GSK2110183 in Subjects with Solid Tumors and
Hematologic Malignancies**

Authors

[REDACTED]

Document type Amended Protocol Version Clean

EUDRACT number 2014-002041-22

Version number 4.0 (Amendment 3.0)

Development phase II

Document status Final

Release date 31-MAR-2016

Novartis internal
reference number CASB183X2X01B

Property of Novartis
Confidential

May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Amendment 03

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GSK2110183, the purpose of this protocol Amendment 03 is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of 24-March-2016:

- 11 patients have received study treatment in 5 countries;
- 7 patients have completed or discontinued study treatment.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

Revision Chronology

GlaxoSmithKline 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 No. 02
	2016-MAR-31	Amendment No. 03 Delete or replace references to GSK or its staff with that of Novartis/Novartis and its authorized agents. Make administrative changes to align with Novartis processes and procedures.

SPONSOR SIGNATORY

[REDACTED], MD
[REDACTED]
[REDACTED]
Phone: [REDACTED]
Email: [REDACTED]

Date

SPONSOR INFORMATION PAGE

Medical Lead Contact Information:

[REDACTED], MD
[REDACTED]
[REDACTED]

Novartis Pharmaceuticals Corporation

One Health Plaza, Bldg 337/ [REDACTED]

East Hanover, NJ 07936-1080 USA

Phone: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

www.novartis.com

[REDACTED] Contact Information:

Novartis Pharmaceuticals Corporation

One Health Plaza

Bldg. 337/ [REDACTED]

East Hanover,

NJ 07936-1080

USA

Phone: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

If you have any questions regarding the protocol, please contact your local Novartis office

Regulatory Agency Identifying Number US [IND 111439]

Health Canada reference number = 9427-G0838-279C

S. Korea: Receipt number = 20110110591

EudraCT number = 2014-002041-22.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number PKB115131/CASB183X2X01B

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	
Investigator Signature	Date

TABLE OF CONTENTS

	PAGE
ABBREVIATIONS	11
PROTOCOL SYNOPSIS	13
1. INTRODUCTION.....	15
1.1. Background	15
1.1.1. Afuresertib	15
1.1.2. Pharmacokinetics of Afuresertib in Humans.....	15
1.1.3. Clinical Safety of Afuresertib	16
1.1.4. PKB116611	18
1.1.5. LCH115397	19
1.1.6. Clinical Activity of Afuresertib.....	19
1.2. Rationale	20
1.2.1. Study Rationale	20
1.2.2. Dose Rationale	20
1.2.3. Population Rationale.....	21
1.2.4. Endpoint Rationale	21
1.3. Summary of Risk Management.....	21
1.3.1. Risk Assessment for Afuresertib	22
2. OBJECTIVE(S)	22
2.1. Primary.....	22
2.2. Secondary	22
3. INVESTIGATIONAL PLAN	23
3.1. Study Design/Schematic.....	23
3.2. Study Design	23
3.2.1. Cohort A and Cohort B: Afuresertib Monotherapy.....	24
3.2.2. Cohort C: Afuresertib Combination Therapy	25
4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA	26
4.1. Subject Selection Criteria.....	26
4.1.1. Number of Subjects	26
4.1.2. Inclusion Criteria	26
4.1.3. Exclusion Criteria.....	27
4.1.4. Other Eligibility Criteria Considerations.....	28
4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria	28
4.2.1. Permanent Discontinuation from Study Treatment.....	28
4.2.2. Subject Completion Criteria	30
5. STUDY ASSESSMENTS AND PROCEDURES	30
5.1. Transition Visit	30
5.2. Continuous Dosing Treatment Period	31
5.2.1. Cohort A and B	31
5.2.2. Cohort C	32
5.3. Final Study Visit.....	32

5.4.	Safety	33
5.4.1.	Physical Examinations	33
5.4.2.	Vital Signs.....	33
5.4.3.	Electrocardiograms.....	33
5.4.4.	Clinical Laboratory Assessments	34
5.5.	Multiple Myeloma Specific Disease Assessments:.....	35
5.6.	Disease Assessments for Malignancies Other Than MM	35
5.7.	Performance Status	35
5.8.	Pregnancy	35
5.8.1.	Time period for collecting pregnancy information	35
5.8.2.	Action to be taken if pregnancy occurs	35
5.8.3.	Action to be taken if pregnancy occurs in a female partner of a male study subject	36
5.9.	Adverse Events (AE) and Serious Adverse Events (SAE).....	36
5.9.1.	Adverse Events.....	36
5.9.1.1.	Definition of an AE.....	36
5.9.1.2.	Definition of a SAE	37
5.9.1.3.	Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs	38
5.9.1.4.	Disease-Related Events and/or Disease- Related Outcomes Not Qualifying as SAEs	39
5.9.1.5.	Time Period and Frequency of Detecting AEs and SAEs	39
5.9.1.6.	Prompt Reporting of Serious Adverse Events and Other Events to Novartis.....	40
5.9.1.7.	Regulatory Reporting Requirements For SAEs.....	41
6.	STUDY TREATMENTS.....	41
6.1.	Afuresertib Investigational Product Dosage/Administration	41
6.2.	Other Anti-Cancer Agents (Cohort C)	43
6.3.	Administration of Study Treatment.....	43
6.4.	Handling and Storage of Study Treatment	43
6.5.	Treatment Assignment.....	43
6.6.	Dose Modifications	44
6.6.1.	Afuresertib Dose Modification	44
6.6.2.	Dose Modification: Other Anti-Cancer Agent(s).....	45
6.7.	Guidelines for Adverse Events of Special Interest.....	45
6.7.1.	Supportive Measures for Nausea or Vomiting.....	46
6.7.2.	Supportive Measures for Hyperglycemia	46
6.7.3.	Management of Diarrhea	46
6.7.4.	Management of Rash.....	46
6.7.5.	Guidelines for Management of Dyspepsia.....	47
6.7.6.	Guidelines for Management of Mucositis	48
6.7.7.	Liver Chemistry Stopping Criteria	48
6.7.7.1.	Actions if Liver Chemistry Stopping Criteria are met.....	49
6.7.7.2.	Liver Event Follow-Up Assessments	50
6.7.7.3.	Liver Chemistry Monitoring Criteria.....	51
6.7.7.4.	Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP.....	51
6.7.8.	QTc Withdrawal Criteria.....	52
6.8.	Blinding.....	52

6.9.	Product Accountability	52
6.10.	Treatment Compliance.....	53
7.	CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES	53
7.1.	Permitted Medication(s) and non-Drug Therapies.....	53
7.2.	Prohibited Medication(s) and Non-Drug Therapies	54
7.2.1.	Drugs Potentially Affected by Afuresertib (afuresertib perpetrator interaction potential	54
7.2.1.1.	Drugs that may potentially affect afuresertib (perpetrators).....	55
8.	LIFESTYLE AND/OR DIETARY RESTRICTIONS	56
8.1.	Contraception Requirements	56
8.1.1.	Female Subjects	56
8.1.2.	Male Subjects	57
8.2.	Meals and Dietary Restrictions	57
8.3.	Activity	57
9.	DATA MANAGEMENT	57
10.	DATA ANALYSIS AND STATISTICAL CONSIDERATIONS.....	58
10.1.	Hypotheses and Treatment Comparisons	58
10.2.	Sample Size Considerations	58
10.2.1.	Sample Size Assumptions	58
10.2.2.	Sample Size Re-estimation.....	58
10.3.	Data Analysis Considerations	58
10.3.1.	Analysis Populations.....	58
10.3.2.	Analysis Data Sets.....	58
10.3.3.	Interim Analysis	58
10.3.4.	Key Elements of Analysis Plan	58
10.3.5.	Safety Analyses	59
10.3.5.1.	Extent of Exposure	59
10.3.5.2.	Adverse Events	59
10.3.5.3.	Clinical Laboratory Evaluations	59
10.3.5.4.	Other Safety Measures.....	59
10.3.5.5.	Clinical Activity Analyses	60
11.	STUDY CONDUCT CONSIDERATIONS	60
11.1.	Posting of Information on Clinicaltrials.gov.....	60
11.2.	Regulatory and Ethical Considerations, Including the Informed Consent Process	60
11.3.	Urgent Safety Measures	60
11.4.	Quality Control (Study Monitoring)	60
11.5.	Quality Assurance.....	61
11.6.	Study and Site Closure	61
11.7.	Records Retention	62
11.8.	Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication	62
12.	REFERENCES.....	63
	APPENDICES.....	65
	Appendix 1: Time and Events Table for Cohort A and B.....	65

Appendix 2: Time and Events Table for Cohort C.....	67
Appendix 3: Liver Safety Drug Restart Guidelines	69
Appendix 4: COCKCROFT-GAULT FORMULA.....	73
Appendix 5: Disease Assessments and Response Criteria	74
Appendix 6: RECIST Guidelines.....	85
Appendix 7: Hy's Law	90
Appendix 8: Protocol Amendment Changes	91
Section: 1.1.1 Afuresertib.....	146

ABBREVIATIONS

β-HCG	Beta-Human Chorionic Gonadotropin
μg	Microgram
μL	Microliter
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BP	Blood pressure
BPM	Beat Per Minute
BUN	Blood urea nitrogen
CBC	Complete blood count
CDMP	Clinical Document Management and Publishing
CIB	Clinical Investigator's Brochure
CO ₂	Carbon dioxide
CPDS	Clinical Pharmacology Data Sciences
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacokinetics Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CRF	Case Report Form
CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical Research Unit
CV	Coefficient of variance
DBP	Diastolic blood pressure
DDS	Drug Development Sciences
DILI	Drug Induced Liver Injury
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EISR	Expedited Investigator Safety Report
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
GCP	Good Clinical Practice
GCPH	Global Clinical Program Head
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
h/hr	Hour(s)

HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IR	Immediate Release Tablet
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
Kg	Kilogram
L	Liter
LFTs	Liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
MUGA	Multi Gated Acquisition Scan
PD	Pharmacodynamic
PK	Pharmacokinetic
QC	Quality control
QD	Once daily
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RBA	Relative Bioavailability
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
TSH	Thyroid stimulating hormone
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBC	White blood cells

PROTOCOL SYNOPSIS

- **PRODUCT:** Afuresertib (GSK2110183)
- **PROTOCOL TITLE:** An Open Label Continuation Study of the Oral AKT Inhibitor GSK2110183 in Subjects with Hematologic or Solid Tumor Malignancy
- **PROTOCOL/AMENDMENT NO.:** PKB115131/Amendment 03
- **U.S. IND NO.:** 111439 **CLINICAL PHASE:** II
- **OBJECTIVES:** To provide continued treatment with afuresertib for subjects who have completed participation in a Novartis-sponsored afuresertib study, or an afuresertib study sponsored by another research organization working on behalf of Novartis. Additional safety information about afuresertib will also be collected.
- **HYPOTHESES:** There are no hypotheses being explored in this treatment continuation or 'rollover' study.
- **STUDY DESIGN AND DURATION:** Multicenter, non-randomized, open-label, rollover study. Eligible subjects will be enrolled in the appropriate cohort based upon the duration and treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. Subjects will receive afuresertib and possibly other anti-cancer agents at the same dose and regimen most recently taken in their parent study. The dose will not exceed the maximum tolerated dose established in prior studies. Subjects may continue treatment in the rollover study until disease progression, unacceptable toxicity, withdrawal of consent, or death.
- **PATIENT SAMPLE:** Approximately 200 subjects worldwide.
- **DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN:**
Afuresertib - Up to 150 mg (provided as 100 mg and 25 mg gelatin capsules or 50 mg and 75 mg Immediate Release (IR) tablets), given orally, once daily in 3 or 4 week cycles, depending on the schedule and treatment used in the parent study. Dose adjustments are allowed to address tolerability and safety issues. Other anti-cancer agents will continue to be given at the same dose and regimen as in the parent study. Any dose modifications will follow parent protocol or most recent prescribing information.
- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS:** There is no serial pharmacokinetic (PK) sampling for this study. Single, safety PK blood draws may be collected for subjects with liver or rash adverse events.
- **EFFICACY MEASUREMENTS:** This study will not collect efficacy data. However, clinical activity will be assessed using local standard of care practices to determine eligibility for continued study participation. Only subjects who are clinically benefitting and tolerating treatment with afuresertib may continue on study.

- **SAFETY MEASUREMENTS:** Routine physical examinations, vital sign measurements, 12-lead electrocardiograms, echocardiograms or multiple-gated acquisition scans, clinical laboratory tests, and monitoring of adverse events. Additional safety assessments may be necessary if a combination treatment regimen is administered to address specific safety concerns with the other agent(s) being administered.
- **DATA ANALYSIS:** Subject demographic and safety data will be collected on eCRFs. All data will be pooled and descriptive safety analyses summarized and listed by cohort at study conclusion.

1. INTRODUCTION

1.1. Background

AKT is a serine/threonine protein kinase with three isoforms (AKT1, AKT2, and AKT3) that participate in multiple pathways regulating several cellular processes, including survival, proliferation, tissue invasion, and metabolism [Tanno, 2001; Morgensztern, 2005]. Aberrant activation of the PI3K/AKT pathway occurs in virtually every type of hematologic malignancy, suggesting that dysregulation of these pathways may be required for carcinogenesis. The importance of AKT-mediated pathways in tumor proliferation and survival render AKT kinases promising targets for therapeutic intervention. Hyperactivation of the AKT pathway can also correlate with chemotherapy resistance and poorer prognosis. Nonclinical data suggest that blocking AKT1 and AKT2 activity can inhibit the proliferation of tumor cells and either induce an apoptotic response or sensitize tumors to undergo apoptosis in response to other cytotoxic agents [DeFeo-Jones, 2005].

1.1.1. Afuresertib

Afuresertib was evaluated in 10 different MM cell lines either alone or in combination with a proteasome inhibitor (either bortezomib or carfilzomib). Six of 10 MM cell lines showed $<1 \mu\text{M}$ gIC_{50} (concentration producing 50% inhibition of growth) for afuresertib as a single agent in a 3-day cell proliferation assay. The combination of afuresertib with bortezomib showed strong synergy in all 10 cell lines tested at concentrations that are clinically achievable. Similar synergy was also observed with combination of afuresertib and carfilzomib. The synergistic anti-proliferative effect of AKT inhibitor and bortezomib is likely mediated by increased induction of apoptosis, as evidenced by increase in caspase 3/7 activity in National Cancer Institute (NCI) H929 cells.

The safety, pharmacokinetic (PK) and pharmacodynamic profiles and activity of afuresertib administered as monotherapy was evaluated in the first time in humans (FTIH) trial PKB112835. Among 34 relapsed/refractory MM subjects treated with afuresertib three have achieved partial response (PR), and a further 3 achieved minimal response (MR) accounting for clinical benefit rate (CBR) of 17.6 in this heavily pretreated population. The combination of afuresertib with bortezomib and dexamethasone is being currently evaluated in PKB115125 study. The preliminary results (data cut-off 29-Jun-2014) in relapsed MM population demonstrate overall response rate (ORR) of 61% (PR or better) and CBR of 78%. The investigator should refer to the current version of the afuresertib Investigator's Brochure (IB) for detailed information regarding all completed and ongoing clinical studies with afuresertib, PK in the target disease populations, as well as observed safety and clinical activity findings.

1.1.2. Pharmacokinetics of Afuresertib in Humans

In the FTIH monotherapy study in subjects with relapsed or refractory hematologic malignancies (PKB112835), afuresertib plasma concentrations following single afuresertib doses were measured over the 72-hour sample collection period in all subjects. Afuresertib accumulated 1.4- to 5.1-fold with repeat daily dosing. Single-dose and

repeat-dose mean area under the plasma concentration-time curve (AUC(0-24)) and maximum observed plasma concentration (C_{max}) values increased with increasing doses; however, given the intersubject variability, there was substantial overlap in the AUC(0-24) and C_{max} values between successive dose groups. The 100 mg and 125 mg multiple-dose exposure data were similar. Median time to C_{max} (t_{max}) across doses was 2 hours. Based on available data from all cohorts, the mean accumulation half life (t_{1/2}) is approximately 1.7 days and the median t_{max} on Day 8 is 2 hours. For details of the PK of afuresertib see the current version of the IB.

Preliminary PK results from the PKB115125 combination study of afuresertib with bortezomib and dexamethasone indicate mean afuresertib exposure (n=7) was similar alone or in combination with bortezomib and dexamethasone, and mean bortezomib exposure (n=7) co-administered with dexamethasone was similar with and without afuresertib. Mean dexamethasone exposure co-administered with bortezomib was 30-50% higher when dosed with afuresertib than without afuresertib; although sample size was small (n=5) and exposure values overlapped.

1.1.3. Clinical Safety of Afuresertib

As of 29-Jun-2013, 226 subjects had received at least 1 dose of afuresertib either as monotherapy or in combination with other agents in the 7 original GSK-sponsored studies with afuresertib. The most common adverse events (AEs) reported in all studies were primarily gastrointestinal (GI) disorders including: diarrhea, nausea, and vomiting, dyspepsia, and constipation.

More detailed safety characteristics from the two most relevant studies are described in greater detail below. The studies are considered most relevant because they were conducted in subjects with hematologic malignancies (PKB112835), and in subjects with MM (PKB115125).

Additional information from all studies where subjects with other diseases are administered afuresertib, as monotherapy or in combination, can be found in the current afuresertib IB.

PKB112835

This was an open-label, 2-part, FTIH study designed to investigate the safety, tolerability, PK, and pharmacodynamics of afuresertib in subjects with hematologic malignancies. A total of 73 subjects were enrolled in this study, 26 in Part 1 (dose escalation), and 47 in Part 2 (expansion). Afuresertib was administered orally once daily at doses of 25 mg, 75 mg, 100 mg, 125 mg, or 150 mg and the maximum tolerated dose (MTD) was established at 125 mg for this dosing based on dose limiting toxicities (DLTs) in 2/6 subjects at the 150 mg dose. Both DLTs were elevations in liver function tests (LFTs). No DLT was reported in any subject enrolled in Part 1 at doses below 150 mg. Both subjects with DLTs had non-Hodgkin's lymphoma (NHL): 1 subject had Grade 3 elevations in alanine aminotransferase (ALT) and alkaline phosphatase (ALP), accompanied by elevations in aspartate aminotransferase (AST), total bilirubin, and eosinophilia, the other subject had liver involvement from lymphoma and experienced Grade 3 elevations in ALT and ALP.

The most frequent type of malignancy in the trial was MM (34 subjects; 47%), followed by NHL (13 subjects, 18%), Hodgkin's lymphoma (HD) (8 subjects, 11%), acute myeloid leukemia (AML) (9 subjects, 12%), chronic lymphocytic leukemia (CLL) (7 subjects, 10%), acute lymphoblast leukemia (ALL) (1 subject, 1%), and Langerhans cell histiocytosis (LCH) (1 subject, 1%). The most frequent ($\geq 10\%$ of subjects) AEs were nausea (35.6%), diarrhea (32.9%), dyspepsia (24.7%), fatigue (20.5%), gastroesophageal reflux disease (GERD; Grade 1) (19.2%), anorexia (19.2%), vomiting (19.2%), anemia (15.1%), upper respiratory tract infection (13.7%), asthenia (13.7%), back pain (12.3%), rash (12.3%), insomnia (12.3%), constipation (11.0%), odynophagia (11.0%), and cough (11.0%). Grade 3 or higher AEs (in ≥ 2 subjects) included anemia (9.6%), neutropenia (9.6%), thrombocytopenia (6.8%), sepsis (4.1%), febrile neutropenia (4.1%), odynophagia (4.1%), rash (4.1%), asthenia (2.7%), diarrhea (2.7%), fatigue (2.7%), pneumonia (2.7%), and abnormal LFTs (2.7%). Grade 5 AEs were observed in 2 subjects: septic shock, considered not related to afuresertib and concomitant pneumonia and sepsis, considered not related to afuresertib in a subject who died from disease progression. There was no obvious relationship between the type of AEs and malignancy type. Three deaths were reported during the study (disease progression, n=2; septic shock, n=1).

PKB115125

This is an ongoing open-label, 2-part, repeat- and escalating-dose study designed to investigate the safety, tolerability, PK, pharmacodynamics, and clinical activity of afuresertib administered once daily in combination with bortezomib and dexamethasone (twice weekly schedule) in subjects with relapsed/refractory MM. In the study's Part 1 dose-escalation, 34 subjects were administered doses of afuresertib in combination with bortezomib and dexamethasone in the following sequence: 75 mg/day (n=4), 100 mg/day (n=6), 125 mg/day (n=6), 150 mg/day (n=12), 175 mg/day (n=6) and plus dexamethasone (40 mg) on days of bortezomib administration (n=6). The MTD for afuresertib was established at 150 mg once daily in combination with bortezomib (1.3 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle) and dexamethasone 40 mg (on days of bortezomib dosing only). Four subjects experienced DLTs during Part 1: 100 mg/day, Grade 2 elevations in ALT; 125 mg/day, Grade 3 erythema multiforme; 175 mg/day, Grade 3 diarrhea, thrombocytopenia, and rash; 175 mg/day, Grade 3 maculo-papular rash. Part 1 was followed by a cohort-expansion phase (Part 2). As of the data cut-off date of 18-Oct-2013, Part 2 included 23 subjects who received 150 mg of afuresertib once daily in combination with bortezomib and dexamethasone. An additional 10 subjects were enrolled into the PK/pharmacodynamic cohort.

The most common AEs ($>10\%$ of subjects) were primarily GI toxicities. No new safety concerns were identified from the use of afuresertib in combination compared with the safety profile observed with afuresertib monotherapy. The most common AEs (in $\geq 10\%$ of subjects) were as follows: fatigue (51% [2% Grade 3, no Grade 4]), diarrhea (49% [14% Grade 3, no Grade 4]), thrombocytopenia 38%, [16% Grade 3, 11% Grade 4]), nausea (37% [1% Grade 3, no Grade 4]), constipation (33% [2% Grade 3, no Grade 4]), dyspepsia (32% [1% Grade 3, no Grade 4]), hyperglycemia (28% [6% Grade 3, 1% Grade 4]), vomiting (27% [2% Grade 3, no Grade 4]), anemia (22% [10% Grade 3, no Grade 4]), peripheral neuropathy (22% [no Grade 3/4]), insomnia (20% [no Grade 3/4]),

rash (20% [7% Grade 3, no Grade 4]), dizziness (20% [no Grade 3/4]), upper respiratory tract infection (17% [no Grade 3/4]), cough (14% [no Grade 3/4]), lymphopenia (14% [5% Grade 3, 2% Grade 4]), pyrexia (14% [no Grade 3/4]), blood creatinine increased (12% [1% Grade 3, 1% Grade 4]), asthenia (11% [2% Grade 3, no Grade 4]), dysgeusia (11% [no Grade 3/4]), headache (11% [no Grade 3/4]), neutropenia (11% [5% Grade 3, 2% Grade 4]), abdominal pain (10% [1% Grade 3, no Grade 4]), ALT increased (10% [2% Grade 3, no Grade 4]), decreased appetite (10% [1% Grade 3, no Grade 4]), exertional dyspnea (10% [no Grade 3/4]), epistaxis (10% [no Grade 3/4]), herpes zoster (10% [no Grade 3/4]), hypotension (10% [2% Grade 3, no Grade 4]), and urinary tract infection (10% [1% Grade 3, no Grade 4]). Grade 5 AEs were observed in 2 subjects: septic shock, and sepsis.

1.1.4. PKB116611

PKB116611 is an ongoing open-label, Phase 1/2 dose-escalation study of afuresertib in combination with carboplatin and paclitaxel in subjects with platinum-resistant/refractory ovarian cancer. The primary objective of the Phase 1 part of the study is to determine the safety and tolerability of the triplet combination, which will be used to define the dosing regimen to be evaluated in Phase 2. The primary objective of the Phase 2 part of the study is to evaluate the clinical efficacy (defined by the overall response rate) of the triplet combination, in patients with platinum-resistant or platinum-refractory ovarian cancer.

Afuresertib doses of 50 to 150 mg/day were explored in combination with carboplatin (IV) AUC 5 and paclitaxel (IV) 175 mg/m² administered day 1 every 21 days for a maximum of 6 doses. Phase 2 expansion cohorts at the recommended Phase 2 afuresertib dose of 125 mg are ongoing in platinum resistant and platinum refractory cohorts.

As of the data cut-off date of 29-Jun-2014, 52 subjects have been enrolled in the study; 29 subjects in Part 1 and 23 subjects in Part 2. Of these, data are available for 49 subjects, including all subjects in Part 1 and 20 subjects in Part 2. For those subjects with available data, 2 subjects who are platinum refractory have been enrolled to Part 2; all other subjects are platinum resistant. Three subjects (6.1%) discontinued study treatment because of AEs and 13 subjects (26.5%) discontinued because of progressive disease.

The most common AEs ($\geq 10\%$ of subjects) were primarily gastrointestinal toxicities, alopecia, and fatigue. The event of fatigue was reported at a similar incidence in Study PKB115125, where afuresertib was administered with bortezomib/dexamethasone.

In total, 18 (36.7%) subjects reported Grade 3 AEs and 12 (24.5%) subjects reported Grade 4 AEs. The following Grade 3 AEs were reported: hypomagnesaemia (8.2%), neutropenia (8.2%), hyperglycaemia (6.1%), vomiting (6.1%), ascites (4.1%), dyspnoea (4.1%), lower respiratory tract infection (4.1%), nausea (4.1%), rash (4.1%), rash maculo-papular (4.1%), small intestinal obstruction (4.1%), and abdominal pain, anaemia, chills, colonic obstruction, dermatitis acneiform, diarrhoea, drug hypersensitivity, escherichia urinary tract infection, fatigue, febrile neutropenia, gastroenteritis viral, hypersensitivity, hypertension, hyperthyroidism, hypophosphataemia, lobar pneumonia, neutropenic sepsis, oesophagitis, platelet count decreased, pneumonia, pyrexia, renal

failure acute, supraventricular tachycardia, syncope, urinary tract infection, and white blood cell count decreased (each reported in 2.0% subjects). In addition, the following Grade 4 AEs were reported: neutropenia (20.4%), thrombocytopenia (4.1%), hypomagnesaemia (2.0%), platelet count decreased (2.0%), and white blood cell count decreased (2.0%). There were also 2 uncoded Grade 3 AEs in the eye disorders SOC (2.0% each).

Five subjects discontinued treatment with afuresertib due to AEs; these were abdominal pain, blood creatinine increased, decreased appetite, dehydration, diarrhea, gastroesophageal reflux disease, headache, muscle spasms, nausea, neutropenia, pleural effusion, syncope, and vomiting (1 subject each).

As of 29-Jun-2014, 1 subject died while on study. Two additional patients died while off study (>30 days after the last dose of afuresertib).

Overall 56 SAEs have been reported in 34 subjects; of these, 18 SAEs in 10 subjects were considered by the investigator to be related to afuresertib.

1.1.5. LCH115397

LCH115397 was an open label, repeat-dose study designed to investigate the efficacy and safety of afuresertib in subjects with LCH. This study is complete.

In total, 17 subjects were enrolled in the study at doses up to 125 mg administered continuously, once daily. Of these, 16 of the 17 subjects completed the study and 1 subject voluntarily withdrew from the study.

One subject, receiving 125 mg/day, discontinued treatment because of an AE (Grade 2 impaired gastric emptying) which was considered to be not related to afuresertib, in the opinion of the investigator.

Five (29%) subjects had AEs of Grade 3 or higher, these were: ALT increased, diarrhea, fatigue, hyponatraemia, impaired gastric emptying, lung infection, esophageal ulcer, pain, perineal pain, pseudomonas infection, soft tissue necrosis, and vulvovaginal pain. None of these occurred in more than 1 subject.

No subject died during the study. Five SAEs have been reported in 3 subjects, only 1 of which (soft tissue necrosis) was considered possibly related to afuresertib

1.1.6. Clinical Activity of Afuresertib

Clinical activity of afuresertib monotherapy was seen in subjects with hematologic malignancies in the PKB112835 FTIH study. Of the 34 subjects with MM, three subjects demonstrated confirmed PR and median time on study for those subjects was 319 days (range 215-541). Three additional subjects had MR and their median time on study was 336 days (range 157-484). The overall CBR for MM subjects (PR+MR) was therefore, 17.6% (6/34). An additional 14 subjects with MM had prolonged stabilization of their

disease for a median 118.5 days (range 48-426). Clinical activity has also been observed in subjects with lymphomas (1 complete response [CR] and 2 partial responses [PRs] in 13 subjects with NHL) and 4/8 subjects with HD achieving unconfirmed PR.

In the ongoing combination study (PKB115125) of afuresertib with bortezomib and dexamethasone, responses have been reported in the dose escalation and expansion phases of the study. In the population of relapsed MM subjects treated at the afuresertib's MTD (150 mg) in Part 2 of the study, the confirmed overall response rate was 61% (14/23 subjects; 3 very good partial responses [VGPR] and 11 PR). Data on duration of responses are not available yet from this ongoing study.

Additional information from all studies where subjects with other diseases are administered afuresertib, as monotherapy or in combination, can be found in the current afuresertib IB.

1.2. Rationale

1.2.1. Study Rationale

The purpose of this study is to allow for continued treatment with afuresertib in subjects who have participated in a 'parent' GSK or Novartis sponsored study of afuresertib, either as monotherapy or as part of a combination regimen, and met the protocol requirements for transitioning to this rollover study. The parent study will have met its primary endpoint and transitioning to this rollover study will allow data to be reported for the parent study. In addition, subjects will be monitored for adverse events, as this study will continue to collect safety information on afuresertib.

Subject enrollment into Cohorts A and B is based on the duration of treatment on a monotherapy parent study with Cohort A enrolling subjects who received less than 24 weeks of treatment, while Cohort B will enroll subjects who have received 24 weeks or greater afuresertib therapy. Cohort C will enroll subjects who have participated on a combination study where afuresertib is given with another anti-cancer agent(s). The purpose of having separate cohorts is to be able to better report and define the safety profile for these subject groups.

1.2.2. Dose Rationale

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 MTD established in the parent study will be allowed in this study.

Cohort A and B:

Subjects who have received <24 weeks (Cohort A) or ≥24 weeks (Cohort B) of afuresertib as monotherapy in the parent study will receive the same continuous dosing regimen of afuresertib at completion of the parent study. If a subject required a dose modification while receiving treatment in the parent study, the subject will enter the rollover study and continue treatment on the modified dose unless after consultation with

the Novartis Medical Lead, it is appropriate to escalate the dose. The dose may be escalated up to the MTD established in the parent study.

Cohort C:

Subjects who have received any duration of a combination regimen with afuresertib and another anti-cancer agent will continue treatment in the rollover study at the current dose level(s) administered in the parent study at the time of transition to the rollover study. If the subject discontinued the anticancer drug, which was studied as a part of a parent study- the subject will enter and continue on the roll over study while receiving monotherapy with afuresertib. Adding additional anticancer drugs is not allowed. If a subject required a dose modification while receiving treatment in the parent study, the subject will enter the rollover study and continue treatment on the modified dose unless after consultation with the Novartis Medical Lead, it is appropriate to escalate the dose. Any dose modifications will follow parent protocol or most recent prescribing information.

1.2.3. Population Rationale

Afuresertib is being explored for its anti-cancer activity in subjects with hematologic and solid tumor malignancies. All subjects enrolled into this study will have participated in a prior afuresertib study. Subjects must meet entry criteria at the time of transition to this study.

1.2.4. Endpoint Rationale

This study will collect additional safety data from prolonged exposure to afuresertib, as monotherapy or in combination with other therapies. Primary endpoints for the study will be: adverse events, changes in laboratory values, and changes in vital signs.

1.3. Summary of Risk Management

Summaries of findings from clinical and nonclinical studies conducted with afuresertib can be found in the current IB. The most common AEs seen to date in afuresertib studies include; nausea, diarrhea, dyspepsia, fatigue, thrombocytopenia, neutropenia, hyperglycemia, upper respiratory infection, anorexia, gastrointestinal reflux and rash. The anticipated resks are listed below.

1.3.1. Risk Assessment for Afuresertib

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal toxicity	GI toxicity has been observed both afuresertib with most frequent events being: diarrhea, nausea, vomiting and dyspepsia.	<ul style="list-style-type: none"> Exclusion of subjects with significant pre-existing GI conditions Close monitoring via continuous assessment of AEs, physical examination, and clinical laboratory assessments (see Section 6.7). Management guidelines and stopping criteria are provided for diarrhea, mucositis, and dyspepsia (see Section 6.7))
Rash	Rash has been frequently observed with afuresertib monotherapy and in combination therapies	<ul style="list-style-type: none"> Monitoring rash via assessment of AEs and physical examination (see Section 6.7.4.). Management guidelines and stopping criteria are provided (see Section 6.7.4.).
Hepatic toxicity	LFT elevations have been observed with afuresertib.	<ul style="list-style-type: none"> Exclusion of subjects with impaired liver function. Monitoring and stopping criteria are provided (see Section 6.7.7))
Hyperglycaemia	Elevated glucose levels have been observed with compounds inhibiting PI3/AKT pathway. Afuresertib can potentially cause hyperglycemia.	<ul style="list-style-type: none"> Only subjects with well-controlled Type 2 diabetes will be enrolled in the study Glucose monitoring will be implemented as clinically indicated. Management guidelines and stopping criteria are provided (see Section 6.7.2))

2. OBJECTIVE(S)

2.1. Primary

The primary objective of the study is to provide treatment with afuresertib for subjects who have previously participated in an afuresertib study sponsored previously by GSK or Novartis or another research organization working on behalf of Novartis.

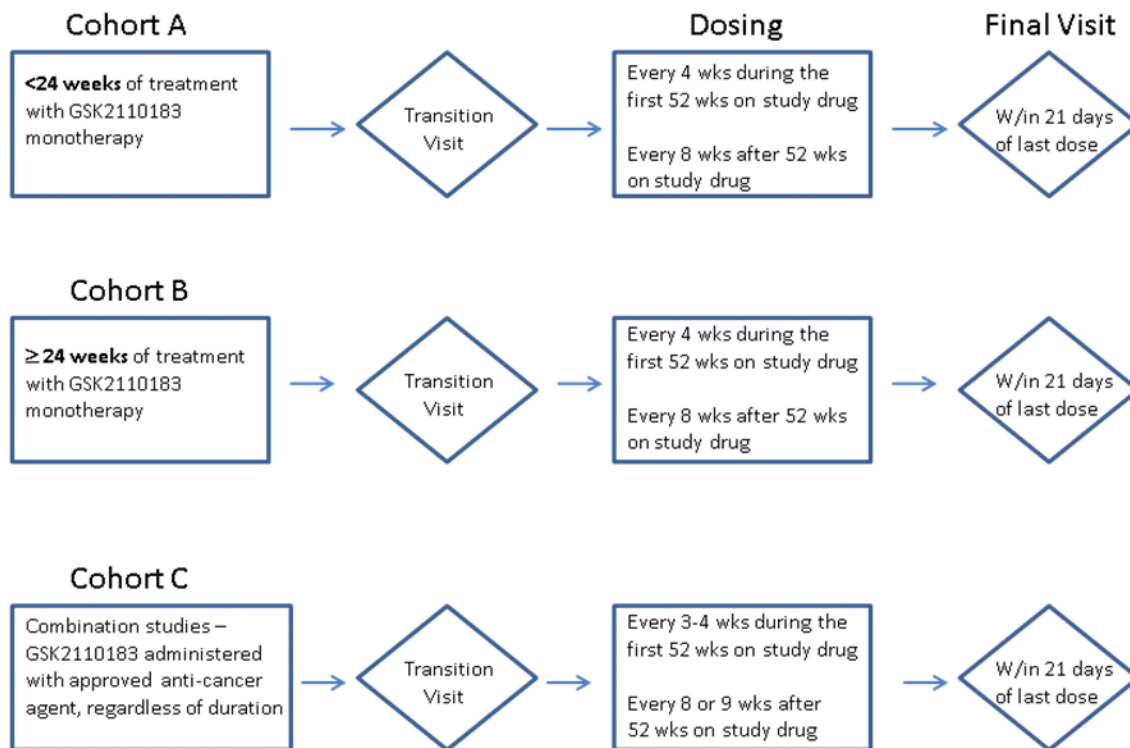
2.2. Secondary

The secondary objective of the study is to collect safety data on continued treatment with afuresertib.

3. INVESTIGATIONAL PLAN

3.1. Study Design/Schematic

Figure 1 Study design



3.2. 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. All subjects enrolling in this study must be tolerating and benefitting from treatment (ie did not meet any of the study discontinuation criteria from the parent study) with afuresertib to be eligible. Subjects will be enrolled into the appropriate cohort (Section 3.2.1) based upon the duration and treatment received in their parent study. Enrollment into this study will be dependent upon the site’s agreement to participate in this study.

Subjects must first provide written informed consent for this rollover study prior to any study-related assessment or procedure being performed and before any treatment with afuresertib can be administered under this protocol. After informed consent is obtained, subjects will be evaluated for study eligibility in PKB115131/CASB183X2X01B.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables for Cohorts A, B and C ([Appendix 1](#), and [Appendix 2](#), respectively), are essential.

The study will consist of a transition visit, continuous dosing treatment period, and a final study visit.

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), clinical laboratory assessments, and monitoring of AEs. Additional safety assessments may be necessary if a combination treatment regimen is administered to address specific safety concerns with the other agent(s).

Assessment of clinical activity will be performed using local standard of care imaging practices and the assessment criteria appropriate for disease type and location to determine eligibility for continued study participation and treatment with afuresertib. Disease assessments must be performed at least every 12 weeks, or more frequently if the investigator decides that it is necessary. Guidelines for solid tumor (RECIST) assessments, and assessments of various hematologic malignancies are provided in [Appendix 5](#) and [Appendix 6](#).

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.

Refer to the Time and Events Table for Cohort A and B ([Appendix 1](#)) or Time and Events Table for Cohort C ([Appendix 2](#)) for timing of all assessments.

Details regarding dose modifications of afuresertib and guidance on additional assessments and procedures following events of special interest can be found in Section [6.6](#) and Section [6.7](#), respectively.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying study procedures manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2.1. Cohort A and Cohort B: Afuresertib Monotherapy

Subjects will receive afuresertib as an oral, daily dose up to 150 mg. Protocol specified guidelines for dose modifications and treatment discontinuation criteria are provided in Section [6.6](#) and Section [6.7](#), respectively. If there are any uncertainties about the dose to be administered in this study, the Novartis Medical Lead should be consulted.

Cohort A:

Cohort A will consist of subjects who have completed <24 weeks of treatment with afuresertib monotherapy during their participation in the parent study. It is anticipated that subjects in this cohort will have participated in a clinical pharmacology or other short-term study of afuresertib. Subjects will complete the Transition Visit; receive instruction and study medication, and then return for their next scheduled visit (Study Week 4) and then every 4 weeks thereafter. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to every 8 weeks with approval from the Novartis Medical Lead. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

Cohort B:

Cohort B will consist of subjects who have completed ≥ 24 weeks of treatment with afuresertib monotherapy during their participation in the parent study. It is expected that subjects in this cohort will have participated in a longer term study of afuresertib. Subjects will complete the Transition Visit, receive study instruction and study medication and then return for their next scheduled visit (Study Week 4), and then every 4 weeks thereafter. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to every 8 weeks with approval from the Novartis Medical Lead. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

3.2.2. Cohort C: Afuresertib Combination Therapy

Cohort C:

Cohort C will consist of subjects who have participated in a combination study where afuresertib is administered with another anti-cancer agent, regardless of duration on study. Subjects who transition from a combination study may continue to receive afuresertib in combination with the anti-cancer agent defined by the parent study, or they may receive afuresertib as monotherapy. If the concomitant anticancer drug has been terminated according to parent study design, or if, in the opinion of the investigator, the subject has received maximum benefit, or is experiencing unacceptable toxicity from the anti-cancer agent, then treatment with the anti-cancer agent may be discontinued and the subject may remain on study for continued treatment with afuresertib monotherapy. Adding any other anticancer drug while on this study, is not allowed. Subjects will complete the Transition Visit, receive study instruction and study medication, and then return for their next scheduled visit (either Study Week 3 or 4) and then every 3 or 4 weeks thereafter, depending on the schedule used in the parent study. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased with approval from the Novartis Medical Lead to every 8 or 9 weeks (whichever is consistent with parent schedule). After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

Approximately 200 subjects from approximately 60 investigative sites worldwide will be transitioned to this study from other afuresertib studies.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on afuresertib or other agent(s) that may impact subject eligibility is provided in the IB for afuresertib or any subsequent IB supplements or in the Prescribing Information for any agent(s) administered as part of a combination treatment regimen, as applicable.

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Has provided signed informed consent for this study.
2. Is currently participating in an afuresertib study (monotherapy or in combination with another anti-cancer agent) sponsored by GSK/Novartis or by another research organization working on behalf of Novartis.
3. Currently tolerating and benefitting from treatment with afuresertib as determined by the investigator following previous treatment with afuresertib either as monotherapy or as part of a combination treatment regimen.
4. Continued ability to swallow and retain orally administered study treatment(s) and does not have any clinically significant GI abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
5. Male subjects with a female partner of childbearing potential must be willing to continue practicing the same acceptable method of contraception as used in the parent study during the rollover study and for at least 16 weeks after the last dose of afuresertib.
6. Female subjects of childbearing potential, as defined in the parent study, must be willing to continue practicing the same acceptable method of contraception as used in the parent study during the rollover study and for at least 4 weeks after the last dose of afuresertib.
7. Female subjects of childbearing potential, as defined in parent study, must have negative serum pregnancy tests at the time of transition to this study.

8. Maintain a performance status score of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale (Section 5.7) at time of transition into this study.
9. Subjects with Type II diabetes are only allowed if their HbA1C \leq 8% at study entry.
10. Have adequate organ system function as defined in Table 1.

Table 1 Definitions of Adequate Organ Function

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	$\geq 1.0 \times 10^9/L$
Hemoglobin	≥ 8.0 g/dL
Platelets	$\geq 50 \times 10^9/L$
PT/INR and PTT	$\leq 1.5x$ ULN
Hepatic	
Total bilirubin	$\leq 1.5x$ ULN (isolated bilirubin $>1.5x$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $<35\%$)
AST and ALT	$\leq 3x$ ULN. If liver involvement is present and ALT and AST levels are $>3x$ UNL and $<5x$ ULN, enrollment into PKB115131 can occur as long as there is no concurrent bilirubin or INR elevation
Renal (Monotherapy)	
Serum creatinine OR Calculated creatinine clearance ¹	≤ 2.5 mg/mL ≥ 30 mL/min
Renal (in combination with nephrotoxic anti-cancer agents)	
Serum creatinine OR Calculated creatinine clearance ¹	$\leq 1.2x$ ULN ≥ 50 mL/min
Cardiac	
Ejection Fraction (LVEF)	$\geq 50\%$ by TTE or MUGA

1. As calculated by Cockcroft-Gault formula (Appendix 4).

4.1.3. Exclusion Criteria

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. Permanent discontinuation of afuresertib in the parent study due to toxicity or disease progression.
2. Concomitant use of any type of anti-cancer treatment other than studied in the parent protocol.
3. Current use of a prohibitive medication(s) as listed in Section 6.2.
4. Current use of anticoagulants is only allowed if PTT/INR values fulfil entry criteria.

5. Any unresolved toxicity > Grade 2 , except for alopecia, (National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.0) from parent study treatment at the time of transition to this study.
6. History of HIV infection.
7. History of hepatitis B or C infection (subjects with evidence of cleared hepatitis B are permitted).
8. Evidence of severe or uncontrolled systemic diseases (e.g., unstable, or uncompensated respiratory, hepatic, renal, metabolic or cardiac disease).
9. QTcF interval > 500 msec at the time of transition to this study.
10. Other clinically significant ECG abnormalities including 2nd degree (Type II) or 3rd degree atrioventricular (AV) block.
11. Evidence of current Class III, or IV heart failure as defined by the New York Heart Association [NYHA, 1994] functional classification system at the time of transition to this study.
12. Symptomatic or untreated leptomeningeal, CNS or brain metastases or spinal cord compression at the time of transition to this study.

NOTE: Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs (EIAEDs). Continued stability of brain metastases must be confirmed with imaging.

13. Lactating female or female who becomes pregnant prior to transition to this study.
14. Previously diagnosed diabetes mellitus Type I. Subjects with Type II diabetes are allowed if entry criteria are fulfilled (see entry criteria #9).
15. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions at the time of transition to this study that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the investigator or Novartis Medical Lead.

4.1.4. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the Novartis investigational product(s) or other study treatment being used in this study: IB for afuresertib, product label(s) for other commercially available co-administered agents.

4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.2.1. Permanent Discontinuation from Study Treatment

Subjects may be permanently discontinued from study treatment in the event of unacceptable toxicity, which include but are not restricted to: meeting stopping criteria for liver chemistry defined in Section 6.7.7 or for hematologic and other non-hematologic

toxicity. In addition, study treatment will be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Adverse Event, including but not limited to clinically significant AE leading to interruption of treatment for >14 consecutive days¹.
- Disease progression (including death due to disease progression)
- Request of the subject or proxy (withdrawal of consent by the subject)
- Investigator's discretion
- Subject is lost to follow-up
- Study is closed or terminated
- Death

The primary reason for permanent study treatment discontinuation must be documented in the subject's medical records and electronic case report form (eCRF).

Once a subject has permanently discontinued from afuresertib, the subject will not be allowed to be retreated with afuresertib.

Every attempt will be made to ensure that subjects who discontinue study treatment will have safety assessments performed at the Final Study Visit within approximately 21 days (± 7 days) of last dose of study treatment(s) as specified in [Appendix 1: Time and Events Table for Cohort A and B](#) or [Appendix 2: Time and Events Table for Cohort C](#).

If the subject withdraws consent for further study treatment, a Final Study Visit should be completed. If the subject withdraws consent for further treatment and data collection, then no additional study visits or data collection should occur.

If the subject discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation of study treatment in the eCRF.

In the event that a subject permanently discontinues study treatment at any time due to an AE (as defined in Section 5.9.1.1, "Definition of an AE") or serious AE (SAE) (as defined in Section 5.9.1.2, "Definition of a SAE"), the procedures stated in Section 5.9 ("Adverse Events") must be followed. All subjects who have a Grade 3 or 4 clinical or laboratory abnormality at the time of permanently discontinuing study treatment must be followed up to 30 days or until resolution, whichever comes first.

If the subject discontinues study treatment from death due to disease progression, 'Disease Progression' will be recorded as the primary reason for permanent study treatment discontinuation in the eCRF. The cause of death should also be documented in

¹ **NOTE:** If the investigator and Novartis Medical Lead agree that continued treatment will benefit the subject, then the subject may continue treatment, with or without a dose reduction, with the approval of the Novartis Medical Lead.

the Death eCRF. If the subject discontinues study treatment from death due to any other cause, then 'AE' will be recorded as the primary reason for permanent discontinuation in the eCRF. In both cases the cause of death should be documented in the Death eCRF.

4.2.2. Subject Completion Criteria

A completed subject is one who took at least one dose of study medication in the rollover study and discontinued the study for any reason. For subjects who permanently discontinue study treatment, date of discontinuation and reason will be collected.

5. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

Refer to the Time and Events Tables for Cohorts A, B or C for the timing of all assessments ([Appendix 1](#) or [Appendix 2](#), respectively). Further details of study procedures and assessments can be found in the SPM.

The study specific assessments and procedures are outlined in the Time and Events Schedule for Cohort A, B or C ([Appendix 1](#) or [Appendix 2](#), respectively). Approximately 3 teaspoons (15 mL) of blood will be collected at each study visit. The total amount of blood collected for the duration of the study is dependent on the length of individual subject participation in the study.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. The change in timing for any planned study assessments must be approved and documented by Novartis, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme.

If vital signs, ECGs and blood draws are scheduled for the same nominal time, the ECG will be obtained first, followed by the vital signs, and then blood draws.

For all cohorts, disease assessments should be performed at regular intervals per local standard practice using criteria appropriate for disease type and location. Refer to the Time and Events Tables for Cohorts A, B or C for the suggested timing of all assessments ([Appendix 1](#) or [Appendix 2](#), respectively).

5.1. Transition Visit

For this study, the Transition Visit may occur on the same day as the last study visit on the parent study. The most recent disease assessment performed under the parent protocol may be used for entry criteria for this rollover protocol, if there are no clinical signs of disease progression. The results of any specified study assessments performed on the day of the Transition Visit will serve as the baseline value for said assessment.

At the Transition Visit, the following assessments will be performed:

- Demographic data, including date of birth, ethnicity, gender, and race.
- Subject-related data from parent study, including parent study protocol number, previous subject number assigned in parent study, start and stop date, dose of afuresertib and other study treatment(s), if applicable, at time of transition to this study; and response based on last disease assessment in parent study. At the time of transition visit the duration of treatment on parent study will be calculated.
- Complete physical examination, including height and weight.
- Vital signs (BP, temperature and pulse rate)
- Clinical laboratory tests: hematology, TSH and clinical chemistry required for study entry, including coagulation tests
- Serum beta-human Chorionic Gonadotropin (β -hCG) pregnancy test for female subjects of childbearing potential only
- Single 12-lead ECG
- Review of adverse events and concomitant medications
- Disease assessments

5.2. Continuous Dosing Treatment Period

5.2.1. Cohort A and B

The following assessments must be performed **every 4 weeks (± 3 days)** while receiving treatment:

- Vital signs (BP, temperature and pulse rate)
- Complete physical examination
- Clinical laboratory tests: hematology and clinical chemistry, including TSH and coagulation tests
- Single, 12-lead ECG

Once the subject has been on study drug for >52 weeks (including the time on parent study), and after confirmation with Medical Lead the frequency of those assessments can be decreased to **every 8 weeks (± 3 days)**.

The disease assessments must be performed at least **every 12 weeks** while receiving treatment.

The following assessments must be performed **continuously (regardless of the time on study)** while receiving treatment:

- Review of Concomitant Medications
- Assessment of study treatment(s) compliance
- Assessment of AEs

5.2.2. Cohort C

The following assessments must be performed either **every 3 or 4 weeks** (± 3 days) (depending on schedule used in parent study) while receiving treatment:

- Vital signs (BP, temperature and pulse rate)
- Complete physical examination
- Clinical laboratory tests: hematology and clinical chemistry, including TSH and coagulation tests
- Single, 12-lead ECG
- Perform assessments needed for safe administration of other anti cancer agents used in combination

Once the subject has been on study drug for >52 weeks (including the time on parent study), and after confirmation with Medical Lead the frequency of these assessments can be decreased to **every 8 or 9 weeks** (± 3 days) (**whichever is consistent with the parent schedule**).

The disease assessments must be performed **at least every 12 weeks** while receiving treatment.

The following assessments must be performed **continuously (regardless of the time on study)** while receiving treatment:

- Review of Concomitant Medications
- Assessment of study treatment(s) compliance
- Assessment of AEs

5.3. Final Study Visit

If a subject is withdrawn from study treatment, the following assessments will be performed within one month from the last dose of study treatment(s) and prior to initiating any other treatment for cancer:

- Complete physical examination
- Vital signs (BP, temperature and pulse rate)
- Clinical laboratory tests: hematology, clinical chemistry, and TSH
- Single, 12-lead ECG
- Review of concomitant medications
- Assessment of AEs
- Disease assessment

5.4. Safety

Measurements used to evaluate safety will include weight, physical examinations, vital signs (BP, temperature and pulse rate), 12-lead ECGs, ECHO or MUGA scan, clinical laboratory tests (hematology and clinical chemistry), and monitoring for AEs. Planned time points for all safety assessments are listed in [Appendix 1](#): Time and Events Table for Cohort A and B or [Appendix 2](#): Time and Events Table for Cohort C.

Additional, unplanned safety assessments may be performed during the course of the study as clinically indicated in the judgment of the investigator. Additional time points for safety tests may also be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

NOTE: Baseline will refer to the value from the day of the transition visit. This definition of baseline will be applicable to all assessments (i.e., physical examination findings, laboratory values) for this study when baseline reference is used. All Adverse Events which have been recorded in the parent study eCRFs and are ongoing at the time of transition into the rollover study will be reported as “AE continued” at the time of transition to the rollover study, i.e., AE status and relationship to the study drug at time of transition into the rollover study will become baseline for the rollover study.

5.4.1. Physical Examinations

Complete physical examinations will be performed at the time points outlined in Section 5.2 and Section 5.3 and in [Appendix 1](#): Time and Events Table for Cohort A and B, [Appendix 2](#): Time and Events Table for Cohort C. Height will also be measured and recorded at the initial physical examination only.

5.4.2. Vital Signs

Vital sign measurements (BP, temperature, and pulse rate) will be taken at the time points outlined in Section 5.2 and Section 5.3 and in [Appendix 1](#): Time and Events Table for Cohort A and B or [Appendix 2](#): Time and Events Table for Cohort C. Vital signs will be measured more frequently if warranted by clinical condition of the subject. Refer to the SPM for details regarding measurement of vital signs.

5.4.3. Electrocardiograms

Single 12-lead ECGs will be obtained at each time point during the study according to [Appendix 1](#): Time and Events Table for Cohort A and B or [Appendix 2](#): Time and Events Table for Cohort C using an ECG machine that automatically calculates the heart rate and measures RR, PR, QRS, QT, and QTc intervals.

If there are any clinically significant abnormalities including, but not limited to, QTcF >500 msec, confirm with 2 additional ECGs taken at least 5 minutes apart.

Refer to Section 6.7.7.4 for QTc withdrawal criteria and additional readings that may be necessary. Refer to the SPM for details regarding ECG procedures.

5.4.4. Clinical Laboratory Assessments

Clinical laboratory tests ([Table 2](#)) will be performed as outlined in [Appendix 1](#): Time and Events Table for Cohort A and B or [Appendix 2](#): Time and Events Table for Cohort C. To address any immediate safety concerns by the investigator, additional laboratory samples may be taken as clinically necessary.

All laboratory tests with values that are significantly abnormal during study participation or within 28 days after the last dose of study treatment(s) should be repeated until the values return to within normal range or baseline. All subjects who have a Grade 3 or 4 laboratory abnormality at time of study withdrawal must be followed until resolution to Grade 2 or less, unless it is unlikely to improve due to underlying disease. If such values do not return to within normal range within a period judged reasonable by the investigator, the etiology should be identified and the Novartis Medical Lead notified.

Table 2 List of Clinical Laboratory Assessments

Hematology

	<i>Automated WBC Differential:</i>
White blood cell (WBC) Count (absolute)	Neutrophils
Hemoglobin	Lymphocytes
RBC	Monocytes
Platelet Count	Eosinophils
	Basophils

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium
Creatinine	Inorganic phosphorus
Sodium	Magnesium
Albumin	Chloride
Calcium	LDH
Bicarbonate	Glucose
Total protein	
AST	
ALT	
Alkaline Phosphatase	
Total bilirubin (bilirubin fractionation recommended if total bilirubin >2 times ULN)	

Other tests

• TSH
• Triglycerides and total cholesterol
• HbA1c
• Coagulation: PT/PTT, INR
• Serum β -hCG pregnancy (female subjects of childbearing potential only; performed at baseline and every 12 weeks while on study)

5.5. Multiple Myeloma Specific Disease Assessments:

The following assessments will be performed to assess disease in subjects with MM only every 4 weeks until week 42 and every 8 weeks thereafter:

Serum M-protein, urine M-protein, serum FLC, urine FLC, imaging for extramedullary MM (only in subjects in whom there is a clinical evidence of extramedullary MM- the imaging technique should be the same throughout the study (ie if subject initially had CT- should be followed by CT, if MRI- follow by MRI, or if PET scan- follow by PET scan.)).

5.6. Disease Assessments for Malignancies Other Than MM

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. The investigator may decide that more frequent disease assessments are needed, and perform them according to medical practice.

5.7. Performance Status

The performance status assessment is based on the ECOG scale [[Oken, 1982](#)]:

- 0 – Fully active, able to carry on all pre-disease performance without restriction.
- 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
- 2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 – Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
- 4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
- 5 – Dead.

5.8. Pregnancy

5.8.1. Time period for collecting pregnancy information

All pregnancies in female subjects will be collected after the start of dosing and until 28 days after the last dose of aforesertib.

5.8.2. Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Novartis within 24 hours of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to

Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to Novartis as described in Section 5.9.1.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating will be withdrawn from the study.

5.8.3. Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Novartis within 24 hours of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

5.9. Adverse Events (AE) and Serious Adverse Events (SAE)

5.9.1. Adverse Events

AEs and SAEs will be monitored from the time of consent until the final study visit. All AEs and SAEs must be recorded and reported as detailed in the following sections and in the SPM. At the time of consent, all ongoing AEs that began during participation in the parent study must be recorded in the eCRF.

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 5.9.1.1 and Section 5.9.1.2, respectively.

5.9.1.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

5.9.1.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

- a. Results in death
- b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT ≥ 3 times ULN and bilirubin ≥ 2 times ULN ($>35\%$ direct) (or ALT ≥ 3 times ULN and INR >1.5 , if INR is measured) termed 'Hy's Law' events ([Appendix 7](#)). INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants.

NOTE: Bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2 times ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

h. Additionally, new primary cancers and laboratory abnormalities as referenced in Section [5.9.1.3](#) are considered to be serious events by virtue of being medically important. These should be reported in the same manner as other SAEs.

5.9.1.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

All events of possible drug-induced liver injury with hyperbilirubinemia (defined as ALT ≥ 3 times ULN **plus** bilirubin ≥ 2 times ULN and/or INR > 1.5) or Hy's Law events, require immediate study treatment cessation and reporting as an SAE.

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick** indicating direct bilirubin elevations and suggesting liver injury.

If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2.0 times ULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations > 1.5 suggest severe liver injury.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

5.9.1.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

5.9.1.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time of first dose of study treatment until 30 days after last study treatment dose.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to Novartis within 24 hours, as indicated in Section [5.9.1.6](#).

5.9.1.6. Prompt Reporting of Serious Adverse Events and Other Events to Novartis

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to Novartis as described in the following table once the investigator determines the event meets the protocol definition for that event.

Table 3 Serious Adverse Events

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities Phase II:				
ALT \geq 3 times ULN and bilirubin \geq 2 times ULN (>35% direct) (or ALT \geq 3 times ULN and INR >1.5	24 hours ¹	SAE data collection tool. Liver Event eCRF and liver imaging and/or biopsy CRFs if applicable ²	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF ²
ALT \geq 3 times ULN with hepatitis or rash or 5 times ULN \geq 2 weeks (if no liver involvement) or ALT \geq 8 times ULN if liver involvement present at enrollment;	24 hours ¹	Liver Event eCRF ²	24 hours	Updated Liver Event eCRF ²
ALT \geq 3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours ¹	Liver event eCRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks ²		

1. Novartis to be notified at onset of liver chemistry elevations to discuss subject safety.
2. Liver event documents should be completed as soon as possible

Methods for detecting, recording, evaluating, and following up on AEs and SAEs are provided in the SPM.

5.9.1.7. Regulatory Reporting Requirements For SAEs

Prompt notification of SAEs by the investigator to Novartis is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6. STUDY TREATMENTS

The term ‘study treatment’ is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

6.1. Afuresertib Investigational Product Dosage/Administration

For early trials in the afuresertib clinical program, study drug was provided in hard gelatin capsules (25 mg and 100 mg strengths; see [Table 6](#) below). The initial patients enrolled to this protocol from the FTIH study PKB112825 continued to receive afuresertib in hard gelatin capsules. Subsequently, afuresertib has been re-formulated as immediate-release (IR) tablets (50 mg and 75 mg strengths). A relative bioavailability study (201039) performed in healthy volunteers showed similar afuresertib pharmacokinetic characteristics between the capsule formulation and the IR tablet formulation (for details of study 201039 see the afuresertib clinical IB). Patients currently receiving afuresertib as hard gelatin capsules in this protocol will be switched to IR tablets from Day 1 of their next treatment cycle following a scheduled clinic visit. Patients newly enrolled to this protocol from a parent afuresertib study in which they received drug in hard gelatin capsules will immediately switch to IR tablets. Patients newly enrolled to this protocol from a parent afuresertib study in which they received drug as IR tablets will continue to receive IR tablets. Patients switching from capsule to tablets will have the change fully explained by their Investigator or Study Nurse.

Table 4 Afuresertib Dosage/Administration

Product name :	Afuresertib	
Formulation description:	Gelatin capsules: Each 25 mg capsule contains 25 mg of afuresertib as free base Each 100 mg capsule contains 100 mg of afuresertib as free base OR: Immediate release tablets (IR tablets): Each 50 mg tablet contains 50 mg of afuresertib as free base Each 75 mg tablet contains 75 mg of afuresertib as free base	
Dosage form :	Gelatin capsule or immediate release tablet	
	CAPSULES	IR TABLETS
Unit dose strength(s)/Dose Level(s):	25 mg capsule or 100 mg capsule	50 mg tablet or 75 mg tablet
Physical Description:	25mg Capsules: Opaque, white, size 4 capsules with no external markings, filled with a white powder. OR: OR: 100mg Capsules: Opaque, Swedish orange, size 1 capsule with no external markings, filled with a white powder.	50mg IR tablets: White, film-coated, round, biconvex tablet 75mg IR tablets: White, film-coated, oval or capsule shaped tablet
Route/ Administration/ Duration:	Oral/ The initial regimen will be once daily dosing continuously.	
Dosing instructions:	Dose with at least 200 mL of water, and taken in the morning. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.) Afuresertib may be given without regard to food.	

Afuresertib will be provided to sites by Novartis. The contents of the label will be in accordance with all applicable regulatory requirements. No special preparation of afuresertib is required.

Afuresertib must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Only authorized site staff may supply or administer afuresertib.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff, although adequate precautions are to be taken to avoid direct contact with study medication. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be

provided to the site staff if required by local laws or will otherwise be available from Novartis upon request.

6.2. Other Anti-Cancer Agents (Cohort C)

When the treatment regimen to be administered includes another anti-cancer agent(s) in combination with afuresertib, the sites will be responsible for obtaining the necessary drug supply for the anti-cancer agent(s) through commercial means; the drug(s) will not be supplied by Novartis. The use of an anti-cancer agent(s) in combination with afuresertib that was not part of the parent study is not permitted. Refer to the Prescribing Information for each anti-cancer agent for information regarding the physical and chemical properties, storage, and dosing/administration guidelines.

6.3. Administration of Study Treatment

Afuresertib will be administered with approximately 200mL of water. If a subject vomits after taking afuresertib, the subject should be instructed NOT to retake the dose and should take the next scheduled dose of study treatment(s). If vomiting persists, the subject should contact the investigator.

If subject misses a dose of afuresertib, the subject should be instructed to skip the missed dose and not make it up, then take the next scheduled dose. The missed dose should be recorded in the eCRF.

6.4. Handling and Storage of Study Treatment

Afuresertib must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the afuresertib will be limited to the investigator and authorized site staff. Afuresertib must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Afuresertib is to be stored at room temperature and should not exceed 30°C in an HDPE white opaque container. Maintenance of a temperature log (manual or automated) is required.

Anti-cancer agents should be handled per manufacturer instructions.

6.5. Treatment Assignment

Subjects will be identified by a new, unique subject number that is assigned upon enrollment into this study and that will remain consistent for the duration of the study.

The parent study number and subject/treatment numbers originally assigned to subjects during their participation in the parent study will be recorded in the eCRF, but will not be used to identify subjects in the rollover study.

Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the Novartis interactive voice response system (IVRS), by the investigator or authorized site staff.

6.6. Dose Modifications

At each study visit, subjects should be carefully evaluated for evidence of treatment-related toxicity. The investigator should refer to parent study guidelines to determine which study treatment may be contributing to the treatment-emergent toxicity and make the appropriate dosing adjustments, which may include reducing the dose of one or all study treatments.

Guidelines for afuresertib dose modifications are provided below. Investigators should also consult the Novartis Medical Lead and refer to the afuresertib IB or the prescribing information for the appropriate anti-cancer combination agent for detailed information regarding warnings, precautions, contraindications, AEs, and recommendations for supportive care in the event of drug-related toxicity.

6.6.1. Afuresertib Dose Modification

Dose modifications for clinically significant toxicities that are considered related to study medication are provided in [Table 5](#). More detailed guidelines for the clinical management of hyperglycemia, diarrhea, rash, dyspepsia, mucositis, and liver function abnormalities are provided in [Section 6.7](#). All dose modifications (delays or reductions) will be recorded on the appropriate eCRF.

Table 5 Dose Modifications for Afuresertib

TOXICITY¹	Afuresertib
Grade 1	Continue afuresertib at current dose level. Consider supportive care recommendations provided in Section 6.7
Grade 2	Withhold treatment with afuresertib until toxicity resolves to Grade 1 or baseline. Upon resolution, restart afuresertib at current dose level. Consider supportive care recommendations provided in Section 6.7. Consider dose reduction if toxicity is intolerable to the subject.
Grade 3	Withhold afuresertib until toxicity resolves to Grade 1 or baseline. Upon resolution, reduce dose of afuresertib by one dose level ² . Consider supportive care recommendations provided in Section 6.7.
Grade 4	Permanently discontinue treatment with afuresertib.

1. Considered related to study treatment.
2. Dose level 1: 150mg, Dose level 2: 125mg, Dose level 3: 100mg, Dose level 4:75mg. If subject requires dose reduction below 75mg, then treatment must be discontinued, and subject withdrawn from the study.

Treatment with afuresertib may be delayed for up to 14 days to allow resolution of toxicity or based on investigator discretion. If the investigator and the Novartis Medical Lead conclude that continued treatment will benefit a subject who has experienced a treatment delay >14 days, then the subject may continue afuresertib therapy with the approval of the Novartis Medical Lead.

A maximum of 2 dose reductions (including reductions from the parent study) of afuresertib is permitted and each of them requires consultation with the Novartis Medical Lead. Dose reductions should be to a lower dose level previously studied in an afuresertib clinical study. If a third dose reduction or a dose reduction below 75mg is required, treatment with afuresertib should be discontinued and subject should be withdrawn from study.

6.6.2. Dose Modification: Other Anti-Cancer Agent(s)

If an anti-cancer agent(s) is being taken in combination with afuresertib at the time of transition to the rollover study, treatment will continue with the current dose administered in the parent study. Any dose modification(s) required while on this study should be made according to the administration and/or dose modification guidelines presented in the protocol of the parent study or in the package insert for the agent, whichever is appropriate. If, in the opinion of the investigator, the subject has received maximum benefit from the additional anti-cancer agent(s), then treatment with the anti-cancer agent(s) may be discontinued.

6.7. Guidelines for Adverse Events of Special Interest

The severity of AEs will be graded utilizing the NCI-CTCAE, version 4.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in this section.

6.7.1. Supportive Measures for Nausea or Vomiting

Supportive care management of nausea or vomiting should be undertaken as clinically indicated.

6.7.2. Supportive Measures for Hyperglycemia

Subjects with clinically significant glucose elevation, with or without ketoacidosis, should be aggressively managed according to standard medical practice. Study sites with a protocol/guideline for management of hyperglycemia should include a copy in the study document file. Early consultation with a diabetes specialist is also encouraged, especially for study participants with a history of diabetes. If significant hyperglycemia (e.g., fasting glucose ≥ 200 mg/dL) persists despite treatment and after stopping systemic glucocorticoids (where applicable), or in the event of life-threatening complications, dose modification of afuresertib should also be considered, after discussion with a Novartis Medical Lead. Dose modification of afuresertib should not be performed for asymptomatic hyperglycemia, or hyperglycemia that responds to other interventions.

6.7.3. Management of Diarrhea

Episodes of diarrhea have been reported in subjects receiving afuresertib and this should be actively managed as soon as an episode has occurred. When starting afuresertib, it is advisable to provide subjects with a prescription for loperamide (or equivalent), along with detailed guidance on how to manage this potential toxicity. If an episode of diarrhea occurs, other potential causes should be promptly ruled out (e.g., concomitant medications like stool softeners, laxatives, antacids, etc., infections, partial bowel obstruction, etc.). Supportive therapy will be provided according to standard medical practice. Supportive measures should include the following as clinically indicated [Benson, 2004]:

- Dietary modifications (e.g., small, frequent meals, low fiber, and lactose avoidance)
- Maintain hydration with clear liquids or IV fluids as needed
- Loperamide and/or oral antibiotics

6.7.4. Management of Rash

Subjects should contact the investigator immediately upon onset of a rash. Full supportive care should be provided to subjects who experience a rash while on study. *Information contained in this section is a guideline. The investigator's best medical judgment should determine medical intervention for rash. Details should be entered into InForm.*

Table 6 Guidelines for Dose Modification and Management of Rash

	1 st occurrence	2 nd occurrence	3 rd occurrence
Grade 1	Symptomatic care ^a Consider oral steroids if multiple recurrences ^b		
Grade 2	Consider oral steroids	Oral steroids Hold drug until <Grade 1, then resume at full dose	Oral steroids Hold drug until <Grade 1, then resume at 25 mg dose reduction
Grade 3	Oral steroids Hold drug until <Grade 1, then resume at full dose	Oral steroids Hold drug until <Grade 1, then resume at 25 mg dose reduction	Oral steroids Hold drug until <Grade 1, then resume at 50 mg dose reduction or discontinue
Grade 4	Oral steroids Hold drug until <Grade 1, then resume at 25 mg dose reduction	Oral steroids Hold drug until <Grade 1, then resume 50 mg dose reduction or discontinue	Discontinue

a. Recommended symptomatic measures (for all grades) includes topical steroids (e.g., hydrocortisone 1% or 2.5% cream), antihistamines, hypoallergenic moisturizers and emollients for dry skin (e.g., 5-10% urea in cetomacrogel cream or soft paraffin).

b. Recommended course of oral steroids is methylprednisolone (or equivalent).

A dermatology consult should be considered for Grade ≥ 3 rash or multiple occurrences of Grade ≤ 2 rash.

6.7.5. Guidelines for Management of Dyspepsia

Based on nonclinical data and current clinical experience, it is possible that afuresertib may be a direct GI mucosal irritant such that subjects with GI dysmotility or GERD may be predisposed to symptoms of dyspepsia. Therefore, if a subject experiences symptoms supportive therapy will be provided according to standard medical practice. If Grade 1-2 dyspepsia, the investigator should consider the following recommendations:

- Afuresertib may be taken with or without food, except where specified (see Section 6.1 and Table 4).
- Capsules should be administered approximately 5 minutes apart with divided amounts of fluid (4-8 oz with each capsule for a total of at least 12 oz), except where specified (see Section 6.1)
- Subjects should remain upright for 30 min after taking afuresertib.

In more severe cases of dyspepsia, consider sucralfate and/or aluminum hydroxide with magnesium carbonate as supportive measures. These should be administered at least 2 hours after dosing to avoid any potential drug-drug interactions (see Section 6.1).

- Histamine H₂-receptor antagonists (H₂ blockers) or proton pump inhibitors may also be considered.

If the recommendations above are insufficient to resolve symptoms, or if active ulceration is suspected, investigators should consider additional tests such as upper endoscopy or barium radiography.

6.7.6. Guidelines for Management of Mucositis

Ulceration throughout the GI tract was observed in nonclinical studies of afuresertib. Mucositis has also been reported as a consequence of treatment with AKT inhibitors. Prophylaxis for mucositis is recommended in subjects who are receiving afuresertib. This should include good oral hygiene (e.g., soft toothbrushes, rinsing and cleaning the oral cavity with water after every meal, and removal of dentures at the first sign of oral pain or inflammation) and preventive measures for lower GI symptoms (e.g., maintaining adequate hydration, reducing dairy intake in the event of lactose intolerance). Afuresertib should be held for episodes of mucositis \geq Grade 2. Recommended supportive measures include the following:

- Institute a soft diet and avoid acidic, salty, or dry foods
- Provide topical analgesics (e.g., 2% lidocaine solution), or coating agents. Parenteral analgesia may be required for more severe events.
- Work-up for infection, including oral candidiasis and viral infections. Empiric antibiotic treatment may be required while awaiting culture results, especially if high-grade neutropenia is present concurrently.
- Administer H2 blockers or proton-pump inhibitor if epigastric symptoms are also present.

Hospitalization may be required for more severe cases, especially if IV hydration, parenteral analgesia, or supplemental nutrition is required. Investigators should discuss afuresertib dosing with a Novartis Medical Lead before reinstating treatment after an episode of Grade 3 or 4 mucositis.

6.7.7. Liver Chemistry Stopping Criteria

Liver chemistry stopping and follow-up criteria have been designed to assure subject safety and evaluate liver event etiology in alignment with the United States (US) Food and Drug Administration (FDA) premarketing clinical liver safety guidance. Liver chemistry stopping criteria 1 to 4 are defined as follows:

1. Alanine aminotransferase (ALT) \geq 3 times upper limit of normal (ULN) **and** bilirubin \geq 2 times ULN (>35% direct bilirubin), or ALT \geq 3 times ULN and INR >1.5, if INR is measured).
 - **NOTE:** Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, study treatment(s) should be discontinued if ALT \geq 3 times ULN **and** bilirubin \geq 2 times ULN. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8 xULN
3. ALT ≥ 3 xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity symptoms (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia); or
4. ALT ≥ 3 xULN persists for more than 4 weeks or ALT ≥ 3 xULN and subject can't be monitored weekly for 4 weeks.

6.7.7.1. Actions if Liver Chemistry Stopping Criteria are met

When any of the liver chemistry stopping criteria are met, do the following:

- **Immediately discontinue** investigational product.
- Report the event to Novartis **within 24 hours** of learning its occurrence.
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE.
- All events of ALT ≥ 3 xULN and bilirubin ≥ 2 xULN (>35% direct bilirubin) (or ALT ≥ 3 xULN and INR >1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE**.
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Follow-up for overall survival is required following permanent discontinuation from investigational product.
- Do not re-challenge with investigational product.

In addition, for criterion 1 in Section 6.7.7:

- Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 6.7.7.2), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin) resolve, stabilize or return to within baseline values.
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin) resolve, stabilize or return to within baseline values.

In addition, for subjects meeting any of the criteria 2-4 in Section 6.7.7:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (refer to Section [6.7.7.2](#)).

Monitor subjects weekly until liver chemistries (ALT, AST, ALP, bilirubin) resolve, stabilize or return to within baseline values.

Also, refer to [Appendix 3, Liver Chemistry Testing Procedures](#), for details of the assessments required if a subject meets any of the above criteria in the absence of disease progression.

6.7.7.2. Liver Event Follow-Up Assessments

For subjects meeting any of the liver chemistry stopping criteria, make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology including:
 - Hepatitis A Immunoglobulin M (IgM) antibody
 - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
 - Hepatitis C RNA.
 - Cytomegalovirus IgM antibody
 - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
 - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within 10 days of last dose of study treatment(s). Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment(s) prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2 times ULN.
- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE report form.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form.

The following assessments are required for subjects with ALT ≥ 3 times ULN and bilirubin ≥ 2 times ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use) (James LP. Drug Metab Disp 2009; 37:1779–1784).
- Liver imaging (ultrasound, magnetic resonance imaging [MRI], or computerized tomography [CT]) to evaluate liver disease.

6.7.7.3. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥ 3 times ULN **but** < 5 times ULN **and** bilirubin < 2 times ULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:

- Notify the Novartis Medical Lead within 24 hours of learning of the abnormality to discuss subject safety.
- Continue study treatment(s).
- Return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline.
- If at any time the subject meets any of the liver chemistry stopping criteria 1 to 5, proceed as described above.
- If, after 4 weeks of monitoring, ALT < 3 times ULN and bilirubin < 2 times ULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

Refer to [Appendix 3](#) for algorithm of liver chemistry stopping and follow-up criteria.

6.7.7.4. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval by Novartis after discussion with Novartis Medical Lead for drug restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required;
- If the restart/rechallenge is approved by Novartis in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death;

- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart;
- Study drug must be administered at the dose specified by Novartis; and
- Subjects approved by Novartis for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

6.7.8. QTc Withdrawal Criteria

QTc should be assessed at the frequency shown in [Appendix 1](#): Time and Events Table for Cohort A and B or [Appendix 2](#): Time and Events Table for Cohort C.

A subject that meets the criteria below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.

- QTcF > 500 msec or uncorrected QT >600 msec
- If subject has underlying bundle branch block then the QTc withdrawal criteria depends on the baseline value:

Baseline QTc value (with underlying bundle branch block)	QTc withdrawal criteria
<450 ms	>500 ms
450-470 ms	≥530 ms

Withdrawal decisions are to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

6.8. Blinding

This is an open-label study.

6.9. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of Novartis investigational product (IP) dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on IP accountability.

6.10. Treatment Compliance

Compliance with afuresertib will be assessed through pill counts, and querying the subject during the site visits and documented in the source documents and eCRF.

When dosing occurs outside of the study site, the subject will return all unused investigational product in the dispensed container on each return visit to the clinic, and study staff will note the number of capsules or tablets returned in the source documents. Subjects will maintain a daily dosing diary.

A record of the number of afuresertib capsules or tablets must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment interruptions and/or dose reductions will also be recorded in the eCRF.

7. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF).

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by Novartis and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

7.1. Permitted Medication(s) and non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Paracetamol or acetaminophen, at the label-recommended dose, is permitted.

Medications which contain paracetamol or acetaminophen should be counted in label recommended dose. Other concomitant medication may be considered on a case by case basis by the Novartis Medical Lead.

Concurrent treatment with bisphosphonates is permitted. Prophylactic use of bisphosphonates in subjects without metastatic bone disease is not permitted, except for the treatment of osteoporosis.

Current use of warfarin for therapeutic anticoagulation is not allowed (Note: low molecular weight heparin is permitted). Their use must be monitored in accordance with local institutional practice.

7.2. Prohibited Medication(s) and Non-Drug Therapies

Subjects should not receive anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormone therapy other than for replacement, surgery, and/or tumor embolization) directed towards the tumor for which they have been enrolled on the trial while on treatment in this study; although palliative radiation to control pain may be used following discussion with the Novartis Medical Lead.

Subjects should abstain from taking any herbal and dietary supplements within 5 half lives (or 14 days if the drug is a potential enzyme inducer) prior to study drug(s) dosing and until completion of the follow-up visit, unless there is little concern for a potential drug-drug interaction with the study drug(s). These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. The investigator should contact a Novartis Medical Lead before initiating study treatment in a subject taking any herbal preparation.

Short courses (up to 7 days) of oral corticosteroids intended to treat study treatment related rash or diarrhea are allowed.

Erythropoiesis-stimulating agents and colony-stimulating factors like filgrastim and pegfilgrastim may be used as clinically indicated.

7.2.1. Drugs Potentially Affected by Afuresertib (afuresertib perpetrator interaction potential)

In vitro data indicate that afuresertib has the potential of being a perpetrator in drug-drug interactions through enzyme inhibition (with substrates of CYP3A4 and 2C8, IC₅₀ estimates of 3.7 to 6.0 μM and 6.3 μM, respectively), through transporter inhibition (with substrates of OATP1B1 and BCRP, IC₅₀ estimates of 1.7 μM and 2.9 μM) (Table 7). Co-administration of afuresertib and medications which are a sensitive substrate of CYP3A4, OATP1B1 and BCRP with a low therapeutic index will be prohibited. Co-administration of afuresertib and medications which are a sensitive substrate of CYP2C8 with a low therapeutic index will be used with caution. Other drugs affected by these enzymes and transporters should be used with caution and please refer to SPM.

Table 7 Drugs potentially affected by afuresertib

AVOID:

CYP3A Substrate	Therapeutic Area
carbamazepine	Anticonvulsants
ergotamine, dihydroergotamine	Antimigraine
pimozide	Antipsychotics
amiodarone, disopyramide, quinidine, bosentan	Cardiovascular Agents
cyclosporine, everolimus, sirolimus, tacrolimus	Immunosuppressive Agents
OAT1B1 Substrate	Therapeutic Area
methotrexate	Anti-cancer

BCRP Substrate	Therapeutic Area
topotecan	Anti-cancer
Note: Boceprevir and telaprevir (anti-HCV drugs) should be used with caution when combining with afuresertib.	

Table 8 Drugs Potentially Affected by Afuresertib:

Use with Caution

Generic Drug Name ¹	Therapeutic Class
CYP3A Substrate	
fentanyl	Analgesics
alfentanil, ropivacaine	Anesthetics
losartan	Angiotensin II inhibitors
ethosuximide, trimethadione	Anticonvulsants
buspirone, roboxetine, sertraline, trazodone, venlafaxine	Antidepressants/Anxiolytics
emadastine, loratadine	Antihistamines
artemether, halofantrine, lumefantrine, quinine	Antimalarial
erythromycin, clindamycin, rifabutin, rifampin	Antimicrobials
eletriptan	Antimigraine
α -dihydroergocriptine, bromocriptine	Anti-Parkinsonians
aripiprazole, bromperidol, clozapine, haloperidol, quetiapine	Antipsychotics
oxybutynin, tolterodine	Antispasmodics
osentan, delaviridine, tipranavir, nelfinavir	Antivirals
amlodipine, barnidipine, diltiazem, dofetilide, dronedarone, eplerenone, felodipine, nifedipine, pranidipine, propafenone, verapamil, vesnarinone	Cardiovascular Agents
sildenafil, tadalafil, vardenafil	Erectile dysfunction treatments
aprepitant, lansoprazole	Gastrointestinal Agents
atrovastatin, lovastatin, simvastatin	HMG CoA reductase inhibitors ²
alprazolam, chlordiazepoxide, diazepam, flunitrazepam, midazolam, propofol, triazolam, zolpidem, zopiclone	Hypnotics and Sedatives
pioglitazone, repaglinide, rosiglitazone	Hypoglycemic agents
temsirolimus	Immunosuppressive Agents

1. Please note some drugs may be listed more than once. This is due to the fact that they are substrates for both CYP and a transporter (e.g., OATP1B1, BCRP).
2. If subjects are on a high dose of a HMG CoA reductase inhibitor, dose reduction should be considered. Monitoring for toxicities (such as rhabdomyolysis) should be considered.

7.2.1.1. Drugs that may potentially affect afuresertib (perpetrators)

The metabolism of afuresertib may be mediated by CYP450 isozymes which may include CYP3A4 with possible contributions from CYP2D6 and CYP1A2. Afuresertib is a substrate of human P-gp and of murine Bcrp1. However, the relative contribution of the various pathways to the elimination of afuresertib is presently unknown. Substances that potently inhibit or induce these enzymes/transporters could lead to alterations in the pharmacologic effects of afuresertib and potentially much higher/lower exposure in subjects. Those medications which may alter afuresertib elimination and should be administered with caution and please refer to SPM.

Table 9 Drugs that may Potentially Affect Afuresertib: Use with Caution

Generic Drug Name	Therapeutic Class
quinidine	Antiarrhythmics
fluvoxamine, fluoxetine, nefazodone, paroxetine	Antidepressants
fluconazole, itraconazole, ketoconazole, terbinafine, voriconazole	Antifungals
ciprofloxacin, clarithromycin, erythromycin, isoniazid, telithromycin, troleandomycin	Anti-infectives
amprenavir, atazanavir, delaviridine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir	Antivirals
all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)	Antibiotics
phenobarbital, oxandrolone, tizanidine, gemfibrozil	Miscellaneous

8. LIFESTYLE AND/OR DIETARY RESTRICTIONS

8.1. Contraception Requirements

8.1.1. Female Subjects

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Contraceptive Methods with a Failure Rate of \leq 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the <1% effectiveness criteria as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

8.1.2. Male Subjects

To prevent pregnancy in a female partner or to prevent exposure of any partner to the investigational product from a male subject's semen, male subjects must use one of the following contraceptive methods:

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Condom (*during non-vaginal intercourse with any partner - male or female*) **OR**
- Condom and occlusive cap (diaphragm or cervical/vault caps (*during sexual intercourse with a female*))

8.2. Meals and Dietary Restrictions

Subjects may take afuresertib without regard to food. For combination medications, please use its meal and dietary restrictions. Subject should take afuresertib dose at approximately same time each day.

In addition, subjects shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pommelos within 7 days prior to the first dose of afuresertib until the end of the study.

8.3. Activity

Subjects will abstain from strenuous exercise for 48 hr prior to each blood collection for clinical laboratory tests.

9. DATA MANAGEMENT

For this study, data will be collected using the eCRFs, transmitted electronically to the sponsor (or designee) and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Novartis standards and data cleaning procedures to ensure the integrity of the data, e.g., resolving errors and inconsistencies in the data. AEs and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and custom drug dictionary.

All laboratory data (i.e., hematology, clinical chemistry, liver function, coagulation, and serum pregnancy tests) will be entered into the eCRF.

10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1. Hypotheses and Treatment Comparisons

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

10.2. Sample Size Considerations

10.2.1. Sample Size Assumptions

As this is a roll-over study, no specific sample size considerations are required. The sample size will be based on the number of subjects completing their parent study of afuresertib and are eligible for inclusion in this rollover study.

10.2.2. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

The **All Treated Subjects Population** will consist of all subjects that receive at least one dose of afuresertib in this rollover study. Safety data will be evaluated based on this population.

10.3.2. Analysis Data Sets

Construction of data sets relating to the reporting and analysis of study data will be performed in accordance with all applicable Novartis standards and procedures.

10.3.3. Interim Analysis

No formal interim analysis is planned for this study.

10.3.4. Key Elements of Analysis Plan

Data will be listed and summarized according to the Novartis reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis. Summaries may be provided grouped by appropriate subject populations.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

Demographic and baseline characteristics will be summarized by cohort and for total subjects. Complete details of the safety analyses will be provided in the RAP.

10.3.5. Safety Analyses

10.3.5.1. Extent of Exposure

The number of subjects administered study treatment(s) will be listed and summarized by cohort according to the duration of therapy.

10.3.5.2. Adverse Events

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

Events will be summarized by frequency, cohort and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, drug-related AEs, serious AEs and AEs leading to discontinuation of study treatment(s).

If the AE is listed in the NCI CTCAE (version 4.0) table, the maximum grade will be summarized.

Characteristics (e.g., number of occurrences, action taken, grade, etc) of the following AEs of special interest, but not restricted to them may be listed or summarized separately: elevated liver enzymes hyperglycemia, nausea, fatigue, vomiting, anemia, diarrhea, abdominal pain, headache, rash, dyspepsia, mucositis and neutropenia.

If the data warrant, the incidence of deaths and the primary cause of death will be listed.

10.3.5.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be listed for each subject and summarized at each scheduled assessment according to NCI-CTCAE grade (version 4.0). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI-CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). 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). Further details will be provided in the RAP.

10.3.5.4. Other Safety Measures

The results of scheduled assessments of vital signs, 12-lead ECG, and ECHO/MUGA scan will be listed for each subject and summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Further details will be provided in the RAP.

10.3.5.5. Clinical Activity Analyses

No efficacy analysis is planned for this study.

11. STUDY CONDUCT CONSIDERATIONS

11.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on clinicaltrials.gov before enrollment of subjects begins.

11.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Novartis will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements including a US IND.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/IEC review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

Novartis will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study. The consent process will be conducted during the Transition Visit.

11.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the IEC/IRB is notified.

11.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, ICH GCP, and Novartis procedures, Novartis personnel (or designated Clinical Research Organization [CRO]) will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and

their responsibilities to satisfy regulatory, ethical, and Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time of their staff to the monitor to discuss any findings and issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.5. Quality Assurance

To ensure compliance with ICH GCP and all applicable regulatory requirements, Novartis may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

11.6. Study and Site Closure

The end of the study will be defined as the date of the final study visit of the last subject enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and Novartis Standard Operating Procedures.

Novartis reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Novartis determines that such action is required, Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, Novartis will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, Novartis will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Novartis will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

11.7. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Novartis audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify Novartis of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

11.8. Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Novartis site or other mutually-agreeable location.

Novartis will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Novartis aims to post a results summary to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) and other publicly available registers no later than twelve (12) months after the last subject's last visit (LSLV). In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication. When publication is not feasible, please refer to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) for a summary of the trial results.

12. REFERENCES

Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. *Oncogene*. 2005;24:7455-64.

Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia recommendations from an expert panel on behalf of the European Leukemia Net. *Blood*. 2006;108 (6):1809-1920.

Bellacosa A, Testa JR, Moore R, Larue L. A portrait of AKT kinases. *Cancer Biol & Ther*. 2004;3(3):268-75.

Benson III A, Jaffer A, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Induced Diarrhea. *J Clin Oncol* 22:2918-2926. 2004 by American Society of Clinical Oncology

Blade J, Samson, D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. *Br J Hematol*. 1998;102:1115-1123.

Cheson BD, Bennett, JM, Kopecky, KJ, et al. Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003;21 (24):4642-9.

Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. *J Clin Oncol*. 2007;25 (5):579-586.

Cohen MH, Johnson, JR, Pazdur, R. U.S. Food and Drug Administration Drug Approval Summary: Conversion of Imatinib mesylate (STI571; Gleevec) Tablets from Accelerated Approval to Full Approval. *Clin Cancer Res*. 2005;12 (11):12-19.

Cortes J, Rousselot, P, Kim, D-W, et al. Dasatinib induces complete hematologic and cytogenic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in blast crisis. *Blood*. 2007;109 (8):3207-3213.

DeFeo-Jones D, Barnett SF, Fu S, et al. Tumor cell sensitization to apoptotic stimuli by selective inhibition of specific AKT/PKB family members. *Mol Cancer Ther*. 2005;4(2):271-9.

Durie BGM, Harousseau J-L, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006;20(12), 1467-73.

GlaxoSmithKline Document Number 2011N112051_02. LCH115397 Protocol Amendment 2. A Phase 2a, Open Label, Multicenter Study to Assess the Efficacy and Safety of the Oral AKT Inhibitor GSK2110183 in Subjects with Langerhans Cell Histiocytosis. Effective date, 02-Aug-2011.

GlaxoSmithKline Document Number 2011N113491_03. GSK2110183 Investigator's Brochure. Report Date: SEP-2014.

GlaxoSmithKline Document Number RM2008/00788/05 Amendment 5.
GlaxoSmithKline protocol PKB112835, A Phase I, Open-Label, Two-Stage Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of the Oral AKT Inhibitor GSK2110183 in Subjects with Any Hematologic Malignancy.
Effective Date: 16-Feb-2010.

Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*, 2008;111:5446-56.

James, L.P., Letzig, L., Simpson, P.M., Capparelli, E., Roberts, D.W., Hinson, J.A., Davern, T.J., and Lee, W.M. Pharmacokinetics of acetaminophen protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metabolism and Disposition* 37:1779-1784, 2009.

Morgensztern D, McLeod HL. PI3K/AKT/Mtor pathway as target for cancer therapy. *Anti-Cancer Drugs*. 2005;16:797-803.

NCI Common Terminology Criteria for Adverse Events, Version 4, DCTD, NCI, NIH, DHHS, 28 May 2009.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*. 1982;5:649-655.

Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117:4691-4695.

Tanno S, Mitsuuchi Y, et al. AKT activation up-regulates insulin-like growth factor I receptor expression and promotes invasiveness of human pancreatic cancer cells. *Cancer Res*. 2001;61:589-93.

The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994:253-256.

Appendices

Appendix 1: Time and Events Table for Cohort A and B

Assessment/ Procedure	Transition Visit ¹	Continuous Dosing Treatment Period		Final Study Visit
		Every 4 weeks ¹¹ (±3 days) during the first 52 weeks of study treatment	Every 8 weeks ¹¹ (±3 days) After 52 weeks on study treatment	Within 21 days (±7 days) of Last Dose of Study Treatment(s)
Informed Consent ²	X			
Demographics and Parent Study Data	X			
Physical Exam	X	X	X	X
Pregnancy test ³	X	Every 12 weeks		
Vital Signs ⁴	X	X	X	X
Body Weight	X	X	X	X
12-Lead ECG ⁵	X	X	X	X
Clinical Chemistry ⁶	X	X	X	X
Hematology	X	X	X	X
Coagulation (PT/PTT, INR)	X	X	X	X
HbA1c	X	Every 8 weeks		X
TSH	X	Every 8 weeks		X
Triglycerides and Total Cholesterol	X	Every 8 weeks		X
Disease Assessment ⁷	X ⁷	X ⁷		
AE Monitoring ^{8, 9}		<i>Continuous</i>		
Review of Concomitant Medications ¹⁰		<i>Continuous</i>		
GSK2110183 Dosing		<i>Continuous</i>		

- All subjects transitioning from parent study will begin the rollover study based on the last treatment visit completed during the parent study. All Transition Visit assessments/procedures must be completed prior to the first dose of study treatment(s). Assessments/procedures may be used to fulfill the requirements of both the final visit on parent study and transition visit on this study. Results from the final visit on parent study should be recorded in the eCRF as transition values.
- Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with afuresertib is to be continued.
- Serum β -hCG pregnancy tests will be performed on female subjects of childbearing potential at the time of transition from the parent study and every 12 weeks thereafter.
- Vital signs (BP, temperature and pulse rate) should be taken in a semi-supine position and after the subject has rested for at least 5 minutes prior to the reading. Vital signs may be measured more frequently as clinically indicated.
- A single 12-Lead ECG will be performed using a standard 12-lead ECG machine. All ECGs will be taken in a supine position after resting in that position for at least 10 minutes prior to testing.
- Refer to Section 5.4.4 for complete list of clinical laboratory assessments to be performed.
- Disease assessments should be performed per local standard practice using criteria appropriate for disease type and location, no less frequent than every 12 weeks (more frequent assessments - as determined by investigator).

Appendix 1: Time and Events Table for Cohort A and B (Continued)

8. AEs/SAEs will be monitored and recorded beginning on the time of consent until the last study visit.
9. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
10. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
11. Subjects who remain on study treatment >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to once every 8 weeks with approval from the Novartis Medical Lead.

Appendix 2: Time and Events Table for Cohort C

Assessment/ Procedure	Transition Visit ¹	Continuous Dosing Treatment Period		Final Study Visit
		Every 3 or 4 weeks ¹² (±3 days) during the first 52 weeks of study treatment	Every 8 or 9 weeks ¹² (±3 days) After 52 weeks on study treatment	Within 21 days (±7 days) of Last Dose of Study Treatment(s)
Informed Consent ²	X			
Demographics and Parent Study Data	X			
Physical Exam	X	X	X	X
Pregnancy test ³	X	Every 12 weeks		
Vital Signs ⁴	X	X	X	X
Body weight	X	X	X	X
12-Lead ECG ⁵	X	X	X	X
	X			X
Clinical Chemistry ⁷	X	X	X	X
Hematology	X	X	X	X
Coagulation (PT/PTT, INR)	X	X	X	X
HbA1c	X	Every 8 or 9 weeks	X	X
TSH	X	Every 8 or 9 weeks	X	X
Triglycerides and Total Cholesterol	X	Every 8 or 9 weeks	X	X
Disease Assessment ⁸	X ⁸	X ⁸		
AE Monitoring ^{9,10}		<i>Continuous</i>		
Review of Concomitant Medications ¹¹		<i>Continuous</i>		
Afuresertib Dosing		<i>Continuous</i>		

- All subjects transitioning from parent study will begin the rollover study based on the last treatment visit completed during parent study. All Transition Visit assessments/procedures must be completed prior to the first dose of study treatment(s). Assessments/procedures may be used to fulfill the requirements of both the final study visit on parent study and transition visit on this study. Results from the final study visit on parent study should be recorded in the eCRF as transition values.
- Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with afuresertib is to be continued.
- Serum β -hCG pregnancy tests will be performed on female subjects of childbearing potential at the time of transition from the parent study and every 12 weeks thereafter
- Vital signs (BP, temperature and pulse rate) should be taken in a semi-supine position and after the subject has rested for at least 5 minutes prior to the reading. Vital signs may be measured more frequently as clinically indicated.
- A single 12-Lead ECG will be performed using a standard 12-lead ECG machine. All ECGs will be taken in a supine position after resting in that position for at least 10 minutes prior to testing.
- ECHO or MUGA scan should be performed at the transition visit (or within 30 days prior to study entry), and the study final visit (if required).
- Refer to Section 5.4.4 for complete list of clinical laboratory assessments to be performed.
- Disease assessments should be performed per local standard practice using criteria appropriate for disease type and location, no less than every 12 weeks.

Appendix 2: Time and Events Table for Cohort C (Continued)

9. AEs/SAEs will be monitored and recorded beginning on the time of consent until the last study visit.
10. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
11. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
12. If the subject was treated on a 3 weeks schedule during parent study- he/she will remain on this schedule for the first 52 weeks of treatment (including the time on parent study). After 52 weeks the frequency of the visits may/can be reduced to every 8 or 9 weeks. If the subject was on 4-week schedule on the parent study he/she will remain on this schedule for the first 52 weeks (including time on parent study). After 52 weeks the frequency of visits can be decreased to every 8 weeks with approval of Novartis Medical Lead.

Appendix 3: Liver Safety Drug Restart Guidelines

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

Background Information on Drug Restart/Rechallenge

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies.**¹ Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity¹ with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin \geq 2xULN or INR $>$ 1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge^{2,3} or evidence of drug-related preclinical liability / mitochondrial impairment³.

Drug Restart/Rechallenge Process (also see [Figure 2](#))

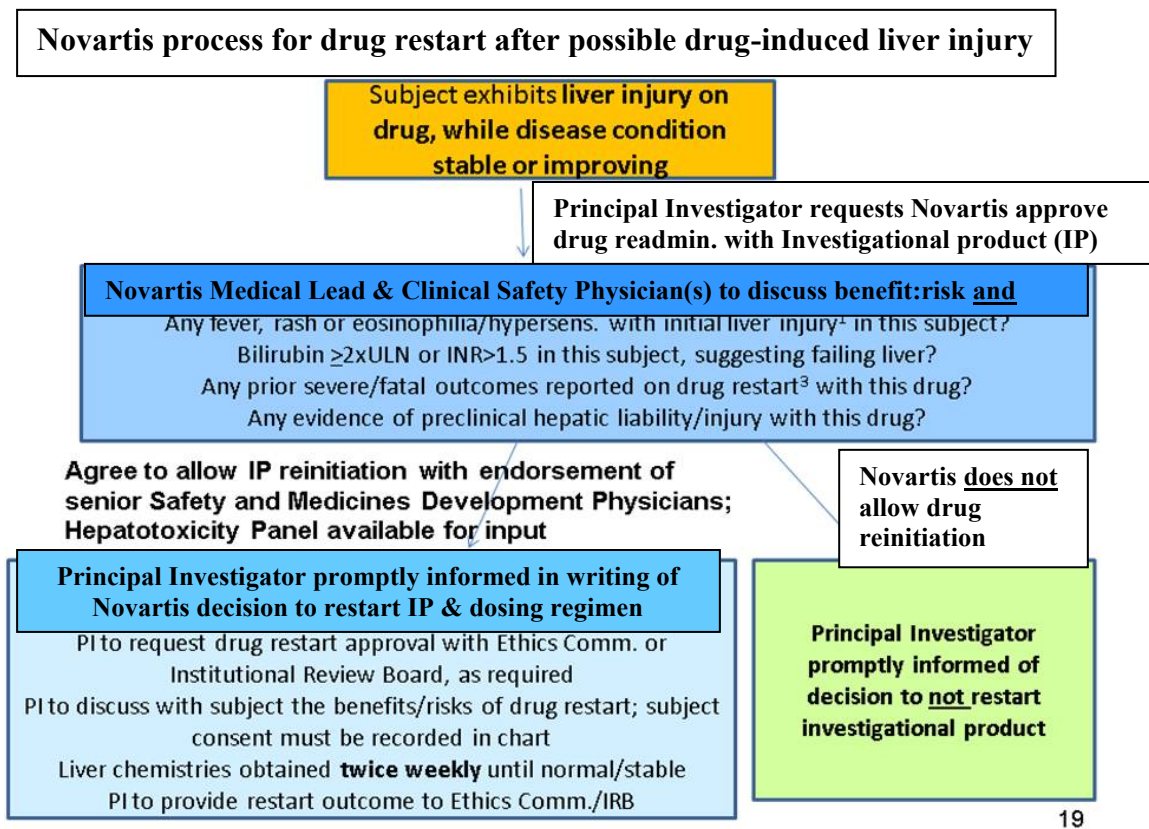
1. Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment.
2. Novartis Medical Lead & Clinical Safety Physician to review the subject's restart/rechallenge risk factors & complete checklist ([Table 10](#))

Table 10 Checklist for drug restart/rechallenge for critical medicine

(Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)		
	Yes	No
Compelling benefit of the investigational product (IP) for this subject and no alternative therapy. Provide brief explanation:		
Relative benefit-risk favorable for drug restart/rechallenge , after considering the following high risk factors:		
• Initial liver injury event included:		
– fever, rash, eosinophilia, or hypersensitivity		
– or bilirubin \geq 2xULN (direct bilirubin $>$ 35% of total)		
• Subject <u>currently</u> exhibits ALT \geq 3xULN, bilirubin \geq 2xULN (direct bilirubin $>$ 35% of total, if available), <u>or</u> INR \geq 1.5		
• Severe or fatal restart/rechallenge has earlier been observed with IP If yes, please provide brief explanation:		
• IP associated with known preclinical hepatic liability/ injury		

3. If Novartis provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:
- The PI is to obtain Ethics Committee or Institutional Review Board review of drug re-initiation, as required.
 - PI must discuss the possible benefits and risks of drug re-initiation with the subject.
 - The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent specifically for the IP restart must be recorded in the study chart.
 - The drug must be reinitiated at Novartis approved dose(s).
 - Subjects approved by Novartis for restart of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.
 - The Ethics Committee or Institutional Review Board is to be informed of the subject's outcome, as required.
 - Novartis is to be notified of any adverse events, as per Section 5.9.

Figure 2 Algorithm for Drug Restart After Possible Drug-induced Liver Injury



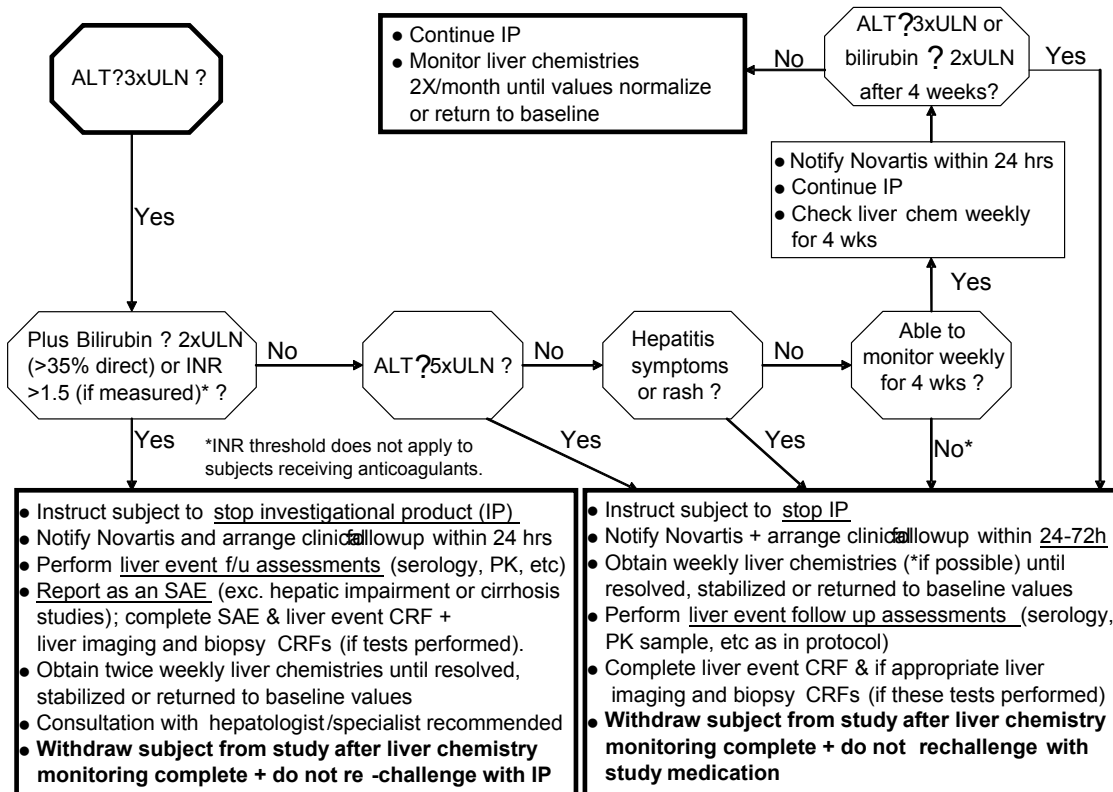
¹Andrade RJ. Expert Opin Drug Saf 2009;8:709-714. ²Papay JI. Regul Tox Pharm 2009;54:84-90. ³Hunt CM. Hepatol 2010;52:2216-2222.

References:

1. Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf 2009;8:709-714.
2. Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. Regul Toxicol Pharmacol 2009;54:84-90.
3. Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: a systematic review. Hepatology 2010;52:2216-2222

Liver Safety Algorithms

Flow chart for Phase II studies:



Appendix 4: COCKCROFT-GAULT FORMULA

$CL_{Cr}(\text{mL}/\text{min}) =$	$Q \times (140 - \text{age}[\text{yr}]) \times \text{ideal body wt} [\text{kg}]^*$ $72 \times \text{serum creatinine} [\text{mg}/\text{dL}]$
$Q = 0.85$ for females	
$Q = 1.0$ for males	
OR	
$CL_{Cr}(\text{mL}/\text{min}) =$	$K \times (140 - \text{age}[\text{yr}]) \times \text{ideal body wt} [\text{kg}]^*$ $\text{Serum creatinine} [\mu\text{mol}/\text{L}]$
$K = 1.0$ for females	
$K = 1.23$ for males	

*Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]

Ideal body weight

Males = $50.0 \text{ kg} + (2.3 \text{ kg} \times \text{each inch over 5 feet})$ or $50.0 \text{ kg} + (0.906 \text{ kg} \times \text{each cm over } 152.4 \text{ cm})$

Females = $45.5 \text{ kg} + (2.3 \text{ kg} \times \text{each inch over 5 feet})$ or $45.5 \text{ kg} + (0.906 \text{ kg} \times \text{each cm over } 152.4 \text{ cm})$

Example 1: Male, actual body weight = 90.0 kg, height = 68 inches.
Ideal body weight = $50.0 + (2.3) (68 - 60) = 68.4 \text{ kg}$.

This subject's actual body weight is > 30% over ideal body weight. Therefore, in this case, the subject's ideal body weight of 68.4 kg should be used in calculating estimated creatinine clearance.

References

Devine, BJ. Case Number 25 Gentamicin Therapy: Clinical Pharmacology Case Studies. Drug Intelligence and Clinical Pharmacy. 1974; 8:650-655

Appendix 5: Disease Assessments and Response Criteria

Chronic Lymphocytic Leukemia (CLL) [Hallek, 2008]		
	Within 4 weeks of transition visit	every 12 weeks ³
Imaging as clinically indicated ¹	X	X
Bone marrow aspirate/biopsy ²	X	X

- Investigator discretion as to type
- Bone marrow evaluation for cellular morphology, cytogenetics, flow cytometry, and molecular studies as clinically indicated.
- The intervals of disease assessments may be shorter if investigator feels that it is necessary

Chronic Myelogenous Leukemia (CML) [Baccarani, 2006; Cohen, 2005; Cortes, 2007]		
	Within 4 weeks of Transition visit	every 12 weeks
BCR-ABL by RT-PCR	X	X
Bone marrow aspirate/ biopsy ¹	X	X

- Bone marrow evaluation for cellular morphology, cytogenetics, flow cytometry, and molecular studies as clinically indicated.

Multiple Myeloma (MM) [Rajkumar, 2011, Durie, 2006, Blade, 1998]		
	Within 4 weeks of Transition visit	Every 4 weeks within the first 52 weeks of treatment and at least every 12 weeks thereafter
SPEP and UPEP or M-protein quantitation & immunofixation	X	x
24h urine collection for M-protein or light chain quantitation	X	X ²
κ/λ ratio	X	X
Imaging ³	X	X
Bone marrow aspirate/biopsy ⁴	X	X ⁵

- Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP); UPEP only if subject has monoclonal paraprotein in urine at original disease assessment prior to Day 1, Cycle 1 dosing.
- 24h urine collection only required for subjects with monoclonal paraprotein found in original disease assessment collection prior to Day 1, Cycle 1 dosing.
- Investigator discretion as to type.
- Bone marrow evaluation for cellular morphology, cytogenetics, flow cytometry, and molecular studies as clinically indicated.
- Not necessary to repeat bone marrow biopsy if monoclonal protein absence in both serum and urine has been sustained for six weeks → except for subjects with non-secretory multiple myeloma.

Malignant Lymphoma (ML) [Cheson, 2007]		
	Within 4 weeks of transition visit	Every 12 weeks
Imaging (Investigator discretion as to type)	X	X
Bone marrow aspirate/biopsy ^{1,2}	X	X

- Bone marrow evaluation for cellular morphology, cytogenetics, flow cytometry, and molecular studies as clinically indicated.
- Needed only if subject with lymphomatous involvement of bone marrow

AML and ALL [Cheson, 2003]			
	Within 4 weeks of transition visit	D1 of each cycle	Every 12 weeks, or more often if needed
CDC with differential ¹	X	x	
Bone marrow aspirate/biopsy ²	X		X

1. Flow cytometry per investigator's discretion.
2. Bone marrow evaluation for cellular morphology, cytogenetics, flow cytometry, and molecular studies as clinically indicated.

Langerhans Cell Histiocytosis (LCH)		
	Within 4 weeks of transition visit	Every 12 weeks
Imaging (Investigator discretion as to type)	X	X
Bone marrow ¹	X	X
Pulmonary function tests ²	X	X

1. Bone marrow evaluation only if clinically indicated
2. Needed in subjects with pulmonary involvement

Response Criteria for Chronic Lymphocytic Leukemia (CLL)

[Hallek, 2008]

Complete remission (CR): The presence of all of the following for ≥ 2 months.

- Peripheral blood lymphocytes $< 4000/\mu\text{L}$
- Absence of lymphadenopathy, hepatomegaly, and splenomegaly by physical exam and appropriate radiographic imaging.
- Absence of constitutional symptoms.
- Normal CBC defined as polymorphonuclear lymphocytes $\geq 1500/\mu\text{L}$ (without growth factors), platelets $> 100,000/\mu\text{L}$ (without growth factors), and hemoglobin $> 11.0\text{g/dL}$ (untransfused).
- Bone marrow aspirate and biopsy (2 months after all the requirements above are met) that is at least normocellular for age with $< 30\%$ of nucleated cells being lymphocytes and has no lymphoid nodules.

Partial remission (PR): The presence of $\geq 50\%$ decrease in peripheral blood lymphocyte count from pre-treatment baseline value and a $\geq 50\%$ reduction in lymphadenopathy, and/or $\geq 50\%$ reduction in the size of the liver and/or spleen, as well as one or more of the following features for ≥ 2 months.

- Polymorphonuclear lymphocytes $\geq 1500/\mu\text{L}$ without growth factors.
- Platelets $> 100,000/\mu\text{L}$ or 50% improvement over baseline without growth factors.
- Hemoglobin $> 11.0\text{g/dL}$ or 50% improvement over baseline without transfusions.

Progressive disease (PD): At least one of the following.

- Appearance of any new lesions such as lymph nodes >1.5 cm or increase of $\geq 50\%$ in the greatest determined diameter
- $\geq 50\%$ increase in the size of the liver and/or spleen as determined by measurement below the respective costal margin or appearance of palpable hepatomegaly/splenomegaly which was not previously present.
- $\geq 50\%$ increase in the absolute number of circulating lymphocytes to at least 5000/ μL B lymphocytes.
- Transformation to a more aggressive histology (e.g., Richter's syndrome or PLL with >55% prolymphocytes).
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL

Stable disease (SD): Not meeting criteria for complete remission, partial remission or progressive disease.

Response Criteria for Chronic Myelogenous Leukemia (CML)

[[Baccarani, 2006](#); [Cohen, 2005](#); [Cortes, 2007](#)]

Hematologic response criteria (all responses to be confirmed after \geq four week):

For blast crisis and accelerated phase:

Complete hematologic response (CHR): <5% blasts in bone marrow, no blasts in peripheral blood, ANC $\geq 1500/\mu\text{l}$ and platelets $\geq 100,000/\mu\text{l}$, no extramedullary involvement (e.g., nonpalpable spleen).

No evidence of leukemia (NEL): As for CHR but without complete recovery of peripheral blood (i.e., $1000 \leq$ absolute neutrophil count [ANC] < $1500/\mu\text{L}$ and $20,000 \leq$ platelets < $100,000/\mu\text{L}$).

Partial (minor) hematologic response (PHR): <15% blasts in peripheral blood and bone marrow, <30% blasts + promyelocytes in peripheral blood and bone marrow, <20% basophils in peripheral blood, no extramedullary involvement other than spleen or liver

Chronic phase:

Complete hematologic response (CHR): Platelet count <450,000/ μl , white blood cell count <10,000/ μl , <5% myelocytes + metamyelocytes in peripheral blood, no blasts + promyelocytes in peripheral blood, <20% basophils in peripheral blood, no extramedullary involvement.

Partial (minor) hematologic response (PHR): White blood cell count <10,000/ μL with persistence of immature cells (myelocytes or metamyelocytes) in peripheral blood, splenomegaly < 50% of the pre-treatment level, and thrombocytosis > 450,000/ μL but <50% of pre-treatment level.

Response categories:

Major hematologic response: CHR + NEL.

Overall hematologic response: CHR + NEL + PHR.

Progressive disease in responding subjects: Subjects with CHR, NEL, or PHR who lose response over 6 weeks.

Progressive disease in non-responders: Subjects with no change in baseline levels of % blasts in peripheral blood or bone marrow on all assessments over 6 week period.

Cytogenetic response:

Complete cytogenetic response: 0% Ph positive cells detectable on metaphase cytogenetic evaluation of bone marrow aspirate with 20 to 25 cells analyzed. Values maintained over 3 week period.

Partial cytogenetic response: 1 to 35% Ph positive cells detectable on metaphase cytogenetic evaluation of bone marrow aspirate with 20 to 25 cells analyzed. Values maintained over 3 week period.

Minor cytogenetic response: 36 to 65% Ph positive cells detectable on metaphase cytogenetic evaluation of bone marrow aspirate with 20 to 25 cells analyzed. Values maintained over 3 week period.

Minimal cytogenetic response: 66 to 95% Ph positive cells detectable on metaphase cytogenetic evaluation of bone marrow aspirate with 20 to 25 cells analyzed. Values maintained over 3 week period.

No cytogenetic response: >95% Ph positive cells detectable on metaphase cytogenetic evaluation of bone marrow aspirate with 20 to 25 cells analyzed. Values maintained over 3 week period.

Molecular response:

Complete molecular response: No evidence of BCR-ABL mRNA by RT-PCR in peripheral blood. Values maintained over 3 week period.

Major molecular response: ≥ 3 log reduction in detectable BCR-ABL mRNA in peripheral blood. Values maintained over 3 week period.

Response Criteria for Multiple Myeloma (MM)

[[Rajkumar, 2011](#)]

sCR (stringent complete response):

Complete response as defined below plus:

- normal free light chain (FLC) ratio and
- absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry

CR (complete response):

- Negative serum and urine immunofixation, and
- Disappearance of any soft tissue plasmacytomas, and
- <5% plasma cells in bone marrow

VGPR (very good partial response):

- Serum and urine M-component detectable by immunofixation but not on electrophoresis **OR**
- 90% or greater reduction in serum M- component plus urine M- component < 100mg/24h

PR (partial response):

- $\geq 50\%$ reduction of serum M-protein and reduction in 24 hour urinary M-protein by $\geq 90\%$ or to < 200 mg/24h, and
- If the serum and urine M-protein are not measurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, $\geq 50\%$ reduction in bone marrow plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$, and
- In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size of the soft tissue plasmacytomas is also required.

SD (stable disease):

- Not meeting criteria for CR, VGPR, PR or PD

PD (progressive disease)^a

Requires any one or more of the following:

- Increase of $\geq 25\%$ from lowest response value in any one or more of the following:
 - serum M-component (absolute increase must be ≥ 0.5 g/dl), or
 - urine M-component (absolute increase must be ≥ 200 mg/24h), or
 - the difference between involved and uninvolved free light chain levels (absolute increase must be > 10 mg/dl): only for patients without measurable serum and urine M-protein levels, or

- bone marrow plasma cell percentage (the absolute % must be $\geq 10\%$) – only for patients without measurable serum and urine M-protein levels and without measurable disease by FLC level
- definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- development of hypercalcemia (corrected calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
- All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.
- Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a $> 90\%$ decrease in the difference between involved and uninvolved FLC levels.
- Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; “25% increase” refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value

References

Durie BGM, Harousseau J-L, Miguel JS, et. al. International uniform response criteria for multiple myeloma. *Leukemia*, 2006;20: 1467-73.

Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117:4691-4695.

Response Criteria for Malignant Lymphoma

[[Cheson, 2003](#); [Cheson, 2007](#)]

General Comments:

- Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0 cm. Lymph nodes $\leq 1.0 \times \leq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.

- Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is assessable but not quantifiable (*e.g.* pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted on imaging studies or physical examination, it is found to be histologically negative.
- Where PET is unavailable, unnecessary, or inappropriate for use, response should be assessed as below, but only using CT scans.

Complete Response: Requires the following:

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- Typically FDG-avid lymphoma: in subjects with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies. Nodules related to lymphoma should disappear.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry (IHC). A sample that is negative by IHC but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in subject outcome.

Partial Response: Requires all of the following

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by $\geq 50\%$ in their SPD or, for single nodules, in the great transverse diameter.
4. With the exception of splenic or hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (*e.g.*, large cell lymphoma or small neoplastic B cells). Subjects who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, subjects should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for subjects with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG avidity unknown: for subjects without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.
9. In subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable disease: Defined as the following

- A subject is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.
- Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- Variably FDG-avid lymphoma/FDG-avidity unknown: for subjects without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR or SD):

- Appearance of any new lesion more than 1.5 cm in size in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapse or progressive disease after confirmation with other modalities. In subjects with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus a therapeutic decision should not be made solely on the basis of the PET without histological confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (*e.g.* splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5 X 1.5 cm or more than 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (<1.5 cm in its long axis by CT)

Response Criteria for Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL)

[[Cheson, 2003](#)]

Morphologic leukemia-free state*: $<5\%$ blasts in a bone marrow aspirate sample with marrow spicules, a count of at least 200 nucleated cells, and no visible Auer rods.

Morphologic complete remission*: absence of peripheral blasts; $<5\%$ blasts in a bone marrow aspirate sample with marrow spicules, a count of at least 200 nucleated cells, and no visible Auer rods; ANC $\geq 1000/\mu\text{L}$; platelets $\geq 100,000/\mu\text{L}$; and transfusion independent.

Morphologic complete remission with incomplete blood count recovery*: absence of peripheral blasts, $<5\%$ blasts in a bone marrow aspirate sample with marrow spicules and a count of at least 200 nucleated cells and no visible Auer rods, residual neutropenia (ANC $<1000/\mu\text{L}$) and/or thrombocytopenia (platelets $<100,000/\mu\text{L}$).

Cytogenetic complete remission*: Subject in morphologic complete remission and normal karyotype on bone marrow aspirate with 20 to 25 metaphase cells analyzed.

Molecular complete remission*: Subject in morphologic and cytogenetic complete remission and no evidence of leukemia by flow cytometry or PCR.

Partial remission: ANC $\geq 1000/\mu\text{L}$; platelets $\geq 100,000/\mu\text{L}$; decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate.

Treatment Failure:

- **Residual disease:** Subject survives ≥ 7 days post treatment; persistent AML/ALL in blood or bone marrow.
- **Aplasia:** Subject survives ≥ 7 days post treatment; death while cytopenic with aplastic bone marrow.
- **Indeterminate cause:** Subject who dies < 7 days post treatment; subject who dies > 7 days post treatment with no peripheral blasts, but no bone marrow examination; subject who doesn't complete the first course of therapy.

*NOTE: Extramedullary leukemia such as CNS or soft tissue involvement must be absent.

Definition of Disease State, Response Criteria and Response Definition for Langerhans Cell Histiocytosis (LCH)

Definition of Disease State

NON ACTIVE DISEASE (NAD)	no evidence of disease	resolution of all signs or symptoms
	regressive disease	regression of signs or symptoms, no new lesions*
ACTIVE DISEASE (AD)	stable disease	persistence of signs or symptoms, no new lesions
	progressive disease	progression of signs or symptoms and/or appearance of new lesions**

*Plus partial or complete response by RECIST [Eisenhauer, 2009]; and/or pulmonary criteria if applicable

*/** Isolated pulmonary LCH: improvement in lung function is $> 10\%$ increase in baseline FEV1 or DLCO at time of disease assessment. Disease progression is $> 15\%$ decline from baseline FEV1 or DLCO or FVC OR progression of symptoms (dyspnea, cough, constitutional symptoms) that cannot be explained by diagnoses other than pulmonary LCH (infection, heart disease, and/or other clinical issues excluded by careful clinical evaluation and testing)

** Isolated bone disease: progression is defined as appearance of new bone lesions or lesions in other organs

Response Criteria

BETTER	Complete Resolution	NAD
	Regression	AD Better
INTERMEDIATE	Mixed	New lesions in one site, regression in another site
	Stable	Unchanged
WORSE	Progression	

Response Definition for Efficacy

	3 Month Assessment	6 Month Assessment (performance relative to 3 month assessment)
Response	NAD or AD Better Mixed Stable	NAD or AD Better or Stable NAD or AD Better NAD or AD Better
Failure	NAD or AD Better NAD or AD Better Mixed or Stable ¹ Progression	Mixed Progression Mixed or Stable ¹ or Progression N/A

NAD = Non Active Disease

AD = Active Disease

Stable = Unchanged

Mixed = New lesions in one site, regression in another site

1. Subjects who are assessed only as stable at the 3 and 6 month assessment are not considered a treatment response; however, they may be considered for continued treatment

Appendix 6: RECIST Guidelines

[Eisenhauer, 2009]

Baseline Disease Assessment

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before the beginning of the treatment.

Measurable lesions

Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
- 20 mm by chest X-ray.

Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

- ‘**Lytic bone lesions or mixed lytic-blastic lesions**’ with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
- ‘**Cystic lesions**’ thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Non-measurable lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- **Blastic bone lesions** are non-measurable.

- **Lesions with prior local treatment**, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for **all target lesions** will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-target Lesions

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as **non-target lesions** and be recorded at baseline. Measurements of these lesions are not required and they should be followed as ‘present’, ‘absent’ or in rare cases, ‘unequivocal progression’.

Response Criteria

Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Response Criteria

Special notes on the assessment of target lesions

- **Lymph nodes** identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- **Target lesions that become ‘too small to measure’.** While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’, in which case a default value of 5 mm should be assigned.
- **Lesions that split or coalesce on treatment.** When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR / Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- When patient has measurable disease. To achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- **When patient has only non-measurable disease.** There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an

increase in a pleural effusion from ‘trace’ to ‘large’ or an increase in lymphangitic disease from localized to widespread.

New lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient’s baseline lesions show partial or complete response).
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

It is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Time Point Response

[Table 1](#) provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Overall Responses for all Possible Combinations of Tumor Responses in Target and Non-target Lesions With or Without the Appearance of New Lesions

Target lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; PR partial response; SD = stable disease; and PD = progressive disease.

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, (i.e., in randomized Phase II or III trials or studies where stable disease or progression are the primary endpoints), confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than six to eight weeks) that is defined in the study protocol.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

References

Eisenhauer, E. A., P. Therasse, et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer **45**(2): 228-247.

Appendix 7: Hy's Law

Hy's law is a prognostic indicator of drug-induced liver injury defined as ALT ≥ 3 times ULN and bilirubin ≥ 2 times ULN (>35% direct) (or ALT ≥ 3 times ULN and INR >1.5, if INR is measured).

Appendix 8: Protocol Amendment Changes

AMENDMENT 1

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study.

Summary of Amendment Changes with Rationale

Updated regulatory agency identifying numbers

Updated Investigator's Brochure information with the most recent IB document number 2011N113491

Added disease assessments to 6.1 Transition Visit

Removed central lab wording from Section 6.4.5 Clinical Laboratory Assessments because we are not using central labs

Incorporated liver function tests into the clinical chemistries table (Table 4, Section 6.4.5) to insure that liver function tests would be administered whenever clinical chemistries were due

Updated AE monitoring language

Updated IP storage wording

Updated Table 7 Dose Modifications for GSK2110183

Added standard Acetaminophen protein adduct testing to Liver Event Follow-up Assessments (Section 7.7.7.1). These had been inadvertently left out.

Updated Section 8.2 Prohibited and Cautionary Meds

Updated Section 8.3 Non Drug Therapies

Updated Time & Events Table

Added LCH and Acetaminophen protein adduct testing reference to Sec 13 References

Added Definition of Disease State, Response Criteria and Response Definition for Langerhans Cell Histiocytosis (LCH). These had been inadvertently left out.

List of Specific Changes

Page 3, Regulatory Agency Identifying Numbers

PREVIOUS TEXT

Regulatory Agency Identifying Number [IND 111439]
OCTAGON: Health Canada reference number = 9427-O1624-21C
Australian CTN number = 2009/272.
S. Korea: Receipt number = 20090399355

REVISED TEXT

Regulatory Agency Identifying Number [IND 111439]
[REDACTED] Health Canada reference number = **9427-G0838-279C**
[REDACTED]
S. Korea: Receipt number = **20110110591**

Section 6.4.5 Clinical Laboratory Assessments

PREVIOUS TEXT

Whenever possible, every effort should be made to ensure that laboratory results submitted to GSK are from the designated central laboratory. If laboratory assessments are performed at the institution's local laboratory, please refer to the SPM for appropriate handling of samples to avoid duplicate and/or additional blood draws.

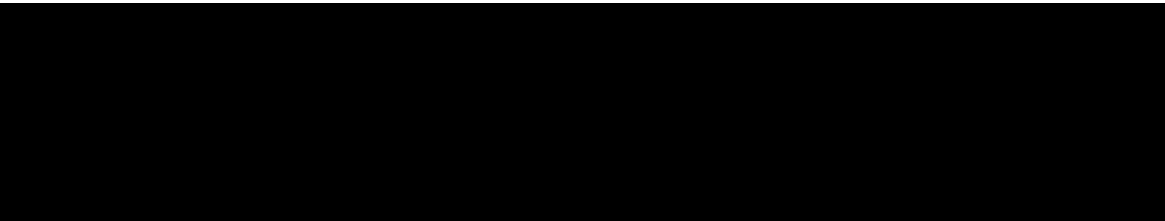


Table 4 List of Clinical Laboratory Assessments, Section 6.4.5 Clinical Laboratory Assessments

PREVIOUS TEXT

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium
Creatinine	Inorganic phosphorus
Sodium	Magnesium
Albumin	Chloride
Calcium	LDH
Bicarbonate	Glucose
Total protein	M-protein ¹

1. For Multiple Myeloma subjects only

Liver Function Tests

AST
ALT
Alkaline Phosphatase
Total bilirubin (bilirubin fractionation recommended if total bilirubin >2 times ULN)

REVISED TEXT

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium
Creatinine	Inorganic phosphorus
Sodium	Magnesium
Albumin	Chloride
Calcium	LDH
Bicarbonate	Glucose
Total protein	M-protein ¹
AST	
ALT	
Alkaline Phosphatase	
Total bilirubin (bilirubin fractionation recommended if total bilirubin >2 times ULN)	

3. For Multiple Myeloma subjects only

Section 6.8.1 Adverse Events

PREVIOUS TEXT

AEs and SAEs will be monitored from the time of consent until 30 days after the last dose of study drug(s). All AEs and SAEs must be recorded and reported as detailed in the following sections and in the SPM. At the time of consent, all ongoing AEs that began during participation in the parent study must be recorded in the eCRF.

REVISED TEXT

AEs and SAEs will be monitored from the time of consent until [REDACTED] -the final study visit. All AEs and SAEs must be recorded and reported as detailed in the following sections and in the SPM. At the time of consent, all ongoing AEs that began during participation in the parent study must be recorded in the eCRF.

Section 6.8.1.5 Time Period and Frequency of Detecting AEs and SAEs

PREVIOUS TEXT

AEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

REVISED TEXT

AEs will be collected from the time the first dose of study treatment is administered until [REDACTED] the final study visit regardless of initiation of a new cancer therapy or transfer to hospice.

Section 7.4 Handling And Storage of Study Treatment

PREVIOUS TEXT

GSK2110183 is to be stored at room temperature and should not exceed 30°C in an opaque bottle.

REVISED TEXT

GSK2110183 is to be stored at room temperature and should not exceed 30°C in an **HDPE white** opaque bottle.

Section 7.6.1 Dose Modifications

PREVIOUS TEXT

Dose Modifications for GSK2110183

TOXICITY ¹	GSK2110183
Grade 1	Continue GSK2110183 at current dose level. Consider supportive care recommendations provided in Section 7.7
Grade 2	Withhold treatment with GSK2110183 until toxicity resolves to Grade 1 or baseline. Upon resolution, restart GSK2110183 at current dose level. Consider supportive care recommendations provided in Section 7.7. Consider dose reduction if toxicity is intolerable to the subject.
Grade 3	Withhold GSK2110183 until toxicity resolves to Grade 1 or baseline. Upon resolution, reduce dose of GSK2110183 to a previously studied lower dose of GSK2110183 ²). Consider supportive care recommendations provided in Section 7.7.
Grade 4	Permanently discontinue treatment with GSK2110183.

1. Considered related to study treatment.
2. Dose level 1: 150mg, Dose level 2: 125mg, Dose level 3: 100mg, Dose level 4:75mg. If subject requires dose reduction below 75mg, then treatment must be discontinued, and subject withdrawn from the study.

Treatment with GSK2110183 may be delayed for up to 14 days to allow resolution of toxicity or based on investigator discretion. If the investigator and the GSK Medical Monitor conclude that continued treatment will benefit a subject who has experienced a treatment delay >14 days, then the subject may continue GSK2110183 therapy with the approval of the GSK Medical Monitor.

A maximum of 2 dose reductions (including reductions from the parent study) of GSK2110183 is permitted and each of them requires consultation with the GSK medical monitor. Dose reductions should be to a lower dose level previously studied in a

GSK2110183 clinical study. If a third dose reduction is required, treatment with GSK2110183 should be discontinued.

REVISED TEXT

Dose Modifications for GSK2110183

TOXICITY ¹	GSK2110183
Grade 1	Continue GSK2110183 at current dose level. Consider supportive care recommendations provided in Section 7.7
Grade 2	Withhold treatment with GSK2110183 until toxicity resolves to Grade 1 or baseline. Upon resolution, restart GSK2110183 at current dose level. Consider supportive care recommendations provided in Section 7.7. Consider dose reduction if toxicity is intolerable to the subject.
Grade 3	Withhold GSK2110183 until toxicity resolves to Grade 1 or baseline. Upon resolution, reduce dose of GSK2110183 by one dose level [REDACTED]. Consider supportive care recommendations provided in Section 7.7.
Grade 4	Permanently discontinue treatment with GSK2110183.

3. Considered related to study treatment.

4. Dose level 1: 150mg, Dose level 2: 125mg, Dose level 3: 100mg, Dose level 4: 75mg. If subject requires dose reduction below 75mg, then treatment must be discontinued, and subject withdrawn from the study.

Treatment with GSK2110183 may be delayed for up to 14 days to allow resolution of toxicity or based on investigator discretion. If the investigator and the GSK Medical Monitor conclude that continued treatment will benefit a subject who has experienced a treatment delay >14 days, then the subject may continue GSK2110183 therapy with the approval of the GSK Medical Monitor.

A maximum of 2 dose reductions (including reductions from the parent study) of GSK2110183 is permitted and each of them requires consultation with the GSK medical monitor. Dose reductions should be to a lower dose level previously studied in a GSK2110183 clinical study. **If a third dose reduction or a dose reduction below 75mg is required, treatment with GSK2110183 should be discontinued and subject should be withdrawn from study.** [REDACTED]

Section 7.7.7.1 Liver Event Follow-up Assessments

PREVIOUS TEXT

The following assessments are required for subjects with ALT ≥ 3 times ULN and bilirubin ≥ 2 times ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance imaging [MRI], or computerized tomography [CT]) to evaluate liver disease.

REVISED TEXT

The following assessments are required for subjects with ALT ≥ 3 times ULN and bilirubin ≥ 2 times ULN (>35% direct) but are optional for other abnormal liver chemistries:


- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- **Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use) (James LP. Drug Metab Disp 2009; 37:1779–1784).**
- Liver imaging (ultrasound, magnetic resonance imaging [MRI], or computerized tomography [CT]) to evaluate liver disease.

Section 8.2 Prohibited and Cautionary Medications

PREVIOUS TEXT

The use of certain medications, and illicit drugs within 5 half-lives or 28 days (if the drug is a potential enzyme inducer) prior to the first dose of study treatment(s) and for the duration of the study will not be allowed. If a prohibited medication is required for single use (such as for a procedure) while study treatment(s) is held, the GSK Medical Monitor can approve such use.

Anticoagulants at therapeutic doses (e.g., warfarin, low molecular weight heparin, direct thrombin inhibitors, etc) are PROHIBITED from seven days prior to the first dose of study drug through completion of the Final Study Visit. Low dose (prophylactic) anticoagulants are permitted provided that subject's PT/PTT meet entry criteria.



The use of certain medications will not be allowed for the duration of the study. If a prohibited medication is required for single use (such as for a procedure) while study treatment(s) is held, the GSK Medical Monitor can approve such use.

Anticoagulants are permitted only if the subject meets PTT and INR entry criteria. Their use must be monitored in accordance with local institutional practice.

Section 8.3 Non-Drug Therapies

PREVIOUS TEXT

The investigator should contact a GSK Medical Monitor before initiating treatment with any herbal preparation.

REVISED TEXT

The investigator should contact a GSK Medical Monitor before initiating treatment with any herbal preparation. **While herbal preparations/medications are prohibited, if one is administered to a subject during the study then that herbal medication will be recorded in the eCRF.**

Section 13 References

PREVIOUS TEXT

GlaxoSmithKline Document Number WM2008/00093/02 Version 2. GSK2110183 Investigator's Brochure. Report Date: 31-AUG-2010.

REVISED TEXT

GlaxoSmithKline Document Number [REDACTED] 2011N113491.
GSK2110183 Investigator's Brochure. Report Date: [REDACTED] 25APR2011.

James, L.P., Letzig, L., Simpson, P.M., Capparelli, E., Roberts, D.W., Hinson, J.A., Davern, T.J., and Lee, W.M. Pharmacokinetics of acetaminophen protein adducts in adults with acetaminophen overdose and acute liver failure. Drug Metabolism and Disposition 37:1779-1784, 2009.

Appendix 1 Time and Events Table

8.Disease assessments should be performed per local standard practice using criteria appropriate for disease type and location, no less frequent than every 12 weeks

9.AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK2110183

8.Disease assessments should be performed per local standard practice using criteria appropriate for disease type and location, no less frequent than every 12 weeks (**more frequent assessments - as determined by investigator**).

9.AEs/SAEs will be monitored and recorded beginning on the time of consent until [REDACTED] [REDACTED] he last study visit.

Appendix 5 Disease Assessments and Response Criteria

REVISED TEXT

Langerhans Cell Histiocytosis (LCH) [Portnoy, 2011]		
	Within 4 weeks of transition visit	Every 12 weeks
Imaging (Investigator discretion as to type)	X	X
Bone marrow ¹	X	X
Pulmonary function tests ²	X	X

3. Bone marrow evaluation only if clinically indicated

4. Needed in subjects with pulmonary involvement

Response Criteria for Multiple Myeloma (MM)

[Rajkumar, 2011, Durie, 2006 ██████████]

sCR (stringent complete response):

Complete response as defined below plus:

- normal free light chain (FLC) ratio and
- absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry

CR (complete response):

- Negative serum and urine immunofixation, and
- Disappearance of any soft tissue plasmacytomas, and
- <5% plasma cells in bone marrow

VGPR (very good partial response):

- Serum and urine M-component detectable by immunofixation but not on electrophoresis OR
- 90% or greater reduction in serum M- component plus urine M- component < 100mg/24h

PR (partial response):

- ≥50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥90% or to < 200 mg/24h, and
- If the serum and urine M-protein are not measurable, a ≥50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria. If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-

**protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$,
and**

- **In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size of the soft tissue plasmacytomas is also required.**

SD (stable disease):

- **Not meeting criteria for CR, VGPR, PR or PD**

PD (progressive disease)^a

Requires any one or more of the following:

- **Increase of $\geq 25\%$ from lowest response value in any one or more of the following:**
 - **serum M-component (absolute increase must be ≥ 0.5 g/dl), or**
 - **urine M-component (absolute increase must be ≥ 200 mg/24h), or**
 - **the difference between involved and uninvolved free light chain levels (absolute increase must be > 10 mg/dl): only for patients without measurable serum and urine M-protein levels, or**
 - **bone marrow plasma cell percentage (the absolute % must be $\geq 10\%$) – only for patients without measurable serum and urine M-protein levels and without measurable disease by FLC level**
- **definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas**
- **development of hypercalcemia (corrected calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder**
- **All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.**
- **Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a $> 90\%$ decrease in the difference between involved and uninvolved FLC levels.**

- **Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; “25% increase” refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the “lowest response value” does not need to be a confirmed value**

References

Durie BGM, Harousseau J-L, Miguel JS, et. al. International uniform response criteria for multiple myeloma. Leukemia, 2006:20: 1467-73.

Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117:4691-4695.

Appendix 5 Disease Assessments and Response Criteria

REVISED TEXT

Definition of Disease State, Response Criteria and Response Definition for Langerhans Cell Histiocytosis (LCH)

Definition of Disease State

NON ACTIVE DISEASE (NAD)	no evidence of disease	resolution of all signs or symptoms
	regressive disease	regression of signs or symptoms, no new lesions*
ACTIVE DISEASE (AD)	stable disease	persistence of signs or symptoms, no new lesions
	progressive disease	progression of signs or symptoms and/or appearance of new lesions**

*Plus partial or complete response by RECIST [Eisenhauer, 2009]; and/or pulmonary criteria if applicable

*/** Isolated pulmonary LCH: improvement in lung function is >10% increase in baseline FEV1 or DLCO at time of disease assessment. Disease progression is >15% decline from baseline FEV1 or DLCO or FVC OR progression of symptoms (dyspnea, cough, constitutional symptoms) that cannot be explained by diagnoses other than pulmonary LCH (infection, heart disease, and/or other clinical issues excluded by careful clinical evaluation and testing)

** Isolated bone disease: progression is defined as appearance of new bone lesions or lesions in other organs

Response Criteria

BETTER	Complete Resolution	NAD
	Regression	AD Better
INTERMEDIATE	Mixed	New lesions in one site, regression in another site
	Stable	Unchanged
WORSE	Progression	

Response Definition for Efficacy

	3 Month Assessment	6 Month Assessment (performance relative to 3 month assessment)
Response	NAD or AD Better Mixed Stable	NAD or AD Better or Stable NAD or AD Better NAD or AD Better
Failure	NAD or AD Better NAD or AD Better Mixed or Stable¹ Progression	Mixed Progression Mixed or Stable¹ or Progression N/A
<p>NAD = Non Active Disease AD = Active Disease Stable = Unchanged Mixed = New lesions in one site, regression in another site 1. Subjects who are assessed only as stable at the 3 and 6 month assessment are not considered a treatment response; however, they may be considered for continued treatment</p>		

AMENDMENT 2

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study.

Summary of Amendment Changes with Rationale

Addition of Immediate Release (IR) tablet description. This description was added because it is now the formulation of Auresertib that is being used. The protocol description, synopsis, study treatments and dosage/administration sections have all been updated to reflect this change.

Since this was an older protocol, GSK2110183 has now been replaced with Auresertib throughout the protocol.

Due to the fact that this is an older protocol, the following updates and changes have been made to bring it up to date:

The introduction, summary of risk management, supportive measures for hyperglycemia, management of diarrhea, rash, dyspepsia, mucositis, liver chemistry stopping criteria, drug restart/rechallenge, con meds and non-drug therapies, meals and dietary restrictions and liver safety drug restart guidelines sections have all been updated with the latest information.

MM specific disease assessments have been added along with the new investigator brochure reference.

AE follow up shortened to 30 days, ECHO/MUGA scans, fasting requirements and combination studies with two investigational compounds ineligibility wording have been removed.

EudraCT number was added.

List of Specific Changes

TITLE PAGE

REVISED TEXT

Description:

Auresertib (GSK2110183) is an orally administered, pan-AKT kinase inhibitor that has demonstrated encouraging clinical activity in hematologic malignancies (especially in multiple myeloma MM), and is currently also being evaluated in clinical trials in solid tumors. This multicenter, non-randomized, open-label, treatment continuation or 'rollover' study is designed to provide continued access to auresertib treatment for eligible subjects who have previously participated in an auresertib 'parent study' sponsored by GlaxoSmithKline (GSK) or another research organization working on behalf of GSK. Eligible subjects must be receiving clinical benefit [REDACTED]

[REDACTED] tolerating treatment with Afuresertib. Subjects who have participated in an afuresertib combination study with another anti-cancer agent will also be eligible to enroll in this rollover study. [REDACTED]

[REDACTED] Subjects will be enrolled by cohort based on the duration and treatment received while in their parent study. Safety assessments (physical examinations, vital sign measurements, 12-lead electrocardiograms, echocardiograms or multiple-gated acquisition scans, clinical laboratory assessments and monitoring of adverse events) will be evaluated during this study. Disease assessment will be performed using local standard of care imaging practices and criteria appropriate for disease type and location.

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

Author (s):

[REDACTED] US [REDACTED],
[REDACTED], US [REDACTED], US
[REDACTED], US
[REDACTED], US
[REDACTED], US

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

REVISED TEXT

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	[REDACTED] MD, PhD	[REDACTED]	[REDACTED]	[REDACTED]	GlaxoSmithKline 1250 South Collegeville Road, Mailstop [REDACTED] Collegeville, PA 19426, USA [REDACTED]
Secondary Medical Monitor	[REDACTED] <u>MD/MPH</u>	[REDACTED]	[REDACTED]	[REDACTED]	GlaxoSmithKline 1250 S Collegeville Road Mailstop [REDACTED] Collegeville, PA USA [REDACTED]

REVISED TEXT

Regulatory Agency Identifying Number US [IND 111439]
Health Canada reference number = 9427-G0838-279C
S. Korea: Receipt number = 20110110591
EudraCT number = **2014-002041-22**

Section ABBREVIATIONS

Added the abbreviation IR (Immediate Release Tablet).

Section PROTOCOL SYNOPSIS

REVISED TEXT

- PRODUCT: Afuresertib (GSK2110183)
- PROTOCOL/AMENDMENT NO.: PKB115131/Amendment 02
- OBJECTIVES: To provide continued treatment with afuresertib for subjects who have completed participation in a GSK-sponsored afuresertib study, or an afuresertib study sponsored by another research organization working on behalf of GSK. Additional safety information about afuresertib will also be collected.
- HYPOTHESES: There are no hypotheses being explored in this treatment continuation or 'rollover' study.
- STUDY DESIGN AND DURATION: Multicenter, non-randomized, open-label, rollover study. Eligible subjects will be enrolled in the appropriate cohort based upon the duration and treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. Subjects will receive afuresertib and possibly ~~or~~ other anti-cancer agents at the same dose and regimen most recently taken in their parent study. The dose will not exceed the maximum tolerated dose established in prior studies. Subjects may continue treatment in the rollover study until disease progression, unacceptable toxicity, withdrawal of consent, or death.
- DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN: Afuresertib - Up to 150 mg (provided as 100 mg and 25 mg gelatin capsules or 50 mg and 75 mg Immediate Release (IR) tablets), given orally, once daily in 3 or 4 week cycles, depending on the schedule and treatment used in the parent study. Dose adjustments are allowed to address tolerability and safety issues. Other anti-cancer agents will continue to be given at the same dose and regimen as in the parent study. Any dose modifications will follow [REDACTED] parent protocol or most recent prescribing information.
- EFFICACY MEASUREMENTS: This study will not collect efficacy data. However, clinical activity will be assessed using local standard of care practices to determine eligibility for continued study participation. Only subjects who are clinically benefitting [REDACTED] and tolerating [REDACTED] treatment [REDACTED] [REDACTED] with afuresertib may continue on study- [REDACTED]

Section 1.1. Background

REVISED TEXT

AKT is a serine/threonine protein kinase with three isoforms (AKT1, AKT2, and AKT3) that participate in multiple pathways regulating several cellular processes, including survival, proliferation, tissue invasion, and metabolism [Tanno, 2001; Morgensztern, 2005]. Aberrant activation of the PI3K/AKT pathway occurs in virtually every type of hematologic malignancy, suggesting that dysregulation of these pathways may be required for carcinogenesis. The importance of AKT-mediated pathways in tumor proliferation and survival render AKT kinases promising targets for therapeutic intervention. Hyperactivation of the AKT pathway can also correlate with chemotherapy resistance and poorer prognosis. Nonclinical data suggest that blocking AKT1 and AKT2 activity can inhibit the proliferation of tumor cells and either induce an apoptotic response or sensitize tumors to undergo apoptosis in response to other cytotoxic agents [DeFeo-Jones, 2005].

1.1.1 Afuresertib

Afuresertib was evaluated in 10 different MM cell lines either alone or in combination with a proteasome inhibitor (either bortezomib or carfilzomib). Six of 10 MM cell lines showed <1 μ M gIC_{50} (concentration producing 50% inhibition of growth) for afuresertib as a single agent in a 3-day cell proliferation assay. The combination of afuresertib with bortezomib showed strong synergy in all 10 cell lines tested at concentrations that are clinically achievable. Similar synergy was also observed with combination of afuresertib and carfilzomib. The synergistic anti-proliferative effect of AKT inhibitor and bortezomib is likely mediated by increased induction of apoptosis, as evidenced by increase in caspase 3/7 activity in National Cancer Institute (NCI) H929 cells.

The safety, pharmacokinetic (PK) and pharmacodynamic profiles and activity of afuresertib administered as monotherapy was evaluated in the first time in humans (FTIH) trial PKB112835. Among 34 relapsed/refractory MM subjects treated with afuresertib three have achieved partial response (PR), and a further 3 achieved minimal response (MR) accounting for clinical benefit rate (CBR) of 17.6 in this heavily pretreated population. The combination of afuresertib with bortezomib and dexamethasone is being currently evaluated in PKB115125 study. The preliminary results (data cut-off 29-Jun-2014) in relapsed MM population demonstrate overall response rate (ORR) of 61% (PR or better) and CBR of 78%. The investigator should refer to the current version of the afuresertib Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113491_02] for detailed information regarding all completed and ongoing clinical studies with afuresertib, PK in the target disease populations, as well as observed safety and clinical activity findings.

1.1.2. Pharmacokinetics of Afuresertib in Humans

In the FTIH monotherapy study in subjects with relapsed or refractory hematologic malignancies (PKB112835), afuresertib plasma concentrations following single afuresertib doses were measured over the 72-hour sample collection period in all subjects. Afuresertib accumulated 1.4- to 5.1-fold with repeat daily dosing. Single-dose and repeat-dose mean area under the plasma concentration-time curve (AUC(0-24)) and

maximum observed plasma concentration (C_{max}) values increased with increasing doses; however, given the intersubject variability, there was substantial overlap in the AUC(0-24) and C_{max} values between successive dose groups. The 100 mg and 125 mg multiple-dose exposure data were similar. Median time to C_{max} (t_{max}) across doses was 2 hours. Based on available data from all cohorts, the mean accumulation half life (t_{1/2}) is approximately 1.7 days and the median t_{max} on Day 8 is 2 hours. For details of the PK of afuresertib see the current version of the IB [GlaxoSmithKline Document Number 2011N113491_02].

Preliminary PK results from the PKB115125 combination study of afuresertib with bortezomib and dexamethasone indicate mean afuresertib exposure (n=7) was similar alone or in combination with bortezomib and dexamethasone, and mean bortezomib exposure (n=7) co-administered with dexamethasone was similar with and without afuresertib. Mean dexamethasone exposure co-administered with bortezomib was 30-50% higher when dosed with afuresertib than without afuresertib; although sample size was small (n=5) and exposure values overlapped [GlaxoSmithKline Document Number 2011N113491_02].

1.1.3. Clinical Safety of Afuresertib

As of 29-Jun-2013, 226 subjects had received at least 1 dose of afuresertib either as monotherapy or in combination with other agents in the 7 GSK-sponsored studies with afuresertib. The most common adverse events (AEs) reported in all studies were primarily gastrointestinal (GI) disorders including: diarrhea, nausea, and vomiting, dyspepsia, and constipation.

More detailed safety characteristics from the two most relevant studies are described in greater detail below. The studies are considered most relevant because they were conducted in subjects with hematologic malignancies (PKB112835), and in subjects with MM (PKB115125).

Additional information from all studies where subjects with other diseases are administered afuresertib, as monotherapy or in combination, can be found in the current afuresertib IB [GlaxoSmithKline Document Number 2011N113491_03].

PKB112835

This was an open-label, 2-part, FTIH study designed to investigate the safety, tolerability, PK, and pharmacodynamics of afuresertib in subjects with hematologic malignancies. A total of 73 subjects were enrolled in this study, 26 in Part 1 (dose escalation), and 47 in Part 2 (expansion). Afuresertib was administered orally once daily at doses of 25 mg, 75 mg, 100 mg, 125 mg, or 150 mg and the maximum tolerated dose (MTD) was established at 125 mg for this dosing based on dose limiting toxicities (DLTs) in 2/6 subjects at the 150 mg dose. Both DLTs were elevations in liver function tests (LFTs). No DLT was reported in any subject enrolled in Part 1 at doses below 150 mg. Both subjects with DLTs had non-Hodgkin's lymphoma (NHL): 1 subject had Grade 3 elevations in alanine aminotransferase (ALT) and alkaline phosphatase (ALP), accompanied by elevations in aspartate aminotransferase (AST), total bilirubin, and

eosinophilia, the other subject had liver involvement from lymphoma and experienced Grade 3 elevations in ALT and ALP.

The most frequent type of malignancy in the trial was MM (34 subjects; 47%), followed by NHL (13 subjects, 18%), Hodgkin's lymphoma (HD) (8 subjects, 11%), acute myeloid leukemia (AML) (9 subjects, 12%), chronic lymphocytic leukemia (CLL) (7 subjects, 10%), acute lymphoblast leukemia (ALL) (1 subject, 1%), and Langerhans cell histiocytosis (LCH) (1 subject, 1%). The most frequent ($\geq 10\%$ of subjects) AEs were nausea (35.6%), diarrhea (32.9%), dyspepsia (24.7%), fatigue (20.5%), gastroesophageal reflux disease (GERD; Grade 1) (19.2%), anorexia (19.2%), vomiting (19.2%), anemia (15.1%), upper respiratory tract infection (13.7%), asthenia (13.7%), back pain (12.3%), rash (12.3%), insomnia (12.3%), constipation (11.0%), odynophagia (11.0%), and cough (11.0%). Grade 3 or higher AEs (in ≥ 2 subjects) included anemia (9.6%), neutropenia (9.6%), thrombocytopenia (6.8%), sepsis (4.1%), febrile neutropenia (4.1%), odynophagia (4.1%), rash (4.1%), asthenia (2.7%), diarrhea (2.7%), fatigue (2.7%), pneumonia (2.7%), and abnormal LFTs (2.7%). Grade 5 AEs were observed in 2 subjects: septic shock, considered not related to afuresertib and concomitant pneumonia and sepsis, considered not related to afuresertib in a subject who died from disease progression. There was no obvious relationship between the type of AEs and malignancy type. Three deaths were reported during the study (disease progression, n=2; septic shock, n=1).

PKB115125

This is an ongoing open-label, 2-part, repeat- and escalating-dose study designed to investigate the safety, tolerability, PK, pharmacodynamics, and clinical activity of afuresertib administered once daily in combination with bortezomib and dexamethasone (twice weekly schedule) in subjects with relapsed/refractory MM. In the study's Part 1 dose-escalation, 34 subjects were administered doses of afuresertib in combination with bortezomib and dexamethasone in the following sequence: 75 mg/day (n=4), 100 mg/day (n=6), 125 mg/day (n=6), 150 mg/day (n=12), 175 mg/day (n=6) and plus dexamethasone (40 mg) on days of bortezomib administration (n=6). The MTD for afuresertib was established at 150 mg once daily in combination with bortezomib (1.3 mg/m² on Days 1, 4, 8, and 11 of a 21-day cycle) and dexamethasone 40 mg (on days of bortezomib dosing only). Four subjects experienced DLTs during Part 1: 100 mg/day, Grade 2 elevations in ALT; 125 mg/day, Grade 3 erythema multiforme; 175 mg/day, Grade 3 diarrhea, thrombocytopenia, and rash; 175 mg/day, Grade 3 maculo-papular rash. Part 1 was followed by a cohort-expansion phase (Part 2). As of the data cut-off date of 18-Oct-2013, Part 2 included 23 subjects who received 150 mg of afuresertib once daily in combination with bortezomib and dexamethasone. An additional 10 subjects were enrolled into the PK/pharmacodynamic cohort.

The most common AEs ($>10\%$ of subjects) were primarily GI toxicities. No new safety concerns were identified from the use of afuresertib in combination compared with the safety profile observed with afuresertib monotherapy. The most common AEs (in $\geq 10\%$ of subjects) were as follows: fatigue (51% [2% Grade 3, no Grade 4]), diarrhea (49% [14% Grade 3, no Grade 4]), thrombocytopenia 38%, [16% Grade 3, 11% Grade 4]), nausea (37% [1% Grade 3, no Grade 4]), constipation (33% [2% Grade 3, no Grade 4]).

dyspepsia (32% [1% Grade 3, no Grade 4]), hyperglycemia (28% [6% Grade 3, 1% Grade 4]), vomiting (27% [2% Grade 3, no Grade 4]), anemia (22% [10% Grade 3, no Grade 4]), peripheral neuropathy (22% [no Grade 3/4]), insomnia (20% [no Grade 3/4]), rash (20% [7% Grade 3, no Grade 4]), dizziness (20% [no Grade 3/4]), upper respiratory tract infection (17% [no Grade 3/4]), cough (14% [no Grade 3/4]), lymphopenia (14% [5% Grade 3, 2% Grade 4]), pyrexia (14% [no Grade 3/4]), blood creatinine increased (12% [1% Grade 3, 1% Grade 4]), asthenia (11% [2% Grade 3, no Grade 4]), dysgeusia (11% [no Grade 3/4]), headache (11% [no Grade 3/4]), neutropenia (11% [5% Grade 3, 2% Grade 4]), abdominal pain (10% [1% Grade 3, no Grade 4]), ALT increased (10% [2% Grade 3, no Grade 4]), decreased appetite (10% [1% Grade 3, no Grade 4]), exertional dyspnea (10% [no Grade 3/4]), epistaxis (10% [no Grade 3/4]), herpes zoster (10% [no Grade 3/4]), hypotension (10% [2% Grade 3, no Grade 4]), and urinary tract infection (10% [1% Grade 3, no Grade 4]). Grade 5 AEs were observed in 2 subjects: septic shock, and sepsis.

1.1.4. PKB116611

PKB116611 is an ongoing open-label, Phase 1/2 dose-escalation study of afuresertib in combination with carboplatin and paclitaxel in subjects with platinum-resistant/refractory ovarian cancer. The primary objective of the Phase 1 part of the study is to determine the safety and tolerability of the triplet combination, which will be used to define the dosing regimen to be evaluated in Phase 2. The primary objective of the Phase 2 part of the study is to evaluate the clinical efficacy (defined by the overall response rate) of the triplet combination, in patients with platinum-resistant or platinum-refractory ovarian cancer.

Afuresertib doses of 50 to 150 mg/day were explored in combination with carboplatin (IV) AUC 5 and paclitaxel (IV) 175 mg/m² administered day 1 every 21 days for a maximum of 6 doses. Phase 2 expansion cohorts at the recommended Phase 2 afuresertib dose of 125 mg are ongoing in platinum resistant and platinum refractory cohorts.

As of the data cut-off date of 29-Jun-2014, 52 subjects have been enrolled in the study: 29 subjects in Part 1 and 23 subjects in Part 2. Of these, data are available for 49 subjects, including all subjects in Part 1 and 20 subjects in Part 2. For those subjects with available data, 2 subjects who are platinum refractory have been enrolled to Part 2; all other subjects are platinum resistant. Three subjects (6.1%) discontinued study treatment because of AEs and 13 subjects (26.5%) discontinued because of progressive disease.

The most common AEs (≥10% of subjects) were primarily gastrointestinal toxicities, alopecia, and fatigue. The event of fatigue was reported at a similar incidence in Study PKB115125, where afuresertib was administered with bortezomib/dexamethasone.

In total, 18 (36.7%) subjects reported Grade 3 AEs and 12 (24.5%) subjects reported Grade 4 AEs. The following Grade 3 AEs were reported: hypomagnesaemia (8.2%), neutropenia (8.2%), hyperglycaemia (6.1%), vomiting (6.1%), ascites (4.1%), dyspnoea (4.1%), lower respiratory tract infection (4.1%), nausea (4.1%), rash (4.1%), rash maculo-papular (4.1%), small intestinal obstruction (4.1%), and abdominal pain, anaemia, chills, colonic obstruction, dermatitis acneiform, diarrhoea, drug hypersensitivity,

escherichia urinary tract infection, fatigue, febrile neutropenia, gastroenteritis viral, hypersensitivity, hypertension, hyperthyroidism, hypophosphataemia, lobar pneumonia, neutropenic sepsis, oesophagitis, platelet count decreased, pneumonia, pyrexia, renal failure acute, supraventricular tachycardia, syncope, urinary tract infection, and white blood cell count decreased (each reported in 2.0% subjects). In addition, the following Grade 4 AEs were reported: neutropenia (20.4%), thrombocytopenia (4.1%), hypomagnesaemia (2.0%), platelet count decreased (2.0%), and white blood cell count decreased (2.0%).«There were also 2 uncoded Grade 3 AEs in the eye disorders SOC (2.0% each).

Five subjects discontinued treatment with afuresertib due to AEs; these were abdominal pain, blood creatinine increased, decreased appetite, dehydration, diarrhea, gastroesophageal reflux disease, headache, muscle spasms, nausea, neutropenia, pleural effusion, syncope, and vomiting (1 subject each).

As of 29-Jun-2014, 1 subject died while on study. Two additional patients died while off study (>30 days after the last dose of afuresertib).

Overall 56 SAEs have been reported in 34 subjects; of these, 18 SAEs in 10 subjects were considered by the investigator to be related to afuresertib.

1.1.5. LCH115397

LCH115397 was an open label, repeat-dose study designed to investigate the efficacy and safety of afuresertib in subjects with LCH. This study is complete.

In total, 17 subjects were enrolled in the study at doses up to 125 mg administered continuously, once daily. Of these, 16 of the 17 subjects completed the study and 1 subject voluntarily withdrew from the study.

One subject, receiving 125 mg/day, discontinued treatment because of an AE (Grade 2 impaired gastric emptying) which was considered to be not related to afuresertib, in the opinion of the investigator.

Five (29%) subjects had AEs of Grade 3 or higher, these were: ALT increased, diarrhea, fatigue, hyponatraemia, impaired gastric emptying, lung infection, esophageal ulcer, pain, perineal pain, pseudomonas infection, soft tissue necrosis, and vulvovaginal pain. None of these occurred in more than 1 subject.

No subject died during the study. Five SAEs have been reported in 3 subjects, only 1 of which (soft tissue necrosis) was considered possibly related to afuresertib

1.1.6. Clinical Activity of Afuresertib

Clinical activity of afuresertib monotherapy was seen in subjects with hematologic malignancies in the PKB112835 FTIH study. Of the 34 subjects with MM, three subjects demonstrated confirmed PR and median time on study for those subjects was 319 days (range 215-541). Three additional subjects had MR and their median time on study was 336 days (range 157-484). The overall CBR for MM subjects (PR+MR) was therefore,

17.6% (6/34). An additional 14 subjects with MM had prolonged stabilization of their disease for a median 118.5 days (range 48-426). Clinical activity has also been observed in subjects with lymphomas (1 complete response [CR] and 2 partial responses [PRs] in 13 subjects with NHL) and 4/8 subjects with HD achieving unconfirmed PR.

In the ongoing combination study (PKB115125) of afuresertib with bortezomib and dexamethasone, responses have been reported in the dose escalation and expansion phases of the study. In the population of relapsed MM subjects treated at the afuresertib's MTD (150 mg) in Part 2 of the study, the confirmed overall response rate was 61% (14/23 subjects; 3 very good partial responses [VGPR] and 11 PR). Data on duration of responses are not available yet from this ongoing study.

Additional information from all studies where subjects with other diseases are administered afuresertib, as monotherapy or in combination, can be found in the current afuresertib IB [GlaxoSmithKline Document Number 2011N113491_03].

Section 1.2. Rationale

REVISED TEXT

1.2.1 Study Rationale

The purpose of this study is to allow for continued treatment with afuresertib in subjects who have participated in a 'parent' GSK sponsored study of afuresertib, either as monotherapy or as part of a combination regimen, and met the protocol requirements for transitioning to this rollover study. The parent study will have met it's primary endpoints and transitioning to this rollover study will allow data to be reported for the parent study. In addition, subjects will be [REDACTED] monitored for adverse events, as this study will continue to collect safety information on afuresertib.

Subject enrollment into Cohorts A and B is based on the duration of treatment on a monotherapy parent study with Cohort A enrolling subjects who received less than 24 weeks of treatment, while Cohort B will enroll subjects who have received 24 weeks or greater afuresertib therapy. Cohort C will enroll subjects who have participated on a combination study where afuresertib is given with another anti-cancer agent(s). The purpose of having separate cohorts is to be able to better report and define the safety profile for these subject groups.

1.2.2 Dose Rationale

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 MTD established in the parent study will be allowed in this study.

Cohort A and B:

Subjects who have received <24 weeks (Cohort A) or ≥24 weeks (Cohort B) of afuresertib as monotherapy in the parent study will receive the same continuous dosing

regimen of afuresertib at completion of the parent study. If a subject required a dose modification while receiving treatment in the parent study, the subject will enter the rollover study and continue treatment on the modified dose unless after consultation with the GSK Medical Monitor, it is appropriate to escalate the dose. The dose may be escalated up to the MTD established in the parent study.

Cohort C:

Subjects who have received any duration of a combination regimen with afuresertib and another anti-cancer agent will continue treatment in the rollover study at the current dose level(s) administered in the parent study at the time of transition to the rollover study. If the subject discontinued the [REDACTED] anticancer drug, which was studied as a part of a parent study- the subject will enter and continue on the roll over study while receiving monotherapy with afuresertib. Adding additional anticancer drugs is not allowed. If a subject required a dose modification while receiving treatment in the parent study, the subject will enter the rollover study and continue treatment on the modified dose unless after consultation with the GSK Medical Monitor, it is appropriate to escalate the dose. Any dose modifications will follow parent protocol or most recent prescribing information [REDACTED]

1.2.4 Endpoint Rationale

This study will collect additional safety data from prolonged exposure to afuresertib, as monotherapy or in combination with other [REDACTED] therapies. Primary endpoints for the study will be: adverse events, changes in laboratory values, and changes in vital signs.

Section 1.3 Summary of Risk Management

REVISED TEXT

Summaries of findings from clinical and nonclinical studies conducted with afuresertib can be found in the current IB [GlaxoSmithKline Document Number 2011N113491_02]. The most common AEs seen to date in afuresertib studies include: nausea, diarrhea, dyspepsia, fatigue, thrombocytopenia, neutropenia, hyperglycemia, upper respiratory infection, anorexia, gastrointestinal reflux and rash. The anticipated resks are listed below. [REDACTED]

1.3.1 Risk Assessment for Afuresertib

<u>Potential Risk of Clinical Significance</u>	<u>Data/Rationale for Risk</u>	<u>Mitigation Strategy</u>
<u>Gastrointestinal toxicity</u>	<u>GI toxicity has been observed both afuresertib with most frequent events being: diarrhea, nausea, vomiting and dyspepsia.</u>	<ul style="list-style-type: none"> • <u>Exclusion of subjects with significant pre-existing GI conditions</u> • <u>Close monitoring via continuous assessment of AEs, physical examination, and clinical laboratory assessments (see Appendix 1.).</u> • <u>Management guidelines and stopping criteria are provided for diarrhea, mucositis, and dyspepsia (see Section 6.7)</u>
<u>Rash</u>	<u>Rash has been frequently observed with afuresertib monotherapy and in combination therapies</u>	<ul style="list-style-type: none"> • <u>Monitoring rash via assessment of AEs and physical examination (see Section 5.8.1)</u> • <u>Management guidelines and stopping criteria are provided (see Section 6.7.4)</u>
<u>Hepatic toxicity</u>	<u>LFT elevations have been observed with afuresertib.</u>	<ul style="list-style-type: none"> • <u>Exclusion of subjects with impaired liver function.</u> • <u>Monitoring and stopping criteria are provided (see Section 6.7.7)</u>
<u>Hyperglycaemia</u>	<u>Elevated glucose levels have been observed with compounds inhibiting PI3/AKT pathway. Afuresertib can potentially cause hyperglycemia.</u>	<ul style="list-style-type: none"> • <u>Only subjects with well-controlled Type 2 diabetes will be enrolled in the study</u> • <u>Glucose monitoring will be implemented as clinically indicated.</u> • <u>Management guidelines and stopping criteria are provided (see Section 6.7.2)</u>

Section 3. INVESTIGATIONAL PLAN

3.2 Study Design

Paragraph 1 and 2:

This multicenter, non-randomized, open-label, rollover study is designed to provide continued access to afuresertib to subjects who have previously participated in an a afuresertib study. All subjects enrolling in this study must be tolerating and benefitting from treatment (ie did not meet any of the study discontinuation criteria from the parent study) with afuresertib to be eligible. Subjects will be enrolled into the appropriate cohort (Section 4.2.1) based upon the duration and treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study.

Subjects must first provide written informed consent for this rollover study prior to any study-related assessment or procedure being performed and before any treatment with afuresertib can be administered under this protocol. After informed consent is obtained, subjects will be evaluated for study eligibility in PKB115131.

Paragraph 7:

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.

3.2.1 Cohort A and Cohort B: Afuresertib Monotherapy

Subjects will receive afuresertib as an oral, daily dose up to 150 mg. Protocol specified guidelines for dose modifications and treatment discontinuation criteria are provided in Section 7.6 and Section 7.7, respectively. If there are any uncertainties about the dose to be administered in this study, the GSK Medical Monitor should be consulted.

Cohort A:

Cohort A will consist of subjects who have completed **<24 weeks** of treatment with afuresertib monotherapy during their participation in the parent study. It is anticipated that subjects in this cohort will have participated in a clinical pharmacology or other short-term study of afuresertib. Subjects will complete the Transition Visit; receive instruction and study medication, and then return for their next scheduled visit (Study Week 4) and then every 4 weeks thereafter. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to every 8 weeks with approval from the GSK Medical Monitor. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs [REDACTED] -for 30 days or until resolution, [REDACTED] whichever comes first.

Cohort B:

Cohort B will consist of subjects who have completed **≥24 weeks** of treatment with afuresertib monotherapy during their participation in the parent study. It is expected that subjects in this cohort will have participated in a longer term study of afuresertib. Subjects will complete the Transition Visit, receive study instruction and study medication and then return for their next scheduled visit (Study Week 4), and then every 4 weeks thereafter. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to every 8 weeks with approval from the GSK Medical Monitor. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first

3.2.2 Cohort C: Afuresertib Combination Therapy

Cohort C:

Cohort C will consist of subjects who have participated in a combination study where afuresertib is administered with another anti-cancer agent, regardless of duration on study. Subjects who transition from a combination study may continue to receive afuresertib in combination with the anti-cancer agent defined by the parent study, or they may receive afuresertib as monotherapy. If the concomitant anticancer drug has been terminated according to parent study design, or if, in the opinion of the investigator, the subject has received maximum benefit, or is experiencing unacceptable toxicity from the anti-cancer agent, then treatment with the anti-cancer agent may be discontinued and the subject may remain on study for continued treatment with afuresertib monotherapy. Adding any other anticancer drug while on this study, is not allowed. Subjects will complete the Transition Visit, receive study instruction and study medication, and then return for their next scheduled visit (either Study Week 3 or 4) and then every 3 or 4 weeks thereafter, depending on the schedule used in the parent study. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor to every 8 or 9 weeks (whichever is consistent with parent schedule). After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

Section 4.1.2. Inclusion Criteria

REVISED TEXT

Paragraph 1:

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on afuresertib or other agent(s) that may impact subject eligibility is provided in the IB for afuresertib [GlaxoSmithKline Document 2011N113491_03] or any

subsequent IB supplements or in the Prescribing Information for any agent(s) administered as part of a combination treatment regimen, as applicable.

Inclusion criteria no 2:

Is currently participating in an afuresertib study (monotherapy or in combination with another anti-cancer agent) sponsored by GSK or by another research organization working on behalf of GSK.

Inclusion criteria no 3:

Currently tolerating and benefitting from treatment with afuresertib as determined by the investigator following previous treatment with afuresertib either as monotherapy or as part of a combination treatment regimen.

Inclusion criteria no 10:

Have adequate organ system function as defined in Table 1.

Table 1 Definitions of Adequate Organ Function

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	$\geq 1.0 \times 10^9/L$
Hemoglobin	≥ 8.0 g/dL
Platelets	$\geq 50 \times 10^9/L$
PT/INR and PTT	$\leq 1.5x$ ULN
Hepatic	
Total bilirubin	$\leq 1.5x$ ULN (isolated bilirubin $>1.5x$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $<35\%$)
AST and ALT	$\leq 3x$ ULN. If liver involvement is present and ALT and AST levels are $>3x$ UNL and $<5x$ ULN, enrollment into PKB115131 can occur as long as there is no concurrent bilirubin or INR elevation
Renal (Monotherapy)	
Serum creatinine OR Calculated creatinine clearance ¹	≤ 2.5 mg/mL ≥ 30 mL/min
Renal (in combination with nephrotoxic anti-cancer agents)	
<u>Serum creatinine</u> <u>OR</u> <u>Calculated creatinine clearance¹</u>	$< 1.2x$ ULN ≥ 50 mL/min
Cardiac	
Ejection Fraction (LVEF)	$\geq 50\%$ by TTE or MUGA

1. As calculated by Cockcroft-Gault formula (Appendix 4).

Section 4.1.4. Other Eligibility Criteria Considerations

REVISED TEXT

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the GSK investigational product(s) or other study treatment being used in this study: IB for afuresertib [GlaxoSmithKline Document 2011N113491_03], product label(s) for other commercially available co-administered agents.

Section 4.2.1. Permanent Discontinuation from Study Treatment

REVISED TEXT

Subjects may be permanently discontinued from study treatment in the event of unacceptable toxicity, which include but are not restricted to: meeting stopping criteria for liver chemistry defined in Section 6.7.7 or for hematologic and other non-hematologic toxicity. In addition, study treatment will be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Adverse Event, including but not limited to clinically significant AE leading to interruption of treatment for >14 consecutive days².
- Disease progression (including death due to disease progression)
- Request of the subject or proxy (withdrawal of consent by the subject)
- Investigator's discretion
- Subject is lost to follow-up
- Study is closed or terminated (such as when afuresertib becomes locally available as commercial product to the subject for continued treatment)
- Death

Paragraph 7:

In the event that a subject permanently discontinues study treatment at any time due to an AE (as defined in Section 6.8.1.1, "Definition of an AE") or serious AE (SAE) (as defined in Section 6.8.1.2, "Definition of a SAE"), the procedures stated in Section 6.8 ("Adverse Events") must be followed. All subjects who have a Grade 3 or 4 clinical or laboratory abnormality at the time of permanently discontinuing study treatment must be followed up to 30 days or until resolution, whichever comes first

² **NOTE:** If the investigator and GSK Medical Monitor agree that continued treatment will benefit the subject, then the subject may continue treatment, with or without a dose reduction, with the approval of the GSK Medical Monitor.

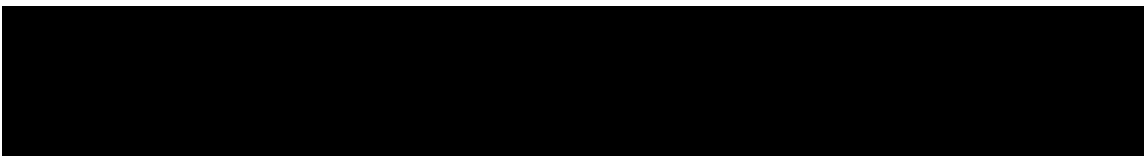
Section 5.1 Transition Visit

REVISED TEXT

For this study, the Transition Visit may occur on the same day as the last study visit on the parent study. The most recent disease assessment performed under the parent protocol may be used for entry criteria for this rollover protocol, if there are no clinical signs of disease progression. The results of any specified study assessments performed on the day of the Transition Visit will serve as the baseline value for said assessment.

At the Transition Visit, the following assessments will be performed:

- Demographic data, including date of birth, ethnicity, gender, and race.
- Subject-related data from parent study, including parent study protocol number, previous subject number assigned in parent study, start and stop date, dose of afuresertib and other study treatment(s), if applicable, at time of transition to this study; and response based on last disease assessment in parent study. At the time of transition visit the duration of treatment on parent study will be calculated.
- Complete physical examination, including height and weight.
- Vital signs (BP, temperature and pulse rate)
- Clinical laboratory tests: hematology, TSH and clinical chemistry required for study entry, including coagulation tests
- Serum beta-human Chorionic Gonadotropin (β -hCG) pregnancy test for female subjects of childbearing potential only
- Single 12-lead ECG



- Review of adverse events and concomitant medications
- Disease assessments

Section 5.2.2 Cohort C

REVISED TEXT

The following assessments must be performed either every 3 or 4 weeks (± 3 days) (depending on schedule used in parent study) while receiving treatment:

- Vital signs (BP, temperature and pulse rate)
- Complete physical examination
- Clinical laboratory tests: hematology and clinical chemistry, including TSH and coagulation tests

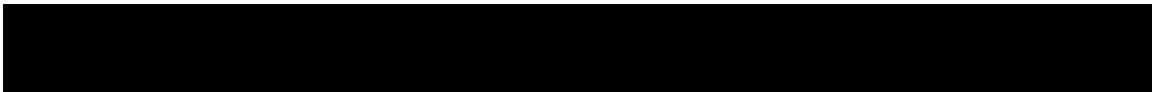
- Single, 12-lead ECG
- Perform assessments needed for safe administration of other anti cancer agents used in combination

Section 5.3 Final Study Visit

REVISED TEXT

If a subject is withdrawn from study treatment, the following assessments will be performed within [REDACTED] one month from the last dose of study treatment(s) and prior to initiating any other treatment for cancer:

- Complete physical examination
- Vital signs (BP, temperature and pulse rate)
- Clinical laboratory tests: hematology, clinical chemistry, and TSH
- Single, 12-lead ECG



- Review of concomitant medications
- Assessment of AEs
- Disease assessment

Table 2 List of Clinical Laboratory Assessments

REVISED TEXT

Clinical Chemistry

Blood urea nitrogen (BUN)	Potassium
Creatinine	Inorganic phosphorus
Sodium	Magnesium
Albumin	Chloride
Calcium	LDH
Bicarbonate	Glucose
Total protein	[REDACTED]
AST	
ALT	
Alkaline Phosphatase	
Total bilirubin (bilirubin fractionation recommended if total bilirubin >2 times ULN)	



Section 5.5 and Section 5.6

REVISED TEXT

Section 5.5 Multiple Myeloma specific disease assessments:

The following assessments will be performed to assess disease in subjects with MM only every 4 weeks until week 42 and every 8 weeks thereafter:

Serum M-protein, urine M-protein, serum FLC, urine FLC, imaging for extramedullary MM (only in subjects in whom there is a clinical evidence of extramedullary MM- the imaging technique should be the same throughout the study (ie if subject initially had CT- should be followed by CT, if MRI- follow by MRI, or if PET scan- follow by PET scan.)).

Section 5.6 Disease assessments for malignancies other than MM

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. The investigator may decide that more frequent disease assessments are needed, and perform them according to medical practice.

Section 5.9.1.5. Time Period and Frequency of Detecting AEs and SAEs

REVISED TEXT

AEs will be collected from the time of [REDACTED] first dose of study treatment until [REDACTED] 30 days after last study treatment dose.

Section 6.1

REVISED TEXT

6.1 Afuresertib Investigational Product Dosage/Administration

For early trials in the afuresertib clinical program, study drug was provided in hard gelatin capsules (25 mg and 100 mg strengths; see Table 6 below). The initial patients enrolled to this protocol from the FTIH study PKB112825 continued to receive afuresertib in hard gelatin capsules. Subsequently, afuresertib has been re-formulated as immediate-release (IR) tablets (50 mg and 75 mg strengths). A relative bioavailability study (201039) performed in healthy volunteers showed similar afuresertib pharmacokinetic characteristics between the capsule formulation and the IR tablet formulation (for details of study 201039 see the afuresertib clinical IB). Patients currently receiving afuresertib as hard gelatin capsules in this protocol will be switched to IR tablets from Day 1 of their next treatment cycle following a scheduled clinic visit. Patients newly enrolled to this protocol from a parent afuresertib study in which they received drug in hard gelatin capsules will immediately switch to IR tablets. Patients newly enrolled to this protocol from a parent afuresertib study in which they received drug as IR tablets will continue to receive IR tablets. Patients switching from capsule to tablets will have the change fully explained by their Investigator or Study Nurse.

Table 4 Afuresertib Dosage/Administration

<u>Product name :</u>	<u>Afuresertib</u>	
<u>Formulation description:</u>	<u>Gelatin capsules: Each 25 mg capsule contains 25 mg of afuresertib as free base</u> <u>Each 100 mg capsule contains 100 mg of afuresertib as free base</u> <u>OR:</u> <u>Immediate release tablets (IR tablets): Each 50 mg tablet contains 50 mg of afuresertib as free base</u> <u>Each 75 mg tablet contains 75 mg of afuresertib as free base</u>	
<u>Dosage form :</u>	<u>Geletin capsule or immediate release tablet</u>	
	<u>CAPSULES</u>	<u>IR TABLETS</u>
<u>Unit dose strength(s)/Dose Level(s):</u>	<u>25 mg capsule or 100 mg capsule</u>	<u>50 mg tablet or 75 mg tablet</u>
<u>Physical Description:</u>	<u>25mg Capsules: Opaque, white, size 4 capsules with no external markings, filled with a white powder.</u> <u>OR:</u> <u>OR: 100mg Capsules: Opaque, Swedish orange, size 1 capsule with no external markings, filled with a white powder.</u>	<u>50mg IR tablets: White, film-coated, round, biconvex tablet</u> <u>75mg IR tablets: White, film-coated, oval or capsule shaped tablet</u>
<u>Route/ Administration/ Duration:</u>	<u>Oral/ The initial regimen will be once daily dosing continuously.</u>	
<u>Dosing instructions:</u>	<u>Dose with [REDACTED] at least 200 mL of water, and taken in the morning. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.) Afuresertib may be given without regard to food.</u>	

Section 6.2 Other Anti-Cancer Agents (Cohort C)

REVISED TEXT

When the treatment regimen to be administered includes another anti-cancer agent(s) in combination with afuresertib, the sites will be responsible for obtaining the necessary drug supply for the anti-cancer agent(s) through commercial means; the drug(s) will not be supplied by GSK. The use of an anti-cancer agent(s) in combination with afuresertib that was not part of the parent study is not permitted. Refer to the Prescribing Information for each anti-cancer agent for information regarding the physical and chemical properties, storage, and dosing/administration guidelines.

Section 6.3 Administration of Study Treatment

REVISED TEXT

Paragraph 1:

Afuresertib will be administered with approximately 200mL of water. [REDACTED]
[REDACTED]

Section 6.4 Handling and Storage of Study Treatment

REVISED TEXT

Paragraph 3:

Anti-cancer agents should be handled per manufacturer instructions.

Section 6.6 Dose Modifications

REVISED TEXT

Paragraph 2:

Guidelines for afuresertib dose modifications are provided below. Investigators should also consult the GSK Medical Monitor and refer to the afuresertib IB [GlaxoSmithKline Document Number 2011N113491_03] or the prescribing information for the appropriate anti-cancer combination agent for detailed information regarding warnings, precautions, contraindications, AEs, and recommendations for supportive care in the event of drug-related toxicity.

Section 6.6.2 Dose Modification: Other Anti-Cancer Agent(s)

REVISED TEXT

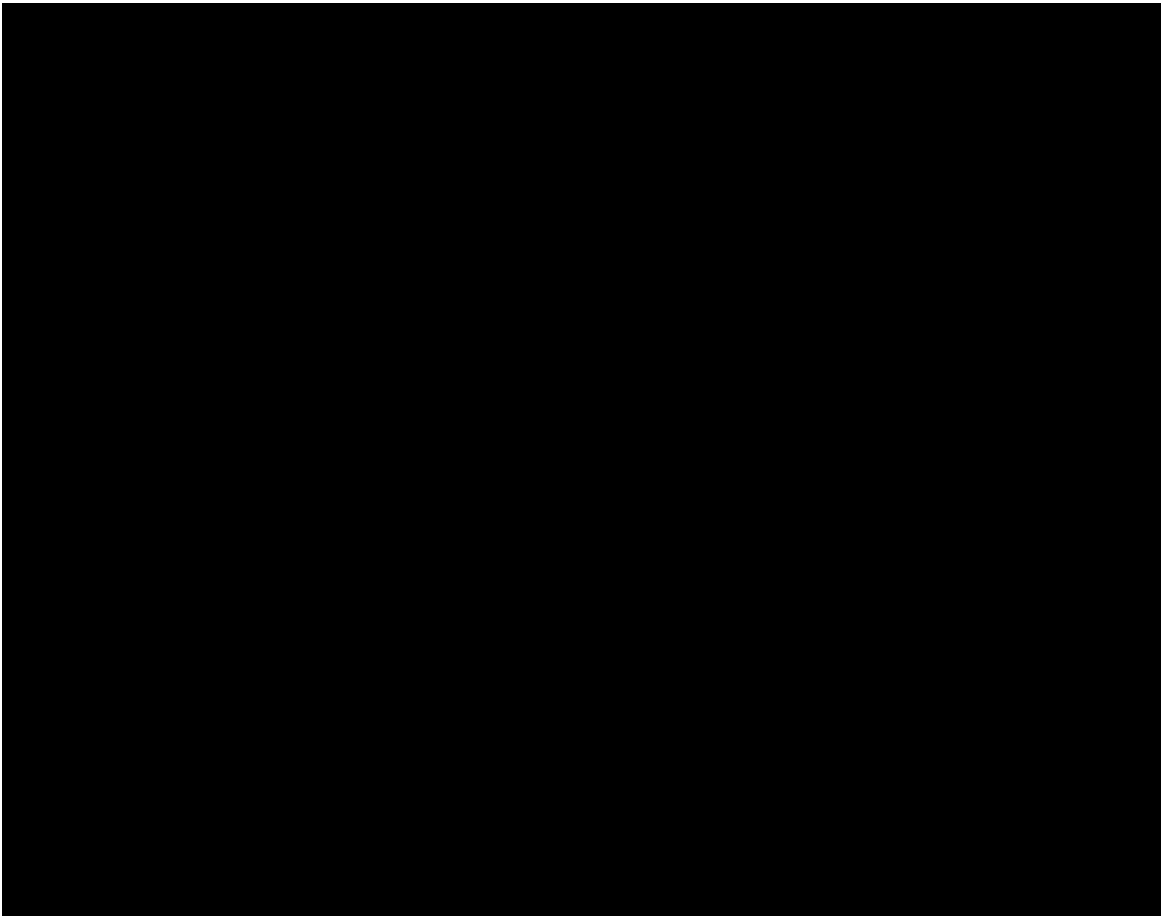
If an [REDACTED]-anti-cancer agent(s) is being taken in combination with afuresertib at the time of transition to the rollover study, treatment will continue with the current dose administered in the parent study.

Section 6.7.2 Supportive Measures for Hyperglycemia

REVISED TEXT

Subjects with clinically significant glucose elevation, with or without ketoacidosis, should be aggressively managed according to standard medical practice. Study sites with a protocol/guideline for management of hyperglycemia should include a copy in the study document file. Early consultation with a diabetes specialist is also encouraged, especially for study participants with a history of diabetes. If significant hyperglycemia (e.g., fasting glucose ≥ 200 mg/dL) persists despite treatment and after stopping systemic glucocorticoids (where applicable), or in the event of life-threatening complications, dose modification of afuresertib should also be considered, after discussion with a GSK

medical monitor. Dose modification of afuresertib should not be performed for asymptomatic hyperglycemia, or hyperglycemia that responds to other interventions.

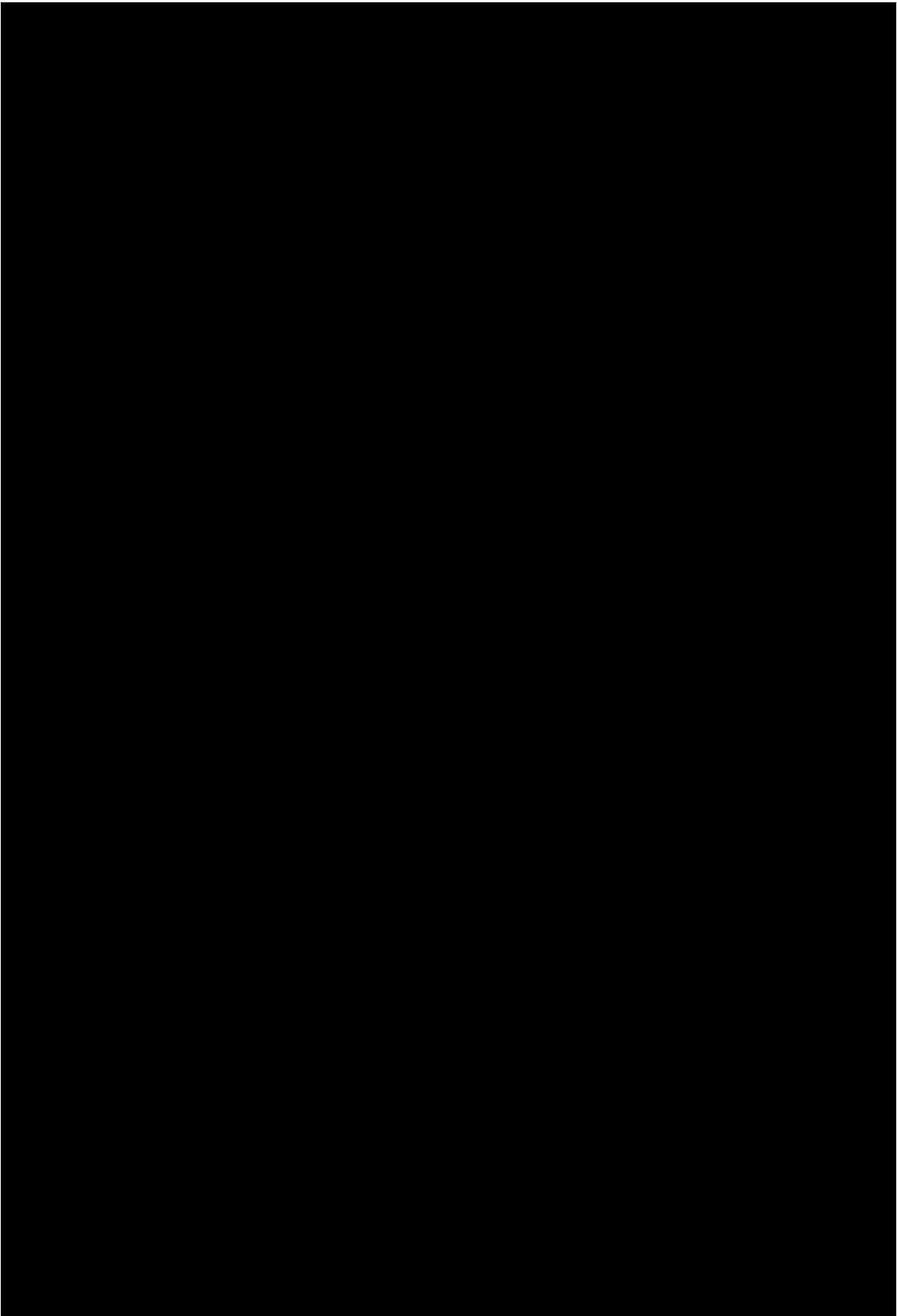


Section 6.7.3 Management of Diarrhea

REVISED TEXT

Episodes of diarrhea have been reported in subjects receiving afuresertib and this should be actively managed as soon as an episode has occurred. When starting afuresertib, it is advisable to provide subjects with a prescription for loperamide (or equivalent), along with detailed guidance on how to manage this potential toxicity. If an episode of diarrhea occurs, other potential causes should be promptly ruled out (e.g., concomitant medications like stool softeners, laxatives, antacids, etc., infections, partial bowel obstruction, etc.). Supportive therapy will be provided according to standard medical practice. Supportive measures should include the following as clinically indicated [Benson, 2004]:

- Dietary modifications (e.g., small, frequent meals, low fiber, and lactose avoidance)
- Maintain hydration with clear liquids or IV fluids as needed
- Loperamide and/or oral antibiotics



Section 6.7.4 Management of Rash

REVISED TEXT

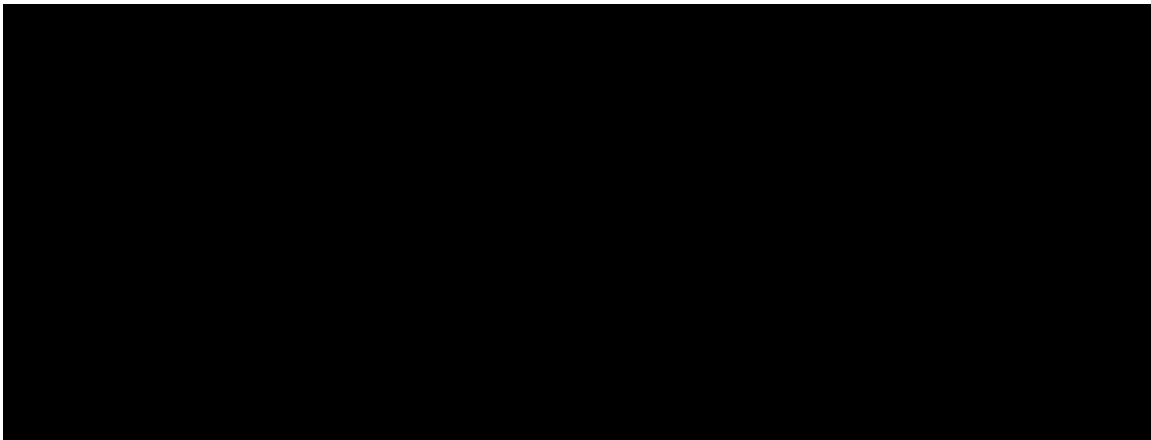
Subjects should contact the investigator immediately upon onset of a rash. Full supportive care should be provided to subjects who experience a rash while on study. *Information contained in this section is a guideline. The investigator's best medical judgment should determine medical intervention for rash. Details should be entered into InForm.*

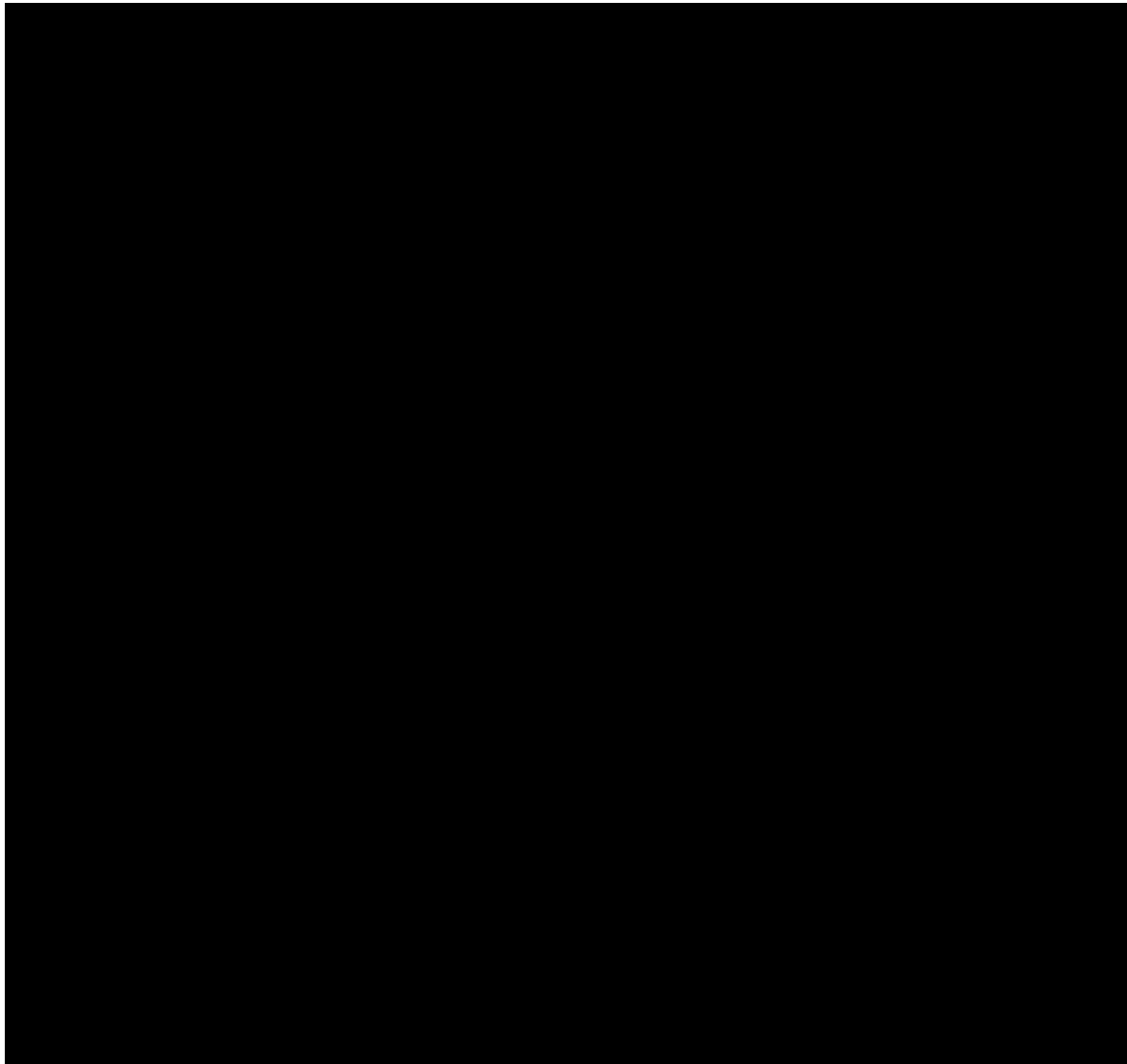
Table 6 Guidelines for Dose Modification and Management of Rash

	1st occurrence	2nd occurrence	3rd occurrence
Grade 1	<u>Symptomatic care^a</u> <u>Consider oral steroids if multiple recurrences^b</u>		
Grade 2	<u>Consider oral steroids</u>	<u>Oral steroids</u> <u>Hold drug until <Grade 1,</u> <u>then resume at full dose</u>	<u>Oral steroids</u> <u>Hold drug until</u> <u><Grade 1, then resume</u> <u>at 25 mg dose reduction</u>
Grade 3	<u>Oral steroids</u> <u>Hold drug until <Grade 1,</u> <u>then resume at full dose</u>	<u>Oral steroids</u> <u>Hold drug until <Grade 1,</u> <u>then resume at 25 mg</u> <u>dose reduction</u>	<u>Oral steroids</u> <u>Hold drug until</u> <u><Grade 1, then resume</u> <u>at 50 mg dose reduction</u> <u>or discontinue</u>
Grade 4	<u>Oral steroids</u> <u>Hold drug until <Grade 1,</u> <u>then resume at 25 mg</u> <u>dose reduction</u>	<u>Oral steroids</u> <u>Hold drug until <Grade 1,</u> <u>then resume 50 mg dose</u> <u>reduction or discontinue</u>	<u>Discontinue</u>

- a. Recommended symptomatic measures (for all grades) includes topical steroids (e.g., hydrocortisone 1% or 2.5% cream), antihistamines, hypoallergenic moisturizers and emollients for dry skin (e.g., 5-10% urea in cetomacrogel cream or soft paraffin).
- b. Recommended course of oral steroids is methylprednisolone (or equivalent).

A dermatology consult should be considered for Grade ≥3 rash or multiple occurrences of Grade ≤2 rash.





Section 6.7.5 Guidelines for Management of Dyspepsia

REVISED TEXT

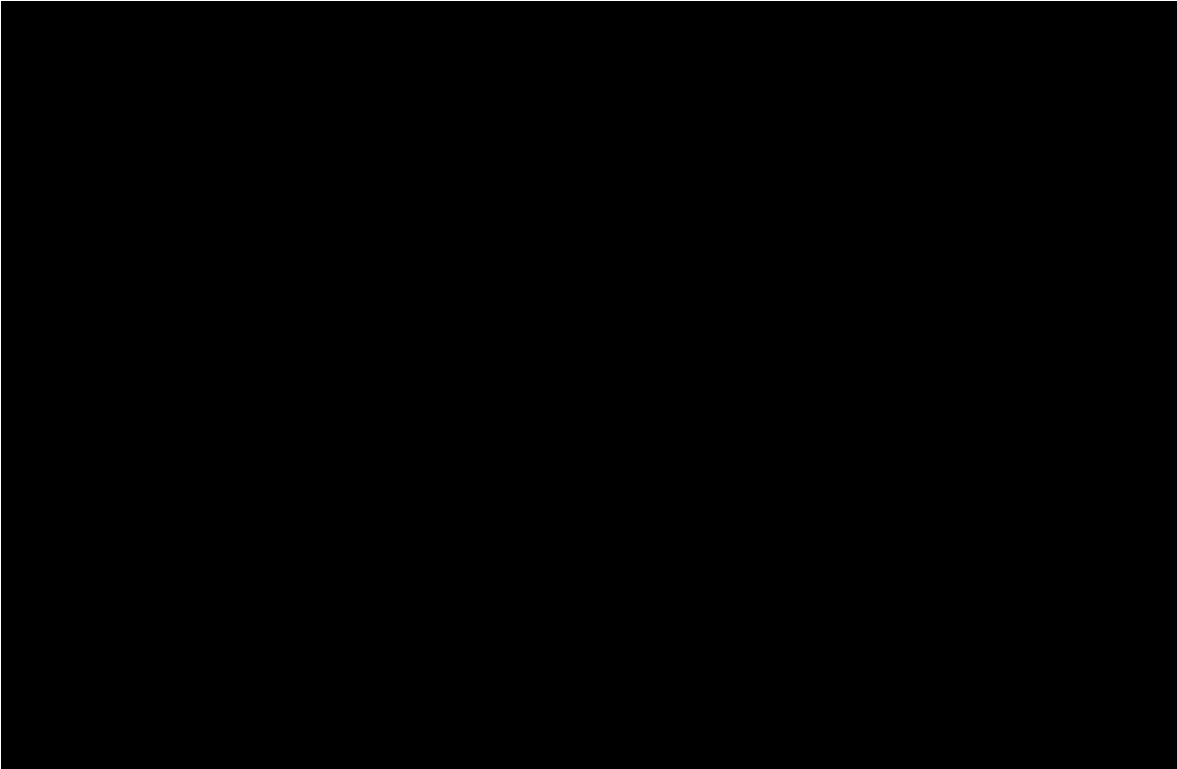
Based on nonclinical data and current clinical experience, it is possible that afuresertib may be a direct GI mucosal irritant such that subjects with GI dysmotility or GERD may be predisposed to symptoms of dyspepsia. Therefore, if a subject experiences symptoms supportive therapy will be provided according to standard medical practice. If Grade 1-2 dyspepsia, the investigator should consider the following recommendations:

- Afuresertib may be taken with or without food, except where specified (see Section 3.8.1 and Table 12).
- Capsules should be administered approximately 5 minutes apart with divided amounts of fluid (4-8 oz with each capsule for a total of at least 12 oz), except where specified (see Section 3.8.1).
- Subjects should remain upright for 30 min after taking afuresertib.

In more severe cases of dyspepsia, consider sucralfate and/or aluminum hydroxide with magnesium carbonate as supportive measures. These should be administered at least 2 hours after dosing to avoid any potential drug-drug interactions (see Section 7.2).

- Histamine H2-receptor antagonists (H2 blockers) or proton pump inhibitors may also be considered.

If the recommendations above are insufficient to resolve symptoms, or if active ulceration is suspected, investigators should consider additional tests such as upper endoscopy or barium radiography.



Section 6.7.6 Guidelines for Management of Mucositis

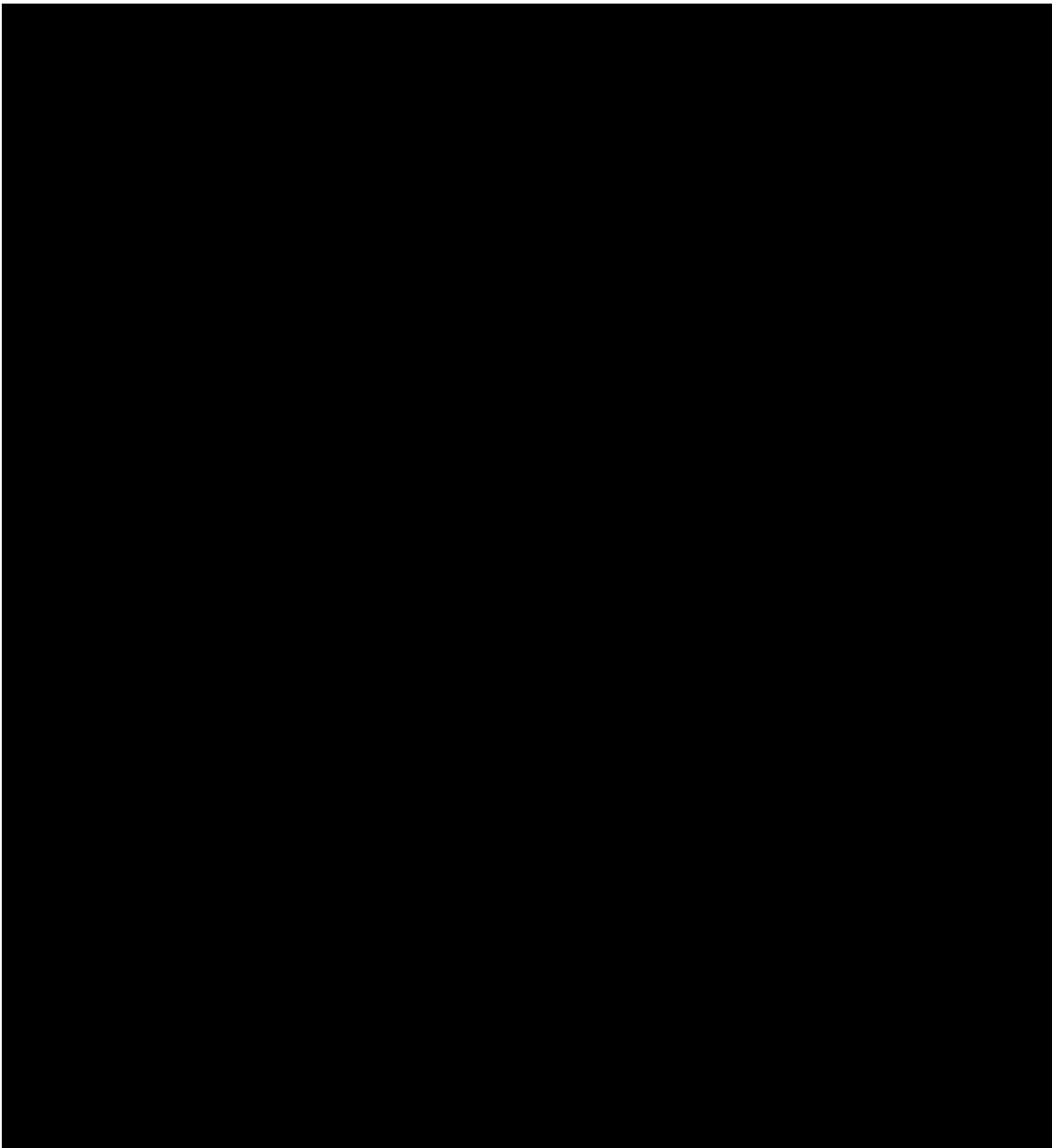
REVISED TEXT

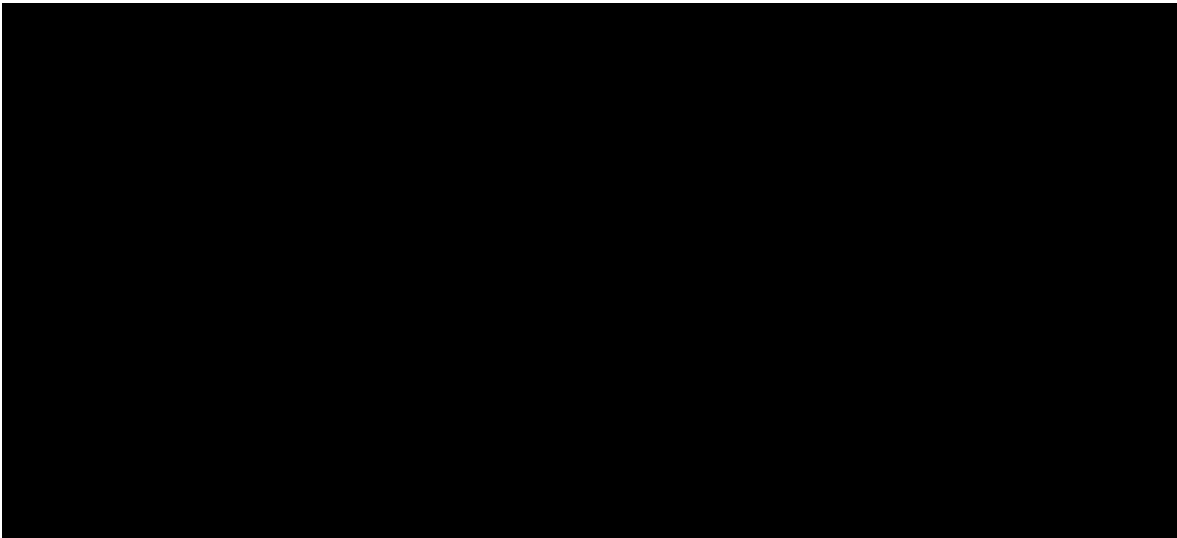
Ulceration throughout the GI tract was observed in nonclinical studies of afuresertib. Mucositis has also been reported as a consequence of treatment with AKT inhibitors. Prophylaxis for mucositis is recommended in subjects who are receiving afuresertib. This should include good oral hygiene (e.g., soft toothbrushes, rinsing and cleaning the oral cavity with water after every meal, and removal of dentures at the first sign of oral pain or inflammation) and preventive measures for lower GI symptoms (e.g., maintaining adequate hydration, reducing dairy intake in the event of lactose intolerance). Afuresertib should be held for episodes of mucositis \geq Grade 2. Recommended supportive measures include the following:

- Institute a soft diet and avoid acidic, salty, or dry foods

- Provide topical analgesics (e.g., 2% lidocaine solution), or coating agents. Parenteral analgesia may be required for more severe events.
- Work-up for infection, including oral candidiasis and viral infections. Empiric antibiotic treatment may be required while awaiting culture results, especially if high-grade neutropenia is present concurrently.
- Administer H2 blockers or proton-pump inhibitor if epigastric symptoms are also present.

Hospitalization may be required for more severe cases, especially if IV hydration, parenteral analgesia, or supplemental nutrition is required. Investigators should discuss afuresertib dosing with a GSK medical monitor before reinstating treatment after an episode of Grade 3 or 4 mucositis.





Section 6.7.7 Liver Chemistry Stopping Criteria

ADDED SECTION

Section 6.7.7.1 Actions if Liver Chemistry Stopping Criteria are met

When any of the liver chemistry stopping criteria are met, do the following:

- Immediately discontinue investigational product.
- Report the event to GSK within 24 hours of learning its occurrence.
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE.
- All events of ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN (>35% direct bilirubin) (or ALT $\geq 3 \times$ ULN and INR >1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE.**
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed.
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.
- Follow-up for overall survival is required following permanent discontinuation from investigational product.
- Do not re-challenge with investigational product.

In addition, for criterion 1 in Section 6.7.7:

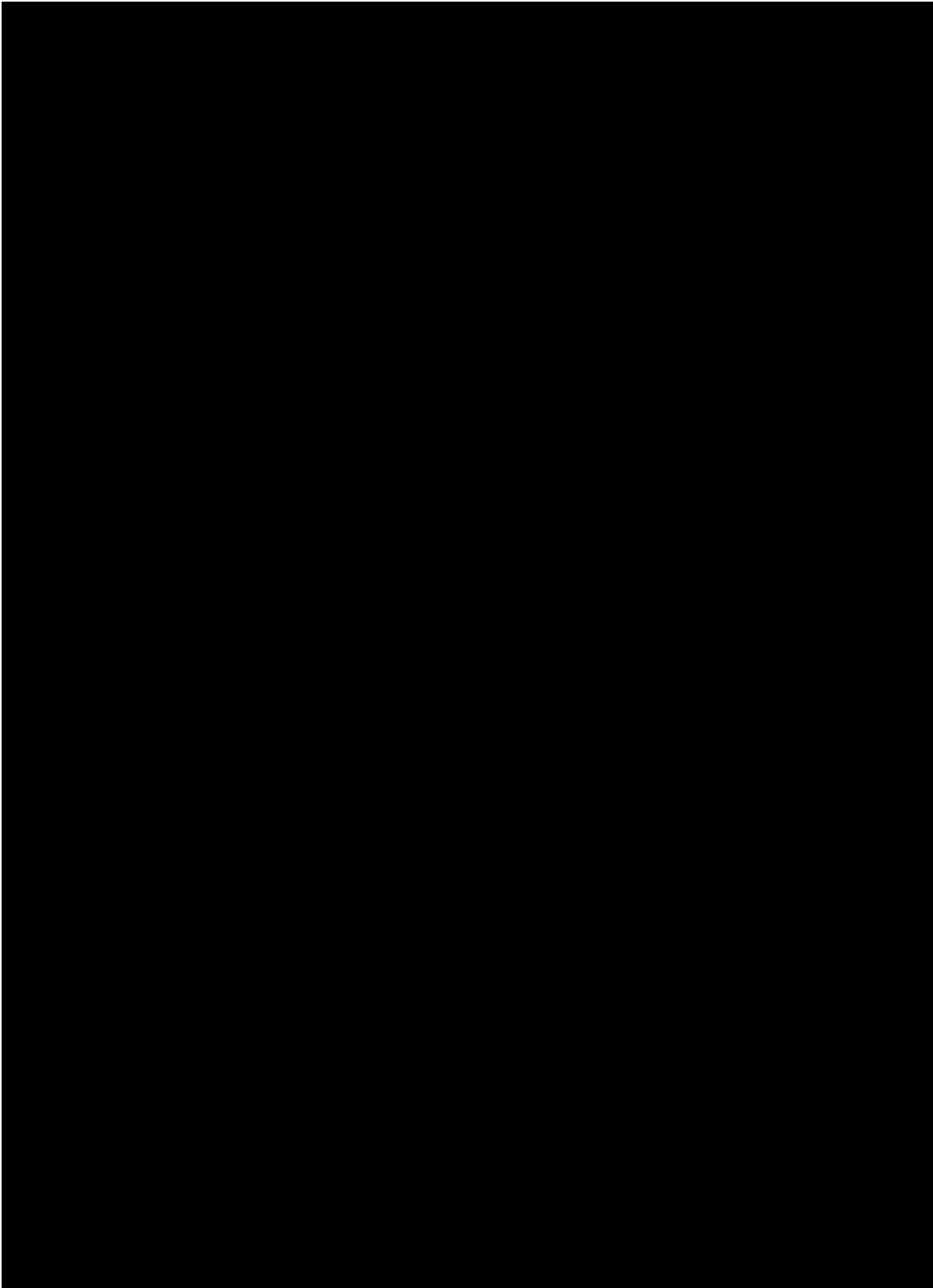
- Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow up assessments (refer to Section 6.7.7.2), and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin) resolve, stabilize or return to within baseline values.
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin) resolve, stabilize or return to within baseline values.

In addition, for subjects meeting any of the criteria 2-4 in Section 6.7.7:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (refer to Section 6.7.7.2).

Monitor subjects weekly until liver chemistries (ALT, AST, ALP, bilirubin) resolve, stabilize or return to within baseline values.

Also, refer to Appendix 3, Liver Chemistry Testing Procedures, for details of the assessments required if a subject meets any of the above criteria in the absence of disease progression.



Section 6.7.7.2 Liver Event Follow-Up Assessments

For subjects meeting any of the liver chemistry stopping criteria [REDACTED] make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology including:
 - Hepatitis A Immunoglobulin M (IgM) antibody
 - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)
 - Hepatitis C RNA.
 - Cytomegalovirus IgM antibody
 - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
 - Hepatitis E IgM antibody
- Blood sample for PK analysis, obtained within [REDACTED] 10 days of last dose of study treatment(s). Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment(s) prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

ADDED SECTION

Section 6.7.7.4 Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval by GSK after discussion with GSK medical monitor for drug restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required;
- If the restart/rechallenge is approved by GSK in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death;
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart;
- Study drug must be administered at the dose specified by GSK; and
- Subjects approved by GSK for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

Section 6.10 Treatment Compliance

REVISED TEXT

Paragraphs 2 and 3:

When dosing occurs outside of the study site, the subject will return all unused investigational product in the dispensed container on each return visit to the clinic, and study staff will note the number of capsules or tablets returned in the source documents. Subjects will maintain a daily dosing diary.

A record of the number of afuresertib capsules or tablets must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment interruptions and/or dose reductions will also be recorded in the eCRF.

Section 7 Concomitant Medications and Non-Drug Therapies

REVISED TEXT

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the electronic case report form (eCRF).

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

7.1 Permitted Medication(s) and non-Drug Therapies

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Paracetamol or acetaminophen, at the label-recommended dose, is permitted.

Medications which contain paracetamol or acetaminophen should be counted in label recommended dose. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

Concurrent treatment with bisphosphonates is permitted. Prophylactic use of bisphosphonates in subjects without metastatic bone disease is not permitted, except for the treatment of osteoporosis.

Current use of warfarin for therapeutic anticoagulation is not allowed (Note: low molecular weight heparin is permitted). Their use must be monitored in accordance with local institutional practice.

7.2 Prohibited Medication(s) and Non-Drug Therapies

Subjects should not receive anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormone therapy other than for replacement, surgery, and/or tumor embolization) directed towards the tumor for which they have been enrolled on the trial while on treatment in this study; although palliative radiation to control pain may be used following discussion with the GSK Medical Monitor.

Subjects should abstain from taking any herbal and dietary supplements within 5 half lives (or 14 days if the drug is a potential enzyme inducer) prior to study drug(s) dosing and until completion of the follow-up visit, unless there is little concern for a potential drug-drug interaction with the study drug(s). These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. The investigator should

contact a GSK Medical Monitor before initiating study treatment in a subject taking any herbal preparation.

Short courses (up to 7 days) of oral corticosteroids intended to treat study treatment related rash or diarrhea are allowed.

Erythropoiesis-stimulating agents and colony-stimulating factors like filgrastim and pegfilgrastim may be used as clinically indicated.

7.2.1 Drugs Potentially Affected by Afuresertib (afuresertib perpetrator interaction potential)

In vitro data indicate that afuresertib has the potential of being a perpetrator in drug-drug interactions through enzyme inhibition (with substrates of CYP3A4 and 2C8, IC₅₀ estimates of 3.7 to 6.0 µM and 6.3 µM, respectively), through transporter inhibition (with substrates of OATP1B1 and BCRP, IC₅₀ estimates of 1.7 µM and 2.9 µM) (Table 14). Co-administration of afuresertib and medications which are a sensitive substrate of CYP3A4, OATP1B1 and BCRP with a low therapeutic index will be prohibited. Co-administration of afuresertib and medications which are a sensitive substrate of CYP2C8 with a low therapeutic index will be used with caution. Other drugs affected by these enzymes and transporters should be used with caution and please refer to SPM.

Table 7 Drugs potentially affected by afuresertib

AVOID:

<u>CYP3A Substrate</u>	<u>Therapeutic Area</u>
carbamazepine	Anticonvulsants
ergotamine, dihydroergotamine	Antimigraine
pimozide	Antipsychotics
amiodarone, disopyramide, quinidine, bosentan	Cardiovascular Agents
cyclosporine, everolimus, sirolimus, tacrolimus	Immunosuppressive Agents
<u>OAT1B1 Substrate</u>	<u>Therapeutic Area</u>
methotrexate	Anti-cancer
<u>BCRP Substrate</u>	<u>Therapeutic Area</u>
topotecan	Anti-cancer
Note: Boceprevir and telaprevir (anti-HCV drugs) should be used with caution when combining with afuresertib.	

Table 8 Drugs Potentially Affected by Afuresertib:

Use with Caution

Generic Drug Name¹	Therapeutic Class
<u>CYP3A Substrate</u>	
<u>fentanyl</u>	<u>Analgesics</u>
<u>alfentanil, ropivacaine</u>	<u>Anesthetics</u>
<u>losartan</u>	<u>Angiotensin II inhibitors</u>
<u>ethosuximide, trimethadione</u>	<u>Anticonvulsants</u>
<u>bupirone, roboxetine, sertraline, trazodone, venlafaxine</u>	<u>Antidepressants/Anxiolytics</u>
<u>emadastine, loratadine</u>	<u>Antihistamines</u>
<u>artemether, halofantrine, lumefantrine, quinine</u>	<u>Antimalarial</u>
<u>erythromycin, clindamycin, rifabutin, rifampin</u>	<u>Antimicrobials</u>
<u>eletriptan</u>	<u>Antimigraine</u>
<u>α-dihydroergocriptine, bromocriptine</u>	<u>Anti-Parkinsonians</u>
<u>aripiprazole, bromperidol, clozapine, haloperidol, quetiapine</u>	<u>Antipsychotics</u>
<u>oxybutynin, tolterodine</u>	<u>Antispasmodics</u>
<u>osentan, delaviridine, tipranavir, nelfinavir</u>	<u>Antivirals</u>
<u>amlodipine, barnidipine, diltiazem, dofetilide, dronedarone, eplerenone, felodipine, nifedipine, pranidipine, propafenone, verapamil, vesnarinone</u>	<u>Cardiovascular Agents</u>
<u>sildenafil, tadalafil, vardenafil</u>	<u>Erectile dysfunction treatments</u>
<u>aprepitant, lansoprazole</u>	<u>Gastrointestinal Agents</u>
<u>atrovastatin, lovastatin, simvastatin</u>	<u>HMG CoA reductase inhibitors²</u>
<u>alprazolam, chlordiazepoxide, diazepam, flunitrazepam, midazolam, propofol, triazolam, zolpidem, zopiclone</u>	<u>Hypnotics and Sedatives</u>
<u>pioglitazone, repaglinide, rosiglitazone</u>	<u>Hypoglycemic agents</u>
<u>temsirolimus</u>	<u>Immunosuppressive Agents</u>

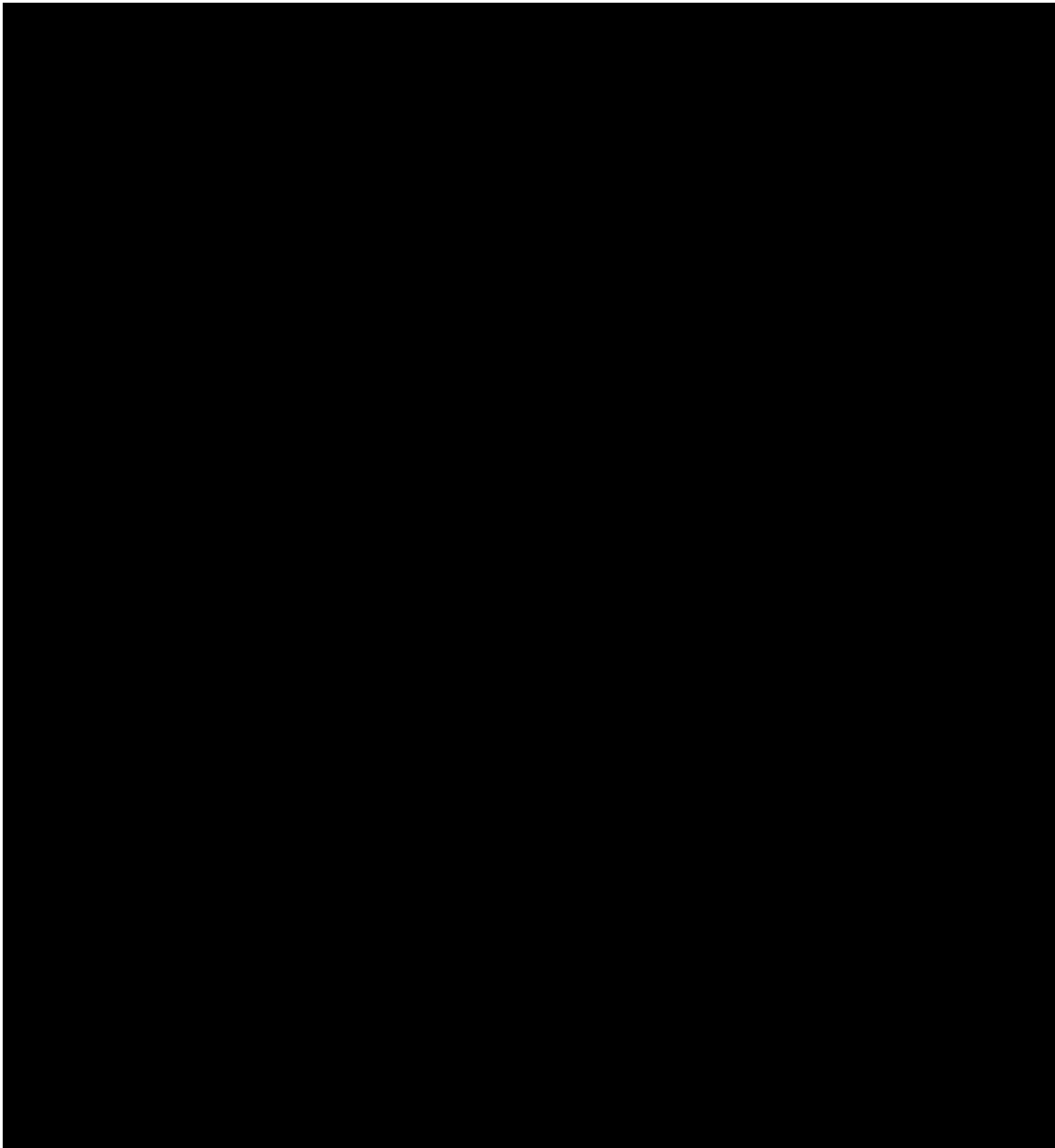
1. Please note some drugs may be listed more than once. This is due to the fact that they are substrates for both CYP and a transporter (e.g., OATP1B1, BCRP).
2. If subjects are on a high dose of a HMG CoA reductase inhibitor, dose reduction should be considered. Monitoring for toxicities (such as rhabdomyolysis) should be considered.

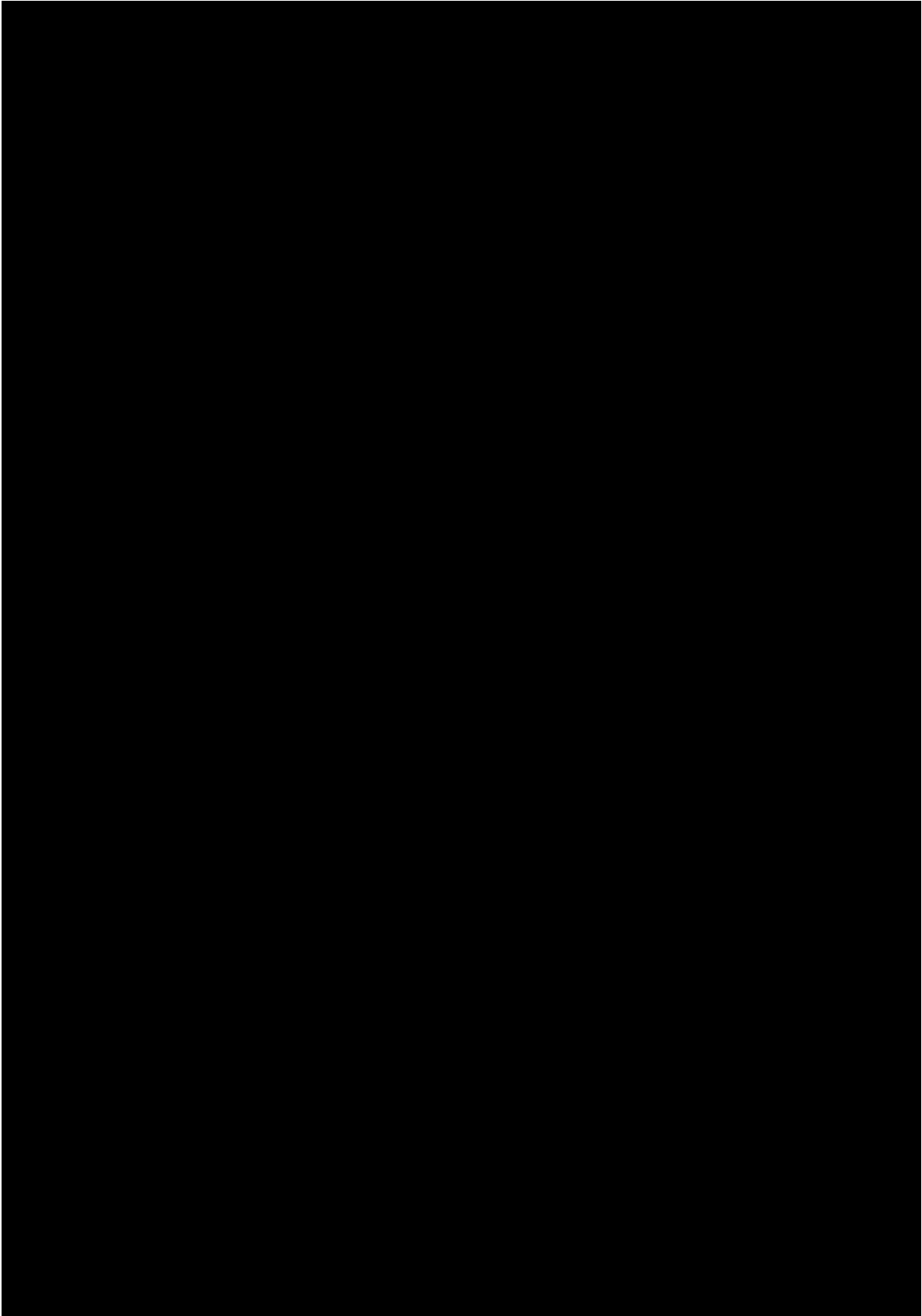
7.2.1.1 Drugs that may potentially affect afuresertib (perpetrators)

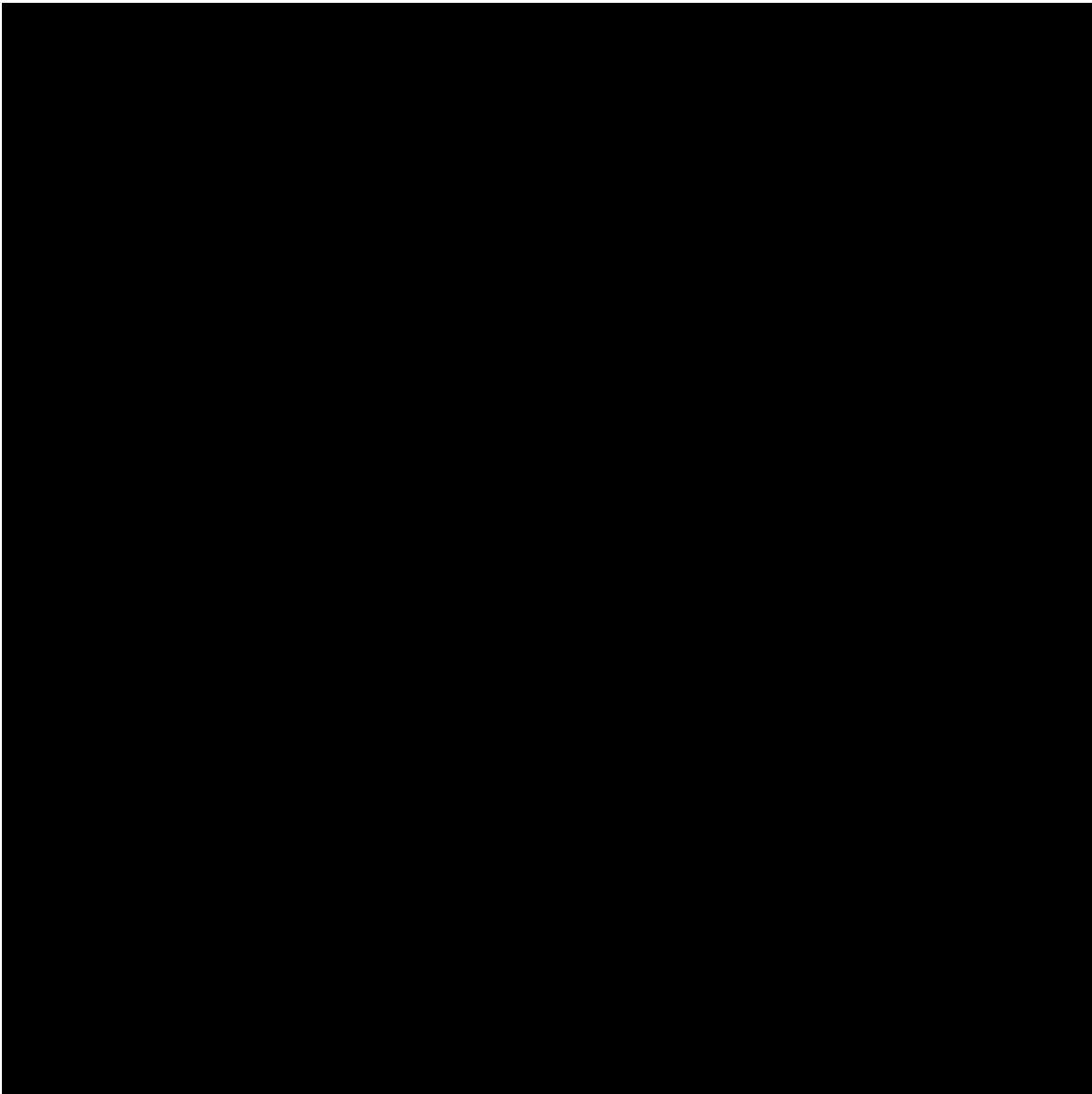
The metabolism of afuresertib may be mediated by CYP450 isozymes which may include CYP3A4 with possible contributions from CYP2D6 and CYP1A2. Afuresertib is a substrate of human P-gp and of murine Bcrp1. However, the relative contribution of the various pathways to the elimination of afuresertib is presently unknown. Substances that potently inhibit or induce these enzymes/transporters could lead to alterations in the pharmacologic effects of afuresertib and potentially much higher/lower exposure in subjects. Those medications which may alter afuresertib elimination and should be administered with caution and please refer to SPM.

Table 9 Drugs that may Potentially Affect Afuresertib: Use with Caution

Generic Drug Name	Therapeutic Class
<u>quinidine</u>	<u>Antiarrhythmics</u>
<u>fluvoxamine, fluoxetine, nefazodone, paroxetine</u>	<u>Antidepressants</u>
<u>fluconazole, itraconazole, ketoconazole, terbinafine, voriconazole</u>	<u>Antifungals</u>
<u>ciprofloxacin, clarithromycin, erythromycin, isoniazid, telithromycin, troleandomycin</u>	<u>Anti-infectives</u>
<u>amprenavir, atazanavir, delaviridine, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir</u>	<u>Antivirals</u>
<u>all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)</u>	<u>Antibiotics</u>
<u>phenobarbital, oxandrolone, tizanidine, gemfibrozil</u>	<u>Miscellaneous</u>



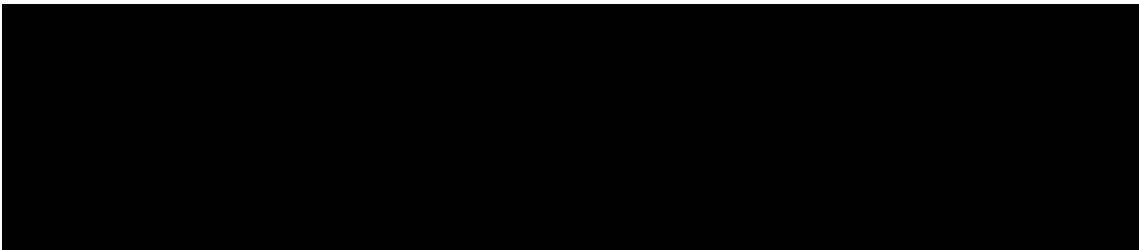




Section 8.3 Meals and Dietary Restrictions

REVISED TEXT

[REDACTED] Subjects may take afuresertib without regard to food. For combination medications, please use its meal and dietary restrictions. Subject should take afuresertib dose at approximately same time each day.



In addition, subjects shall abstain from ingestion of any food or drink containing grapefruit and grapefruit juice, Seville oranges, or pommelos within 7 days prior to the first dose of afureserib until the end of the study.

Section 12 References

REVISED REFERENCE

GlaxoSmithKline Document Number 2011N113491_03. GSK2110183 Investigator's Brochure. Report Date: SEP-2014.

Appendix 2 Time and Events Table for Cohort C

ECHO/MUGA scan assessments were deleted from the table.

Appendix 3: Liver Safety Drug Restart Guidelines

REVISED TEXT

Drug restart may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if there is favorable benefit: risk ratio and no alternative medicine available.

Background Information on Drug Restart/Rechallenge

Following drug-induced liver injury, **drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies.**¹ Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity¹ with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin \geq 2xULN or INR $>$ 1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge^{2,3} or evidence of drug-related preclinical liability / mitochondrial impairment³.

Drug Restart/Rechallenge Process (also see Figure 2)

1. Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment.
2. GSK Medical Monitor & Clinical Safety Physician to review the subject's restart/rechallenge risk factors & complete checklist (Table 10).

Table 10 Checklist for drug restart/rechallenge for critical medicine

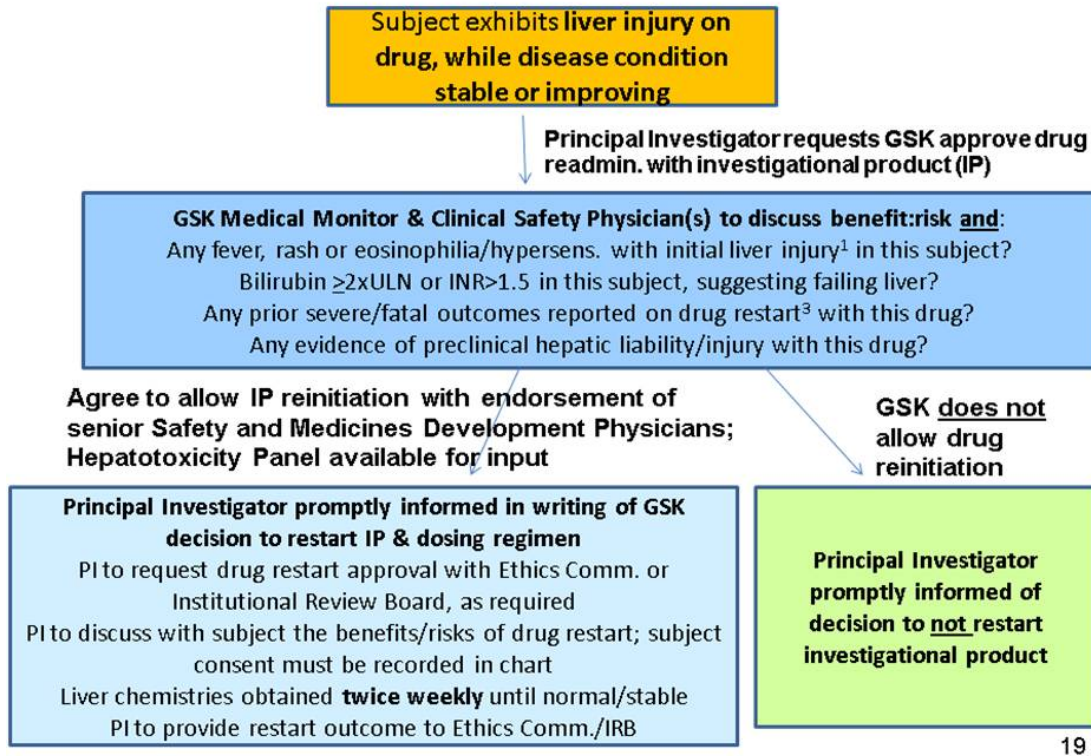
<u>(Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)</u>		
	<u>Yes</u>	<u>No</u>
<u>Compelling benefit of the investigational product (IP) for this subject and no alternative therapy. Provide brief explanation:</u>		
<u>Relative benefit-risk favorable for drug restart/rechallenge, after considering the following high risk factors:</u>		
• <u>Initial liver injury event included:</u>		
– <u>fever, rash, eosinophilia, or hypersensitivity</u>		
– <u>or bilirubin ≥2xULN (direct bilirubin >35% of total)</u>		
• <u>Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR ≥1.5</u>		
• <u>Severe or fatal restart/rechallenge has earlier been observed with IP If yes, please provide brief explanation:</u>		
• <u>IP associated with known preclinical hepatic liability/ injury</u>		

3. If GSK provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:
- The PI is to obtain Ethics Committee or Institutional Review Board review of drug re-initiation, as required.
 - PI must discuss the possible benefits and risks of drug re-initiation with the subject.
 - The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent specifically for the IP restart must be recorded in the study chart.
 - The drug must be reinitiated at GSK approved dose(s).
 - Subjects approved by GSK for restart of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.
 - The Ethics Committee or Institutional Review Board is to be informed of the subject's outcome, as required.

- GSK is to be notified of any adverse events, as per Section 8.5.2.

Figure 2 Algorithm for Drug Restart After Possible Drug-induced Liver Injury

GSK process for drug restart after possible drug-induced liver injury



19

¹Andrade RJ. Expert Opin Drug Saf 2009;8:709-714. ²Papay JI. Regul Tox Pharm 2009;54:84-90. ³Hunt CM. Hepatol 2010;52:2216-2222.

References:

1. Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf 2009;8:709-714.
2. Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. Regul Toxicol Pharmacol 2009;54:84-90.
3. Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: a systematic review. Hepatology 2010;52:2216-2222

AMENDMENT 3

Where the Amendment Applies

This amendment applies to all investigator sites participating in this study.

Summary of Amendment Changes with Rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound GSK2110183, the purpose of this protocol Amendment 03 is to:

- Delete or replace references to GlaxoSmithKline or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

List of Specific Changes

Title Page:

REVISED TEXT

The title page replaced as per Novartis requirements.

Section: Sponsor Signatory

REVISED TEXT

[REDACTED]

[REDACTED]

Date

OGD OCD INC/PKC

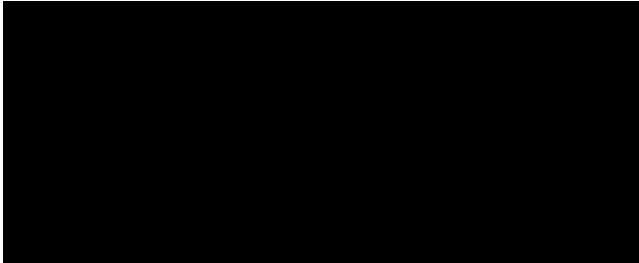
Phone:

Email:

Section: Sponsor Information Page

REVISED TEXT

[REDACTED] **Medical Lead Contact Information:**
[REDACTED]



Novartis Pharmaceuticals Corporation

One Health Plaza, Bldg 337/

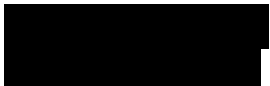
East Hanover, NJ 07936-1080 USA

Phone:

Mobile:

Email:

www.novartis.com



Contact Information:

Novartis Pharmaceuticals Corporation

One Health Plaza

Bldg. 337/

East Hanover,

NJ 07936-1080

USA

Phone:

Mobile:

Email:

If you have any questions regarding the protocol, please contact your local Novartis office

Section: Abbreviations

TEXT ADDED:

GCPH	Global Clinical Program Head
-------------	-------------------------------------

Section: PROTOCOL SYNOPSIS

REVISED TEXT

- PROTOCOL/AMENDMENT NO.: PKB115131/Amendment 03

- OBJECTIVES: To provide continued treatment with afuresertib for subjects who have completed participation in a [REDACTED] Novartis sponsored afuresertib study, or an afuresertib study sponsored by another research organization working on behalf of [REDACTED] Novartis. Additional safety information about afuresertib will also be collected.

Section: 1.1.1 Afuresertib

REVISED TEXT

The investigator should refer to the current version of the afuresertib Investigator's Brochure (IB) [REDACTED] [REDACTED] for detailed information regarding all completed and ongoing clinical studies with afuresertib, PK in the target disease populations, as well as observed safety and clinical activity findings.

Section: 1.1.2 Pharmacokinetics of Afuresertib in Humans

For details of the PK of afuresertib see the current version of the IB [REDACTED]

Mean dexamethasone exposure co-administered with bortezomib was 30-50% higher when dosed with afuresertib than without afuresertib; although sample size was small (n=5) and exposure values overlapped [REDACTED]

Section: 1.1.3 Clinical Safety of Afuresertib

REVISED TEXT

As of 29-Jun-2013, 226 subjects had received at least 1 dose of afuresertib either as monotherapy or in combination with other agents in the 7 original GSK-sponsored studies with afuresertib.

Additional information from all studies where subjects with other diseases are administered afuresertib, as monotherapy or in combination, can be found in the current afuresertib IB- [REDACTED]

Section 1.1.6 Clinical Activity of Afuresertib

REVISED TEXT

Additional information from all studies where subjects with other diseases are administered afuresertib, as monotherapy or in combination, can be found in the current afuresertib IB- [REDACTED]

Section 1.2.1 Study Rationale

REVISED TEXT

The purpose of this study is to allow for continued treatment with afuresertib in subjects who have participated in a 'parent' GSK **or Novartis** sponsored study of afuresertib, either as monotherapy or as part of a combination regimen, and met the protocol requirements for transitioning to this rollover study.

Section 1.2.2 Dose Rationale

REVISED TEXT

If a subject required a dose modification while receiving treatment in the parent study, the subject will enter the rollover study and continue treatment on the modified dose unless after consultation with the [REDACTED] **Novartis Medical [REDACTED] Lead**, it is appropriate to escalate the dose.

If a subject required a dose modification while receiving treatment in the parent study, the subject will enter the rollover study and continue treatment on the modified dose unless after consultation with the [REDACTED] **Novartis Medical [REDACTED] Lead**, it is appropriate to escalate the dose. Any dose modifications will follow parent protocol or most recent prescribing information.

Section: 1.3 Summary of Risk Management

REVISED TEXT

Summaries of findings from clinical and nonclinical studies conducted with afuresertib can be found in the current IB- [REDACTED]

Section: 2.1 Primary

REVISED TEXT

The primary objective of the study is to provide treatment with afuresertib for subjects who have previously participated in an afuresertib study sponsored **previously** by GSK **or Novartis or** another research organization working on behalf of [REDACTED] **Novartis**.

Section: 3.2. Study Design

REVISED TEXT

After informed consent is obtained, subjects will be evaluated for study eligibility in PKB115131/CASB183X2X01B.

Section: 3.2.1 Cohort A and Cohort B: Afuresertib Monotherapy

REVISED TEXT

Subjects will receive afuresertib as an oral, daily dose up to 150 mg. Protocol specified guidelines for dose modifications and treatment discontinuation criteria are provided in Section 6.6 and Section 6.7, respectively. If there are any uncertainties about the dose to be administered in this study, the [REDACTED] Novartis Medical [REDACTED] Lead should be consulted.

Subjects will complete the Transition Visit; receive instruction and study medication, and then return for their next scheduled visit (Study Week 4) and then every 4 weeks thereafter. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to every 8 weeks with approval from the [REDACTED] Novartis Medical [REDACTED] Lead. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

Subjects will complete the Transition Visit, receive study instruction and study medication and then return for their next scheduled visit (Study Week 4), and then every 4 weeks thereafter. Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to every 8 weeks with approval from the [REDACTED] Novartis Medical [REDACTED] Lead. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

Section: 3.2.2 Cohort C: Afuresertib Combination Therapy

REVISED TEXT

Subjects who remain on study treatment for >52 weeks (including time on parent study) may have the frequency of their interim visits decreased with approval from the [REDACTED] Novartis Medical [REDACTED] Lead to every 8 or 9 weeks (whichever is consistent with parent schedule). After discontinuation of study treatment, the investigator will monitor all AEs/SAEs for 30 days or until resolution, whichever comes first.

Section: 4.1.2 Inclusion Criteria

REVISED TEXT

- 2 Is currently participating in an afuresertib study (monotherapy or in combination with another anti-cancer agent) sponsored by GSK/Novartis or by another research organization working on behalf of [REDACTED] Novartis.

Section: 4.1.3 Exclusion Criteria

REVISED TEXT

- 15 Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions at the time of transition to this study that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the investigator or [REDACTED] Novartis Medical [REDACTED] Lead.

Section: 4.1.4 Other Eligibility Criteria Considerations

REVISED TEXT

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the [REDACTED] Novartis investigational product(s) or other study treatment being used in this study: IB for afuresertib [REDACTED], product label(s) for other commercially available co-administered agents.

Section: 5 Study Assessments and Procedures

REVISED TEXT

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. The change in timing for any planned study assessments must be approved and documented by [REDACTED] Novartis, but this will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme.

Section: 5.2.1 Cohort A and B

REVISED TEXT

Once the subject has been on study drug for >52 weeks (including the time on parent study), and after confirmation with Medical [REDACTED] Lead the frequency of those assessments can be decreased to every 8 weeks (±3 days).

Section: 5.2.2 Cohort C

REVISED TEXT

Once the subject has been on study drug for >52 weeks (including the time on parent study), and after confirmation with Medical [REDACTED] Lead the frequency of these assessments can be decreased to every 8 or 9 weeks (± 3 days) (whichever is consistent with the parent schedule).

Section: 5.4.4 Clinical Laboratory Assessments

REVISED TEXT

All laboratory tests with values that are significantly abnormal during study participation or within 28 days after the last dose of study treatment(s) should be repeated until the values return to within normal range or baseline. All subjects who have a Grade 3 or 4 laboratory abnormality at time of study withdrawal must be followed until resolution to Grade 2 or less, unless it is unlikely to improve due to underlying disease. If such values do not return to within normal range within a period judged reasonable by the investigator, the etiology should be identified and the [REDACTED] Novartis Medical [REDACTED] Lead notified.

Section: 5.8.2 Action to be taken if pregnancy occurs

REVISED TEXT

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to [REDACTED] Novartis within [REDACTED] 24 hours of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to [REDACTED] Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to [REDACTED] Novartis as described in Section 5.9.1.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Section: 5.8.3 Action to be taken if pregnancy occurs in a female partner of a male study subject

REVISED TEXT

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to [REDACTED] Novartis within [REDACTED] 24 hours of learning of the partner's pregnancy. The

partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to [REDACTED] Novartis. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Section: 5.9.1.5 Time Period and Frequency of Detecting AEs and SAEs

REVISED TEXT

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment [REDACTED] [REDACTED] must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to [REDACTED] Novartis within 24 hours, as indicated in Section- [5.9.1.6](#).

Section: 5.9.1.6 Prompt Reporting of Serious Adverse Events and Other Events to GSK

REVISED TEXT

5.9.1.6 Prompt Reporting of Serious Adverse Events and Other Events to [REDACTED] Novartis

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to [REDACTED] Novartis as described in the following table once the investigator determines the event meets the protocol definition for that event.

Table 11 Serious Adverse Events

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry abnormalities Phase II:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5	24 hours ¹	SAE data collection tool. Liver Event eCRF and liver imaging and/or biopsy CRFs if applicable ²	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF ²
ALT ≥3 times ULN with hepatitis or rash or 5 times ULN ≥2 weeks (if no liver involvement) or ALT ≥8 times ULN if liver involvement present at enrollment;	24 hours ¹	Liver Event eCRF ²	24 hours	Updated Liver Event eCRF ²
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours ¹	Liver event eCRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks ²		

1 [REDACTED] Novartis to be notified at onset of liver chemistry elevations to discuss subject safety.

2 Liver event documents should be completed as soon as possible

Section: 5.9.1.7 Regulatory Reporting Requirements For SAEs

REVISED TEXT

Prompt notification of SAEs by the investigator to [REDACTED] Novartis is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

[REDACTED] Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

██████ Novartis will comply with country specific regulatory requirements relating to safety reporting to regulatory authorities, IRBs/IECs and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and ██████ Novartis policy and are forwarded to investigators as necessary. An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from ██████ Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Section: 6.1 Afuresertib Investigational Product Dosage/Administration

REVISED TEXT

Afuresertib will be provided to sites by ██████ Novartis. The contents of the label will be in accordance with all applicable regulatory requirements. No special preparation of afuresertib is required.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff, although adequate precautions are to be taken to avoid direct contact with study medication. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to the site staff if required by local laws or will otherwise be available from ██████ Novartis upon request.

Section: 6.2 Other Anti-Cancer Agents (Cohort C)

REVISED TEXT

When the treatment regimen to be administered includes another anti-cancer agent(s) in combination with afuresertib, the sites will be responsible for obtaining the necessary drug supply for the anti-cancer agent(s) through commercial means; the drug(s) will not be supplied by ██████ Novartis. The use of an anti-cancer agent(s) in combination with afuresertib that was not part of the parent study is not permitted. Refer to the Prescribing Information for each anti-cancer agent for information regarding the physical and chemical properties, storage, and dosing/administration guidelines.

Section: 6.5 Treatment Assignment

REVISED TEXT

Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the ██████ Novartis interactive voice response system (IVRS), by the investigator or authorized site staff.

Section: 6.6 Dose Modifications

REVISED TEXT

Guidelines for afuresertib dose modifications are provided below. Investigators should also consult the [REDACTED] Novartis Medical [REDACTED] Lead and refer to the afuresertib IB [REDACTED] or the prescribing information for the appropriate anti-cancer combination agent for detailed information regarding warnings, precautions, contraindications, AEs, and recommendations for supportive care in the event of drug-related toxicity.

Section: 6.6.1 Afuresertib Dose Modification

REVISED TEXT

Treatment with afuresertib may be delayed for up to 14 days to allow resolution of toxicity or based on investigator discretion. If the investigator and the [REDACTED] Novartis Medical [REDACTED] Lead conclude that continued treatment will benefit a subject who has experienced a treatment delay >14 days, then the subject may continue afuresertib therapy with the approval of the [REDACTED] Novartis Medical [REDACTED] Lead.

A maximum of 2 dose reductions (including reductions from the parent study) of afuresertib is permitted and each of them requires consultation with the [REDACTED] [REDACTED] -Novartis Medical Lead. Dose reductions should be to a lower dose level previously studied in an afuresertib clinical study. If a third dose reduction or a dose reduction below 75mg is required, treatment with afuresertib should be discontinued and subject should be withdrawn from study.

Section: 6.7.2 Supportive Measures for Hyperglycemia

REVISED TEXT

If significant hyperglycemia (e.g., fasting glucose ≥ 200 mg/dL) persists despite treatment and after stopping systemic glucocorticoids (where applicable), or in the event of life-threatening complications, dose modification of afuresertib should also be considered, after discussion with a [REDACTED] -Novartis Medical Lead. Dose modification of afuresertib should not be performed for asymptomatic hyperglycemia, or hyperglycemia that responds to other interventions.

Section: 6.7.6 Guidelines for Management of Mucositis

REVISED TEXT

Hospitalization may be required for more severe cases, especially if IV hydration, parenteral analgesia, or supplemental nutrition is required. Investigators should discuss afuresertib dosing with a [REDACTED] Novartis Medical Lead before reinstating treatment after an episode of Grade 3 or 4 mucositis.

Section: 6.7.6 Guidelines for Management of Mucositis

REVISED TEXT

Hospitalization may be required for more severe cases, especially if IV hydration, parenteral analgesia, or supplemental nutrition is required. Investigators should discuss afuresertib dosing with a [REDACTED] **Novartis Medical Lead** before reinstating treatment after an episode of Grade 3 or 4 mucositis.

Section: 6.7.7.1 Actions if Liver Chemistry Stopping Criteria are met

REVISED TEXT

- Report the event to [REDACTED] **Novartis** within 24 hours of learning its occurrence.

Section: 6.7.7.3 Liver Chemistry Monitoring Criteria

REVISED TEXT

- Notify the [REDACTED] **Novartis Medical [REDACTED] Lead** within 24 hours of learning of the abnormality to discuss subject safety.

Section: 6.7.7.4 Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

REVISED TEXT

Approval by [REDACTED] **Novartis** after discussion with [REDACTED] **Novartis Medical Lead** for drug restart can be considered where:

- If the restart/rechallenge is approved by [REDACTED] **Novartis** in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death;
- Study drug must be administered at the dose specified by [REDACTED] **Novartis**; and
- Subjects approved by [REDACTED] **Novartis** for restart/rechallenge of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

Section: 6.9 Product Accountability

REVISED TEXT

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of [REDACTED] **Novartis** investigational product (IP) dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to [REDACTED] **Novartis**, when applicable. Product accountability records must be

maintained throughout the course of the study. Refer to the SPM for further detailed instructions on IP accountability.

Section: 7 Concomitant Medications and Non-Drug Therapies

REVISED TEXT

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by [REDACTED] **Novartis** and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

Section: 7.1 Permitted Medication(s) and non-Drug Therapies

REVISED TEXT

Medications which contain paracetamol or acetaminophen should be counted in label recommended dose. Other concomitant medication may be considered on a case by case basis by the [REDACTED] **Novartis Medical [REDACTED] Lead**.

Section: 7.2 Prohibited Medication(s) and Non-Drug Therapies

REVISED TEXT

Subjects should not receive anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormone therapy other than for replacement, surgery, and/or tumor embolization) directed towards the tumor for which they have been enrolled on the trial while on treatment in this study; although palliative radiation to control pain may be used following discussion with the [REDACTED] **Novartis Medical [REDACTED] Lead**.

Subjects should abstain from taking any herbal and dietary supplements within 5 half lives (or 14 days if the drug is a potential enzyme inducer) prior to study drug(s) dosing and until completion of the follow-up visit, unless there is little concern for a potential drug-drug interaction with the study drug(s). These herbal medications include, but are not limited to, St. John's wort, kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng. The investigator should contact a [REDACTED] **Novartis Medical [REDACTED] Lead** before initiating study treatment in a subject taking any herbal preparation.

Section: 9 Data Management

REVISED TEXT

For this study, data will be collected using [REDACTED] **the eCRFs**, transmitted electronically to [REDACTED] **the sponsor (or designee)** and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable [REDACTED] **Novartis** standards and data cleaning procedures to ensure the integrity of the data, e.g., resolving errors and inconsistencies in the data. AEs and concomitant medications

terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and [REDACTED] custom drug dictionary [REDACTED]

All laboratory data (i.e., hematology, clinical chemistry, liver function, coagulation, and serum pregnancy tests) will be entered into the eCRF.

[REDACTED]

Section: 10.3.2 Analysis Data Sets

REVISED TEXT

Construction of data sets relating to the reporting and analysis of study data will be performed in accordance with all applicable [REDACTED] [REDACTED] Novartis standards and procedures.

Section: 10.4 Analysis Data Sets

REVISED TEXT

Data will be listed and summarized according to the [REDACTED] Novartis reporting standards, where applicable. Complete details will be documented in the Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

Section: 11.2 Regulatory and Ethical Considerations, Including the Informed Consent Process

REVISED TEXT

Prior to initiation of a study site, [REDACTED] Novartis will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements including a US IND.

[REDACTED] Novartis will provide full details of the above procedures, either verbally, in writing, or both.

Section: 11.4 Quality Control (Study Monitoring)

REVISED TEXT

In accordance with applicable regulations, ICH GCP, and [REDACTED] Novartis procedures, [REDACTED] [REDACTED] Novartis personnel (or designated Clinical Research Organization [CRO]) will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and [REDACTED] Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

Section: 11.5 Quality Assurance

REVISED TEXT

To ensure compliance with ICH GCP and all applicable regulatory requirements, [REDACTED] Novartis may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

Section: 11.6 Study and Site Closure

REVISED TEXT

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and [REDACTED] Novartis Standard Operating Procedures.

GSKNovartis reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If [REDACTED] Novartis determines that such action is required, [REDACTED] Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, [REDACTED] Novartis will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, [REDACTED] Novartis will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. [REDACTED] Novartis will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

Section: 11.7 Records Retention.

REVISED TEXT

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a [REDACTED] Novartis audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

[REDACTED]

[REDACTED]

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify [REDACTED] Novartis of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

Section: 11.8 Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

REVISED TEXT

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a [REDACTED] Novartis site or other mutually-agreeable location.

GSKNovartis will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

[REDACTED] Novartis aims to post a results summary [REDACTED] to the Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) [REDACTED] and other publicly available registers no later than twelve (12) months [REDACTED] after the last subject's last visit (LSLV). In addition, [REDACTED] upon study completion and finalization of study report, Novartis aims to submit results of the study for publication. [REDACTED] When [REDACTED] -publication [REDACTED] -is not feasible, [REDACTED] please refer to the [REDACTED] Novartis Clinical Trial Results website (www.novartisclinicaltrials.com) [REDACTED] for a summary of the trial results.

Section: Appendix 1: Time and Events Table for Cohort A and B

REVISED TEXT

11 Subjects who remain on study treatment >52 weeks (including time on parent study) may have the frequency of their interim visits decreased to once every 8 weeks with approval from the [REDACTED] Novartis Medical [REDACTED] Lead

Section: Appendix 2: Time and Events Table for Cohort C

REVISED TEXT

- 12 If the subject was treated on a 3 weeks schedule during parent study- he/she will remain on this schedule for the first 52 weeks of treatment (including the time on parent study). After 52 weeks the frequency of the visits may/can be reduced to every 8 or 9 weeks. If the subject was on 4-week schedule on the parent study he/she will remain on this schedule for the first 52 weeks (including time on parent study). After 52 weeks the frequency of visits can be decreased to every 8 weeks with approval of [REDACTED] Novartis Medical [REDACTED] Lead.

Section: Appendix 3: Liver Safety Drug Restart Guidelines

REVISED TEXT

- 2 [REDACTED] Novartis Medical [REDACTED] Lead & Clinical Safety Physician- to review the subject's restart/rechallenge risk factors & complete checklist ([Table 10](#))
- 3 If [REDACTED] Novartis provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:
 - The drug must be reinitiated at [REDACTED] Novartis approved dose(s).
 - Subjects approved by [REDACTED] Novartis for restart of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.
 - [REDACTED] Novartis is to be notified of any adverse events, as per [Section 5.9](#).