TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A rollover study to provide continued treatment with GSK1120212 to subjects with solid tumors or leukemia

Compound Number: GSK1120212 / NCT01376310

Effective Date: 06-FEB-2014

Protocol Amendment Number: 7

Subject: GSK1120212 **(Trametinib)**, MEK inhibitor, solid tumors, leukemia, safety, cancer.

Author:

[redacted]

Copyright 2014 the GlaxoSmithKline group of companies. All rights reserved.
Unauthorised copying or use of this information is prohibited.

MEMORANDUM

Protocol: MEK114375

Title: A rollover study to provide continued treatment with GSK1120212 to subjects with solid tumors or leukemia

To: [redacted], Investigators, and LOCs

From: [redacted], GSK) [redacted]

Date: 27 February 2014

RE: MEK114375 Amendment 7, 06 February 2014, Protocol Section 5.7.5. Stopping Criteria Visual Changes, Grade 2 or Grade 3 Visual Changes, Sub-Bullet #2

An error of omission occurred in the above referenced section for Protocol Amendment 7. Currently the second sub-bullet under Grade 2 or Grade 3 Visual Changes reads:

- If RPED is diagnosed (symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL, perform retinal evaluation monthly and if improves to ≤ Grade 1, resume treatment with GSK1120212 at lower dose (reduced by 0.5 mg) or discontinue in subjects taking GSK1120212 1 mg daily.

The second sub-bullet should read:

- If RPED is diagnosed (symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL**), report as a SAE,** perform retinal evaluation monthly and if improves to ≤ Grade 1, resume treatment with GSK1120212 at lower dose (reduced by 0.5 mg) or discontinue in subjects taking GSK1120212 1 mg daily.

Section 5.7.5. Stopping Criteria Visual Changes, Grade 2 or Grade 3 Visual Changes, will be revised in the next protocol amendment.

Revision Chronology:

RM2010/00127/00	2010-NOV-15	Original
RM2010/00127/01	2011-MAY-26	Amendment No.:1

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Removed reference to "a GSK-sponsored" GSK1120212 study throughout document as subjects may be transitioned to the rollover study from studies conducted/sponsored by other groups such as NCI
- Revised the following sections to reflect revision in study objective stating intent of study is to allow subjects to continue treatment if clinically benefitting (allowing for continued treatment for subjects who have clinically progressed if agreed upon by treating physician and GSK Medical Monitor : description, protocol summary, objective, study design, and inclusion criteria (#4)
- Added Section 5.7.6.1, French specific QTc stopping criteria
- Revised text in Section 5.1 and Section 7.1 to clarify administration of GSK1120212

		in a fasting state as "1 hour before or 2 hours after a meal". • Revised list of References and removed those references not cited in protocol • Added country specific requirements for Australia (investigational product availability) and France (QTc stopping criteria)
RM2010/00127/02	2011-DEC-15	Amendment 2: • [redacted] • Updated the fax number for the Primary Medical Monitor • Section 1.1, Background: revised to reflect updated information from Investigator's Brochure • Section 1.2, Summary of Risk Management: inserted new section and text to include risk management of potential risks of ocular toxicity, cardiac function and GI toxicity and cutaneous toxicity. • Section 1.2, Study Rationale: renumbered to Section 1.3. • Section 5.1, GSK1120212 GSK Investigational Product: title of section revised to "Investigational Product"; inserted new table for GSK1120212 GSK Investigational Product (Commercial Image Product). • Section 5.7.7.1 Left Ventricular Ejection Fraction Stopping

		Criteria: revised to provide a parameter for LVEF when lower limit of normal does not exist • Section 8.2.1 Cohort A, Section 8.2.2 Cohort B, and Section 8.3 Final Visit: clarified text describing timing of ECHO or MUGA scans to clearly indicate that ECHO or MUGA should be performed 12 weeks from date of last assessment and not from the date of transition to rollover unless ECHO or MUGA is performed at that time. • Section 12, References: revised citation for GSK1120212 IB version 03, issued on 23 Jun 2011 • Section 13.1 and Section 13.2, Time and Events Tables for Cohort A and Cohort B, respectively: table revised to show liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) as separate assessments from rest of clinical chemistry laboratory tests. Footnote added to clarify tests included in liver function tests; footnotes renumbered due to insertion of new footnote. • Appendix 7 added to capture changes in Amendment 02.
RM2010/00127/03	2012-FEB-06	Amendment No. 3: • Abbreviations: updated to include abbreviations used in revised text • Protocol Summary: revised to reflect changes made in the Background section • Section 1.1, Background,

paragraph 2: revised text describing GSK1120212 in regards to its inhibitory activity and kinase activity

- Section 4.1.3, Exclusion Criteria: added criteria outlining additional criteria to be used in assessing the cardiovascular risk of a subject at the time of determining eligibility for treatment with GSK1120212
- Section 5.4, Handling and Storage of Study Treatment: revised temperature for storage of GSK1120212 based on clarification received from GSK Pharmaceutical Development.
- Section 5.7.1, Monitoring and Management of Hypertension: added new section with guidelines for monitoring and managing hypertension in subjects undergoing treatment with GSK1120212
- Section 7.1, Meals and Dietary Restrictions: revised to clarify that fasting times were based upon the time of meal rather than dosing of GSK1120212 and for consistency with Section 5.1
- Appendix 1, Footnote #9: revised to clarify when an ECHO or MUGA scan should be performed during the Final Study Visit
- Appendix 2, Footnote #9: revised to clarify when an ECHO or MUGA scan should be performed during the Final Study Visit

RM2010/00127/04	2012-SEP-12	Amendment No. 4: United Kingdom (UK) only. • Abbreviations: updated to include abbreviations used in revised text. • Page 14: Study Design revised to clarify how long subjects may continue to receive treatment in the MEK114375 study once GSK1120212 is commercially available. • Section 3: Study Design revised to clarify how long subjects may continue to receive treatment in the MEK114375 study once GSK1120212 is commercially available. • Section 5.7.7.1: Revised to include the UK (QTc stopping criteria) • Section 13.5 Appendix 5: Country Specific Requirements: page revised to include UK specific requirements regarding QTc withdrawal criteria and study duration
RM2010/00127/05	2012-SEP-25	Amendment No. 5: • Page 1: Subject: added 'trametinib' the commercial name of GSK1120212. • Section 4.1.2: Inclusion Criteria Bullet #7: revised the time span for female contraceptive use as standard language requirement. • Section 4.1.3: Exclusion Criteria revised to be more in

		line with the criteria of the parent studies from which the subject is transitioning. • Section 5.7.7: QTc Withdrawal Criteria revised to show specific actions for a Grade 3 or Grade 4 prolonged QTc event at the request of the FDA. • Section 6.2: Prohibited Medications and Non-Drug Therapies revised by removing medications and non-drug therapies that are no longer prohibited. • Section 7.3: Contraception Requirements, Section 7.3.1: Female Subjects revised the time span for female contraceptive use as standard language requirement. • Section 12: References updated to include the most recent edition date of Investigator's Brochure. • Section 13.1: Appendix 1: Time and Event Table for Cohort A deleted ECHO/MUGA Scan at 8 weeks to match the language in the body of the protocol and revised footnote #8 to match. Additionally revised footnote #6 to reflect the change in the upper limit of the QTc interval. • Section 13.2: Appendix 2: Time and Event Table for Cohort B: Footnote #6 revised to reflect the change in the upper limit of the QTc interval.
RM2010/00127/06	2013-FEB-14	Amendment No.: 6 • Revised Section: 3.1 Cohorts, Section 13.1 Time & Events Table Cohort A footnote # 20 and Section 13.2 Time & Event

			Table Cohort B footnote #20 to provide clarification on decreasing interim visit schedule for those subject on study >52 weeks. • Revised language to incorporate standard language changes in Section: 4.1.2 Inclusion Criteria, Section 5.7.1.2 Managing Hypertension, Section 5.7.7 QTc Withdrawal Criteria, Section 5.7.8.1 Left Ventricular Ejection Fraction Stopping Criteria, and Section 8.5.5 Pregnancy. • Section 5.1. Investigational Product: Table 1 GSK1120212 GSK Investigational Product: Deleted description of the 1mg tablet as this strength is no longer available for use. • Section 7.2.Contraception Requirements: Section 7.3.2 Male Subjects: Deleted as it no longer applies. • Made administrative changes for typographical (punctuation) omissions and errors.
RM2010/00127/07	2014-FEB-06	Amendment No.: 7	• [redacted]

[redacted]

- [redacted]
- [redacted]

- List of Abbreviations: Added Retinal Pigment Epithelial Detachment (RPED).

- Section 4.1.3. Exclusion Criteria: Deleted criterion #2 as local access to commercially available GSK1120212 is no longer considered a major exclusion to enroll in study.

- Section 5.1. Investigational Product, Table 1 GSK1120212GSK Investigational Product: Table 1 was deleted. Protocol tables and table references throughout the protocol were renumbered accordingly.

- Section 5.4. Handling and Storage of Study Treatment: Revised section to reference the label and the Study Procedure Manual for study treatment storage conditions.

- Section5.7.5. Stopping Criteria for Visual Changes: Paragraph #1 revised to reflect current

standard language.

- Section 5.7.5 Stopping Criteria for Visual Changes: Grade 1 visual changes: Grade 2 or 3 visual changes; Grade 4 visual changes: Revised to reflect current standard language.

- Section 8.4.2. Ophthalmologic Examinations: revised to reflect current standard language.

- Section 12 References: Added Investigator's Brochure, 5th edition, 25 September 2013 to Clinical Investigator's Brochure reference.

- Section13.1. Appendix 1: Time and Events Table for Cohort A: Annotation #12 corrected symbol from > to ≥.

- Section13.2. Appendix 2: Time and Events Table for Cohort B: Annotation #12 corrected symbol from > to ≥.

- Made administrative changes for typographical (punctuation) omissions and errors.

Sponsor Signatory:	Signature:	Date:
[redacted], MD, PhD [redacted] [redacted] GlaxoSmithKline	[redacted]	02/06/14

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Clinical Study Identifier: MEK114375

GlaxoSmithKline
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: [redacted]

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Sponsor Medical Monitor 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 UP 4410 Collegeville, PA 19426-0989, US** [redacted]
Secondary Medical Monitor	[redacted], **MD**	[redacted]	[redacted]	[redacted]	**GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4210 Collegeville, PA 19426-0989, US** [redacted]

Regulatory Agency Identifying Numbers: US IND #102,175

EudraCT # 2010-023015-33

GlaxoSmithKline

French Information Page

Title of Protocol:	MEK114375: A rollover study to provide continued treatment with GSK1120212 to subjects with solid tumors or leukemia
Protocol Reference:	RM2010/00127/07
Effective Date of Protocol:	**06-FEB-2014**
Study Identifier:	**MEK114375**

French Contacts: **GLAXOSMITHKLINE**
100, route de Versailles
78163 MARLY-LE-ROI Cedex

Medical Project Leader: **Dr** [redacted]
Tel : [redacted]
Fax: [redacted]

Study Team Leader: [redacted]
Tel : [redacted]
Fax : [redacted]

Safety Contact: **Dr** [redacted]
Tel : [redacted]
Fax [redacted]

Clinical Research Associate

FRENCH SIGNATORY

[redacted]
GSK FRANCE

Date & Signature: [redacted] 06 March 2014

Page inserted in study protocol for GSK France requirement

GlaxoSmithKline

French Coordinating Investigator Statement

Title of Protocol: MEK114375: A rollover study to provide continued treatment with GSK1120212 to subjects with solid tumors or leukemia

Protocol Reference : **RM2010/00127/07**

Effective Date of Protocol: **06-FEB-2014**

Study Identifier: **MEK114375**

Compound Number: **GSK1120212**

I agree to act as the coordinating investigator for this clinical trial in France, according to the French law (n°2004-806 of 09 August 2004) "Article L1121-1 du Code de la Santé Publique".

[redacted]

.....

INVESTIGATOR AGREEMENT PAGE

For protocol MEK114375

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 clinical 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 Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

ADL	Activities of daily living
AE(s)	Adverse Event(s)
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
ATS	All Treated Subjects
β-HCG	Beta-Human Chorionic Gonadotropin
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
°C	Degrees Celsius
cfDNA	Circulating free DNA
cm	Centimeter(s)
CPK	Creatine phosphokinase
CPP	Calcium phosphate product
CR	Complete response
CSR	Central serous retinopathy
CT	Computed tomography
CYP	Cytochrome
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosterone
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG(s)	Electrocardiogram(s)
ECHO(s)	Echocardiogram(s)
eCRF(s)	Electronic case report form(s)
EIAED(s)	Enzyme-inducing anti-epileptic drug(s)
ERK	Extracellular signal-regulated kinase
°F	Degrees Fahrenheit
FDA	Food and Drug Administration
fl oz	Fluid ounces
GCP	Good Clinical Practice
G-CSF	Granulocyte-cell stimulating factor
GM-CSF	Granulocyte-macrophage-cell stimulating factor
GSK	GlaxoSmithKline
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board

IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram(s)
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAA	**Marketing Application Authorization**
MAPK	Mitogen-activated protein kinase
MedDRA	Medical dictionary for regulatory activities
MEK	Mitogen-activated protein kinase
MHRA	**Medicines and Healthcare products Regulatory Agency**
mg	Milligrams
mL	Milliliter
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
MUGA	Multiple-gated acquisition scan
NC	North Carolina
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute – Common Toxicity Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
PA	Pennsylvannia
PD	Progressive disease or pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
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
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
RPED	**Retinal Pigment Epithelial Detachment**
RVO	Retinal vein occlusion
SAE	Serious adverse event(s)
SBP	Systolic blood pressure
SD	Stable disease
SPF	Skin protection factor
SPM	Study Procedures Manual

TSH	Thyroid stimulating hormone
UK	**United Kingdom**
ULN	Upper limit of normal
US/USA	United States of America
WBC	White blood cells
WNL	Within normal limits

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
None

PROTOCOL SUMMARY

Rationale

GSK1120212 is a potent**, reversible** and highly selective inhibitor of MEK**1/MEK2 activation and** kinase activity. This multicenter, non-randomized, open-label rollover study will provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212.

Objectives

The primary objective of the study is to provide continued treatment with GSK1120212 for subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212.

Study Design

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study (parent study) and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212. Subjects will be enrolled into the appropriate cohort based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. It is estimated that approximately 250 subjects will be enrolled in this study. Subjects may continue treatment in the rollover study until no longer clinically benefitting, unacceptable toxicity, withdrawal of consent, or **have access to local** commercial supply of GSK1120212.

Study Assessments

Safety will be evaluated through 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.

Assessment of clinical activity will be performed throughout the study using local standard of care imaging practices and the appropriate assessment criteria as determined by the investigator to determine continued study participation and treatment with GSK1120212. Only subjects considered by the investigator to be receiving clinical benefit may continue on study treatment.

1. INTRODUCTION

1.1. Background

The RAS/RAF/MEK/ERK or MAPK pathway is a critical signal transduction cascade implicated in the uncontrolled proliferation of many human cancers. Multiple genetic alterations in components of this cascade resulting in constitutive pathway activation have been well characterized over the past several decades [Davies, 2002; Allen, 2003]. Given the critical location of MEK in this signalling pathway, it has been recognized as an important target for anti-cancer therapy. Drug development efforts to inhibit MEK demonstrated clinical benefit, although with limited success. For example, PD-0325901, CI-1040, and AZD6244, have achieved objective responses in melanoma, pancreatic cancer, and non-small cell lung cancer [LoRusso, 2010; LoRusso, 2005; GlaxoSmithKline Document Number RM2007/00642/03; Tzekova, 2008], but none have demonstrated significant single-agent activity in these tumor types.

GSK1120212 is a **potent,** reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. **The specificity of GSK1120212 to MEK1 and MEK2 was confirmed against a large panel of kinases and no significant inhibitory activity was measured.** A detailed summary of *in vitro* and *in vivo* non-clinical pharmacology studies is provided in the GSK1120212 Investigator Brochure (IB) [GlaxoSmithKline Document Number HM2009/00151/**02**].

As of 14 April 2011, 657 subjects with cancer have received at least one dose of GSK1120212 in 14 ongoing Phase I/II/III clinical studies. Six of the 14 studies administer GSK1120212 as monotherapy, whereas the other 8 studies are designed to administer GSK112012 as combination therapy. As of 14 April 2011, 206 subjects in MEK111054, the first-time-in-human (FTIH) study of GSK1120212, had been dosed with GSK1120212. Dose-related MAP kinase inhibition was demonstrated between daily doses of 0.5 and 2.0 mg with immunohistochemistry on tumor biopsies. Modulation of MAP kinase pathways was consistent with changes observed with fluorodeoxyglucose-positron emission tomography imaging. Based on the AEs observed in the FTIH MEK111054 study, the maximum tolerated dose (MTD) was determined to be 3.0 mg once-daily and the recommended Phase II dose (RP2D) of GSK1120212 was identified as 2.0 mg once-daily. An unconfirmed response rate of 43% (6 out of 14 subjects) had an objective response, including 2 complete responses (CRs) was observed. The recommended monotherapy dose (2 mg once-daily) was well-tolerated. Most notable adverse events (AEs) at this dose (n = 96) included class effects of rash (78%; 4% Grade 3) and diarrhea (54%; 1% Grade 3). In all subjects dosed (n = 206), 5 cases of Grade 3 left ventricular systolic dysfunction, 3 cases of central serous retinopathy (CSR), and 1 case of retinal vein occlusion (RVO) were observed. Among the 5 left ventricular ejection fraction (LVEF) cases, only 2 were considered related to study treatment and neither subject was symptomatic. All 3 cases of CSR resolved upon study treatment interruption, and the subject with RVO has experienced significant improvement in visual acuity after intraocular bevacizumab treatments.

GSK1120212 is absorbed rapidly with median tmax generally occurring within 1 to 3 hours after administration of GSK1120212. After repeat dosing (Study Day 15), the mean area under the concentration-time curve (AUC(0-τ)) and maximum observed concentrations (Cmax) increased in a dose proportional manner (i.e., a 2-fold increase in dose resulted in a 2-fold increase in exposure). Between-subject variability (CV%) in exposure ranged from 27 to 50% for Cmax and 20 to 41% for area under the concentration-time curve from time zero (pre-dose) to 24 hrs after the last dose of study treatment (AUC(0-24)) across all dosing regimens. GSK1120212 accumulates with repeat dose with an effective half-life (t1/2) of approximately 5 days.

Further information on the safety, PK, and efficacy is described in the IB for GSK1120212 [GlaxoSmithKline Document Number HM2009/00151/02].

1.2. Summary of Risk Management

The assessment of the risk of GSK1120212 is based on clinical data from the ongoing FTIH study in which subjects have been dosed daily for >21 days, as well as preclinical toxicity data. In study MEK111054, the most common AEs experienced by ≥20% of all subjects with daily dosing were rash, diarrhea, fatigue, nausea, peripheral edema, and vomiting. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and LVEF reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with GSK1120212 as well as other MEK inhibitors. Systemic toxicity of GSK1120212 has been evaluated following oral dosing in rats and dogs for up to 13 weeks. In the most sensitive non-clinical species, rat, the principal adverse effects seen in oral toxicity studies of up to 13 weeks with daily dosing were skin and stomach erosions, skin ulcerations, which were secondary to reduced proliferation, altered phosphate homeostasis that resulted in soft tissue mineralization, hepatocellular necrosis, bone marrow degeneration/necrosis and ovarian perturbations. The skin and stomach findings and phosphatemia demonstrated reversibility with 4 weeks of recovery. Additional details are provided in the IB for GSK1120212 [GlaxoSmithKline Document Number HM2009/00151/02].

Procedures to minimize or monitor potential risks are listed below:

- **To reduce the risk of ocular toxicity, subjects with history of RVO, or CSR, subjects with predisposing factors for RVO or CSR or predisposing retinal pathology as determined by ophthalmologic exams are excluded. Ophthalmologic exams will be performed at baseline and as clinically warranted.**
- **To monitor cardiac function, echocardiogram (ECHO) or multigated acquisition (MUGA) scans will be performed.**
- **To reduce the risk of excessive gastrointestinal (GI) toxicity (diarrhea) and cutaneous toxicity (rash), subjects will be monitored closely and supportive care guidelines will be implemented.**

1.3. Study Rationale

This open-label rollover study will permit subjects with solid tumors or leukemia, who are currently receiving GSK1120212 either as monotherapy or as part of a combination regimen in a GSK1120212 study that has met its study objective(s), to continue receiving treatment with GSK1120212. In addition, this study will continue to collect safety information. Subject may continue treatment in this study if they are demonstrating clinical benefit as well as an acceptable safety profile with GSK1120212.

2. OBJECTIVE

2.1. Primary

The primary objective of the study is to provide continued treatment with GSK1120212 for subjects who have previously participated in a GSK1120212 study and who continue to receive clinical benefit as well as have an acceptable safety profile with GSK1120212.

3. STUDY DESIGN

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects who have previously participated in a GSK1120212 study (parent study). All subjects enrolling in this study must be receiving clinical benefit from continued treatment as well as have an acceptable safety profile with GSK1120212 to be eligible. Subjects will be stratified into the appropriate cohort (see Section 3.1) based upon the 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 provide written informed consent prior to any study-related assessment or procedure being performed or treatment with GSK1120212 for this study. After informed consent is obtained, subjects will be evaluated for study eligibility.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B, is 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 the evaluation of physical examinations, vital sign measurements (blood pressure [BP], pulse rate, and temperature), 12-lead electrocardiograms (ECGs), echocardiograms (ECHOs) or MUGA scans, 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 appropriate assessment criteria (e.g. Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) as determined by the investigator to determine continued study participation and treatment with GSK1120212. Only subjects who continue to receive clinical benefit as determined by the investigator as well as having an acceptable toxicity safety profile will be allowed to continue treatment on study.

Subjects may continue treatment in this rollover study until lack of clinical benefit, unacceptable toxicity, withdrawal of consent, or **have access to local** commercial supply of GSK1120212.

Refer to Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B for timing of all assessments.

NOTE: Subjects participating in a BRAF/MEK combination study (receiving GSK1120212 in combination with GSK2118436 [a BRAF inhibitor]) should continue treatment in the GSK2118436 rollover study, BRF114144.

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.

3.1. Cohorts

Cohort A:

Cohort A will consist of subjects who have completed <24 weeks of treatment with GSK1120212 monotherapy during their participation in the parent study. It is anticipated that subjects in this cohort will have participated in a clinical pharmacology or another short-term study of GSK1120212. Subjects will complete the Transition Visit and return for their next scheduled visit (Study Week 4), and then every 4 weeks thereafter. Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

Subjects will receive GSK1120212 as an oral, daily dose of 2 mg or less. Protocol specified guidelines for dose modifications and treatment discontinuation criteria are provided in Section 5.6 and Section 5.7, respectively. If there are any uncertainties about the dose to be administered in this study, the GSK Medical Monitor should be consulted. Once treatment with GSK1120212 is discontinued the subject is to be withdrawn from the rollover study.

Cohort B:

Cohort B will consist of subjects who have completed ≥24 weeks of treatment with GSK1120212 (either as monotherapy or combination therapy with an approved anti-cancer agent) during their participation in the parent study. Subjects who transition from a combination study may continue to receive GSK1120212 in combination with the approved anti-cancer agent defined by the parent study or if, in the opinion of the

investigator, the subject has received maximum benefit or is experiencing unacceptable toxicity from the approved anti-cancer agent, then treatment with the approved anti-cancer agent may be discontinued and the subject may remain on study for continued treatment with GSK1120212 alone. Once treatment with GSK1120212 is discontinued the subject is to be withdrawn from the rollover study.

Subjects will complete the Transition Visit assessments and then return for their next scheduled visit (Study Week 3 or 4), then every 3 or 4 weeks thereafter (depending on the schedule used in the parent study). Subjects **who have tolerated therapy well with limited toxicities** and remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

All subjects will receive GSK1120212 at the current dose level administered in the parent study at the time of the Transition Visit. If this starting dose of GSK1120212 is below the recommended Phase 2 dose (RP2D) previously defined for the given treatment regimen (e.g., dose modification following recovery from toxicity), the investigator, after consultation with the GSK Medical Monitor, may consider escalating the dose to the RP2D. If there are any uncertainties about the dose(s) to be administered in this study, the GSK Medical Monitor should be consulted.

3.2. Discussion of Design

The purpose of this study is to allow for continued treatment with GSK1120212 in subjects with solid tumors or leukemia who have participated in a GSK1120212 study of GSK1120212 and meet the protocol requirements for transitioning to the rollover study. Subjects will be closely monitored for known dose-limiting toxicities associated with GSK1120212. The schedule of assessments and procedures to be performed during this study is provided in Appendix 1: Time and Events Table for Cohort A and Appendix 2: Time and Events Table for Cohort B. To manage known side effects, and unless otherwise stated, supportive care therapies, such as growth colony stimulating factors, will be allowed and dosed in accordance with local institutional practices. The details regarding dose modifications of GSK1120212 and guidance on additional assessments and procedures following events of special interest can be found in Section 5.6 and Section 5.7, respectively.

3.2.1. Dose Rationale

For this study, 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 the rollover study.

1. Subjects who have received <24 weeks of GSK1120212 monotherapy in the parent study (Cohort A) will receive the same continuous dosing regimen of GSK1120212 at completion of the parent study. Subjects must be at a starting dose of 2 mg or less once-daily in the rollover study.

Dose selection for Cohort A was based on the preliminary results from the first-time-in-human trial, MEK111054 [GlaxoSmithKline Document Number RM2007/00642/03]. Based on the preliminary AEs observed and protocol-defined dose-finding criteria in MEK111054, the single-agent maximum tolerated dose (MTD) was established at 3 mg once-daily, and the current recommended Phase II dose as monotherapy is 2 mg once-daily.

2. Subjects who have received ≥24 weeks of continuous treatment with GSK1120212 as monotherapy or combination therapy with another approved anti-cancer agent (Cohort B) will continue treatment in the rollover study at the current dose level administered in the parent study at the time of transition to the rollover 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.

4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

4.1. Subject Selection Criteria

4.1.1. Number of Subjects

Approximately 250 subjects from approximately 80 investigative sites will be transitioned to this study from other GSK1120212 studies.

4.1.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on GSK1120212 or other approved agent(s) that may impact subject eligibility is provided in the IB for GSK1120212 [GlaxoSmithKline Document Number HM2009/00151/**02**] or any subsequent IB supplements or in the Prescribing Information for any approved 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. Has demonstrated compliance during the parent study with study treatment(s), treatment visit schedules, and the requirements and restrictions listed in the consent form.

3. Is currently participating in GSK1120212 study and is receiving treatment with GSK1120212.
4. Is currently receiving clinical benefit as determined by the investigator from previous treatment with GSK1120212 either as monotherapy or as part of a combination treatment regimen.
5. 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.
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 months after the last dose of GSK1120212.**
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. **Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.**

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.

Subjects meeting any of the following criteria must not be enrolled in this study:

1. Permanent discontinuation of GSK1120212 in the parent study due to toxicity or disease progression.
2. **Current use of a prohibitive medication(s) as listed in Section 6.2.**

   NOTE: Use of anticoagulants such as warfarin is permitted; however, the international normalization ratio (INR) must be monitored in accordance with local institutional practice.
3. **Any unresolved toxicity that meets the study treatment discontinuation or study withdrawal criteria from the parent study at the time of transition to this study.**
4. **Bazett-corrected QT (QTcB) interval ≥501 msec at the time of transition to this study**
5. **Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.**
6. **Nursing female.**
7. **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 GSK Medical Monitor.

4.1.4. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.1.4.1. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until death or unacceptable AE, including meeting stopping criteria for liver chemistry defined in Section 5.7.4 or for hematologic and other non-hematologic toxicity. In addition, study treatment may be permanently discontinued for any of the following reasons:

- Deviation(s) from the protocol
- Clinically significant AE leading to interruption of treatment for >21 consecutive days.

  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.
- 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 GSK1120212 becomes locally available as commercial product to the subject for continued treatment)

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

Once a subject has permanently discontinued from GSK1120212, the subject will not be allowed to be retreated.

All subjects who discontinue study treatment will have safety assessments performed at the Final Study Visit within approximately 28 days (±7 days) of last dose of study treatment(s) as specified in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B.

If the subject withdraws consent for further study treatment, a Final Study Visit should be completed (see Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B). 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 in the eCRF.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 8.5.1, "Definition of an AE") or serious AE (SAE) (as defined in Section 8.5.2, "Definition of a SAE"), the procedures stated in Section 8.5, ("Adverse Events") must be followed. All subjects who have a Grade 3 or 4 clinical or laboratory abnormality at the time of withdrawal from the study must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of underlying disease.

If the subject discontinues from study treatment due to disease progression, 'Disease Progression' will be recorded as the primary reason for permanent study treatment discontinuation in the eCRF.

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

4.1.4.2. Subject Completion Criteria

A subject will be considered to have completed the study if the subject progresses during study treatment or at the Final Study Visit, or dies.

A subject will be considered to have withdrawn from the study if the subject has not died or progressed and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.

The end of study is defined as the last subject, last visit.

5. 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.

5.1. Investigational Product

Table 1 GSK1120212 GSK Investigational Product

	Commercial Image Product	
Product name :	**GSK1120212 0.5 mg Tablet**	**GSK11210212 2 mg Tablet**
Formulation description:	**Each tablet contains GSK1120212B equivalent to 0.5 mg of GSK1120212 as drug substance blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with yellow opaque film* (*Opadry yellow, a titanium dioxide-based formulation with yellow iron oxide as colorant).**	**Each tablet contains GSK1120212B equivalent to 2 mg of GSK1120212 as drug substance blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with pink opaque film* (*Opadry Pink, a titanium dioxide-based formulation with red iron oxide as colorant).**
Dosage form :	**Tablet**	**Tablet**
Unit dose strength(s):	**Tablet strength: 0.5 mg**	**Tablet strength: 2 mg**
Physical Description:	**Yellow, modified oval, biconvex, film-coated tablets (4.85 x 8.86 mm)**	**Pink, biconvex, round film-coated tablets 7.5 mm in diameter**
Route/ Administration:	**Oral/once-daily single dose**	**Oral/once-daily single dose**
Dosing Instructions:	**GSK1120212 should be administered with approximately 240 mL (8 fl oz) of water, under fasting conditions, either 1 hour before or 2 hours after a meal**	

GSK1120212 will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. No special preparation of GSK1120212 is required.

GSK1120212 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 GSK1120212.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. 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 GSK upon request.

Adequate precautions are to be taken to avoid direct contact with the study treatment. The occupational hazards and recommended handling procedures are provided in the MSDS.

5.2. Other Approved Anti-Cancer Agents (Cohort B)

When the treatment regimen to be administered includes an approved anti-cancer agent(s) in combination with GSK1120212, the sites will be responsible for obtaining the necessary drug supply for the approved 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 GSK1120212 that was not part of the parent study is not permitted. Refer to the Prescribing Information for each approved anti-cancer agent for information regarding the physical and chemical properties, storage, and dosing/administration guidelines.

5.3. Administration of Study Treatment

If a subject vomits after taking study treatment(s), 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 study treatment(s), the subject should be instructed to skip the missed dose and not make it up, then take the next scheduled dose.

5.4. Handling and Storage of Study Treatment

GSK1120212 must be stored in **an opaque bottle, protected from light and moisture** in a secure area under the appropriate physical conditions for the product **at the temperature specified on the label. Maintenance of a temperature log (manual or automatic) is required.** Access to and administration of the GSK1120212 will be limited to the investigator and authorized site staff. GSK1120212 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. **Additional guidance can be found in the SPM.**

5.5. Treatment Assignment

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

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 GSK interactive voice response system (IVRS), by the investigator or authorized site staff.

5.6. Dose Modifications

At each study visit, subjects should be carefully evaluated for evidence of treatment-related toxicity. The investigator should use clinical judgment 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 1 or all study treatments.

Guidelines for GSK1120212 dose modifications are provided below. Investigators should also refer to the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/**02**] or the prescribing information for the appropriate approved anti-cancer combination agent for detailed information regarding warnings, precautions, contraindications, AEs, and recommendations for supportive care in the event of drug-related toxicity.

5.6.1. GSK1120212 Dose Modification

For clinically significant toxicities that are considered related to GSK1120212 (i.e., diarrhea, peripheral and periorbital edema), **except** for rash (Section 5.7.1), ejection fraction changes (Section 5.7.8.1), pneumonitis (Section 5.7.4), or visual changes (Section 5.7.5), the dose modification guidelines for GSK1120212 are provided in Table 2 All dose modifications (delays or reductions) will be recorded on the appropriate eCRF.

Table 2 Dose Modifications for GSK1120212

TOXICITY[a]	GSK1120212
Grade 1	Continue GSK1120212 at current dose level. Consider supportive care recommendations provided in Section 5.7.
Grade 2	Withhold treatment with GSK1120212 until toxicity resolves to Grade 1 or baseline. Upon resolution, restart GSK1120212 at current dose level. Consider supportive care recommendations provided in Section 5.7. Consider dose reduction if toxicity is intolerable to the subject.
Grade 3	Withhold GSK1120212 until toxicity resolves to Grade 1 or baseline. Upon resolution, consider reducing dose of GSK1120212 by ≥0.5 mg. Consider supportive care recommendations provided in Section 5.7.
Grade 4	Permanently discontinue treatment with GSK1120212.

a. Considered related to study treatment.

Treatment with GSK1120212 may be delayed for up to 21 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 >21 days, then the subject may continue GSK1120212 therapy with the approval of the GSK Medical Monitor.

A maximum of 2 dose reductions of GSK1120212 is permitted. If a third dose reduction is required, treatment with GSK1120212 should be discontinued.

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

If an approved anti-cancer agent(s) is being taken in combination with GSK1120212 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 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 approved anti-cancer agent(s), then treatment with the approved anti-cancer agent(s) may be discontinued.

5.7. Guidelines for Events of Special Interest

The severity of AEs will be graded utilizing the NCI-CTCAE, version 4.0 [NCI, 2009]. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment are provided in this section.

5.7.1. Monitoring and Management of Hypertension

5.7.1.1. Monitoring of Hypertension

All BP assessments should be performed under optimal conditions i.e. after (1) subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor, (2) subject is relaxed comfortably for at least 5 minutes, (3) preparatory steps including removal of any restrictive clothing over the cuff area and selection of the proper cuff size have been ensured, (4) the arm is supported so that the middle of the cuff is at the heart level, and (5) the subject remains quiet during the measurement. In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final BP measurement.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mm Hg and/or diastolic blood pressure (DBP) >90 mmHg in up to 3 subsequent visits with BP assessments from 2 readings under the optimal conditions described above. Visits to monitor increased BP should be scheduled independently from the per-protocol visits outlined in the time-and-events schedule; ideally, subsequent BP assessments should be performed within 7 days.

Asymptomatic hypertension is defined as an increase of SBP >140 mmHg and/or DBP > 90 mmHg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension which would disappear after the BP is controlled within the normal range.

5.7.1.2. Management of Hypertension

For subjects experiencing an increase in SBP and/or DBP that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Hypertension	
(A) Asymptomatic and persistent[1] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	**Step 1. Continue study treatment at the current dose.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[2] BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).**
(B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	**Step 1.Consider reducing or interrupting study treatment, as clinically indicated.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP.** **Step 4. Once BP is well-controlled[2], restart study treatment dose-reduced by one dose level**
(C) Symptomatic hypertension or recurring[3] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite modification of antihypertensive medication(s)	**Step 1. Interrupt study treatment.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended.** **Step 4. Once BP is well-controlled, restart study treatment dose-reduced by one dose level**
(D) Refractory hypertension unresponsive to above interventions.	**Permanently discontinue study treatment and continue follow-up per protocol.**

1. Hypertension detected in 2 separate readings during up to 3 subsequent visits
2. BP reading of SBP ≤140 mmHg and DBP ≤90 mmHg in 2 separate readings during up to 3 subsequent visits
3. Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention.

5.7.2. Management of Dermatological AEs

5.7.2.1. Supportive Measures for Rash

General considerations in rash management:

- Encourage subjects to avoid unnecessary exposure to sunlight.

- Employ a proactive approach (i.e., prophylactic treatment; see below for recommendations).
- If a subject develops rash, verify treatment intervention and follow steps outlined under "Reactive Management".

5.7.2.2. Prophylactic Treatment of Rash

The exact prophylactic regimen should be based on the investigator's experience; however, the following regimen is recommended:

- Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with an skin protection factor (SPF) ≥15;
- Thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogel cream) on dry areas of the body;
- Mild topical steroid (1% hydrocortisone cream), with escalation to higher strength and/or oral steroid as detailed below.
- Offer topical antibiotics or oral doxycycline 100 mg twice daily (BID) or oral minocycline 100 mg BID for the first 2 to 3 weeks of GSK1120212 administration.

Topical agents should be applied on a daily basis starting on Study Day 1 of study treatment, and more often as needed. Oral antibiotics should be started on Study Day 1.

5.7.2.3. Reactive Management of Rash

It is strongly recommended that subjects who develop dermatological reactions receive evaluations for management on the specific side effect.

- For **pruritic lesions**, the use of cool compresses and oral antihistamine agents may be helpful.
- For **fissuring**, the use of Monsel's solution, silver nitrate, or zinc oxide cream is advised.
- For **desquamation**, thick emollients and mild soap are recommended.
- For **paronychia**, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.
- For **infected lesions**, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

Consider the following algorithm in a stepwise manner **(**Table 3**).**

Table 3 Guidelines for Skin Rash Management

Step	Grade	Severity	Management	GSK1120212 Dose Adjustment
1	Mild	• Localized • Minimally symptomatic • No impact on activities of daily living (ADL) • No sign of superinfection	• Initiate prophylactic regimen if not already started. Consider using moderate strength topical steroids (e.g. hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2.	• Continue current dose. • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2.
2	Moderate	• Generalized • Mild symptoms (e.g., pruritis, tenderness) • Minimal impact on ADL • No sign of superinfection	• Initiate prophylactic regimen if not already started, but using moderate strength topical steroids (e.g. hydrocortisone 2.5% cream or fluticasone propionate 0.5% cream) • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3	• Reduce dose by ≥ 0.5mg • Consider holding treatment until rash improves • Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3
3	Severe	• Generalized • Severe symptoms (e.g. pruritis, tenderness) • Significant impact on ADL • Sign of or potential for superinfection	• Initiate prophylactic regimen if not already started, but using moderate strength topical steroids PLUS methylprednisolone dose pack. • Consider obtaining dermatology consultation. • Manage rash per dermatologist's recommendation.	• Hold treatment until rash improves (moderate, mild) or resolves, then follow steps outlined for the appropriate grading. • Reassess after 2 weeks; if rash worsens or does not improve, discontinue treatment with GSK1120212.

For subjects with an extensive or symptomatic Grade 3 or 4 dermatologic events, or for subjects with chronic, persistent or recurring lower grade skin events, a dermatology consultation is encouraged.

5.7.3. Management of Diarrhea

General considerations for diarrhea management:

Rule out other or concomitant causes. These include medications (e.g., stool softeners, laxatives, antacids, etc), infection by *C. difficile* or *Candida* species, partial bowel obstruction, malabsorption/lactose intolerance, fecal impaction, diets high in fiber or lactose.

For uncomplicated Grade 1 to 2 diarrhea (i.e., mild to moderate defined as NCI-CTCAE [NCI, 2009] Grade 1 or 2 with no complicating signs or symptoms):

- Administer standard dose of loperamide:
  - Initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool; maximum of 16 mg (8 tablets) per day.
  - Continuation of loperamide is suggested until diarrhea-free for 12 hours
- Dietary modifications: stop all lactose containing products and eat small meals. A BRAT (banana, rice, apples, toast) diet may be helpful.
- Hydration: drink 8 to 10 large glasses of clear liquids per day (e.g., Gatorade or broth)
- Consider a temporary GSK1120212 dose interruption until symptoms have resolved to baseline or Grade 1. Re-treatment with GSK1120212 may then be resumed at 100% of current dose level.
- If mild to moderate diarrhea persists for >24 hours, administer loperamide 2 mg every 2 hours; maximum 16 mg (8 tablets) per day. Consider adding oral antibiotics.
- If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, start second-line agents (octreotide, budesonide or tincture of opium). Consider adding oral antibiotics.

Grade 3 to 4 diarrhea or complicated Grade 1 to 2 diarrhea (i.e., cramping, nausea/vomiting ≥Grade 2, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding and/or dehydration):

- Subject must call the investigator immediately for any complicated severe diarrhea event.
- Discontinue GSK1120212 treatment and hold until symptoms resolve to ≤Grade 1 or baseline. Consider re-starting therapy at a reduced dose level.
- If loperamide has not been initiated, initiate loperamide immediately. Initial dose 4 mg followed by 2 mg every 2 hours or after every unformed stool; maximum of 16 mg (8 tablets) per day.
- For dehydration, use IV fluids as appropriate; if severe dehydration, administer octreotide.

- Administer antibiotics as needed (e.g. fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 or 4 neutropenia.
- Intervention should be continued until the subject is diarrhea free for at least 24 hours.

Intervention may require hospitalization for subjects most at risk for life-threatening complications.

5.7.4. Management of Pneumonitis

To reduce the risk of pneumonitis, subjects will be monitored closely for symptoms, evaluated with imaging and/or functional studies, and stopping/interruption criteria will be implemented. Dose modification and supportive care guidelines for pneumonitis will also be implemented.

Table 4 Pneumonitis Guidelines for GSK1120212

Grade	Required Investigations	Management	Dose Adjustment for GSK1120212
1	• CT scans with lung windows (high resolution CT recommended). • Consider evaluation by pulmonologist. • Consider room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 minutes apart). Repeat every 8 to 12 weeks until values return to WNL	No specific therapy is required.	Administer 100% of study treatment dose.
2	• CT scan with lung windows (high resolution CT recommended). • Consider evaluation by pulmonologist. • Consider pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 minutes apart). Repeat every 8 to 12 weeks until values return to WNL. • Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage.	Symptomatic only. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤Grade 1, then reduce by 0.5 mg. Discontinue treatment if no recovery to ≤Grade 1 within 4 weeks. May consider escalation to pre-event dose after discussion with GSK Medical Monitor.
3	• CT scan with lung windows (high resolution CT recommended). • Evaluation by pulmonologist. • Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (times 2, 5 minutes apart). Repeat every 8 to 12 weeks until values return to WNL. • Bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤Grade 1. Discontinue treatment if no recovery to ≤Grade 1 within 4 weeks. May consider restarting GSK1120212 at a dose reduced by 0.5 mg after discussion with GSK Medical Monitor if there is clinical benefit.
4	• CT scan with lung windows (high resolution CT recommended). • Evaluation by pulmonologist. • Required pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 minutes apart). Repeat every 8 to 12 weeks until values return to WNL. • Bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

Table 5 Pneumonitis Guidelines for GSK1120212 and Gemcitabine Combination Therapy

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Dose Adjustment for GSK1120212	Dose Adjustment for Gemcitabine
Grade 1	CT scans with lung windows (high resolution CT scan is recommended). Consider evaluation by pulmonologist. Consider room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat every 8 to 12 weeks until return to within normal limits (WNL).	No specific therapy is required.	Administer 100% of study treatment dose.	Hold treatment until improvement in CT scan results, then re-start at same dose level.
Grade 2	CT scan with lung windows (high resolution CT scan is recommended). Consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat every 8 to 12 weeks until return to WNL. Consider a bronchoscopy with biopsy and/or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated.	Reduce by 0.5mg until recovery to ≤ Grade 1. Treatment may also be interrupted if symptoms are troublesome. Discontinue treatment if no recovery to ≤ Grade 1 within 4 weeks. May consider escalation to pre-event dose after discussion with GSK Medical Monitor.	Hold treatment until recovery to ≤ Grade 1, then re-start with at least 25% dose reduction. Discontinue treatment if no recovery to ≤ Grade 1 within 4 weeks.
Grade 3	CT scan with lung windows (high resolution CT scan is recommended). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat at least every 8 weeks until return to WNL. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart study treatment within 4 weeks at a reduced dose (by 0.5mg) if symptoms improve and evidence of clinical benefit after discussion with GSK Medical Monitor.	Hold treatment until recovery to ≤ Grade 1, then re-start with at least 25% dose reduction. Discontinue study treatment if no recovery to ≤ Grade 1 within 4 weeks.
Grade 4	CT scan with lung windows (high resolution CT recommended). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat at least every 8 weeks until return to WNL. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.	Discontinue treatment.

Table 6 Pneumonitis Guidelines for GSK1120212 and Everolimus Combination Therapy

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Dose Adjustment for GSK1120212	Dose Adjustment for Everolimus
Grade 1	CT scans with lung windows (high resolution CT scan is recommended). Consider evaluation by pulmonologist. Consider room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat every 8 to 12 weeks until return to WNL.	No specific therapy is required.	Administer 100% of study treatment dose.	Administer 100% of study treatment dose.
Grade 2	CT scan with lung windows (high resolution CT scan is recommended). Consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat every 8 to 12 weeks until return to WNL. Consider a bronchoscopy with biopsy and/or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated.	Reduce by 0.5mg until recovery to ≤ Grade 1. Treatment may also be interrupted if symptoms are troublesome. Discontinue treatment if no recovery to ≤ Grade 1 within 4 weeks. May consider escalation to pre-event dose after discussion with GSK Medical Monitor.	Reduce study treatment dose by 1 dose level until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Subjects will discontinue study treatment if they fail to recover to ≤ Grade 1 within 4 weeks.
Grade 3	CT scan with lung windows (high resolution CT scan is recommended). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat at least every 8 weeks until return to WNL. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart study treatment within 4 weeks at a reduced dose (by 0.5mg) if symptom improve and evidence of clinical benefit after discussion with GSK Medical Monitor.	Hold treatment until recovery to ≤ Grade 1. May restart study treatment within 4 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows (high resolution CT scan recommended). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DL_{CO}, and room air O_2 saturation at rest via pulse oximetry reading (times 2, 5 mins apart). Repeat at least every 8 weeks until return to WNL. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.	Discontinue treatment.

5.7.5. Stopping Criteria for Visual Changes

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. An ophthalmologist should be consulted if changes in vision develop. If the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO)). For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Visual change events should be graded using Table 7 based on the NCI-CTCAE, version 4.0 [NCI, 2009]).

Table 7 Grading of Visual Changes

Grade	Description
1	Asymptomatic or symptomatic but not limiting activities of daily living (ADL); clinical or diagnostic observations only; intervention not indicated
2	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL; local or non-invasive intervention indicated (e.g., topical or oral agents)
3	Symptomatic with marked decrease in visual acuity or marked visual field defect (worse than 20/40 but better than 20/200 in the affected eye); Severe pain or medically significant but not immediately sight-threatening; operative intervention indicated; disabling; limiting self care ADL
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye

Grade 1 visual changes:

- For Grade 1 visual changes that do not affect vision and which, in the option of the treating physician, are clearly unrelated to study treatment (e.g., conjunctivitis), treatment with GSK1120212 may continue with close observation.
- If attribution to study treatment is unclear, immediately refer the subject for ophthalmic exam; **if a dilated fundus examination cannot be performed within 7 days of onset, interrupt treatment with GSK1120212 until RPED and RVO can be excluded by retina specialist/ophthalmologist. Follow the guidance below depending on the results.**

  If a retinal abnormality is noted, interrupt treatment with GSK1120212 immediately and referral to a retinal specialist should be considered for further evaluation.
- **If RPED suspected or diagnosed (asymptomatic; clinical or diagnostic observations only) continued treatment with retinal evaluation monthly until resolved. Report as an SAE. If worsens see grade 2-3 guidance.**

- **If RVO is diagnosed, report as a SAE and permanently discontinue treatment with GSK1120212**
- If there is no evidence of **RPED or RVO**, resume treatment with GSK1120212 at the same dose level.

Grade 2 or Grade 3 visual changes:

- Immediately interrupt treatment with GSK1120212 and refer subject to an ophthalmologist for evaluation with an ophthalmic exam. For all subjects with findings consistent with **RPED or RVO** based on the ophthalmic exam, referral to retinal specialist, if available, should be considered for further evaluation.
  - **If RVO is diagnosed report as a SAE and permanently discontinue GSK1120212**
  - If **RPED is diagnosed (symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL, perform retinal evaluation monthly and if improves to ≤ Grade 1, resume treatment with GSK1120212 at lower dose (reduced by 0.5 mg) or discontinue in subjects taking GSK1120212 1 mg daily.**
  - If **RPED and RVO are excluded and visual changes are clearly unrelated to study treatment, restart** GSK1120212 at the same dose level.

Grade 4 visual changes:

- **Interrupt GSK1120212, consult ophthalmologist immediately and report as SAE.**
- **If RPED and RVO are excluded, may consider restarting GSK1120212 at same or reduced dose after discussion with the study medical monitor**
- **If RPED or RVO diagnosed permanently discontinue treatment with GSK1120212.**

5.7.6. Liver Chemistry Stopping Criteria

Phase II 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 Food and Drug Administration (US FDA) premarketing clinical liver safety guidance. Phase II liver chemistry stopping criteria 1 to 5 are defined as follows:

1. Alanine aminotransferase (ALT) ≥3 times upper limit of normal (ULN) **and** bilirubin ≥2 times ULN (>35% direct bilirubin) (or ALT ≥3 times ULN and INR >1.5, if INR is measured).

NOTE: If serum bilirubin fractionation is not immediately available, study treatment(s) should be discontinued if ALT ≥3 times ULN **and** bilirubin ≥2 times ULN. Serum bilirubin fractionation should be 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.

2. ALT ≥5 times ULN.
3. ALT ≥3 times ULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
4. ALT ≥3 times ULN persists for ≥4 weeks.
5. ALT ≥ 3 times ULN and cannot be monitored weekly for 4 weeks.

When any of the liver chemistry stopping criteria 1 through 5 is met, do the following:

- **Immediately discontinue** study treatment(s).
- Report the event to GSK **within 24 hours** of learning its occurrence.
- Complete the liver event eCRF and SAE data collection tool if the event also meets the criteria for an SAE.
    - All events of ALT ≥3 times ULN **and** bilirubin ≥2 times ULN (>35% direct bilirubin) (or ALT ≥ times ULN and INR >1.5, if INR is 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 (excluding studies of hepatic impairment or cirrhosis)**.
    - NOTE: if serum bilirubin fractionation is not immediately available, study drug(s) should be discontinued if ALT ≥3 times ULN **and** bilirubin ≥2 times ULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting livery injury.
- Complete the liver imaging and/or liver biopsy eCRFs 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.
- Withdraw the subject from the **study** (unless further safety follow-up is required) after completion of the liver chemistry monitoring as described below.
- Do not rechallenge with study treatment(s).

In addition, for criterion 1:

- 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 5.7.6.1), and close monitoring.
- A specialist or hepatology consultation is recommended.

- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase, and bilirubin) resolve, stabilize or return to within baseline values.

In addition, for subjects meeting any of the criteria 2 to 5:

- Make every reasonable attempt to have subjects return to clinic **within 24 to 72 hours** for repeat liver chemistries and liver event follow-up assessments (refer to Section 5.7.6.1)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values;
    - Any subject who meets criterion 5 should be monitored as frequently as possible.

5.7.6.1. Liver Event Follow-Up Assessments

For subjects meeting any of the liver chemistry stopping criteria 1 through 5, 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 96 hours 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.
- Liver imaging (ultrasound, magnetic resonance imaging [MRI], or computerized tomography [CT]) to evaluate liver disease.

5.7.6.2. 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 GSK Medical Monitor 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 4 for algorithm of liver chemistry stopping and follow-up criteria.

5.7.7. QTc Withdrawal Criteria

QTc should be assessed at the frequency shown in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B.

A subject **who experiences a QTc prolongation**[1] defined as **QTcB ≥501 msec or uncorrected QT>600 msec or (QTcB>530 msec or QTcB>530 msec for subjects with bundle branch block** will have study treatment with GSK1120212 withheld:

[1] based on average QTc value of triplicate ECGs (confirmed via manual over-read). For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to **grade 1 (450 - 480 msec) or baseline**, the subject may be re-started on the study treatment **at current dose level** if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment. **If the event does not resolve or recurs, permanently discontinue study treatment.**

5.7.7.1. French and the United Kingdom Specific QTc Stopping Criteria

In line with local requirements, a subject in France **or the United Kingdom** that meets the QTc[1] criteria below will have study treatment withheld:

QTcB >500 msec

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

5.7.8. Criteria for Evaluating Cardiac Function and Electrical Activity

5.7.8.1. Left Ventricular Ejection Fraction Stopping Criteria

ECHO or MUGA scans should include an evaluation for LVEF and both right- and left-sided valvular lesions. For each subject, the same procedure should be performed at the time of transition and at the Final Study Visit to allow direct comparison. Additional ECHO assessments may be performed if clinically warranted.

Subject who have an asymptomatic, absolute decrease of >10% in LVEF compared with baseline (baseline value from parent study) and the ejection fraction is below the institution's LLN should have treatment with GSK1120212 withheld and a repeat evaluation of LVEF within 2 weeks.

- If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline [baseline value from parent study]) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK1120212 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks, and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK1120212 should be permanently discontinued **and have a cardiology consult**. Ejection fraction should be monitored in 2 weeks and then every 4 weeks for a total of 16 weeks or until resolution.

Subjects with **symptomatic** Grade 3 **(resting LVEF 39-20% or >20% absolute reduction from baseline)** or **symptomatic Grade 4 (resting LVEF <20%)** left ventricular systolic dysfunction must discontinue treatment with GSK1120212 **and have a cardiology consult.** Ejection fraction should be monitored at 2 weeks, at 4 weeks, and then every 4 weeks for a total of 16 weeks or until resolution. **Symptomatic Grade 3 and symptomatic Grade 4 left ventricular systolic dysfunctions are to be reported as SAEs.**

The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s). Copies of all ECHOs and/or MUGA scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline **and** LVEF <LLN **(or <50% when LLN does not exist)** will be required by GSK for review. Instructions for submission of qualifying ECHOs/MUGA scans are provided in the SPM.

5.8. Blinding

This is an open-label study.

5.9. 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 GSK investigational product (IP) dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, 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.

5.10. Treatment Compliance

Compliance with GSK1120212 and other investigational or approved anti-cancer agent(s) used in combination with GSK1120212 dosing will be assessed through pill counts, and querying the subject during the site visits and documented in the source documents and eCRF.

A record of the number of GSK1120212 tablets and other investigational or approved anti-cancer agent(s) used in combination with GSK1120212 dosing dispensed to and taken by each subject 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.

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of the Transition Visit until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations, taken at the time of transition from the parent study and during the study will be recorded in the 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.

6.1. Permitted Medications

All concomitant medications taken during the study will be recorded in the eCRF with information regarding reason for use, route of administration and dates of administration.

The following will be recorded on the concomitant medications eCRF page:

- A complete list of prescription and over-the-counter medications (including herbal remedies) taken at the time of transition to the rollover study.
- All concomitant medications taken during the study will also be recorded in the eCRF.

Subjects should receive full supportive care during the study including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Acetaminophen at doses of ≤2 grams/day is permitted. Use of anticoagulants such as warfarin is also permitted provided that INR is monitored according to local standard clinical practice.

Supplementation with growth factors such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and erythropoietin-based agents are allowed as clinically indicated. Growth factors will be administered according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology version 1, 2010.

6.1.1. Drug to Be Used with Caution

Medications that may alter the elimination of GSK1120212 **(**Table 8**)** or medications that may have their elimination altered by GSK1120212 **(**Table 9**)** should be administered **WITH CAUTION**.

6.1.1.1. GSK1120212 as a Victim

Drugs that potently inhibit or induce CYP3A4 should be administered **WITH CAUTION** as it may increase or decrease exposure to GSK1120212. Table 8 provides a list of possible medications including, but not limited to, those drug substances that may alter GSK1120212 elimination.

Table 8 Drugs Potentially Affecting GSK1120212 Elimination Resulting in Increased or Decreased GSK1120212 Exposure

Drug Class	Generic Drug Name
	Drugs that may increase exposure of GSK1120212 (CYP3A4 inhibitors)
Antivirals	amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir
Antibiotics	clarithromycin, erythromycin, telithromycin, troleandomycin
Antifungals	fluconazole, itraconazole, ketoconazole, voriconazole
Antidepressants	nefazodone
Calcium Channel Blockers	mibefradil, diltiazem, verapamil
Miscellaneous	aprepitant
	Drugs that may decrease exposure of GSK1120212 (CYP3A4 inducers)
Antivirals	efavirenz, nevirapine,
Antibiotic	rifampin
Anticonvulsants	carbamazepine, phenobarbital, phenytoin

6.1.1.2. GSK1120212 as a Perpetrator

Drugs with a narrow therapeutic index that are substrates of CYP2C8 should be used **WITH CAUTION (**Table 9**).**

Table 9 Drug Metabolism Potentially Affected by GSK1120212 Resulting in Increased Exposure of These Substrates

Drug Class	Generic Drug Name
	Substrates for CYP2C8
HMG CoA-reductase inhibitors	cerivastatin
Thiazolidinediones	repaglinide, rosiglitazone, pioglitazone
Miscellaneous	chloroquine, zopiclone

6.2. Prohibited Medications and Non-Drug Therapies

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.

The following medications or non-drug therapies are prohibited while participating in this study:

- Other anti-cancer agents (e.g., chemotherapy, immunotherapy, biologic therapy, and/or hormone therapy other than for replacement)
- Other non-drug anti-cancer therapy (e.g. radiation therapy, surgery, and/or tumor embolization)

NOTE: Subjects may receive palliative radiation treatment during this study. The study treatment must be held for at least 2 days prior to the start of palliative radiation treatment and for at least 2 days after palliative treatment or longer

(depending upon the extent of palliative treatment and recovery from any acute toxicities to ≤ Grade 1).

- **Herbal products include, but are not limited to:**
  - **marijuana**

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

6.3. Treatment after Discontinuation of Study Treatment or Discontinuation from /Completion of Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical conditions whether or not GSK is providing specific post-study treatment.

Subjects will receive standard of care treatment as determined by their healthcare provider after withdrawal from this study.

Post-study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non-protocol) therapy at the discretion of the treating physician. New therapy should be documented in the eCRF. Every effort should be made to complete the required post-treatment follow-up evaluations prior to initiating further anti-cancer therapy or dosing of an investigational agent (see Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B for Final Study Visit assessments and procedures).

6.4. Treatment of Study Treatment Overdose

6.4.1. GSK1120212

In the event of a GSK1120212 overdose defined as administration of more than the highest dose administered in clinical studies to date, the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

Subjects suspected of overdose should be monitored until study treatment(s) can no longer be detected systemically (at least 7 days).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the subject.

A plasma sample for PK analysis may be requested by the GSK Medical Monitor on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 7 days from the date of the last dose of on-study dosing.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

6.4.2. Other Anti-Cancer Agent(s)

In the event of an overdose of another anti-cancer agent(s) used in combination with GSK1120212, the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AE/SAEs and laboratory abnormalities based upon the prescribing information for the agent(s).

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

7. LIFESTYLE OR DIETARY RESTRICTIONS

7.1. Meals and Dietary Restrictions

GSK1120212 should be **administered** with approximately **240 mL (**8 fl oz) of water**, under fasting conditions, either** 1 hour before **or** 2 hours after **a meal**.

If diet recommendations change with emerging data (i.e. the planned food-effect study) 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 without amendment to the protocol.

7.2. Activity

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

7.3. Contraception Requirements

7.3.1. Female Subjects

Females of non-childbearing potential (i.e., physiologically incapable of becoming pregnant), as defined in the parent study, are any female who has had a documented hysterectomy, bilateral oophorectomy (ovariectomy), or bilateral tubal ligation; or post-menopausal.

Female subjects of childbearing potential, as defined in the parent study and determined not to be post-menopausal, must continue to use the same adequate method of contraception as used in the parent study during the rollover study and for **4 months*** following the last dose of study treatment(s).

GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- An intrauterine device with a documented failure rate of <1% per year

- Vasectomized partner who is sterile prior to the female subject's entry in the study and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to the first dose of study treatment, through the dosing period, and for at least **4 months*** after the last dose of study treatment
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

NOTE: Hormonal-based methods (e.g., oral contraceptives) are not permitted due to potential drug-drug interaction with GSK1120212.

***NOTE**: Contraception requirement may last for a time period longer than what is required for single-agent GSK1120212 since female subjects may be exposed to cytotoxic chemotherapy during study treatment. Investigators should reference the product label for the appropriate chemotherapeutic agent(s) for additional clarification.

Refer to Section 8.5.5 for details on reporting any pregnancy that occurs during participation in the rollover study.

8. STUDY ASSESSMENTS AND PROCEDURES

The study specific assessments and procedures are outlined in Appendix 1: Time and Events Table for Cohort A and Appendix 2: Time and Events Table for Cohort B. Further details of study assessments and procedures are provided in the SPM.

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

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. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

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.

8.1. Transition Visit

For this study, the Transition Visit may occur on the same day as the last study visit on the parent study. The 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, sex, and race.
- Subject-related data from parent study, including parent study protocol number, parent study subject treatment number, previous subject number assigned in parent study, start date and dose of GSK1120212 treatment regimen in parent study, dose of GSK1120212 and other study treatment(s), if applicable, at time of transition to this study; and best response based on last disease assessment in parent study.
- Complete physical examination, including height and weight.
- Vital signs (BP, temperature, respiratory rate, and pulse rate)
- Clinical laboratory tests: hematology and clinical chemistry
- Serum beta-human Chorionic Gonadotropin (β-hCG) pregnancy test for female subjects of childbearing potential only
- 12-lead ECG
- ECHO (preferred) or MUGA scan (if ECHO or MUGA scan was performed within 12 to 16 weeks of transition to rollover study as part of the parent study assessments, the results of that assessment may be recorded as transition values for the rollover study)
- Review of concomitant medications

8.2. Continuous Dosing Treatment Period

8.2.1. Cohort A

The following assessments must be performed **every 4 weeks** while receiving treatment:

- Vital signs (BP, temperature, respiratory rate, and pulse rate)
- Clinical laboratory tests: hematology and clinical chemistry(for the first 2 years of treatment with GSK1120212, including time on parent study)

The following assessments must be performed **at Week 8** while receiving treatment:

- Complete physical examination

The following assessment must be performed while receiving treatment:

- ECHO (preferred) or MUGA scan should be performed within 12 weeks from the date of the subject's last ECHO or MUGA scan which may have been performed in the parent study or at the time of transition to the rollover study.
- Subsequent ECHO (preferred) or MUGA scans must be performed every 12 weeks thereafter while the subject is receiving treatment.

NOTE: Refer to Section 5.7.5 for stopping criteria and follow-up for abnormal results).

The following assessments must be performed **every 12 weeks** while receiving treatment:

- Complete physical examination (after Week 8)
- 12-lead ECG (for first 2 years of treatment with GSK1120212, including time on parent study)
- Clinical laboratory tests: hematology and clinical chemistry (>2 years of treatment with GSK1120212, including time on parent study)

The following assessments must be performed **every 24 weeks** while receiving treatment:

- 12-lead ECG (>2 years of treatment with GSK1120212, including time on parent study)

The following assessments must be performed **continuously** while receiving treatment:

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

8.2.2. Cohort B

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

- Vital signs (BP, temperature, respiratory rate, and pulse rate)
- Clinical laboratory tests: hematology and clinical chemistry (for first 2 years of treatment with GSK1120212, including time on parent study)

The following assessments must be performed **every 9 or 12 weeks** (depending on schedule used in parent study) while receiving treatment:

- 12-lead ECG (for first 2 years of treatment with GSK1120212, including time on parent study)
- Clinical laboratory tests: hematology and clinical chemistry (>2 years of treatment with GSK2118436, including time on parent study)

The following assessments must be performed **every 12 weeks** while receiving treatment:

- Complete physical examination

The following assessments must be performed while receiving treatment:

- **ECHO (preferred) or MUGA scan should be performed within 12 weeks from the date of the subject's last ECHO or MUGA scan which may have been performed in the parent study or at the time of transition to the rollover study.**

- **Subsequent ECHO (preferred) or MUGA scans must be performed <u>every 12 weeks</u> thereafter while the subject is receiving treatment.**

  NOTE: Refer to Section 5.7.5 for stopping criteria and follow-up for abnormal results).

The following assessments must be performed **<u>every 24 weeks</u>** while receiving treatment:

- 12-lead ECG (>2 years of treatment with GSK1120212, including time on parent study)

The following assessments must be performed **<u>continuously</u>** while receiving treatment:

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

8.3. Final Study Visit

If a subject is withdrawn from study treatment, the following assessments will be performed within 28 days (±7 days) from the last dose of study treatment(s) and prior to initiating any other treatment for cancer:

- Complete physical examination
- Vital signs (BP, temperature, respiratory rate, and pulse rate)
- Clinical laboratory tests: hematology and clinical chemistry
- 12-lead ECG
- ECHO (preferred) or MUGA scan (only required if there was an abnormal finding **reported from the last ECHO or MUGA scan performed**)
- Review of concomitant medications
- Assessment of AEs

8.4. Safety

Measurements used to evaluate safety will include physical examinations, vital signs (BP, temperature, respiratory rate, 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 Appendix 2: Time and Events Table for Cohort B.

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 time of first dose of study treatment(s) on the rollover study as baseline for some AEs may have occurred in parent study as AE continued at the time of transition to the rollover study). This definition of baseline will be applicable to other assessments (i.e., physical examination findings, laboratory values) for this study when baseline reference is used.

8.4.1. Physical Examinations

Complete physical examinations will be performed at the time points outlined in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B. Height and weight will also be measured and recorded at the initial physical examination only.

8.4.1.1. Assessment of Skin Changes

All physical examinations should include examination of skin and assessment of any skin changes. Post-baseline skin examinations by a referral dermatologist or other appropriate physician should be conducted if clinically indicated. Biopsy of skin lesions related to treatment may be performed if clinically indicated.

8.4.2. Ophthalmologic Examinations

All subjects transitioning to the rollover study are expected to have had a standard ophthalmic exam performed by an ophthalmologist during Screening in their parent study. Ophthalmologic examinations will be conducted during the rollover study if clinically indicated (refer to Section 5.7.5 for stopping criteria for visual changes). If an ophthalmologic examination is necessary, it should include **dilated** indirect fundoscopic examination, **best corrected** visual acuity, visual field examination, tonometry, **slit lamp biomicroscopic examination** and direct fundoscopy, with special attention to retinal abnormality. **Optical coherence tomography is strongly recommended at scheduled visits, and if** retinal abnormalities **are suspected. Other types of ancillary testing including** color fundus **photography and** fluorescein angiography **are also recommended if clinically indicated.**

8.4.3. Vital Signs

Vital sign measurements (BP, temperature, respiratory rate, and pulse rate) will be taken at the time points outlined in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B. 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.

8.4.4. 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 or Appendix 2: Time and Events Table for Cohort B 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, QTcB >500 msec, confirm with 2 additional ECGs taken at least 5 minutes apart.

Refer to Section 5.7.7 for QTc withdrawal criteria and additional readings that may be necessary. Refer to the SPM for details regarding ECG procedures.

8.4.5. Echocardiograms/MUGA Scans

ECHO or MUGA scans (preferably ECHO) will be performed to assess cardiac ejection fraction and cardiac valve abnormalities at the time points specified in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B. The procedure (either ECHO or MUGA, although ECHO is preferred) to document the subject's baseline LVEF status must be used consistently throughout the study. If possible, it is also preferred that interpretation of LVEF status be performed consistently by the same reviewer throughout the study.

Copies of all ECHOs and/or MUGA scans performed on subjects who experience an absolute >10% decrease in LVEF compared to baseline and LVEF <LLN will be required by GSK for review. Instructions for submission of qualifying ECHOs/MUGA scans are provided in the SPM

Refer to Section 5.7.8.1 for details regarding LVEF evaluation.

8.4.6. Clinical Laboratory Assessments

Clinical laboratory tests **(**Table 10**)** will be performed as outlined in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B. At the discretion of the investigator, additional laboratory samples may be taken as clinically necessary.

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 and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are significantly abnormal during study participation or within 30 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 GSK Medical Monitor notified.

Table 10 List of Clinical Laboratory Assessments

Hematology	
Platelet Count	*Automated WBC Differential:*
White blood cell (WBC) Count (absolute)	Neutrophils
Hemoglobin	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical Chemistry	
Blood urea nitrogen (BUN)	Potassium
Creatinine	Inorganic phosphorus
Sodium	Magnesium
Albumin	Chloride
Calcium	LDH
Bicarbonate	Glucose
Liver Function Tests	
AST	
ALT	
Alkaline Phosphatase	
Total bilirubin (bilirubin fractionation recommended if total bilirubin >2 times ULN)	
Other tests	
Serum β-hCG pregnancy (female subjects of childbearing potential only; performed only at baseline unless clinically indicated)	

8.5. Adverse Events

AEs and SAEs will be monitored from the time of consent until 30 days after the last dose of study treatment(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.

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 8.5.1 and Section 8.5.2, respectively.

8.5.1. 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.

8.5.2. Definition of a SAE

A SAE 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 fulfils 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 (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 a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury

h. Protocol-specific SAEs: LVEF meeting the stopping criteria (see Section 5.7.8).

i. Additionally, new primary cancers and laboratory abnormalities as referenced in Section 8.5.3 are considered to be serious events by virtue of being medically important. These should be reported in the same manner as other SAEs.

8.5.3. 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.

8.5.3.1. 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 a SAE.

8.5.4. 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 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.

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 or GSK concomitant medication 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 GSK within 24 hours, as indicated in Section 8.5.4.1.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 30 days the investigator may report any AE that they believe possibly related to study treatment.

8.5.4.1. Prompt Reporting of Serious Adverse Events and Other Events to GSK

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

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 Weeks	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, if INR measured)[3]	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 ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash **or** 3 times ULN ≥4 weeks	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]		
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. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. Liver event documents should be completed as soon as possible
3. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

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

8.5.4.2. Regulatory reporting requirements for SAEs

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

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

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.5.5. Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as a SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

8.5.6. Optional Tumor and/or Skin Biopsy and Biomarker Assessments

All sites are required to participate in the collection of tumor or skin biopsies and tumor marker sampling; however, participation by the individual subject is optional. Samples will only be collected only from subjects who provide consent for tumor biopsy, skin biopsy and/or blood sampling for tumor marker assessment at the time of transition to this study. If consent is provided, tumor tissue sample(s), skin sample(s), and/or blood samples (2 x 10 mL) will be collected at the time of disease progression.

Further details on tissue and/or blood requirements for specific tumor biopsy or tumor marker assessments will be provided in the SPM.

8.5.7. Optional Tumor Biopsy

Some subjects may have had pre- and/or post-dose tumor biopsies collected during their participation in their parent study. However, an additional tumor tissue sample from a

lesion not required for disease assessment may be requested during this study. Total mutations in BRAF, MEK1 or 2, PIK3Ca, PTEN and other genes may be assessed.

8.5.8. Optional Skin Biopsy

Some subjects may have had skin biopsies collected during their participation in their parent study. However, additional biopsy or initial biopsies in or around skin lesions that change on treatment may be taken during this study. Testing of these biopsies may include analysis of proteins related to the action of GSK1120212. Deoxyribonucleic acid (DNA) analysis of these biopsy specimens will be restricted to cancer-related genes.

8.5.9. Optional Blood Sampling for Biomarker Analysis

In subjects whose disease may be followed by well-characterized tumor markers, assessment of clinical activity should include results of tumor marker measurements.

Blood samples may be collected for analysis of potential surrogate markers of GSK1120212 activity (e.g. interleukin-8) at the time of disease progression. Additional blood proteins or tumor DNA related to the activity of GSK1120212 may be analyzed. Biomarker sample collection may be altered or terminated based on emerging data. Tumor marker values will be recorded in the eCRF.

8.5.9.1. Optional Circulating Free DNA (cfDNA)

Blood samples may be collected for the analysis of circulating free-DNA (cfDNA). Tumor-specific cfDNA has the potential to be a useful biomarker of therapeutic response to correlate increasing cfDNA levels with increasing tumor burden.

9. DATA MANAGEMENT

For this study, data will be collected using defined eCRFs, transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data. AEs and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSK Drug. Electronic CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

Laboratory data (i.e., hematology and clinical chemistry) will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1. Hypotheses

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

10.2. Study Design Considerations

10.2.1. Sample Size Considerations

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 GSK1120212 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 (ATS) Population** will consist of all subjects that receive at least one dose of GSK1120212. Safety and response 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 GSK Integrated Data Standards Library (IDSL) 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

The final analysis will take place after the last subject last visit has occurred.

Data will be listed and summarized by cohort and for total subjects according to the GSK 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 and/or cohorts.

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

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized by cohort and for total subjects. The ATS population will be used for the analysis of safety data. 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) [NCI, 2009].

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) [NCI, 2009] table, the maximum grade will be summarized.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the following AEs of special interest will be summarized separately: rash, visual changes, diarrhea, pneumonitis, and LVEF.

The incidence of deaths and the primary cause of death will be summarized by cohort and for total subjects.

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) [NCI, 2009]. 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 by cohort. 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. To assess clinical activity, the overall response based on investigator assessments will be listed and summarized by cohort. If the data warrant, the response data will be summarized by cohort.

11. STUDY CONDUCT CONSIDERATIONS

11.1. Posting of Information on Clinicaltrials.gov

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

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

Prior to initiation of a study site, GSK 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.

GSK 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 GSK procedures, the site 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 GSK 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 to their staff to monitor to discuss findings and any 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, GSK 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 last 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 GSK Standard Operating Procedures.

GSK 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 GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK 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**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK 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 GSK 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.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK 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

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK 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.

The results summary will be posted to the Clinical Study Register at the time of the first regulatory approval or within 12 months of any decision to terminate development. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 12 months of the first approval or within 12 months of any decision to terminate development. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

12. REFERENCES

Allen LF, Sebolt-Leopold J, Meyer MB. CI-140 (PD184352), a targeted signal transduction inhibitor of MEK (MAPKK). *Seminars in Oncology.* 2003; 30:105-166.

Davies H, Bignell, GR, Cox, C, Stephens, P, Edkins, S, et al. Mutations of the BRAF gene in human cancer. *Nature.* 2002; 417:949-954.

Friday BB, Adjei AA. Advances in targeting the Ras/Raf/MEK/Erk mitogen-activated protein kinase cascade with MEK inhibitors for cancer therapy. *Clin Cancer Res.* 2008; 14:342-346.

GlaxoSmithKline Document Number HM2009/00151/02. Clinical Investigator Brochure for GSK1120212, 3rd edition. 23-Jun-2011. 4th edition. 05-Sep-2012**. 5th edition. 25-Sep-2013.**

GlaxoSmithKline Document Number RM2007/00642/03. MEK111054: An open-label, multiple-dose, dose escalation study to investigate the safety, pharmacokinetics, and pharmacodynamics of the MEK inhibitor GSK1120212 in subjects with solid tumors or lymphoma. Dated: 10-Jun-2009.

LoRusso PM, Adjei AA, Varterasian M, Gadgeel S, Reid J, et al. Phase I and pharmacodynamic study of the oral MEK inhibitor CI-1040 in patients with advanced malignancies. *J Clin Oncol.* 2005; 23:5281-93.

LoRusso PM, Krishnamurthi SS, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral MAPK/ERK kinase inhibitor PD-0325901 in patients with advanced cancers. *Clin Cancer Res*. 2010; 16:1924-1937.

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

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.

Tzekova V, Cebotaru C, et al. Efficacy and safety of AZD6244 (ARRY-142886) as second/third-line treatment of patients (pts) with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2008;26:431s.

13. APPENDICES

13.1. Appendix 1: Time and Events Table for Cohort A

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 4 weeks[17] (±7 days)	**Week 8[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Liver Function Tests[10,12]	X	X		X		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be **>500** msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should **be performed every 12 weeks** (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is **≥2 times** ULN.
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of **GSK1120212.**
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The **Week** 8", "Every 12 Weeks" or "Every 24 Weeks" columns are NOT a separate visit but instead a listing of assessments required to be completed **at week** 8 **and every** 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

13.2. Appendix 2: Time and Events Table for Cohort B

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 3 or 4 weeks[17] (± 7 days)	**Every 9 or 12 weeks[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X			X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X		X[7]		X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]	X[11]			X
Hematology[10]	X	X[11]	X[11]			X
Liver Function Tests[10,12]	X	X	X			X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

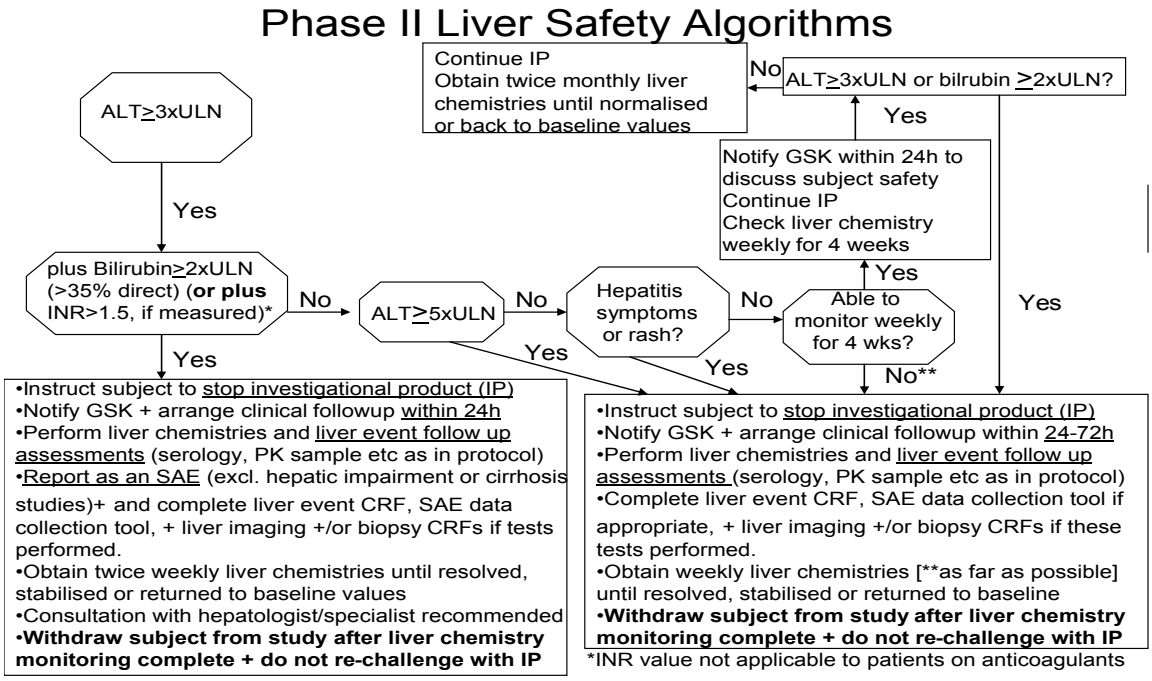
1. All subjects transitioning from parent study will begin the rollover study based on the last treatment visit completed during the parent study. All Transition Visit assessments/procedures must be completed prior to the first dose of study treatment(s). Assessments/procedures may be used to fulfill the requirements of both the parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be **>500** msec.
7. 12-lead ECGs will be performed every 9 or 12 weeks (depending on the schedule used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should be performed every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment.
12. Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is **≥2 times** ULN**.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK1120212.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 9 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 9, 12 or 24 weeks or every second or third clinic visit that is recurring at 3 or 4-week intervals, depending on the schedule used in the parent study.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

13.3. Appendix 3: NYHA Functional Classification System

The **New York Heart Association (NYHA) Functional Classification: Class I, II, III or IV Heart Failure** [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Class	Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

13.4. Appendix 4: Liver Chemistry Stopping and Follow-up Criteria



13.5. Appendix 5: Country Specific Requirements

Australia: Supply of GSK1120212 should continue until the drug is available under subsidy on the Pharmaceutical Benefits Scheme (PBS).

France and the United Kingdom: French **and United Kingdom** specific QTc Stopping Criteria has been added to Section 5.7.1.1.

No other known country specific requirements are currently required.

FRENCH ADMINISTRATIVE CONSIDERATIONS

This appendix includes all the requirements of the French law (n° 2004-806 of 9th August 2004), and identifies, item per item, the mandatory modifications or additional information to the study protocol.

1. Concerning the « STUDY POPULATION»

- In line with the local regulatory requirements, the following text in section **«OTHER STUDY ELIGIBILITY CRITERIA CONSIDERATIONS »** is added :

  A subject will be eligible for inclusion in this study if he /she is either affiliated to or beneficiary of a social security category.
  It is the investigator's responsibility to ensure and to document (in source document - patient notes) that the patient is either affiliated to or beneficiary of a social security category.

≈≈≈≈≈≈≈≈≈≈≈

2. Concerning the "DATA ANALYSIS AND STATISTICAL CONSIDERATIONS" and specially in the "SAMPLE SIZE ASSUMPTION"

The expected number of patients to be recruited in France is declared to the French regulatory authority.

≈≈≈≈≈≈≈≈≈≈≈

3. Concerning the "STUDY CONDUCT CONSIDERATIONS"

- **In section "Regulatory and Ethical Considerations, Including the Informed Consent Process"**

  ⇒ Concerning **the process for informing the patient** or his/her legally authorized representative, the following text is added :

  French Patient Informed Consent form is a document in triplicate which summarizes the main features of the study and allows collection of the patient's written consent. It also contains a reference to the authorisation of Afssaps and the approval from the French Ethic committee and the maintenance of confidentiality of the returned consent form by GSK France.

  ⇒ **Concerning the management of the Patient Informed Consent forms**, the following text is added :

  The first copy of the Patient Informed Consent form is kept by the investigator. The second copy is kept by the Medical Direction of GlaxoSmithKline France and the last copy is given to the patient or his/her legally authorized representative.

  The second copy of all the consent forms will be collected by the investigator under the Clinical Research Assistant's (CRA's) control, and placed in a sealed envelope bearing only:

  - ♦ the study number,
  - ♦ the identification of the Centre : name of the principal investigator and centre number),
  - ♦ the number of informed consents,

- ♦ the date,
- ♦ and the principal investigator's signature.

Then, the CRA hands the sealed envelope over to the Medical Direction, for confidential recording, under the responsibility of the Medical Director.

-*-*-*-*-*-*-*-

- In section concerning the **" NOTIFICATION TO THE HOSPITAL DIRECTOR "** the following text is added:

  In accordance with Article L1123-13 of the Public Health Code, the Hospital Director is informed of the commitment to the trial in his establishment. The Hospital Director is supplied with the protocol and any information needed for the financial disposition, the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial (R.1123-63).

≈≈≈≈≈≈≈≈≈≈≈

- In section concerning the **" INFORMATION TO THE HOSPITAL PHARMACIST "** the following text is added:

  In accordance with Article R.1123-64 of the Public Health Code, the Hospital Pharmacist is informed of the commitment to the trial in his establishment. The Pharmacist is supplied with a copy of the protocol (which allows him to dispense the drug(s) of the trial according to the trial methodology), all information concerning the product(s) of the trial (e.g. included in the CIB), the name of the investigator(s), the number of sites involved in his establishment and the estimated time schedule of the trial.

≈≈≈≈≈≈≈≈≈≈≈

- **In section " DATA MANAGEMENT " the following text is added:**

  Within the framework of this clinical trial, data regarding the identity of the investigators and/or co-investigators and/or the pharmacist if applicable, involved in this clinical trial, and data regarding the patients recruited in this clinical trial (patient number, treatment number, patient status with respect to the clinical trial, dates of visit, medical data) will be collected and computerized in GSK data bases by GlaxoSmithKline Laboratory or on its behalf, for reasons of follow up, clinical trial management and using the results of said clinical trial. According to the Act n° 78-17 of 6th January 1978 further modified, each of these people aforesaid has a right of access, correction and opposition on their own data through GlaxoSmithKline Laboratory (Clinical Operations Department).

≈≈≈≈≈≈≈≈≈≈≈

4. . Concerning the « SAE »

In section **"TRANSMISSION OF THE SAE REPORTS"**:

In case of paper CRF, the SAE Reports have to be transmitted to the GSK France Drug Safety Department, which name, address and phone number are:

Département de Pharmacovigilance
Laboratoire GlaxoSmithKline
100 Route de Versailles
78163 MARLY LE ROI
Tel : [redacted] **Fax :** [redacted]

13.6. Appendix 6: Protocol Changes

AMENDMENT 7

Where the Amendment Applies

Amendment 07 applies to all sites that are or will be conducting this study.

Summary of Amendment Changes with Rationale

In this amendment, standard language changes based on CIB V 05 report date 25 Sept 2013 were made to Stopping Criteria for Visual Changes and Ophthalmologic Examinations. Exclusion Criteria number 2 was deleted as local commercial availability of the study drug is no longer considered to be a major exclusion criterion. Table 1 GSK1120212 Investigation Product (description) was deleted as only the commercial drug is now being used in studies. Tables and table references throughout the protocol were renumbered accordingly. The Handling and Storage of Study Treatment was revised to refer investigators to the drug label and SPM for detailed handling and storage directions. CIB V 05 report date 25 Sep 2013 was added to the CIB reference. Authors, Sponsor Signatory and Sponsor/Medical Monitor Information pages were revised to reflect changes in GSK study team members. Administrative changes were made for typographical (punctuation) omissions and errors.

Title Page

PREVIOUS TEXT:

Author:

[redacted]

REVISED TEXT:

Author:

[redacted]

Sponsor Signatory Page

PREVIOUS TEXT:

[redacted], ~~MD~~
[redacted],
GlaxoSmithKline

REVISED TEXT:

[redacted] **, MD, PhD**
[redacted] **GlaxoSmithKline**

Sponsor/Medical Monitor Information Page

PREVIOUS TEXT:

Sponsor Medical Monitor 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 UP 4215 Collegeville, PA 19426, US~~ [redacted]
Secondary Medical Monitor	[redacted], ~~MD, PhD~~	[redacted]	[redacted]	[redacted]	~~GlaxoSmithKline 1250 South Collegeville Road Mailstop: UP 4340 Collegeville, PA 19426, US~~ [redacted]
~~Tertiary Medical Monitor~~	[redacted], ~~MD~~	[redacted]	[redacted]	[redacted]	~~GlaxoSmithKline 1250 South Collegeville Road Mailstop: UP4340 Collegeville, PA 19426, US~~ [redacted]

REVISED TEXT:

Sponsor Medical Monitor 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 UP 4410 Collegeville, PA 19426-0989, US** [redacted]
Secondary Medical Monitor	[redacted], **MD**	[redacted]	[redacted]	[redacted]	**GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4210 Collegeville, PA 19426-0989, US** [redacted]

List of Abbrevations

ADDED:

RPED	**Retinal Pigment Epithelial Detachment**

Section 4.1.3. Exclusion Criteria #2

PREVIOUS TEXT:

1. Permanent discontinuation of GSK1120212 in the parent study due to toxicity or disease progression.
2. ~~Local access to commercially available GSK1120212.~~
3. Current use of a prohibitive medication(s) as listed in Section 6.2.

   NOTE: Use of anticoagulants such as warfarin is permitted; however, the international normalization ratio (INR) must be monitored in accordance with local institutional practice.
4. Any unresolved toxicity that meets the study treatment discontinuation or study withdrawal criteria from the parent study at the time of transition to this study.
5. **Bazett-corrected QT (QTcB) interval ≥501 msec at the time of transition to this study**

6. **Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.**
7. **Nursing female.**
8. **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 GSK Medical Monitor.**

REVISED TEXT:

1. Permanent discontinuation of GSK1120212 in the parent study due to toxicity or disease progression.
2. **Current use of a prohibitive medication(s) as listed in Section 6.2.**

   NOTE: Use of anticoagulants such as warfarin is permitted; however, the international normalization ratio (INR) must be monitored in accordance with local institutional practice.
3. **Any unresolved toxicity that meets the study treatment discontinuation or study withdrawal criteria from the parent study at the time of transition to this study.**
4. **Bazett-corrected QT (QTcB) interval ≥501 msec at the time of transition to this study**
5. **Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.**
6. **Nursing female.**
7. **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 GSK Medical Monitor.**

Section 5.1. Investigational Product, Table 1

PREVIOUS TEXT:

Table 1 GSK1120212 GSK Investigational Product

	~~Investigational Product~~		
Product name :	~~GSK1120212~~		
Formulation description:	~~Each tablet is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. Tablets are then coated with either a white or pink opaque film* (*Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant as applicable).~~		
Dosage form :	~~Tablet~~		
Unit dose strength(s):	~~**0.5 mg**~~		~~**2.0 mg**~~
Physical Description:	~~**0.5mg: White, oval, biconvex film-coated tablet with dose proportional diameter**~~ ~~**2.0 mg: Pink, round, biconvex film-coated tablet with dose proportional diameter**~~		
~~Route/Regimen~~:	~~Oral/Cohort A: Subjects will receive GSK1120212 2.0 mg or less once-daily. Cohort B: Subjects will receive continuous oral dosing of GSK1120212 at the current dose administered in the parent study at the time of transition to the rollover study.~~		
Dosing Instructions:	~~GSK1120212 should be administered with approximately 240 mL (8 fl oz) of water, under fasting conditions, either 1 hour before or 2 hours after a meal.~~		

REVISED TEXT:

Table 1 GSK1120212 GSK Investigational Product

	Commercial Image Product	
Product name :	**GSK1120212 0.5 mg Tablet**	**GSK11210212 2 mg Tablet**
Formulation description:	**Each tablet contains GSK1120212B equivalent to 0.5 mg of GSK1120212 as drug substance blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with yellow opaque film* (*Opadry yellow, a titanium dioxide-based formulation with yellow iron oxide as colorant).**	**Each tablet contains GSK1120212B equivalent to 2 mg of GSK1120212 as drug substance blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with pink opaque film* (*Opadry Pink, a titanium dioxide-based formulation with red iron oxide as colorant).**
Dosage form :	**Tablet**	**Tablet**
Unit dose strength(s):	**Tablet strength: 0.5 mg**	**Tablet strength: 2 mg**
Physical Description:	**Yellow, modified oval, biconvex, film-coated tablets (4.85 x 8.86 mm)**	**Pink, biconvex, round film-coated tablets 7.5 mm in diameter**
Route/ Administration:	**Oral/once-daily single dose**	**Oral/once-daily single dose**
Dosing Instructions:	**GSK1120212 should be administered with approximately 240 mL (8 fl oz) of water, under fasting conditions, either 1 hour before or 2 hours after a meal**	

Section 5.4. Handling and Storage of Study Treatment

PREVIOUS TEXT:

GSK1120212 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK1120212 will be limited to the investigator and authorized site staff. GSK1120212 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

~~GSK1120212 is to be stored at a temperature up to **25**°C in an opaque bottle, **protected from light and moisture**. Maintenance of a temperature log (manual or automated) is required.~~

REVISED TEXT:

GSK1120212 must be stored **in an opaque bottle, protected from light and moisture** in a secure area under the appropriate physical conditions for the product **at the temperature specified on the label. Maintenance of a temperature log (manual or automatic) is required.** Access to and administration of the GSK1120212 will be limited to the investigator and authorized site staff. GSK1120212 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. **Additional guidance can be found in the SPM.**

Section 5.7.5. Stopping Criteria for Visual Changes, paragraph 1

PREVIOUS TEXT:

~~For all visual changes, regardless of grade~~, a blood sample for PK analysis must be drawn as close as possible to the time of the event. Visual change events should be graded using ~~Table 8~~ based on the NCI-CTCAE, version 4.0 [NCI 2009]).

REVISED TEXT:

Episodes of visual changes have been observed in subjects receiving trametinib, and ocular adverse events are known to be related to trametinib. An ophthalmologist should be consulted if changes in vision develop. If the visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), then monitor closely as it may be reasonable to defer ophthalmic examination. Special attention should be given to retinal findings (e.g., retinal pigment epithelial detachment (RPED) or retinovascular abnormalities (i.e., branch or central retinal vein occlusions (RVO). For events of visual changes (regardless of severity) for which an ophthalmic examination is conducted, a blood sample for PK analysis must be drawn as close as possible to the time of the event.

Visual change events should be graded using **Table 7** based on the NCI-CTCAE, version 4.0 [NCI 2009]).

Section 5.7.5. Stopping Criteria for Visual Changes, Grade 1, Grade 2 or 3 and Grade 4 Visual Changes

PREVIOUS TEXT:

Grade 1 visual changes:

- For Grade 1 visual changes that do not affect vision and which, in the option of the treating physician, are clearly unrelated to study treatment (e.g., conjunctivitis), treatment with GSK1120212 may continue with close observation.
- If attribution to study treatment is unclear, immediately refer the subject for ophthalmic exam; **if ~~an ophthalmic exam~~ cannot be performed within 7 days, interrupt treatment with GSK1120212 until ~~exam can be performed and f~~ollow the guidance below depending on the results.**

  If a retinal abnormality is noted, interrupt treatment with GSK1120212 immediately and referral to a retinal specialist should be considered for further evaluation.
- **If RVO is diagnosed, report as a SAE and permanently discontinue treatment with GSK1120212**
- ~~If CSR is diagnosed, interrupt treatment with GSK1120212 until signs and symptoms have resolved. Resume treatment with GSK1120212 at a dose reduced by 1 dose level.~~
- If there is no evidence of RVO ~~or CSR~~, resume treatment with GSK1120212 at the same dose level.

Grade 2 or Grade 3 visual changes:

- Immediately interrupt treatment with GSK1120212 and refer subject to an ophthalmologist for evaluation with an ophthalmic exam. For all subjects with findings consistent with RVO ~~or CSR~~ based on the ophthalmic exam, referral to retinal specialist, if available, should be considered for further evaluation.
  - **If RVO is diagnosed, report as a SAE and permanently discontinue GSK1120212**
  - If ~~CSR~~ is diagnosed~~, interrupt treatment with GSK1120212 until signs and symptoms have resolved and then resume treatment with GSK1120212 at reduced dose by at least one dose level.~~
  - If ~~there is no evidence of~~ RVO ~~or CSR, interrupt treatment with GSK1120212 until signs and symptoms have returned to Grade 1 or resolved. Resuming treatment with~~ GSK1120212 at the same dose level ~~may be considered~~ if visual changes are clearly unrelated to study treatment.

Grade 4 visual changes:

- ~~**requires permanent discontinuation of**~~ **treatment with GSK1120212.**

REVISED TEXT:

Grade 1 visual changes:

- For Grade 1 visual changes that do not affect vision and which, in the option of the treating physician, are clearly unrelated to study treatment (e.g., conjunctivitis), treatment with GSK1120212 may continue with close observation.
- If attribution to study treatment is unclear, immediately refer the subject for ophthalmic exam; **if a dilated fundus examination cannot be performed within 7 days of onset, interrupt treatment with GSK1120212 until RPED and RVO can be excluded by retina specialist/ophthalmologist. Follow the guidance below depending on the results.**

  If a retinal abnormality is noted, interrupt treatment with GSK1120212 immediately and referral to a retinal specialist should be considered for further evaluation.
- **If RPED suspected or diagnosed (asymptomatic; clinical or diagnostic observations only) continued treatment with retinal evaluation monthly until resolved. Report as an SAE. If worsens see grade 2-3 guidance.**
- **If RVO is diagnosed, report as a SAE and permanently discontinue treatment with GSK1120212**
- If there is no evidence of **RPED or RVO**, resume treatment with GSK1120212 at the same dose level.

Grade 2 or Grade 3 visual changes:

- Immediately interrupt treatment with GSK1120212 and refer subject to an ophthalmologist for evaluation with an ophthalmic exam. For all subjects with findings consistent with **RPED** or RVO based on the ophthalmic exam, referral to retinal specialist, if available, should be considered for further evaluation.
  - **If RVO is diagnosed report as a SAE and permanently discontinue GSK1120212**
  - If **RPED** is diagnosed **(symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL), perform retinal evaluation monthly and if improves to ≤ Grade 1, resume treatment with GSK1120212 at lower dose (reduced by 0.5 mg) or discontinue in subjects taking GSK1120212 1 mg daily.**
  - If **RPED and RVO,** are excluded and visual changes are clearly unrelated to study treatment restart GSK1120212 at the same dose.

Grade 4 visual changes:

- **Interupt GSK1120212, consult ophthalmologist immediately and report as as SAE.**
- **If RPED and RVO are excluded, may consider restarting GSK1120212 at same or reduced dose after discussion with the study medical monitor**
- **If RPED or RVO diagnosed permanently discontinue treatment with GSK1120212.**

Section 8.4.2. Ophthalmologic Examinations

PREVIOUS TEXT:

All subjects transitioning to the rollover study are expected to have had a standard ophthalmic exam performed by an ophthalmologist during Screening in their parent study. Ophthalmologic examinations will be conducted during the rollover study if clinically indicated (refer to Section 5.7.5 for stopping criteria for visual changes). If an ophthalmologic examination is necessary, it should include indirect fundoscopic examination, visual acuity, visual field examination, tonometry, and direct fundoscopy, ~~with special attention to retinal abnormality that are predisposing factors for RVO or CSR~~.

~~For subjects with clinical suspicion of RVO or CSR, additional color fundus photos are recommended if they can be acquired, and fluorescein angiography and/or optical coherence tomography are highly recommended~~.

REVISED TEXT:

All subjects transitioning to the rollover study are expected to have had a standard ophthalmic exam performed by an ophthalmologist during Screening in their parent study. Ophthalmologic examinations will be conducted during the rollover study if clinically indicated (refer to Section 5.7.5 for stopping criteria for visual changes). If an ophthalmologic examination is necessary, it should include **dilated** indirect fundoscopic examination, **best corrected** visual acuity, visual field examination, **tonometry, slit lamp biomicroscopic examination** and direct fundoscopy, with special attention to retinal abnormality. **Optical coherence tomography is strongly recommended at scheduled visits, and if retinal abnormalities are suspected. Other types of ancillary testing including color fundus photography and fluorescein angiography are also recommended if clinically indicated.**

Section 12. References

PREVIOUS TEXT:

GlaxoSmithKline Document Number HM2009/00151/**02**. Clinical Investigator Brochure for GSK1120212, 3rd edition. 23-Jun-2011. **4th edition. 05-Sep-2012**

REVISED TEXT:

GlaxoSmithKline Document Number HM2009/00151/02. Clinical Investigator Brochure for GSK1120212, 3rd edition. 23-Jun-2011. 4th edition. 05-Sep-2012**. 5th edition. 25-Sep-2013.**

Section 13.1. Appendix 1: Time and Events Table for Cohort A, annotation #12

PREVIOUS TEXT:

12. Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is ~~>2 times~~ ULN

REVISED TEXT:

12. Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is **≥ 2 times**-ULN

Section 13.2. Appendix 2: Time and Events Table for Cohort B, annotation #12

PREVIOUS TEXT:

12. Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is ~~>2 times~~ ULN

REVISED TEXT:

12. Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is **≥ 2 times**-ULN

AMENDMENT 6

Where the Amendment Applies

Amendment 06 applies to all sites that are or will be conducting this study.

Summary of Amendment Changes with Rationale

In this amendment, standard language changes based on CIB V 04 report date 05 Sep 2012 were made to QTc Withdrawal Criteria, LVEF Stopping Criteria, Management of Hypertension, Inclusion Criteria, Pregnancy and Contraception. The requirements for male contraception were deleted from the Inclusion Criteria and sections on Pregnancy and Contraception as the use of contraception with female partners of childbearing potential is not recommended based on the absence of genotoxicity, no effects on male reproductive tissues in nonclinical toxicity studies, and the minimal potential for trametinib exposure of females via semen. The decreased frequency of interim visits for those subjects who have been on study >52 weeks was more clearly define to be for those subjects who have in addition to being on study >52 weeks have also tolerated therapy well with limited toxicities and to be with the approval and direction of the GSK medical monitor. The 1mg tablet was deleted from Table 1 GSK1120212 Investigational Product as the 1mg tablet is no longer available. Typographical errors were corrected.

Section 3.1. Cohorts

PREVIOUS TEXT:

Cohort A:

Cohort A will consist of subjects who have completed <24 weeks of treatment with GSK1120212 monotherapy during their participation in the parent study. It is anticipated that subjects in this cohort will have participated in a clinical pharmacology or another short-term study of GSK1120212. Subjects will complete the Transition Visit and return for their next scheduled visit (Study Week 4), and then every 4 weeks thereafter. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

Subjects will receive GSK1120212 as an oral, daily dose of 2 mg or less. Protocol specified guidelines for dose modifications and treatment discontinuation criteria are provided in Section 5.6 and Section 5.7, respectively. If there are any uncertainties about the dose to be administered in this study, the GSK Medical Monitor should be consulted. Once treatment with GSK1120212 is discontinued the subject is to be withdrawn from the rollover study.

Cohort B:

Cohort B will consist of subjects who have completed ≥24 weeks of treatment with GSK1120212 (either as monotherapy or combination therapy with an approved anti-cancer agent) during their participation in the parent study. Subjects who transition from

a combination study may continue to receive GSK1120212 in combination with the approved anti-cancer agent defined by the parent study or if, in the opinion of the investigator, the subject has received maximum benefit or is experiencing unacceptable toxicity from the approved anti-cancer agent, then treatment with the approved anti-cancer agent may be discontinued and the subject may remain on study for continued treatment with GSK1120212 alone. Once treatment with GSK1120212 is discontinued the subject is to be withdrawn from the rollover study.

Subjects will complete the Transition Visit assessments and then return for their next scheduled visit (Study Week 3 or 4), then every 3 or 4 weeks thereafter (depending on the schedule used in the parent study). Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

All subjects will receive GSK1120212 at the current dose level administered in the parent study at the time of the Transition Visit. If this starting dose of GSK1120212 is below the recommended Phase 2 dose (RP2D) previously defined for the given treatment regimen (e.g., dose modification following recovery from toxicity), the investigator, after consultation with the GSK Medical Monitor, may consider escalating the dose to the RP2D. If there are any uncertainties about the dose(s) to be administered in this study, the GSK Medical Monitor should be consulted.

REVISED TEXT

Cohort A:

Cohort A will consist of subjects who have completed <24 weeks of treatment with GSK1120212 monotherapy during their participation in the parent study. It is anticipated that subjects in this cohort will have participated in a clinical pharmacology or another short-term study of GSK1120212. Subjects will complete the Transition Visit and return for their next scheduled visit (Study Week 4), and then every 4 weeks thereafter. Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

Subjects will receive GSK1120212 as an oral, daily dose of 2 mg or less. Protocol specified guidelines for dose modifications and treatment discontinuation criteria are provided in Section 5.6 and Section 5.7, respectively. If there are any uncertainties about the dose to be administered in this study, the GSK Medical Monitor should be consulted. Once treatment with GSK1120212 is discontinued the subject is to be withdrawn from the rollover study.

Cohort B:

Cohort B will consist of subjects who have completed ≥24 weeks of treatment with GSK1120212 (either as monotherapy or combination therapy with an approved anti-cancer agent) during their participation in the parent study. Subjects who transition from a combination study may continue to receive GSK1120212 in combination with the approved anti-cancer agent defined by the parent study or if, in the opinion of the investigator, the subject has received maximum benefit or is experiencing unacceptable

toxicity from the approved anti-cancer agent, then treatment with the approved anti-cancer agent may be discontinued and the subject may remain on study for continued treatment with GSK1120212 alone. Once treatment with GSK1120212 is discontinued the subject is to be withdrawn from the rollover study.

Subjects will complete the Transition Visit assessments and then return for their next scheduled visit (Study Week 3 or 4), then every 3 or 4 weeks thereafter (depending on the schedule used in the parent study). Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

All subjects will receive GSK1120212 at the current dose level administered in the parent study at the time of the Transition Visit. If this starting dose of GSK1120212 is below the recommended Phase 2 dose (RP2D) previously defined for the given treatment regimen (e.g., dose modification following recovery from toxicity), the investigator, after consultation with the GSK Medical Monitor, may consider escalating the dose to the RP2D. If there are any uncertainties about the dose(s) to be administered in this study, the GSK Medical Monitor should be consulted.

Section 4.1.2. Inclusion Criteria, #6

PREVIOUS TEXT:

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. Has demonstrated compliance during the parent study with study treatment(s), treatment visit schedules, and the requirements and restrictions listed in the consent form.
3. Is currently participating in GSK1120212 study and is receiving treatment with GSK1120212.
4. Is currently receiving clinical benefit as determined by the investigator from previous treatment with GSK1120212 either as monotherapy or as part of a combination treatment regimen.
5. 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.
6. ~~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 GSK1120212.~~
7. 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 months** after the last dose of GSK1120212.

8. Female subjects of childbearing potential, as defined in parent study, must have negative serum pregnancy tests at the time of transition to this study.
9. Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

REVISED TEXT:

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. Has demonstrated compliance during the parent study with study treatment(s), treatment visit schedules, and the requirements and restrictions listed in the consent form.
3. Is currently participating in GSK1120212 study and is receiving treatment with GSK1120212.
4. Is currently receiving clinical benefit as determined by the investigator from previous treatment with GSK1120212 either as monotherapy or as part of a combination treatment regimen.
5. 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.
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 months after the last dose of GSK1120212.**
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. **Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.**

Section 5.1. Investigational Product: Table 1

PREVIOUS TEXT:

Table 12 GSK1120212 GSK Investigational Product

	Investigational Product		
Product name :	**GSK1120212**		
Formulation description:	Each tablet is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. Tablets are then coated with either a white or pink opaque film* (*Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant as applicable).		
Dosage form :	Tablet		
Unit dose strength(s):	0.5 mg	~~1.0 mg~~	2.0 mg
Physical Description:	0.5mg: White, oval, biconvex film-coated tablet with dose proportional diameter ~~1.0 mg: White, round, biconvex film-coated tablet with dose proportional diameter~~ 2.0 mg: Pink, round, biconvex film-coated tablet with dose proportional diameter		
Route/Regimen:	Oral/Cohort A: Subjects will receive GSK1120212 2.0 mg or less once-daily. Cohort B: Subjects will receive continuous oral dosing of GSK1120212 at the current dose administered in the parent study at the time of transition to the rollover study.		
Dosing Instructions:	GSK1120212 should be administered with approximately 240 mL (8 fl oz) of water, under fasting conditions, either 1 hour before or 2 hours after a meal.		

REVISED TEXT:

Table 13 GSK1120212 GSK Investigational Product

	Investigational Product		
Product name :	**GSK1120212**		
Formulation description:	Each tablet is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. Tablets are then coated with either a white or pink opaque film* (*Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant as applicable).		
Dosage form :	Tablet		
Unit dose strength(s):	**0.5 mg**		**2.0 mg**
Physical Description:	**0.5mg: White, oval, biconvex film-coated tablet with dose proportional diameter** **2.0 mg: Pink, round, biconvex film-coated tablet with dose proportional diameter**		
Route/Regimen:	Oral/Cohort A: Subjects will receive GSK1120212 2.0 mg or less once-daily. Cohort B: Subjects will receive continuous oral dosing of GSK1120212 at the current dose administered in the parent study at the time of transition to the rollover study.		
Dosing Instructions:	GSK1120212 should be administered with approximately 240 mL (8 fl oz) of water, under fasting conditions, either 1 hour before or 2 hours after a meal.		

Section 5.7.1.2. Managing Hypertension

PREVIOUS TEXT:

For subjects experiencing an increase in SBP and/or DBP that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Hypertension	
(A) Asymptomatic and persistent[1] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	**Step 1. Continue study treatment at the current dose.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[2] BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).**
(B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	**Step 1.Consider reducing or interrupting study treatment, as clinically indicated.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP.** **Step 4. Once BP is well-controlled, restart study treatment dose-reduced**
(C) Symptomatic hypertension or recurring[3] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite modification of antihypertensive medication(s)	**Step 1. Interrupt study treatment.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended.** **Step 4. Once BP is well-controlled, restart study treatment dose-reduced.**
(D) Refractory hypertension unresponsive to above interventions.	**Discontinue study treatment and continue follow-up per protocol.**

Hypertension detected in 2 separate readings during up to 3 subsequent visits

a. BP reading of SBP ≤140 mmHg and DBP ≤90 mmHg in 2 separate readings during up to 3 subsequent visits

b. Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention.

REVISED TEXT:

For subjects experiencing an increase in SBP and/or DBP that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Hypertension	
(A) Asymptomatic and persistent[1] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	**Step 1. Continue study treatment at the current dose.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[2] BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).**
(B) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	**Step 1.Consider reducing or interrupting study treatment, as clinically indicated.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP.** **Step 4. Once BP is well-controlled[2], restart study treatment dose-reduced by <u>one dose level</u>**
(C) Symptomatic hypertension or recurring[3] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite modification of antihypertensive medication(s)	**Step 1. Interrupt study treatment.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended.** **Step 4. Once BP is well-controlled, restart study treatment dose-reduced by <u>one dose level</u>**
(D) Refractory hypertension unresponsive to above interventions.	**<u>Permanently</u> discontinue study treatment and continue follow-up per protocol.**

1. Hypertension detected in 2 separate readings during up to 3 subsequent visits
2. BP reading of SBP ≤140 mmHg and DBP ≤90 mmHg in 2 separate readings during up to 3 subsequent visits
3. Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention.

Section 5.7.7 QTc Withdrawal Criteria

PREVIOUS TEXT:

QTc should be assessed at the frequency shown in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B.

A subject ~~that~~ **experiences a ~~Grade 3 (QTcB ≥501 msec on at least two separate ECGs)~~ or ~~Grade 4 (QTcB≥501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) prolongation of the corrected QT[1] interval~~** will have study treatment with GSK1120212 withheld:

[1] based on average QTc value of triplicate ECGs (confirmed via manual over-read). For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to **grade 1 (450 - 480 msec) or baseline**, the subject may be re-started on the study treatment **at current dose level** if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

REVISED TEXT:

QTc should be assessed at the frequency shown in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B.

A subject **<u>who</u> experiences a QTc prolongation**[1] defined as **<u>QTcB ≥501 msec or uncorrected QT>600 msec or QTcB>530 msec for subjects with bundle branch block</u>** will have study treatment with GSK1120212 withheld:

[1] based on average QTc value of triplicate ECGs (confirmed via manual over-read). For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to **grade 1 (450 - 480 msec) or baseline**, the subject may be re-started on the study treatment **at current dose level** if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment. **<u>If the event does not resolve or recurs, permanently discontinue study treatment.</u>**

Section 5.7.8.1 Left Ventricular Ejection Fraction Stopping Criteria, Second Paragraph, Bullet #2 and Third Paragraph

PREVIOUS TEXT:

Subject who have an asymptomatic, absolute decrease of >10% in LVEF compared with baseline (baseline value from parent study) and the ejection fraction is below the institution's LLN should have treatment with GSK1120212 withheld and a repeat evaluation of LVEF within 2 weeks.

- If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline [baseline value from parent study]) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK1120212 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks, and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK1120212 should be permanently discontinued. Ejection fraction should be monitored in 2 weeks and then every 4 weeks for a total of 16 weeks or until resolution.

Subjects with Grade 3 or 4 ~~(symptomatic)~~ left ventricular systolic dysfunction must discontinue treatment with GSK1120212. Ejection fraction should be monitored at 2 weeks, at 4 weeks, and then every 4 weeks for a total of 16 weeks or until resolution. ~~Evaluation by a cardiologist should be considered.~~

REVISED TEXT

Subject who have an asymptomatic, absolute decrease of >10% in LVEF compared with baseline (baseline value from parent study) and the ejection fraction is below the institution's LLN should have treatment with GSK1120212 withheld and a repeat evaluation of LVEF within 2 weeks.

- If the LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared with baseline [baseline value from parent study]) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK1120212 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks, and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK1120212 should be permanently discontinued **and have a cardiology consult.** Ejection fraction should be monitored in 2 weeks and then every 4 weeks for a total of 16 weeks or until resolution.

Subjects with **symptomatic** Grade 3 **(resting LVEF 39-20% or >20% absolute reduction from baseline)** or **symptomatic Grade** 4 **(resting LVEF<20%)** left ventricular systolic dysfunction must discontinue treatment with GSK1120212 **and have a cardiology consult.** Ejection fraction should be monitored at 2 weeks, at 4 weeks, and then every 4 weeks for a total of 16 weeks or until resolution. **Symptomatic Grade 3 and symptomatic Grade 4 left ventricular systolic dysfunctions are to be reported as SAEs.**

Section 7.3. Contraception Requirements

PREVIOUS TEXT:

~~7.3.2. Male Subjects~~

~~Male subjects with a female partner of childbearing potential must have had a prior vasectomy or must agree to use the same method of contraception as used in the parent study during the rollover study and for 16 weeks after the last dose of study treatment(s).~~

REVISED TEXT:

None

Section 8.5.5. Pregnancy

PREVIOUS TEXT:

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as a SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

~~In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.~~

REVISED TEXT

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as a SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

Section 13.1. Appendix 1: Time and Events Table Cohort A, Footnotes #14, #17 and #20

PREVIOUS TEXT:

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 4 weeks[17] (±7 days)	**Week 8[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Liver Function Tests[10,12]	X	X		X		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be **>500** msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should **be performed every 12 weeks** (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of ~~GSK2118436.~~
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The ~~"Every~~ 8 ~~Weeks"~~, "Every 12 Weeks" or "Every 24 Weeks" columns are NOT a separate visit but instead a listing of assessments required to be completed ~~every~~ 8, 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

REVISED TEXT:

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 4 weeks[17] (±7 days)	**Week 8[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Liver Function Tests[10,12]	X	X		X		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be **>500** msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should **be performed every 12 weeks** (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of **GSK1120212.**
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The "'**Week** 8", "Every 12 Weeks" or "Every 24 Weeks" columns are NOT a separate visit but instead a listing of assessments required to be completed at **week** 8, **and every** 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

Section 13.2 Appendix 2: Time and Events Table Cohort B, Footnote #20

PREVIOUS TEXT:

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 3 or 4 weeks[17] (± 7 days)	**Every 9 or 12 weeks[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X			X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X		X[7]		X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]	X[11]			X
Hematology[10]	X	X[11]	X[11]			X
Liver Function Tests[10,12]	X	X	X			X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be **>500** msec.
7. 12-lead ECGs will be performed every 9 or 12 weeks (depending on the schedule used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should be performed every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK1120212.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 9 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 9, 12 or 24 weeks or every second or third clinic visit that is recurring at 3 or 4-week intervals, depending on the schedule used in the parent study.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

REVISED TEXT

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 3 or 4 weeks[17] (± 7 days)	**Every 9 or 12 weeks[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X			X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X		X[7]		X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]	X[11]			X
Hematology[10]	X	X[11]	X[11]			X
Liver Function Tests[10,12]	X	X	X			X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be **>500** msec.
7. 12-lead ECGs will be performed every 9 or 12 weeks (depending on the schedule used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should be performed every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK1120212.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 9 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 9, 12 or 24 weeks or every second or third clinic visit that is recurring at 3 or 4-week intervals, depending on the schedule used in the parent study.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who **have tolerated therapy well with limited toxicities and** remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval **and direction** from the GSK Medical Monitor.

AMENDMENT 5

Where the Amendment Applies

Amendment 05 applies to all sites that are or will be conducting this study.

Summary of Amendment Changes with Rationale

In this amendment, actions regarding study treatment, GSK1120212 (Trametinib), should the subject experience a Grade 3 or Grade 4 prolongation of the QTc interval was provided in greater detail at the request of the FDA. The time span for females to use contraception was revised; prohibited medications and non-drug therapies were revised to reflect recent changes in the standard language. Additionally, the Exclusion Criteria were revised to be more in line with those of the subject's parent study and less restrictive for eligible subjects who are transitioning to the MEK114375 study. Trametinib, the commercial name of GSK1120212, was added to the subject line on the title page.

Title Page

PREVIOUS TEXT:

GSK1120212, MEK inhibitor, solid tumors, leukemia, safety, cancer

REVISED TEXT

GSK1120212 **(Trametinib),** MEK inhibitor, solid tumors, leukemia, safety, cancer

Section 4.1.2 Inclusion Criteria, Bullet #7

PREVIOUS TEXT:

7. 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 ~~30 days~~ after the last dose of GSK1120212.

REVISED TEXT:

7. 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 months** after the last dose of GSK1120212.

Section 4.1.3 Exclusion Criteria

PREVIOUS TEXT:

Subjects meeting any of the following criteria must not be enrolled in this study:

1. Permanent discontinuation of GSK1120212 in the parent study due to toxicity or disease progression.
2. Local access to commercially available GSK1120212.
3. Current use of a prohibitive medication(s) as listed in Section 6.2.
    - **NOTE**: Use of anticoagulants such as warfarin is permitted; however, the international normalization ratio (INR) must be monitored in accordance with local institutional practice.
4. Any unresolved toxicity that meets the study treatment discontinuation or study withdrawal criteria from the parent study at the time of transition to this study.

~~5. Evidence of severe or uncontrolled systemic diseases (e.g. unstable, or uncompensated respiratory, hepatic, renal **or** metabolic disease)~~

~~6. History or evidence of cardiovascular risk including any of the following:~~

- Bazett-corrected QT (QTcB) interval **≥~~480~~ msec at the time of transition to this study**
- **~~History or evidence of current clinically significant uncontrolled arrhythmias~~**
    - **~~i. Exception: Subjects with controlled atrial fibrillation for >30 days prior to transition to this study are eligible.~~**
- **~~History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to transition to this study~~**
- **~~History or evidence of current Class II congestive heart failure as defined by the New York Heart Association (NYHA; Appendix 3)~~**
- **~~Treatment refractory hypertension defined as a BP reading of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by antihypertensive therapy~~**
- **~~Subjects with intra-cardiac defibrillator or permanent pacemaker~~**
- **~~Cardiac metastases~~**

7. Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.

~~8. Symptomatic or untreated leptomeningeal 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 (EIAEDs).~~

9. Nursing female.
10. 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 GSK Medical Monitor.

REVISED TEXT:

Subjects meeting any of the following criteria must not be enrolled in this study:

1. Permanent discontinuation of GSK1120212 in the parent study due to toxicity or disease progression.
2. Local access to commercially available GSK1120212.
3. Current use of a prohibitive medication(s) as listed in Section 6.2.
    - **NOTE**: Use of anticoagulants such as warfarin is permitted; however, the international normalization ratio (INR) must be monitored in accordance with local institutional practice.
4. Any unresolved toxicity that meets the study treatment discontinuation or study withdrawal criteria from the parent study at the time of transition to this study.
5. Bazett-corrected QT (QTcB) interval **≥501 msec at the time of transition to this study**
6. Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.
7. Nursing female.
8. 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 GSK Medical Monitor.

Section 5.7.7 QTc Withdrawal Criteria

PREVIOUS TEXT:

QTc should be assessed at the frequency shown in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B.

A subject that ~~meets the QTc[1] criteria below~~ will have study treatment with GSK1120212 withheld:

- ~~QTcB >530 msec, or uncorrected QT >600 msec~~

[1] based on average QTc value of triplicate ECGs (confirmed via manual over-read). For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to ~~<500 msec~~, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

REVISED TEXT:

QTc should be assessed at the frequency shown in Appendix 1: Time and Events Table for Cohort A or Appendix 2: Time and Events Table for Cohort B.

A subject that **experiences a Grade 3 (QTcB ≥501 msec on at least two separate ECGs) or Grade 4 (QTcB ≥501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia) prolongation of the corrected QT[1] interval** will have study treatment with GSK1120212 withheld:

[1] based on average QTc value of triplicate ECGs (confirmed via manual over-read). For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to **grade 1 (450 – 480 msec) or baseline**, the subject may be re-started on the study treatment **at current dose level**, if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

Section 6.2 Prohibited Medications and Non-Drug Therapies, 2nd Paragraph

PREVIOUS TEXT:

The following medications or non-drug therapies are prohibited while participating in this study:

- Other anti-cancer agents (e.g., chemotherapy, immunotherapy, biologic therapy, and/or hormone therapy other than for replacement)
- Other non-drug anti-cancer therapy (e.g. radiation therapy, surgery, and/or tumor embolization)

NOTE: Subjects may receive palliative radiation treatment during this study. The study treatment must be held for at least 2 days prior to the start of palliative radiation treatment and for at least 2 days after palliative treatment or longer (depending upon the extent of palliative treatment and recovery from any acute toxicities to ≤ Grade 1).

- ~~Enzyme-inducing anti-epileptic drugs (EIAEDs)~~
- Herbal products include, but are not limited to:
  - ~~St. John's Wort~~
  - ~~kava~~
  - ~~ephedra (ma huang~~)
  - ~~gingko biloba~~

- ~~dehydroepiandrosterone (DHEA)~~
- ~~yohimbe~~
- ~~saw palmetto~~
- ~~ginseng~~
- marijuana

REVISED TEXT:

The following medications or non-drug therapies are prohibited while participating in this study:

- Other anti-cancer agents (e.g., chemotherapy, immunotherapy, biologic therapy, and/or hormone therapy other than for replacement)
- Other non-drug anti-cancer therapy (e.g. radiation therapy, surgery, and/or tumor embolization)

NOTE: Subjects may receive palliative radiation treatment during this study. The study treatment must be held for at least 2 days prior to the start of palliative radiation treatment and for at least 2 days after palliative treatment or longer (depending upon the extent of palliative treatment and recovery from any acute toxicities to ≤ Grade 1).

- Herbal products include, but are not limited to:
  - marijuana

Section 7.3 Contraceptive Requirements: 7.3.1 Female Subjects, 2nd Paragraph & Bullet #3 of the 3rd Paragraph

PREVIOUS TEXT:

Female subjects of childbearing potential, as defined in the parent study and determined not to be post-menopausal, must continue to use the same adequate method of contraception as used in the parent study during the rollover study and for ~~30 days~~* following the last dose of study treatment(s).

GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- An intrauterine device with a documented failure rate of <1% per year
- Vasectomized partner who is sterile prior to the female subject's entry in the study and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to the first dose of study treatment, through the dosing period, and for at least ~~30 days~~* after the last dose of study treatment

- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

REVISED TEXT:

Female subjects of childbearing potential, as defined in the parent study and determined not to be post-menopausal, must continue to use the same adequate method of contraception as used in the parent study during the rollover study and for **4 months*** following the last dose of study treatment(s).

GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

- An intrauterine device with a documented failure rate of <1% per year
- Vasectomized partner who is sterile prior to the female subject's entry in the study and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days prior to the first dose of study treatment, through the dosing period, and for at least **4 months*** after the last dose of study treatment
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).

Section 12: References

PREVIOUS TEXT:

GlaxoSmithKline Document Number HM2009/00151/**02**. Clinical Investigator Brochure for GSK1120212, 3rd edition. 23-Jun-2011

REVISED TEXT:

GlaxoSmithKline Document Number HM2009/00151/**02**. Clinical Investigator Brochure for GSK1120212, 3rd edition. 23-Jun-2011. **4th edition. 05-Sep-2012.**

Section 13.1 Appendix 1: Time and Events Table for Cohort A

PREVIOUS TEXT:

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 4 weeks[17] (±7 days)	**Week 8[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X		~~X~~[8]	X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Liver Function Tests[10,12]	X	X		X		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be ~~>480~~ msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should ~~first~~ be performed ~~at Week 8 and then~~ every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK2118436.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 8 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 8, 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

REVISED TEST:

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 4 weeks[17] (±7 days)	**Week 8[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Liver Function Tests[10,12]	X	X		X		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be >**500** msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA **scan should be performed every 12 weeks** (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported **from the last ECHO or MUGA scan performed**
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK2118436.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 8 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 8, 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

Section 13.2 Appendix 2: Time and Events Table for Cohort B, Footnote #6

PREVIOUS TEXT:

6. 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. QTc interval must not be ~~>480~~ msec.

REVISED TEXT:

6. 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. QTc interval must not be **>500** msec.

AMENDMENT 4

Where the Amendment Applies

Amendment 04 applies to all sites located in the UK that are or will be conducting this study.

Summary of Amendment Changes with Rationale

List of Specific Changes

Abbreviations

Added abbreviations for the United Kingdom (UK), Medicines and Healthcare products Regulatory Agency (MHRA) and Marketing Application Authorization (MAA).

Study Design, page 14

PREVIOUS TEXT

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study (parent study) and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212. Subjects will be enrolled into the appropriate cohort based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. It is estimated that approximately 250 subjects will be enrolled in this study. Subjects may continue treatment in the rollover study until no longer clinically benefitting, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK1120212 becomes available to the subject.

REVISED TEXT

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study (parent study) and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212. Subjects will be enrolled into the appropriate cohort based upon the treatment received in their parent study. Enrollment into this study will be dependent

upon the site's agreement to participate in this study. It is estimated that approximately 250 subjects will be enrolled in this study. Subjects may continue treatment in the rollover study until no longer clinically benefitting, unacceptable toxicity, withdrawal of consent, or **have access to local** commercial supply of GSK1120212 ~~becomes available to the subject.~~.

Section 3 Study Design, paragraph 7

PREVIOUS TEXT

Subjects may continue treatment in this rollover study until lack of clinical benefit, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK1120212 becomes available to the subject.

REVISED TEXT

Subjects may continue treatment in this rollover study until lack of clinical benefit, unacceptable toxicity, withdrawal of consent, or **have access to local** commercial supply of GSK1120212 ~~becomes available to the subject.~~

Section 5.7.7.1 French and the United Kingdom Specific QTc Stopping Criteria

PREVIOUS TEXT

Section 5.7.7.1 French Specific QTc Stopping Criteria

In line with local requirements, a subject in France that meets the QTc[1] criteria below will have study treatment withheld:

QTcB >500 msec

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

REVISED TEXT

Section 5.7.7.1 French and United Kingdom Specific QTc Stopping Criteria

In line with local requirements, a subject in France **or the United Kingdom** that meets the QTc[1] criteria below will have study treatment withheld:

QTcB >500 msec

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

Section 13.5 Appendix 5 Country Specific Requirements

PREVIOUS TEXT

France: French specific QTc Stopping Criteria has been added to Section 5.7.7.1.

REVISED TEXT

France <u>and the United Kingdom</u>: French **<u>and United Kingdom</u>** specific QTc Stopping Criteria has been added to Section 5.7.7.1.

Section 13.5 Appendix 5 Country Specific Requirements

PREVIOUS TEXT

None

REVISED TEXT

AMENDMENT 3

Where the Amendment Applies

This amendment applies to all site and countries.

Summary of Amendment Changes with Rationale

In this amendment, new hypertension guidelines were added based on recent reports of hypertensive events in subjects receiving GSK1120212. In addition, the exclusion criteria based on cardiovascular risk was expanded to include additional criteria based upon recent cardiac events reported in an ongoing MEK study. The protocol section providing background information on GSK1120212 was also revised to remove text that does not correctly summarize the mechanism of action noted preclinically; additional text was inserted to provide a more accurate description of the specificity of GSK1120212. Other changes were made to correct inconsistencies between sections regarding administration of GSK1120212 and the need to perform an ECHO or MUGA at the final study visit outlined in the study assessments section and the Time and Events Tables.

List of Specific Changes

Abbreviations

Added abbreviations for diastolic blood pressure (DBP) and systolic blood pressure (SBP).

Protocol Summary – Rationale

PREVIOUS TEXT

GSK1120212 is a potent and highly selective inhibitor of MEK kinase activity. This multicenter, non-randomized, open-label rollover study will provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212.

REVISED TEXT

GSK1120212 is a potent**, reversible** and highly selective inhibitor of MEK**1/MEK2 activation and** kinase activity. This multicenter, non-randomized, open-label rollover study will provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK1120212 study and who are clinically benefitting from continued treatment and have an acceptable safety profile with GSK1120212.

Section 1.1 Background, Paragraph 2

PREVIOUS TEXT

GSK1120212 is a reversible, highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. A detailed summary of *in vitro* and *in vivo* non-clinical pharmacology studies is provided in the GSK1120212 Investigator Brochure (IB) [GlaxoSmithKline Document Number HM2009/00151/**02**].

REVISED TEXT

GSK1120212 is a **potent,** reversible and highly selective allosteric inhibitor of MEK1/MEK2 activation and kinase activity. **The specificity of GSK1120212 to MEK1 and MEK2 was confirmed against a large panel of kinases and no significant inhibitory activity was measured.** A detailed summary of *in vitro* and *in vivo* non-clinical pharmacology studies is provided in the GSK1120212 Investigator Brochure (IB) [GlaxoSmithKline Document Number HM2009/00151/**02**].

Section 4.1.3 Exclusion Criteria

The new criteria were inserted with some original criteria placed within this new criteria as sub-bullets; subsequent criteria were renumbered as appropriate.

PREVIOUS TEXT

5. Evidence of severe or uncontrolled systemic diseases (e.g. unstable or uncompensated respiratory, hepatic, renal, metabolic or cardiac disease).
6. Bazett-corrected QT (QTcB) interval >530 msec or uncorrected QT >600 msec at the time of transition to this study.
7. Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.
8. Evidence of current Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system at the time of transition to this study (Appendix 3).

REVISED TEXT

5. Evidence of severe or uncontrolled systemic diseases (e.g. unstable, or uncompensated respiratory, hepatic, renal **or** metabolic ~~or cardiac~~ disease).
6. History or evidence of cardiovascular risk including any of the following:
    - Bazett-corrected QT (QTcB) interval **≥480 msec** at the time of transition to this study
    - Bazett-corrected QT (QTcB) interval **≥480 msec at the time of transition to this study**
    - **History or evidence of current clinically significant uncontrolled arrhythmias**

Exception: Subjects with controlled atrial fibrillation for >30 days prior to transition to this study are eligible.

- **History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to transition to this study**
- **History or evidence of current Class II congestive heart failure as defined by the New York Heart Association (NYHA; Appendix 3)**
- **Treatment refractory hypertension defined as a BP reading of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by antihypertensive therapy**
- **Subjects with intra-cardiac defibrillator or permanent pacemaker**
- **Cardiac metastases**

7. Left ventricular ejection fraction (LVEF) < institutional lower limit of normal (LLN) by ECHO (preferred) or MUGA scan at the time of transition to this study.

~~8. Evidence of current Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system at the time of transition to this study (Appendix 3).~~

Section 5.4 Handling and Storage of Study Treatment

The storage temperature for GSK1120212 was clarified by GSK Pharmaceutical Development and is consistent with information provided in IND and IMPD for GSK1120212.

PREVIOUS TEXT

GSK1120212 is to be stored at a temperature up to 30°C in an opaque bottle. Maintenance of a temperature log (manual or automated) is required.

REVISED TEXT

GSK1120212 is to be stored at a temperature up to ~~30~~**25**°C in an opaque bottle, **protected from light and moisture**. Maintenance of a temperature log (manual or automated) is required.

Section 5.7.1 Monitoring and Management of Hypertension

New section was inserted and subsequent sections were renumbered in Section 5.7.

NEW TEXT

Section 5.7.1 Monitoring and Management of Hypertension

Section 5.7.1.1 Monitoring of Hypertension

All BP assessments should be performed under optimal conditions i.e. after (1) subject has been seated with back support, ensuring that legs are uncrossed and flat on the floor, (2) subject is relaxed comfortably for at least 5 minutes, (3) preparatory steps including removal of any restrictive clothing over the cuff area and selection of the proper cuff size have been ensured, (4) the arm is supported so that the middle of the cuff is at the heart level, and (5) the subject remains quiet during the measurement. In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 1 minute later, with the 2 readings averaged to obtain a final BP measurement.

Persistent hypertension is defined as an increase of systolic blood pressure (SBP) >140 mm Hg and/or diastolic blood pressure (DBP) >90 mmHg in up to 3 subsequent visits with BP assessments from 2 readings under the optimal conditions described above. Visits to monitor increased BP should be scheduled independently from the per-protocol visits outlined in the time-and-events schedule; ideally, subsequent BP assessments should be performed within 7 days.

Asymptomatic hypertension is defined as an increase of SBP >140 mmHg and/or DBP > 90 mmHg in the absence of headache, light-headedness, vertigo, tinnitus, episodes of fainting or other symptoms indicative of hypertension which would disappear after the BP is controlled within the normal range.

Section 5.7.1.2 Management of Hypertension

For subjects experiencing an increase in SBP and/or DBP that is persistent and may be associated with the study treatment, recommendations for the clinical management of hypertension are described below:

Hypertension	
(A). Asymptomatic and persistent[1] SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	**Step 1. Continue study treatment at the current dose.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[2] BP. I f BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).**
(B). Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	**Step 1.Consider reducing or interrupting study treatment, as clinically indicated.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP.** **Step 4. Once BP is well-controlled, restart study treatment dose-reduced**
(C). Symptomatic hypertension or recurring[3] SBP ≥160 mmHg, or DBP ≥100 mmHg, despite modification of antihypertensive medication(s)	**Step 1. Interrupt study treatment.** **Step 2. Adjust current or initiate new antihypertensive medication(s).** **Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended.** **Step 4. Once BP is well-controlled, restart study treatment dose-reduced**
(D). Refractory hypertension unresponsive to above interventions.	**Discontinue study treatment and continue follow-up per protocol.**

1. **Hypertension detected in 2 separate readings during up to 3 subsequent visits**
2. **BP reading of SBP ≤140 mmHg and DBP ≦90 mmHg in 2 separate readings during up to 3 subsequent visits**
3. **Persistent asymptomatic hypertension after initially successful anti-hypertensive intervention**

Section 7.1 Meals and Dietary Restrictions

PREVIOUS TEXT

GSK1120212 should be taken orally, once-daily with approximately 8 fl oz of water. Subjects should fast for at least 1 hour before and for at least 2 hours after dosing with GSK1120212.

REVISED TEXT

GSK1120212 should be **administered** ~~taken orally, once-daily~~ with approximately **240 mL (**8 fl oz) of water**, under fasting conditions, either**~~. Subjects should fast for at least~~ 1 hour before **or** ~~and for at least~~ 2 hours after **a meal** ~~dosing with~~ ~~GSK1120212~~.

Appendix 1: Time and Events Table for Cohort A, Footnote #9

PREVIOUS TEXT

9. ECHO is only required at the Final Study Visit if an abnormal finding is reported at a prior visit.

REVISED TEXT

9. ECHO is only required at the Final Study Visit if an abnormal finding is reported ~~at a prior visit~~ **from the last ECHO or MUGA scan performed.**

Appendix 2: Time and Events Table for Cohort B, Footnote #9

PREVIOUS TEXT

9. ECHO is only required at the Final Study Visit if an abnormal finding is reported at a prior visit.

REVISED TEXT

9. ECHO is only required at the Final Study Visit if an abnormal finding is reported ~~at a prior visit~~ **from the last ECHO or MUGA scan performed.**

AMENDMENT 2

Where the Amendment Applies

This amendment applies to all site and countries.

Summary of Amendment Changes with Rationale

In this amendment, the background information and risk management sections of the protocol were revised to provide updated safety information included in the most recent version of the GSK1120212 IB. In addition, since the new commercial image investigational product will be administered to subjects participating in this protocol, it was necessary to add the product description.

The language describing the timing of the ECHOs and MUGA scans was revised to further clarify that ECHO/MUGA should be completed 12 weeks from the subject's last scan not necessarily 12 weeks from the date of the transition visit.

Administrative changes were made to update contact information for the primary and secondary medical monitors.

List of Specific Changes

Sponsor Medical Monitor Contact Information:

updated Fax number for primary Medical Monitor.

Section 1.1 Background, Paragraph 2

PREVIOUS TEXT

A detailed summary of *in vitro* and *in vivo* non-clinical pharmacology studies is provided in the GSK1120212 Investigator Brochure (IB) [GlaxoSmithKline Document Number HM2009/00151/].

REVISED TEXT

A detailed summary of *in vitro* and *in vivo* non-clinical pharmacology studies is provided in the GSK1120212 Investigator Brochure (IB) [GlaxoSmithKline Document Number HM2009/00151/**02**].

Section 1.1 Background, Paragraphs 3 to 6

PREVIOUS TEXT

The safety, pharmacokinetic (PK) and pharmacodynamic (PD) profiles and activity of GSK1120212 administered either as monotherapy or in combination with other anti-cancer agents are currently being evaluated in multiple clinical trials involving subjects

with a variety of cancers. The investigator should refer to the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/] for detailed information regarding ongoing GSK1120212 clinical studies, PK in the target disease population, as well as observed safety and efficacy findings.

The adverse event (AE) profile of GSK1120212 observed to date is comparable to other MEK inhibitors [Friday, 2008]. For example, rash and diarrhea, experienced by 70% and 41% of subjects, respectively, are the most common toxicities reported in the first-time-in-human study, MEK111054 [GlaxoSmithKline Document Number RM2007/00642/03]. Rash was considered a dose-limiting toxicity (DLT) in 2 subjects (Grade 2 and Grade 3), whereas a DLT for Grade 3 diarrhea occurred once. Other AEs commonly reported (≥20%) include fatigue, nausea, peripheral edema, and vomiting. Although observed at lower frequencies, visual impairment and left ventricular ejection fraction (LVEF) reduction have been observed with GSK1120212 as well as other MEK inhibitors. Visual impairment includes 2 cases of dose-limiting Grade 2 central serous retinopathy (CSR) and 1 case of Grade 3 retinal vein occlusion (RVO). Pneumonitis has also been seen in subjects treated with GSK1120212 in combination with gemcitabine.

GSK1120212 has demonstrated anti-tumor activity in a variety of solid tumors as well as in 1 subject with acute myelogenous leukemia. Importantly, 1 out of 2 subjects with KRAS-mutant metastatic non-small cell lung cancer (NSCLC) has achieved a partial response (PR; 49% tumor reduction) and one out of 18 advanced pancreatic subjects has a sustained PR (on study >40 weeks) following treatment with GSK1120212 monotherapy.

Although tumor response appears to higher in those subjects whose cancer harbors mutations in the MAPK signalling pathway, clinical benefit is still observed in subjects with wild-type disease or disease where the mutation status is unknown. For example, multiple NSCLC and pancreatic cancer subjects have achieved stable disease (SD).

REVISED TEXT

~~The safety, pharmacokinetic (PK) and pharmacodynamic (PD) profiles and activity of GSK1120212 administered either as monotherapy or in combination with other anti-cancer agents are currently being evaluated in multiple clinical trials involving subjects with a variety of cancers. The investigator should refer to the GSK1120212 IB [GlaxoSmithKline Document Number HM2009/00151/] for detailed information regarding ongoing GSK1120212 clinical studies, PK in the target disease population, as well as observed safety and efficacy findings.~~

~~The adverse event (AE) profile of GSK1120212 observed to date is comparable to other MEK inhibitors [Friday, 2008]. For example, rash and diarrhea, experienced by 70% and 41% of subjects, respectively, are the most common toxicities reported in the first-time-in-human study, MEK111054 [GlaxoSmithKline Document Number RM2007/00642/03]. Rash was considered a dose-limiting toxicity (DLT) in 2 subjects (Grade 2 and Grade 3), whereas a DLT for Grade 3 diarrhea occurred once. Other AEs commonly reported (≥20%) include fatigue, nausea, peripheral edema, and vomiting. Although observed at lower frequencies, visual impairment and left ventricular ejection fraction (LVEF) reduction have been observed with GSK1120212 as well as other MEK inhibitors. Visual impairment includes 2 cases of dose-limiting Grade 2 central serous retinopathy (CSR) and 1 case of Grade 3 retinal vein occlusion (RVO). Pneumonitis has also been seen in subjects treated with GSK1120212 in combination with gemcitabine.~~

~~GSK1120212 has demonstrated anti-tumor activity in a variety of solid tumors as well as in 1 subject with acute myelogenous leukemia. Importantly, 1 out of 2 subjects with KRAS-mutant metastatic non-small cell lung cancer (NSCLC) has achieved a partial response (PR; 49% tumor reduction) and one out of 18 advanced pancreatic subjects has a sustained PR (on study >40 weeks) following treatment with GSK1120212 monotherapy.~~

~~Although tumor response appears to higher in those subjects whose cancer harbors mutations in the MAPK signalling pathway, clinical benefit is still observed in subjects with wild-type disease or disease where the mutation status is unknown. For example, multiple NSCLC and pancreatic cancer subjects have achieved stable disease (SD).~~

As of 14 April 2011, 657 subjects with cancer have received at least one dose of GSK1120212 in 14 ongoing Phase I/II/III clinical studies. Six of the 14 studies administer GSK1120212 as monotherapy, whereas the other 8 studies are designed to administer GSK112012 as combination therapy. As of 14 April 2011, 206 subjects in MEK111054, the first-time-in-human (FTIH) study of GSK1120212, had been dosed with GSK1120212. Dose-related MAP kinase inhibition was demonstrated between daily doses of 0.5 and 2.0 mg with immunohistochemistry on tumor biopsies. Modulation of MAP kinase pathways was consistent with changes observed with fluorodeoxyglucose-positron emission tomography imaging. Based on the AEs observed in the FTIH MEK111054 study, the maximum tolerated dose (MTD) was determined to be 3.0 mg once-daily and the recommended Phase II dose (RP2D) of GSK1120212 was identified as 2.0 mg once-daily. An unconfirmed response rate of 43% (6 out of 14 subjects) had an objective response, including 2 complete responses (CRs) was observed. The recommended monotherapy dose (2 mg once-daily) was well-tolerated. Most notable adverse events (AEs) at this dose (n = 96) included class effects of rash (78%; 4% Grade 3) and diarrhea (54%; 1% Grade 3). In all subjects dosed (n = 206), 5 cases of Grade 3 left ventricular systolic dysfunction, 3 cases of central serous retinopathy (CSR), and 1 case of retinal vein occlusion (RVO) were observed. Among the 5 left ventricular ejection fraction (LVEF) cases, only 2 were considered related to study treatment and neither subject was symptomatic. All 3 cases of CSR resolved upon study treatment interruption, and the subject with RVO has experienced significant improvement in visual acuity after intraocular bevacizumab treatments.

GSK1120212 is absorbed rapidly with median tmax generally occurring within 1 to 3 hours after administration of GSK1120212. After repeat dosing (Study Day 15), the mean area under the concentration-time curve (AUC0-τ)) and maximum observed concentrations (Cmax) increased in a dose proportional manner (i.e., a 2-fold increase in dose resulted in a 2-fold increase in exposure). Between-subject variability (CV%) in exposure ranged from 27 to 50% for Cmax and 20 to 41% for area under the concentration-time curve from time zero (pre-dose) to 24 hrs after the last dose of study treatment (AUC(0-24)) across all dosing regimens. GSK1120212 accumulates with repeat dose with an effective half-life (t1/2) of approximately 5 days.

Further information on the safety, PK, and efficacy is described in the IB for GSK1120212 [GlaxoSmithKline Document Number HM2009/00151/02].

Section 1.2 Summary of Risk Management

Added new Section 1.2 and renumbered old Section 1.2 to Section 1.3.

NEW TEXT

The assessment of the risk of GSK1120212 is based on clinical data from the ongoing FTIH study in which subjects have been dosed daily for >21 days, as well as preclinical toxicity data. In study MEK111054, the most common AEs experienced by ≥20% of all subjects with daily dosing were rash, diarrhea, fatigue, nausea, peripheral edema, and vomiting. Rash and diarrhea are common, class-effect toxicities for MEK inhibitors. In addition, visual impairment and LVEF reduction, although observed at lower frequencies, are also considered class-effect toxicities as they have been observed with GSK1120212 as well as other MEK inhibitors. Systemic toxicity of GSK1120212 has been evaluated following oral dosing in rats and dogs for up to 13 weeks. In the most sensitive non-clinical species, rat, the principal adverse effects seen in oral toxicity studies of up to 13 weeks with daily dosing were skin and stomach erosions, skin ulcerations, which were secondary to reduced proliferation, altered phosphate homeostasis that resulted in soft tissue mineralization, hepatocellular necrosis, bone marrow degeneration/necrosis and ovarian perturbations. The skin and stomach findings and phosphatemia demonstrated reversibility with 4 weeks of recovery. Additional details are provided in the IB for GSK1120212 [GlaxoSmithKline Document Number HM2009/00151/02HM2009/00151/**].**

Procedures to minimize or monitor potential risks are listed below:

- **To reduce the risk of ocular toxicity, subjects with history of RVO, or CSR, subjects with predisposing factors for RVO or CSR or predisposing retinal pathology as determined by ophthalmologic exams are excluded. Ophthalmologic exams will be performed at baseline and as clinically warranted.**
- **To monitor cardiac function, echocardiogram (ECHO) or multigated acquisition (MUGA) scans will be performed.**

- **<u>To reduce the risk of excessive gastrointestinal (GI) toxicity (diarrhea) and cutaneous toxicity (rash), subjects will be monitored closely and supportive care guidelines will be implemented.</u>**

Section 5.1 GSK1120212 GSK Investigational Product

Changed title of Section 5.1 from GSK1120212 GSK Investigational Product to Investigational Product. Labelled the original table as Table 1 (previously unlabelled) and inserted Table 2, a new table for GSK1120212 GSK Investigational Product (Commercial Image Product).

PREVIOUS TEXT

Product name :	GSK1120212		
Formulation description:	The drug substance is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with either a white or pink opaque film* (*Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant as applicable).		
Dosage form :	Tablet		
Unit dose strength(s)/ Dosage levels	0.5 mg	1.0 mg	2.0 mg
Physical Description:	0.5mg: White, oval, biconvex film-coated tablet with dose proportional diameter 1.0 mg: White, round, biconvex film-coated tablet with dose proportional diameter 2.0 mg: Pink, round, biconvex film-coated tablet with dose proportional diameter		
Route/Regimen:	Oral/Cohort A: Subjects will receive GSK1120212 2.0 mg or less once-daily. Cohort B: Subjects will receive continuous oral dosing of GSK1120212 at the current dose administered in the parent study at the time of transition to the rollover study.		
Dosing Instructions:	GSK1120212 **<u>should be administered</u>** with approximately 240 mL (8 fl oz) of water, **<u>under fasting conditions, either 1 hour before or 2 hours after a meal</u>**.		

REVISED and NEW TEXT

Section 5.1 ~~GSK1120212 GSK~~ <u>Investigational Product</u>

Table 1 GSK1120212 GSK Investigational Product

Product name :	GSK1120212		
Formulation description:	The drug substance is blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with either a white or pink opaque film* (*Opadry White or Pink, a titanium dioxide-based formulation with iron oxide as colorant as applicable).		
Dosage form :	Tablet		
Unit dose strength(s)/ Dosage levels	0.5 mg	1.0 mg	2.0 mg
Physical Description:	0.5mg: White, oval, biconvex film-coated tablet with dose proportional diameter 1.0 mg: White, round, biconvex film-coated tablet with dose proportional diameter 2.0 mg: Pink, round, biconvex film-coated tablet with dose proportional diameter		
Route/Regimen:	Oral/Cohort A: Subjects will receive GSK1120212 2.0 mg or less once-daily. Cohort B: Subjects will receive continuous oral dosing of GSK1120212 at the current dose administered in the parent study at the time of transition to the rollover study.		
Dosing Instructions:	GSK1120212 **should be administered** with approximately 240 mL (8 fl oz) of water, **under fasting conditions, either 1 hour before or 2 hours after a meal**.		

Table 2 GSK1120212 GSK Investigational Product (Commercial Image Product)

	Commercial Image Product	
Product name :	**GSK1120212 0.5 mg Tablet**	**GSK11210212 2 mg Tablet**
Formulation description:	Each tablet contains GSK1120212B equivalent to 0.5 mg of GSK1120212 as drug substance blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with yellow opaque film* (*Opadry yellow, a titanium dioxide-based formulation with yellow iron oxide as colorant as applicable).	Each tablet contains GSK1120212B equivalent to 2 mg of GSK1120212 as drug substance blended with inert ingredients (mannitol, sodium lauryl sulfate, colloidal silicon dioxide, microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate) and compressed into tablets. The tablets are then coated with pink opaque film* (*Opadry Pink, a titanium dioxide-based formulation with red iron oxide as colorant).
Dosage form :	Tablet	Tablet
Unit dose strength(s):	Tablet strength: 0.5 mg	Tablet strength: 2 mg
Physical Description:	Yellow, modified oval, biconvex, film-coated tablets (4.85 x 8.86 mm)	Pink, biconvex, round film-coated tablets 7.5 mm in diameter
Route/ Administration:	Oral/once-daily single dose	Oral/once-daily single dose
Dosing Instructions:	GSK1120212 should be administered with approximately 240 mL (8 fl oz) of water, under fasting conditions, either 1 hour before or 2 hours after a meal.	

Section 5.7.7.1, Left Ventricular Ejection Fraction Stopping Criteria, 4th paragraph:

PREVIOUS TEXT

The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s). Copies of all ECHOs and/or MUGA scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline **and** LVEF <LLN will be required by GSK for review. Instructions for submission of qualifying ECHOs/MUGA scans are provided in the SPM.

REVISED TEXT

The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s). Copies of all ECHOs and/or MUGA scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline **and** LVEF <LLN **(or <50% when LLN does not exist)** will be required by GSK for review. Instructions for submission of qualifying ECHOs/MUGA scans are provided in the SPM.

Section 8.2.1 Cohort A:

PREVIOUS TEXT

The following assessments must be performed **at Week 8** while receiving treatment:

- Complete physical examination
- ECHO (preferred) or MUGA scan (see Section 5.7.4 for stopping criteria and follow-up for abnormal results)

The following assessments must be performed **every 12 weeks** while receiving treatment:

- Complete physical examination (after Week 8)
- ECHO (preferred) or MUGA scan (after Week 8)
- 12-lead ECG (for first 2 years of treatment with GSK1120212, including time on parent study)
- Clinical laboratory tests: hematology and clinical chemistry (>2 years of treatment with GSK1120212, including time on parent study)

REVISED TEXT

The following assessment~~s~~ must be performed **at Week 8** while receiving treatment:

- Complete physical examination
- ~~ECHO (preferred) or MUGA scan (see Section 5.7.4 for stopping criteria and follow-up for abnormal results)~~

The following assessment must be performed while receiving treatment:

- **ECHO (preferred) or MUGA scan should be performed within 12 weeks from the date of the subject's last ECHO or MUGA scan which may have been performed in the parent study or at the time of transition to the rollover study.**

- **Subsequent ECHO (preferred) or MUGA scans must be performed every 12 weeks thereafter while the subject is receiving treatment.**

  NOTE: Refer to Section 5.7.4 for stopping criteria and follow-up for abnormal results).

The following assessments must be performed **every 12 weeks** while receiving treatment:

- Complete physical examination (after Week 8)
- ~~ECHO (preferred) or MUGA scan (after Week 8)~~
- 12-lead ECG (for first 2 years of treatment with GSK1120212, including time on parent study)
- Clinical laboratory tests: hematology and clinical chemistry (>2 years of treatment with GSK1120212, including time on parent study)

Section 8.2.2 Cohort B:

PREVIOUS TEXT

The following assessments must be performed **every 12 weeks** while receiving treatment:

- Complete physical examination
- ECHO (preferred) or MUGA scan (see Section 5.7.7)

REVISED and NEW TEXT

The following assessments must be performed **every 12 weeks** while receiving treatment:

- Complete physical examination
- ~~ECHO (preferred) or MUGA scan (see Section 5.7.7)~~

The following assessment must be performed while receiving treatment:

- **ECHO (preferred) or MUGA scan should be performed within 12 weeks from the date of the subject's last ECHO or MUGA scan which may have been performed in the parent study or at the time of transition to the rollover study.**

- **Subsequent ECHO (preferred) or MUGA scans must be performed <u>every 12 weeks</u> thereafter while the subject is receiving treatment.**

  NOTE: Refer to Section 5.7.4 for stopping criteria and follow-up for abnormal results).

Section 8.3 Final Visit

PREVIOUS TEXT

If a subject is withdrawn from study treatment, the following assessments will be performed within 28 days (±7 days) from the last dose of study treatment(s) and prior to initiating any other treatment for cancer:

- Complete physical examination
- Vital signs (BP, temperature, respiratory rate, and pulse rate)
- Clinical laboratory tests: hematology and clinical chemistry
- 12-lead ECG
- ECHO (preferred) or MUGA scan (only required if there was an abnormal finding reported at a prior visit)
- Review of concomitant medications
- Assessment of AEs

REVISED TEXT

If a subject is withdrawn from study treatment, the following assessments will be performed within 28 days (±7 days) from the last dose of study treatment(s) and prior to initiating any other treatment for cancer:

- Complete physical examination
- Vital signs (BP, temperature, respiratory rate, and pulse rate)
- Clinical laboratory tests: hematology and clinical chemistry
- 12-lead ECG
- ECHO (preferred) or MUGA scan (only required if there was an abnormal finding ~~reported at a prior visit~~ **<u>reported from the last ECHO or MUGA scan performed</u>**)
- Review of concomitant medications
- Assessment of AEs

Section 12 References

PREVIOUS TEXT

GlaxoSmithKline Document Number HM2009/00151/01. Clinical Investigator Brochure for GSK1120212, 2nd edition. 04-Jun-2010.

REVISED TEXT

GlaxoSmithKline Document Number HM2009/00151/**02**. Clinical Investigator Brochure for GSK1120212, **3rd** edition. **23-Jun-2011**.

Section 13.1 Appendix 1: Time and Events Table for Cohort A

PREVIOUS TEXT

Assessment/ Procedure[17]	Transition Visit[1]	Continuous Dosing Treatment Period[19]				Final Study Visit
		Every 4 weeks[16] (±7 days)	Week 8[16] (± 7 days)	Every 12 weeks[16] (± 7 days)	Every 24 weeks[16] (± 7 days)	With 28 days of Last Dose of Study Treatment(s) (± 7 days)[18]
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X		X[8]	X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[12]						O
cfDNA Sample[12]						O
AE Monitoring[13,14]	*Continuous*					
Review of Concomitant Medications[15]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate 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.
6. 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. QTc interval must not be >480 msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should first be performed at Week 8 and then every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported at a prior visit.
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
13. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK2118436.
14. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
15. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
16. The “Every 8 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 8, 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
17. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
18. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
19. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

REVISED TEXT

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 4 weeks[17] (±7 days)	**Week 8[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X		X	X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X			X[7]	X[7]	X
ECHO/MUGA scan	X		X[8]	X[8]		X[9]
Clinical Chemistry[10]	X	X[11]		X[11]		X
Hematology[10]	X	X[11]		X[11]		X
Liver Function Tests[10,12]	X	X		X		X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Physical examination will be completed at the Transition Visit, Week 8 and every 12 weeks thereafter while on treatment, and at the Final Study Visit. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate 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.
6. 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. QTc interval must not be >480 msec.
7. 12-lead ECGs will be performed every 12 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should first be performed at Week 8 and then every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported at a prior visit.
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 4 weeks (at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 12 weeks for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK2118436.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 8 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 8, 12 or 24 weeks or every second or third clinic visit that is recurring at 4-week intervals, respectively.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

Section 13.2 Appendix 2: Time and Events Table for Cohort B

PREVIOUS TEXT

Assessment/ Procedure[17]	Transition Visit[1]	Continuous Dosing Treatment Period[19]				Final Study Visit
		Every 3 or 4 weeks[16] (± 7 days)	Every 9 or 12 weeks[16] (± 7 days)	Every 12 weeks[16] (± 7 days)	Every 24 weeks[16] (± 7 days)	With 28 days of Last Dose of Study Treatment(s) (± 7 days)[18]
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X			X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X		X[7]		X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]	X[11]			X
Hematology[10]	X	X[11]	X[11]			X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[12]						O
cfDNA Sample[12]						O
AE Monitoring[13, 14]	*Continuous*					
Review of Concomitant Medications[15]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be >480 msec.
7. 12-lead ECGs will be performed every 9 or 12 weeks (depending on the schedule used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should be performed every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported at a prior visit.
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment.
12. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
13. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK1120212.
14. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
15. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
16. The “Every 9 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 9, 12 or 24 weeks or every second or third clinic visit that is recurring at 3 or 4-week intervals, depending on the schedule used in the parent study.
17. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
18. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
19. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

REVISED TEXT

Assessment/ Procedure[18]	**Transition Visit[1]**	**Continuous Dosing Treatment Period[20]**				**Final Study Visit**
		Every 3 or 4 weeks[17] (± 7 days)	**Every 9 or 12 weeks[17] (± 7 days)**	**Every 12 weeks[17] (± 7 days)**	**Every 24 weeks[17] (± 7 days)**	**With 28 days of Last Dose of Study Treatment(s) (± 7 days)[19]**
Informed Consent[2]	X					
Demographics and Parent Study Data	X					
Physical Exam[3]	X			X		X
Pregnancy test[4]	X					
Vital Signs[5]	X	X				X
12-Lead ECG[6]	X		X[7]		X[7]	X
ECHO/MUGA scan	X			X[8]		X[9]
Clinical Chemistry[10]	X	X[11]	X[11]			X
Hematology[10]	X	X[11]	X[11]			X
Liver Function Tests[10,12]	X	X	X			X
Tumor Tissue /Skin Biopsy or Blood Sample for Biomarker Analysis[13]						O
cfDNA Sample[13]						O
AE Monitoring[14, 15]	*Continuous*					
Review of Concomitant Medications[16]	*Continuous*					
GSK1120212 Dosing	*Continuous*					

Abbreviations: O, optional

1. 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 parent study and this study. Results from the parent study should be recorded in the eCRF as transition values.
2. Informed consent must be obtained prior to performing any assessments or procedures for this study and before treatment with GSK1120212 is to be continued.
3. Height (cm) and weight (kg) will be measured only at the Transition Visit.
4. Serum β–hCG pregnancy tests will be performed on female subjects of childbearing potential only at the time of transition from the parent study.
5. Vital signs (BP, temperature, respiratory rate, 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.
6. 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. QTc interval must not be >480 msec.
7. 12-lead ECGs will be performed every 9 or 12 weeks (depending on the schedule used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years of treatment 12-lead ECGs will be performed every 24 weeks for the duration of treatment.
8. ECHO or MUGA scan should be performed every 12 weeks (at a minimum or more frequently per local practice). If LVEF decreases ≥20 percentage points, repeat testing is required within 2 weeks. If decline is sustained, the investigator, in consultation with GSK Medical Monitor, should consider withdrawal of subject from the study.
9. ECHO is only required at the Final Study Visit if an abnormal finding is reported at a prior visit.
10. Refer to Section 8.4.5 for complete list of clinical laboratory assessments to be performed.
11. Hematology and clinical chemistry laboratory assessments will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years hematology and clinical chemistry laboratory assessments will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment.
12. **Liver function tests (AST, ALT, alkaline phosphatase and total bilirubin) will be performed every 3 or 4 weeks (depending on the scheduled used in the parent study; at a minimum or more frequently per local practice) for the first 2 years of treatment (including time on parent study). After 2 years liver function tests will be performed every 9 or 12 weeks (depending on schedule used in the parent study) for the duration of treatment. Bilirubin fractionation is recommended if total bilirubin is >2 times ULN.**
13. Optional tumor tissue, skin or blood sample from a lesion not required for disease assessment and/or optional blood sample for cfDNA may be obtained if subject has provided consent.
14. AEs/SAEs will be monitored and recorded beginning on the time of consent until 30 days after the last dose of GSK1120212.
15. All ongoing (unresolved) AEs at the time of the transition to this study will be recorded in the eCRF.
16. All concomitant medication(s) at the time of the transition to this study will be recorded in the eCRF.
17. The “Every 9 Weeks”, “Every 12 Weeks” or “Every 24 Weeks” columns are NOT a separate visit but instead a listing of assessments required to be completed every 9, 12 or 24 weeks or every second or third clinic visit that is recurring at 3 or 4-week intervals, depending on the schedule used in the parent study.
18. After a subject has been on study for a total of 2 years, including time on parent study, the frequency of assessments will be modified. If more frequent assessments are needed, these should be done per local practice.
19. The Final Study Visit should occur within 28 days (±7 days) following the last dose of study treatment(s) and prior to initiating any new treatment.
20. Subjects who remain on study treatment >52 weeks may have the frequency of their interim visits decreased with approval from the GSK Medical Monitor.

AMENDMENT 1

WHERE THE AMENDMENT APPLIES

This amendment applies to all site and countries.

Summary of Amendment Changes with Rationale

It was noted that there was inconsistent language regarding the intent of the study stated in the rationale and study objective sections of the protocol. The true intent of this protocol is, as stated in the rationale, to allow subjects to continue on drug who are clinically benefitting and have an acceptable toxicity profile. Some subjects who have clinically progressed (e.g., isolated progression in brain, requiring treatment with gamma knife) but continue to receive benefit and who are allowed as per the primary protocol to continue on the study treatment if both the treating physician and GSK Medical Monitor agree, should have continued access to the study treatment. However, as per the above inclusion criteria these subjects would not be allowed to roll over to open-label rollover study which is inconsistent with the rationale of the study.

The directions for administering GSK1120212 in a fasting state were clarified to state "1 hour before or 2 hours after a meal".

Country specific requirements for Australia and France were added in the event the protocol is opened in these countries. General administrative changes (i.e., authors, sponsor signatory, assignment of medical monitors, etc.) were also made. List of references was revised to remove documents that were not cited in document but listed erroneously in list of references.

List of Specific Changes

Page 1, Description

PREVIOUS TEXT

Description: GSK1120212 is an orally administered, potent and highly selective small molecule inhibitor of MEK1/MEK2 activation and kinase activity. As monotherapy, GSK1120212 has shown an acceptable risk-benefit profile with encouraging efficacy in various oncologic settings. This multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to eligible subjects who have previously participated in a GlaxoSmithKline (GSK)-sponsored GSK1120212 study (referred to as the parent study) and have no evidence of progressive disease as well as an acceptable safety profile with GSK1120212. Subjects will be enrolled into an appropriate cohort based on the treatment received 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 throughout the study. Clinical activity will be assessed using local standard of care imaging practices and the appropriate assessment criteria as determined by the investigator.

REVISED TEXT

Description: GSK1120212 is an orally administered, potent and highly selective small molecule inhibitor of MEK1/MEK2 activation and kinase activity. As monotherapy, GSK1120212 has shown an acceptable risk-benefit profile with encouraging efficacy in various oncologic settings. This multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to eligible subjects who have previously participated in a ~~GlaxoSmithKline (GSK)-sponsored~~ GSK1120212 study (referred to as the parent study) and ~~have no evidence of progressive disease as well as~~ **who are clinically benefitting from continued treatment and have** an acceptable safety profile with GSK1120212. Subjects will be enrolled into an appropriate cohort based on the treatment received 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 throughout the study. Clinical activity will be assessed using local standard of care imaging practices and the appropriate assessment criteria as determined by the investigator.

Protocol Summary

PREVIOUS TEXT

Rationale

GSK1120212 is a potent and highly selective inhibitor of MEK kinase activity. This multicenter, non-randomized, open-label rollover study will provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GlaxoSmithKline (GSK)-sponsored GSK1120212 study and who have no evidence of progressive disease as well as an acceptable safety profile with GSK1120212.

Objectives

The primary objective of the study is to provide continued treatment with GSK1120212 for subjects with solid tumors or leukemia who have previously participated in a GSK-sponsored GSK1120212 study and who have no evidence of progressive disease as well as an acceptable safety profile with GSK1120212.

Study Design

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a GSK-sponsored GSK1120212 study (parent study) and who have no evidence of progressive disease as well as an acceptable safety profile with GSK1120212. Subjects will be enrolled into the appropriate cohort based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. It is estimated that approximately 250 subjects will be enrolled in this study. Subjects may continue treatment in the rollover study until disease progression, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK1120212 becomes available to the subject.

Study Assessments

Assessment of clinical activity will be performed throughout the study using local standard of care imaging practices and the appropriate assessment criteria as determined by the investigator to determine continued study participation and treatment with GSK1120212. Only subjects considered by the investigator to be without progressive disease may continue on study treatment

REVISED TEXT

Rationale

GSK1120212 is a potent and highly selective inhibitor of MEK kinase activity. This multicenter, non-randomized, open-label rollover study will provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a ~~GlaxoSmithKline (GSK) sponsored~~ GSK1120212 study ~~and who have no evidence of progressive disease~~ **and who are clinically benefitting from continued treatment and have** an acceptable safety profile with GSK1120212.

Objectives

The primary objective of the study is to provide continued treatment with GSK1120212 for subjects with solid tumors or leukemia who have previously participated in a ~~GSK-sponsored~~ GSK1120212 study ~~and who have no evidence of progressive disease as~~ **and who are clinically benefitting from continued treatment and have** an acceptable safety profile with GSK1120212.

Study Design

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects with solid tumors or leukemia who have previously participated in a ~~GSK sponsored~~ GSK1120212 study (parent study) and ~~who have no evidence of progressive disease~~ **who are clinically benefitting from continued treatment and have** an acceptable safety profile with GSK1120212. Subjects will be enrolled into the appropriate cohort based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study. It is estimated that approximately 250 subjects will be enrolled in this study. Subjects may continue treatment in the rollover study ~~until disease progression~~ **until no longer clinically benefitting**, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK1120212 becomes available to the subject.

Study Assessments

Assessment of clinical activity will be performed throughout the study using local standard of care imaging practices and the appropriate assessment criteria as determined by the investigator to determine continued study participation and treatment with GSK1120212. Only subjects considered by the investigator to be ~~without progressive disease~~ **to be receiving clinical benefit** may continue on study treatment

Section 2.1 Objectives

PREVIOUS TEXT

The primary objective of the study is to provide continued treatment with GSK1120212 for subjects who have previously participated in a GSK-sponsored GSK1120212 study and who have no evidence of progressive disease as well as an acceptable safety profile with GSK1120212.

REVISED TEXT

The primary objective of the study is to provide continued treatment with GSK1120212 for subjects who have previously participated in a ~~GSK-sponsored~~ GSK1120212 study and ~~who have no evidence of progressive disease~~ **who continue to receive clinical benefit** as well as have an acceptable safety profile with GSK1120212.

Section 3 Study Design, Paragraph 1, Paragraph 6 and Paragraph 7

PREVIOUS TEXT

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects who have previously participated in a GSK-sponsored GSK1120212 study (parent study). All subjects enrolling in this study must have no evidence of progressive disease as well as an acceptable safety profile with GSK1120212 to be eligible. Subjects will be stratified into the appropriate cohort (see Section 3.1) based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study.

Assessment of clinical activity will be performed using local standard of care imaging practices and the appropriate assessment criteria (e.g. Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) as determined by the investigator to determine continued study participation and treatment with GSK1120212. Only subjects without progressive disease as determined by the investigator as well as an acceptable toxicity safety profile will be allowed to continue treatment on study.

Subjects may continue treatment in this rollover study until disease progression, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK1120212 becomes available to the subject.

REVISED TEXT

This Phase II, multicenter, non-randomized, open-label, rollover study is designed to provide continued access to GSK1120212 to subjects who have previously participated in a ~~GSK-sponsored~~ GSK1120212 study (parent study). All subjects enrolling in this study must ~~have no evidence of progressive disease~~ **be receiving clinical benefit from continued treatment as well as have** an acceptable safety profile with GSK1120212 to be eligible. Subjects will be stratified into the appropriate cohort (see Section 3.1) based upon the treatment received in their parent study. Enrollment into this study will be dependent upon the site's agreement to participate in this study.

Assessment of clinical activity will be performed using local standard of care imaging practices and the appropriate assessment criteria (e.g. Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) as determined by the investigator to determine continued study participation and treatment with GSK1120212. Only subjects ~~without progressive disease~~ **who continue to receive clinical benefit as determined by the investigator as well as having** an acceptable toxicity safety profile will be allowed to continue treatment on study.

Subjects may continue treatment in this rollover study until ~~disease progression~~ **lack of clinical benefit**, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK1120212 becomes available to the subject.

Section 4.1.2 Inclusion Criteria, Criteria #3

PREVIOUS TEXT

Is currently participating in a GSK-sponsored study of GSK1120212 and receiving treatment with GSK1120212.

REVISED TEXT

Is currently participating in GSK1120212 study and is receiving treatment with GSK1120212.

Section 4.1.2, Inclusion Criteria, Criteria #4

PREVIOUS TEXT

Currently has no evidence of progressive disease as determined by the investigator from previous treatment with GSK1120212 either as monotherapy or as part of a combination treatment regimen

REVISED TEXT

Is currently receiving clinical benefit as determined by the investigator from previous treatment with GSK1120212 either as monotherapy or as part of a combination treatment regimen.

Section 4.1.2 Inclusion Criteria, Criteria #9

PREVIOUS TEXT

French Subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

REVISED TEXT

Subjects enrolled in France: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Section 4.1.3 Exclusion Criteria, Criteria #4

PREVIOUS TEXT

Current evidence or risk of RVO or CSR:

- Visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO or CSR such as:
  - Evidence of new optic disc cupping
  - Evidence of new visual field defects
  - Intraocular pressure >21 mmHg

REVISED TEXT

Previous text deleted and list of exclusion criteria were renumbered.

Section 4.1.3 Exclusion Criteria, Criteria #5

PREVIOUS TEXT

Any unresolved toxicity > Grade 2, except for alopecia, (National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI Common Terminology Criteria for Adverse Events, 2009], version 4.0) from parent study treatment at time of transition to this study.

REVISED TEXT

Any unresolved toxicity ~~> Grade 2, except for alopecia, (National Cancer Institute-Common Toxicity Criteria for Adverse Events [NCI Common Terminology Criteria for Adverse Events, 2009], version 4.0) from parent study treatment at time of transition to this study~~ **that meets the study treatment discontinuation or study withdrawal criteria from the parent study** at the time of transition to this study.

Section 4.1.3 Exclusion Criteria, Criteria #7

PREVIOUS TEXT

Bazett-corrected QT (QTcB) interval ≥480 msec at the time of transition to this study.

REVISED TEXT

Bazett-corrected QT (QTcB) interval **>530** msec **or uncorrected QT >600 msec** at the time of transition to this study.

Section 4.1.3 Exclusion Criteria, Criteria #10

PREVIOUS TEXT

Symptomatic or untreated leptomeningeal 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 (EIAEDs). Continued stability of brain metastases must be confirmed with imaging.

REVISED TEXT

Symptomatic or untreated leptomeningeal 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 (EIAEDs). ~~Continued stability of brain metastases must be confirmed with imaging.~~

Section 5.1 GSK1120212 GSK Investigational Product

PREVIOUS TEXT

Dosing Instructions:	GSK1120212 will be taken with approximately 240 mL (8 fl oz) of water. Subjects will be expected to fast for at least 1 hour before and 2 hours after dosing unless further instructed based on food-effect assessment.

REVISED TEXT

Dosing Instructions:	GSK1120212 **should be administered** ~~will be taken~~ with approximately 240 mL (8 fl oz) of water, **under fasting conditions, either 1 hour before or 2 hours after a meal**. ~~Subjects will be expected to fast for at least 1 hour before and 2 hours after dosing unless further instructed based on food-effect assessment.~~

Section 5.7.6.1 French Specific QTc Stopping Criteria added

NEW TEXT

In line with local requirements, a subject in France that meets the QTc[1] criteria below will have study treatment withheld:

QTcB >500 msec

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, 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 subjects should have study treatment withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

Section 7.1 Meals and Dietary Restrictions

PREVIOUS TEXT

GSK1120212 should be taken orally, once-daily with approximately 8 fl oz of water. Subjects should fast from other food consumption for at least 1 hour prior to daily dosing through at least 2 hours after daily dosing due to a potential food-effect on GSK1120212 absorption. GSK1120212 should be taken orally, once-daily with approximately 8 fl oz of water. Subjects should fast from other food consumption for at least 1 hour prior to daily dosing through at least 2 hours after daily dosing due to a potential food-effect on GSK1120212 absorption.

REVISED TEXT

GSK1120212 should be taken orally, once-daily with approximately 8 fl oz of water. Subjects should fast ~~from other food consumption~~ for at least 1 hour ~~prior to daily dosing through~~ **before and for** at least 2 hours after ~~daily~~ dosing **with** GSK1120212 ~~due to a potential food-effect on GSK1120212 absorption~~.

References

DELETED TEXT

~~GlaxoSmithKline Document Number RM2010/00127/00. MEK114375: An Open-Label, Phase Ib Continuation Study of GSK1120212 Monotherapy or GSK1120212 in Combination with other Anti-cancer Treatment in Patients with Solid Tumors. 2010~~

~~Lacouture ME, Basti S, Patel J, et al. The SERIES clinic: an interdisciplinary approach to the management of toxicities of EGFR inhibitors. *J Support Oncol*. 2006 May;4(5):236-8.~~

~~Lynch TJ Jr, Kim ES, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. *Oncologist*. 2007 May;12(5):610-21.~~

~~Pérez-Soler R, Delord JP, Halpern A, et al. HER1/EGFR inhibitor-associated rash: future directions for management and investigation outcomes from the HER1/EGFR inhibitor rash management forum. *Oncologist*. 2005 May;10(5):345-56.~~

Appendix 5: Country Specific Requirements

PREVIOUS TEXT

No known country specific requirements are currently required.

REVISED TEXT

Australia: Supply of GSK1120212 should continue until the drug is available under subsidy on the Pharmaceutical Benefits Scheme (PBS).

France: French specific QTc Stopping Criteria has been added to Section 5.7.6.1.

No **other** known country specific requirements are currently required.