

## TITLE PAGE

**Division:** Worldwide Development

**Retention Category:** GRS019

**Information Type:** Protocol Amendment

<b>Title:</b>	Multi-arm, Non-randomized, Open-Label Phase IB Study to Evaluate GSK3052230 in Combination with Paclitaxel and Carboplatin, or Docetaxel or as Single Agent in Subjects with Solid Malignancies and Deregulated FGF Pathway Signaling
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**Compound Number:** GSK3052230

**Effective Date:** 14-DEC-2015

**Protocol Amendment Number:** 05

**Subject:** squamous non-small cell lung cancer, FGFR, GSK3052230, HGS1036, FP1039, paclitaxel, carboplatin, docetaxel, FGFR1, FGF2, permetrexed, cisplatin

**Author:**

PPD

Oncology Clinical Development, USA  
Precision Medicine and Diagnostics, Oncology, USA  
Quantitative Sciences-Oncology, USA  
Biotransformation and Drug Disposition, PTS, USA  
Global Clinical Safety and Pharmacovigilance, USA  
Cancer Research, USA  
Clinical Pharmacology Modeling & Simulation, USA  
Quantitative Sciences-Genetics, USA  
Clinical Immunology, USA  
GMP Operations Biopharm R&D, USA  
Oncology Clinical Development, USA

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## Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2013N165256_00	2013-APR-16	Original
2013N165256_01	2013-OCT-17	Amendment No. 1
This amendment is a country-specific amendment for the UK. Stopping criteria based on QTc interval and contraceptive requirements have been revised.		
2013N165256_02	2013-NOV-07	Amendment No. 2
Amendment No.2: This amendment applies to all sites. Sponsor medical monitor information was updated, the inclusion criterion for FGFR gene amplification was modified, clarifications were made to the Time and Events Table, vital sign measurements, and permitted concomitant medications; and contraceptive requirements were corrected.		
2013N165256_03	2014-FEB-03	Amendment No. 3
Amendment No.3: This amendment changed Arm C of the protocol from GSK3052230 monotherapy of subjects with solid tumors to combination chemotherapy (GSK3052230 plus pemetrexed and cisplatin) of subjects with mesothelioma. Associated additions to the protocol include safety precautions for pemetrexed and cisplatin, use of modified RECIST for evaluation of clinical response, assessment of forced vital capacity. Patient reported outcomes using the Lung Cancer Symptom Scale (LCSS) was added for subjects with lung cancer and LCSS-meso for subjects with mesothelioma. Additional background and rationale were added. Stopping rules and sample size were modified. Translational research objectives were clarified		
2013N165256_04	2014-FEB-03	Amendment No. 3
Amendment No.3 version 2: A minor correction to Amendment 3 was made on Page 24 to correct ototoxicity monitoring for consistency with the changes listed on page 114. As Amendment 3 was published prior to discovery of this inconsistency, the correction increases the document number from 03 to 04.		
2013N165256_05	2014-OCT-15	Amendment No. 4
Amendment No.4: The protocol medical monitor contact information was updated and information will be provided during the study to prevent protocol amendments if there are staff changes. Additional information on preclinical studies in mesothelioma was added in the background section, and clarifications were provided for modified RECIST, the time & event tables, concomitant medications and Cockcroft-gault formula description. In Arm B, the criteria for entry has been broaden to greater than two prior lines of therapy. The protocol was expanded to allow intra-subject dose escalation or de-escalation. This allows subjects who receive benefit during the dose escalation to transition to the recommended expansion dose. In addition, additional wording has been added to allow alternative dosing and schedules to be explored.		

2013N165256_06	2015-DEC-14	Amendment No. 5
Amendment No.5: Changes including (1) the medical monitors contacts, (2) synopsis wording clarified to be consistent with the changes in Amendment 4 regarding confirmed diagnosis being Stage IIIB or IV for subjects in Arm A or B; (3) provide additional wording that chemotherapy such as cisplatin should be administered per local standards, (4) providing additional guidance for GSK3052230 dosing with extended infusion timings and pre-medication per local institutional standard practice, (5) providing more flexible timing for subjects in Arm A screening who desire to start chemotherapy prior to GSK3052230 first dose, (6) providing new PK sampling for cisplatin for Arm C subjects, and (7) requiring total calcium instead of total calcium and ionized calcium at selected sites in the UK.		

**SPONSOR SIGNATORY:**

PPD

Li Yan, MD PhD  
VP, Head Unit Physician, Oncology R  
GlaxoSmithKline

PPD

14 Dec 2015

**Date**

## MEDICAL MONITOR INFORMATION PAGE

### Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Medical Monitor	PPD MD, PhD	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426-0989, United States Email: PPD
Secondary Medical Monitor	PPD PPD MD	PPD	PPD	PPD	GlaxoSmithKline 1250 S. Collegeville Road, Collegeville, PA 19426-0989, United States Email: PPD
Additional medical monitor or sponsor contacts may be provided in a letter to investigator during the course of the study conduct without involving a protocol amendment.					

### Sponsor Registered Address:

GlaxoSmithKline Research & Development Limited  
980 Great West Road  
Brentford  
Middlesex, TW8 9GS  
UK

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

### Regulatory Agency Identifying Number(s):

Compound Number	IND Number	EudraCT Number
GSK3052230	IND#114083	2013-000354-21

**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number FGF117360:

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

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

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

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

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## LIST OF ABBREVIATIONS

AE(s)	Adverse Event(s)
ADA	Anti-drug antibody
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC(0- $\tau$ )	Area under the concentration-time curve over the dosing interval
$\beta$ -HCG	Beta-Human Chorionic Gonadotropin
BSA	Body surface area
BUN	Blood urea nitrogen
CAF	Cytokines and Angiogenic Factors
Cav	Average concentration
CBC	Complete blood count
CfDNA	Circulating cell free DNA
CL	Systemic clearance of parent drug
CLCR	Creatinine clearance
Cmax	Maximum observed concentration
CT	Computed tomography
C $\tau$	Pre-dose (trough) concentration at the end of the dosing interval
CO <sub>2</sub>	Carbon dioxide
CPMS	Clinical Pharmacokinetic Modeling and Simulation
CNS	Central nervous system
CR	Complete response
C <sub>t</sub>	Last observed quantifiable concentration
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
EC	Ethics committee
ECG(s)	Electrocardiogram(s)
ECHO	Echocardiogram
ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGF	Endothelial growth factor
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR1	Fibroblast growth factor receptor 1
FISH	Fluorescence <i>in situ</i> hybridization
FSH	Follicle Stimulating Hormone
FTIM	First time in man
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyltransferase

GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International normalization ratio
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
kg	Kilogram
L	Liter
LDT/IUO	Laboratory developed test for investigational use only
LLN	Lower limit of normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
msec	Milliseconds
MFD	Maximum Feasible Dose
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung cancer
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	Overall response rate
PD	Progressive disease or pharmacodynamics
PET	Probability of early termination
PFS	Progression-free survival
PGx	Pharmacogenetics
PK	Pharmacokinetic
PO	Per os, by mouth
PR	Partial response
PTT	Partial thromboplastin time
QTc	Corrected QT interval duration
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RBC	Red blood cells

RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SCCHN	Squamous cell carcinoma of the head and neck
SD	Standard deviation or stable disease
SMRP	Soluble mesotheline-related peptides
SPM	Study Procedures Manual
t	Time of last observed quantifiable concentration
$t_{1/2}$	Terminal phase half-life
$\tau$	Dosing interval
TGI	tumor growth inhibition
TSH	Thyroid stimulating hormone
TTG	Time to tumor growth
ULN	Upper limit of normal
UK	United Kingdom
UPC	Urine protein creatinine
US/USA	United States/United States of America
Vd	Apparent volume of distribution after IV administration
WBC	White blood cells

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## PROTOCOL SYNOPSIS

**Title:** Multi-arm, Non-randomized, Open-Label Phase IB Study to Evaluate GSK3052230 in Combination with Paclitaxel and Carboplatin, or Docetaxel or as Single Agent in Subjects with Solid Malignancies and Deregulated FGF Pathway Signaling

**Protocol Number:** FGF117360

**Clinical Phase:** IB

**Compound:** GSK3052230

**Study Rationale:** FGF receptor 1 (*FGFR1*) amplification has been identified in approximately 20% of squamous non-small cell lung cancer (NSCLC) with suggested tumor dependence on fibroblast growth factor (FGF) pathway signaling in this subset. *FGFR1* amplification has been associated with significantly shorter disease free and overall survival in NSCLC [Kim, 2013]. GSK3052230 inhibits the FGF pathway through binding and sequestering of FGF ligands and has demonstrated tumor growth inhibition in several tumor xenograft models [Harding, 2013]. Carboplatin and paclitaxel can be used in first line therapy of metastatic NSCLC and docetaxel is a standard second line agent. Additive antitumor effect was demonstrated in tumor xenograft models treated with the combination of GSK3052230 and chemotherapy including paclitaxel and carboplatin as well as docetaxel. Based on the clinical and preclinical data, the combination of GSK3052230 in combination with chemotherapy will be investigated in patients with metastatic squamous NSCLC in Arms A and B.

FGF ligand-dependent signaling plays an important role in cancer development and tumor maintenance. GSK3052230 has been shown to inhibit tumor growth in non-amplified *FGFR1* tumor xenograft models where FGF2 mRNA was overexpressed [Harding, 2013]. Malignant pleural mesothelioma (MPM) is a tumor type where FGF2 ligand overexpression has been observed in a high percentage of primary specimens and where GSK3052230 preclinical efficacy has been observed in xenograft models. Pemetrexed and cisplatin are standard agents used in first line therapy of MPM. In Arm C, the combination of GSK3052230 and pemetrexed + cisplatin will be investigated in patients with MPM who are not surgically resectable or have relapsed after surgery or localized treatment.

**Study Design:** This will be a multi-arm, multicenter, non-randomized, parallel-group, uncontrolled, open-label Phase IB study designed to evaluate the safety, tolerability and preliminary activity of GSK3052230 in combination with paclitaxel + carboplatin in previously untreated metastatic squamous NSCLC (Arm A), in combination with docetaxel in metastatic squamous NSCLC that has progressed after at least 1 line of chemotherapy (Arm B), or in combination with pemetrexed + cisplatin in MPM previously untreated with chemotherapy or investigational agents (Arm C).

### Objectives and Endpoints:

The primary objectives and endpoints are noted below. The full objectives and endpoints (primary, secondary and exploratory) are located in the main protocol in Section 2.

**Primary Objectives:**

- To characterize the safety and tolerability of GSK3052230 in combination with chemotherapy regimens.
- To determine the regimen of GSK3052230 in combination with chemotherapy for evaluation in future studies based on the maximum tolerated dose (or maximum feasible dose).
- To assess the overall response rate (ORR) in each treatment arm.

**Primary Endpoints:**

- Measurements used to evaluate safety and tolerability will include rate and severity of adverse events (AEs), withdrawals due to AEs, dose interruptions and reductions, treatment duration, and dose-limiting toxicities (DLTs) as well as change from baseline for the following: physical examinations, vital signs, 12-lead electrocardiograms (ECGs), echocardiograms (ECHO), clinical laboratory tests.
- Maximum tolerated dose (MTD) or maximum feasible dose (MFD).
- Best response defined as complete or partial response, stable disease or progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

ORR defined as the proportion of subjects with investigator-assessed confirmed complete response or partial response per RECIST 1.1.

**Hypotheses:**

Arm A: H0:  $p \leq 25\%$  versus HA:  $p \geq 45\%$

Arm B: H0:  $p \leq 10\%$  versus HA:  $p \geq 25\%$

Arm C: H0:  $p \leq 40\%$  versus HA:  $p \geq 60\%$

**Number of Subjects:** Approximately 70 subjects (minimum of 38 and up to 120, alternative dosing cohorts could potentially add another 6 to ~40 subjects).

**Inclusion Criteria:** A high level summary of the inclusion and exclusion criteria are denoted below. The full details of inclusion and exclusion criteria are located in the main protocol Section 3.2.

1. Histologically or cytologically confirmed diagnosis:

**Arms A and B:** Stage IIIB or IV or recurrent metastatic squamous NSCLC (TNM Staging for NSCLC, 7<sup>th</sup> Edition) with *FGFR1* gene amplification by central laboratory testing.

**Arm C:** recurrent after local treatment or unresectable MPM with measurable lesions.

- For specific arms the following requirements:

**Arm A:** Subjects who have received no prior therapy for Stage IV or recurrent metastatic disease. Note, to avoid any undue delay of initiating systemic chemotherapy for these subjects with newly diagnosed metastatic disease, it is allowed to initiate the first cycle of chemotherapy while eligibility for the study is

still being determined, as long as the first dose of GSK3052230 is given no later than Cycle 2 Day 1 of chemotherapy.

**Arm B:** Subjects who have documented tumor progression (based on radiological imaging), or intolerance, after receiving only at least prior line of platinum containing combination chemotherapy for metastatic disease.

**Arm C:** Subjects who have received no prior systemic therapy for MPM.

2. Availability of archival tumor tissue required. If archival tissue is not available, a fresh biopsy is required.
3. Measurable disease per RECIST version 1.1 for Arms A & B and by modified RECIST for Arm C.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 for Arm A and C and 0-2 for Arm B.

**Exclusion Criteria:**

1. For Arms A, C: Treatment with any FGFR inhibitor.  
For Arm B: Treatment with any anti-cancer therapy (for biological anti-cancer therapies see criteria 2.) during the preceding 4 weeks or within 4 half-lives of the therapy, whichever is longer.
2. Receipt of any biological therapy within 6 weeks of the first dose of GSK3052230.
3. Conditions likely to increase the potential for abdominal perforation or fistula formation.
4. Symptomatic leptomeningeal or brain metastases or spinal cord compression.

**Study Treatment Dose/Route/Regimen:** GSK3052230 will be administered via intravenous infusion (i.v.) once weekly in each 21-day cycle. GSK3052230 will be diluted in a 250 mL (nominal volume) i.v. bag containing either 5% dextrose solution or normal saline and administered over 30 minutes. Paclitaxel and carboplatin (Arm A), docetaxel (Arm B), and pemetrexed and cisplatin (Arm C) will be administered per product label on Day 1 of each cycle.

**Study Assessments:** Prior to starting the study informed consent will be obtained from all subjects. Safety assessments and study procedures include: medical history, review inclusion/exclusion criteria, physical exam, vital signs, weight, height, ophthalmologic exam, ECHO, Eastern Cooperative Oncology Group Performance Status (ECOG PS), laboratory assessments (hematology, coagulation, pancreatic markers, chemistry, thyroid, pregnancy, urinalysis), ECG, and immunogenicity sampling. Radiologic and disease assessments include brain scan and bone scan. Patient reported outcomes will be assessed using the Lung Cancer Symptom Scale or Lung Cancer Symptom Scale Mesothelioma [LCSS(-meso)]. Additional samples (blood, plasma or tissue) will be obtained for pharmacokinetic, pharmacodynamic, or translational research. An optional pharmacogenetic blood sample may be obtained if subject consents.

## 1. INTRODUCTION

### 1.1. The FGF Pathway in Cancer

Preclinically, the fibroblast growth factor (FGF) pathway plays many roles in the development of cancer, including regulation of cell growth and differentiation, regulation of angiogenesis and participation in tumor-stroma interactions. FGFs can stimulate the proliferation of tumor cells and tumor cell lines. Blockade of FGF signaling can prevent tumor cell growth [Lamont, 2011].

There are 22 known human FGFs (for a review on FGFs and their role in cancer see [Beenken, 2009]. The expression of the FGFs is restricted to specific tissues, cell types, and/or developmental stages with the exception of FGF-1 and FGF-2, both of which are expressed in essentially all adult tissues. FGF signaling is mediated by a family of trans-membrane receptor tyrosine kinases encoded by four distinct genes producing FGF receptor subtypes termed FGFR1-4. Many FGFs bind with high affinity to multiple FGF receptors, and as such, each FGF receptor has a characteristic binding profile. The FGF proteins trigger their 4 cognate receptor tyrosine kinases (FGFRs) to generate a range of cellular proliferation, survival, and differentiation responses [Itoh, 2007].

FGFR1 is the best characterized of the 4 FGFRs. FGFR1 acts through multiple mechanisms in the promotion of tumor cell growth and survival. FGFR1 signaling increases the mitotic rate of tumor cells, promotes tumor angiogenesis, and helps maintain the tumorigenicity of tumor stem cells. Many tumor cell lines are responsive to and dependent on FGFR1 signaling for growth in vitro, and tumor cell lines become resistant to cytotoxic agents when stimulated with FGF2 [Song, 2000].

FGF ligand-dependent signaling occurs through autocrine production of FGFs directly from cancer cells or through paracrine production of FGFs from the local stroma [Turner, 2010]. FGF2-FGFR1 autocrine feedback loops have been characterized in several tumor types and may have a role in drug resistance upon exposure to chemotherapy or targeted agents such as gefitinib [Sharpe, 2011; Marek, 2009]. Overexpression of FGFs is readily detectable by immunohistochemical approaches, as several studies have shown high levels of FGF2 protein in MPM tumor specimens [Kumar-Singh, 1999; Davidson, 2004; Li, 2011]. Further, overexpression or high systemic levels of FGF ligands correlate with tumorigenesis and poor patient outcome. These discoveries support the notion that specific treatments targeting FGF pathway alterations may provide benefit in this population.

### 1.2. Lung Cancer

Various *in vitro* studies utilizing non-small cell lung cancer (NSCLC) cell lines reveal that specific FGFs (FGF2 and FGF9) as well as FGFR1 and FGFR2 are frequently co-expressed [Berger, 1999; Chandler, 1999; Fischer, 2008; Kono, 2009]. In addition, frequent expression of FGF2, FGFR1 and FGFR2 mRNA and protein in primary NSCLC specimens have been demonstrated [Kono, 2009]. Further it has been shown that *FGFR1* gene amplification is associated with sensitivity to FGFR1 inhibition in non-small cell lung cancer (NSCLC) cell lines [Dutt, 2011].

Increased expression of FGFRs, *FGFR1* gene amplification, or production of FGFs correlates with poor prognosis in a variety of tumor types including NSCLC [Nguyen, 1994; Kim, 2013]. A focal amplification of the *FGFR1* gene has been detected in approximately 20% of subjects with squamous NSCLC [Weiss, 2010], a histological subtype of NSCLC which previously had very limited evidence of molecular alterations amenable to targeted drug therapy.

### **1.3. Mesothelioma**

Malignant mesothelioma remains a deadly disease with few effective therapies. Although the incidence of mesothelioma is leveling off in the United States, the incidence in Western Europe, China, Russia, and India continues to rise [Ettinger, 2012]. The median overall survival ranges from 9-17 months regardless of disease stage [Tsao, 2009]. The standard of care for the front-line treatment of mesothelioma remains cisplatin and pemetrexed with the combination regimen having a 41% response rate, a median time to progression of 5.7 months, a median overall survival of 12.1 months, and significant improvements in quality of life [Vogelzang, 2003; Gralla, 2003]. There remains no widely approved regimen for recurrent mesothelioma although pemetrexed (if not used in the front-line), vinorelbine, and gemcitabine are agents that have been used with limited success [Jassem, 2008; Stebbing, 2009; Manegold, 2005]. A recently completed Phase III study of vorinostat versus placebo in 660 patients with recurrent mesothelioma reported a median progression-free survival (PFS) of 6.3 versus 6.1 weeks and median overall survival (OS) of 31 versus 27 weeks in vorinostat vs. placebo respectively, which represents the largest Phase III study completed to date in recurrent mesothelioma [Krug, 2011]. These poor PFS and OS data underscore the need for more effective therapies in recurrent mesothelioma.

### **1.4. GSK3052230**

#### **1.4.1. Background**

GSK3052230 was originally developed as FP1039 and was also briefly known as HGS1036. All three names refer to the same molecular entity and differ only in the extinction coefficient used to calculate the concentration of drug. Please refer to the Investigators Brochure (IB) for additional details [GlaxoSmithKline Document Number 2013N160379\_00].

GSK3052230 is a soluble fusion protein consisting of the extracellular domains of human fibroblast growth factor receptor 1 (FGFR1) isoform  $\alpha$ -IIIc linked to the modified hinge and native Fc regions of human immunoglobulin G1 (IgG1). GSK3052230 acts as a fusion protein “trap” that sequesters FGFs that may be involved in the growth of tumor cells or the associated vasculature mediated by FGFRs. In this manner, GSK3052230 may have anti-tumor activity either by inhibiting tumor cell proliferation and/or by inhibition of tumor associated angiogenesis.

##### **1.4.1.1. Preclinical data on GSK3052230**

Seventy-eight tumor-derived xenograft models were treated with GSK3052230 (FP1039) as a single agent. Twenty-eight models were found to show significant tumor growth

inhibition (TGI), including models of NSCLC, small cell lung cancer, mesothelioma, squamous cell carcinoma of the head and neck (SCCHN), endometrial, colon and breast cancer [Harding, 2010; Harding, 2013]. In lung cancer xenografts, GSK3052230-treated tumors harboring *FGFR1* gene amplification displayed an average of 56% TGI compared to 22% TGI in non-amplified *FGFR1* xenografts ( $p=0.03$ )[Harding, 2013]. FGF2 mRNA levels displayed the highest ratio (247.7-fold) of median gene expression between GSK3052230 responder and nonresponder xenograft models and was the only marker that correlated with response in the subset of non-amplified *FGFR1* lung cancer xenografts where significant tumor growth inhibition was observed [Harding, 2013].

To further extend this observation, GSK3052230 was tested in models of mesothelioma, a tumor type shown to express high levels of FGF2 mRNA in cell lines and in primary tumor specimens [DeYoung, 2014]. GSK3052230 inhibited MAPK signaling as evidenced by decreased phospho-ERK levels in both NCI-H226 and MSTO-211H cells. When both cell lines were grown as tumor xenografts in mice, GSK3052230 inhibited tumor growth in a dose-dependent manner (NCI-H226: 16 – 78% TGI; MSTO-211H: 20 – 50% TGI). Because FGFs also play a key role in angiogenesis, the effects of GSK3052230 on tumor vessel formation in NCI-H226 xenografts were explored [DeYoung, 2014]. Dose-dependent and statistically-significant reductions in tumor vessel density were observed in GSK3052230-treated tumors compared to vehicle-treated tumors using MECA-32 endothelial cell IHC staining. Therefore, *FGFR1* amplification or FGF2 overexpression served as predictive markers of response to GSK3052230.

An additional thirty tumor xenograft models were treated with GSK3052230 in combination with other anti-cancer agents including chemotherapy and targeted agents. In general, the combination of GSK3052230 and a second agent was more effective than either GSK3052230 or the other agent when administered alone. In A549 lung xenografts, GSK3052230 treatment (15 mg/kg) alone resulted in 42% tumor inhibition (not significant). Carboplatin (25 mg/kg) plus paclitaxel (30 mg/kg) alone resulted in 73% tumor inhibition ( $p < 0.001$ ), and carboplatin plus paclitaxel and GSK3052230 resulted in 86% tumor inhibition ( $p < 0.001$ ) compared to vehicle treated animals. In two prophylactic models (A549 and NCI-H1703) the combination of GSK3052230 and docetaxel showed tumor growth inhibition of 58% ( $p < 0.01$ ) and 97% ( $p < 0.001$ ) compared to 46% and 26% with GSK3052230 alone (both not significant). In these three models, the addition of GSK3052230 did not confer additional toxicity compared to chemotherapy alone [GlaxoSmithKline Document Number [2013N160379\\_00](#)].

#### **1.4.2. First-time-in-human study FP1039-001**

GSK3052230 has been studied in a Phase 1, open-label, dose-escalation study (Protocol FP1039-001, please refer to Investigator Brochure, GlaxoSmithKline Document Number [2013N160379\\_00](#)). No maximum tolerated dose (MTD) was identified in this study exploring a dose range from 0.6 to 20 mg/kg/week of GSK3052230. The 20 mg/kg once weekly dosing schedule was determined to be safe and was declared the ‘maximum feasible dose’ (MFD) taking into account the high absolute dose of drug as well as achievement of the desired target concentration based on preclinical studies.

#### **1.4.2.1. Clinical Pharmacokinetics of GSK3052230**

In study FP1039-001, the GSK3052230 PK profiles were assessed following the 1st and 4th doses and were found to be typical of a large protein, with an initial distribution phase and a terminal elimination phase. The profile in humans is similar to that observed in rats, dogs, and chimpanzees. After the 1st dose, the mean terminal phase half-life ( $t_{1/2}$ ) ranged from 63 to 92 h, while after the 4th dose  $t_{1/2}$  ranged from 87 to 125 h. Systemic clearance (CL) ranged from 0.0648 to 0.101 L/h across the dose range and appears to be independent of dose. The maximum plasma GSK3052230 concentration (Cmax) and area under the plasma GSK3052230 concentration-time curve during a dosing interval (AUC(0- $\tau$ )) increased proportionally to dose. Some accumulation was observed after 4 weekly doses; Cmax after the 4th infusion was 11% to 42% higher than Cmax after the 1st dose, and AUC(0- $\tau$ ) was 30% to 61% higher after the 4th dose compared to the 1st dose. The pharmacokinetic analysis supports a weekly IV dosing schedule of between 10 and 20 mg/kg, when used as monotherapy, achieving the desired target concentration throughout the dosing interval.

#### **1.4.2.2. Clinical Safety of GSK3052230**

GSK3052230 has been investigated as monotherapy in a first-time-in-man (FTIM) study (FP1039-001) including a total of 39 subjects with different tumor types. It should be noted that the study population was heavily pretreated with a median of 4 prior anticancer therapies (range 0-11). GSK3052230 IV once every week was considered tolerable over the dose range studied (0.6-20 mg/kg/week). Mean duration of exposure was 54 days (13-203 days). One subject required a dose reduction (Grade 3 neutropenia event described below) and a total of 6 subjects experienced dose interruptions at any timepoint during the study.

A total of 4 dose-limiting toxicities (DLTs) were reported over the course of the study and occurred at doses of 1.0 mg/kg (urticaria), 1.3 mg/kg (intestinal perforation and neutropenia each counted as an event), and 20 mg/kg (muscular weakness). After seeing 2 DLTs at 1.3 mg/kg/week, 2 dose levels below 1.3 mg/kg were explored in 6 subjects each. Both these dose levels were considered tolerable. Since the DLT of intestinal perforation was confounded by several known risk factors and of questionable relation to GSK3052230 (see below) and the DLT of neutropenia was a brief Grade 3 event, further exploration of this dose-level for a total of 6 subjects was carried out. Since there were no further DLTs at this dose level, dose escalation continued. No clear evidence of dose-related toxicity limiting the dose escalation was found, hence a MTD was not identified, rather, a 'maximum feasible dose' of 20 mg/kg was determined.

The most common toxicities were diarrhea (44%), fatigue (44%) and nausea (26%), with no clear dose-related increases in frequency of any adverse events (AEs) except low grade nausea/vomiting seen at the highest dose-level.

The more commonly reported Grade 3 (severe) AEs involved metabolism and nutrition disorders as reflected in abnormal clinical chemistry values, reported for 7 subjects (17.9%) and consisted of hyperglycemia, hypokalemia, and hypophosphatemia (each reported by 2 subjects [5.1%]). Of note, hyperphosphatemia that has been previously reported with agents targeting the FGF pathway was not identified in the study. Other

Grade 3 AEs reported by more than 1 subject were abdominal pain and dyspnea (each reported by 2 subjects [5.1%]). A total of 2 subjects had Grade 4 and/or fatal AEs (1 subject with Grade 4 pulmonary embolism and 1 subject with Grade 4 leukopenia, Grade 4 neutropenia, and Grade 5 respiratory failure).

A total of 12 serious adverse events (SAEs) were reported in 11 subjects during the course of this study. Two SAEs, intestinal perforation and worsening bilateral leg weakness/peripheral neuropathy, were considered at least possibly related to GSK3052230. Intestinal perforation occurred in a subject with malignant liposarcoma of the retroperitoneum treated with several resections and abdominal radiotherapy, who died of intestinal perforation 17 days after last dose of GSK3052230. The tumor mass involved the bowel at study entry; this was also a DLT event. The second subject developed exacerbation of pre-existing bilateral leg weakness and died of acute respiratory failure secondary to pneumonia 43 days after last dose of GSK3052230. The subject had colon cancer with metastatic spread to the lungs, and had pre-existing peripheral neuropathy since 2005. After 3 weeks on study the neuropathy worsened and GSK3052230 was discontinued. MRI of brain and spinal cord was normal and the subject was transferred to a rehabilitation facility where he died 19 days later.

A total of five deaths were reported in the study. Please refer to the Investigator Brochure, GlaxoSmithKline Document Number [2013N160379\\_00](#), for further details.

#### **1.4.2.3. Anti-tumor Activity with GSK3052230**

No activity in terms of objective tumor responses were seen in the FTIM study which was carried out in a population unselected for deregulation of FGF signaling pathway. For subjects with evaluable disease, the best overall tumor response (Response Evaluation Criteria in Solid Tumors [RECIST] 1.0) was stable disease (SD) for 15/36 subjects (41.7%) and progressive disease (PD) for 17/36 subjects (47.2%). One subject with hormone resistant prostate cancer rapidly progressing on prior docetaxel, experienced a 20% reduction in tumor diameter and stable disease of 7 months duration.

### **1.5. Chemotherapy (Paclitaxel, Carboplatin, Docetaxel, Pemetrexed, Cisplatin)**

#### **1.5.1. Paclitaxel/Carboplatin**

Paclitaxel, a mitotic inhibitor originally extracted from the pacific yew (*Taxus brevifolia*), has been shown to be active as a single agent and/or in combination with other chemotherapeutic drugs in subjects with ovarian cancer, breast cancer, NSCLC, and Kaposi's sarcoma. Paclitaxel causes side effects that are generally predictable and manageable. Neutropenia, the most frequent side effect, is generally of short duration. Peripheral neuropathy, myalgia, and arthralgia are usually noted with the administration of higher doses of paclitaxel ( $\geq 175$  mg/m<sup>2</sup>) for several cycles. Paclitaxel causes rapid and usually complete alopecia. Other toxicities include: mild to moderate nausea, vomiting, diarrhea, and mucositis [[Taxol USPI](#), 2011].

Carboplatin is an analog of cisplatin with an improved toxicity profile. Bone marrow suppression is the major dose-limiting toxicity of carboplatin. Carboplatin has been

shown to be active as a single agent and/or in combination with other chemotherapeutic drugs in subjects with ovarian cancer, NSCLC, bladder cancer, esophageal and other upper gastrointestinal cancer [Paraplatin USPI, 2010]. Nausea, vomiting, and loss of appetite are usually mild to moderate. The pharmacokinetics (area under the time concentration curve [AUC] and the pharmacodynamic effects (hematologic toxicity) of carboplatin are much better predicted by glomerular filtration rate (GFR) based dosing as compared with the more traditional body surface area (BSA) dosing method [Calvert, 1994].

The combination of paclitaxel and carboplatin has been developed to avoid overlapping neurotoxicity of paclitaxel with cisplatin and for its easier administration. Several Phase 2 and Phase 3 studies of the combination of paclitaxel and carboplatin have shown that the drug combination is active in subjects with NSCLC, ovarian cancer, bladder cancer, esophageal cancers, SCCHN cancers and other tumor types [NCCN Guidelines, 2012].

### **1.5.2. Docetaxel**

Docetaxel, a semi-synthetic analog of paclitaxel, acts by disrupting the microtubule network leading to apoptosis and cell death. Docetaxel is used as a single agent in the treatment of NSCLC, breast cancer, and in combination with multiple other chemotherapies in the treatment of breast cancer, NSCLC, gastric cancer and SCCHN. The most common adverse events associated with the administration of docetaxel are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia [Taxotere PI, 2010].

### **1.5.3. Pemetrexed/Cisplatin**

Pemetrexed is a folate analog inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, which are folate-dependent enzymes involved in de novo biosynthesis of thymidine and purine nucleotides. Cisplatin is a heavy-metal complex containing a central platinum atom with 2 chloride atoms and 2 ammonia molecules in the cis position. Pemetrexed in combination with cisplatin is recommended for the treatment of mesothelioma [Alimta PI, 2004].

The most common adverse reactions (incidence  $\geq 20\%$ ) with single-agent use of pemetrexed are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation [Alimta PI, 2004].

Common adverse reactions (incidence  $\geq 20\%$ ) associated with cisplatin include nephrotoxicity, ototoxicity, myelosuppression, and nausea/vomiting. Other toxicities include vascular complications, serum electrolyte imbalance, Hyperuricemia, neurotoxicity, ocular toxicity, anaphylactic-type reactions, and hepatotoxicity [Platinol PI, 2010].

## 1.6. Summary of Risk Management

Further information on these potential risks can be found in the Investigator Brochure (IB) for GSK3052230 [GlaxoSmithKline Document Number [2013N160379\\_00](#)].

Based on preclinical data and experience from the clinical study, as well as the toxicity profile of the combination agents, the following are events of interest:

### Infusion-related reactions/Edema/Hypersensitivity:

- Generalized edema of unknown cause (not associated with measurable increase in histamine or cytokines) was a prominent observation in preclinical toxicology studies
- Edema and hypersensitivity are potential overlapping toxicities between GSK3052230 and taxanes such as paclitaxel and docetaxel.
- Subjects will be closely monitored for infusion-related reactions.
- Subjects in the combination chemotherapy arms will already be receiving premedication with glucocorticoids (for the paclitaxel combination also antihistamines and H2 receptor antagonists) as part of the standard of care. Epinephrine for subcutaneous injection, diphenhydramine for IV injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in the room where the infusions are being performed.
- If infusion reactions are noted in subjects not already premedicated with glucocorticoids, antihistamines and H2 receptor antagonists, appropriate premedication against hypersensitivity reactions may be initiated prior to the next infusions at the discretion of the investigator according to the institution's standard practice. All subjects who have experienced an infusion reaction should have GSK3052230 infused over 60 minutes instead of 30 minutes and pre-treated with appropriate local pretreatment guidelines. If the subject continues to have a reaction on re-challenge, the infusion of GSK3052230 may be prolonged for 90 minutes.

### Anti-drug antibodies:

- The antidrug antibody response in study FP1039-001 was generally weak with no apparent associated changes in drug exposure or clinical sequelae. Anti-drug antibodies will be monitored throughout the study.

### Anterior uveitis:

- Bilateral acute anterior uveitis was seen in preclinical toxicology studies. This is believed to be secondary to anti-drug antibody (ADA) immune complexes deposited in the eyes of the animals. No events of anterior uveitis were reported in study FP1039-001.
- Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin.

- An ophthalmologic exam will be performed at screening and at Cycle 4 (Section 7.3.7). If at any time the subject complains of photophobia, changes in vision, or eye pain; the ophthalmic examination finding are abnormal; or visual acuity has worsened by 3 lines or more since the start of the study the subject will be referred for a formal evaluation, including a slit-lamp examination and intraocular pressure, by a qualified ophthalmologist.

**Wound healing:**

- Abnormal wound healing is a theoretical risk associated with inhibition of the FGF signaling pathway. No events of abnormal wound healing have been reported previously. Subjects with non-healing wounds that, in the opinion of the investigator, would pose a significant medical risk to the subject should wound healing be further impaired, will be excluded from participation in this study.
- Interruption of therapy is recommended in subjects undergoing surgical procedures; treatment with GSK3052230 should be stopped at least 14 days prior to scheduled surgery and restarted only after complete healing has occurred and been documented in subject's notes.

**Bowel perforation:**

- One subject developed fatal bowel perforation in Study FP1039-001. The subject's history was notable for several risk factors for perforation. However, GSK3052230 may have anti-angiogenic activity that has previously been associated with a risk of bowel perforation, so subjects with conditions with an increased risk for bowel perforation are excluded from participation in this study.

**Heart valve fibrosis:**

- Heart valve thickening due to fibrosis was noted at necropsy in 2 rats in a 4-week toxicology study. This finding was consistent with chronic persistent irritation and attributed to infusion catheter complications.
- Subjects participating will undergo echocardiography at screening and Cycle 4 for evaluation of cardiac valve abnormalities and left ventricular ejection fraction (LVEF) changes (note, additional assessments may be obtained as clinically indicated or if the subject discontinues prior to Cycle 4).

**Peripheral Neuropathy**

- One event of worsening bilateral leg neuropathy/muscle weakness was reported as a possibly related SAE in a subject with pre-existing neuropathy in Study FP1039-001.
- Peripheral neuropathy is a potentially overlapping toxicity between GSK3052230, taxanes such as paclitaxel and docetaxel, and cisplatin.
- Complete physical exam will be performed at screening. Also, disease-oriented physical examination will be performed on Day 1 of each cycle, Day 22 of the last cycle on treatment or 7 days after last visit off treatment, and 30 days after discontinuation of GSK3052230 therapy

**Hypothyroidism:**

- Slightly reduced weight of the thyroid gland was seen in preclinical toxicology studies. In study FP1039-001, 2 events of hypothyroidism/increased thyroid stimulating hormone (TSH) were reported.
- Subjects participating in clinical studies with GSK3052230 will be assessed for TSH at baseline and periodically during the study. If TSH is abnormal, additional thyroid assessments (total T3, total T4, free T4) along with appropriate clinical assessments are warranted.

**Hematologic toxicity:**

- Two events of neutropenia (Grade 3 and grade 4) were reported in Study FP1039-001 for an overall rate of 5.1%. Furthermore, paclitaxel, docetaxel, and cisplatin have known bone-marrow toxicity.
- All subjects in the study will have their blood counts monitored regularly, and supportive therapy including blood transfusions and growth factor support is encouraged (Section 9.1).

**Nephrotoxicity:**

- Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m<sup>2</sup>. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.
- One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B12 died of drug-related toxicity following administration of pemetrexed alone.

**Ototoxicity:**

- Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m<sup>2</sup>, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Careful monitoring per standard of care should be performed.

## 2. OBJECTIVES AND ENDPOINTS

### 2.1. Primary

	Objectives	Endpoints
Primary	To characterize the safety and tolerability of GSK3052230 in combination with chemotherapy regimens.	Measurements used to evaluate safety and tolerability will include rate and severity of AEs, withdrawals due to AEs, dose interruptions and reductions, treatment duration, and DLTs as well as change from baseline for the following: physical examinations, vital signs,:12-lead ECGs, ECHO, clinical laboratory tests.
	To determine the regimen of GSK3052230 in combination with chemotherapy for evaluation in future studies based on the maximum tolerated dose (or maximum feasible dose).	Maximum tolerated dose (MTD) or maximum feasible dose (MFD).
	To assess the overall response rate (ORR) in each treatment arm.	Best response defined as complete or partial response, stable disease or progressive disease according to RECIST 1.1 or modified RECIST (for MPM)  ORR defined as the proportion of subjects with investigator-assessed confirmed complete response or partial response per RECIST 1.1 or modified RECIST (for MPM)

### 2.2. Secondary

	Objectives	Endpoints
Secondary	To assess progression free survival (PFS) for each treatment arm.	PFS is defined as the interval between first dose of GSK3052230 and the earliest date of disease progression or death due to any cause by investigator assessment per RECIST 1.1 or modified RECIST (for MPM)
Secondary	To characterize the population pharmacokinetics of GSK3052230 and identify important determinants of variability.	GSK3052230 population pharmacokinetic parameters such as clearance (CL) and volume of distribution (Vd), and relevant covariates which may influence exposure (e.g. age, weight, or disease related covariates).
Secondary	Assess improvement in Pulmonary Function Tests in Patients with MPM	Change from baseline in Forced Vital Capacity (FVC) in patients with MPM

## 2.3. Exploratory

	Objectives	Endpoints
<b>Exploratory</b>	To describe the kinetics of tumor growth in the presence of GSK3052230 for each treatment arm and investigate the relationship between tumor growth kinetics and clinical activity.	Tumor size over time, tumor growth rate constants, and time to tumor growth (TTG) predicted with the model parameters. Additional analysis will be performed utilizing volumetric analysis.
<b>Exploratory</b>	To identify biomarkers that may predict response or resistance.	Evaluate potential predictive/prognostic biomarkers (DNA, RNA, or protein) of response in circulation and/or in tumor.
<b>Exploratory</b>	To evaluate the pharmacodynamic response in circulation following treatment.	Changes in circulating biomarkers (eg, proteins) implicated in FGFR or disease biology signalling in pre and post dose blood samples.
<b>Exploratory</b>	To explore the relationship between PK, pharmacodynamic response, and clinical endpoints.	Predicted/observed exposure (AUC), trough concentrations (C <sub>T</sub> ), or other PK endpoints as compared to pharmacodynamic and clinical endpoints.
<b>Exploratory</b>	To develop and validate an assay to measure FGFR1 gene amplification status such as, but not limited to, a Fluorescence <i>in situ</i> hybridization (FISH) -based assay..	Association of FGFR1 gene amplification with clinical response to support the development of an investigation use only test (IUO) and potential companion diagnostic for subject selection.
<b>Exploratory</b>	To investigate additional measures of FGF signaling pathway deregulation as potential predictive biomarkers for GSK3052230 in tissue.	Identification and validation of alternative measures of FGF signaling pathway deregulation retrospectively such as ligand or receptor overexpression for example but not limited to FGF2 or FGFR1 expression FGF2 overexpression) as predictive biomarkers for subject selection and potential development of a companion diagnostic.
<b>Exploratory</b>	To evaluate changes in patient reported outcomes	Change from baseline and association with ORR in observer and patient assessed components of the Lung Cancer Symptom Scale (LCSS) and LCSS-meso
<b>Pharmacogenetics</b>	To investigate the relationship between genetic variants in the host DNA and the pharmacokinetics of GSK3052230 and/or the relationship between genetic variants in the host DNA and the efficacy, safety and tolerability of GSK3052230.	Refer to <a href="#">Appendix 1</a> .

### 3. STUDY POPULATION

#### 3.1. Number of Subjects

Approximately 70 subjects will be enrolled in the study (minimum of 38 and up to approximately 120, alternative dosing cohorts could potentially add another 6 to ~ 40 subjects). In addition to minimum and maximum sample sizes for each arm, sample sizes that would be expected under the null and alternative hypothesis rates are provided in Section 12.3.

#### 3.2. Subject Selection Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK study treatment or other study treatment(s) that may impact subject eligibility is provided in the Investigator Brochure [GlaxoSmithKline Document Number [2013N160379\\_00](#)] and the individual product labels [[Taxol](#) PI, 2011], [[Paraplatin](#) PI, 2010], [[Taxotere](#) PI, 2010], [[Alimta](#) PI, 2004], [[Platinol](#) PI, 2010].

Deviations from inclusion/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.

##### 3.2.1. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. Signed written informed consent;
2. Histologically or cytologically confirmed diagnosis:

**Arms A and B:** Stage IV or recurrent metastatic squamous NSCLC [[TNM classification](#) of malignant tumors, 7<sup>th</sup> edition, 2009; [Edge](#), 2010] with *FGFR1* gene amplification by central laboratory testing.

**Arm C:** recurrent after local therapy or unresectable malignant pleural mesothelioma (MPM) with measurable lesions.

- For specific arms the following requirements:

**Arm A:** Subjects who have received no prior therapy for Stage IIIB or Stage IV or recurrent metastatic disease. Note, to avoid any undue delay of initiating systemic chemotherapy for these subjects with newly diagnosed advanced or metastatic disease, it is allowed to initiate the first cycle of chemotherapy while eligibility for the study is still being determined, as long as the first dose of GSK3052230 is given no later than Cycle 2 Day 1 of chemotherapy. In addition, subjects with Stage IIIB or Stage IV disease and recurrence after previous NSCLC that has been treated with surgery and adjuvant chemotherapy or a radio-chemotherapy regimen with curative intent are eligible, provided 6 months has passed since this treatment ended [[TNM classification](#) of malignant tumors, 7<sup>th</sup> edition, 2009; [Edge](#), 2010].

**Arm B:** Subjects who have documented tumor progression (based on radiological imaging) or intolerance after receiving at least one prior line of platinum containing combination chemotherapy for Stage IIIB, Stage IV or recurrent metastatic disease [[TNM classification](#) of malignant tumors, 7<sup>th</sup> edition, 2009; [Edge](#), 2010].. Note: Prior treatment should not include docetaxel but may have included paclitaxel.

**Arm C:** Subjects who have received no prior systemic therapy for MPM.

3. Availability of archival tumor tissue required for assessment of deregulated FGF pathway signaling eg, *FGFR1* amplification or FGF2 or FGFR1 expression. If archival tissue is not available, a fresh biopsy is required. Please refer to Section [7.7.1](#)

**In Arms A and B**, subjects will be prospectively screened for *FGFR1* gene amplification using a FISH assay (note, local testing is permitted for pre-screening of subjects prior to central testing) for the dose expansion and the MTD/MFD cohorts only. For inclusion in this study, based on the central laboratory testing, *FGFR1* gene amplification must meet one of the following criteria: a ratio of *FGFR1*/CEN 8 of  $\geq 2$ ; or average number of *FGFR1* signals per tumor nucleus of  $\geq 6$ ; or the percentage of tumor nuclei containing  $\geq 5$  *FGFR1* signals is  $\geq 50\%$ .

**In Arm C**, FGF2 expression by IHC will be evaluated retrospectively in tissue samples by a central laboratory and is not a requirement for study entry.

4. Measurable disease per RECIST version 1.1 (Arm A and B) and modified RECIST for Arm C.
5. Male or female  $\geq 18$  years of age.
6. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section [10](#), from 14 days prior to the first dose of study treatment, throughout the study, and for 6 months following the last dose of chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest.
7. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section [10.1.2](#) for at least 2 weeks prior to administration of the first dose of study treatment and for at least 6 months after the last dose of chemotherapy, to allow for clearance of any altered sperm.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 for Arms A and C subjects and 0-2 for Arm B.
9. 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.
10. Must have adequate organ function as defined by the following baseline values:

**Table 1      Inclusion Criteria: Adequate Organ Function**

SYSTEM	LABORATORY VALUES
Hematologic	
ANC	$\geq 1.5 \times 10^9/L$
Hemoglobin <sup>a</sup>	$\geq 9 \text{ g/dL}$
Platelets	$\geq 100 \times 10^9/L$
Partial thromboplastin time (PTT)	$\leq 1.25 \times \text{ULN}$ .
Hepatic	
Albumin	$\geq 2.5 \text{ g/dL}$
Serum total bilirubin <sup>b</sup>	$\leq 1.25 \text{ times ULN}$ (for Arm B: $\leq \text{ULN}$ )
AST and ALT	$\leq 2.5 \text{ times ULN}$ (for Arm B: $\leq 1.5 \text{ times ULN}$ )
Renal	
Serum Creatinine	$\leq 1.5 \times \text{ULN}$
Or	<u>Or</u>
Measured or Calculated Creatinine Clearance <sup>c</sup>	$\geq 45 \text{ mL/min}$ (Arm A or B) $\geq 65 \text{ mL/min}$ (Arm C)
Cardiac	
Left ventricular ejection fraction	$\geq 50\%$ by ECHO

a. Subjects should meet criteria in the absence of hematopoietic growth factors or transfusions.

b. If the serum total bilirubin is elevated at screening but the direct bilirubin is  $\leq \text{ULN}$  then the subject may be allowed to enter study.

c. Calculated by the Cockcroft and Gault formula.

NOTE: Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the investigator may opt to retest the subject and the subsequent within range screening result may be used to confirm eligibility.

### 3.2.2.      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 the study:

1. For Arms A and C: Treatment with any FGFR inhibitor.  
For Arm B: Treatment with any anti-cancer therapy (for biological anti-cancer therapies see criteria 2) during the preceding 4 weeks or within 4 half-lives of the therapy, whichever is longer.
2. Receipt of any biological therapy within 6 weeks of the first dose of GSK3052230.
3. Unresolved toxicity of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v4.03) [[NCI](#), 2010] Grade 2 or higher from previous anti-cancer therapy, except alopecia
4. Active malignancy other than the cancer under study. Subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible.
5. Presence of uncontrolled infection.

6. Prior major surgery or trauma within 28 days before first dose of study drug.
7. Presence of any non-healing wound, fracture, or ulcer.
8. Any prohibited medication(s) as described in Section 9.2.
9. Conditions likely to increase the potential for abdominal perforation or fistula formation, including but not limited to:
  - Luminal intestinal cancers or bulky abdominal disease.
  - Presence or history of abdominal fistula, gastrointestinal perforation, peptic ulcer disease or intra-abdominal abscess within the six months prior to the first dose of GSK3052230.
  - Other risk factors for perforation, such as acute diverticulitis, obstruction or previous abdominal or pelvic radiation.
10. Symptomatic leptomeningeal or brain metastases or spinal cord compression.

**NOTE:** Subjects previously treated for these conditions are eligible if they meet **both** of the criteria below:

- (1) have had stable CNS disease for at least 4 weeks after local therapy as assessed by imaging (contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT)) prior to Day 1, **and**
- (2) are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 4 weeks prior to Day 1.

11. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drugs (GSK3052230, docetaxel, paclitaxel, carboplatin, pemetrexed, cisplatin) or their excipients that contraindicates their participation.
12. Known human immunodeficiency virus (HIV)-positive serology, acquired immunodeficiency syndrome (AIDS), or an AIDS-related illness.
13. Prior organ or allogeneic stem cell transplant.
14. The following cardiac abnormalities:
  - Corrected QT (QTc) interval  $\geq 480$  msec
  - History of acute coronary syndromes (including unstable angina) within the past 24 weeks
  - Coronary angioplasty, or stenting within the past 24 weeks
  - Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
  - Abnormal cardiac valve morphology ( $\geq$  Grade 2) documented by echocardiogram (subjects with Grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study).
  - History of known arrhythmias (except sinus arrhythmia and atrial fibrillation that is controlled) within the past 24 weeks

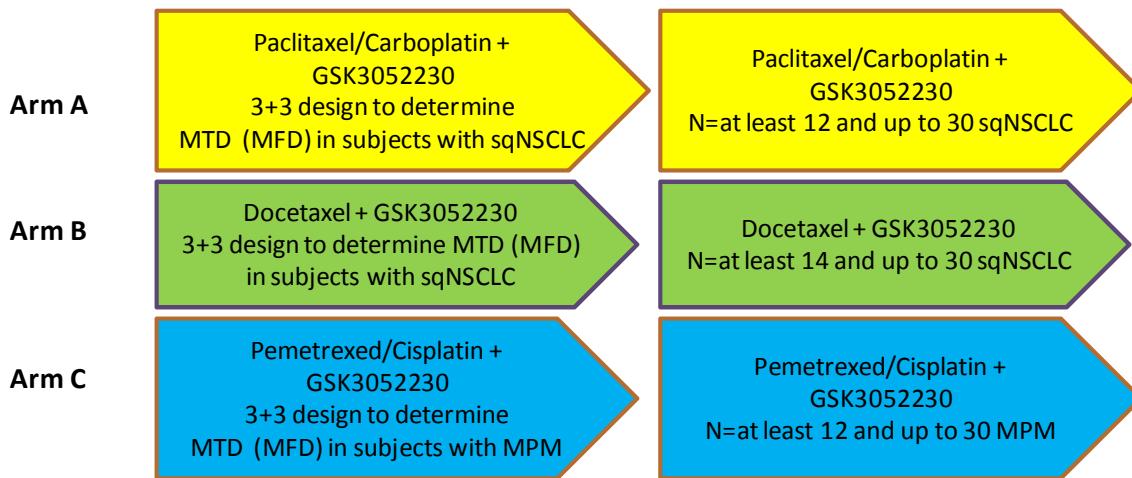
15. Presence or history of hemoptysis ( $>1/2$  teaspoon of red blood) 2 weeks prior to the first dose of GSK3052230.
16. Any serious and/or unstable pre-existing medical, psychiatric disorder or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
17. Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases or otherwise stable chronic liver disease per investigator's assessment).
18. Pregnant, lactating or actively breast feeding females.
19. French subjects: The French subject has participated in any study using an investigational study treatment(s) during the previous 30 days.

## 4. INVESTIGATIONAL PLAN

### 4.1. Discussion of Study Design

This will be a multi-arm, multicenter, non-randomized, parallel-group, uncontrolled, open-label Phase IB study designed to evaluate the safety, tolerability and preliminary activity of GSK3052230 in combination with paclitaxel + carboplatin (Arm A), in combination with docetaxel (Arm B), or in combination with pemetrexed + cisplatin (Arm C).

**Figure 1** Study Schema



Dose escalation will follow a 3+3 design as outlined in Section 4.2 for determination of MTD (or MFD). A cohort expansion of at least 12 subjects will be treated at the MTD (or MFD) in each arm, with the option of expanding to a maximum of 30 subjects. Stopping rules based on anti-tumor activity were derived according to a predictive probability design for each arm of the study and are detailed in Section 4.2.1, Section 4.2.2, and Section 4.2.3.

GSK3052230 will be administered as a 30-minute intravenous (i.v.) infusion once a week (Day 1, Day 8, Day 15) of each 21-day cycle. Paclitaxel/carboplatin, docetaxel, and pemetrexed/cisplatin will be administered i.v. on Day 1 of each 21-day cycle. The number of cycles of paclitaxel/carboplatin will be limited to 4 to 6 cycles. Subjects may continue to receive docetaxel and pemetrexed/cisplatin until disease progression or as long as they are considered to derive benefit from treatment. Subjects on pemetrexed/cisplatin may have their cisplatin stopped after 4 cycles per local clinical standards. Subjects who discontinue chemotherapy for reasons other than disease progression, may continue to receive GSK3052230 as long as they are considered to derive benefit from the treatment according to the criteria in Section 6.3. After discontinuation of GSK3052230, subjects will return after approximately 30 days (see Time and Events Table Section 7.1) for a follow-up visit to collect safety assessments, after which they will be considered to have completed the study.

Blood samples for pharmacokinetic, pharmacogenetic, and translational research will be obtained at specified times during the study. Efficacy will be assessed every 2 cycles during the first year and every 4 cycles thereafter.

All study treatments, including investigational product, will be referred to as ‘study treatment’ for ease of presentation throughout the protocol. For EU regulatory purposes, the term ‘investigational product’ will only be used in Section 5 when describing the GSK3052230.

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential.

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.

## 4.2. GSK3052230 plus Chemotherapy

Dose escalation will follow a 3 + 3 dose-escalation procedure, described in Table 2. Dose limiting toxicities (DLTs) are based on any observed toxicity in the first 21 days of treatment (please see Section 4.2.4). An additional (4<sup>th</sup>) subject is allowed in each cohort of 3 to ensure 3 evaluable subjects for determination of DLTs. Evaluation of available safety data from at least 3 subjects who have completed a minimum of 21 days (1 cycle) is required prior to expanding a cohort or escalating to the next higher dose cohort.

Dose escalation will be explored in cohorts of 3 to 6 subjects to determine the MTD (or MFD), defined in Section 4.2.4. The cohort may be expanded up to 9 subjects to further evaluate safety, pharmacokinetics and tolerability before dose escalation or reduction decision is determined.

**Table 2 Dose Escalation 3+3 Design Process for Arms A, B**

Number of subjects at given dose level with DLT	Action
0 out of 3 subjects	Proceed to next relevant dose-level or expand cohort to a total of 6 evaluable subjects as appropriate
1 out of 3 subjects	Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects
1 out of 6 subjects	Proceed to next relevant dose-level or expand cohort to 9 as appropriate.
2 or more out of 3 or 6 subjects in a dosing cohort <sup>a</sup>	The MTD has been exceeded. Dose reduction in this Arm should be considered. Either evaluate an intermediate dose lower than current dose or expand a prior cohort.

a. If 9 subjects in a cohort, then 3 or more out of 9

#### 4.2.1. Arm A

The starting dose (Dose Level 0) and escalation/de-escalation schema for GSK3052230 in combination with paclitaxel + carboplatin is presented in [Table 3](#). Depending on emerging data, additional intermediate or lower dose-levels beyond those described may be explored.

**Table 3 Combination Therapy: Arm A GSK3052230 + Paclitaxel + Carboplatin**

Dose Level	Dose of GSK3052230 (Weekly)	Paclitaxel + Carboplatin <sup>a</sup> (once every 21 days)
Dose Level -2	5 mg/kg	135 mg/m <sup>2</sup> + AUC 4
Dose Level -1	5 mg/kg	175 mg/m <sup>2</sup> + AUC 5
<b>Starting Dose Level 0</b>	<b>5 mg/kg</b>	<b>200 mg/m<sup>2</sup> + AUC 6</b>
Dose Level 1	10 mg/kg	200 mg/m <sup>2</sup> + AUC 6
Dose Level 2	20 mg/kg	200 mg/m <sup>2</sup> + AUC 6

a. Carboplatin dose based on Calvert's formula.

A total of at least 12 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 12 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm A are 0/12, 1/14, 2/17, 3/20, 4/22, 5/24, 6/26, 7/27, 8/28, 9/29, and 10/30 subjects and are shown in tabular format in [Section 12.7](#). Up to 30 subjects will be enrolled in Arm A. All available data will be considered in making enrollment decisions.

#### Arm A: Screening procedure for subjects on chemotherapy

To avoid any undue delay in initiating systemic chemotherapy for subjects with newly diagnosed Stage IV or recurrent metastatic disease, the first cycle of chemotherapy may be initiated while determination of eligibility is being completed for the present study.

The first dose of GSK3052230 should be given no later than Cycle 2 Day 1 of chemotherapy.

Subjects who have started with the initial dose of systemic chemotherapy will have the following done:

- Complete full screening procedures for FGF117360 as outlined in Section [7.1](#).
- All treatment related toxicities (>Grade 2) should be resolved prior to starting GSK3052230.
- Ensure documentation of all medical history (adverse events pre-baseline) in eCRF prior to start of treatment with GSK3052230.

#### 4.2.2. Arm B

The starting dose (Dose Level 0) and escalation/de-escalation schema for GSK3052230 in combination with docetaxel is presented in [Table 4](#). Depending on emerging data, additional intermediate or lower dose-levels beyond those described may be explored.

**Table 4 Combination Therapy: Arm B GSK3052230 + Docetaxel**

Dose Level	Dose of GSK3052230 (weekly)	Docetaxel (once every 21 days)
Dose Level -2	5 mg/kg	40 mg/m <sup>2</sup>
Dose Level -1	5 mg/kg	55 mg/m <sup>2</sup>
<b>Starting Dose Level 0</b>	<b>5 mg/kg</b>	<b>75 mg/m<sup>2</sup></b>
Dose Level 1	10 mg/kg	75 mg/m <sup>2</sup>
Dose Level 2	20 mg/kg	75 mg/m <sup>2</sup>

A total of at least 14 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 14 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm B are 0/14, 1/22, 2/26, 3/28, 4/29, and 5/30 subjects and are shown in tabular format in Section [12.7](#). Up to 30 subjects will be enrolled in Arm B. All available data will be considered in making enrollment decisions.

#### 4.2.3. Arm C

Arm C will open for enrollment subsequent to Amendment 3. The starting dose of GSK3052230 (Dose Level 0) in Arm C will be 10 mg/kg, as long as the 5 mg/kg dose in combination with chemotherapy in Arm A did not exceed the MTD. Otherwise, the starting dose level in Arm C will be Dose Level -1. Dose levels and escalation/de-escalation schema for GSK3052230 in combination with pemetrexed and cisplatin is presented in [Table 5](#). Depending on emerging data, additional intermediate or lower dose-levels beyond those described may be explored.

**Table 5 Combination Therapy: Arm C GSK3052230 + Pemetrexed + Cisplatin**

<b>Dose Level</b>	<b>Dose of GSK3052230 (Weekly)</b>	<b>Pemetrexed + Cisplatin (once every 21 days)</b>
Dose Level -2	5 mg/kg	400 mg/m <sup>2</sup> + 60 mg/m <sup>2</sup>
Dose Level -1	5 mg/kg	500 mg/m <sup>2</sup> + 75 mg/m <sup>2</sup>
<b>Starting Dose Level 0</b>	<b>10 mg/kg</b>	<b>500 mg/m<sup>2</sup> + 75 mg/m<sup>2</sup></b>
Dose Level 1	20 mg/kg	500 mg/m <sup>2</sup> + 75 mg/m <sup>2</sup>

A total of at least 12 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 12 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm C are 2/12, 3/14, 4/16, 5/18, 6/20, 7/21, 8/23, 9/24, 10/25, 11/26, 12/27, 13/28, 14/29 and 15/30 subjects and are shown in tabular format in Section 12.7 Up to 30 subjects will be enrolled in Arm C. All available data will be considered in making enrollment decisions.

#### **4.2.4. Dose-Limiting Toxicity**

DLT will be defined as toxicities due to GSK3052230 or due to the combination of GSK3052230 with chemotherapy within Cycle 1 (first 21 days of period on study) that are unlikely to be due to another cause, such as the known effects of cytotoxics chemotherapy alone, disease progression, or accident, according to the criteria below:

- Grade 3 or 4 clinically significant non-hematological toxicity (excluding: Grade 3 nausea/vomiting or Grade 3 diarrhea that responds to optimal medical care within 3 days; Grade 3 infusion reactions that can be medically managed without the use of systemic pressors and allow completion of infusion.)
- Grade 4 neutropenia lasting more than 7 days
- Grade 4 febrile neutropenia
- Grade 4 thrombocytopenia (of any duration)
- Grade 4 clinically significant laboratory abnormalities with duration greater than 48hrs
- Treatment delay of 14 days or greater due to unresolved drug-related toxicity.
- Any grade 2 toxicity which in the judgement of the investigator and GSK medical monitor is considered a DLT

Clinically significant toxicities that persist or occur beyond Cycle 1 that the investigator and GSK medical monitor consider dose-limiting may also be designated a DLT for the purpose of establishing MTD.

#### **4.2.5. Maximum Tolerated Dose**

The MTD for the combination regimens will be defined as the highest dose level tested at which < 33% of subjects experience a DLT. Up to 30 subjects for each regimen may be treated at the MTD or at the highest dose evaluated if the MTD is not reached (this dose

will be described as the MFD). The dose recommended for Phase 2 studies will take into consideration toxicity and tolerability from all dose levels and treatment cycles.

#### **4.2.6. Intra-Subject Dose Escalation or Dose De-escalation**

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the higher dose level cohort from the 3+3 phase of the study has been cleared without a DLT, and after review of all safety data and approval by a GSK Medical Study Physician and discussion with the investigator. The subject on a lower dose level may be increased up to the highest dose level tested. In this case, the subject may begin dosing at the higher dose level as it will have already been demonstrated to be tolerable and monitoring will be performed as described in the protocol. For example, a subject who enrolled at a dose level below the MTD (or MFD) and may be eligible for dose increases if the investigator believes the subject could benefit.

##### **4.2.6.1. Alternative Dosing and Schedule Cohorts**

Additional doses and schedules may be explored based on emerging pharmacokinetic and safety data. Alterations may be made to the schedule of PK/PD sampling based on emerging PK data.

The sample size of the “alterative dosing and schedule cohorts” will be based on the 3 + 3 design with potential to expand to up to 30 subjects in this regimen.

The rationale for exploring this alterative dosing and/or schedule is to expand on the safety, tolerability and preliminary efficacy.

### **4.3. Rationale**

#### **4.3.1. Rationale for Evaluation of GSK3052230 in Chemotherapy Combinations**

*FGFR1* amplification has been associated with significantly shorter disease free and overall survival in NSCLC [Kim, 2013; Heist, 2012]. Carboplatin and paclitaxel can be used in first line therapy of NSCLC and docetaxel is a standard second line agent. Pemetrexed and cisplatin is the standard first line therapy for mesothelioma. Additive antitumor effect was demonstrated in tumor xenograft models treated with the combinations of GSK 3052230 and chemotherapy including paclitaxel and carboplatin as well as docetaxel. Malignant pleural mesothelioma (MPM) is a tumor type where FGF2 ligand overexpression has been observed in a high percentage of primary specimens and where GSK3052230 preclinical efficacy has been observed in xenograft models. Based on the clinical and preclinical data, the combination of GSK3052230 with chemotherapy will be investigated in patients with NSCLC or with mesothelioma.

#### **4.3.2. Rationale for Dose of GSK3052230**

The highest dose tested in the Phase 1 study FP1039-001 was 20 mg/kg. A maximum tolerated dose was not determined in the Phase 1 trial; the 20 mg/kg dose was determined to be safe and was declared the maximum feasible dose. This dose was not associated

with toxicity in rat and dog toxicity studies of 13 weeks duration. A 10 to 20 mg/kg dose is estimated to be the dose range needed to achieve clinical activity based on exposure/efficacy relationships in preclinical xenograft models. In these efficacy models, trough plasma levels of GSK3052230 associated with tumor growth inhibition of 54% to 69% ranged from approximately 0.2 to 23.3 µg/mL for preclinical doses of 1.3 mg/kg to 12.8 mg/kg. Levels within the upper part or above that range were achieved at clinical doses of GSK3052230 of 10 and 20 mg/kg. Weekly dosing is required to maintain levels within the expected range for activity, based on PK analysis from the completed Phase 1 study (GlaxoSmithKline Document Number [2013N160379\\_00](#)).

#### **4.3.3. Rationale for Endpoints**

Safety, tolerability and efficacy (ORR) are being assessed to address the primary objectives of the study. The safety assessments along with the PK will be important for determining the MTD (or MFD). The efficacy and pharmacodynamic assessments will further support the recommended phase II dose and expand the understanding regarding mechanism of action. Response rate stopping rules were determined separately for Arms A, B and C. In each case, the null hypothesis rate was determined using available literature and the alternative hypothesis rate constituted an improvement in therapy. Details of null and alternative hypothesis rates are provided in Section [12.3](#). Symptom assessments as measured by the LCSS and LCSS-meso were added to increase the understanding of the patient experience and perceptions.

### **4.4. Study Treatment Assignment**

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System).

### **4.5. Dosage and Administration of Study Treatments**

#### **4.5.1. GSK3052230**

Subjects in all arms will receive GSK3052230 administered as a 30-minute infusion once a week (Day 1, Day 8, and Day 15) of each 21-day cycle at the dosages specified in Section [4.2](#). Following infusion of GSK3052230, subjects should be observed for 1 hour prior to infusion of chemotherapeutic agents. If infusion reactions are noted, subjects should be treated with antiemetics, steroids, or antihistamines at the discretion of the investigator and premedication according to institutional standards before further infusions of GSK3052230 should be considered. Dose modifications should follow the guidelines in Section [4.7.4](#). Start and stop times of all infusions must be recorded.

##### **4.5.1.1. Study treatments: Alternative Dosing and Schedule cohorts**

Subjects in these expansion cohorts will be dosed based on the pharmacokinetic and safety data from the ongoing study. This will be determined at FGF117360 Study Investigator meetings (example: dose escalation meeting) and the minutes and

agreements would be provided to IRB/Ethics prior to dosing in this “Alternative Dosing and Schedule” Cohorts.

#### 4.5.2. Paclitaxel + Carboplatin

Subjects in Arm A will receive pre-treatment for paclitaxel and carboplatin according to institutional standards. Paclitaxel according to the dose level being investigated as described in [Table 3](#) will be administered intravenously over 3 hours (or according to local clinical standards) in a constant rate infusion on Day 1 of each 21 day treatment cycle immediately followed by i.v. carboplatin at a dose calculated for a target maximum AUC of AUC=6 as a 30 to 60 minute constant rate infusion (or according to local clinical standards). A total of 4 to 6 cycles of paclitaxel/carboplatin will be administered per local clinical practice.

Carboplatin will be dosed using the Calvert Formula [[Calvert](#), 1989]. This approach uses a mathematical formula, which is based on a subject’s pre-existing renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin. The formula calculates the dose based on a subject’s glomerular filtration rate (GFR in mL/min) as measured by Cr-EDTA clearance and carboplatin target area under the concentration versus time curve (AUC in mg/ml•min). With the Calvert formula, the total dose of carboplatin is expressed in mg, NOT mg/m<sup>2</sup>:

$$\text{Total Carboplatin Dose (mg)} = (\text{target AUC}) \times (\text{GFR}^1 + 25)$$

**<sup>1</sup>NOTE: The GFR used in the above Calvert formula to calculate AUC-based carboplatin dosing should not exceed 125 mL/min.** Therefore, the maximum carboplatin dose (mg) equals the target AUC (mg/ml•min) multiplied by 150 mL/min.

$$\text{Maximum Carboplatin Dose (mg)} = \text{target AUC (mg/ml•min)} \times (150 \text{ mL/min})$$

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is  $6 \times 150 = 900$  mg

For a target AUC = 5, the maximum dose is  $5 \times 150 = 750$  mg

For a target AUC = 4, the maximum dose is  $4 \times 150 = 600$  mg

The maximum target AUC explored in any cohort in this study is AUC=6. **Therefore, using the Calvert formula above, the maximum carboplatin dose in mg should not exceed 900 mg.**

The Cockcroft-Gault formula (see [Appendix 3](#)) can be used to calculate the creatinine clearance (CLCR), which can be substituted for the GFR in the Calvert formula.

Additional information, packaging, preparation and administration information can be found in the prescribing information for carboplatin [[Paraplatin](#) USPI, 2010].

Dose modifications should follow the guidelines in Section [4.7](#). Start and stop times of all infusions must be recorded.

#### 4.5.3. Docetaxel

Subjects in Arm B will receive pre-treatment for docetaxel according to institutional standards. Docetaxel will be administered according to the dose level being explored as described in [Table 4](#) as an i.v. infusion over 1 hour (or according to local clinical standards) on Day 1 of each 21 day cycle. The subject is treated until progression or until the subject has been determined to have received maximum benefit.

For additional formulation, packaging, preparation and administration information, please refer to the current product labeling (e.g. US package insert or product monograph) for country specific docetaxel dosing guidelines.

Dose modifications should follow the guidelines in Section [4.7](#). Start and stop times of all infusions must be recorded.

#### 4.5.4. Pemetrexed and Cisplatin

Subjects in Arm C will receive pre-treatment for pemetrexed and cisplatin according to institutional standards. Pemetrexed according to the dose level being investigated ([Table 5](#)) will be administered intravenously over 10 minutes (or according to local clinical standards) on Day 1 of each 21 day treatment cycle followed 30 minutes later by i.v. cisplatin infused over 2 hours.

Subjects will be hydrated and pre-medicated with folic acid and vitamin B12 supplements in order to reduce the incidence and severity of hematologic and gastrointestinal toxicities as well as cutaneous hypersensitivity reactions as per institutional guidelines.

Recommendations for pre-medication are as follows:

- 1-2 liters of fluid infused for 8-12 hours prior to cisplatin dose (or hydration per local standard)
- 350-1000 µg folic acid, once daily, by mouth for seven days preceding the first dose of pemetrexed, during treatment, and for 21 days following the last dose of pemetrexed
- 1000 µg vitamin B12 by intramuscular injection in the week preceding the first dose of pemetrexed and every three cycles thereafter (subsequent vitamin B12 injections may be given on the same day as pemetrexed)
- 4 mg dexamethasone (or equivalent), twice daily, by mouth the day before, the day of, and the day after pemetrexed administration

Additional information can be found in the prescribing information for pemetrexed [[Alimta Package Insert, 2004](#)] and cisplatin [[Platinol, 2010](#)]..

## 4.6. Safety Management Guidelines

### 4.6.1. Liver Chemistry Stopping Criteria

Specific liver dose modification and discontinue guidance for docetaxel is presented in [Table 8](#) (see Section [4.7.3](#)). For subjects who are not being treated with docetaxel, please follow the guidelines below.

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. Alanine aminotransferase (ALT)  $\geq 3$  times upper limit of normal (ULN) and bilirubin  $\geq 2$  times ULN (or ALT  $\geq 3$  times ULN and international normalization ratio [INR]  $> 1.5$ )

**NOTE:** Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

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

Subjects with ALT  $\geq 3$  times ULN **and**  $< 5$  times ULN **and** bilirubin  $< 2$  times ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. See following section for details on weekly follow-up procedures for these subjects.

#### 4.6.1.1. Liver Chemistry Follow-up Procedures

Refer to the diagram in [Appendix 5](#) for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section [4.6.1](#):

- Immediately and permanently withdraw the subject from study treatment.
- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.

- Complete the liver event electronic case report forms (eCRFs). If the event also meets the criteria of a serious adverse event (SAE) (see Section 8.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s).

**Safety Follow-Up Procedures for subjects with ALT  $\geq$ 3 times ULN:**

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

**Safety Follow-Up Procedures for subjects with ALT  $\geq$ 3 times ULN and bilirubin  $\geq$ 2 times ULN (or ALT  $\geq$ 3 times ULN and INR  $>$ 1.5):**

- **This event is considered an SAE** (see Section 8.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

**In addition, for all subjects with ALT  $\geq$ 3 times ULN, every attempt must be made to also obtain the following:**

- Viral hepatitis serology including:
  - Hepatitis A Immunoglobulin M (IgM) antibody.
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM).
  - Hepatitis C ribonucleic acid (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 2 weeks of last dose. 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 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 included in the SPM. A subject may be requested to provide 2 samples for PK analysis (4mL sample per compound)

if the samples are taken less than 2 days after the last dose of paclitaxel (Arm A) or docetaxel (Arm B).

- Serum creatine phosphokinase and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin  $\geq 2$  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, on the AE eCRF.
- Record use of concomitant medication(s), acetaminophen, herbal remedies, other over-the-counter medication(s), or putative hepatotoxins on the Concomitant Medications eCRF.
- Record alcohol use on the Liver Events eCRF.

The following are required for subjects with ALT  $\geq 3$  times ULN **and** bilirubin  $\geq 2$  times ULN 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 computed tomography [CT] scan) to evaluate liver disease.
- Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

#### **4.6.2. QTc Stopping Criteria**

If a subject meets the corrected QT (QTc)<sup>1</sup> interval duration criteria below following manual over-read of the ECG, study treatment(s) will be withheld.

- QT interval corrected for heart rate by Fridericia's formula (QTcF)  $> 530$  msec

<sup>1</sup>Based on average QTc value of triplicate electrocardiograms (ECGs) with manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment(s) withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment(s) if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment. Dose reduction should be considered if the signs or symptoms are indicative of a proarrhythmic potential.

For subjects recruited in France or the UK, please refer to [Appendix 7](#) for the country specific QTc stopping criteria.

#### **4.6.3. Left Ventricular Ejection Fraction (LVEF) and Valvular Toxicity Stopping Criteria**

##### **4.6.3.1. LVEF Stopping Criteria**

Echocardiography must be performed at Screening and at Cycle 4 visit as outlined in the Time and Events Table (Section 7.1). Subjects who have an asymptomatic, absolute decrease of >10% in left ventricular ejection fraction (LVEF) compared with baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue GSK3052230 and have a repeat evaluation of LVEF within 1 week. Echocardiogram (ECHO) should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to above institutional LLN and within 10% of baseline.

- If the LVEF recovers (defined as  $\geq$ LLN and absolute decrease  $\leq$ 10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK3052230 at a reduced dose. For such subjects, monitoring of LVEF will be performed 3 weeks after rechallenge, and every 3 weeks thereafter for 6 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK3052230 should be permanently discontinued. Ejection fraction should be monitored 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 GSK3052230. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Copies of all ECHOs and cardiology consultations performed on subjects who experience a >10% decrease in LVEF from baseline and whose cardiac ejection fraction is <institutional LLN may be required by GSK for review. Additionally, the decrease in LVEF is to be reported as an SAE. Instructions for submitting qualifying ECHOs may be found in the SPM.

##### **4.6.3.2. Cardiac Valve Toxicity Stopping Criteria**

Subjects who have a new asymptomatic, moderate regurgitation or stenosis by echocardiogram (ECHO) (Grade 2 mitral/tricuspid/aortic valvular toxicity per National Cancer Institute- Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.03) should temporarily discontinue GSK3052230 and have a repeat evaluation by ECHO within 1 week. Echocardiogram should be repeated every 1 to 2 weeks for 4 weeks or until valve recovery to baseline.

- If the valve recovers to baseline any time during the treatment cycle, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK3052230 at a reduced dose(s). For such subjects, monitoring of the valve via ECHO will then be performed 3 weeks after rechallenge, as clinically appropriate.

- If repeat ECHO does not reveal valve recovery to baseline within a treatment cycle, then the subject should permanently discontinue GSK3052230. The valve should continue to be monitored via ECHO every 3 weeks after rechallenge, as clinically appropriate, until resolution.

Subjects with a Grade 3 or 4 (symptomatic, severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention) valvular toxicity must discontinue GSK3052230. Valvular toxicity should continue to be monitored every 3 weeks, as clinically appropriate, until resolution.

ECHO must be performed at baseline and at Cycle 4. Copies of all ECHO(s) and cardiology consultations performed on subjects who experience valvular toxicity may be required by GSK for review. Additionally, the valvular toxicity is to be reported as an SAE. Instructions for submitting qualifying ECHOs are provided in the SPM.

#### **4.6.4. Management of Diarrhea**

Diarrhea was reported in 44% of subjects participating in Study FP1039-001. The majority of these events were CTC grade 1 (88%) and no events of severe diarrhea were reported. A baseline assessment of stool pattern is recommended in order to establish potential treatment emerging changes. Subjects should be instructed to immediately notify their physician/healthcare provider at onset of diarrhea and prompt investigation of potential causes should be initiated. When infectious causes have been excluded, anti-diarrheals (e.g. loperamide) should be considered. For recommended dose modifications, see Section 4.7.

#### **4.6.5. Management of Fluid Retention**

Fluid retention should be graded as outlined in [Table 6](#). No dose reduction is planned for fluid retention. Patients developing new onset or symptomatic edema or other signs of increasing fluid retention should be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below. Diuretic therapy may be initiated in the order listed at the discretion of the investigator:

- Spironolactone 50 mg by mouth (PO), once to three times daily.
- Furosemide 40 mg PO daily if not responsive to spironolactone.  
Potassium supplementation may be given as needed.
- If, after a trial of > 2 weeks, this is ineffective, treat with furosemide 20 mg PO daily plus metolazone 2.5 mg PO daily with potassium supplementation as needed.

Further therapy following fluid retention should be customized depending upon the clinical situation.

**Table 6      Grading and Management of Fluid Retention**

Severity Grading	Edema <sup>a</sup>	Effusion <sup>a</sup>
Mild (1)	Asymptomatic	Asymptomatic
Moderate (2)	Symptomatic	Symptomatic – intervention may be required
Severe (3)	Symptomatic – discontinue study drugs	Symptomatic – intervention required

a. Report the highest grade.

## 4.7.      Dose Modifications

The severity of adverse events (AEs) will be graded utilizing the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section. These include general guidelines based on the severity (CTCAE grade) of adverse events for GSK3052230 and key recommendations provided in the package insert for paclitaxel, carboplatin, and docetaxel [Taxol PI, 2011], [Paraplatin PI, 2010], [Taxotere PI, 2010].

### 4.7.1.      Dose Delays

Chemotherapy administration in all arms may be reduced or delayed for toxicity, or in the interest of subject safety per investigator discretion. Requirement for more than 2 dose reductions will result in permanent discontinuation of chemotherapy. If chemotherapy is discontinued due to toxicity, subjects may continue to receive GSK3052230 (Section 6.3).

### 4.7.2.      Hematologic Toxicity Related to Chemotherapy

Guidelines for management of hematologic toxicity attributed to chemotherapy are given in Table 7. For severe cytopenias (grade 4), frequent follow-up of hematology should be performed (at least every 3 days until improved to at least Grade 3) and supportive therapy including G-CSF (per ASCO guidelines) is encouraged. These are recommended reductions. Local guidelines for dose reductions may vary. Dose reductions that differ from the following table should be discussed with the GSK Study Physician

**Table 7      Chemotherapy Dose Delay and Modifications for Hematologic Toxicity**

Hematologic Toxicity		Modification Instructions
Absolute Neutrophil Count (ANC) Nadir	Platelets Nadir	
≥500 to <1500 mm <sup>3</sup> (or <500/mm <sup>3</sup> for <7 days and no neutropenic fever)	AND/OR ≥75,000 to <100,000/mm <sup>3</sup>	Withhold chemotherapy until ANC ≥1500/mm <sup>3</sup> and Platelets ≥ 100,000/mm <sup>3</sup> Restart treatment with no dose reductions If treatment must be held for more than 2 weeks, discuss potential retreatment or discontinuation with GSK Study Physician
<500/mm <sup>3</sup> for ≥7 days and no neutropenic fever OR Neutropenic fever		Withhold chemotherapy until ANC ≥1500/mm <sup>3</sup> and Platelets ≥ 100,000/mm <sup>3</sup> Arm A: Restart combination chemotherapy at dose levels reduced by 1 level for both agents according to <a href="#">Table 3</a> . Arm B: Restart docetaxel reduced by 1 level according to <a href="#">Table 4</a> Arm C: Restart combination chemotherapy reduced by 1 level for the chemotherapy dose according to <a href="#">Table 5</a> Note, 2 dose reductions are allowed in case of recurring toxicity. If neutropenic fever occurs prophylactic G-CSFs should be used with further chemotherapy treatment.

#### 4.7.3.      Non-hematologic Toxicity Related to Chemotherapy

Guidelines for management of non-hematologic toxicity attributed to chemotherapy are given in [Table 8](#).

**Table 8      Chemotherapy Dose Delay and Modifications for Non-hematologic Toxicity**

Adverse Event	Action
Non-hematological, Grade 1 or 2	Continue chemotherapy.
Non-hematological, drug-related Grade 3 or 4 (except alopecia)	Hold chemotherapy until recovery to Grade $\leq$ 1. Arm A: Restart at dose levels reduced by 1 level for both agents according to <a href="#">Table 3</a> . Arm B: Restart docetaxel reduced by 1 level according to <a href="#">Table 4</a> Arm C: Restart combination chemotherapy reduced by 1 level for the chemotherapy dose according to <a href="#">Table 5</a>
<b>Exceptions</b>	
Grade 3 or 4 hypersensitivity reactions	For Grade 3 hypersensitivity/infusion reactions that can be medically managed without the use of systemic pressors and allow completion of infusion, subjects are allowed to continue treatment at current dose with appropriate hypersensitivity prophylaxis. Grade 4: discontinue study treatment
Grade 2 neurotoxicity	<b>Arm C:</b> Withhold study treatment until recovery to Grade 1; then resume treatment with cisplatin reduced by 50% of previous dose
Grade 3 or 4 Neurotoxicity	Withhold study treatment until recovery to Grade 1; then resume treatment at dose reduced by 2 levels according to <a href="#">Table 3</a> (Arm A) or <a href="#">Table 4</a> (Arm B). Permanently discontinue chemotherapy in Arm C. If treatment delay is more than 2 weeks, re-initiation of treatment should be agreed with the GSK study physician.
Severe or cumulative cutaneous reaction (any Grades)	Hold until $\leq$ Grade 1 or to baseline and restart with reduction in dose by 1 level according to <a href="#">Table 3</a> (Arm A) or <a href="#">Table 4</a> (Arm B).
AST/ALT $>1.5 \times$ ULN <b>and</b> ALP $>2.5 \times$ ULN <sup>a</sup>	<b>Arm B:</b> Hold docetaxel. Monitor liver chemistries weekly. When recovered, docetaxel may be restarted reduced by 1 level according to <a href="#">Table 4</a> . Also consult Section <a href="#">4.6.1</a> for actions with GSK3052230
Bilirubin $>$ ULN	<b>Arm B:</b> Hold docetaxel. Monitor liver chemistries weekly. When recovered, docetaxel may be restarted reduced by 1 level according to <a href="#">Table 4</a> . Also consult Section <a href="#">4.6.1</a> for actions with GSK3052230
2.5x ULN $<$ AST/ALT $<$ 5xULN <b>and</b> 1 X ULN $<$ bilirubin $<$ 1.25 X ULN <sup>a</sup>	<b>Arm A:</b> At time of event, if the subject is dosing $>175 \text{ mg/m}^2$ of paclitaxel then dose reduce to $175 \text{ mg/m}^2$ ; if the subject is currently at $175 \text{ mg/m}^2$ then maintain the current dose level (remain at $175 \text{ mg/m}^2$ ). Also consult Section <a href="#">4.6.1</a> for actions with GSK3052230
2.5x ULN $<$ AST/ALT $<$ 5xULN <b>and</b> bilirubin 1.26-2.0 X ULN <sup>a</sup>	<b>Arm A:</b> Reduce paclitaxel to $135 \text{ mg/m}^2$ (or dose level below if already treated at this level). Also consult Section <a href="#">4.6.1</a> for actions with GSK3052230
2.5x ULN $<$ AST/ALT $<$ 3xULN <b>and</b> bilirubin 2.01-5.0 X ULN <sup>a</sup>	<b>Arm A:</b> Reduce paclitaxel to $90 \text{ mg/m}^2$ . If this is the second dose reduction required for liver toxicity, discontinue treatment. Also consult Section <a href="#">4.6.1</a> for actions with GSK3052230
AST/ALT $>$ 3 X ULN <b>and</b> bilirubin 2.01-5.0 X ULN <sup>a</sup>	<b>Arm A:</b> This requires discontinuation of GSK3052230 and, hence, discontinuation from study after appropriate safety follow up.
Mucositis, Grade 3 or 4	<b>Arm C:</b> Reduce pemetrexed only by 50% of previous dose
Serum creatinine $>1.5 \text{ mg/100mL}$ or BUN $>25\text{mg/100mL}$	<b>Arm C:</b> Hold chemotherapy until serum creatinine $<1.5 \text{ mg/100mL}$ or BUN $<25\text{mg/100mL}$
Creatinine clearance $<45 \text{ mL/min}$	<b>Arm C:</b> Hold chemotherapy until creatinine clearance $\geq 45 \text{ mL/min}$

a. Day 1 value to be used in determining elevation. Note that dose reductions for liver toxicity are permanent. Liver chemistry following-up procedures see Section [4.6.1.1](#).

#### 4.7.4. GSK3052230 Dose Modifications

For toxicities at least possibly related to GSK3052230, dosing may be interrupted or delayed up to 14 days. Approval from the GSK Study Physician is required to restart a dose after 14 days of dose interruption.

If necessary, 5 mg will be the minimum dose level. Following a dose reduction and resolution of toxicity to baseline levels, individual subjects may be re-escalated to a higher dose level with the approval of the GSK Study Physician.

Guidelines for dose modifications are outlined in [Table 9](#).

**Table 9 GSK3052230 Dose Modification Guidelines**

Grade	Action
Grade 1 drug related event	No delay or modification
Grade 2 drug related event	May hold until reduced to Grade 1 or baseline at the discretion of the investigator, no dose reduction.
Grade 3 or higher drug related event (except Grade 3 nausea that resolves with clinical intervention)	Hold until Grade 1 or baseline, dose reduce 50%

If the toxicity is potentially related to both GSK3052230 and chemotherapy as given in all arms, please refer to dose modification for chemotherapy in Section [4.7.2](#) and Section [4.7.3](#) for potential dose reduction of both study treatments.

Subjects who experience a toxicity related to GSK3052230 that precludes further treatment with GSK3052230 will be withdrawn from the study treatment.

##### 4.7.4.1. GSK3052230 Dose Modifications regarding infusion related reactions

Subjects should be closely monitored for GSK3052230 infusion-related reactions. All subjects who have experienced an infusion reaction due to GSK3052230 (and not chemotherapy) should have GSK3052230 infused over 60 minutes instead of 30 minutes and pre-treated with appropriate local institutional pre-treatment guidelines (example: medications such as steroids, antihistamines, acetaminophen, H-2 antagonists, and antiemetics, according to local pre-treatment guidelines). If the subject continues to have a reaction on re-challenge, the infusion of GSK3052230 may be prolonged to 90 minutes. Epinephrine for subcutaneous injection, diphenhydramine for IV injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions should be quickly available during subject infusions.

## 5. INVESTIGATIONAL PRODUCT

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

Refer to the SPM (the FGF117360 Pharmacy Manual) for additional details on investigational product procedures.

### 5.1. Description of Investigational Products

#### 5.1.1. GSK3052230

Product name :	<b>GSK3052230, 12.8 mg/mL</b>
Formulation description:	The product is formulated in 0.94 mg/mL sodium phosphate monobasic, 1.9 mg/mL sodium phosphate dibasic, 8.8 mg/mL sodium chloride, 0.2 mg/mL polysorbate 80, pH 7.0 at a GSK3052230 (HGS1036) concentration of 12.8 mg/mL. GSK3052230 contains no preservative.
Dosage form:	Solution for infusion
Unit dose strength(s)/Dose Level(s):	20 mg/kg 15 mg/kg 10 mg/kg 5 mg/kg
Physical Description:	The drug product is a clear to opalescent, colorless to pale yellow solution that may contain small amounts of translucent to white proteinaceous particles.
Route/ Administration/ Duration:	Intravenous infusion once weekly (Day 1, Day 8, Day 15) in each 21-day cycle administered using a 0.2 µm in-line filter
Dosing instructions:	Administer as a 30 minute infusion
Manufacturer:	GSK

GSK3052230 will be provided to sites by GSK. GSK3052230 is supplied in a sterile 25 mL glass vial. Each vial is intended for single use. The deliverable volume per vial is 20 mL. The contents of the label will be in accordance with all applicable regulatory requirements.

#### 5.1.2. Chemotherapeutic Agents

Paclitaxel, carboplatin, docetaxel, pemetrexed, and cisplatin will be sourced locally from commercial stock, except in countries where Regulatory Authorities mandate that the Sponsor must supply all non-investigational product (IPs) required for study participation. Investigators are responsible for ensuring that subjects receive supplies of paclitaxel, carboplatin, docetaxel, pemetrexed, and cisplatin for the entire duration of the study, as appropriate. The contents of the label will be in accordance with all applicable regulatory requirements.

## **5.2. Preparation/Handling/Storage of GSK3052230**

### ***Preparation***

Using aseptic techniques, GSK3052230 will be diluted in a 250 mL (nominal volume) i.v. bag containing either 5% dextrose solution or normal saline. GSK3052230 is stable after dilution in 5% dextrose solution or normal saline for up to 8 hours at ambient temperature (~25°C). GSK3052230 infusion must be completed within 8 hours of the dilution. Please refer to SPM for recommended IV supplies.

### ***Handling***

Under normal conditions of handling and administration, IP 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 site staff if required by local laws or will otherwise be available from GSK upon request.

Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists.

In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Refer to the SPM (the FGF117360 Pharmacy Manual) for detailed procedures for the disposal and/or return of unused study treatment(s).

### ***Storage***

Access to and administration of the GSK3052230 will be limited to the investigator and authorized site staff. GSK3052230 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. Refer to the SPM (the FGF117360 Pharmacy Manual) for storage conditions.

## **5.3. 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 IP dispensed and/or administered to 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 (the FGF117360 Pharmacy Manual) for further detailed instructions on product accountability.

## **5.4. Treatment Compliance**

GSK3052230 and chemotherapy will be intravenously administered to subjects at the study site. Administration will be documented in the source documents and reported in the eCRF.

## 5.5. Treatment of Study Treatment Overdose

In the event of an overdose (defined as administration of more than the protocol-specified dose) of GSK3052230, the investigator should:

- contact the GSK Medical Monitor immediately
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK3052230 can no longer be detected systemically (at least 14 days)
- obtain a plasma sample for PK analysis if requested by the GSK Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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.

In the event of an overdose of chemotherapy agents, please consult product label as well as following the above procedures.

## 6. COMPLETION OR WITHDRAWAL OF SUBJECTS

### 6.1. Screen Failures

Data for screen failures will be collected in source documentation at the site. Subjects who did not meet all eligibility requirements but whose tumor tissue was tested for *FGFR1* amplification by the central laboratory will be entered to the Assay Validation Population.

### 6.2. Subject Completion Criteria

A completed subject is one who has discontinued study treatment for reasons listed in Section 6.3 and completed the follow-up visit 30 days after last dose, or has died while on study.

### 6.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 4.6.1. In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion (which may include safety, behavioral or administrative reasons)

- a dose delay of >14 days unless the investigator or GSK Medical Monitor agree that further treatment may benefit the subject
- intercurrent illness that prevents further administration of study treatment(s)
- termination of the study by Sponsor
- Subject is lost to follow-up.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

Subjects who permanently discontinue chemotherapy may continue GSK3052230 until meeting one of the reasons for discontinuation stated above. The primary reason each study treatment was discontinued must be documented in the medical record and on the eCRF. The reason for discontinuing GSK3052230 may differ from the reason chemotherapy was discontinued.

If the subject voluntarily discontinues from treatment due to toxicity, 'adverse event (AE)' will be recorded as the primary reason for permanently discontinuation on the eCRF.

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

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Table (see Section 7.1).

#### **6.4. Study Completion**

The study will be considered completed when at least 80% of subjects have completed the study. Upon completion of the study, if subjects are still continuing to receive benefit from GSK3052230, plans will be developed to provide continued access to GSK3052230 for those subjects.

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit.

#### **6.5. Treatment after the End of the Study**

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

### **7. STUDY ASSESSMENTS AND PROCEDURES**

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

The timing of each assessment is listed in the Time and Events Table (Section 7.1). The timing and number of the planned samples may be altered to a minor extent (no more than 1 to 3 additional samples) during the course of the study based on newly available data (e.g. to obtain samples closer to the time of peak plasma concentrations). The change in timing or addition of time points for any of the planned samples must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee will be informed of any safety issues that require alteration of the safety monitoring scheme. Specific blood volumes for analysis will be specified in the SPM.

Whenever vital signs, 12-lead electrocardiograms (ECGs) and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SPM.

## **7.1. Time and Events Table**

This section consists of the Time and Events Table to describe assessment windows and sequencing of study-specific assessments and procedures.

**Table 10 Time and Events Schedule**

Time and Events Schedule for FGF117360		Screen	Cycle 1			Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U
			D1	D8	D15	D1	D8	D15	D1	D8	D15			
Visit Window	Once the subject provides consent, a tumor sample may be submitted for Arms A and B for FGFR1 amplification at any time (there is no time limit or window). All other screening assessments should be conducted within 30 days of C1D1. Visit windows of $\pm 2$ days during study through EOT, +7 days for F/U. For Arm A subjects who wish to start chemotherapy prior to GSK3052230 screening period is 30 days +3 to allow baseline imaging scans to be performed prior to chemotherapy but within 30 +3 days of GSK3052230 first dose.													
Informed consent	Main study and PGx optional consent; register subject	X												
Medical History,	Medical history, review of inclusion & exclusion criteria	X												
Physical exam and height (baseline only)	Not needed C1D1 if screening assessments within prior 72 hrs. Complete physical exam at screening. Abbreviated disease-oriented physical exam subsequently.	X	X			X			X				X	X
Weight	Note, during dosing period weight should be captured on Day 1 of each cycle. It can be obtained more frequently per institutional standards (example: if required at each infusion)	X	X			X			X				X	X
Ophthalmologic Exam	To be performed by ophthalmologist or qualified optometrist. (Visit windows of $\pm 7$ days post baseline).	X											C4 only	
ECHO	Perform at EOT if subject discontinues prior to C4. Visit windows of $\pm 7$ days post baseline.	X											C4 only	early disc
ECOG PS	Obtain prior to infusion	X				X			X					X
Vital Signs	Within 20 min before start of first chemotherapy infusion and within 20 min before start of GSK3052230 infusion.	X	X			X			X					
Forced Vital Capacity	Assess D1 of every odd cycle, Arm C only, Visit windows of $\pm 7$ days post baseline.	X	X						Odd X					
Hematology and Chemistry	Not needed C1D1 if screening assessments within prior 72 hrs. See Table 12 for analytes. In	X	X	X	X	X	X		X	A only			X	

Time and Events Schedule for FGF117360		Screen	Cycle 1			Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U
			D1	D8	D15	D1	D8	D15	D1	D8	D15			
	addition Arm A: D8 of additional cycles while receiving paclitaxel + carboplatin only													
Coagulation and pancreatic markers	See <a href="#">Table 12</a> for analytes	X										X	X	
Thyroid	TSH at Screening.	X	TSH every 2 cycles for the first year and then every 4 cycles. If TSH is positive, then test total T3, total T4, and free T4.											
Pregnancy	serum test +7 days of first dose; urine or serum test onward	X											X	
Urinalysis	Obtain prior to infusion of GSK3052230 on C1D1	X	X									X	X	
ECG (single read)	Prior to GSK3052230 infusion and 1 hr ( $\pm 10$ min) after end of GSK3052230 i.v. on C1D1. Prior to GSK3052230 i.v. onward	X	X	X		X			As clinically indicated			X	X	
Pharmacokinetics	See <a href="#">Table 11</a>		X	X		X			X			X	X	
Immunogenicity	Obtain prior to infusion of GSK3052230		X		X				D1 of every 2 cycle, C4 to C15				X	
Archival Tumor Tissue	Archived tumor tissue (or fresh biopsy if no archival tissue). Once the subject provides consent, a tumor sample may be submitted for Arms A and B for FGFR1 amplification at any time (there is no time limit or window).	X												
Circulating cell-free DNA Sample	Predose. First sample +7 days prior to C1D1			X									X	
Circulating Biomarkers	Plasma sample collected predose (+7 days prior to C1D1)			X			X		Arm C: D1 every cycle ( $\pm 1$ week) for 1 year, then D1 every 2 cycles ( $\pm 2$ weeks)				X	
Blood sample for PGx	Collect any time on study but only if PGx informed consent has been signed; preferred on C1D1 after dosing.			X										
Brain Scan	Obtain only if symptomatic	X	every 12 weeks $\pm 1$ week if positive at Screening, or as clinically indicated											
Bone Scan		X	As clinically indicated											

Time and Events Schedule for FGF117360		Screen	Cycle 1			Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U
			D1	D8	D15	D1	D8	D15	D1	D8	D15			
Radiologic and Disease Assessment	CT scan, PET-CT scan or MRI. Imaging modality consistent during study and not change	X							Every 2 cycles ( $\pm 1$ week) for 1 year; thereafter every 4 cycles ( $\pm 2$ week)			X		
LCSS (Arms A and B); LCSS-meso (Arm C)	Must be administered first before any other tests or procedures. Study staff should check for completeness.	X	X			X			X				X	X
GSK3052230	30 minute infusion.		X	X	X	X	X	X	X	X	X			
ARM A: Paclitaxel + Carboplatin	GSK3052230 infused & observed 1 hr prior to chemotherapy doses. May start chemotherapy during screening period, see inclusion #2				X				X					
ARM B: Docetaxel	GSK3052230 infused & observed 1 hr prior to chemotherapy infusions.			X		X			X					
ARM C: Pemetrexed + Cisplatin	GSK3052230 infused & observed 1 hr prior to chemotherapy infusions.			X		X			X					
Adverse Event Assessment		X	Continuous monitoring during study											
Concomitant Medications		X	Continuous monitoring during study											

**Table 11 Pharmacokinetic Sampling Schedule**

FGF117360 Pharmacokinetic Sampling Schedule			Limited PK	Extensive PK	Extensive PK	Extensive PK
Time	When	Window		n=20pts in each arm	Arm A	Arm B
Cycle 1 Day 1	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230		GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	1hr after end of infusion of GSK3052230	±10 min but after ECG		GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	2hr after end of infusion of GSK3052230 or end of docetaxel infusion	±10 min or up to 5 min prior to end of docetaxel infusion		GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230		GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
Cycle 1 Day 8	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230		GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	1 hr after start of paclitaxel infusion or end of docetaxel or pemetrexed infusion	±10 min for paclitaxel or up to 5 min prior to end of docetaxel infusion or up to 1 min prior to end of pemetrexed infusion		GSK3052230 PK Paclitaxel PK	GSK3052230 PK Docetaxel PK	GSK3052230 PK Pemetrexed PK Cisplatin PK
	1 hr after end of pemetrexed infusion	± 20 min				Pemetrexed PK Cisplatin PK
	End of paclitaxel infusion or 2 hr after end of docetaxel or pemetrexed infusion	up to 5 min prior to end of paclitaxel infusion or ± 20 min for docetaxel and pemetrexed		Paclitaxel PK	Docetaxel PK	Pemetrexed PK Cisplatin PK
Cycle 2 Day 1	2 hr after end of paclitaxel infusion or 5 hr after end of docetaxel or pemetrexed infusion	±30 min		(selected sites) GSK3052230 PK Paclitaxel PK	(selected sites) GSK3052230 PK Docetaxel PK	(selected sites) GSK3052230 PK Pemetrexed PK Cisplatin PK

FGF117360 Pharmacokinetic Sampling Schedule			Limited PK	Extensive PK	Extensive PK	Extensive PK
Time	When	Window		Arm A	Arm B	Arm C
Cycle 4 Day 1						
Cycle 6 Day 1						
Cycle 12 Day 1	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
Cycle 4 Day 1						
Cycle 6 Day 1						
Cycle 12 Day 1	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
EOT			GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
30 days FU		At time of immunogenicity sample	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK

All subjects will have PK sampling performed (either Limited PK or Extensive PK). Serial PK samples will be performed on at least the first 10 subjects in Arm A and B with at least 6 subjects having serial PK at the MTD/MFD. For Arm C, at least 6 subjects will have serial PK sampling. After an adequate PK profile data has been achieved, the remaining subjects will participate in the population PK sampling. Depending on emerging data, the timing of PK samples may change and PK samples may not be required from every subject in the study.

## 7.2. Demographic/Medical History and Baseline Assessments

The following demographic parameters will be captured during Screening: date of birth, gender, race and ethnicity.

Medical/medication history assessed as related to the eligibility criteria listed in Section 3.2.

Baseline (Screening) assessments obtained will include:

- Complete physical examination, including height (in cm) and weight (in kg).
- Vital signs (i.e., blood pressure, temperature, respiratory rate, pulse rate)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Clinical laboratory tests: hematology, clinical chemistry [and urinalysis]
- Serum beta-human chorionic gonadotropin ( $\beta$ -HCG) pregnancy test for female subjects of childbearing potential only
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO)
- LCSS for Arms A & B
- For Arm C only: LCSS (meso) and forced vital capacity
- Review of concomitant medications

Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for Screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the timeframe of the study.

### 7.2.1. Critical Baseline Assessments

Ophthalmologic examination, ocular, and cardiovascular medical history/risk factors will be assessed at baseline.

Assessment regarding deregulation of FGF signaling pathway (e.g. FGFR gene amplification, FGF ligand overexpression, etc) is required during screening. Archival tissue may be used for this analysis. If archival tissue is not available, a fresh biopsy will be required. This will be assessed by a central laboratory for Arms A and B.

For Arm C, forced vital capacity will be assessed at screening.

## 7.3. Safety Evaluations

Planned time points for all safety assessments are provided in the Time and Events Table (Section 7.1).

### **7.3.1. Physical Examinations**

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities. Height and weight will also be measured and recorded.

A brief physical examination will include assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).

### **7.3.2. ECOG Performance Status**

The performance status will be assessed using the ECOG scale (see [Appendix 4](#)) as specified in the Time and Events Table (Section [7.1](#)).

### **7.3.3. Vital Signs**

Vital sign measurements will include systolic and diastolic blood pressure, temperature, respiration rate and pulse rate. All vital sign measurements will be obtained after the subject has rested for at least 5 minutes in a semi-supine position. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Whenever blood pressure and heart rate are measured at the same nominal time as a blood draw, the blood pressure and heart rate will be prior to the blood draw. Refer to the SPM for details regarding measurement of vital signs.

### **7.3.4. Forced Vital Capacity**

Forced vital capacity will be measured in Arm C at each scheduled disease assessment using standard methods (Refer to the SPM for details)

### **7.3.5. Electrocardiogram**

Single 12-lead ECGs will be obtained at designated time points during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5 minute rest and is in a semi-recumbent position.

The QT interval should be corrected for heart rate by Fridericia's formula (QTcF). Additional QTc readings may be necessary.

Refer to the SPM for details regarding ECG procedures.

### **7.3.6. Echocardiogram**

ECHOs will be performed at baseline to assess cardiac ejection fraction and cardiac valve morphology for the purpose of study eligibility and Cycle 4, as specified in the Time and Events Table (Section [7.1](#)). Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an

evaluation for left ventricular ejection fraction (LVEF) and both right and left-sided valvular lesions.

Copies of all ECHOs performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF <lower limit of normal (LLN), or who experience valvular toxicity, may be required by GSK for review.

### **7.3.7. Ophthalmologic Examinations**

An ophthalmologic exam will be performed at baseline and at Cycle 4 (or as clinically appropriate), as specified in the Time and Events Table (Section 7.1). These exams will be performed by an ophthalmologist or qualified optometrist and includes a slit-lamp examination and intraocular pressure. During the study, ophthalmologic assessments performed by the investigator will include inspection of the external eye to assess for redness and query of subjects for symptoms of photophobia, vision problems, or eye pain. If at any time the subject complains of photophobia, changes in vision, or eye pain; the ophthalmic examination finding are abnormal; or visual acuity has worsened by 3 lines or more since the start of the study, the subject will be referred for a formal evaluation, including a slit-lamp examination and intraocular pressure, by a qualified ophthalmologist.

### **7.3.8. Laboratory Assessments**

All protocol required laboratory assessments, as defined in (Table 12) should be performed according to the Time and Events Table (Section 7.1). Details for the preparation and shipment of samples to the central laboratory will be provided in the SPM.

Prior to administration of the first dose of study treatment, results of laboratory assessments should be reviewed. Any laboratory test with a value outside the normal range may be repeated (prior to the first dose) at the discretion of the investigator.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinical significant by the investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All laboratory tests with values that are significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

**Table 12 List of Clinical Laboratory Tests**

<b>Hematology</b>	
Platelet Count	<i>Automated WBC Differential:</i>
Red blood cell (RBC) Count	Neutrophils (absolute)
White blood cell (WBC) Count (absolute)	Lymphocytes (absolute)
Hemoglobin	Monocytes (absolute)
	Eosinophils (absolute)
	Basophils (absolute)
<b>Clinical Chemistry</b>	
Potassium, Sodium, Chloride, Total carbon dioxide, total Calcium, ionized calcium*, magnesium, phosphate, albumin, glucose (fasting),	
Blood urea nitrogen (BUN), Creatinine, Uric Acid, creatinine clearance	
Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT), Alkaline phosphatase, Total bilirubin (if elevated also test direct bilirubin)	
Thyroid hormone: TSH at Screening; every 2 cycles for the first year and then every 4 cycles. If TSH is positive, also test total T3, total T4, and free T4.	
Pancreatic tests (amylase and lipase)	
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)	
<b>Routine Urinalysis</b>	
pH, glucose, protein, blood and ketones by dipstick	
Microscopic examination (if blood or protein is abnormal)	
<b>Other screening tests</b>	
Pregnancy test for females (serum at screening, urine or serum post dose)	
*Ionized calcium collected may not be collected in some selected sites and only total calcium is collected for subjects regarding safety monitoring.	

### 7.3.9. Pregnancy Testing and Reporting

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum  $\beta$ -HCG pregnancy test performed within 7 days prior to the first dose of study treatments. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described in Section 10.1 during the study until 6 months following the last dose of chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest.

Any pregnancy that occurs during study participation (note, study participation is defined as the time of the first dose of study drug GSK3052230 is administered) 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 up 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 an 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(s), must be promptly reported to GSK.

## 7.4. Evaluation of Anti-Cancer Activity

Disease assessment will include imaging (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI]) as appropriate for the specific tumor type. Disease assessment will be completed within 30 days prior to the first dose of GSK3052230, then every other treatment cycle for the first year. Subsequent assessments will follow the Time and Events Table (Section 7.1), which also should be consulted for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of  $\pm 7$  days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 2 cycles or a maximum of 8 weeks prior to the subject's withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

Disease progression and response evaluations will be determined according to the definitions established in RECIST 1.1 [Eisenhauer, 2009]. Subjects whose disease responds (either complete response [CR] or partial response [PR]) should have a confirmatory disease assessment performed no earlier than 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator. Please see Section 7.4.1.5 for the evaluation of best overall response. To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same technique will be used when assessing response.

Disease response will also be quantified by change in volume to support the exploratory objectives. Comparison between RECIST evaluations, linear tumor dimensions, and variations in tumor volume will be performed [O'Connor, 2008].

Inclusion of up to three pre-study tumor imaging scans performed prior to baseline scans at study entry will also be encouraged in subjects whose scans are available for review. Prior tumor imaging scans will be analyzed (see SPM for additional details) and quantitative tumor data (e.g., tumor measurements, tumor volumes) will be generated. Depending on data availability, the slope of tumor growth prior to study entry and following treatment may be calculated and compared in an exploratory analysis. Such comparisons may be important in evaluation of the clinical significance of subjects achieving a clinical response, particularly in those subjects achieving SD.

Research sites will be trained in volumetric analysis using a standardized review platform. Depending on the outcome of site based assessments, images may be collected centrally for further analysis.

Please see the SPM for specific guidelines for CT and MRI acquisitions and analysis.

**CT:** For contrast enhanced CT, contiguous slices (no gap) may be no greater than 5mm. However, 3mm slice thickness or less is strongly preferred for volume analysis. MRI is

acceptable, but when used, scanning should be optimized for the evaluation of the type and site of disease and must be measured in a consistent anatomic plane for each timepoint. Whenever possible, the same scanner should be used [Eisenhauer, 2009].

For Arms A and B, RECIST 1.1 analysis, the minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. The Image Acquisition Guidelines portion of the SPM should be consulted for additional details on imaging protocols.

For Arm C, modified RECIST will be used. Tumor thickness perpendicular to the chest wall or mediastinum will be measured in two positions at three separate levels on thoracic CT scans. The sum of the six measurements defines a pleural unidimensional measure. Bidimensionally measureable lesions will be measured unidimensionally as for RECIST 1.1. All measurements were added to obtain the total tumor measurement. The Image Acquisition Guidelines portion of the SPM should be consulted for additional details on imaging protocols.

**Brain Scan:** In subjects with known brain metastases (criteria outlined in Section 3.2), a contrast-enhanced MRI (preferred) or CT of the brain must be obtained within 30 days prior to receiving the first dose of the study medication. Assessment of brain metastases must be repeated as part of the regular assessment of target and non target lesions, and the same imaging method should be used.

In subjects with no history of brain metastases at baseline and no clinical signs or symptoms indicative of the presence of brain metastases, no baseline MRI or CT of the brain is necessary, nor is any routine brain imaging necessary. MRI or CT of the brain will be required in case of new clinical signs and symptoms indicative of brain metastases.

**Bone Scan:** Including evaluation of skull, total spine, clavicle, ribs, pelvis and long bones. Other imaging modalities are allowed such as PET or MRI.

If a subject's bone-scan lesions are consistent with tumor metastases, or are consistent with non-malignant lesions, confirmatory imaging assessments are not necessary. The anatomic sites and nature of the lesions must be documented in the eCRF.

If bone scan lesions are equivocal for tumor metastases, a confirmatory imaging assessment must be performed using X-ray, CT, or MRI to determine the nature of the lesions. The lesion sites and nature of lesions must be documented in the eCRF. For lesions that are confirmed as tumor metastases, the same imaging modality must be used for all subsequent follow-up bone lesion assessments.

**Volumetric Analysis:** Retrospective evaluation of tumor volumes will also be performed in subjects with sufficient CT or MRI imaging data. Comparison between RECIST evaluations, linear tumor dimensions, and variations in tumor volume will be performed [O'Connor, 2008].

### 7.4.1. Evaluation of Response in Arm A and Arm B (RECIST 1.1)

#### 7.4.1.1. Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- **Not Applicable (NA):** No target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the five preceding definitions.

#### NOTE:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

#### 7.4.1.2. Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- **Complete Response (CR):** The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g. <10 mm short axis).
- **Non-CR/Non-PD:** The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline  $\geq 10$  mm short axis.
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.
- **Not Applicable (NA):** No non-target lesions at baseline.
- **Not Evaluable (NE):** Cannot be classified by one of the four preceding definitions.

#### NOTE:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of non-target lesions, which are not assessed at a particular time point based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

#### 7.4.1.3. New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

#### 7.4.1.4. Evaluation of overall response

**Table 13** presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

**Table 13      Evaluation of Overall Response for Subjects with Measurable Disease at Baseline**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

#### **NOTE:**

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

#### **Confirmation Criteria:**

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than four weeks (28 days) after the criteria for response are first met.

#### **7.4.1.5.      Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the response assessment at each time point.

- To be assigned a status of SD, the post-baseline disease assessment must have met the SD criteria no less than 10 weeks (per Time and Events schedule Section 7.1).
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

## **Tips on Lymph Node Measurements:**

Lymph nodes are considered as a separate organ to measure, and up to two lymph nodes can be measured per patient by RECIST v1.1. For unidimensional lymph node measurements, use the short axis of the lymph node at baseline and then at every followup scan. To be considered as pathologically enlarged and measurable at baseline, the lymph node short axis diameter should be  $\geq 15$  mm.

### **7.4.2. Evaluation of Response in Arm C: Mesothelioma**

#### **7.4.2.1. Mesothelioma Tumor Imaging**

Clinical trials of therapeutic agents in MPM may be compromised by inaccuracy of tumor measurements due to the unique pattern of growth of mesothelioma [Byrne, 2004; Tsao, 2011]. Malignant mesothelioma commonly grows as a rind and thus may not produce spherical lesions with bidimensional, measurable diameters [Byrne, 2004]. Modification of RECIST criteria have been recommended to address the difficulties in measurement of lesions [Byrne, 2004; Tsao, 2011]. In subjects with mesothelioma, it is requested that disease assessments using both RECIST v1.1 criteria AND modified RECIST criteria be performed.

Uni-dimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites at 3 different levels on the CT scan. Transverse cuts used for measurement must be at least 1 cm apart, and related to anatomical landmarks in the thorax, preferably above the level of division of the main bronchi. At reassessment, pleural thickness must be measured at the same position and level. Nodal, subcutaneous, and other bidimensionally measurable lesions are measured unidimensionally as per the RECIST v1.1 criteria. Unidimensional measurements are added to produce the total tumor measurements (e.g., the sum of 6 pleural thickness measurements = one univariate diameter).

Overall tips for measurement of mesothelioma by modified RECIST [Tsao, 2011]:

1. Larger lesions are easier and more accurate to measure. Choose the larger or thickest of the pleural disease to measure. Magnifying the image may make an easier measurement.
2. The short-axis diameter is defined as the shortest pathway from the tip of the tumor to the chest wall.
3. Ensure that that differentiation of normal chest wall from tumor is easy at the point of measurement
4. To ensure accuracy, all measurements must be performed electronically in the same window setting on consecutive studies. It is recommended that the “soft tissue” setting (not lung windows) be used, as it enables accurate pleural mass measurements with the electronic calipers and avoids the incorporation of chest wall or mediastinal fat within the calculations.

5. CT scan slices up to 5 mm can be used, but for greater accuracy, thinner slices such as 2.5 mm are preferable. Ideally, all subsequent CT scans should use the same slice thickness.
6. To limit interobserver variability, in measuring tumor response, it is preferred that the same clinician measure the tumors at baseline and on all subsequent CT scans.
7. The pleural disease to be measured should have a short-axis diameter of at least 1 cm, as lesions less than 1 cm are considered nonmeasurable.
8. To obtain the short axis of the disease, with electronic calipers, measure the distance between the point where the tumor abuts the chest or the mediastinal border and the point where the pleural disease touches the lung. The shortest route possible is the one perpendicular to the chest wall/mediastinum.
9. Avoid measuring regions where the tumor infiltration obscures the interface of tumor to normal tissue. A good interface for measurement usually is one where the tumor abuts fat or an intact rib/vertebral body, as the density of the pleural tumor differs significantly from bone or fat and the difference can be easily observed. Avoid choosing an interface of tumor with muscle, as muscle and tumor have similar CT densities and are often difficult to distinguish when they abut one another.
10. Following the instructions in #5, choose three different axial slices, preferably above the level of the main bronchi and record two measurements per slice, thus resulting in six separate measurements.
11. If any nodal, subcutaneous or other bidimensionally measurable lesions are available, they should undergo unidimensional measurements by RECIST v1.1 and be added to the total obtained in #7 above.

#### **7.4.2.2. Prior Scan collection**

Collection of up to three prior tumor imaging scans performed prior to baseline scans at study entry will also be encouraged in subjects whose scans are available for review. These scans may be collected and sent to an independent radiologist for review. The slope of tumor growth prior to study entry and following treatment may be compared in subsequent analyses. Such comparisons may be important in evaluation of the clinical significance of subjects achieving a clinical response, particularly in those subjects achieving SD.

#### **7.4.3. Patient Reported Outcomes**

The Lung Cancer Symptom Scale (LCSS) or the Lung Cancer Symptom Scale-mesothelioma (LCSS-meso) will be self-administered by subjects (patient scales) and completed by the investigator (observer scales) as indicated in the Time and Events schedule ([Table 10](#)). The LCSS consists of 9 patient-reported items and 6 observer reported items, the LCSS-meso consists of 8 patient-reported items, and are validated in lung cancer and in mesothelioma patients [[Hollen, 2006](#)]. Using visual analogue scales (range from 0 to 100), the patient scale measures the intensity of patient responses for appetite, fatigue, cough, dyspnea, hemoptysis, pain, and summary items symptoms of lung cancer, activity level and quality of life. An example questionnaire can be found in the SPM. The LCSS and LCSS-meso was chosen because of its focus on disease-related

symptoms, the possibility to combine the patient's perception with the investigator's contextual knowledge, its demonstrated concept and content validity, ease of application and minimal burden to patients.

It is important that the LCSS and LCSS-meso patient scale is administered at the start of the clinic visit before any other study assessments are performed.

## **7.5. Pharmacokinetics**

### **7.5.1. Blood Sample Collection for Pharmacokinetics**

Blood samples of approximately 4 mL for PK analysis of GSK3052230 will be collected at the time points indicated in the Time and Events Schedule (Section 7.1). For subjects in Arm A, a 4mL blood sample for PK analysis of paclitaxel may be collected and subjects in Arm B, a 4mL blood sample for PK analysis of docetaxel may be collected (see Section 7.1). Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

The timing and frequency of the PK sampling may be adjusted based on emerging data. Details on PK blood sample collection, processing, storage and shipping procedures are provided in the SPM.

### **7.5.2. Pharmacokinetic Sample Analysis**

Plasma analysis will be performed under the management of Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, GSK. Concentrations of GSK3052230 and selected chemotherapy will be determined in plasma samples using the currently approved analytical methodologies. Raw data will be stored in the Good Laboratory Practice Archives, GSK.

## **7.6. Immunogenicity**

Plasma samples for determination of anti- GSK3052230 antibodies will be taken from all subjects in this study as a safety measurement for GSK3052230 at the time-points specified in the Time and Events Table in Section 7.1. Timing of the assessments may be adjusted based on emerging data.

Samples will be analyzed for the presence of anti- GSK3052230 antibodies by immuno-electrochemiluminescent (ECL) screening assays. If samples contain anti- GSK3052230 antibodies as determined by the ECL screening assay, they will be further characterized for specificity and antibody titers. The immunogenicity assessment report will include the incidence and levels of anti- GSK3052230 binding antibodies.

Samples obtained for immunogenicity will be retained in long term storage and may be characterized for neutralizing activity if a positive response is observed.

## 7.7. Translational Research

### 7.7.1. Central Confirmation of FGF Signalling Pathway Status and Translational Research

Collection of archival tumor tissue is required for all subjects (see Time and Events Table; Section 7.1); if not available a fresh sample will be required. A formalin fixed paraffin embedded tumor block is requested or if not available, approximately 15 sections will be needed. Details of the tumor biopsy collection including amount, processing, storage, and shipping procedures are provided in the SPM.

In Arms A and B, a requirement for inclusion is evidence of *FGFR1* gene amplification in tumor tissue as determined by a central laboratory (CLIA or appropriate certification) using a laboratory developed test.

In Arm C, FGF2 and/or FGFR1 expression will be evaluated retrospectively by IHC to determine if expression levels of these proteins are associated with response to GSK3052230

Any remaining tissue from this study may be used for:

- Development and validation of a potential IUO assay and companion diagnostic test, e.g., but not limited to *FGFR1* gene amplification by FISH or FGF2 and/or FGFR1 expression by IHC.
- Alternative biomarkers of FGF pathway signalling such as other ligands or receptors.
- Biomarker research (protein, RNA and DNA) including status of RTK/PI3K/AKT pathways and cancer development and additional testing of DNA, RNA, or protein biomarkers related to the function of GSK3052230 if ongoing research identifies or defines additional predictive and prognostic biomarkers

It is essential that the required amount of tumor tissue is obtained in order to perform the FISH assay for entry into the study in Arms A and B, explore other potential measures of FGF signaling pathway deregulation in all arms including Arm C, and complete the necessary equivalency and precision testing requirements for the development of an IUO and potential companion diagnostic test.

Tissue samples/sections will be retained for the further confirmation using the IUO validated assay or potential companion diagnostic test, when available. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

### 7.7.2. Peripheral Blood

#### 7.7.2.1. Plasma for Soluble Markers

Clusters of markers (e.g. cytokines and angiogenic factors [CAF]) circulating in the plasma have been found to correlate with tumor pathway activation. Soluble mesotheline-related peptides (SMRP) have been shown to be clinical markers of MPM. Blood-based markers have the important advantage that specimens are readily available, simple to prepare and store, and can be taken prior to and during treatment. This allows for the

assessment of predictive markers based on the baseline evaluation as well as markers of activity and resistance based on changes that occur during treatment. Therefore, a broad panel of CAF, including FGF ligands, and SMRP will be evaluated in plasma and correlated with clinical outcome to treatment with GSK3052230.

Plasma will be collected at multiple times to evaluate circulating cytokines, angiogenesis and other soluble factors. Details of the blood collection (including volume to be collected), processing, storage and shipping procedures will be provided in the SPM.

#### **7.7.2.2. Circulating cell free DNA (cfDNA) Analysis**

Tumor-specific circulating nucleic acid (cfDNA) levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting subjects for certain treatments. Given the promise of cfDNA blood based test for subject selection, this test will be explored to determine whether mutations in cfDNA correlate with that in the tumor tissue from which it is derived. This test will also be explored to correlate increasing cfDNA levels with increasing tumor burden.

Plasma samples collected at timepoints described in Time and Events Schedule (Section 7.1) will be analyzed for mutations in genes relevant to RTK/MAPK/PI3K pathway and cancer biology in cfDNA. Details of the blood collection (including volume to be collected), processing, storage and shipping procedures will be provided in the SPM.

### **7.8. Pharmacogenetics**

An important objective of the clinical study is pharmacogenetic (PGx) research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in selected candidate genes in DNA from blood will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics (PK) and efficacy) to treatment with GSK2052230.

Information regarding PGx research is included in [Appendix 1](#). The institutional review board (IRB)/ethics committee (EC) and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of [Appendix 1](#)). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then

the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

## 8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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 8.1 and Section 8.2, respectively.

### 8.1. 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.

## 8.2. 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 out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

- d. Results in disability/incapacity, or

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

- e. Is a congenital anomaly/birth defect.

- f. Medical or scientific judgment 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. Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia as defined as alanine aminotransferase (ALT)  $\geq 3$  times upper limit of normal (ULN) **and** bilirubin  $\geq 2$  times ULN ( $>35\%$  direct) (or ALT  $\geq 3$  times ULN and international normalization ratio (INR)  $>1.5$ , if INR is measured) or 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 not available, 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  $\geq 2$  times ULN, then the event is still reported as a serious adverse event (SAE). If INR is obtained, include values on the SAE form. INR elevations  $>1.5$  suggest severe liver injury.

- Any new primary cancers.
- Cardiac toxicity including LVEF changes or treatment emergent cardiac valve toxicity.
- Treatment emergent acute anterior uveitis.

### **8.3. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**

An event that 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 a SAE. Death due to disease under study is to be recorded on the Death eCRF. 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 or procedures and the disease progression, then this must be reported as a SAE.

### **8.4. 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.

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 an 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. 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 8.5.2.

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.

#### **8.5.1. Method of Detecting AEs and SAEs**

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?”

“Have you had any (other) medical problems since your last visit/contact?”

“Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

#### **8.5.2. Prompt Reporting of SAEs 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.

Type of Event	Initial Reports		Follow-up Information on a Previous Report	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
<b>Liver chemistry abnormalities:</b>				
ALT $\geq$ 3 times ULN and bilirubin $\geq$ 2 times ULN ( $>35\%$ direct) (or ALT $\geq$ 3 times ULN and INR $>1.5$ , if INR is measured) <sup>c</sup>	24 hours <sup>a</sup>	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable <sup>b</sup>	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF <sup>b</sup>
ALT $\geq$ 5 times ULN; ALT $\geq$ 3 times ULN with hepatitis or rash <b>or</b> 3 times ULN $\geq$ 4 weeks	24 hours <sup>a</sup>	Liver Event eCRF <sup>b</sup>	24 hours	Updated Liver Event eCRF <sup>b</sup>
ALT $\geq$ 3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours <sup>a</sup>	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks <sup>b</sup>		

- a. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
- b. Liver event documents should be completed as soon as possible
- c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

Please refer to Section 4.6.1 for liver chemistry stopping criteria and follow-up procedures.

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

### 8.5.3. Regulatory reporting requirements for SAEs

Prompt notification of serious adverse events (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, institutional review board (IRB)/ethics committee (EC) 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/EC, if appropriate according to local requirements.

## **9. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES**

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. Additionally, a complete list of all prior anti-cancer therapies 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.

### **9.1. Permitted Medication(s)**

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Pre-medication for chemotherapy is allowed per institutional guidelines.

The prophylactic use of hematopoietic colony stimulating factors is not recommended in Cycle 1 of the dose escalation portion of the study. Local institutional practices vary globally, please discuss with the GSK medical team if there is a need to have prophylactic use for subjects during the dose escalation period or alternative dose finding period. During expansion phase, growth factor support therapy (e.g., G-CSF, GM-CSF) may be administered as a prophylaxis for chemotherapy-related neutropenia according to the NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors v.1.2010 [NCCN, 2010] or the European Organisation for Research and Treatment of Cancer guidelines for the use of G-CSFs [Aapro, 2011]. All growth factor use must be recorded as concomitant medication.

Aromatase inhibitors, octreotide, and GnRH analogues are permitted if the subject has been receiving these therapies and continued therapy is deemed to be clinically indicated. Other non-investigational concomitant medications are discouraged unless medically indicated.

### **9.2. Prohibited Medications**

Investigational medications other than GSK3052230 are prohibited throughout the study. Anti-cancer agents other than those described within this protocol are prohibited.

Use of oral contraceptives (either combined or progesterone only)/estrogenic vaginal ring/percutaneous contraceptive patches/implants of levonorgestrel/injectable progesterone is prohibited in this study as it is not known if there is the potential of inhibition/induction of enzymes that affect the metabolism of estrogens and/or progestins.

Agents known to alter the metabolism of the baseline chemotherapies, including non-traditional medications such as herbal remedies, should be avoided. If such use is identified, then use should be properly recorded.

Pre-medication (such as anti-histamines or corticosteroids) prior to infusion of GSK3052230 should not be used unless the subject has experienced an infusion reaction to previous administration or it is a required component of concomitant chemotherapy.

### **9.3. Permitted Non-Drug Therapies**

Concurrent radiation therapy and surgery for solid tumors, including advanced or metastatic NSCLC, including resection of non-dominant metastases, is prohibited.

In exceptional cases, palliative radiation of bone metastasis may be allowed during the screening or treatment period if all of the following conditions are met:

- There is no evidence of disease progression for subjects on study treatment
- Intention of palliation is only for symptom control of bone pain and does not include any “target” lesion.
- Single-dose palliation is planned ( $\leq 8$  GY allowed; no prolonged or fractionated RT is allowed)
- The investigator has reviewed the case with the GSK medical monitor.

GSK3052230 should be stopped 2 weeks prior to radiation and then restarted post-radiation.

## **10. LIFESTYLE AND/OR DIETARY RESTRICTIONS**

### **10.1. Contraception**

#### **10.1.1. Female Subjects**

**A female of non-childbearing potential** (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate,  $>45$  years in the absence of hormone replacement therapy. In questionable cases, the subject must have a follicular stimulating hormone (FSH) value  $>40$  mIU/mL and an estradiol value  $< 40$  pg/mL ( $<140$  pmol/L).

**A female of childbearing potential** is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

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

**Abstinence**

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

**Contraceptive Methods with a Failure Rate of <1%**

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

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

Complete abstinence from sexual intercourse or contraception must be practiced for 14 days prior to first dose of study treatment, through the dosing period, and for at least 4 weeks after the last dose of GSK3052230 or 6 months after the last dose of chemotherapy, whichever is latest.

**10.1.2. Male Subjects**

For male subjects, to prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods until 6 months after the last dose of chemotherapy:

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse prior to first dose of chemotherapy treatment, through the dosing period, and for at least 6 months after the last dose of chemotherapy treatment.

- Condom (during non-vaginal intercourse with any partner - male or female) **OR**  
Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)

## 11. 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.

Patient reported data will be collected via paper questionnaires and will be entered into the eCRF centrally. Data will be checked for completeness by study staff immediately after completion by the subject and reasons for non-compliance will be noted.

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 (eCRFs), including queries and audit trails, will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

## 12. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

### 12.1. Considerations of statistical design

The sections below show the planned dose cohorts as well as the decision rules, by study arm, specifying the number of subjects with a confirmed objective response (according to RECIST 1.1 or modified RECIST for Arm C) needed for continuing enrolment or stopping for futility. The methodology is based on the predictive probability of success if enrolment continues to 30 subjects [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility but the design allows evaluation of futility after every subject once a minimum enrolment has been reached whereas the Green-Dahlberg design does this at one fixed interim and at the end of enrolment. While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design. A randomized Phase II or Phase III study may be conducted based on the results from this study.

### 12.2. Hypotheses

No formal statistical hypotheses are being tested during the dose escalation portions of Arms A, B, and C. Analysis of the data obtained from the dose escalation parts of the study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data.

For the dose expansion portions of the study, hypothesized response rates are provided in Section 12.3. In each case, a test that the response rate is less than or equal to the null hypothesis rate versus the response rate is greater than or equal to the alternative rate is being performed using the stopping rules provided. Descriptive statistics will be used to describe the observed response rates at the dose used in the expanded cohorts for each of the arms.

## 12.3. Sample Size Determination

### 12.3.1. Arm A: GSK3052230 + Paclitaxel + Carboplatin

An initial dose escalation will be used to establish the MTD (or MFD) for GSK3052230. Once the final dose is confirmed, at least 12 and up to 30 subjects in total will be enrolled at that dose, guided by decision rules defined in Section 4.2.1. The assumptions underlying the design are detailed below and are based on the most recent phase 3 evaluation of this regimen in NSCLC subjects including the squamous subset [Socinski, 2012].

The null hypothesis is:

$$H_0: p \leq 25\%$$

The alternative hypothesis is:

$$H_A: p \geq 45\%$$

Starting with a cohort of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate ( $\alpha$ ) of 0.11 and 86% power. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.3, 0.7), a relatively non-informative prior with a mean response rate of 30%. Under the null hypothesis, the expected sample size is 24.2 subjects and probability of early termination is 83.5%. Under the alternative hypothesis, the expected sample size is 29.7 subjects and the probability of early termination is 9%.

### 12.3.2. Arm B: GSK3052230 + Docetaxel

An initial dose escalation will be used to establish the MTD. Once the final dose is confirmed, at least 14 and up to 30 subjects in total will be enrolled at that dose, using decision rules defined in Section 4.2.2. The assumptions underlying the design are detailed below and are based on previously published randomized phase 3 data in the 2<sup>nd</sup> line setting of metastatic NSCLC [Hanna, 2004].

The null hypothesis is:

$$H_0: p \leq 10\%$$

The alternative hypothesis is:

$$H_A: p \geq 25\%$$

Starting with a cohort of 14 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate ( $\alpha$ ) of 0.07 and 79% power. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a relatively non-informative prior with a mean response rate of 15%. Under the null hypothesis, the expected sample size is

24.0 subjects and probability of early termination is 84.5%. Under the alternative hypothesis, the expected sample size is 29.5 subjects and the probability of early termination is 12.2%.

### **12.3.3. Arm C: GSK3052230 + Pemetrexed + Cisplatin**

An initial dose escalation will be used to establish the MTD. Once the final dose is confirmed, at least 12 and up to 30 subjects in total will be enrolled at that dose, using decision rules defined in Section 4.2.3. The assumptions underlying the design are detailed below and are based on previously published randomized phase 3 data in the 1st line setting of malignant pleural mesothelioma [Vogelzang, 2003].

The null hypothesis is:

$$H_0: p \leq 40\%$$

The alternative hypothesis is:

$$H_A: p \geq 60\%$$

Starting with a cohort of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate ( $\alpha$ ) of 0.10 and 82% power. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.5, 0.5), a relatively non-informative prior with a mean response rate of 50%. Under the null hypothesis, the expected sample size is 23.1 subjects and probability of early termination is 86.4%. Under the alternative hypothesis, the expected sample size is 29.5 subjects and the probability of early termination is 13.7%.

## **12.4. Sample Size Sensitivity**

No analysis of sample size sensitivity was performed.

### **12.4.1. Sample Size Re-estimation**

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

## **12.5. Data Analysis Considerations**

### **12.5.1. Analysis Populations**

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK3052230. Safety and anti-cancer activity will be evaluated based on this analysis population.

The **PK Population** will consist of all subjects from the All Treated Population for whom a PK sample is obtained and analyzed.

The **Assay Validation Population** is defined as all subjects who were consented, screened for the study (regardless if the subject met eligibility requirements for study

enrollment) and whose tissue was assayed by the central laboratory for *FGFR1* amplification. Data from this population may be used for future validation of the assay.

## **12.6. Treatment Comparisons**

No statistical comparisons will be made between doses for a given study arm. Safety, PK, PD, biomarker, and anti-tumor activity summaries will be provided by dose level of GSK3052230 for each study arm.

## **12.7. Interim Analysis**

Preliminary safety data, including adverse events, changes in laboratory values and other safety parameters will be evaluated for each dose escalation cohort prior to making dose escalation decisions.

For each study arm, after the initial 12 (Arms A and C) or 14 (Arm B) subjects have enrolled at the final dose, response data will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 4.2.1 (Arm A), Section 4.2.2 (Arm B), and Section 4.2.3 (Arm C).

For Arm C only, the totality of the data will be reviewed prior to stopping for futility and the futility stopping rules are non-binding. The final analysis for Arm C will require 16/30 responses as specified in [Table 16](#). This is equivalent to a binomial test at the final analysis with alpha level 0.10 and power of 82%.

The rules for Parts A, B and C are also shown in a tabular format below:

**Table 14      Stopping Rules for Arm A: GSK3052230 + Paclitaxel + Carboplatin**

Number of Patients Enrolled	$\leq$ This Number of Objective Responses to Stop Early for Futility
12	0
13	0
14	1
15	1
16	1
17	2
18	2
19	2
20	3
21	3
22	4
23	4
24	5
25	5
26	6
27	7
28	8
29	9
30	10

**Table 15      Stopping Rules for Arm B: GSK3052230 + Docetaxel**

Number of Patients Enrolled	≤ This Number of Objective Responses to Stop Early for Futility
14	0
15	0
16	0
17	0
18	0
19	0
20	0
21	0
22	1
23	1
24	1
25	1
26	2
27	2
28	3
29	4
30	5

**Table 16      Stopping Rules for Arm C: GSK3052230 + Pemetrexed + Cisplatin**

Number of Patients Enrolled	≤ This Number of Objective Responses to Stop Early for Futility
12	2
13	2
14	3
15	3
16	4
17	4
18	5
19	5
20	6
21	7
22	7
23	8
24	9
25	10
26	11
27	12
28	13
29	14
30	15

## 12.8.      Key Elements of Analysis Plan

Data will be listed and summarized 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.

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.

### **12.8.1. Anti-Cancer Activity Analyses**

The All Treated Population will be used for anti-cancer activity analyses. Anti-cancer activity will be evaluated using RECIST, version 1.1 for Arms A and B and modified RECIST for Arm C. The response data will be summarized by study arm and dose level. Full details will be specified in the RAP.

For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g. assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of events, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. PFS will be summarized using the Kaplan-Meier method.

### **12.8.2. Safety Analyses**

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g. laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the RAP.

#### **12.8.2.1. Extent of Exposure**

The number of subjects administered study treatment will be summarized according to the duration of therapy.

#### **12.8.2.2. Adverse Events**

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the National Cancer Institute- Common Toxicity Criteria for Adverse Events (NCI-CTCAE), (version 4.03).

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (version 4.03) will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

The incidence of deaths and the primary cause of death will be summarized.

For the dose-escalation portions of the study, dose-limiting toxicities (DLTs) will be listed for each subject and summarized by dose cohort according to International Data Standards Library standards.

#### **12.8.2.3. Clinical Laboratory Evaluations**

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to National Cancer Institute-Common Toxicity Criteria for

Adverse Events (NCI-CTCAE) (version 4.03). Laboratory test results outside the reference range that do not have an associated NCI-CTCAE criteria will be summarized using proportions. Further details will be provided in the Reporting and Analysis Plan (RAP).

#### **12.8.2.4. Other Safety Measures**

Data for vital signs, ECGs, and ECHOs will be summarized based on predetermined criteria identified to be of potential clinical concern. Immunogenicity data will be summarized and listed. Further details will be provided in the RAP.

#### **12.8.3. Patient Reported Outcomes**

Change from baseline scores in LCSS and LCSS-meso will be calculated for all scales and timepoints. Change from baseline of 10mm was previously identified as clinically meaningful (P. Hollen, personal communication). The number of subjects achieving a 10mm improvement at any timepoint will be tabulated for each component of the LCSS. For each component of the LCSS, plots of individual and/or mean/median values and change from baseline values over time will be produced. If warranted, mixed-effects models may be used to model subject data over time for components of particular interest. Associations with efficacy assessments and between patient reported and clinician reported symptomatic will be explored when warranted. Further details will be provided in the RAP.

#### **12.8.4. Pharmacokinetic Analyses**

PK analyses will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Plasma GSK3052230 concentration-time data may be combined with data from other studies and will be analyzed using a population pharmacokinetic approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (clearances, CL and volumes of distribution, V) and identify important covariates (e.g., age, weight, or disease related covariates). Summary exposure measures (Cmax, AUC and average concentration Cav defined as time corrected AUC [AUC/τ]) will also be computed. Results of this analysis may be provided in a separate report.

Plasma concentration-time data will be listed and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum).

#### **12.8.5. Pharmacokinetic/Pharmacodynamic Analyses**

Observed or predicted concentrations or summary exposure measure (eg; Cmax, Ctrough, and Cav) may be combined with safety and efficacy pharmacodynamic measures of interest to examine potential exposure response relationships. Graphical evaluation will first be performed.

Where evidence of activity is seen, linear and/or non-linear mixed effect models may be fitted to the data to estimate PK/PD parameters of interest (e.g. slope, baseline (E0), concentration for 50% of maximum effect (EC50) and maximum effect (Emax)).

Overall efficacy data, as assessed by conventional RECIST 1.1 criteria (best confirmed response) and overall tumor burden, may be described using ordered categorical model and continuous models with summary exposure parameters (eg; Cmax, Ctrough, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the Reporting and Analysis Plan.

### **12.8.6. Tumor Kinetics Analysis**

Data from some arms of the study may be combined to describe the kinetics of tumor growth based on the sum of longest diameters and/or volume of target lesions.

The kinetics of tumor growth may be described as a function of time using the NSCLC model described by the FDA [[Wang](#), 2009]. The tumor size (TS) is expressed as:

$$TS(t) = BSL \cdot e^{-SRt} + PR \cdot t$$

where  $TS(t)$  denotes the tumor size measured as the sum of longest distance (mm) of lesions or volume ( $mm^3$ ) at time  $t$ , BSL is the baseline tumor size, SR is the exponential tumor shrinkage rate constant and PR is the linear tumor progression rate.

The kinetics of tumor growth may also be described as a function of time using the model described by Claret [[Claret](#), 2009]. The model is expressed as:

$$dTS(t)/dt = (KL - KD \cdot e^{-\lambda t}) \cdot TS(t)$$

where  $TS(t)$  denotes the sum of longest distance (mm) of lesions or volume ( $mm^3$ ) at time  $t$ , with  $TS(0)$  being the baseline tumor size, KL represents the exponential tumor growth rate, KD represents the exponential rate of tumor shrinkage (i.e. drug effect on total tumor size),  $\lambda$  is the rate constant for drug resistance/disease progression. A measure of exposure of one or more of the administered medications may be included in the models.

The equation proposed by Wang and/or Claret will be fit to the observed data using a mixed-effects model with NONMEM VII. Other models of the kinetics of tumor growth, such as a 2-parameter model, may be used to analyze the data [[Stein](#), 2011; [Stein](#), 2012].

The time to tumor growth (TTG) may be estimated with parameters from the appropriate model. Subject characteristics such as baseline tumor size, performance status, LDH, age, sex, race, prior therapies, or radiotherapy, may be evaluated to determine which covariates have a significant effect on the kinetics of tumor growth.

### **12.8.7. Translational Research Analyses**

Exploratory analysis may be performed to examine potential relationships between anticancer activity and changes in markers of deregulation of FGF signaling pathway (example: *FGFR1* gene amplification) or tumor biology (e.g. cytokines, acute phase proteins, relevant transcripts and/or proteins) or between anticancer activity and potential markers of sensitivity.

The results of translational research investigations may be reported separately from the main clinical study report or as an amendment. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. Further details on the translational research analyses will be addressed in the RAP.

### **12.8.8. Pharmacogenetic Analyses**

Further details on pharmacogenetic (PGx) analyses will be addressed in [Appendix 1](#) and the PGx Reporting and Analysis Plan (RAP).

## **13. STUDY CONDUCT CONSIDERATIONS**

### **13.1. Posting of Information on Clinicaltrials.gov**

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

### **13.2. 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 Good Clinical Practice (ICH GCP) and applicable country-specific regulatory requirements.

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:

- Institutional review board (IRB)/ethics committee (EC) 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.

### **13.3. 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 Institutional review board (IRB)/ethics committee (EC) is notified.

### **13.4. Quality Control (Study Monitoring)**

In accordance with applicable regulations, Good Clinical Practice (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.

### **13.5. Quality Assurance**

To ensure compliance with International Conference on Harmonization Good Clinical Practice (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.

### **13.6. 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, International Conference on Harmonization Good Clinical Practice (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/EC promptly and provide the reason(s) for the suspension/termination.

GSK may also close study sites which fail to recruit subjects within a predefined timeframe, as defined within the SPM.

### **13.7. 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.

### **13.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers 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 GSK Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition a manuscript will be submitted to a peer-reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV).

When manuscript publication in a peer-reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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## 15. APPENDICES

### 15.1. Appendix 1: Pharmacogenetics (PGx)

#### PGx Research

##### PGx – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (PK) (absorption, distribution, metabolism, and elimination), pharmacodynamics (PD) (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [ <a href="#">Hetherington</a> , 2002; <a href="#">Mallal</a> , 2002]	Human Leukocyte Antigen B (HLA- B*5701)	Individuals with HLA-B*5701 variant may be at increased risk for experiencing hypersensitivity to abacavir. Clinical assays are available for HLA-B*5701 but none has been validated. HLA-B*5701 screening would supplement but never replace abacavir clinical risk management strategies aimed at minimizing rare but serious outcomes associated with abacavir hypersensitivity
Carbamazepine	Seizure, Bipolar disorders & Analgesia <a href="#">Chung</a> , 2010; <a href="#">Ferrell</a> , 2008.	HLA-B*1502	Independent studies indicated that patients of East Asian ancestry who carry HLA-B*1502 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
Warfarin	Cardiovascular [ <a href="#">Neergard</a> , 2006; <a href="#">Wilke</a> , 2005]	CYP2C9	SAEs experienced by some subjects on warfarin may be explained by variations in the CYP2C9 gene that influences the degree of anticoagulation achieved.
Irinotecan	Cancer FDA News Release, 2005	UGT1A1	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation might be too high for another subject without this variation, raising the risk of certain side effectsA genetic blood test (Invader UGT1A1molecular assay) is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to GSK3052230.

## **PGx Research Objectives**

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a possible genetic relationship to handling or response to GSK3052230. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK3052230 that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the PK and/or PD of study treatment
- Relationship between genetic variants and safety and/or tolerability of study treatment
- Relationship between genetic variants and efficacy of study treatment.

## **Study Population**

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives study treatment may take part in the PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

## **Study Assessments and Procedures**

In addition to any blood samples taken for the clinical study, a whole blood sample (~6 mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labeled (or “coded”) with a study specific number that can be traced or linked back to the subject only by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK3052230 has been completed and the study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to GSK3052230.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

### **Subject Withdrawal from Study**

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- The sample is retained for PGx research.
- Any PGx sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up to that point.

### **Screen and Baseline Failures**

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

### **PGx Analyses**

The aim of pharmacogenetic analyses will be to investigate the relationship between genetic variations in germline DNA and response to study treatment. The specific type of genetic investigation to be applied will be dependent on the most scientifically feasible approach available to address understanding of the response to the study treatment.

Generally, two approaches may be utilized to explore the association of genetic variation.

1. Candidate gene analysis where variations in specific genes may be studied that encode the drug target, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response.

These candidate genes that may be investigated in this study include the following: the GSK Absorption, Distribution, Metabolism and Excretion genes. These play a central role in drug PK and PD. In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to GSK3052230. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) located throughout the genome. This approach is often employed when potential genetic effects are not well understood.

The results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. In all cases, appropriate statistical methods will be used to analyze the genetic markers in the context of other clinical data. Statistical methods may include, but are not limited to Hardy-Weinberg Equilibrium testing, Comparison of Demographic and Baseline Characteristics by Genotype, Evaluation of Genotypic Effects, Evaluation of Treatment by Genotype and Gene-Gene Interaction, Linkage Disequilibrium, Multiple Comparison and Multiplicity and/or Power and Sample Size Considerations. A detailed description of the analyses to be performed will be documented in the pharmacogenetics RAP.

### **Informed Consent**

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

### **Provision of Study Results and Confidentiality of Subject's PGx Data**

GSK may summarize the cumulative PGx research results in the clinical study report,.

In general, GSK does not inform the investigator, subject or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results unless required by law. The information generated from PGx research is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research.

## References

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Ferrell PB, McLeod HL. Carbamazepine, HLA-B\*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics.* 2008; 9: 1543-46.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet.* 2002; 359:1121-2.

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## 15.2. Appendix 2: 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.

**15.3. Appendix 3: COCKCROFT-GAULT FORMULA**

ClCr (mL/min) = 
$$\frac{Q \times (140 - \text{age[yr]}) \times \text{ideal body weight [kg]}^*}{72 \times \text{serum creatinine [mg/dL]}}$$

Q = 0.85 for females

Q = 1.0 for males

OR

ClCr (mL/min) = 
$$\frac{K \times (140 - \text{age[yr]}) \times \text{ideal body weight [kg]}^*}{\text{Serum creatinine [umol/L]}}$$

K = 1.0 for females

K = 1.23 for males

\*Calculation of Ideal Body Weight Using the Devine Formula [[Devine](#), 1974]

Ideal body weight:

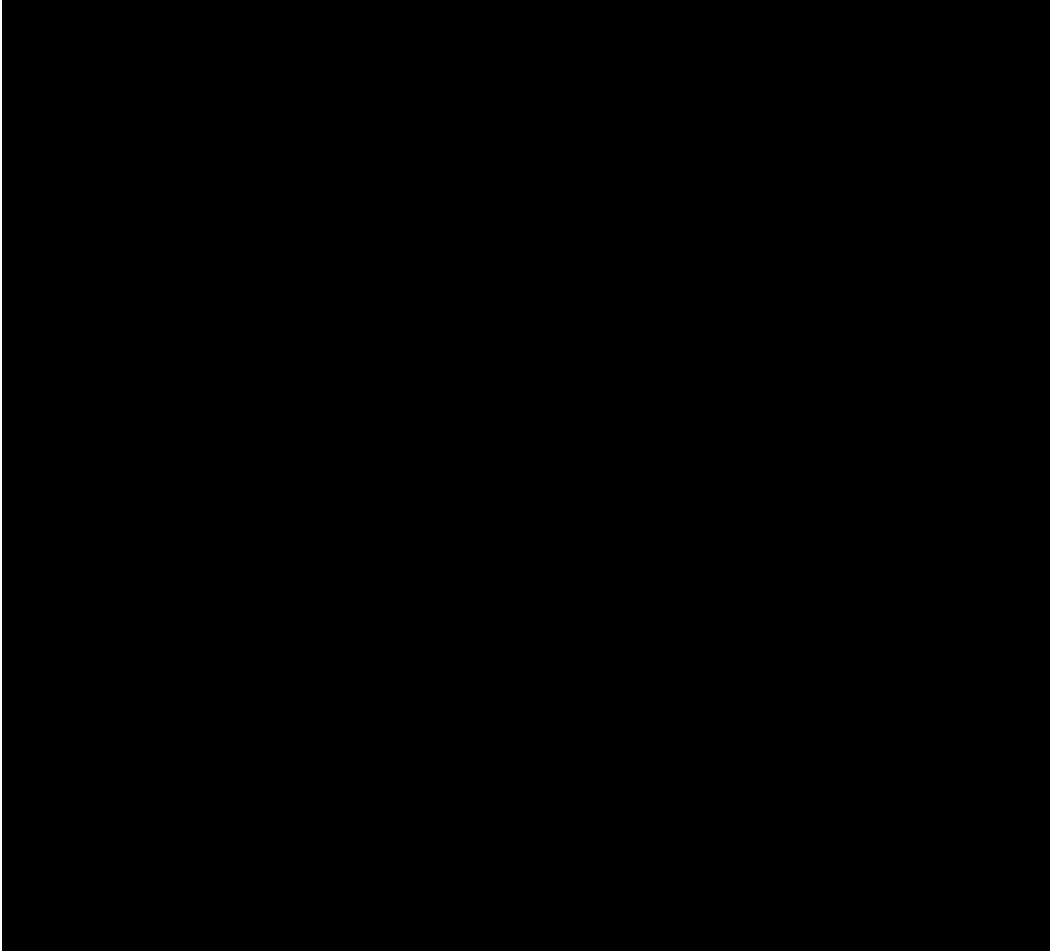
Males =  $50.0 \text{ kg} + (2.3 \text{ kg} \times \text{each inch over 5 feet})$  or  $50.0 \text{ kg} + (0.906 \text{ kg} \times \text{each cm over 152.4 cm})$

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

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

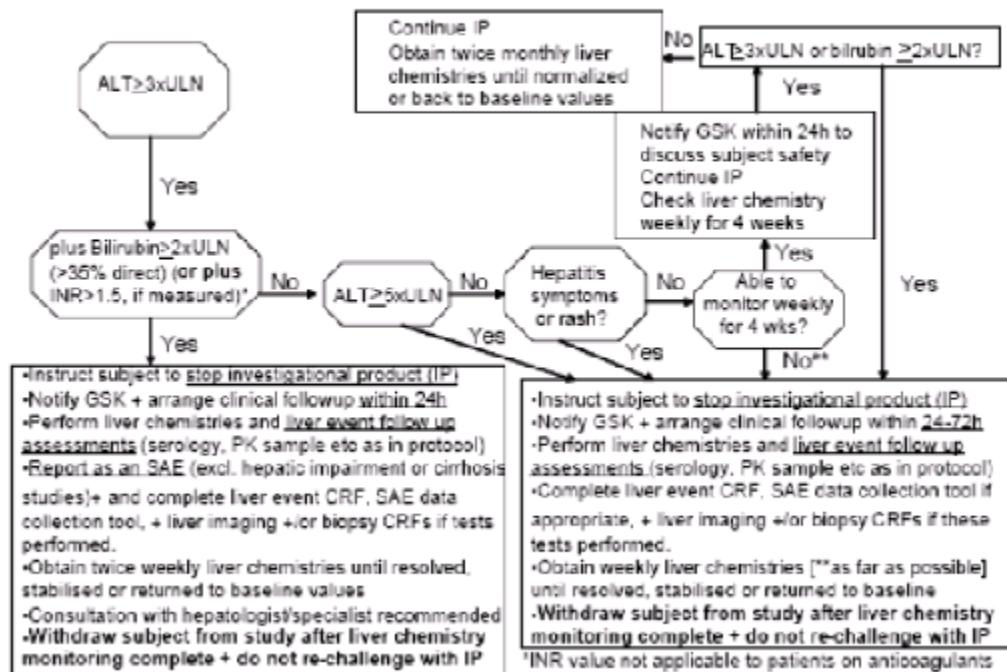
**15.4. Appendix 4: ECOG Performance Status<sup>1</sup>**

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



## 15.5. Appendix 5: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

### Phase I Liver Safety Algorithms



## 15.6. Appendix 6: Urine Protein Creatinine (UPC) Ratio

### Clinical meaning of UPC

There is a good correlation between the ratio of protein concentration to creatinine concentration in a random urine sample and the amount of protein excreted over 24 hours. Creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate.

Normal protein excretion is <150 mg/24 hours and is similar for men and women.

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day.

Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day.

### Calculating UPC

UPC ratio = Urine protein (mg/dL) / Urine creatinine (mg/dL).

UPC ratio  $\approx$  equivalent to grams of protein excreted in urine over 24 hrs.

**Example:** Patient has a urine protein = 90 mg/dL and urine creatinine = 30 mg/dL.

UPC ratio =  $(90 \text{ mg/dL}) / (30 \text{ mg/dL}) = 3$

The calculated UPC ratio is 3, which correlates to roughly 3 g protein excretion in a 24-hour period.

### Units for UPC ratio

**Note:** To calculate UPC, protein and creatinine concentrations must be expressed in the same units (mg/dL, g/L, or  $\mu\text{mol/L}$ ). If, for example, protein concentration is expressed in mg/dL and creatinine concentration is expressed in  $\mu\text{mol/L}$ , conversion of one of the concentration values is required. Conversion factors are:

From	To	Conversion Factor
Conventional Units: mg/dL	SI Units: $\mu\text{mol/L}$	Multiply by 88.4
SI Units: $\mu\text{mol/L}$	Conventional Units: mg/dL	Divide 88.4

[[Xin](#), 2004] [[NKF](#) Guidelines, 2002]

## 15.7. Appendix 7: Country Specific Requirements

### France or UK:

#### French or UK Specific QTc Stopping Criteria:

In line with local requirements, **French subjects** that meet the criteria QTc<sup>1</sup> below will have GSK3502230 withheld:

QTcB > 500 msec

In line with local requirements, **UK subjects** that meet the criteria QTc<sup>1</sup> below will have study treatment withheld:

QTc > 500 msec

<sup>1</sup>Based on average corrected QT (QTc) interval value of triplicate electrocardiograms (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 GSK3502230 withheld.

QT interval (corrected for HR)  $\geq$  500 msec; GSK3502230 will be permanently discontinued.

QTc interval increase from baseline  $\geq$  60 msec and maximum QTc < 500 msec; GSK3502230 may be restarted at a reduced dose level after discussion with the medical monitor once the QTc returns to baseline. If QTc prolongation meeting stopping criteria recurs after re-challenge, GSK3502230 must be permanently discontinued.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on GSK3502230 if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

No other known country specific requirements are currently required.

## 15.8. Appendix 8: Protocol Amendment Changes

### Amendment 5

#### Where the Amendment Applies

This amendment applies to all sites.

#### Summary of Amendment Changes with Rationale

Amendment 5 updates the GSK medical physician contacts for safety questions. The synopsis is being clarified to be consistent with the changes in Amendment 4 regarding histologically or cytologically confirmed diagnosis being Stage IIIB or IV for subjects in Arm A or B. Additional wording has been provided regarding cisplatin dosing and hydration practices to clarify this should be per local standards. The FGF117360 study team has been providing updates and information on infusion reactions during the program. The team has been monitoring GSK3052230 related dosing events and have added guidance for pre-medication per local standards if an infusion reaction is observed. The GSK3052230 infusion time should be extended from 30 minutes to 60 minutes if initial reaction is observed or up to 90 minutes if a second reaction is observed. This guidance in dosing was based on joint discussions between investigators and GSK team to determine most appropriate path forward for these subjects. The Time and Event schedule has been modified to allow more flexible screening timing for subjects in Arm A who desire to start chemotherapy prior to GSK3052230 initial dose. The Time and Event schedule for pharmacokinetics has been modified to include cisplatin sampling for subjects in Arm C. Finally, in the United Kingdom at selected sites total calcium would be utilized instead of monitoring for both total calcium and ionized calcium. At this point in time, there has been no safety signals observed in any arms regarding calcium assessments.

#### List of Specific Changes

##### CHANGE 1: Medical monitor contact information

###### PREVIOUS TEXT:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Medical Monitor	PPD MD	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426 Email: PPD

Medical Monitor	PPD MD	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426 Email: PPD
Additional medical monitor or sponsor contacts may be provided in a letter to investigator during the course of the study conduct without involving a protocol amendment.					

**NEW TEXT:**(new text **bold and underlined**, deleted text in ~~strikethrough~~)

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Medical Monitor	PPD MD	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426 Email: PPD
Medical Monitor	PPD MD, <u>PhD</u>	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426- <u>0989</u> , <u>United States</u> Email: PPD
<u>Secondary Medical Monitor</u>	PPD PPD MD	PPD	PPD	PPD	GlaxoSmithKline <u>1250 S. Collegeville Road</u> , <u>Collegeville, PA 19426-0989</u> , <u>United States</u> Email: PPD
Additional medical monitor or sponsor contacts may be provided in a letter to investigator during the course of the study conduct without involving a protocol amendment.					

**CHANGE 2: Clarifications to be consistent with previous amendments****PREVIOUS TEXT, Synopsis:**

Rationale for change: This was modified was made in Amendment 4 changes and body of protocol but not in synopsis. This change is to ensure consistency within protocol.

1. Histologically or cytologically confirmed diagnosis:

**Arms A and B:** Stage IV or recurrent metastatic squamous NSCLC (TNM Staging for NSCLC, 7<sup>th</sup> Edition) with *FGFR1* gene amplification by central laboratory testing.

**NEW TEXT, Synopsis:**(new text **bold and underlined**, deleted text in ~~strikethrough~~)

1. Histologically or cytologically confirmed diagnosis:

**Arms A and B:** Stage **IIIB or IV** or recurrent metastatic squamous NSCLC (TNM Staging for NSCLC, 7<sup>th</sup> Edition) with *FGFR1* gene amplification by central laboratory testing.

Rationale for change: This was modified was made in Amendment 4 changes but not within the text. This change is to ensure consistency within protocol.

**NEW TEXT, Sectino 1.4.1.1. Preclinical data on GSK3052230**

Added reference **[DeYoung, 2014]**.

Which was updated in REFERENCES, Section 14

**DeYoung MP, Shenk C, Bleam M, Barnette M, Ganji G, Hoang B, Tunstead J, Bellovin D, Los G, Minthorn E, Kumar R. Preclinical efficacy of targeting FGF autocrine signaling in mesothelioma with the FGF ligand trap, FP-1039/GSK3052230. AACR 2014.**

**PREVIOUS TEXT, Section 3.2.1, Inclusion criteria:**

Availability of archival tumor tissue required for assessment of deregulated FGF pathway signaling eg, *FGFR1* amplification or FGF2 expression.

**NEW TEXT, Section 3.2.1, Inclusion criteria:**

Availability of archival tumor tissue required for assessment of deregulated FGF pathway signaling eg, *FGFR1* amplification or FGF2 **or FGFR1** expression.

**Change 3: Chemotherapy treatment per local standards****NEW TEXT, Section 4.1.**

**Subjects on pemetrexed/cisplatin may have their cisplatin stopped after 4 cycles per local clinical standards.**

**NEW TEXT, Section 4.5.4.**

- 1-2 liters of fluid infused for 8-12 hours prior to cisplatin dose **(or hydration per local standard)**

**CHANGE 4: Infusion Reactions and dosing timings****PREVIOUS TEXT, Exclusion criteria, Section 1.6, Summary of Risk Management:**

If infusion reactions are noted in subjects not already premedicated with glucocorticoids, antihistamines and H2 receptor antagonists, appropriate premedication against

hypersensitivity reactions may be initiated prior to the next infusions at the discretion of the investigator according to the institution's standard practice.

**NEW TEXT, Exclusion criteria, Section 1.6, Summary of Risk Management:**  
(new text **bold and underlined**, deleted text in ~~strikethrough~~)

If infusion reactions are noted in subjects not already premedicated with glucocorticoids, antihistamines and H2 receptor antagonists, appropriate premedication against hypersensitivity reactions may be initiated prior to the next infusions at the discretion of the investigator according to the institution's standard practice. **All subjects who have experienced an infusion reaction should have GSK3052230 infused over 60 minutes instead of 30 minutes and pre-treated with appropriate local pretreatment guidelines. If the subject continues to have a reaction on re-challenge, the infusion of GSK3052230 may be prolonged for 90 minutes”**

**NEW TEXT, Section 4.7.4 GSK3052230 Dose Modification**

**4.7.4.1        GSK3052230 Dose Modifications regarding infusion related reactions**

**Subjects should be closely monitored for GSK3052230 infusion-related reactions.**  
**All subjects who have experienced an infusion reaction due to GSK3052230 (and not chemotherapy) should have GSK3052230 infused over 60 minutes instead of 30 minutes and pre-treated with appropriate local institutionl pre-treatment guidelines (example: medications such as steroids, antihistamines, acetaminophen, H-2 antagonists, and antiemetics, according to local pretreatment guidelines). If the subject continues to have a reaction on re-challenge the infusion of GSK3052230 may be prolonged to 90 minutes. Epinephrine for subcutaneous injection, diphenhydramine for IV injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions should be quickly available subject infusions.**

**CHANGE 5: Time and Events Screening Window for Arm A subjects****PREVIOUS TEXT, Section 7 Study Assessments and Procedures:****Table 10 Time and Events Schedule**

Time and Events Schedule for FGF117360	Screen	Cycle 1				Cycle 2				Additional Cycles				Every 4 Cycles, D1	EOT	30 day F/U
		D1	D8	D9	D15	D1	D8	D15	D1	D8	D15	D1	D8			
Visit Window	Once the subject provides consent, a tumor sample may be submitted for Arms A and B for FGFR1 amplification at any time (there is no time limit or window). All other screening assessments should be conducted within 30 days of C1D1. Visit windows of $\pm 2$ days during study through EOT, $+7$ days for F/U.															

Ophthalmologic Exam	To be performed by ophthalmologist or qualified optometrist.	X	Perform assessment if subject discontinues prior to C4.								C4 only						
ECHO	Perform at EOT if subject discontinues prior to C4. Visit windows of $\pm 7$ days during study.	X										C4 only	early disc				
Forced Vital Capacity	Assess D1 of every odd cycle, Arm C only, Visit windows of $\pm 7$ days during study.	X	X								Odd X						

**REVISED TEXT, Section 7 Study Assessments and Procedures:**  
 (new text **bold and underlined**, deleted text in ~~strikethrough~~)

**Table 10 Time and Events Schedule**

Time and Events Schedule for FGF117360	Screen	Cycle 1				Cycle 2				Additional Cycles				Every 4 Cycles, D1	EOT	30 day F/U	
		D1	D8	<del>D9</del>	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
Visit Window		Once the subject provides consent, a tumor sample may be submitted for Arms A and B for FGFR1 amplification at any time (there is no time limit or window). All other screening assessments should be conducted within 30 days of C1D1. Visit windows of $\pm$ 2 days during study through EOT, +7 days for F/U. <b><u>For Arm A subjects who wish to start chemotherapy prior to GSK3052230 screening period is 30 days +3 to allow baseline imaging scans to be performed prior to chemotherapy but within 30+3days of GSK3052230 first dose.</u></b>															

Rationale for change: This was modified was made in Amendment 4 changes but not within the text. This change is to ensure consistency within protocol regarding ophthalmologic exams.

Ophthalmologic Exam	To be performed by ophthalmologist or qualified optometrist. <b><u>(Visit windows of <math>\pm</math>7 days post baseline)</u></b> .	X	Perform assessment if subject discontinues prior to C4.								C4 only						
ECHO	Perform at EOT if subject discontinues prior to C4. Visit windows of $\pm$ 7 days <b><u>during study post baseline</u></b> .	X									C4 only	early disc					
Forced Vital Capacity	Assess D1 of every odd cycle, Arm C only, Visit windows of $\pm$ 7 days <b><u>during study post baseline</u></b> .	X	X							Odd X							

**CHANGE 6: Time and Events PK Sampling for Cisplatin in Arm C subjects****PREVISION TEXT, Section 7: Table 11 Pharmacokinetic Sampling Schedule**

FGF117360 Pharmacokinetic Sampling Schedule			Limited PK	Extensive PK	Extensive PK	Extensive PK
Time	When	Window		Arm A	Arm B	Arm C
Cycle 2 Day 1	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	1 hr after start of paclitaxel infusion or end of docetaxel or pemetrexed infusion	±10 min for paclitaxel or up to 5 min prior to end of docetaxel infusion or up to 1 min prior to end of pemetrexed infusion		GSK3052230 PK Paclitaxel PK	GSK3052230 PK Docetaxel PK	GSK3052230 PK Pemetrexed PK
	1 hr after end of pemetrexed infusion	± 20 min				Pemetrexed PK
	End of paclitaxel infusion or 2 hr after end of docetaxel or pemetrexed infusion	up to 5 min prior to end of paclitaxel infusion or ± 20 min for docetaxel and pemetrexed		Paclitaxel PK	Docetaxel PK	Pemetrexed PK
	2 hr after end of paclitaxel infusion or 5 hr after end of docetaxel or pemetrexed infusion	±30 min		(selected sites) GSK3052230 PK Paclitaxel PK	(selected sites) GSK3052230 PK Docetaxel PK	(selected sites) GSK3052230 PK Pemetrexed PK

**REVISED TEXT, Section 7: Table 11 Pharmacokinetic Sampling Schedule**

FGF117360 Pharmacokinetic Sampling Schedule			Limited PK	Extensive PK	Extensive PK	Extensive PK
Time	When	Window		Arm A	Arm B	Arm C
Cycle 2 Day 1	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK
	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK	GSK3052230 PK

FGF117360 Pharmacokinetic Sampling Schedule			Limited PK	Extensive PK	Extensive PK	Extensive PK
Time	When	Window		Arm A	Arm B	Arm C
	1 hr after start of paclitaxel infusion or end of docetaxel or pemetrexed infusion	±10 min for paclitaxel or up to 5 min prior to end of docetaxel infusion or up to 1 min prior to end of pemetrexed infusion		GSK3052230 PK Paclitaxel PK	GSK3052230 PK Docetaxel PK	GSK3052230 PK Pemetrexed PK <b>Cisplatin PK</b>
	1 hr after end of pemetrexed infusion	± 20 min				Pemetrexed PK <b>Cisplatin PK</b>
	End of paclitaxel infusion or 2 hr after end of docetaxel or pemetrexed infusion	up to 5 min prior to end of paclitaxel infusion or ± 20 min for docetaxel and pemetrexed		Paclitaxel PK	Docetaxel PK	Pemetrexed PK <b>Cisplatin PK</b>
	2 hr after end of paclitaxel infusion or 5 hr after end of docetaxel or pemetrexed infusion	±30 min		(selected sites) GSK3052230 PK Paclitaxel PK	(selected sites) GSK3052230 PK Docetaxel PK	(selected sites) GSK3052230 PK Pemetrexed PK <b>Cisplatin PK</b>

**CHANGE 7: Ionized Calcium monitoring for sites in United Kingdom****PREVIOUS TEXT, Section 7.3.8 Laboratory Assessments::**

Table 12 List of Clinical Laboratory Tests

<b>Hematology</b>	
Platelet Count	<i>Automated WBC Differential:</i>
Red blood cell (RBC) Count	Neutrophils (absolute)
White blood cell (WBC) Count (absolute)	Lymphocytes (absolute)
Hemoglobin	Monocytes (absolute)
	Eosinophils (absolute)
	Basophils (absolute)
<b>Clinical Chemistry</b>	
Potassium, Sodium, Chloride, Total carbon dioxide, total Calcium, ionized calcium, magnesium, phosphate, albumin, glucose (fasting),	

**REVISED TEXT, Section 7.3.8 Laboratory Assessments:**  
(new text **bold and underlined**, deleted text in ~~strikethrough~~)

Table 12 List of Clinical Laboratory Tests

<b>Hematology</b>	
Platelet Count	<i>Automated WBC Differential:</i>
Red blood cell (RBC) Count	Neutrophils (absolute)
White blood cell (WBC) Count (absolute)	Lymphocytes (absolute)
Hemoglobin	Monocytes (absolute)
	Eosinophils (absolute)
	Basophils (absolute)
<b>Clinical Chemistry</b>	
Potassium, Sodium, Chloride, Total carbon dioxide, total Calcium, <u>ionized calcium*</u> , magnesium, phosphate, albumin, glucose (fasting),	

**\*Ionized calcium collected may not be collected in some selected sites and only total calcium is collected for subjects regarding safety monitoring.**

## Amendment 4

### Where the Amendment Applies

This amendment applies to all sites.

### Summary of Amendment Changes with Rationale

The protocol medical monitor contact information was updated and information will be provided during the study to prevent protocol amendments if there are staff changes. In addition, based on investigator feedback, some sections of the protocol needed further clarification or broader assessment windows for subject assessments. Therefore additional information on preclinical studies in mesothelioma was added in the background section, and clarifications were provided for modified RECIST, the time & event tables, concomitant medications and Cockcroft-gault formula description.

We have expanded the lines of treatment to address the changing parameters in the NSCLC development and treatments. We have broadened the lines of therapy to allow for additional subjects to benefit from GSK3052230 in combination with chemotherapy. In addition, the mechanism of resistance for current FGF inhibitors may be different from GSK3052230 and therefore those who previously failed FGFR inhibitor treatment will be included.

The protocol was expanded to allow intra-subject dose escalation or de-escalation. This allows subjects who receive benefit during the dose escalation to transition to the recommended expansion dose. In addition, additional wording has been added to allow alternative dosing and schedules to be explored. Example, if a MTD is not obtained the study could explore lower doses or MFD levels based on the totality of the data (eg, safety, pharmacokinetics, pharmacodynamics, etc).

### List of Specific Changes

#### CHANGE 1: Medical monitor contact information

##### PREVIOUS TEXT:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD PPD MD	PPD PPD	PPD PPD	PPD PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426 Email: PPD

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Secondary Medical Monitor	PP PPD MD	PPD PPD	PPD PPD	PPD PPD	GlaxoSmithKline Five Moore Drive, Mailstop 17.2225.2B Research Triangle Park, NC 27709 Email: PPD

NEW TEXT:

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD PPD MD	PPD PPD	PPD PPD	PPD PPD	GlaxoSmithKline 1250 South Collegeville Road PO Box 5089 Collegeville, PA 19426 Email: PPD
Secondary Medical Monitor	PP PPD MD	PPD PPD	PPD PPD	PPD PPD	GlaxoSmithKline Five Moore Drive, Mailstop 17.2225.2B Research Triangle Park, NC 27709 Email: PPD
<u>Medical Monitor</u>	PPD PPD <u>MD</u>	PPD PPD	PPD PPD	PPD PPD	<u>GlaxoSmithKline</u> <u>1250 South Collegeville Road</u> <u>PO Box 5089</u> <u>Collegeville, PA 19426</u> Email: PPD
<u>Medical Monitor</u>	PPD <u>MD</u>	PPD PPD	PPD PPD	PPD PPD	<u>GlaxoSmithKline</u> <u>1250 South Collegeville Road</u> <u>PO Box 5089</u> <u>Collegeville, PA 19426</u> Email: PPD
<u>Additional medical monitor or sponsor contacts may be provided in a letter to investigator during the course of the study conduct without involving a protocol amendment.</u>					

**CHANGE 2: Abbreviations**(new text **bold and underlined**, deleted text in ~~strikethrough~~)**NEW TEXT:**

TGI	tumor growth inhibition
-----	-------------------------

**CHANGE 3: Study Design**(new text **bold and underlined**, deleted text in ~~strikethrough~~)**PREVIOUS TEXT:**

**Study Design:** This will be a multi-arm, multicenter, non-randomized, parallel-group, uncontrolled, open-label Phase IB study designed to evaluate the safety, tolerability and preliminary activity of GSK3052230 in combination with paclitaxel + carboplatin in previously untreated metastatic squamous NSCLC (Arm A), in combination with docetaxel in metastatic squamous NSCLC that has progressed after 1 line of chemotherapy (Arm B), or in combination with pemetrexed + cisplatin in MPM previously untreated with chemotherapy or investigational agents (Arm C).

**REVISED TEXT:**

**Study Design:** This will be a multi-arm, multicenter, non-randomized, parallel-group, uncontrolled, open-label Phase IB study designed to evaluate the safety, tolerability and preliminary activity of GSK3052230 in combination with paclitaxel + carboplatin in previously untreated metastatic squamous NSCLC (Arm A), in combination with docetaxel in metastatic squamous NSCLC that has progressed after **at least** 1 line of chemotherapy (Arm B), or in combination with pemetrexed + cisplatin in MPM previously untreated with chemotherapy or investigational agents (Arm C).

**CHANGE 4: Exploratory Endpoints and Objectives**(new text **bold and underlined**, deleted text in ~~strikethrough~~)**Section Summary****PREVIOUS TEXT:****Objectives and Endpoints:**

The primary objectives and endpoints are noted below. The full objectives and endpoints (primary, secondary and translational) are located in the main protocol in Section 2.

**REVISED TEXT:****Objectives and Endpoints:**

The primary objectives and endpoints are noted below. The full objectives and endpoints (primary, secondary and translational exploratory) are located in the main protocol in Section 2.

Section: 2.3 Exploratory

**PREVIOUS TEXT:**

	<b>Objectives</b>
<b>Exploratory</b>	To develop and validate a Fluorescence <i>in situ</i> hybridization (FISH) -based assay to measure <i>FGFR1</i> gene amplification status..

	<b>Endpoint</b>
<b>Exploratory</b>	Identification and validation of alternative measures of FGF signaling pathway deregulation retrospectively (eg, FGF2 overexpression) as predictive biomarkers for subject selection and potential development of a companion diagnostic

**REVISED TEXT:**

	<b>Objectives</b>
<b>Exploratory</b>	To develop and validate <u>an assay to measure of <i>FGFR1</i> gene amplification status such as, but not limited to</u> , a Fluorescence <i>in situ</i> hybridization (FISH) -based assay <u>to measure <i>FGFR1</i> gene amplification status</u> .

	<b>Endpoint</b>
<b>Exploratory</b>	Identification and validation of alternative measures of FGF signaling pathway deregulation retrospectively <u>such as ligand or receptor overexpression for example but not limited to FGF2 or FGFR1 expression</u> FGF2 overexpression as predictive biomarkers for subject selection and potential development of a companion diagnostic

**CHANGE 5: Number of subjects**  
(new text **bold and underlined**, deleted text in ~~strikethrough~~)

Section: Summary

**NEW TEXT, Summary section:**

**Number of Subjects:** Approximately 70 subjects (minimum of 38 and up to 120, alternative dosing cohorts could potentially add another ~6 to ~40 subjects).

**NEW TEXT, Section 3.1:**

**Number of Subjects:** Approximately 70 subjects (minimum of 38 and up to 120, alternative dosing cohorts could potentially add another ~6 to ~40 subjects).

**CHANGE 6: Preclinical data on GSK3052230**

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

**PREVIOUS TEXT:**

**1.4.1.1 Preclinical data on GSK3052230**

Seventy-eight tumor-derived xenograft models were treated with GSK3052230 (FP1039) as a single agent. Twenty-eight models were found to show significant tumor growth inhibition (TGI), including models of NSCLC, small cell lung cancer, mesothelioma, squamous cell carcinoma of the head and neck (SCCHN), endometrial, colon and breast cancer [Harding, 2010; Harding, 2013]. In lung cancer xenografts, GSK3052230-treated tumors harboring *FGFR1* gene amplification displayed an average of 56% TGI compared to 22% TGI in non-amplified *FGFR1* xenografts (p=0.03)[ Harding, 2013]. FGF2 mRNA levels displayed the highest ratio (247.7-fold) of median gene expression between GSK3052230 responder and nonresponder xenograft models and was the only marker that correlated with response in the subset of non-amplified *FGFR1* lung cancer xenografts where significant tumor growth inhibition was observed [Harding, 2013].

To further extend this observation, GSK3052230 was tested in models of mesothelioma, a tumor type shown to express high levels of FGF2 mRNA in cell lines and in primary tumor specimens [DeYoung, 2014]. GSK3052230 inhibited MAPK signaling as evidenced by decreased phospho-ERK levels in both NCI-H226 and MSTO-211H cells. When both cell lines were grown as tumor xenografts in mice, GSK3052230 inhibited tumor growth in a dose-dependent manner (NCI-H226: 16 – 78% TGI; MSTO-211H: 20 – 50% TGI). Because FGFs also play a key role in angiogenesis, the effects of GSK3052230 on tumor vessel

formation in NCI-H226 xenografts were explored [DeYoung, 2014]. Dose-dependent and statistically-significant reductions in tumor vessel density were observed in GSK3052230-treated tumors compared to vehicle-treated tumors using MECA-32 endothelial cell IHC staining. Therefore, *FGFR1* amplification or FGF2 overexpression served as predictive markers of response to GSK3052230.

**REVISED TEXT:****1.4.1.1 Preclinical data on GSK3052230**

Seventy-eight tumor-derived xenograft models were treated with GSK3052230 (FP1039) as a single agent. Twenty-eight models were found to show significant tumor growth inhibition (**TGI**), including models of NSCLC, small cell lung cancer, mesothelioma, squamous cell carcinoma of the head and neck (SCCHN), endometrial, colon and breast cancer [Harding, 2010; Harding, 2013]. In lung cancer xenografts, GSK3052230-treated tumors harboring *FGFR1* gene amplification displayed an average of 56% tumor growth inhibition **TGI** compared to 22% tumor growth inhibition **TGI** in non-amplified *FGFR1* xenografts (p=0.03)[ Harding, 2013]. FGF2 mRNA levels displayed the highest ratio (247.7-fold) of median gene expression between GSK3052230 responder and nonresponder xenograft models and was the only marker that correlated with response in the subset of non-amplified *FGFR1* lung cancer xenografts where significant tumor growth inhibition was observed [Harding, 2013].

**To further extend this observation, GSK3052230 was tested in models of mesothelioma, a tumor type shown to express high levels of FGF2 mRNA in cell lines and in primary tumor specimens [DeYoung, 2014]. GSK3052230 inhibited MAPK signaling as evidenced by decreased phospho-ERK levels in both NCI-H226 and MSTO-211H cells. When both cell lines were grown as tumor xenografts in mice, GSK3052230 inhibited tumor growth in a dose-dependent manner (NCI-H226: 16 – 78% TGI; MSTO-211H: 20 – 50% TGI). Because FGFs also play a key role in angiogenesis, the effects of GSK3052230 on tumor vessel formation in NCI-H226 xenografts were explored [DeYoung, 2014]. Dose-dependent and statistically-significant reductions in tumor vessel density were observed in GSK3052230-treated tumors compared to vehicle-treated tumors using MECA-32 endothelial cell IHC staining.** Therefore, *FGFR1* amplification or FGF2 overexpression served as predictive markers of response to GSK3052230.

**CHANGE 7: Subject selection criteria, Section 3.2**

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

**PREVIOUS TEXT:**

Inclusion criteria 2:

**Arm C:** recurrent after local therapy or unresectable malignant pleural mesothelioma (MPM) with measurable lesions.

**Arm A:** Subjects who have received no prior therapy for Stage IV or recurrent metastatic disease. Note, to avoid any undue delay of initiating systemic chemotherapy for these subjects with newly diagnosed metastatic disease, it is allowed to initiate the first cycle of chemotherapy while eligibility for the study is still being determined, as long as the first dose of GSK3052230 is given no later than Cycle 2 Day 1 of chemotherapy. In addition, subjects with Stage IV disease and recurrence after previous NSCLC that has been treated with surgery and adjuvant chemotherapy or a radio-chemotherapy regimen with curative intent are eligible, provided 6 months has passed since this treatment ended [TNM classification of malignant tumors, 7<sup>th</sup> edition, 2009; Edge, 2010].

**Arm B:** Subjects who have documented tumor progression (based on radiological imaging) or intolerance after receiving only one prior line of platinum containing combination chemotherapy for Stage IV or recurrent metastatic disease [TNM classification of malignant tumors, 7<sup>th</sup> edition, 2009; Edge, 2010]. Continued ‘maintenance’ chemotherapy will be considered part of the first line regimen if the same agents are used. If new agents are used for maintenance treatment, this will be considered a second line of therapy. Note: first line treatment should not include docetaxel but may have included paclitaxel.

Inclusion criteria 3:

Availability of archival tumor tissue required for assessment of deregulated FGF pathway signalling, eg, *FGFR1* amplification or FGF2 expression. If archival tissue is not available, a fresh biopsy is required. Please refer to Section 7.7.1.

**In Arms A and B,** subjects will be prospectively screened for *FGFR1* gene amplification using a FISH assay (note, local testing is permitted for pre-screening of subjects prior to central testing). For inclusion in this study, based on the central laboratory testing, *FGFR1* gene amplification must meet one of the following criteria: a ratio of *FGFR1*/CEN 8 of  $\geq 2$ ; or average number of *FGFR1* signals per tumor nucleus of  $\geq 6$ ; or the percentage of tumor nuclei containing  $\geq 5$  *FGFR1* signals is  $\geq 50\%$ .

Inclusion criteria 3:

Measurable disease per RECIST version 1.1.

Inclusion criteria 8:

Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 for Arm A subjects and 0-2 for Arms B and C.

Inclusion criteria 10, Table 1:

Serum Creatinine Or Measured or Calculated Creatinine Clearance <sup>c</sup>	$\leq 1.5 \times \text{ULN}$ Or $\geq 45 \text{ mL/min}$
Cardiac	
Left ventricular ejection fraction	$\geq \text{LLN}$ (according to local institutional norms) by ECHO

Exclusion criteria 1:

For Arms A, B, C: Treatment with any FGFR inhibitor.

Exclusion criteria 10:

Symptomatic leptomeningeal or brain metastases or spinal cord compression.

**NOTE:** Subjects previously treated for these conditions are eligible if they meet **both** of the criteria below:

(1) have had stable CNS disease for at least 4 weeks after local therapy as assessed by imaging (contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT)),

#### REVISED TEXT:

Inclusion criteria 2:

**Arm C:** recurrent after local therapy or unresectable malignant pleural mesothelioma (MPM) with measurable lesions.

**Arm A:** Subjects who have received no prior therapy for Stage IIIB or Stage IV or recurrent metastatic disease. Note, to avoid any undue delay of initiating systemic chemotherapy for these subjects with newly diagnosed metastatic disease, it is allowed to initiate the first cycle of chemotherapy while eligibility for the study is still being determined, as long as the first dose of GSK3052230 is given no later than Cycle 2 Day 1 of chemotherapy. In addition, subjects with Stage IIIB or Stage IV disease and recurrence after previous NSCLC that has been treated with surgery and adjuvant chemotherapy or a radio-chemotherapy regimen with curative intent are eligible, provided 6 months has passed since this treatment ended [TNM classification of malignant tumors, 7<sup>th</sup> edition, 2009; Edge, 2010].

**Arm B:** Subjects who have documented tumor progression (based on radiological imaging) or intolerance after receiving only one or at least one prior line of platinum containing combination chemotherapy for Stage IIIB or Stage IV or recurrent metastatic disease [TNM classification of malignant tumors, 7<sup>th</sup> edition, 2009; Edge, 2010]. ~~Continued 'maintenance' chemotherapy will be considered part of the first line regimen if the same agents are used. If new agents are used for maintenance treatment, this will be considered a second line of therapy.~~ Note: first line Prior treatment should not include docetaxel but may have included paclitaxel.

Inclusion criteria 3:

Availability of archival tumor tissue required for assessment of deregulated FGF pathway signalling, eg but not limited to, FGFR1 amplification or FGF2 or FGFR1 expression. If archival tissue is not available, a fresh biopsy is required. Please refer to Section 7.7.1.

**In Arms A and B,** subjects will be prospectively screened for *FGFR1* gene amplification using a FISH assay (note, local testing is permitted for pre-screening of subjects prior to central testing) for the dose expansion and the MTD/MFD cohorts only. For inclusion in this study, based on the central laboratory testing, *FGFR1* gene amplification must meet one of the following criteria: a ratio of

*FGFR1/CEN 8 of  $\geq 2$ ; or average number of *FGFR1* signals per tumor nucleus of  $\geq 6$ ; or the percentage of tumor nuclei containing  $\geq 5$  *FGFR1* signals is  $\geq 50\%$ .*

Inclusion criteria 4:

Measurable disease per RECIST version 1.1 **(Arm A and B) and modified RECIST for Arm C.**

Inclusion criteria 8:

Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 for Arms A **and C** subjects and 0-2 for Arms **B and C**.

Inclusion criteria 10, Table 1:

Serum Creatinine Or Measured or Calculated Creatinine Clearance <sup>c</sup>	$\leq 1.5 \times ULN$ Or $\geq 45 \text{ mL/min (Arm A or B)} \geq 65 \text{ mL/min (Arm C)}$
Cardiac	
Left ventricular ejection fraction	$\geq 50\% LLN$ (according to local institutional norms) by ECHO

Exclusion criteria 1:

For Arms A, **B, and C**: Treatment with any FGFR inhibitor.

Exclusion criteria 10:

Symptomatic leptomeningeal or brain metastases or spinal cord compression.

**NOTE:** Subjects previously treated for these conditions are eligible if they meet **both** of the criteria below:

(1) have had stable CNS disease for at least 4 weeks after local therapy as assessed by imaging (contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT)) **prior to Day 1**,

**CHANGE 8: Intra-subject dosing and alternative dosing and schedule cohorts**  
(new text **underlined**, deleted text in ~~strikethrough~~)

**NEW TEXT:**

#### 4.2.6 Intra-Subject Dose Escalation or Dose De-escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the higher dose level cohort from the 3+3 phase of the study has been cleared without a DLT, and after review of all safety data and approval by a GSK Medical Study Physician and discussion with the investigator. The subject on a lower dose level may be increased up to the highest dose level tested. In this case, the subject may begin dosing at the higher dose level as it will have already been demonstrated to be tolerable and monitoring will be performed as described in the protocol. For example, a subject who enrolled at a dose level below the MTD (or MFD) and may be eligible for dose increases if the investigator believes the subject could benefit.

#### 4.2.6.1 Alternative Dosing and Schedule Cohorts

Additional doses and schedules may be explored based on emerging pharmacokinetic and safety data. Alterations may be made to the schedule of PK/PD sampling based on emerging PK data.

The sample size of the “alterative dosing and schedule cohorts” will be based on the 3 + 3 design with potential to expand to up to 30 subjects in this regimen.

The rationale for exploring this alterative dosing and/or schedule is to expand on the safety, tolerability and preliminary efficacy.

#### 4.5.1.1 Study treatments: Alternative Dosing and Schedule cohorts

Subjects in these expansion cohorts will be dosed based on the pharmacokinetic and emerging safety data from the ongoing study. This will be determined at FGF117360 Study Investigator meetings (example: dose escalation meeting) and the minutes and agreements would be provided to IRB/Ethics prior to dosing in this “Alternative Dosing and Schedule” Cohorts.

**CHANGE 9: Subject selection criteria, Section 3.2**  
(new text **bold and underlined**, deleted text in ~~strikethrough~~)

#### PREVIOUS TEXT:

##### 4.7.1 Dose Delays

Chemotherapy be reduced or delayed for toxicity, or in the interest of administration in Arm A and Arm B may subject safety per investigator discretion.

##### 4.7.4 GSK3052230 Dose Modifications

If the toxicity is potentially related to both GSK3052230 and chemotherapy as given in Arm A or B, please refer to dose modification for chemotherapy in Section 4.7.2 and Section 4.7.3 for potential dose reduction of both study treatments.

#### REVISED TEXT:

##### 4.7.1 Dose Delays

Chemotherapy administration in all arms Arm A and Arm B may be reduced or delayed for toxicity, or in the interest of subject safety per investigator discretion.

##### 4.7.4 GSK3052230 Dose Modifications

If the toxicity is potentially related to both GSK3052230 and chemotherapy as given in ~~Arm A or B~~, all arms, please refer to dose modification for chemotherapy

in Section 4.7.2 and Section 4.7.3 for potential dose reduction of both study treatments.

**CHANGE 10: Section 7, Time and Events**

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

**PREVIOUS TEXT:****Table 10 Time and Events Schedule**

<b>Time and Events Schedule for FGF117360</b>		Screen	Cycle 1				Cycle 2				Additional Cycles				Every 4 Cycles, D1	EOT	30 day F/U
			D1	D8	D9	D15	D1	D8	D15	D1	D8	D15					
Visit Window	Tissue prescreen for Arms A and B within 60 days and all other screening assessments within 30 days of C1D1. Visit windows of $\pm 2$ days during study through EOT, +7 days for F/U. Cycle 1 Day 9 assessments for Arm C only.																
Physical exam, weight, and height (baseline only)	Not needed C1D1 if screening assessments within prior 72 hrs. Complete physical exam at screening. Abbreviated disease-oriented physical exam subsequently.	X	X					X			X					X	X
Ophthalmologic Exam	To be performed by ophthalmologist or qualified optometrist.	X	Perform assessment if subject discontinues prior to C4.										C4 only				
ECHO	Perform at EOT if subject discontinues prior to C4.	X											C4 only	early disc			
Forced Vital Capacity	Assess D1 of every odd cycle, Arm C only	X	X							O							
Archival Tumor Tissue	Archived tumor tissue (or fresh biopsy if no archival tissue).	X															
Brain Scan		X	every 12 weeks $\pm 1$ week if positive at Screening, or as clinically indicated														

## REVISED TEXT:

Table 10 Time and Events Schedule

Time and Events Schedule for FGF117360	Screen	Cycle 1				Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U
		D1	D8	D9	D15	D1	D8	D15	D1	D8	D15			
Visit Window														
Physical exam, weight, and height (baseline only)	Not needed C1D1 if screening assessments within prior 72 hrs. Complete physical exam at screening. Abbreviated disease-oriented physical exam subsequently.	X	X				X			X			X	X
Weight	<u>Note, during dosing period weight should be captured on Day 1 of each cycle. It can be obtained more frequently per institutional standards (example: if required at each infusion)</u>	X	X				X			X			X	X
Ophthalmologic Exam	To be performed by ophthalmologist or qualified optometrist. ( <u>Visit windows of <math>\pm 7</math> days post baseline</u> ).	X											C4 only	
ECHO	Perform at EOT if subject discontinues prior to C4. ( <u>Visit windows of <math>\pm 7</math> days post baseline</u> ).	X											C4 only	early disc
Forced Vital Capacity	Assess D1 of every odd cycle, Arm C only. ( <u>Visit windows of <math>\pm 7</math> days post baseline</u> ).	X	X									<u>Odd</u>		
Archival Tumor Tissue	Archived tumor tissue (or fresh biopsy if no archival tissue). <u>Once the subject provides consent, a tumor sample may be submitted for Arms A and B for FGFR1 amplification at any time (there</u>	X												

Time and Events Schedule for FGF117360		Screen	Cycle 1			Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U	
			D1	D8	D9	D15	D1	D8	D15	D1	D8	D15			
	<u>is no time limit or window).</u>														
Brain Scan	<u>Obtain only if symptomatic</u>	X													

**CHANGE 11: Section 7.3.9, Pregnancy Testing and Reporting**  
(new text **bold and underlined**, deleted text in ~~strikethrough~~)**PREVIOUS TEXT:**

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form.

**REVISED TEXT:**

Any pregnancy that occurs during study participation (**note, study participation is defined as the time of the first dose of study drug GSK3052230 is administered**) must be reported using a clinical trial pregnancy form.

**CHANGE 12: Section 7.4.1.5**

**MOVE TEXT:** Move section below from protocol Section 7.4.2.1 to Section 7.4.1.5

**Tips on Lymph Node Measurements:**

Lymph nodes are considered as a separate organ to measure, and up to two lymph nodes can be measured per patient by RECIST v1.1. For unidimensional lymph node measurements, use the short axis of the lymph node at baseline and then at every followup scan. To be considered as pathologically enlarged and measurable at baseline, the lymph node short axis diameter should be  $\geq 15$  mm.

**CHANGE 13: Section 7.7.1, Central Confirmation of FGF Signalling Pathway Status and Translational Research**

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

**PREVIOUS TEXT:**

In Arm C, FGF2 and/or FGFR1 expression will be evaluated retrospectively by IHC to determine if expression levels of these proteins are associated with response to GSK3052230

Any remaining tissue from this study may be used for:

- Development and validation of a potential IHC assay and companion diagnostic test, e.g., but not limited to *FGFR1* gene amplification by FISH or FGF2 and/or FGFR1 expression by IHC.
- Alternative biomarkers of FGF pathway signalling such as other ligands or receptors.

**REVISED TEXT:**

In Arm C, FGF2 **and/or FGFR1 expression** will be evaluated retrospectively by IHC to determine if expression levels of ~~FGF2~~these proteins are associated with response to GSK3052230

Any remaining tissue from this study may be used for:

- Development and validation of a potential IUO assay and companion diagnostic test, e.g., but not limited to *FGFR1* gene amplification by FISH or FGF2 and/or *FGFR1* expression by IHC.
- Alternative biomarkers of FGF pathway signalling such as other ligands or receptors.

**CHANGE 14: Section 9.1,**

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

**PREVIOUS TEXT:**

In Arm A and Arm B, the prophylactic use of hematopoietic colony stimulating factors is not allowed in Cycle 1. However, growth factor support therapy (e.g., G-CSF, GM-CSF) may be administered as a prophylaxis for chemotherapy-related neutropenia according to the NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors v.1.2010 [NCCN, 2010] or the European Organisation for Research and Treatment of Cancer guidelines for the use of G-CSFs [Aapro, 2011]

**REVISED TEXT:**

~~In Arm A and Arm B, The prophylactic use of hematopoietic colony stimulating factors is not recommended allowed in Cycle 1~~ of the dose escalation portion of the study. Local institutional practices vary globally, please discuss with the GSK medical team if there is a need to have prophylactic use for subjects during the dose escalation period or alternative dose finding period. During expansion phase, However, growth factor support therapy (e.g., G-CSF, GM-CSF) may be administered as a prophylaxis for chemotherapy-related neutropenia according to the NCCN Clinical Practice Guidelines in Oncology: Myeloid Growth Factors v.1.2010 [NCCN, 2010] or the European Organisation for Research and Treatment of Cancer guidelines for the use of G-CSFs [Aapro, 2011].

**CHANGE 14: Section 12.7, Interim Analysis,**

(new text **bold and underlined**, deleted text in ~~strikethrough~~)

The rules are also shown in a tabular format below:

**REVISED and NEW TEXT:**

For Arm C only, the totality of the data will be reviewed prior to stopping for futility and the futility stopping rules are non-binding. The final analysis for Arm C will require 16/30 responses as specified in Table 16. This is equivalent to a binomial test at the final analysis with alpha level 0.10 and power of 82%.

The rules for Parts A, B and C are also shown in a tabular format below:

**CHANGE 15: Section 15.3, Appendix 3: Cockcroft-Gault Formula**(new text **bold and underlined**, deleted text in ~~strikethrough~~)**PREVIOUS TEXT:**

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

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

**REVISED TEXT:**

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

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

## Amendment 3

### Where the Amendment Applies

This amendment applies to all sites.

### Summary of Amendment Changes with Rationale

Amendment 3 changed Arm C of the protocol from GSK3052230 monotherapy of subjects with solid tumors to combination chemotherapy (GSK3052230 plus pemetrexed and cisplatin) of subjects with mesothelioma. Associated additions to the protocol include safety precautions for pemetrexed and cisplatin, use of modified RECIST for evaluation of clinical response, assessment of forced vital capacity. Patient reported outcomes using the Lung Cancer Symptom Scale (LCSS) was added for subjects with lung cancer and LCSS-meso for subjects with mesothelioma. Additional background and rationale were added. Stopping rules and sample size were modified. Translational research objectives were clarified.

### List of Specific Changes

#### *Section 1.1 The FGF Pathway in Cancer*

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The last 3 paragraphs of this section have been re-arranged into a new section, Section 1.2. New text added to the end of the first 3 paragraphs:

**FGF ligand-dependent signaling occurs through autocrine production of FGFs directly from cancer cells or through paracrine production of FGFs from the local stroma [Turner, 2010]. FGF2-FGFR1 autocrine feedback loops have been characterized in several tumor types and may have a role in drug resistance upon exposure to chemotherapy or targeted agents such as gefitinib [Sharpe, 2011; Marek, 2009]. Overexpression of FGFs is readily detectable by immunohistochemical approaches, as several studies have shown high levels of FGF2 protein in MPM tumor specimens [Kumar-Singh, 1999; Davidson, 2004; Li, 2011]. Further, overexpression or high systemic levels of FGF ligands correlate with tumorigenesis and poor patient outcome. These discoveries support the notion that specific treatments targeting FGF pathway alterations may provide benefit in this population.**

#### *Section 1.1 Lung Cancer*

This is a new section that was made from the last 3 paragraphs in Section 1.1.

PREVIOUS TEXT:

In animal models, activation of an inducible FGFR1 gene in a mouse mammary tumor virus-Wnt-1 transgenic mouse dramatically enhanced mammary tumorigenesis [Pond, 2010]. Further it has been shown that FGFR1 gene amplification is associated with

sensitivity to FGFR1 inhibition in non-small cell lung cancer (NSCLC) cell lines [Dutt, 2011].

Various in vitro studies utilizing NSCLC cell lines reveal that specific FGFs (FGF2 and FGF9) as well as FGFR1 and FGFR2 are frequently co-expressed [Berger, 1999; Chandler, 1999; Fischer, 2008; Kono, 2009]. In addition, frequent expression of FGF2, FGFR1 and FGFR2 mRNA and protein in primary NSCLC specimens have been demonstrated [Kono, 2009].

The relevance of the FGF pathway in cancer has also been studied in human primary specimens. First, it has been demonstrated that FGFR1 gene is amplified at the genomic level in a subset of breast, ovarian, and lung cancer subjects [Knights, 2010]. This amplification contributes to the characteristics that allow tumor formation. Further, it has been shown that increased expression of FGFRs, FGFR1 gene amplification, or production of FGFs correlates with poor prognosis in a variety of tumor types including NSCLC [Nguyen, 1994; Kim, 2013]. For example, reduced metastasis-free survival was found in a subset of breast cancer subjects carrying the 8p11-12 amplification containing the FGFR1 gene [Gelsi-Boyer, 2005; Grose, 2005]. Recently, a focal amplification of the FGFR1 gene has been detected in approximately 20% of subjects with squamous NSCLC [Weiss, 2010], a histological subtype of NSCLC which previously had very limited evidence of molecular alterations amenable to targeted drug therapy. This discovery supports the notion that specific treatments targeting FGF pathway alterations may provide benefit in this population.

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~~In animal models, activation of an inducible FGFR1 gene in a mouse mammary tumor virus Wnt 1 transgenic mouse dramatically enhanced mammary tumorigenesis [Pond, 2010].~~

Various in vitro studies utilizing NSCLC cell lines reveal that specific FGFs (FGF2 and FGF9) as well as FGFR1 and FGFR2 are frequently co-expressed [Berger, 1999; Chandler, 1999; Fischer, 2008; Kono, 2009]. In addition, frequent expression of FGF2, FGFR1 and FGFR2 mRNA and protein in primary NSCLC specimens have been demonstrated [Kono, 2009]. Further it has been shown that FGFR1 gene amplification is associated with sensitivity to FGFR1 inhibition in non-small cell lung cancer (NSCLC) cell lines [Dutt, 2011].

~~The relevance of the FGF pathway in cancer has also been studied in human primary specimens. First, it has been demonstrated that FGFR1 gene is amplified at the genomic level in a subset of breast, ovarian, and lung cancer subjects [Knights, 2010]. This amplification contributes to the characteristics that allow tumor formation. Further, it has been shown that Increased expression of FGFRs, FGFR1 gene amplification, or production of FGFs correlates with poor prognosis in a variety of tumor types including NSCLC [Nguyen, 1994; Kim, 2013]. For example, reduced metastasis free survival was found in a subset of breast cancer subjects carrying the 8p11-12 amplification containing the FGFR1 gene [Gelsi-Boyer, 2005; Grose, 2005]. Recently, A focal amplification of the FGFR1 gene has been detected in approximately 20% of subjects with squamous NSCLC [Weiss, 2010], a histological subtype of NSCLC which previously had very~~

limited evidence of molecular alterations amenable to targeted drug therapy. This discovery supports the notion that specific treatments targeting FGF pathway alterations may provide benefit in this population.

### ***Section 1.3 Mesothelioma***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~) New section added:

**Malignant mesothelioma remains a deadly disease with few effective therapies. Although the incidence of mesothelioma is leveling off in the United States, the incidence in Western Europe, China, Russia, and India continues to rise [Ettinger, 2012]. The median overall survival ranges from 9-17 months regardless of disease stage [Tsao, 2009]. The standard of care for the front-line treatment of mesothelioma remains cisplatin and pemetrexed with the combination regimen having a 41% response rate, a median time to progression of 5.7 months, a median overall survival of 12.1 months, and significant improvements in quality of life [Vogelzang, 2003; Gralla, 2003]. There remains no widely approved regimen for recurrent mesothelioma although pemetrexed (if not used in the front-line), vinorelbine, and gemcitabine are agents that have been used with limited success [Jassem, 2008; Stebbing, 2009; Manegold, 2005]. A recently completed Phase III study of vorinostat versus placebo in 660 patients with recurrent mesothelioma reported a median progression-free survival (PFS) of 6.3 versus 6.1 weeks and median overall survival (OS) of 31 versus 27 weeks in vorinostat vs. placebo respectively, which represents the largest Phase III study completed to date in recurrent mesothelioma [Krug, 2011]. These poor PFS and OS data underscore the need for more effective therapies in recurrent mesothelioma.**

#### ***Section 1.4.1.1 Preclinical data on GSK3052230***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~) New text added:

Seventy-eight tumor-derived xenograft models were treated with GSK3052230 (FP1039) as a single agent. Twenty-eight models were found to show significant tumor growth inhibition, including models of NSCLC, small cell lung cancer, **mesothelioma**, squamous cell carcinoma of the head and neck (SCCHN), endometrial, colon and breast cancer [Harding, 2010; Harding, 2013]. In lung cancer xenografts, GSK3052230-treated tumors harboring FGFR1 gene amplification displayed an average of 56% tumor growth inhibition compared to 22% tumor growth inhibition in non-amplified FGFR1 xenografts (p=0.03)[ Harding, 2013]. **FGF2 mRNA levels displayed the highest ratio (247.7-fold) of median gene expression between GSK3052230 responder and nonresponder xenograft models and was the only marker that correlated with response in the subset of non-amplified FGFR1 lung cancer xenografts where significant tumor growth inhibition was observed [Harding, 2013]. Therefore, FGFR1 amplification or FGF2 overexpression served as predictive markers of response to GSK3052230.**

### ***Section 1.5.3 Pemetrexed/cisplatin***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~) New section added:

**Pemetrexed is a folate analog inhibitor that disrupts folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, and glycynamide ribonucleotide formyltransferase, which are folate-dependent enzymes involved in de novo biosynthesis of thymidine and purine nucleotides. Cisplatin is a heavy-metal complex containing a central platinum atom with 2 chloride atoms and 2 ammonia molecules in the cis position. Pemetrexed in combination with cisplatin is recommended for the treatment of mesothelioma [Alimta PI, 2004].**

**The most common adverse reactions (incidence >20%) with single-agent use of pemetrexed are fatigue, nausea, and anorexia. Additional common adverse reactions when used in combination with cisplatin include vomiting, neutropenia, leukopenia, anemia, stomatitis/pharyngitis, thrombocytopenia, and constipation [Alimta PI, 2004].**

**Common adverse reactions (incidence >20%) associated with cisplatin include nephrotoxicity, ototoxicity, myelosuppression, and nausea/vomiting. Other toxicities include vascular complications, serum electrolyte imbalance, Hyperuricemia, neurotoxicity, ocular toxicity, anaphylactic-type reactions, and hepatotoxicity [Platinol PI, 2010].**

### ***Section 1.6 Summary of Risk Management***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~) New text added:

Anterior uveitis:

- Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of cisplatin.**

Peripheral neuropathy:

- Peripheral neuropathy is a potentially overlapping toxicity between GSK3052230 and, taxanes such as paclitaxel and docetaxel, **and cisplatin**.

Hematologic toxicity:

Furthermore, paclitaxel or, docetaxel, **and cisplatin** have known bone-marrow toxicity

**Nephrotoxicity:**

- **Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of cisplatin. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m<sup>2</sup>. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given.**
- **One patient with severe renal impairment (creatinine clearance 19 mL/min) who did not receive folic acid and vitamin B12 died of drug-related toxicity following administration of pemetrexed alone.**

**Ototoxicity:**

- **Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m<sup>2</sup>, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of cisplatin has been reported. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Careful monitoring per standard of care should be performed.**

***Section 2 Objectives and Endpoints and Synopsis***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

***Primary Objectives:***

To characterize the safety and tolerability of GSK3052230 in combination with chemotherapy regimens (~~Arm A and B~~) or as ~~single agent~~ (~~Arm C~~).

To determine the regimen of GSK3052230 in combination with chemotherapy (~~Arm A and B~~) for evaluation in future studies based on the maximum tolerated dose (or maximum feasible dose).

***Primary Endpoints:***

Best response defined as complete or partial response, stable disease or progressive disease according to RECIST 1.1 **or modified RECIST (for MPM)**

ORR defined as the proportion of subjects with investigator-assessed confirmed complete response or partial response per RECIST 1.1 **or modified RECIST (for MPM)**

***Secondary Objectives***

**Assess improvement in Pulmonary Function Tests in Patients with MPM.**

*Secondary Endpoints*

PFS is defined as the interval between first dose of GSK3052230 and the earliest date of disease progression or death due to any cause by investigator assessment per RECIST 1.1 **or modified RECIST (for MPM)**

**Change from baseline in Forced Vital Capacity (FVC) in patients with MPM.***Exploratory Objectives*

To identify biomarkers that may predict response **or resistance**

To evaluate the pharmacodynamic response in ~~tumors~~ **circulation** following treatment (~~re-biopsy is required for tumors that are accessible for biopsy~~ for Arm C)

To investigate additional measures of FGF signaling pathway deregulation as potential predictive biomarkers for GSK3052230 **in tissue**.

**To evaluate changes in patient reported outcomes.***Exploratory Endpoints*

Changes in ~~proteins/RNA~~ **circulating** biomarkers **(eg, proteins)** implicated in FGFR **or disease biology** signaling (eg. MAPK/PI3K pathways) and/or cancer development **signalling** in pre- and post -dose ~~tumor tissue~~ **blood samples**.

Association of FGFR1 gene amplification with clinical response to support the development of a laboratory developed test for an investigation use (LDT/only test (IUO) **and potential companion diagnostic** for subject selection.

Identification and validation of alternative measures of FGF signaling pathway deregulation as **retrospectively (eg, FGF2 overexpression) as predictive** biomarkers for subject selection **and potential development of a companion diagnostic**

**Change from baseline and association with ORR in observer and patient assessed components of the Lung Cancer Symptom Scale (LCSS) and LCSS-mesothelioma*****Section 3.1 Number of Subjects***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Approximately 70 subjects will be enrolled in the study (minimum of ~~~36~~**38** and up to ~~~104~~ **approximately 120**). In addition to minimum and maximum sample sizes for each arm, sample sizes that would be expected under the null and alternative hypothesis rates ~~for Arms A and B~~ are provided in Section 12.3.

### ***Section 3.2.1 Inclusion Criteria and Synopsis***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Inclusion criterion 2:

~~Arm C: advanced solid tumor with deregulated FGF pathway signaling, for which all lines of standard therapies have been exhausted or for which no standard treatment is available.~~

#### **Arm C: recurrent after local therapy or unresectable MPM with measurable lesions**

~~Arm C: Subjects who have exhausted all lines of standard therapies or for whom there is no standard treatment for the specific tumor. Note: squamous NSCLC subjects who have documented tumor progression (based on radiological imaging) after receiving two or more prior lines of systemic therapy (including platinum containing chemotherapy regimens) for Stage IV or recurrent metastatic disease may be enrolled [ of malignant tumors, 7th edition, 2009; , 2010]. Subjects with ER positive breast cancer having disease progression while on aromatase inhibitor therapy are allowed to continue aromatase inhibitor therapy, subjects with prostate cancer may continue to be treated with GnRH as clinically appropriate, and subjects with carcinoid cancer may continue treatment with octreotide.~~

#### **Arm C: Subjects who have received no prior systemic therapy for MPM.**

Inclusion criterion 3:

3. Availability of archival tumor tissue required for assessment of deregulated FGF pathway signaling e.g. FGFR1 amplification **or FGF2 expression**.

#### **In Arm C, FGF2 expression by IHC will be evaluated retrospectively in tissue samples by a central laboratory and is not required for study entry.**

Inclusion criterion 7:

~~For Arm A and B: Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 10.1.2 for at least 2 weeks prior to administration of the first dose of study treatment and for at least 6 months after the last dose of chemotherapy, to allow for clearance of any altered sperm. Arm C: No male contraception restrictions.~~

### ***Section 3.2.2 Exclusion Criteria and Synopsis***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Exclusion Criterion 1:

For Arms B, C: Treatment with any anti-cancer therapy (for biological anti-cancer therapies see criteria 2.) during the preceding 4 weeks or within 4 half-lives of the

therapy, whichever is longer (except: anti-cancer hormonal treatment of prostate cancer, breast cancer or octreotide for treatment of carcinoid cancer).

Exclusion criterion 11:

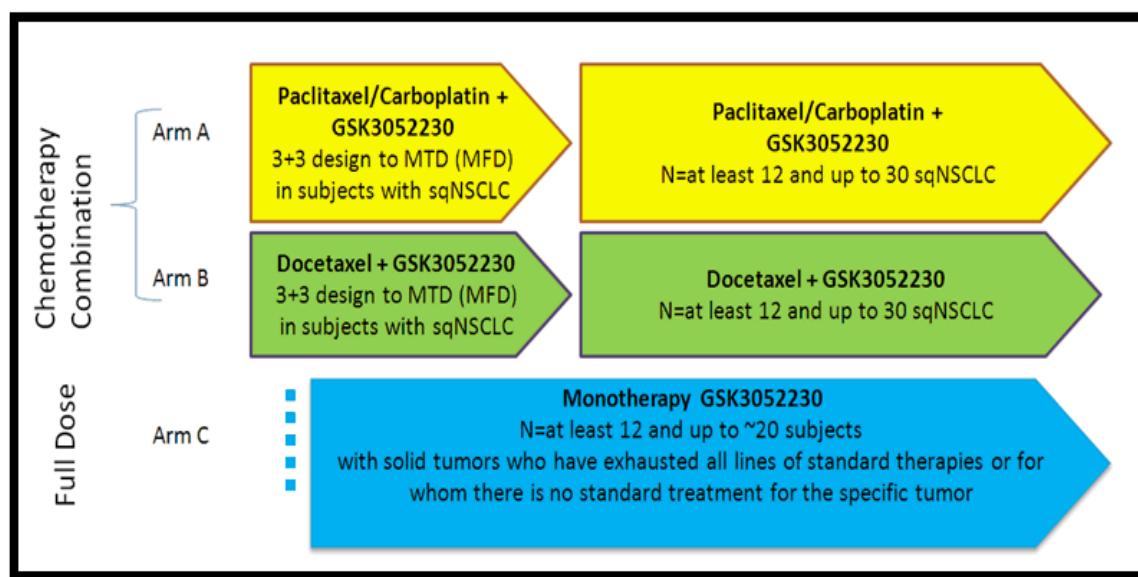
Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to study drugs (GSK3052230, docetaxel, paclitaxel, carboplatin, **pemetrexed, cisplatin**) and/or their excipients that contraindicates their participation

#### ***Section 4.1 Discussion of Study Design and Synopsis***

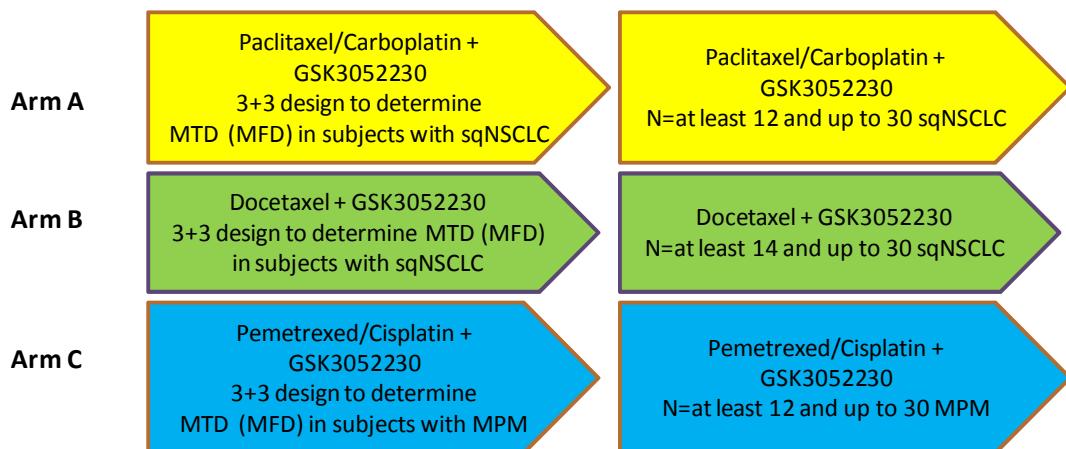
REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

This will be a multi-arm, multicenter, non-randomized, parallel-group, uncontrolled, open-label Phase IB study designed to evaluate the safety, tolerability and preliminary activity of GSK3052230 in combination with paclitaxel + carboplatin (Arm A), in combination with docetaxel (Arm B), or ~~GSK3052230 as monotherapy~~ **in combination with pemetrexed + cisplatin (Arm C)**. All subjects enrolled will have documented deregulation of FGF pathway signaling (e.g. FGFR gene amplification).

Previous Figure 1, Study Schema:



## Revised Figure 1, Study Schema:

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

~~Enrollment to Arms A and B will open first and simultaneously.~~ Dose escalation in Arm A and Arm B will follow a 3+3 design as outlined in Section 4.2 for determination of MTD (or MFD). A cohort expansion of at least 12 subjects will be treated at the MTD (or MFD) in each arm, with the option of expanding to a maximum of 30 subjects. Stopping rules based on anti-tumor activity ~~are outlined in Section 4.2.1 and Section 4.2.2~~ **were derived** according to a predictive probability design for each arm of the study **and are detailed in Section 4.2.1, Section 4.2.2** that allows for evaluation of success, **and 4.2.3** futility after each patient rather than at only two stages as in traditional designs. The decision on the timing of the initiation of Arm C will be determined by GSK and will be communicated to investigative centers directly and expediently in the form of a letter. ~~At least 12 subjects and up to a maximum of 20 subjects will be treated in Arm C.~~

GSK3052230 will be administered as a 30-minute intravenous (i.v.) infusion once a week (Day 1, Day 8, Day 15) of each 21-day cycle. Paclitaxel/carboplatin ~~and~~, docetaxel, **and pemetrexed/cisplatin** will be administered i.v. on Day 1 of each 21-day cycle. The number of cycles of paclitaxel/carboplatin will be limited to 4 to 6 cycles. Subjects may continue to receive docetaxel **and pemetrexed/cisplatin** until disease progression or as long as they are considered to derive benefit from treatment. Subjects who discontinue chemotherapy (Arm A and Arm B) for reasons other than disease progression, may continue to receive GSK3052230 as long as they are considered to derive benefit from the treatment according to the criteria in Section 6.3. After discontinuation of GSK3052230, subjects will return after approximately 30 days (see Time and Events Table Section 7.1) for a follow-up visit to collect safety assessments, after which they will be considered to have completed the study.

Blood samples for pharmacokinetic, pharmacogenetic, and translational research will be obtained at specified times during the study. Efficacy will be assessed every 2 cycles during the first year and every 4 cycles thereafter. ~~Paired tumor biopsies pre-dose and post-dose will be required from a minimum of 6 subjects with accessible tumors for~~

~~repeated biopsy in Arm C. Additional subjects may be asked to provide biopsies based on emerging data.~~

### ***Section 4.2 GSK3052230 plus Chemotherapy in Arm A and Arm B***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

~~Arm A and Arm B~~ Dose escalation will follow a 3 + 3 dose-escalation procedure . . .

#### ***Section 4.2.1 Arm A***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

A total of at least 12 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 12 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the ~~stopping rules. The futility boundaries (inclusive) for ORR for Arm A are 0/12, 1/14, 2/17, 3/20, 4/22, 5/24, 6/26, 7/27, 8/28, 9/29, and 10/30 subjects and are shown in tabular format in Section 12.7 rules summarized in Section . . .~~ Up to 30 subjects will be enrolled in Arm A. All available data will be considered in making enrollment decisions

#### ***Section 4.2.2 Arm B***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

A total of at least ~~42~~14 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After ~~42~~14 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules summarized. ~~The futility boundaries (inclusive) for ORR for Arm B are 0/14, 1/22, 2/26, 3/28, 4/29, and 5/30 subjects and are shown in tabular format~~ in Section 12.7.. Up to 30 subjects will be enrolled in Arm B. All available data will be considered in making enrollment decisions.

#### ***Section 4.2.3 Arm C (new section)***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

~~Arm C will open for enrollment subsequent to Amendment 3. The starting dose of GSK3052230 (Dose Level 0) in Arm C will be 10 mg/kg as long as the 5 mg/kg dose in combination with chemotherapy in Arm A did not exceed the MTD. Otherwise the starting dose level in Arm C will be Dose Level -1. Dose levels and escalation/de-escalation schema for GSK3052230 in combination with pemetrexed and cisplatin is presented in Table 3. Depending on emerging data, additional intermediate or lower dose-levels beyond those described may be explored.~~

**Table 5 Combination Therapy: Arm C GSK3052230 + Pemetrexed + Cisplatin**

<u>Dose Level</u>	<u>Dose of GSK3052230</u> <u>(Weekly)</u>	<u>Pemetrexed + Cisplatin</u> <u>(once every 21 days)</u>
<u>Dose Level -2</u>	<u>5 mg/kg</u>	<u>400 mg/m<sup>2</sup> + 60 mg/m<sup>2</sup></u>
<u>Dose Level -1</u>	<u>5 mg/kg</u>	<u>500 mg/m<sup>2</sup> + 75 mg/m<sup>2</sup></u>
<u>Starting Dose Level 0</u>	<u>10 mg/kg</u>	<u>500 mg/m<sup>2</sup> + 75 mg/m<sup>2</sup></u>
<u>Dose Level 1</u>	<u>20 mg/kg</u>	<u>500 mg/m<sup>2</sup> + 75 mg/m<sup>2</sup></u>

A total of at least 12 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 12 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm C are 2/12, 3/14, 4/16, 5/18, 6/20, 7/21, 8/23, 9/24, 10/25, 11/26, 12/27, 13/28, 14/29 and 15/30 subjects and are shown in tabular format in Section 12.7. Up to 30 subjects will be enrolled in Arm C. All available data will be considered in making enrollment decisions.

#### *Section 4.3 GSK3052230 in Arm C*

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

#### *Section 4.3 GSK3052230 in Arm C*

~~At least 6 and up to 18-20 subjects will be treated in Arm C at a dose of 20 mg/kg. Other doses may be explored in this arm~~

#### *Section 4.3.1 Rationale for Evaluation of GSK3052230 in Chemotherapy Combinations*

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

##### *4.3.1 Rationale for Evaluation of GSK3052230 in Chemotherapy Combination (Paclitaxel + Carboplatin, or Docetaxel) in NSCLC with deregulated FGF pathway signaling Combinations*

~~FGFR1 amplification has been identified in approximately 20% of squamous NSCLC with suggested tumor dependence on FGF pathway signaling [, 2010]. FGFR1 amplification has been associated with significantly shorter disease free and overall survival in NSCLC [Kim, 2013; Heist, 2012]. Carboplatin and paclitaxel can be used in first line therapy of NSCLC and docetaxel is a standard second line agent. **Pemetrexed and cisplatin is the standard first line therapy for mesothelioma.** Additive antitumor effect was demonstrated in tumor xenograft models treated with the combinations of GSK 3052230 and chemotherapy including paclitaxel and carboplatin as well as docetaxel. **Malignant pleural mesothelioma (MPM) is a tumor type where FGF2 ligand overexpression has been observed in a high percentage of primary specimens and where GSK3052230 preclinical efficacy has been observed in xenograft models.**~~

Based on the clinical and preclinical data, the combination of GSK3052230 in

combination with chemotherapy will be investigated in patients with NSCLC or with mesothelioma.

#### ***Section 4.3.2 Rationale for Evaluation of GSK3052230 Monotherapy***

REVISED TEXT: (new text **bold and underlined**, deleted text in strikethrough)

#### **Section 4.3.2 Rationale for Evaluation of GSK3052230 Monotherapy**

~~It is anticipated that GSK3052230 monotherapy will only demonstrate anti-tumor activity in the presence of deregulated FGF signaling pathway, specifically amplification or overexpression of FGF ligand(s) and/or receptor(s). Arm C will enroll subjects with deregulated FGF pathway signaling (e.g. FGFR gene amplification, FGF ligand overexpression, etc.). These subjects should have failed available standard therapies or have a cancer for which no standard therapies exists~~

#### ***Section 4.3.3 Rationale for Endpoints***

REVISED TEXT: (new text **bold and underlined**, deleted text in strikethrough)

**Symptom assessments as measured by the LCSS and LCSS-meso were added to increase the understanding of the patient experience and perceptions.**

#### ***Section 4.5.4 Pemetrexed and Cisplatin***

REVISED TEXT: (new text **bold and underlined**, deleted text in strikethrough)

#### **Section 4.5.4 Pemetrexed and Cisplatin**

**Subjects in Arm C will receive pre-treatment for pemetrexed and cisplatin according to institutional standards. Pemetrexed according to the dose level being investigated (Table 5) will be administered intravenously over 10 minutes (or according to local clinical standards) on Day 1 of each 21 day treatment cycle followed 30 minutes later by i.v. cisplatin infused over 2 hours.**

**Subjects will be hydrated and pre-medicated with folic acid and vitamin B12 supplements in order to reduce the incidence and severity of hematologic and gastrointestinal toxicities as well as cutaneous hypersensitivity reactions as per institutional guidelines. Recommendations for pre-medication are as follows:**

- 1-2 liters of fluid infused for 8-12 hours prior to cisplatin dose**
- 350-1000 µg folic acid, once daily, by mouth for seven days preceding the first dose of pemetrexed, during treatment, and for 21 days following the last dose of pemetrexed**
- 1000 µg vitamin B12 by intramuscular injection in the week preceding the first dose of pemetrexed and every three cycles thereafter (subsequent vitamin B12 injections may be given on the same day as pemetrexed)**

- 4 mg dexamethasone (or equivalent), twice daily, by mouth the day before, the day of, and the day after pemetrexed administration**

**Additional information can be found in the prescribing information for pemetrexed [Alimta Package Insert, 2012] and cisplatin [Platinol, 2010].**

***Section 4.7.2 Hematologic Toxicity Related to Chemotherapy***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~) Added to last row of Modification Instructions, Table 7

**Arm C: Restart combination chemotherapy reduced by 1 level for the chemotherapy dose according to Table 5.**

***Section 4.7.3 Non-hematologic Toxicity Related to Chemotherapy***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Table 8 Chemotherapy Dose Delay and Modifications for Non-hematologic Toxicity

Adverse Event	Action
Non-hematological, drug-related Grade 3 or 4 (except alopecia)	Hold chemotherapy until recovery to Grade $\leq 1$ . Arm A: Restart at dose levels reduced by 1 level for both agents according to Table 3. Arm B: Restart docetaxel reduced by 1 level according to Table 4 <b><u>Arm C: Restart combination chemotherapy reduced by 1 level for the chemotherapy dose according to Table 5</u></b>
<b>Exceptions</b>	
<u>Grade 2 neurotoxicity</u>	<b><u>Arm C: Withhold study treatment until recovery to Grade 1; then resume treatment with cisplatin reduced by 50% of previous dose</u></b>
<u>Grade 3 or 4 Peripheral neuropathy</u> <u>Neurotoxicity</u>	Withhold study treatment until patient recovers <u>recovery</u> to Grade 1; then resume treatment at dose reduced by 2 levels according to Table 3 (Arm A) or Table 4 (Arm B). <b><u>Permanently discontinue chemotherapy in Arm C</u></b> . If treatment delay is more than 2 weeks, re-initiation of treatment should be agreed with the GSK study physician.
<u>Mucositis, Grade 3 or 4</u>	<b><u>Arm C: Reduce pemetrexed only by 50% of previous dose</u></b>
<u>Serum creatinine <math>&lt;1.5</math> mg/100mL</u> <u>or BUN <math>&lt;25</math> mg/100mL</u>	<b><u>Arm C: Hold chemotherapy until serum creatinine <math>&gt;1.5</math> mg/100mL or BUN <math>&gt;25</math> mg/100mL</u></b>
<u>Creatinine clearance <math>&lt;45</math> mL/min</u>	<b><u>Arm C: Hold chemotherapy until creatinine clearance <math>\geq 45</math> mL/min</u></b>

### ***Section 5.1.2 Chemotherapeutic Agents***

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#### **Section 5.1.2 Paclitaxel + Carboplatin and Docetaxel Chemotherapeutic Agents**

Paclitaxel, carboplatin, ~~and~~ docetaxel, **pemetrexed, and cisplatin** will be sourced locally from commercial stock, except in countries where Regulatory Authorities mandate that the Sponsor must supply all non-investigational product (IPs) required for study participation. Investigators are responsible for ensuring that subjects receive supplies of paclitaxel, carboplatin, ~~and~~ docetaxel, **pemetrexed, and cisplatin** for the entire duration of the study, **as appropriate**. The contents of the label will be in accordance with all applicable regulatory requirements.

### ***Section 5.2 Preparation/Handling/Storage of GSK3052230***

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#### **Refer to the SPM (the FGF117360 Pharmacy Manual) for storage conditions.**

### ***Section 6.1 Screen Failures***

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#### Section 6.1 Screen ~~and Baseline~~ Failures

Data for screen ~~and baseline~~ failures....

### Section 7.1 Time and Event Schedules

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

<b>Table 10. Time and Events Schedule for FGF117360</b>		Screen	Cycle 1				Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U
			D1	D8	D9	D15	D1	D8	D15	D1	D8	D15			
Vital Signs	Arms A + B: Within 20 min before start of first chemotherapy infusion and within 20 min before start of GSK3052230 infusion. Arm C: Before start of GSK3052230 infusion.	X	X				X			X					
Forced Vital Capacity	<b><u>Assess D1 of every odd cycle</u></b>	X	X							O					
Tumor Tissue (fresh biopsy) for biomarker research	Arm C only: (minimum of 6 subjects). Predose sample +7 days prior to C1D1. EOT sample only upon progression.		*		*									*	
Circulating Biomarkers	Plasma sample collected predose (+7 days prior to C1D1)		X		X		X			<b><u>Arm C: D1 every cycle 1 year, then D1 every 2 cycles</u></b>			X		
LCSS (Arms A and B); LCSS-meso (Arm C)	<b><u>Must be administered first before any other tests or procedures. Study staff should check for completeness.</u></b>	X	X				X			X				X	X
ARMS A, B, C: GSK3052230	30 minute infusion.		X	X		X	X	X	X	X	X	X			
ARM B: Docetaxel	GSK3052230 infused & observed 1 hr prior to docetaxel <b><u>chemotherapy</u></b> infusions.		X				X			X					
ARM C: Pemetrexed + Cisplatin	<b><u>GSK3052230 infused &amp; observed 1 hr prior to chemotherapy infusions.</u></b>		X				X			X					

<b>Table 10. Time and Events Schedule for FGF117360</b>			Screen	Cycle 1			Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U	
				D1	D8	D9	D15	D1	D8	D15	D1	D8	D15			
<b>Table 11. FGF117360 Pharmacokinetic Sampling Schedule</b>			<b>Limited PK</b>			<b>Extensive PK</b>			<b>Extensive PK</b>			<b>Limited PK</b>		<b>Extensive PK</b>		
Time	When	Window	<b>Arm A or Arm B</b>			<b>Arm A</b>			<b>Arm B</b>			<b>Arm C</b>		<b>Arm C</b>		
<b>Cycle 1 Day 1</b>			<b>n=20pts in Arm A n=20pts in Arm B each arm</b>			<b>n&gt;=10pts</b>			<b>n&gt;=10pts</b>			<b>Remaining patients</b>		<b>n&gt;= 6-10pts</b>		
	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK		GSK3052230 PK		
	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230	GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK		GSK3052230 PK		
	1hr after end of infusion of GSK3052230	±10 min but after ECG				GSK3052230 PK			GSK3052230 PK			-		GSK3052230 PK		
<b>Cycle 1 Day 8</b>	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230				GSK3052230 PK			GSK3052230 PK			-		GSK3052230 PK		
<b>Cycle 1 Day 9</b>	(time relationship to tumor biopsy not infusion time)	<u>within ±1 hr of tumor biopsy</u>	-			-			-			GSK3052230 PK		GSK3052230 PK		
<b>Cycle 2 Day 1</b>	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230	GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK		GSK3052230 PK		
	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230	GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK		GSK3052230 PK		
	1 hr after start of paclitaxel infusion or end of docetaxel <b>or</b> pemetrexed infusion	±10 min for paclitaxel or up to 5 min prior to end of docetaxel infusion <b>or up to 1 min prior to end of pemetrexed infusion</b>				GSK3052230 PK Paclitaxel PK			GSK3052230 PK Docetaxel PK					<b>GSK3052230 PK Pemetrexed PK</b>		
	<b>1 hr after end of pemetrexed infusion</b>	<b>± 20 min</b>												<b>Pemetrexed PK</b>		
		up to 5 min prior to end of				Paclitaxel PK			Docetaxel PK					<b>Pemetrexed PK</b>		

<b>Table 10. Time and Events Schedule for FGF117360</b>			Screen	Cycle 1			Cycle 2			Additional Cycles			Every 4 Cycles, D1	EOT	30 day F/U		
				D1	D8	D9	D15	D1	D8	D15	D1	D8	D15				
	End of paclitaxel infusion or 2 hr after end of docetaxel <b>or pemtrexed</b> infusion	paclitaxel infusion or $\pm$ 20 min for docetaxel <b>and pemtrexed</b>															
	2 hr after end of paclitaxel infusion or 5 hr after end of docetaxel <b>or pemtrexed</b> infusion	$\pm$ 30 min					(selected sites) GSK3052230 PK Paclitaxel PK			(selected sites) GSK3052230 PK Docetaxel PK			(selected sites) GSK3052230 PK Pemetrexed PK				
Cycle 4 Day 1																	
Cycle 6 Day 1																	
Cycle 12 Day 1	Prior to infusion of GSK3052230	Up to 12 hr prior to infusion of GSK3052230		GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK				
Cycle 4 Day 1																	
Cycle 6 Day 1																	
Cycle 12 Day 1	End of infusion of GSK3052230	Up to 5 min prior to end of infusion of GSK3052230		GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK				
EOT				GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK				
30 days FU		At time of immunogenicity sample		GSK3052230 PK			GSK3052230 PK			GSK3052230 PK			GSK3052230 PK				

***Section 7.2 7.2. Demographic/Medical History and Baseline Assessments***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

- **LCSS for Arms A & B**
- **For Arm C only LCSS (meso) and forced vital capacity**

***Section 7.2.1 Critical Baseline Assessments***

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... For Arm C, deregulation of FGF pathway signaling pathway may be assessed locally or centrally (additional details will be in SPM).

**For Arm C, forced vital capacity will be assessed at screening.**

***Section 7.3.4 Forced Vital Capacity***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

**7.3.4. Forced Vital Capacity**

**Forced vital capacity will be measured in Arm C at each scheduled disease assessment using standard methods (Refer to the SPM for details).**

***Section 7.3.8 Laboratory Assessments***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Table 12 List of Clinical Laboratory Tests

Blood urea nitrogen (BUN), Creatinine, Uric Acid, <b><u>creatinine clearance</u></b>
--

***Section 7.4 Evaluation of Anti-cancer Activity***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

CT: (second paragraph) For **Arms A and B**, RECIST 1.1 analysis. . . .

**For Arm C, modified RECIST will be used. Tumor thickness perpendicular to the chest wall or mediastinum will be measured in two positions at three separate levels on thoracic CT scans. The sum of the six measurements defines a pleural unidimensional measure. Bidimensionally measureable lesions will be measured unidimensionally as for RECIST 1.1. All measurements were added to obtain the total tumor measurement. The Image Acquisition Guidelines portion of the SPM should be consulted for additional details on imaging protocols.**

Brain Scan: In subjects with known brain metastases (criteria outlined in Section 3.2), a contrast-enhanced MRI (preferred) or CT of the brain must be obtained within 35~~30~~ days prior to receiving the first dose of the study medication

#### ***Section 7.4.1 Evaluation of Response in Arm A and Arm B (RECIST 1.1)***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

#### Section 7.4.1 **Evaluation of Response Criteria in Arm A and Arm B** (RECIST 1.1)

#### ***Section Evaluation of Response in Arm C: Mesothelioma***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

#### **7.4.2. Evaluation of Response in Arm C: Mesothelioma**

##### **7.4.2.1. Mesothelioma Tumor Imaging**

Clinical trials of therapeutic agents in MPM may be compromised by inaccuracy of tumor measurements due to the unique pattern of growth of mesothelioma [Byrne, 2004; Tsao, 2011]. Malignant mesothelioma commonly grows as a rind and thus may not produce spherical lesions with bidimensional, measurable diameters [Byrne, 2004]. Modification of RECIST criteria have been recommended to address the difficulties in measurement of lesions [Byrne, 2004; Tsao, 2011]. In subjects with mesothelioma, it is requested that disease assessments using both RECIST v1.1 criteria AND modified RECIST criteria be performed.

Uni-dimensional measurements of tumor thickness perpendicular to the chest wall or mediastinum should be performed, measured in 2 sites at 3 different levels on the CT scan. Transverse cuts used for measurement must be at least 1 cm apart, and related to anatomical landmarks in the thorax, preferably above the level of division of the main bronchi. At reassessment, pleural thickness must be measured at the same position and level. Nodal, subcutaneous, and other bidimensionally measurable lesions are measured unidimensionally as per the RECIST v1.1 criteria. Unidimensional measurements are added to produce the total tumor measurements (e.g., the sum of 6 pleural thickness measurements = one univariate diameter).

Overall tips for measurement of mesothelioma by modified RECIST [Tsao, 2011]:

1. Larger lesions are easier and more accurate to measure. Choose the larger or thickest of the pleural disease to measure. Magnifying the image may make an easier measurement.
2. The short-axis diameter is defined as the shortest pathway from the tip of the tumor to the chest wall.
3. Ensure that that differentiation of normal chest wall from tumor is easy at the point of measurement

- 4. To ensure accuracy, all measurements must be performed electronically in the same window setting on consecutive studies. It is recommended that the “soft tissue” setting (not lung windows) be used, as it enables accurate pleural mass measurements with the electronic calipers and avoids the incorporation of chest wall or mediastinal fat within the calculations.**
- 5. CT scan slices up to 5 mm can be used, but for greater accuracy, thinner slices such as 2.5 mm are preferable. Ideally, all subsequent CT scans should use the same slice thickness.**
- 6. To limit interobserver variability, in measuring tumor response, it is preferred that the same clinician measure the tumors at baseline and on all subsequent CT scans.**
- 7. The pleural disease to be measured should have a short-axis diameter of at least 1 cm, as lesions less than 1 cm are considered nonmeasurable.**
- 8. To obtain the short axis of the disease, with electronic calipers, measure the distance between the point where the tumor abuts the chest or the mediastinal border and the point where the pleural disease touches the lung. The shortest route possible is the one perpendicular to the chest wall/mediastinum.**
- 9. Avoid measuring regions where the tumor infiltration obscures the interface of tumor to normal tissue. A good interface for measurement usually is one where the tumor abuts fat or an intact rib/vertebral body, as the density of the pleural tumor differs significantly from bone or fat and the difference can be easily observed. Avoid choosing an interface of tumor with muscle, as muscle and tumor have similar CT densities and are often difficult to distinguish when they abut one another.**
- 10. Following the instructions in #5, choose three different axial slices, preferably above the level of the main bronchi and record two measurements per slice, thus resulting in six separate measurements.**
- 11. If any nodal, subcutaneous or other bidimensionally measurable lesions are available, they should undergo unidimensional measurements by RECIST v1.1 and be added to the total obtained in #7 above.**

**Tips on Lymph Node Measurements:**

**Lymph nodes are considered as a separate organ to measure, and up to two lymph nodes can be measured per patient by RECIST v1.1. For unidimensional lymph node measurements, use the short axis of the lymph node at baseline and then at every followup scan. To be considered as pathologically enlarged and measurable at baseline, the lymph node short axis diameter should be  $\geq 15$  mm.**

#### 7.4.2.2. Prior Scan collection

Collection of up to three prior tumor imaging scans performed prior to baseline scans at study entry will also be encouraged in subjects whose scans are available for review. These scans may be collected and sent to an independent radiologist for review. The slope of tumor growth prior to study entry and following treatment may be compared in subsequent analyses. Such comparisons may be important in evaluation of the clinical significance of subjects achieving a clinical response, particularly in those subjects achieving SD.

#### *Section 7.4.3 Patient Reported Outcomes*

REVISED TEXT: (new text **bold and underlined**, deleted text in strikethrough)

#### 7.4.3. Patient Reported Outcomes

The Lung Cancer Symptom Scale or the Lung Cancer Symptom Scale-mesothelioma [LCSS (-meso)] will be self-administered by subjects (patient scales) and completed by the investigator (observer scales) as indicated in the Time and Events schedule (Table 10). The LCSS(-meso) consists of nine (meso: eight) patient-reported items (visual analogue scale with a range from 0 to100) and six observer reported items and is validated in lung cancer and in mesothelioma patients [Hollen, 2006]. Using visual analogue scales, the patient scale measures the intensity of patient responses for appetite, fatigue, cough, dyspnea, hemoptysis, pain, and summary items symptoms of lung cancer, activity level and quality of life. An example questionnaire can be found in the SPM. The LCSS-meso was chosen because of its focus on disease-related symptoms, the possibility to combine the patient's perception with the investigator's contextual knowledge, its demonstrated concept and content validity, ease of application and minimal burden to patients.

It is important that the LCSS patient scale is administered at the start of the clinic visit before any other study assessments are performed.

#### *Section 7.5.2 Pharmacokinetic Sample Analysis*

REVISED TEXT: (new text **bold and underlined**, deleted text in strikethrough)

Concentrations of GSK3052230 and selected chemotherapy will be determined...

#### *Section 7.7 Translational Research*

REVISED TEXT: (new text **bold and underlined**, deleted text in strikethrough)

##### 7.7.1.—Tumor Biomarker Analysis

###### 7.7.1.1. Fresh Pre and Post dose Tumor Tissues

Pre and post dose tissues, as well as tissues collected at progression will be analyzed for the appropriate protein and/or RNA biomarkers of FGFR pathway and proliferation/apoptosis (e.g. Ki67, CC3, etc). Collected tissues may also be used to

analyze the protein and DNA markers of RTK/MAPK/PI3K pathway activation and cancer development. Additional testing of DNA, RNA, or protein biomarkers related to the function of GSK3052230 may be done if ongoing research identifies or defines additional biomarkers for therapy failure or predictive and prognostic biomarkers.

Paired pre- and post-dose fresh biopsies will be obtained from a minimum of 6 subjects with accessible tumors in Arm C. These biopsies will be taken during the screening period, e.g., within 7 days prior to treatment (preferably pre-dose on day 1), and on Day 9 in those subjects who have signed the corresponding section of the informed consent. A biopsy is also required, when feasible, upon disease progression. The timing of the collections may be adjusted on the basis of emerging pharmacokinetic or pharmacodynamic data from this study or other new information in order to ensure optimal evaluation of the pharmacodynamic endpoints. Details of the tumor biopsy collection including processing, storage and shipping procedures will be provided in the SPM.

#### 7.7.1. Determination of Deregulation Central Confirmation of FGF Signaling Signalling Pathway Status and Translational Research

A requirement for inclusion into this study is deregulated FGF pathway signaling (e.g. FGFR gene amplification) in tumor tissue. As part of the development and validation of this assay, additional measures to FGFR1 gene amplification will be collected to determine if these increase the discriminatory potential of the assay for future development of the IUO. Tumor alterations, such as FGFR1 gene amplification testing, will be conducted using a certified laboratory (e.g. CLIA or appropriate certification) and validated laboratory developed test (LDT) in a central laboratory. In addition, an exploratory objective of this study is to develop and further validate the deregulated FGF pathway signaling assay towards an investigational use only (IUO) assay that can be used for future subject selection and for regulatory approval and registration. The regulatory approved assay will be used in the future to precisely identify the specific deregulated FGF signaling marker such as FGFR gene amplification or over expression, FGF ligand overexpression, etc., status in subjects who may benefit from treatment with GSK3052230. It is essential that the required amount of tumor tissue is obtained in order to perform the FISH assay for entry into the study in Arms A and B, explore other potential measures of FGF signaling pathway deregulation, and complete the necessary equivalency and precision testing requirements for the development of an IUO.

Collection of archival primary tumor tissue is required for all subjects (see Time and Events Table; Section 7.1;); if not available a fresh sample will be required. A formalin fixed paraffin embedded tumor block is requested or if not available, approximately 15 sections will be needed. Details of the tumor biopsy collection including amount, processing, storage, and shipping procedures will be are provided in the SPM.

In addition, these samples may be Arms A and B, a requirement for inclusion is evidence of FGFR1 gene amplification in tumor tissue as determined by a central laboratory (CLIA or appropriate certification) using a laboratory developed test.

**In Arm C, FGF2 expression will be evaluated for the markers retrospectively by IHC to determine if expression levels of FGF2 are associated with response to GSK3052230**

**Any remaining tissue from this study may be used for:**

- **Development and validation of a potential IUO assay and companion diagnostic test, e.g., FGFR1 gene amplification by FISH or FGF2 expression by IHC.**
- **Alternative biomarkers of FGF pathway signalling.**
- **Biomarker research** (protein, RNA and DNA) and status of RTK/PI3K/AKT pathways and cancer development and additional testing of DNA, RNA, or protein biomarkers related to the function of GSK3052230 if ongoing research identifies or defines additional predictive and prognostic biomarkers.

Samples will be collected as indicated **It is essential that the required amount of tumor tissue is obtained in the Timeorder to perform the FISH assay for entry into the study in Arms A and** Events Table (Section ). After determination B, **explore other potential measures of FGF signaling pathway alterations, tissue deregulation in all arms including Arm C, and complete the necessary equivalency and precision testing requirements for the development of an IUO and potential companion diagnostic test.**

**Tissue** samples/sections will be retained for the further confirmation using the IUO validated assay **or potential companion diagnostic test**, when available. All samples will be retained for a maximum of 15 years after the last subject completes the trial.

#### ***Section 7.7.2.1 Plasma for Soluble Markers***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Clusters of markers (e.g. cytokines and angiogenic factors [CAF]) circulating in the plasma have been found to correlate with tumor pathway activation. **Soluble mesotheline-related peptides (SMRP) have been shown to be clinical markers of MPM**.... Therefore, a broad panel of CAF, including FGF ligand, **and SMRP** will be evaluated....

#### ***Section 7.7.2.2 Circulating cell free DNA (CFDNA) Analysis***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

...will be analyzed for mutations in genes relevant to RTK/MAPK/PI3K pathway **and cancer biology** in cell free DNA...

#### ***Section 10.1.2 Male Subjects***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For male subjects ~~in Arm A and B~~, to prevent pregnancy in a female partner...

~~For male subjects in Arm C, there are no contraception restrictions.~~

### ***Section 11 Data Management***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

**Patient reported data will be collected via paper questionnaires and will be entered into the eCRF centrally. Data will be checked for completeness by study staff immediately after completion by the subject and reasons for non-compliance will be noted.**

### ***Section 12.1 Considerations of statistical design***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The sections below show the planned dose cohorts as well as the decision rules, by study arm, specifying the number of subjects with a confirmed objective response (according to RECIST 1.1) needed for continuing enrolment, or stopping for futility, ~~and stopping for efficacy~~. The methodology is based on the predictive probability of success if enrolment continues to 30 subjects [Lee, 2008]. The predictive probability design is similar to a Green-Dahlberg design in that it allows for early stopping for futility. ~~The differences are that but the predictive probability design allows for evaluation of stopping rules futility after each every subject rather than once a minimum enrolment has been reached whereas the Green-Dahlberg design does this at only two stages one fixed interim and that the predictive probabilities methodology allows for stopping for success as well as for futility. at the end of enrolment.~~ While the two designs have similar type I and type II error rates, the probability of early termination is greater with the predictive probability design. A randomized Phase II or Phase III study may be conducted based on the results from this study

### ***Section 12.2 Hypotheses***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

No formal statistical hypotheses are being tested during the dose escalation portions of Arms A, B, and B ~~or for Arm C~~. Analysis of the data obtained from the dose escalation parts of ~~Arms A and B~~ the study will be focused...

For the dose expansion portions of ~~Arms A and B~~ the study, hypothesized response rates...

#### ***Section 12.3.1 Arm A: GSK3052230 + Paclitaxel + Carboplatin***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Starting with a cohort of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate ( $\alpha$ ) of 0.15 and 88% power. The trial is designed to stop early for efficacy when the predictive probability of success if the trial were to continue to the total sample size of 30 is greater than or equal to 90%. **11 and 86% power**. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.3, 0.7), a relatively non-informative prior with a mean response rate of 30%. Under the null hypothesis, the expected sample size is **22.7****24.2** subjects and probability of early termination (PET) is **94.8****3.5**%. Under the alternative hypothesis, the expected sample size is **4.7****29.7** subjects and the **probability of early termination PET** is **94.6****9**%.

### ***Section 12.3.2 Arm B: GSK3052230 + Docetaxel***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

An initial dose escalation will be used to establish the MTD. Once the final dose is confirmed, at least **12****14** and up to 30 subjects...

Starting with a cohort of **12****14** subjects and allowing for a maximum sample size of 30, this design will have a type I error rate ( $\alpha$ ) of **0.0907** and **84.79**% power. The trial is designed to stop early for efficacy when the predictive probability of success if the trial were to continue to the total sample size of 30 is greater than or equal to 90%. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a relatively non-informative prior with a mean response rate of 15%. **Under the null hypothesis, the expected sample size is 24.0 subjects and probability of early termination is 84.5%.** **Under the alternative hypothesis, the expected sample size is 29.5 subjects and the probability of early termination is 12.2%.**

### ***Section 12. Arm C: GSK3052230 + Pemetrexed + Cisplatin***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

#### **12.3.3. Arm C: GSK3052230 + Pemetrexed + Cisplatin**

**An initial dose escalation will be used to establish the MTD. Once the final dose is confirmed, at least 12 and up to 30 subjects in total will be enrolled at that dose, using decision rules defined in Section 4.2.3. The assumptions underlying the design are detailed below and are based on previously published randomized phase 3 data in the 1st line setting of malignant pleural mesothelioma [Vogelzang, 2003].**

**The null hypothesis is:**

**H0: p<40%**

**The alternative hypothesis is:**

**HA:p≥60%**

Starting with a cohort of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate ( $\alpha$ ) of 0.10 and 82% power. The trial is stopped early for futility if the predictive probability of success is less than 0.1%.  
The Bayesian prior used in determining the design was Beta (0.5, 0.5), a relatively non-informative prior with a mean response rate of 50%. Under the null hypothesis, the expected sample size is 23.1 subjects and probability of early termination (PET) is 92.3~~86.4~~129.5%. Under the alternative hypothesis, the expected sample size is 19.1~~129.5~~ subjects and the probability of early termination PET is 90.6~~13.7~~13.7%.

#### 12.3.3. Arm C: GSK3052230

~~A sample size of 18-20 subject is based on the first futility decision timepoint for a test of the null hypothesis  $H_0: p \leq 5\%$  vs  $H_A: p \geq 20\%$  again using predictive probability design. This arm will not stop for success, but will stop for futility if no responses are observed in 18 subjects.~~

#### ***Section 12.7 Interim Analysis***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For each study arm, after the initial 12 (**Arms A and C** or **14 (Arm B)**) subjects have enrolled at the final dose, response data will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 4.2.1 (**Arm A**), Section 4.2.2 (**Arm B**), and Section 4.2.3. and Section (**Arm C**). **The rules are also shown in a tabular format below:**

TABLE 14: Deleted right hand column for stopping for success.

TABLE 15: Deleted right hand column for stopping for success. Deleted top 2 rows for 12 and 13 patients.

FIGURE 2 and FIGURE 3: Deleted figures because no longer stopping for success.

TABLE 16: Added new table for Arm C.

#### ***Section 12.8.2.2 Adverse Events***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For the dose-escalation portions of ~~Arms A and B~~ **the study**, dose-limiting toxicities...

#### ***Section 12.8.3 Patient Reported Outcomes***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

#### **12.8.3. Patient Reported Outcomes**

Change from baseline scores in LCSS and LCSS-meso will be calculated for all scales and timepoints. 10mm in change from baseline were previously identified as clinically meaningful (P. Hollen, personal communication). Associations with

efficacy assessments and between patient reported and clinician reported symptomatic will be explored when warranted. Further details will be provided in the RAP.

***Section 12.8.5. Pharmacokinetic/Pharmacodynamic Analyses***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Where evidence of activity is seen, linear and/or non-linear mixed effect models may be fitted to the data to estimate ~~PKPD~~**PK/PD** parameters of interest (e.g. slope, baseline (E0), ~~location~~ **concentration for 50% of maximum effect** (EC50) and maximum effect (Emax)).

***Section 12.8.6 Tumor Kinetics Analysis***

REVISED TEXT: (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Data from ~~all~~ **some** arms of the study...

## Amendment 2

### Where the Amendment Applies

This amendment applies to all sites.

### Summary of Amendment Changes with Rationale

Amendment No.2: Sponsor medical monitor information was updated, the inclusion criterion for FGFR gene amplification was modified, clarifications were made to the Time and Events Table, vital sign measurements, and permitted concomitant medications; and male contraceptive requirements were corrected.

### List of Specific Changes

#### **Change 1: Inclusion criterion for FGFR gene amplification modified.**

##### *Section 3.2.1 Inclusion Criteria*

##### **PREVIOUS TEXT:**

3. Availability of archival tumor tissue required for assessment of deregulated FGF pathway signaling e.g. FGFR1 amplification or FGF2 over expression status based on emerging GSK3052230 preclinical data), provided no systemic therapy has been given since the biopsy was obtained. If archival tissue is not available, a fresh biopsy is required. Please refer to Section 7.7.1.2. In Arms A and B, subjects will be prospectively screened for FGFR1 gene amplification using a FISH assay. For inclusion in this study, a ratio of FGFR1/CEN 8 of > 2 will be required. FGFR1 gene amplification will be determined by central laboratory testing.

##### **REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

3. Availability of archival tumor tissue required for assessment of deregulated FGF pathway signaling e.g. FGFR1 amplification ~~or FGF2 over expression status based on emerging GSK3052230 preclinical data), provided no systemic therapy has been given since the biopsy was obtained.~~ If archival tissue is not available, a fresh biopsy is required. Please refer to Section 7.7.1.2. In Arms A and B, subjects will be prospectively screened for FGFR1 gene amplification using a FISH assay (**note, local testing is permitted for pre-screening of subjects prior to central testing**). For inclusion in this study, based on the central laboratory testing, FGFR1 gene amplification must meet one of the following criteria: a ratio of FGFR1/CEN 8 of  $\geq 2$ ; **or average number of FGFR1 signals per tumor nucleus of  $\geq 6$ ; or the percentage of tumor nuclei containing  $\geq 5$  FGFR1 signals is  $\geq 50\%$ . FGFR1 gene amplification will be determined by central laboratory testing.**

**Change 2: Clarification for stage of disease and chemotherapy in Arm A.*****Protocol Synopsis, Section 3.2.1 Inclusion Criteria*****PREVIOUS TEXT:**

2. Histologically or cytologically confirmed diagnosis:

**Arms A and B:** Stage IV squamous NSCLC...

**Arm A:** Subjects who have received no prior therapy for Stage IV disease....

**Arm B:** Subjects who have ... Stage IV disease...

**Arm C:** Subjects who have ... Stage IV disease...

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

2. Histologically or cytologically confirmed diagnosis:

**Arms A and B:** Stage IV or recurrent metastatic squamous NSCLC...

**Arm A:** Subjects who have received no prior therapy for Stage IV or recurrent metastatic disease....

**Arm B:** Subjects who have ... Stage IV or recurrent metastatic disease...

**Arm C:** Subjects who have ... Stage IV or recurrent metastatic disease...

**PREVIOUS TEXT:**

2. **Arm A:** Subjects who have received no prior therapy for Stage IV disease. Note, to avoid any undue delay of initiating systemic chemotherapy for these subjects with newly diagnosed metastatic disease, it is allowed to initiate the first cycle of chemotherapy while the subject is still in screening for the present study. The first dose of GSK3052230 should then be given no later than the day of the second cycle of chemotherapy.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

2. Arm A: Subjects who have received no prior therapy for Stage IV or recurrent metastatic disease. Note, to avoid any undue delay of initiating systemic chemotherapy for these subjects with newly diagnosed metastatic disease, it is allowed to initiate the first cycle of chemotherapy ~~whilst the subject is still in screening for the present study while eligibility for the study is still being determined, as long as the first dose of GSK3052230 is given no later than Cycle 2 Day 1 of chemotherapy.~~

***Section 4.2.1 Arm A*****PREVIOUS TEXT:**

Arm A: Screening procedure for subjects on chemotherapy

To avoid any undue delay in initiating systemic chemotherapy for subjects with newly diagnosed Stage IV disease, the first cycle of chemotherapy may be initiated while subjects are still in screening for the present study.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

Arm A: Screening procedure for subjects on chemotherapy

To avoid any undue delay in initiating systemic chemotherapy for subjects with newly diagnosed Stage IV or recurrent metastatic disease, the first cycle of chemotherapy may be initiated while ~~subjects are still in screening~~ determination of eligibility is being completed for the present study.

**Change 3: Other clarifications to Inclusion/Exclusion criteria.*****Section 3.2.1 Inclusion Criteria***

10. Added footnotes for hemoglobin (a) and serum total bilirubin (b):

- a. Subjects should meet criteria in the absence of hematopoietic growth factors or transfusions.
- b. If the serum total bilirubin is elevated at screening but the direct bilirubin is ≤ULN then the subject may be allowed to enter study.

***Section 3.2.2 Exclusion Criteria*****PREVIOUS TEXT:**

10. Symptomatic leptomeningeal or brain metastases or spinal cord compression.

NOTE: Subjects previously treated for these conditions that have had stable CNS disease (verified with consecutive imaging studies) for >1 month, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 1 month prior to study Day 1 are permitted. Stability of brain metastases must be confirmed with imaging. If subjects have been treated with gamma knife they can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications. In addition, subjects treated or currently taking enzyme-inducing anticonvulsant are allowed on study.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

10. Symptomatic leptomeningeal or brain metastases or spinal cord compression.

**NOTE: Subjects previously treated for these conditions are eligible if they meet both of the criteria below:**

**(1) have had stable CNS disease for at least 4 weeks after local therapy as assessed by imaging (contrast enhanced magnetic resonance imaging (MRI) or computed tomography (CT)), and**

**(2) are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 4 weeks prior to Day 1.**

**Change 4: Clarifications to preparation of GSK3052230, Time and Events Table, vital sign measurements, permitted concomitant medications.**

***Section 5.2 Preparation/Handling/Storage of GSK3052230***

Added to end of paragraph on Preparation:

**Please refer to SPM for recommended IV supplies.**

***Section 7.1 Time and Events Table (footnotes)***

**PREVIOUS TEXT:**

Visit Window                    Must occur within the window specified. D=day

Physical exam, weight, and height (baseline only)    Complete physical exam at screening. Abbreviated disease-oriented physical exam subsequently.

Ophthalmologic Exam            To be performed by ophthalmologist.

Vital Signs                    Within -20/+10mins of GSK3052230 i.v. Arm A: -10mins of i.V. start

Hematology and Chemistry    See Table 11 for analytes. In addition Arm A: additional cycles D8 while dosing on paclitaxel + carboplatin only

Circulating Biomarkers            Plasma sample collected predose.

Blood sample for PGx            Collect only if PGx informed consent has been signed.

Brain Scan                    within 8 weeks of C1D1

Bone Scan                    within 12 weeks of C1D1

ARM A: Paclitaxel + Carboplatin    GSK3052230 infused & observed 1 hr prior to chemotherapy doses.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

Visit Window                    Tissue prescreen for Arms A and B within 60 days and all other screening assessments within 30 days of C1D1. Visit windows of  $\pm 2$  days during study through EOT, +7 days for F/U. Cycle 1 Day 9 assessments for Arm C only.

Physical exam, weight, and height (baseline only) **Not needed C1D1 if screening assessments within prior 72 hrs.** Complete physical exam at screening. Abbreviated disease-oriented physical exam subsequently.

Ophthalmologic Exam To be performed by ophthalmologist **or qualified optometrist.**

Vital Signs **Arms A + B: Within 20 min before start of first chemotherapy infusion and within 20 min before start of GSK3052230 infusion. Arm C: Before start of GSK3052230 infusion**

Hematology and Chemistry **Not needed C1D1 if screening assessments within prior 72 hrs.** See Table 11 for analytes. In addition Arm A: additional cycles D8 while dosing on paclitaxel + carboplatin only

Circulating Biomarkers Plasma sample collected predose **(+7 days prior to C1D1)**

Blood sample for PGxCollect **any time on study** but only if PGx informed consent has been signed; **preferred on C1D1 after dosing.**

Brain Scan **within 35 days of C1D1**

Bone Scan **within 4 weeks of C1D1**

ARM A: Paclitaxel + Carboplatin GSK3052230 infused & observed 1 hr prior to chemotherapy doses. **May start chemotherapy during screening period, see inclusion #2**

### ***Section 7.3.3 Vital Signs***

#### **PREVIOUS TEXT:**

Vital sign measurements will include systolic and diastolic blood pressure, temperature, respiration rate and pulse rate. Vital signs should be measured after resting for at least 5 minutes .... Refer to the SPM for details regarding measurement of vital signs.

#### **REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

Vital sign measurements will include systolic and diastolic blood pressure, temperature, respiration rate and pulse rate. **All vital sign measurements will be obtained after the subject has rested** for at least 5 minutes .... **Whenever blood pressure and heart rate are measured at the same nominal time as a blood draw, the blood pressure and heart rate will be prior to the blood draw.** Refer to the SPM for details regarding measurement of vital signs

### ***Section 7.3.6 Ophthalmologic Examinations***

#### **PREVIOUS TEXT:**

These exams will be performed by an ophthalmologist and includes...

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

These exams will be performed by an ophthalmologist or qualified optometrist and includes...

**Section 9.1 Permitted Medications****PREVIOUS TEXT:**

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. **Pre-medication for chemotherapy is allowed per institutional guidelines.**

**Change 3: Correction of contraceptive requirements.****Section 3.2.1 Inclusion Criteria****PREVIOUS TEXT:**

6. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10, during the study and for 6 months following the last dose of chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest.
7. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 10.1.2 for at least 2 weeks prior to administration of the first dose of study treatment and for at least 6 months after the last dose of chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest, to allow for clearance of any altered sperm.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

6. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10, ~~during the study from 14 days prior to the first dose of study treatment, throughout the study~~, and for 6 months following the last dose of chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest
7. **For Arm A and B:** Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 10.1.2 for at least 2 weeks prior to administration of the first dose of study treatment and for at least 6 months after the last dose of chemotherapy ~~or 4 weeks~~

~~after the last dose of GSK3052230, whichever is latest, to allow for clearance of any altered sperm.~~ **Arm C: No male contraception restrictions.**

### Section 10.1.2

#### PREVIOUS TEXT:

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods until 4 weeks after the last dose of GSK3052230 or 6 months after the last dose of chemotherapy, whichever is latest...

**REVISED TEXT:** (new text underlined, deleted text in ~~strikethrough~~)

**For male subjects in Arm A and B,** to prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods ~~until 4 weeks after the last dose of GSK3052230 or 6 months after the last dose of chemotherapy, whichever is latest~~

**For male subjects in Arm C, there are no contraception restrictions.**

## Amendment 1

### Where the Amendment Applies

This amendment is applicable to UK site(s) only.

### Summary of Amendment Changes with Rationale

Amendment No.1: This amendment modified contraceptive practice and adjusted QTc stopping criteria for the UK to comply with MHRA guidelines.

### List of Specific Changes

#### Change 1: Contraception Guidelines

#### RATIONALE FOR CHANGE:

The protocol has been clarified to reflect the SPC for paclitaxel, carboplatin, and docetaxel which recommend using effective contraception methods for a period of 6 months. In addition, the protocol has been clarified regarding the contraception timing for GSK3052230 to allow 5 half-lives for drug clearance. The GSK3052230 half life is 5.2 days. The protocol has been modified to implement the use of an effect contraception methods for 4 weeks post-therapy of GSK3052230 given there are no genotoxicity concerns.

#### Section 3.2.1 Inclusion Criteria:

#### PREVIOUS TEXT

6. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10, during the study and for 21 days following the last dose of study treatment.

7. For Arms A and B: Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 10.1.2 for at least 2 weeks prior to administration of the first dose of study treatment [and for at least 4 weeks after the last dose of chemotherapy given in this study] to allow for clearance of any altered sperm. Arm C: No male contraception restrictions.

#### REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)

6. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 10, during the study and for 21 days 6 months following the last dose of chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest.

7. ~~For Arms A and B:~~ Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 10.1.2 for at least 2 weeks prior to administration of the first dose of study

treatment [and for at least ~~4 weeks~~ **6 months** after the last dose of **chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest**, to allow for clearance of any altered sperm. Arm C: No male contraception restrictions.

### **Section 7.3.8 Pregnancy Testing and Reporting:**

#### **PREVIOUS TEXT**

If a female subject is of childbearing potential, she must have a serum  $\beta$ -HCG pregnancy test performed within 7 days prior to the first dose of study treatments. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described in Section 10.1 during the study until 25 days following the last dose of study treatments.

#### **REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

If a female subject is of childbearing potential, she must have a serum  $\beta$ -HCG pregnancy test performed within 7 days prior to the first dose of study treatments. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described in Section 10.1 during the study until ~~25 days~~ **6 months** following the last dose of ~~study treatments~~ **chemotherapy or 4 weeks after the last dose of GSK3052230, whichever is latest**.

### **Section 10.1.1 Female Subjects**

Moved to end of section:

#### **PREVIOUS TEXT**

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 25 days after the last dose of study treatment.

#### **REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

Complete abstinence from sexual intercourse ~~or contraception~~ must be practiced for 14 days prior to first dose of study treatment, through the dosing period, and for at least ~~25 days~~ **4 weeks after the last dose of study treatment GSK3052230 or 6 months after the last dose of chemotherapy, whichever is latest**.

### **Section 10.1.2 Male Subjects**

#### **PREVIOUS TEXT**

For subjects on Arm A and B, to prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods.....

For subject in Arm C, there are no restrictions.

**REVISED TEXT: (new text underlined, deleted text in ~~strikethrough~~)**

~~For subjects on Arm A and B, To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods until 4 weeks after the last dose of GSK3052230 or 6 months after the last dose of chemotherapy, whichever is latest.....~~

~~For subject in Arm C, there are no restrictions.~~

**Change 2: QTc stopping rules for the UK****RATIONALE FOR CHANGE:**

Country Specific Requirements previously specified the QTc stopping criteria as 500msec for France. The QTc stopping rules and the Country specific appendix have been modified to include UK along for France for the QTc stopping criteria to comply with the MHRA guidelines.

**Section 4.7.2, QTc Stopping Criteria****PREVIOUS TEXT**

For subjects recruited in France, please refer to Appendix 7 for the French specific QTc stopping criteria.

**REVISED TEXT (new text underlined, deleted text in ~~strikethrough~~):**

For subjects recruited in France or the UK, please refer to Appendix 7 for the ~~French country~~ specific QTc stopping criteria.

**15.8 Appendix 7: Country Specific Requirements****PREVIOUS TEXT****France:****French Specific QTc Stopping Criteria:**

In line with local requirements, a **French subject** that meets the criteria QTc<sup>1</sup> below will have study treatment withheld...

**REVISED TEXT (new text underlined, deleted text in ~~strikethrough~~):****France or UK:****French or UK Specific QTc Stopping Criteria:**

In line with local requirements, **French subjects** that meet the criteria QTc<sup>1</sup> below will have study treatment **GSK3502230** withheld:

QTcB > 500 msec

**In line with local requirements, UK subjects that meet the criteria QTc<sup>1</sup> below will have study treatment withheld:**

**QTc > 500 msec**

<sup>1</sup>Based on average corrected QT (QTc) interval value of triplicate electrocardiograms (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 **GSK3502230** withheld.

**QT interval (corrected for HR) >500 msec; GSK3502230 will be permanently discontinued.**

**QTc interval increase from baseline ≥ 60 msec and maximum QTc < 500 msec; GSK3502230 may be restarted at a reduced dose level after discussion with the medical monitor once the QTc returns to baseline. If QTc prolongation meeting stopping criteria recurs after re-challenge, GSK3502230 must be permanently discontinued.**

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on study treatment **GSK3502230** if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment