TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A phase I/II open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK525762 in subjects with NUT midline carcinoma (NMC) and other cancers

Compound Number: GSK525762

Development Phase: I

Effective Date: 24-FEB-2017

Author (s):

PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2011N118599_00	2011-NOV-11	Original
2011N118599_01	2012-JAN-09	Amendment No. 1
Amendment 1 applies to all study sites. Modifications include updated medical monitoring information due to a personnel change on the GSK team. In addition, the following review of the protocol by the FDA, the following changes are made: For Part 1, the starting dose of GSK525762 is reduced from 5 mg/day to 2 mg/day. Cardiac troponin T level assessments are required as a part of the inclusion criteria and thereafter. An observation of CTCAE Grade 2 drug related toxicity, including grade 2 troponin T elevation, in one subject will end accelerated dose titration in Part 1. Subjects with a history of gastrointestinal bleeding or active bleeding (positive guaiac fecal occult blood monitoring) will be excluded. In addition, wording for dose escalation decisions has been modified to state that no more than a 2-fold increase in dose will occur between successive cohorts. A staggered dosing approach will be implemented in the 3+3 dosing design to minimize potential for toxicity in multiple subjects. Alternative dosing regimens will not be implemented without consultation with FDA and a protocol amendment. For Part 2 of the trial, stopping rules based on lack of efficacy and the futility rule have been modified. Additionally the disease assessment scans may be reviewed retrospectively by an independent radiologist. Finally, multiple Time and Event Tables have been revised for consistency across Part 1 and Part 2 of the protocol.		
2011N118599_02	2012-AUG-29	Amendment No. 2
Amendment 02 applies to all study sites. Changes via Amendment 02 include the addition of subjects with tumor types other than NMC [including multiple myeloma (MM), small cell lung cancer (SCLC), colorectal cancer (CRC), neuroblastoma (NB), and any solid tumor that demonstrates N-Myc amplification or over expression (such as NSCLC with N-myc amplification)] and associated changes in the study design and inclusion criteria; definition of adult subjects as those 16 and older; addition of pediatric subjects 12 to ≤15 years old; modification of the initial staggered dosing schedule to shorten the dose escalation period from 6 weeks to 4 weeks; allowance for treatment beyond tumor progression (decision made in consultation with GSK Medical Monitor); minor clarifications to the Risk Assessment section; updates to Exploratory Objectives/Endpoints to ensure adequate assessment of the effect of drug on tumor biology; and addition of drug preparation guidelines for GSK525762 administered via an enteral feeding tube.		
2011N118599_03	2014-FEB-04	Amendment No. 03
Amendment 3 applies to all study sites and includes the addition of the NMC Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamic effects of		

GSK525762 across the predicted efficacious dose range at doses that have been previously cleared during 3+3 dose escalation. The collection of ECGs, PK samples and liver chemistry were clarified or corrected. The inclusion of a pediatric cohort in Part1B, implemented in protocol amendment 2, was clarified and emphasis was added regarding the preservation of reproductive capacity.		
2011N118599_04	2014-OCT-06	Amendment No 04
Amendment 4 applies to all study sites and includes the addition of subjects with the following solid tumor types: castration-resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive breast cancer (ER positive), and non-small cell lung cancer (NSCLC). Multiple myeloma (MM), a haematological malignancy previously included in the trial, is now removed from this trial as it is included in a separate trial open for hematologic malignancies with dose escalation to better define the benefit/risk balance. Additional details of twice daily (BID) dosing during dose escalation have been included. A Besylate Sub-Study has been added to determine the relative bioavailability (BA), food effect, and dose proportionality of the besylate formulation of GSK525762 at or near the MTD. An update to inclusion criteria has been made to allow subjects with evaluable disease to be enrolled in the NMC PD cohort. An updated imaging schedule for NMC subjects has been included.		
2011N118599_05	2015-MAR-24	Amendment No. 5
Amendment 5 applies to all study sites and includes the following additional expansion cohorts for Part 2 of the trial: castration-resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive breast cancer (ER positive) and small cell lung cancer (SCLC). An update was included regarding the Besylate Sub-Study to clarify that this sub-study would only be conducted at centers in the United States. The pediatric cohort in Part 1B was removed for further evaluation in a separate study. An update to the QTc management guidelines has been included.		
2011N118599_06	2015-JUN-19	Amendment No. 6
Amendment 6 applies to all study sites and includes updated guidance on contraception use based on emerging data from preclinical studies. Section 6.4.6 was updated to clarify how the Holter monitoring data will be reviewed and analyzed. Additionally, updates were made throughout to correct minor inconsistencies and provide further clarification, specifically with the Time and Events Tables. Furthermore, the dosing schedule was updated from a staggered (1,3,5,7) dosing schedule in the first two weeks to a continuous daily dosing schedule. Finally, after an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 100 mg QD cohort available by May 15 2015, the 48-hour telemetry requirement has been removed for all parts of the study and the frequency of Holter monitoring has been decreased in Part 1.		
2011N118599_07	2016-MAR-10	Amendment No. 7
Amendment 07 updates were made, to include the final dose and regimen for Part 2, which was determined to be 75 mg once daily based on emerging data from Part 1 and		

Besylate Sub-Study; to clarify that the besylate salt tablets will be the formulation used for subjects enrolled in Part 2 (and potentially for ongoing or newly enrolled subjects in Part 1); to update required number of subjects to be enrolled in the Part 1; to update the subject and study completion details; to update the Visit window for Discontinuation and End of Treatment; to update diagnosis criteria of NMC for Part 1 and 2 for NMC subjects; to update dosing, handling and storage instruction for GSK525762 Besylate tablet; to modify the meals and dietary restrictions based on the results of the besylate sub-study, the fasting requirement is being lifted , except on Serial PK sampling days in Part 2 (Week 1 and Week 4); to include the details about interim and final analysis. Additionally, following updates were in the time and event table, 12-lead ECGs monitoring for prolonged QTcF for Part 1 and 2 was updated, tumor sampling time point was updated for Part 1 and 2; optional Sweat PK sampling for Part1 was removed; optional saliva sampling for time points for part 1 was updated; pain assessments was included for Part 2; W1D1, ECHO was made optional for Part 2; and CT Scan, MRI and PET scan detail were updated for Part 2.		
2011N118599_08	2016-DEC-02	Amendment No. 8
Amendment 8 includes changes as the result of the Dear Investigator Letter, dated 16 November 2016 which outlines the updated thrombocytopenia management guidelines, as outlined in the Dear Investigator Letter, dated 16 November 2016. This amendment also includes increased coagulation monitoring for Part 2 (added at W2D1, W3D1 and changed from q8W to q4W after Week 13), addition of Factor VII monitoring in Part 2 (at Screening, W3D1 and reflex testing if PT or INR are ≥1.5XULN) and addition of laboratory values required prior to performing the post-dose biopsy.		
2011N118599_09	2017-FEB-24	Amendment No. 9
Amendment 9 applies to all global sites. Updates were made throughout the protocol to correct minor inconsistencies, spelling errors and provide further clarification. The following changes have been made based on comments from regulatory agencies during review of this protocol and other GSK525762 protocols: addition of exclusion criteria for exclusionary medications; updated exclusion of bleeding to include all history of bleeding and added known bleeding disorders; addition of laboratory monitoring required prior to surgeries, as described in Section 6.4.6.2 and Section 6.8.1; addition of guidance for dose reduction levels, as described in Section 7.7.1; updated dose adjustment/stopping safety criteria, as described in Table 24 and Table 25; updated prohibited medications in Section 8.2.1. In addition, other changes include: addition of a GIST cohort in Part 2, including background information, updated endpoints, overall Part 2 sample size, futility information, eligibility criteria and Section 11, Data Analysis and Statistical Considerations; updated Section 1.5 Risk Assessment to include current available data; removal of cytokines throughout protocol; updated sample size for MTD dose level in Part 1; update to contraception use in Inclusion 9 and 10 and clarifications in Section 9 Lifestyle Requirements; removal of Holter monitoring; changes to Part 1 Time and Events Tables which includes removal of certain ECG time points, change from required to optional for urine PK samples and certain PK/ECG/biomarker tests (see Table 12 to Table 14), addition of Factor VII assay testing, additional lab samples at Week 7 and Week 11, change in timing of on-treatment biopsy; changes to Part 2 Time and Events		

Tables which includes additional lab samples at Week 7 and 11 and increase in Factor VII testing, addition of pregnancy/testosterone test at W1D1; change in timing of on-treatment biopsy and removal of an ECHO time point; change to the pregnancy reporting guidelines to 24 hours; addition of wording that subjects are to abstain from consuming certain fruits in Section 7.3; updates to Section 8, Concomitant Medications and Non-Drug Therapies to reorganize and update the prohibited, cautionary medication tables and drug interaction information; removal of fever and diarrhea information from Appendix 3. Additionally, Appendix 3 was updated with the current GSK Liver Event and follow-up information, but the liver event criteria did not change.

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24 Feb 2017
Date

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SPONSOR/MEDICAL MONITOR INFORMATION PAGE

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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): Investigational New Drug (IND) # IND112942

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BET115521

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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ABBREVIATIONS

1,5 AG	1,5-Anhydroglucitol
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
BCS	Bio-pharmaceutics Classification System
BET	Bromodomain and extra-terminal
BID	Twice Daily
BP	Blood pressure
BQL	Below the quantitative limit
BRD	Bromodomains
CBC	Complete blood count
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentrations
CPK	Creatine phosphokinase
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form
CRP	C reactive protein
CRPC	Castrate-Resistant Prostate Cancer
CV	Coefficient of variance
DLT	Dose limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
EIAC	Enzyme-inducing anticonvulsant
ER positive	Estrogen receptor positive (breast cancer)
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
Fu	Fraction unbound
GCP	Good Clinical Practice
GIST	Gastrointestinal Stromal Tumor
GSK	GlaxoSmithKline
HbA1C	Hemoglobin A1C
HBsAg	Hepatitis B surface antigen
hERG	Human ether a go-go-related gene
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely toxic dose
hr	Hour(s)
HR	Heart rate

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-6	Interleukin 6
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IVRS	Interactive voice response system
Kg	Kilogram
L	Liter
LCNEC	Large cell neuroendocrine carcinoma tumor
LFTs	Liver function tests
LLN	Lower limit of normal
LO(A)EL	Lowest observed (adverse) effect level
LPS	Lipopolysaccharide
µg	Microgram
MABEL	Minimum anticipated biological effect level
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
Mins	Minute(s)
mL	Milliliter
MM	Multiple Myeloma
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
N-CRM	Neuenschwander- Continuous Reassessment Method
nT-proBNP	N-terminal pro–B-Type natriuretic peptide
NMC	NUT Midline Carcinoma
NO(A)EL	No observed (adverse) effect level
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSCLC	Non-small cell lung cancer
OS	Overall Survival
PD	Progressive disease
PGx	Pharmacogenetics
PK	Pharmacokinetic
PSA	Prostate-Specific Antigen
PT	Prothrombin time
QD	Once Daily
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
Resp	Respiration rate
RP2D	Recommended Phase II Dose
RR	Response rate

RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SCLC	Small cell lung cancer
SD	Stable disease
SPM	Study Procedures Manual
STD 10	10% mortality over the duration of the study
T	Temperature
τ	Dosing interval
t1/2	Terminal phase half-life
tmax	Time of occurrence of Cmax
TNBC	Triple Negative Breast Cancer
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UK	United Kingdom
USA	United States
V/F	Apparent Volume of distribution following oral dosing

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PROTOCOL SYNOPSIS

PRODUCT: GSK525762

PROTOCOL TITLE: A Phase I/II Open-Label, Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of GSK525762 in Subjects with NUT Midline Carcinoma (NMC) and Other Cancers

PROTOCOL NO.: BET115521

U.S. IND NO.: IND112942 **CLINICAL PHASE:** I/II

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following Once Daily (QD) and/or BID dosing schedules. • To evaluate the clinical activity of GSK525762 in NMC and other solid tumors. • To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, Electrocardiogram (ECG), cardiotoxicity, gastrointestinal, etc.) to determine the MTD in subjects 16 years or older • Assess overall response rate (RR) using RECIST 1.1 in NMC and other solid tumors or PSA50 response rate using PCWG2 guidelines in CRPC or DCR (CR+PR+ SD ≥ 16 weeks in duration) in GIST. • Pharmacokinetic (PK) parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.
	• The primary goal of Part 2 is to demonstrate a clinically meaningful response, defined as follows:
	  • NMC: this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 20%.
	  • Small cell lung cancer (SCLC) and Castrate-Resistant Prostate Cancer (CRPC): this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 30%.
	  • ER+BC: this will be determined by testing the null hypothesis that the response rate is ≤15%, with about 80% power when the true response rate is 30%.
	  • Triple Negative Breast Cancer (TNBC): this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 25%.

	• Gastrointestinal stromal tumor (GIST): this will be determined by testing the null hypothesis that the disease control rate is ≤15%, with about 80% power when the true disease control rate is 40%.
Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • To evaluate cardiac safety, including the potential for QT duration corrected for heart rate by Fridericia's formula (QTcF) changes with GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival.
Endpoints	• PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 16 years or older. • Changes in cardiac safety including QTcF following single and repeat-dose oral administration GSK525762. • Progression free survival (PFS), time to response, duration of response, overall survival (OS), and exploratory analysis for antitumor response by various imaging modalities.

Exploratory (Objectives and Endpoints only)	
Objectives	• To evaluate the effect of GSK525762 on tumor biology. • Correlation of GSK525762 exposure to changes in PD markers in tumor and/or surrogate tissue. • To identify potential indicators of sensitivity or response to GSK525762. • To evaluate systemic and ex vivo on-target BET inhibitory effects.
Endpoints	• Dose related changes in markers of cell proliferation and/or cell differentiation in tumor and/or surrogate tissue. • Dose related changes in transcription of genes and/or changes in expression of proteins regulated by BRD proteins in tumor and/or surrogate tissue. • PK/PD parameter values for exposure response (by RECIST and ^{18}FDG-PET [if data allows]) relationship between GSK525762 exposure and QTcF, troponin and tumor response following single and repeat-dose oral administration. • Changes from baseline and dose/response relationship in ex vivo Lipopolysaccharide (LPS) induced cytokines including Interleukin 6 (IL-6) in whole blood and systemic cytokines including IL-6.

- **STUDY DESIGN AND DURATION**: This study is divided into 2 parts:
  - Part 1 of the study is a dose escalation phase to determine the maximum tolerated dose (MTD) and select a recommended dose for Part 2 or a recommended Phase 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma (NMC), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects with NMC will also be enrolled in a pharmacodynamic dose expansion cohort during Part 1. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent.
  - Part 1 besylate sub-study will explore the relative bioavailability, food effect and dose proportionality of besylate formulation. The sub-study will be conducted at active centers in the United States in subjects eligible for Part 1 at the MTD or a dose near the MTD or RP2D. This will be an open-label, randomized, single dose, four period, cross over sub-study to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as besylate tablets.
  - Part 2 is an expansion cohort planned to further explore clinical activity at the MTD in NMC, SCLC, CRPC, TNBC, ER positive BC and GIST subjects.
  - Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).
- **SUBJECT SAMPLE**: Worldwide approximately 110 subjects will be enrolled in Part 1, and approximately 170 subjects will be enrolled in Part 2.
- **DOSAGE/DOSAGE FORM, ROUTE AND DOSE REGIMEN**: Starting dose will be 2 mg, orally (tablets), once a day. Dose escalations will be performed in Part 1 and dose adjustments are allowed to address tolerability and safety issues. Alternate dosing schedules (BID or intermittent dosing) may be used based on PK and safety.
- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There is extensive pharmacokinetic (PK) sampling in Part 1 and limited PK sampling in Part 2 for this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Blood samples will be collected for analysis of protein biomarkers (cytokines and acute phase proteins) and mRNA. Ex-vivo LPS induction of cytokines in whole blood will be assessed. In addition, pre-treatment and post-treatment tumor samples will also be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

- **EFFICACY MEASUREMENTS**: Response Rate (RR), Disease Control Rate (DCR), PSA50 response rate, Progression Free Survival (PFS) and Overall Survival (OS), time to response and duration of response.
- **SAFETY MEASUREMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. Cardiac safety monitoring will be required, consisting of triplicate 12-lead ECGs in Part 1 prior to dosing on selected days and prior to drawing PK samples on serial PK sampling days (overnight stays in research facility may be necessary in Part 1). Extensive laboratory testing includes, in addition to standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels, testing for troponin, c-peptide, 1,5-Anhydroglucitol (1,5 AG), HbA1c, and thyroid monitoring. Additional safety assessments may be necessary if a combination treatment regimen is administered to address specific safety concerns with the other agent(s) being administered.
- **DATA ANALYSIS**: Subject demographic and safety data will be collected on electronic case report forms (eCRFs). All data will be pooled and descriptive safety analyses summarized and listed by cohort at conclusion of Part 2 expansion cohorts. Additional analyses may occur between Part 1 and Part 2 and details will be included in the Reporting Analysis Plan (RAP). Part 2 of the study is powered to test overall Response Rate (RR). A futility assessment will be conducted after data are available from the first 10 subjects in each expansion cohort in Part 2.

1. INTRODUCTION

1.1. Background

Bromodomains: Bromodomains (BRDs) are small protein domains found in a variety of proteins that recognize and bind to acetylated histone tails. This binding affects chromatin structure, and thereby regulates epigenetically controlled processes including gene transcription and mRNA elongation [Nicodeme, 2010; French, 2008]. The bromodomain extra-terminal (BET) family of bromodomain proteins includes the BRD2, BRD3, BRD4 and BRDT [testes] proteins.

Investigational Product: GSK525762 is an orally bioavailable small molecule that is a potent inhibitor of the binding of BET proteins to acetylated histones. Binding of GSK525762 induces squamous differentiation and inhibits proliferation of patient-derived NMC cell lines both in culture and in murine xenografts. The phenotypic changes induced in vitro (flattening, keratin production, and the loss of proliferation markers) persist for more than 2 weeks after washout of GSK525762.

Nonclinical data suggest a narrow therapeutic window relative to reproductive, cardiac, and gastrointestinal toxicities which may be observed clinically with GSK525762 (see Section 1.5). However, the major cardiac and gastrointestinal toxicities observed in the animal studies can be clinically monitored and are largely reversible.

1.2. Study Population Rationale

1.2.1. NUT midline carcinoma

Nuclear protein in testis (NUT) midline carcinoma (NMC) is a newly described aggressive carcinoma that arises from a NUT gene translocation that generates a fusion protein with BRD proteins (BRD4 or BRD3) that is retained strictly in the cell nucleus via interactions with chromatin [Stelow, 2008; French, 2004]. NMC is a poorly differentiated malignant neoplasm, often with squamous differentiation, without pathognomonic features. As a newly described disease, and without specific histology, it is not surprising that NMC is often not diagnosed, or mistaken for other entities, including thymic carcinoma, squamous cell carcinoma of the head and neck, lung carcinoma, and Ewing sarcoma. NMCs are invariably lethal and despite aggressive chemotherapeutic regimens, subjects have a median life expectancy of only 6.7 months (N=63 patients) [Bauer, 2012].

Functional studies in subject-derived NMC cell lines have validated the essential role of the BRD4–NUT oncoprotein in maintaining the characteristic proliferation advantage and differentiation block of this uniformly fatal malignancy. The siRNA-mediated BRD knockdown arrests the proliferation and prompts terminal squamous differentiation in subject-derived NMC cells [French, 2008]. Additionally, BET inhibitors induce differentiation and growth arrest in NMC, and possess anti-tumor activity in NMC mouse xenograft models [Filippakopoulos, 2010].

NMC tumors may occur in multiple organ sites and are histologically indistinguishable from other undifferentiated squamous cell carcinomas. Subjects for the study will be selected based on the ectopic expression of NUT protein by Immunohistochemistry (IHC) [Haack, 2009] rather than on tumor histopathology or organ site. Fluorescence in situ hybridization (FISH) can also be used as a method to detect the presence of BRD-NUT fusion protein in NMC diagnosis. However, due to the fast progression of NMC, there is a practical limitation to the extent of FISH testing that can be completed, especially for delineating cryptic BRD rearrangements, prior to patient inclusion.

Recent studies have delineated the NUT variant sub population (n=4) through bespoke FISH experiments to, in all but one case, a cryptic rearrangement of the BRD3 locus. Retrospective analysis of the survival data observed in the NUT variant sub-population has indicated there is no apparent difference in progression free or overall survival based on this variant diagnosis compared to BRD4 or BRD3.

NMC is extremely rare with approximately 20 cases being reported in the United States annually, however due to misdiagnosis or underdiagnosis, the exact incidence and frequency of NMC are not well established (http://www.nmcregistry.org/). NMC may affect subjects of all ages (age range 0-78 yrs). The only known long-term survivor had a complete tumor resection. Therefore, patients with this rare tumor have a significant unmet medical need for more effective therapy.

1.2.2. Other tumor types

Recently published data as well as data generated internally at GlaxoSmithKline (GSK) and by collaborators have demonstrated the potential application of BRD extra-terminal (BET) inhibitors in tumor types other than NMC, including small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC); estrogen receptor positive (ER positive) breast cancer, neuroblastoma (NB), acute leukemias, gastrointestinal stromal tumors (GIST), and other N-Myc driven tumors. Studies in leukemia and Multiple Myeloma (MM) have shown that small molecule inhibition of BET protein binding to chromatin can directly block both c-Myc expression and its downstream transcriptional functions, resulting in significant anti-tumor effects [Delmore, 2011; Mertz, 2011]. Myc family proteins play a central role in the regulation of gene expression and cell cycle control. Their enhanced expression has been implicated in all aspects of tumor cell biology [Adhikary, 2005].

Based on the preclinical findings within GSK and with collaborators, subjects with small cell lung cancer, non-small cell lung cancer (NSCLC), colorectal cancer, castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, neuroblastoma, and N-Myc amplified solid tumors will be enrolled to the dose finding part of the study. In addition, Part 2 expansion cohorts will enrol subjects with NMC, SCLC, CRPC, TNBC, ER+BC and GIST.

Small Cell Lung Cancer

GSK525762 was found to inhibit growth in a subset of SCLC cell lines, with 46% (18 of 39) of cell lines possessing a $gIC_{50} < 1$ μM. It was confirmed in several of the cell lines

that apoptosis (assessed by caspase cleavage) is induced at concentrations above the gIC_{100}. Additionally, significant tumor growth inhibition was observed in a subset of cell line and patient-derived subcutaneous xenograft models of SCLC.

No correlation between status of c-Myc or L-Myc and sensitivity was found. N-Myc amplified cell lines were found to be sensitive, though the low number (N=2) of lines tested with this amplification does not allow for a firm conclusion to be drawn. Although no predictive marker of GSK525762 sensitivity in SCLC has been identified and considering the high percentage of cell lines that are sensitive, enrolment will be opened to all relapsed refractory SCLC patients in the dose escalation part of the study while collecting data retrospectively on potential predictive biomarkers from the available tissues.

Non-Small Cell Lung Cancer

GSK525762 inhibited cell growth in a subset of NSCLC cell lines, with 46% (33/72) of cell lines tested exhibiting a gIC_{50} <1μM. Median gIC_{50} across the NSCLC cell line panel was 1.1μM. *MYCN* amplified cell lines and large cell neuroendocrine carcinoma (LCNEC) cell lines were among the most sensitive to GSK525762, with a median gIC_{50} of 0.17μM and 0.24μM (n=4 for each sub-type). A subset of NSCLC cell lines, including *MYCN*-amplified and LCNEC lines, exhibited a cytotoxic response to GSK525762. Given the broad sensitivity of NSCLC cell lines to GSK525762, a selection marker will not be used for entry into the dose escalation part of the study.

Colorectal Cancer

In colorectal cell lines, initial data using the same criterion of sensitivity indicates that GSK525762 inhibits growth in a high percentage of lines tested (58%, 25/43 with gIC_{50} < 1 μM). No markers of sensitivity in these lines has been identified yet and, as with SCLC, enrolment will be opened to all relapsed refractory CRC patients without a selection marker in an initial clinical trial.

Neuroblastoma

NB cell lines are sensitive to GSK525762, with 83% of cell lines tested (15/18) exhibiting a gIC_{50} < 1μM. Median gIC_{50} across the NB cell line panel was 0.48μM, with a subset of cell lines exhibiting a cytotoxic response to GSK525762. The agent is sensitive in *MYCN* amplified cell lines, as 10 of the 15 sensitive cell lines possess the copy number increase. As with SCLC, NSCLC, and CRC, a selection marker will not be used in NB patients for entry into the dose escalation part of the study.

Castration-Resistant Prostate Cancer

A subset of prostate cancer cell lines were found to be sensitive to GSK525762, with 57% (4/7) of cell lines exhibiting a gIC_{50} <1μM. Apoptosis was observed in a subset of prostate cancer cell lines as measured by poly ADP ribose polymerase (PARP) cleavage and accumulation of cells in sub-G1 phase of cell cycle. Prostate cancer lines cell lines, including models of CRPC, with high androgen receptor (AR) and high c-Myc protein expression were found to be the most sensitive (lowest gIC_{50}) to GSK525762A.

Consistent with *in vitro* observations, significant tumor growth inhibition was observed in a subcutaneous patient-derived xenograft model of CRPC expressing high levels of *AR* and *MYC*. In contrast, no significant inhibition of tumor growth was observed in a second model expressing low levels of *AR* and *MYC*. Given the limited availability of pre-clinical prostate models and the broad sensitivity of prostate cancer cell lines to GSK525762, no selection marker will be used for entry into the dose escalation part of the study.

Triple Negative and ER-positive Breast Cancer

A subset of breast cancer cell lines representing the ER-positive and triple negative sub-types were found to be sensitive to GSK525762, with 55% (17/31) cell lines tested exhibiting a gIC_{50} < 1μM. Median gIC_{50} across the breast cancer cell line panel was 980nM, with a subset of cell lines exhibiting a cytotoxic response to GSK525762.

The activity observed with GSK525762 in ER+ breast cancer cell lines is consistent with data reported in two recent publications using the tool BET inhibitor JQ1 [Feng Q, 2014; Nagarajan, 2014]. Given the broad activity of BET inhibitors across the ER+ and triple negative subtypes, no selection marker will be used for entry into the dose escalation part of the study for ER-positive and TNBC patients.

N-Myc amplified solid tumors

A large majority of N-Myc amplified cell lines from various tumor types, including SCLC, NSCLC, and neuroblastoma, are highly sensitive to GSK525762. Across the three tumor types, 16 of 19 (84%) *MYCN*-amplified cell lines possess a gIC_{50} < 1μM, and 11 of 19 (58%) exhibit a cytotoxic response to GSK525762. Expression of *MYCN* was suppressed by GSK525762 in SCLC and NB cell lines, which is consistent with published reports [Puissant, 2013; Wyce, 2013].

Given the high percentage of responsive cell lines in small cell lung cancer, non-small cell lung cancer, colorectal, castration-resistant prostate cancer, triple-negative breast cancer, ER-positive breast cancer, and neuroblastoma it is appropriate to include refractory patients who have failed prior treatments regimens into the dose escalation phase of this study where this medicine may prolong survival. In addition subjects with any solid tumor that demonstrates N-Myc amplification will be eligible for the dose escalation phase of the study.

GIST (Gastrointestinal Stromal Tumor)

The super-enhancer profiling of sarcoma tumor samples and cell lines identified conserved super-enhancer program in GIST tumors. Some of the genes associated with super-enhancers in GIST tumors include well-established drivers, such as *KIT* and *PDGFRA*, but also potential novel targets, such as *ETV1* and *HAND1*. GIST-specific *KIT* super-enhancer regulating *KIT* gene activity is remarkably sensitive to bromodomain inhibition. KIT-dependent GIST cell lines have an IC50 to the prototypical bromodomain inhibitor, JQ1, ranging from 150 – 470nM (Matthew Hemming, personal communication, December 2016). Other bromodomain inhibitors, including GSK525762, demonstrate similar selective toxicity in KIT-dependent GIST cell lines. At the gene and protein

expression levels, BET bromodomain inhibitors attenuate the expression of genes, associated with superenhancers, such as *KIT, ETV1* and *HAND1*, suggesting that BET proteins are required for the maintenance of GIST super-enhancer associated transcriptional program and are critical regulators of GIST growth and survival. In support of this mechanism, uncoupling *KIT* expression from its native super-enhancer leads to resistance to bromodomain inhibition. In KIT-dependent GIST cells, bromodomain inhibition shows synergistic toxicity with KIT-inhibition, further suggesting an independent and complimentary mechanism of action in GIST (Matthew Hemming, personal communication, December 2016). These evolving data have driven strong enthusiasm in developing bromodomain inhibitors in GIST.

1.3. Dose Rationale

1.3.1. Human Pharmacokinetics

Whole blood human clearance was predicted from three species (mouse, rat and dog) using simple power-law allometry (in the absence of detectable in vitro metabolism) to be 2.8 mL/min/kg. Volume of distribution was predicted from Gastroplus to be 2.6 L/kg and half-life 10 hours (GlaxoSmithKline Document Number 2010N108204_00, 2011). As the in vitro blood to plasma ratio was 0.86, a 70 kg adult therefore had a predicted total clearance of 10.1 L/hr and a total plasma volume of distribution of 157 L.

Information on the pharmacokinetics of GSK525762 in humans can be found in the Investigator's Brochure (GlaxoSmithKline Document Number 2011N113741_05, 2016). In summary, GSK525762 pharmacokinetics are characterized by a rapid absorption with maximum concentration occurring mostly within the first hour after dosing. GSK525762 is eliminated rapidly with an average terminal phase half-life of 3 to 7 hours, leading to a lack of accumulation following once daily oral administration. Following single oral administration and repeated once daily administration of 2 mg to 100 mg of GSK525762, Maximum observed concentrations (C_{max}) and Area under concentration-time curve (AUC) tended to increase in a dose proportional fashion with a large overlap for individual AUC between 30, 60, 80 and 100 mg cohorts.

1.3.2. Starting dose

Four approaches have been considered to establish the starting dose for GSK525762:

- One tenth of the rat 10% mortality over the duration of the study (STD) 10 as per International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9 guidance

For GSK525762, the STD10 was defined as 30 mg/kg in the rat following ICH S9 guidelines. 1/10 rat STD10 is 18 mg/m^2; this dose is not severely toxic to dogs; therefore starting dose is 1/10 rat STD10 which translates to a starting dose in man of 30 mg, assuming a 70 kg adult and adult surface area of 1.7 m^2.

- One sixth of the dog Highest non-severely toxic dose (HNSTD) as per ICH S9 guidance

Based on tolerability and QT prolongation, the HNSTD was defined as 0.3 mg/kg in the dog. 1/6 dog HNSTD is 1 mg/m^2 which translates to a starting dose in man of 1.7 mg (rounded to a starting dose of 2 mg based on tablet strength), assuming a 70 kg adult and adult surface area of 1.7 m^2.

- Average exposure at the QTc NOEL in the dog

Average exposure at the QTc NOEL (0.3 mg/kg) was as follows: AUC 642 ng.hr/ml (total), 167 ng.hr/ml (free), Cmax 80 ng/ml (total), 20.8 ng/ml (free). Extrapolating the AUC to humans, the dose required for parity is given by Dose = AUC x CL/Fu, where Fu is fraction unbound in humans (22%). Using this expression, the predicted starting dose would be 167 ng.hr/ml x 11.8 (L/hr)/0.22 = 9 mg, assuming 100% absolute bioavailability. Using an absorption rate of 1/hr predicted from Gastroplus, the predicted free drug Cmax is 8.2 ng/ml.

- The dose predicted to deliver a Cmax of less than the IC20 for the most sensitive known human pharmacology (Minimum anticipated biological effect level [MABEL] dose)

The most sensitive human pharmacology is defined as the inhibition of growth in patient derived NMC cells. Free drug IC50 is approximately 40 ng/ml with maximal inhibition at 1000 ng/ml. IC20 for this pharmacology, defined as MABEL, is 10 ng/ml. The dose to achieve this MABEL concentration at Cmax is 11mg (MABEL dose).

Taking all four approaches into consideration, a starting dose of 2 mg is proposed. This dose will provide a 5-fold safety margin to the QTc prolongation observed on repeat dosing in the dog. Table 1 provides the predicted safety cover for the proposed 2 mg starting dose.

Table 1 Predicted Safety Cover for proposed 2mg starting dose (data from most sensitive NOAEL/NOEL from 4 week toxicology studies)

Clinical starting dose Dose (2 mg)	**Total AUC**	**Free AUC**	**Total Cmax**	**Free Cmax**
Predicted human exposure	197 ng.h/mL	36.6 ng.h/mL	9.80 ng/mL	36.6 ng.h/mL
Cardiotoxicity				
QTc from single dose*	94.1x (NOEL)	130x (NOEL)	336x (NOEL)	130x (NOEL)
QTc on repeat dosing	3.97x (NOEL) 10.7x (LOEL)	5.45x (NOEL) 14.8x (LOEL)	10.9x (NOEL) 32.7x (LOEL)	5.45x (NOEL) 14.8x (LOEL)
Troponin	No cover		No cover	
Gastrointestinal toxicity				
In life changes	0.863x (NOAEL) 9.44x (LOAEL)		8.25x (NOAEL) 121x (LOAEL)	
Microscopic changes	9.44x (NOAEL) 45.3x (LOAEL)		32.7x (NOAEL) 134x (LOAEL)	
Hepatic toxicity (single rat)	9.44x (NOAEL) 62.6x (LOAEL)		121x (NOAEL) 337x (LOAEL)	
Hematopoietic toxicity	1.64x (NOAEL) 9.44x (LOAEL)		14.7x (NOAEL) 121x (LOAEL)	
Lymphoid toxicity	9.44x (NOAEL) 62.6x (LOAEL)		121x (NOAEL) 337x (LOAEL)	
Hemolysis (rat specific)	9.44x (NOAEL) 62.6x (LOAEL)		121x (NOAEL) 337x (LOAEL)	
Clotting effects	10.7x (NOAEL) 45.3x (LOAEL)		32.7x (NOAEL) 134x (LOAEL)	
Pancreatic toxicity (male rat specific)	7.39x (NOAEL) 62.3x (LOAEL)		64.2x (NOAEL) 338x (LOAEL)	
Pulmonary effects (rat specific)	1.64x (NOEL) 9.44x (LOEL)		14.7x (NOEL) 121x (LOEL)	
Testicular toxicity	No cover		No cover	

NO(A)EL = No observed (adverse) effect level
LO(A)EL = Lowest observed (adverse) effect level
*Calculated from single dose GLP dog Coefficient of variance (CV) study

1.3.3. Predicted therapeutic dose range

The potential therapeutic dose for GSK525762 in human was derived using available preclinical PK, in vitro data, and efficacy data from several tumor xenograft studies. Based on modeling, maximal efficacy of GSK525762 may require ≥ 50% target inhibition. The predicted human effective daily dose is 25 to 100 mg assuming 50 to 100% oral bioavailability.

1.3.4. Dose escalation steps

Human PK predictions suggest that exceeding the systemic exposure of the preclinical 4 week MTD (1 mg/kg in dogs and 10 mg/kg in rats) may be required to achieve ≥ 50% target inhibition in the majority of subjects. The start of the predicted therapeutic range in humans is at parity with the 4 week MTD exposure range in preclinical species. The toxicities observed at exposures greater than the preclinical MTD are clinically monitorable and largely reversible (excluding testicular effects), therefore semi-semi-log (≤ 2-fold) dose escalation above this preclinical MTD, conditional on acceptable tolerability, is permitted until the clinical MTD is established.

1.3.5. BID Dose Cohort

1.3.5.1. Preclinical Rationale

Pre-clinical pharmacokinetic and pharmacodynamic data suggests a potential benefit of a BID dosing regimen compared to QD dosing. In mice, GSK525762 has a short half-life of about 1.5 hours. Single dose pharmacodynamic experiments were performed in three SCLC and one CRC mouse xenograft model. Dose-dependent changes in gene expression were observed in all models at early time points post-dose; however, expression returned to pre-treatment levels within 8-12 hours. Additionally, in a subcutaneous multiple myeloma cell line xenograft study, c-Myc protein levels were significantly reduced 2 and 5 hours post-dose, and returned to baseline by 8 hours. The transient effects on gene expression observed in these studies with QD dosing highlights the potential benefit of BID dosing by extending the duration of gene silencing within a 24 hour period.

QD and BID dosing have been further explored in efficacy studies in the above-mentioned SCLC and CRC xenograft models. In a subcutaneous, patient-derived model of SCLC, BID dosing at 12.5mg/kg resulted in improved tumor growth inhibition compared to 25 mg/kg QD (74% versus 60%, respectively). Improved efficacy with BID dosing was also observed in the cell line xenograft model of CRC. BID dosing at 12.5 mg/kg resulted in 48% tumor growth inhibition, whereas 25 mg/kg QD dosing resulted in 34% inhibition. In a third model, a cell line xenograft of SCLC, there was no significant difference in tumor growth inhibition resulting from 12.5mg/kg BID versus 25mg/kg QD dosing. Thus, we observed equivalent or improved efficacy with BID dosing in all xenograft models tested.

1.3.5.2. Clinical Rationale

Based on the pharmacokinetics of GSK525762 observed to date, with the short half-life of about 5 hours, it is predicted that even 100 mg QD doses would result in the trough

concentrations falling below the average in vitro IC50 (0.08 uM to 1.3 uM) for the tumor types selected for this study. Dividing the daily dose into two doses administered about 12 hours apart would maintain the concentrations above the lower in vitro IC50 for doses around 30 mg BID.

1.3.6. Doses for Besylate Bioavailability/Food Effect/Dose Proportionality Sub-Study

A dose at or near the maximum tolerated dose or the recommended Phase 2 dose will be used to evaluate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet.

As GSK525762 is a compound with high solubility but low permeability, it is expected that administration with food will have no effect or possibly a negative effect on its absorption [C-H Gu, 2007] and a dose at or near the MTD or RP2D will be used to evaluate the effect of food on the relative BA of GSK525762 administered as the besylate salt tablet.

In addition, to evaluate the dose proportionality of the PK of GSK525762 after fasted administration as besylate salt tablet, a lower dose of half to one-third of the MTD or RP2D will be evaluated.

1.4. Rationale for Study and Endpoints

Safety and efficacy (RR) 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 of once daily and/or twice daily dosing. The pharmacodynamic assessments will further support the recommended Phase II doses (RP2D) and expand the understanding regarding mechanism of action. The response rate hurdle of 20% in NMC was determined based on 3 parameters: NMC is a rare population, there is currently no standard of care therapy for NMC, and NMC carries a poor prognosis (median survival of 6.7 months [Bauer, 2012].

Given the poor prognosis and high unmet medical need of NMC, as well as in other tumor types such as relapsed/refractory SCLC, NSCLC, CRC, CRPC, TN and ER+ BC, GIST, NB and N-Myc amplified tumors and the exceptional drug-to-target alignment of GSK525762, a combined Phase I/II study (BET115521) is proposed. The BET115521 study comprises an accelerated dose titration (Part 1), which will include subjects with NMC and other tumor types that are predicted to be responsive to GSK525762, to determine a maximum tolerated dose (MTD). The besylate sub-study will be an open-label, randomized, single dose, four period, crossover sub-study to investigate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet at a dose at or near the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate salt tablet at or near the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate salt tablets. Results of the besylate sub-study will enable the use of the besylate salt tablet formulation later in this study and provide recommendation around the need for fasting status when administering GSK525762. The besylate sub-study will be conducted at centers in the United States.

The recommended phase II dose (RP2D) of GSK525762 with possible adjustment based on the relative bioavailability of the besylate salt formulation, will be studied in the cohort expansion (Part 2) to determine efficacy, safety and tolerability in NMC and other tumor types including SCLC, CRPC, TNBC, ER+BC and GIST.

1.5. Risk Assessment

Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK525762 are gastrointestinal, cardiovascular, pancreatic, hematologic and reproductive (see GlaxoSmithKline Document Number 2011N113741_05, 2016, Section 3.4). These toxicities are addressed below, together with the proposed safety monitoring and risk mitigation activities that are included in the planned study.

Gastrointestinal: Evidence of degeneration/regeneration and/or erosion/ulceration in the gastrointestinal tract was seen at non-tolerated doses in 7 and 14 day studies in rat and dog, respectively. Microscopic examination included degenerative changes in the esophagus, stomach, small and large intestine, including erosion or ulceration, mucosal congestion, hemorrhage and edema, crypt dilatation and focal inflammatory cell infiltration in the toxicology studies of up to 3 month duration in the dog and rat. Recovery was evident after a minimum of 3 weeks off dose. During clinical studies, medical history, physical examination (including weight) and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided as per standard medical practice. In the event of clinically significant toxicity, treatment will be withheld and supportive therapy provided according to standard medical practice.

Cardio-vascular: Although there were minimal effects of GSK525762 on current density and no effects on trafficking in HEK-293 cells or on ECG rhythms or arrhythmias in the *ex vivo* rabbit wedge assay, QT and QTc prolongation (maximum 41 milliseconds at 3 mg/kg for 12 days) was seen in dogs after a single oral dose of 30 mg/kg or repeat dosing at ≥1 mg/kg/day in toxicology studies of up to 3 month duration. No effect was seen in the dog at 0.3 mg/kg (6 mg/m2) where exposure is estimated to be approximately equivalent to that achieved by a 10 mg dose in humans if 100% bioavailability is assumed. However, the starting dose in this First time in humans (FTIH) study is 2 mg. Increases in biomarkers of cardiac damage (cardiac troponin I and T, myosin light chain and NT-proANP) were also seen in the rat and cardiac troponin I in the dog. Despite these QTc and cardiac biomarker changes, there was no evidence of compound-related myocardial necrosis or other histopathological changes in cardiac tissue of either species. No significant arrhythmias were detected in preclinical studies.

Given the risks of long QTc associated arrhythmias, and of compound associated cardiomyopathy, subjects will be monitored closely for changes in QTc with triplicate 12-lead ECGand for elevations in plasma Troponin. Inpatient 48-hour telemetry was originally required for all subjects following the first dose of study drug, as part of the cardiac monitoring. Evaluation of cardiac safety data from subjects treated up to the 100 mg QD cohort by the cut-off date of May 15, 2015 demonstrated no significant QTc prolongation after single and repeat dose administration. Therefore, the 48-hour telemetry requirement was removed and the frequency of Holter monitoring was reduced with

Protocol Amendment 6 and upon further review of the totality of data, Holter monitoring was removed in Amendment 9. Specific stopping criteria and management guidelines are provided for cardiac toxicities.

Electrolytes, including potassium and magnesium will be checked at baseline and at regular intervals or when clinically indicated. Appropriate medical management will be instituted to assure that electrolytes are kept within the normal range.

Safety ECGs

Safety ECGs will be performed at the time points specified in Time and Events Tables using a standard 12-lead ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF intervals. The mean from triplicate ECGs (when indicated) will be evaluated at each time point. Safety ECGs will be reviewed by the investigator and a Cardiologist on an ongoing basis for safety purposes and will be over-read at a central site (eRT). The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected.

Serum Markers

In addition to the safety ECGs performed during the study, laboratory evaluations for cardiac troponins and electrolytes will be performed and NT-pro-brain natriuretic peptide (BNP) will be checked at baseline, regular intervals (as specified in the Time and Events Tables), and when clinically warranted during the study treatment. Troponin I or T (based on availability) levels will be tested by a local laboratory and monitoring for troponin T at a central laboratory. Appropriate medical therapy will be provided by the investigator for any clinically significant increase in troponins including withholding or discontinuing the study medication.

Pancreatic: Islet cell fibrosis/fibroplasias and peri-islet hemorrhage, pigmented macrophages and inflammation were seen at 30 mg/kg in male rats and acinar cell apoptosis, vacuolation and/or degranulation were seen at 3 mg/kg in female dogs. Glucose (serum and urine), insulin, 1,5-AG and c-peptide will be monitored clinically for changes associated with islet cell toxicity and signs of gastric distress or abdominal pain that may serve as a sign and/or symptom of acinar cell dysfunction. In addition, amylase and lipase levels will be obtained. Subjects will be monitored for clinical signs of malabsorption.

Hematologic and lymphoid: Lymphoid toxicity was observed in rats and dogs manifested by bone marrow hypo-cellularity and variable and inconsistent changes in total white cell lymphocyte and decreased platelet counts. There were variable and inconsistent changes in multiple red blood cell parameters and reticulocytes in the periphery, and decreased organ weight, thymus, spleen, and lymph node hypocellularity. Higher activated partial thromboplastin time (aPTT) and increased fibrinogen were seen at 3 mg/kg in dogs indicative of abnormal clotting. In clinical studies, the complete blood count (CBC) and coagulation factors (INR, prothrombin time [PT], aPTT) will be measured frequently to monitor for these toxicities. Supportive therapy will be provided

according to standard medical practice, and treatment will be held for clinically significant toxicity.

Pulmonary: Aggregates of foamy macrophages in peri-bronchiolar areas were evident in rats given ≥10 mg/kg/day for 28 days. Following the 3 week off-dose period, these changes were decreased in incidence. This effect may be a result of unintended lung exposure due to the dosing procedure and an exacerbation of the finding by GSK525762. This finding is unlikely to affect pulmonary function; no effects were observed in the 3 month studies in rats and dogs.

In the study, patients will have pulmonary function assessments at baseline and as clinically appropriate. In addition, a chest x-ray will be obtained at baseline along with physical exams that will be performed throughout the study (see Section 5).

Hepatic Toxicity: Non-adverse liver changes were observed in rats and dogs including increases in bilirubin levels and transient increases in AST in rats. Necrosis was observed in one rat at 30 mg/kg/day in the 4 week study. GSK525762 has been demonstrated to undergo bioactivation in vitro which indicates potential for idiosyncratic hepatotoxicity. The precursor metabolite has been observed in clinical plasma samples.

The BET115521 protocol includes frequent monitoring of liver biochemistry along with stopping criteria for dose limiting toxicity (DLT), liver monitoring guidelines and management (see Section 3.2.3, Section 7.7.2, and Appendix 3).

Reproductive and Developmental: In toxicology studies of up to 3 month duration, bilateral sperm retention, germ cell degeneration and tubular vacuolization, and depletion of testicular germinal epithelium occurred in male dogs receiving ≥ 0.01 mg/kg and male rats receiving ≥ 10 mg/kg doses of GSK525762. Exposures associated with reproductive toxicity in male dogs overlap with the proposed 5 mg starting dose in this FTIH study. These changes were accompanied in rats and dogs by changes in sperm morphology, motility and number and hormonal changes (decreased testosterone and Inhibin B in rats and increased FSH in rats and dogs). Reduced prostate weight and secretory content was also evident in the rat. An effect on spermatogenesis is anticipated. Full or partial reversibility of the testicular effects was observed in the 3 month rat and dogs studies following a 17 week off dose period.

GSK525762 at 0, 1, 3, 10, or 30 mg/kg/day (total dose; doses expressed as parent compound) was given orally by gavage BID (doses given 6 hours apart) to pregnant rats on Days 0 through 17 post-coitus. Dose-dependent maternal toxicity (reduced body weight gain and reduced food consumption) was evident at ≥10 mg/kg/day. Embryo-fetal toxicity was evident as both pre-implantation loss and increased fetal resorptions leading to complete loss of litters at 30 mg/kg/day, and dose-dependent increased fetal resorptions at doses ≥1 mg/kg/day. Developmental toxicity was evident as decreased fetal weights at 10 mg/kg/day and fetal malformations and/or variations at all doses (membranous ventricular septal defects in the heart ≥1 mg/kg/day; great vessel, heart, kidney, ovary, uterus, and ureter malformations and/or variations at 10 mg/kg/day). The AUC0-t and Cmax at 1 mg/kg/day (the lowest dose tested) in non-mated female rats after 5 doses were 54 ng.h/mL and 18 ng/mL, respectively.

No ovarian histologic changes were observed in the 4 week toxicology studies, however female fertility (disrupted estrous cyclicity, delays to mating and/or reduced fertility index) was affected in rats given 30 mg/kg/day GSK525762 for 15 days prior to mating and 15 days prior to mating through to Day 6 post coitus (pc). Systemic exposure in rats was approximately 2-fold higher than current exposure in late stage cancer patients (at 60 mg/day). No fertility effects were observed when 30 mg/kg/day was given for 6 weeks followed by 6 weeks off-dose prior to mating.

Reproductive and developmental toxicity (decreased fetal body weight, fetal malformations or variations and / or pre- and post-implantation loss) occurred in rats given GSK525762 ≥1mg/kg/day from conception through gestation day 17 (of 21 days) and when dosed at ≥10 mg/kg/day for 14 days and dosing stopped prior to mating or continued until Day 6 pc. Systemic exposure in rats was approximately 80-fold lower than current exposure in late stage cancer patients (at 60 mg/day). These results are consistent with observations that BRD2, BRD3, BRD4 and BRDT have crucial roles in reproduction and development [see the GSK525762 IB, GlaxoSmithKline Document Number 2011N113741_05, 2016]] for references.

Based on the findings in these reproductive and developmental toxicity studies in rats with GSK525762, there is a substantiated risk for adverse effects on embryofetal development and impacts on female fertility.

In the BET11521 study, specific contraceptive guidelines and precautions for males and females are provided in the protocol. In addition, the informed consent will include potential reproductive risks and precautions in addition to recommendations for the preservation of reproductive capacity.

Potential drug-drug interactions based on nonclinical studies: There is low potential for GSK525762 to induce or inhibit cytochrome P450 (CYP) enzymes or to inhibit Pgp or BCRP. Use of concurrent drugs with potential to prolong QTcF will be used with extreme caution or prohibited (as outlined in Section 8.2.2 of the protocol). Regarding drugs for hyperemesis, palonosetron (administered per the prescribing information) and ondansetron (at a maximum oral dose of 8 mg TID) will be the only allowed serotonin 5-HT3 receptor antagonist drugs.

2. OBJECTIVES, ENDPOINTS, HYPOTHESES FOLLOWING QD AND/OR BID DOSING SCHEDULES

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • To evaluate the clinical activity of GSK525762 in NMC and other solid tumors. • To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc.) to determine the MTD in subjects 16 years or older • Assess overall response rate (RR) using RECIST 1.1 in NMC and other solid tumors or PSA50 response rate using PCWG2 guidelines in CRPC or DCR (CR+PR+SD ≥ 16 weeks in duration) in GIST. • PK parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet.

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.
	• The primary goal of Part 2 is to demonstrate a clinically meaningful response, defined as follows:
	  • NMC: this will be determined by testing the null hypothesis that the response rate is ≤5%, with about 80% power when the true response rate is 20%.
	  • SCLC and CRPC: this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 30%.
	  • ER+BC: this will be determined by testing the null hypothesis that the response rate is ≤15%, with about 80% power when the true response rate is 30%.
	  • TNBC: this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 25%.
	  • GIST: this will be determined by testing the null hypothesis that the disease control rate is ≤15%, with about 80% power when the true disease control rate is 40%.

Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • To evaluate cardiac safety, including the potential for QTcF changes with GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival.
Endpoints	• PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 16 years or older • Changes in cardiac safety including QTcF following single and repeat-dose oral administration GSK525762. • Progression free survival (PFS), time to response, duration of response, overall survival (OS), and exploratory analysis for antitumor response by various imaging modalities.
Exploratory (Objectives and Endpoints only)	
Objectives	• To evaluate the effect of GSK525762 on tumor biology. • Correlation of GSK525762 exposure to changes in PD markers in tumor and/or surrogate tissue. • To identify potential indicators of sensitivity or response to GSK525762. • To evaluate systemic and ex vivo on-target BET inhibitory effects.
Endpoints	• Dose related changes in markers of cell proliferation and/or cell differentiation in tumor and/or surrogate tissue. • Dose related changes in transcription of genes and/or changes in expression of proteins regulated by BRD proteins in tumor and/or surrogate tissue. • PK/PD parameter values for exposure response (by RECIST and ^{18}FDG-PET [if data allows]) relationship between GSK525762 exposure and QTcF, troponin and tumor response following single and repeat-dose oral administration. • Changes from baseline and dose/response relationship in ex vivo LPS induced cytokines including IL-6 in whole blood and systemic cytokines including IL-6.

3. INVESTIGATIONAL PLAN

3.1. Study Design/Schematic

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables, is essential.

This is an open-label, single and repeat dose, 2-part study to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily orally. Twice daily dosing may also be explored upon evaluation of safety, PK, and PD data from once-daily dosing. Part 1 will be conducted in adult subjects with NMC, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and MYCN driven solid tumors. During the dose escalation of Part 1, additional subjects with NMC will be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamic effects of GSK525762 at lower doses that have been previously cleared during dose escalation. This will enable collection of pharmacodynamic data across the predicted efficacious dose range and contribute to the evaluation of a biologically efficacious dose. A sub-study will be opened to approximately 10 to 12 subjects in the United States to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet at the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet at the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate tablet. This sub-study will also use a stable isotope of GSK525762 in order to reduce the variability in the measurement of drug exposure caused by day-to-day biologic variations. Expansion cohorts (Part 2) are planned to further explore clinical activity of GSK525762 in subjects with NMC, SCLC, CRPC, TNBC, ER+BC and GIST as shown in Figure 1. The expansion cohorts will enroll adult (16 years old and above) subjects at the appropriate R2PD dose.

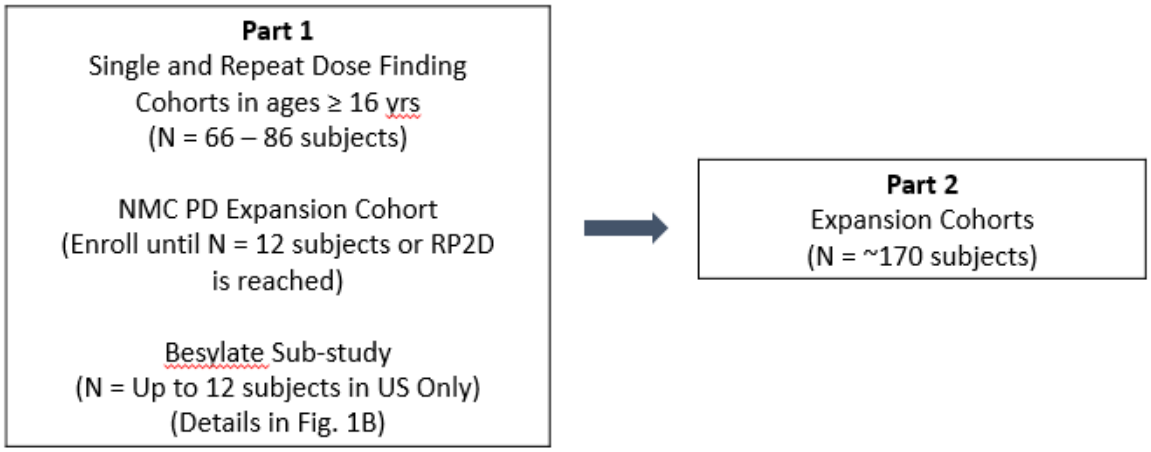
In Part 1, an accelerated dose titration will be employed with one subject per dose level until the first instance of a Grade 2 drug related toxicity occurs. Thereafter, subjects will be enrolled in a standard 3+3 design.

After the MTD has been determined in Part 1, Part 2 will be opened for the SCLC, TNBC, ER+BC and CRPC expansion cohorts. The NMC expansion cohort will be opened with the pivotal besylate tablet after results from the besylate study are available. The GIST expansion cohort is being added in Amendment 9 due to pre-clinical evidence for bromodomain inhibition in GIST.

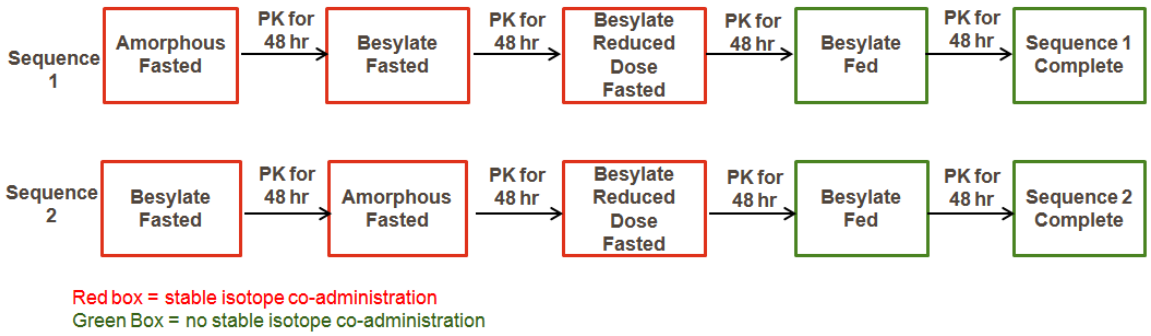
In Part 1, all subjects will be evaluated for systemic and ex-vivo on-target BET inhibitory effects in blood. In addition, pre-treatment and post-treatment tumor samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Figure 1 Study Schema

A. Part 1 and 2



B. Besylate Sub-Study (N=up to 12 subjects in the United States)



After completion of either sequence all subjects enrolled in the sub-study will be allowed to continue in the study with a continuous daily schedule.

3.2. Discussion of Design

3.2.1. Part 1 Dose Escalation

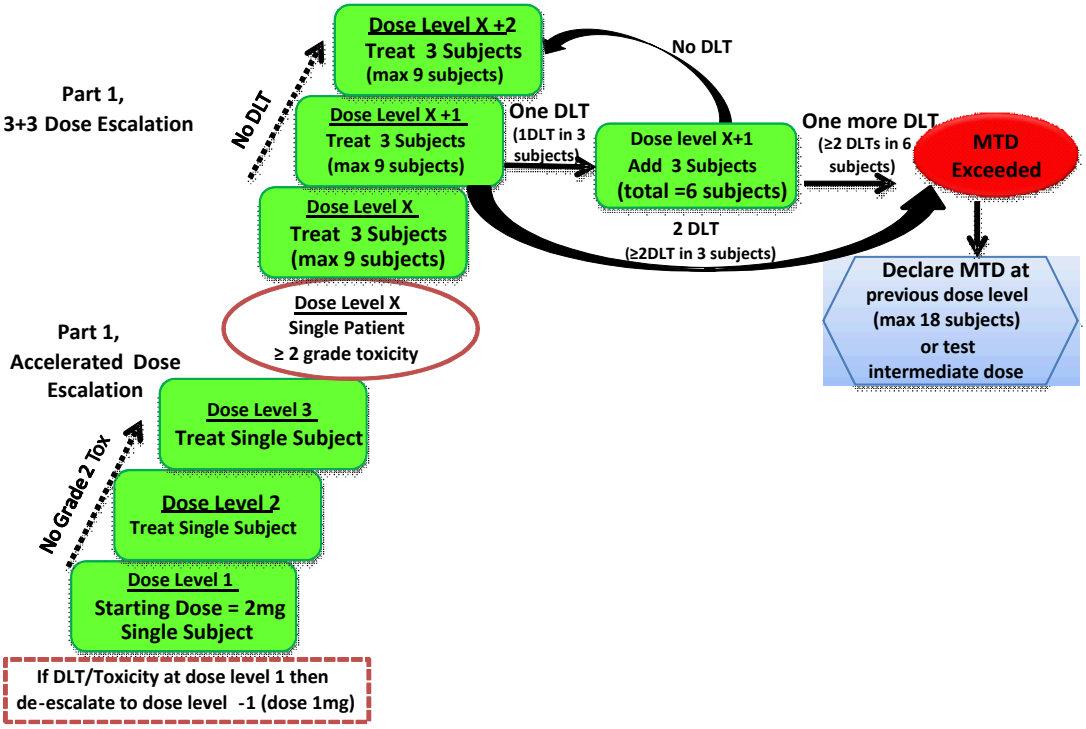
Part 1 will start with an accelerated dose escalation schema in subjects ≥16 years old with one subject per dose level. Accelerated dose titration will stop once a single Grade 2 or higher drug-related adverse event is observed in one subject, at which point a standard 3+3 dose escalation design will be implemented to define the MTD. The details of these 2 dose escalation strategies are in Figure 2.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the recommended dose from the Neuenschwander- Continuous Reassessment Method (N-CRM) design [Neuenschwander, 2009]. N-CRM design is a type of Bayesian adaptive dose escalation scheme. The method is fully adaptive and

makes use of all the Dose Limiting Toxicity (DLT) information available at the time of each dose assignment. The DLT information of all subjects enrolled in the trial are used to update the dose-toxicity relationship and provide supportive information in addition to 3+3 design in the next escalation/de-escalation decision.

Dose escalation will continue until an MTD is determined or until a dose of 200mg per day is reached.

Figure 2 Dose Escalation Schema



(Dose increase at any dose escalation will be < 2 fold)

3.2.2. Dose Escalation and Schedule

In Part 1, subjects will dose once or twice daily, depending on the cohort. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data.

Monitoring for cardiac safety signals will be performed, with triplicate 12-lead ECGs to be performed on the days indicated in the Time and Events Tables.

Subjects will be evaluated for dose limiting toxicities (DLTs) during the first 4 weeks of treatment (Section 3.2.3).

3.2.2.1. Accelerated Dose Escalation in Part 1

One subject per dose level in the accelerated dose escalation schema will be treated to minimize suboptimal drug exposures, starting with Dose Level 1 (Table 2) and continuing until one subject experiences a Grade 2 or higher (based on CTCAE v. 4.0) drug related adverse event or a DLT. Once this occurs, the accelerated dose escalation will terminate, and subjects will be enrolled under a standard 3+3 design (i.e., 3 subject cohorts) (Section 3.2.2.2).

Table 2 Accelerated Dose Escalation Procedures in Part 1

Dose Level	Change in Dose
Dose Level -1	Lower doses may be used if Dose Level 1 is not tolerated. This may be achieved by reducing the dose or by alternate dosing (e.g. every other day)
Dose Level 1	Starting Dose at 2 mg once daily
Subsequent dose levels	Increase by ≤2-fold (No subjects with ≥ Grade 2 drug related toxicity AND no subjects with any DLTs in first 4 weeks of treatment)
End of Accelerated Titration Phase	Begin 3+3 Dose Escalation Phase (1 subject ≥ Grade 2 drug related toxicity in the first 4 weeks of treatment)

NOTE: Route/Administration/Duration: Oral QD or BID (specific dosing instructions will be provided to each subject).

3.2.2.2. 3+3 Dose Escalation in Part 1

Two additional subjects will be enrolled to the dose level at which accelerated dose titration ends, for a total of at least 3 subjects at that dose level. If no DLTs are observed in any of the 3 patients then dosing will proceed to the next higher dose level (≤2 fold increase in dose). Subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects. Dose escalation decisions will be made as outlined in Table 3. Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. If 2 or more DLTs are observed at any dose level, the MTD will have been exceeded.

Once the MTD is reached, up to 20 additional subjects may be enrolled at the MTD to further evaluate safety and tumor PD. Up to an additional 6 subjects may be enrolled at any dose level below the MTD in order to obtain additional dose/response information related to tumor PD. Additional cohorts (with daily exposure not exceeding QD MTD exposure) may also be initiated to explore alternative dosing schedules to optimize the PK, safety and tolerability profile (see Section 3.2.2.4). The enrolment of additional subjects as described could be in parallel with Part 2 enrolment.

Table 3 3+3 Dose Escalation Decision Process in Part 1

Number of subjects at given dose level with DLT	Action
0 out of 3 subjects	Escalate to next dose level
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	Escalate to the next dose level (Increase by ≤2-fold)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort.

3.2.2.3. Biopsy and PET Cohorts during Dose Escalation Phase

During the accelerated dose escalation phase ^{18}FDG-PET and biopsy assessments will be optional until the standard 3+3 design is implemented. At this point, the sites will be required to obtain biopsies (when accessible) and required to perform ^{18}FDG-PET assessments when appropriate. Additional details on biopsy collection are provided in Section 6.8.1.

3.2.2.4. Alteration of Schedule

Alterations may be made to the schedule of administration and/or PK/PD sampling schedule based on the results of emerging PK and safety data.

Schedules that incorporate a recovery period may be explored (e.g. every other day or two weeks on treatment followed by one week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using 3 + 3 dose escalation. If alternative dosing schedules are explored, PK sampling times and other safety assessments may be modified to reflect the new dosing schedule.

On completion of the besylate sub-study for relative bioavailability of besylate formulation in tablet form, and having determined a dose for Part 2, all subjects in Part 1 daily dosing cohorts and in Part 2 will be administered the besylate tablets at the recommended Part 2 dose of 75 mg once daily. Those subjects in Part 1 daily dosing cohort who were on amorphous tablet dosing before availability of besylate tablets, they will be switched to the equivalent besylate tablet dose and will have limited PK samples drawn after start on besylate tablets.

In Part 2, subjects approved to alter their current dose level with either a dose reduction or dose escalation may require additional limited PK sampling, after discussion with the GSK Medical Monitor.

3.2.2.5. BID Dosing Cohort

BID dosing will be explored, based on the short half-life. The initial dose level for BID will be 20mg BID or "x"mg BID (where 2x is equivalent to the last once daily dose cleared for dose escalation in Part 1) – whichever is lower. Dosing will be separated by approximately 12 hours (± 1 hr). Escalation can then proceed as described using the 3 + 3 dose escalation. Additional blood samples will be collected for PK, PD, and safety as described in Table 7.

Subjects may need to undergo dose modification(s) to manage toxicities. A dose adjustment (e.g., BID dose level with a minimum 25% reduction in total daily dosing or QD at the same or lower dose level) may be explored after consultation with GSK Medical Monitor. The investigator should use clinical judgment to determine whether the dosing scheduling may be contributing to any potential toxicity necessitating dose adjustment, and make the appropriate change after consultation with the GSK Medical Monitor.

3.2.2.6. Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced any Grade 2 or higher drug related toxicity during the first 4 weeks of investigational therapy in the accelerated dose escalation phase or a DLT in the 3+3 dose escalation phase and contingent upon one of the following:

- If additional subject(s) have been enrolled at a higher dose in the dose escalation phase and at least one subject has completed 4 weeks of dosing on that regimen without a DLT, and after review of all safety data and approval by a GSK Medical Monitor, a subject on a lower dose level may be increased up to the highest dose level tested. In this case the subject may begin daily dosing at the higher dose level as it will have already been demonstrated to be tolerable.
- If no further subjects have been identified for a subsequent higher dose level and after a subject has completed 4 weeks of dosing on that regimen without a DLT, that subject may be escalated to the next higher dose level after an additional 4 weeks of dosing (total of 8 weeks of dosing), review of all safety data and approval by a GSK Medical Monitor. In this case the subject must follow the dosing/monitoring schedule for the first 4-weeks as outlined in the Time and Events Tables, as he/she will be the first subject exposed to the higher dose.

In Part 1, subjects approved for intra-subject dose escalation will require additional limited PK sampling (pre-dose, 0.5, 3 and 6-8 hours) at the higher dose, as determined by GSK Clinical Pharmacology. Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

3.2.3. Dose Limiting Toxicity (DLT)

An event will be considered a DLT if it occurs within the first 4 weeks of therapy and meets one of the following criteria:

- Neutropenia:

  - Grade 4 neutropenia lasting ≥7days.

  - Febrile neutropenia: as defined by CTCAE version 4.0 lasting for >24 hours despite adequate treatment.

- Grade 4 thrombocytopenia.
- Drug related Grade 3 or 4 non-hematologic toxicity (including QTcF) as described in the Common Terminology Criteria for Adverse Events v 4.0 (excluding abnormalities of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (see criteria below). In addition, the DLT exceptions include: rash, diarrhea, fatigue, mucositis, nausea, and vomiting that do respond to standard medical care within 72 hours or for electrolyte disturbances within 24 hours).
- Drug related Grade 2 non-hematological toxicity (at any time during treatment) that in the judgment of the investigator and GSK Medical Monitor is dose-limiting.
- Grade 2 Troponin T elevation (central laboratory > Upper limit of normal [ULN]), measured on two separate occasions within 48 hours in order to confirm elevation and with other clinical signs, symptoms, laboratory tests consistent with cardiac toxicity. (In the event a troponin T (central laboratory assessment) is not performed or a laboratory error occurs, considerations for a DLT criteria will involve review of two separate local troponin (I or T) assays done within 48 hours at a local investigator site. Troponin I or T elevations greater than the upper limit of normal, and > 10% coefficient of variance (CV) for that assay will be considered as a grade 2 elevation.)
- Treatment delay of 14 days or greater due to unresolved drug-related toxicity.
- ALT ≥3x ULN + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin < 2xULN but with hepatitis symptoms or rash or ALT ≥5xULN.

3.2.4. Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

The MTD will be exceeded if 2 or more subjects in a cohort of up to 6 subjects experience a DLT.

The recommended Phase 2 (Part 2) dose (RP2D) will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile and available pharmacodynamic data generated from all subjects in Parts 1. The MTD will be the RP2D for Part 2 of the study unless there is a lower dose that provides a more favorable safety/tolerability profile while providing adequate exposure, biomarker inhibition or clinical activity. If necessary, alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

3.2.5. Part 1

3.2.5.1. NMC Pharmacodynamic Expansion Cohort

In the event there are no available enrollment slots during 3+3 dose escalation, eligible subjects with NMC (Section 6.2) may be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamics of GSK525762 at doses that have previously been cleared during 3+3 dose escalation. Three subjects with NMC will be allowed to enroll at the last cleared dose level only if subjects with NMC or other solid tumor types (Section 4.2.1 Inclusion Criteria) have already enrolled in 3+3 dose escalation. Enrollment in the PD Expansion Cohort will continue until either 12 subjects with NMC are enrolled in the PD Expansion Cohort, or until the RP2D is determined in Part 1, whichever occurs first. Eligibility criteria for subjects diagnosed with NMC to enroll in this cohort are described in Section 4.2 (Part 1). NMC subjects with non-measurable disease by RECIST 1.1 but clinically evaluable for progression or response may be considered for enrollment after discussion with the GSK Medical Monitor. Biopsy collection will be mandatory as described in Section 3.2.2.3, unless a waiver is granted by the GSK medical monitor. ^{18}FDG-PET will be required for all subjects in this cohort.

Subjects in the NMC PD Expansion Cohort will start with same dosing schedule described in Section 3.2.2 ; Monitoring for cardiac safety signals will be performed as required in Part 1 with triplicate 12-lead ECGs to be performed on the days indicated in the Time and Events Table. All safety and PK evaluations will be performed as outlined in the Time and Events Tables for Part 1 (Section 5). Safety data from subjects in the NMC PD Expansion Cohort will be reviewed on an ongoing basis by the GSK medical monitor, GSK Safety Review Team, and investigators for consideration during 3+3 dose escalation decisions.

Subjects will be eligible for intra-subject dose escalation to a higher approved dose as described in Section 3.2.2.6, upon completion of the 4 week observation period, tumor biopsy collection, and approval by the investigator and GSK medical monitor in consultation with the GSK study team. Subjects approved for intra-subject dose escalation will require additional limited PK sampling (pre-dose, 0.5, 3 and 6-8 hours) at the higher dose, as determined by GSK Clinical Pharmacology. Subjects may continue on daily administration of GSK525762 until permanent discontinuation or completion of the study as described in Section 4.2.4.1.

3.2.6. Bioavailability, Food Effect, and Dose Proportionality Besylate Sub-Study

Part 1 will include a besylate sub-study that will be an open-label, randomized, single dose, four period, cross over study to investigate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet at or near the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate salt tablet at or near the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate salt tablets. GSK525762 dosing will be separated by at least 48 hours. Up to 12 subjects in the United States may be enrolled in besylate sub-study. A subject requiring dose reduction or discontinuation from study before completion of the Besylate Sub-Study will be replaced by a new enrollment. All subjects enrolled to the Besylate Sub-Study, on completion of their participation in this segment

of the study, will continue on a daily dosing schedule till disease progression or discontinuation due to investigational agent related toxicity or withdrawal of informed consent. The high-fat (approximately 50% of the total caloric content of the meal), high-calorie meal (approximately 800 to 1000 calories) will be the representative example given by the 2002 US Food and Drug Administration (FDA) guidance [FDA, 2002]. It includes the following: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk.

In order to reduce variability in measurement of drug exposure caused by day-to-day biologic variation, a small (<10% of total dose) liquid dose of a stable, non-radioactive ^{13}C isotope labeled version of GSK525762 besylate salt, will be coadministered orally with each fasted treatment in besylate sub-study to serve as an internal standard for quantitation purposes (Refer to Section 7.1 for additional information). Use of this stable isotope approach will allow better characterization of the impact of the besylate salt and dose on GSK525762 bioavailability, if any (Parr, 2012).

Table 4 Besylate Sub-Study Design: BA, Food Effect and Dose Proportionality Evaluation

Besylate Sub-Study: Single Dose PK Evaluation					
Sample Size	Sequence	Period 1 (Week 1 Day 1)	Period 2 (Week 1 Day 3)	Period 3 (Week 2 Day 1)	Period 4 (Week 2 Day 3)
6	1	Treatment A2	Treatment B	Treatment C	Treatment D
6	2	Treatment B	Treatment A2	Treatment C	Treatment D

Treatment A2: RP2D (or MTD) as amorphous free-base tablet + low dose stable isotope in solution, fasted administration
Treatment B: RP2D (or MTD) as besylate tablet + low dose stable isotope in solution, fasted administration
Treatment C: half to one-third of RP2D (or MTD) as besylate tablet + low dose stable isotope in solution, fasted administration
Treatment D: RP2D (or MTD) as besylate tablet, fed administration with FDA recommended high fat breakfast

3.2.7. Part 2 Expansion Cohort

Based on the analysis and evaluation of the safety profile and available pharmacodynamic, pharmacokinetic and efficacy data generated from all subjects enrolled in Part 1 as of January 28, 2016, including the analysis of subjects enrolled in the Besylate Sub-Study, the final dose and regimen for Part 2 is determined to be 75 mg once daily. The besylate salt tablets will be the formulation used for subjects enrolled in Part 2 (and potentially for ongoing or newly enrolled subjects in Part 1). Additional details and supporting information are provided under separate cover in a companion document and dose decision memo. Approximately 170 subjects with NMC, SCLC, CRPC, TNBC, ER+BC and GIST will be enrolled in expansion cohort at the RP2D to gather more safety data and to further assess anti-tumor activity.

Subjects in Part 2 will start with a continuous daily dosing schedule unless safety, PK or PD data necessitate a different dosing schedule.

The statistical design and number of subjects to be enrolled in a cohort is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. The predictive probability design allows for evaluation of stopping rules after each subject once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. Final decisions on stopping enrollment will depend on the totality of the data collected.

For NMC, to test for 20% ORR relative to a 5% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look may be conducted once 10 evaluable subjects have been enrolled into the expansion cohort or treated at the same dose level to examine safety and efficacy; if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of 25 subjects in this cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 3 Diagram of Stopping Rules for NMC Cohort Expansion

	Number of Responses			
Number of Subjects	**0**	**1**	**2**	**3**
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				

Figure 3: The shaded regions are the specific regions for stopping enrollment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 10% or less (the futility criterion) and further enrollment into this cohort will be stopped.

For SCLC and CRPC, to test for 30% ORR relative to a 10% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conducted once 10 evaluable subjects have been enrolled in either cohort or treated at the same dose level to examine safety and efficacy, if 0 responses are observed in either cohort, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4. A maximum of 22 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 4 Diagram of Stopping Rules for SCLC and CRPC Cohort Expansion

	Number of Responses				
Number of Subjects	**0**	**1**	**2**	**3**	**4**
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					

Figure 4 Legend: The shaded regions are the specific regions for stopping enrollment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and further enrolment in this cohort will be stopped.

For TNBC, to test for 25% ORR relative to a 10% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conducted once 10 evaluable TNBC subjects have been enrolled in the cohort or treated at the same dose level to examine safety and efficacy, if 0 responses are observed in the cohort, Part 2 of the trial may be terminated with no further enrolment in this cohort. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 5. A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 5 Diagram of Stopping Rules for TNBC Cohort Expansion

	Number of Responses						
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**
10							
11							
12							
13							
14							

	Number of Responses						
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							
29							
30							
31							
32							
33							
34							
35							
36							
37							

Figure 5 Legend: The shaded regions are the specific regions for stopping enrollment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and further enrolment in this cohort will be stopped.

For ER+BC, to test for 25% ORR relative to a 10% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conducted once 10 evaluable ER+BC subjects have been enrolled in this cohort or treated at the same dose level to examine safety and efficacy, if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 6. A maximum of 37 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 6 Diagram of Stopping Rules for ER+BC Cohort Expansion

	Number of Responses								
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
10	■								
11	■								
12	■								
13	■								
14	■								
15	■								
16	■	■							
17	■	■							
18	■	■							
19	■	■							
20	■	■							
21	■	■	■						
22	■	■	■						
23	■	■	■						
24	■	■	■						
25	■	■	■	■					
26	■	■	■	■					
27	■	■	■	■					
28	■	■	■	■					
29	■	■	■	■	■				
30	■	■	■	■	■				
31	■	■	■	■	■				
32	■	■	■	■	■	■			
33	■	■	■	■	■	■			
34	■	■	■	■	■	■	■		
35	■	■	■	■	■	■	■		
36	■	■	■	■	■	■	■	■	
37	■	■	■	■	■	■	■	■	■

Figure 6 Legend: The shaded regions are the specific regions for stopping enrollment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and further enrolment in this cohort will be stopped.

For GIST, to test for 40% DCR relative to a 15% DCR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conducted once 8 evaluable GIST subjects have been enrolled in this cohort or treated at the same dose level to examine safety and efficacy, if 0 confirmed response or SD with at least 16 weeks is observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Table 5. A maximum of 25 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Table 5 Decision Making Criteria for Futility of GIST

Number of Evaluable Subjects	≤ This Number of Confirmed Responses/SD to Stop Early for Futility	Probability of continuing enrolling when DCR=0.4	Probability of continuing enrolling when DCR=0.15
8	0	0.0000	0.7275
9	0	0.0000	0.7275
10	1	0.0000	0.4496
11	1	0.0000	0.4496
12	1	0.0000	0.4496
13	1	0.0000	0.4496
14	2	0.0000	0.3087
15	2	0.0000	0.3087
16	2	0.0000	0.3087
17	2	0.0000	0.3087
18	3	0.0000	0.2215
19	3	0.0000	0.2215
20	3	0.0000	0.2215
21	4	0.0000	0.1532
22	4	0.0000	0.1532
23	4	0.0000	0.1532
24	5	0.0000	0.1047
25	6	0.0585	0.0000

Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified. Plasma samples for pharmacokinetic evaluation will be collected in all subjects. Plasma samples and tumor biopsies will be collected pre- and post-treatment for the pharmacodynamic evaluation.

4. STUDY POPULATION

4.1. Number of Subjects

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) and schedule(s) of GSK525762 for further study. To complete Part 1, it is estimated 90 to 110 evaluable subjects will be enrolled. The besylate sub-study will enroll approximately 10 to 12 subjects in the United States only. Part 2 will enroll approximately 170 subjects.

If a subject discontinues the study before completing Week 4 during Part 1 due to reasons other than toxicity, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator to ensure adequate population for DLT and MTD evaluations.

If subjects discontinue the study before completing Week 8 during Part 2, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator to ensure adequate population for determination of response within NMC and other expansion cohorts.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential. Additional details regarding the enrollment and registration process for this study can be found in the Study Procedures Manual.

A subject will be eligible for inclusion in this study only if all of the following criteria apply and after consultation with GSK:

1. Male or female 16 years or older, at the time of signing the informed consent.
2. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. If the subject is less than 18 years old, an Assent form and parental/guardian Consent form (replacing “you will” with “your child will” will be required).
3. Diagnosis of one of the following:
    - Part 1 Only:
        - NUT Midline Carcinoma based on ectopic expression of NUT protein as determined by IHC and/or detection of NUT gene translocation as determined by FISH. Subjects may be treatment naïve or have had prior therapy.
        - SCLC, CRC, NB, TNBC, ER positive BC, CRPC, NSCLC, and any other solid tumor which has been confirmed by clinical testing to be MYCN

amplified (defined as a MYCN gene copy number gain of ≥5). Subjects should have tumor progression after receiving at least one prior standard/approved chemotherapy, or where there is no approved therapy, or where standard therapy is refused.

- Part 2 Only:
  - NUT Midline Carcinoma as diagnosed by the Central Laboratory. Subjects may be treatment naïve or have had prior therapy.
  - SCLC, CRPC, TNBC, ER+BC and GIST

4. Subjects with solid tumors, with the exception of CRPC, must demonstrate measurable disease, per RECIST v1.1. NOTE: Subjects with NMC that do not meet the RECIST v1.1 criteria for measurable disease, but have evaluable disease may be considered for enrollment after discussion with the GSK medical monitor.
5. All prior treatment- related toxicities must be CTCAE (Version 4.0) ≤ Grade 1 (except alopecia and peripheral neuropathy) at the time of treatment allocation [NCI-CTCAE, 2009].
6. ECOG Performance Status score of 0-2 for subjects with NMC; 0-1 for subjects with other tumor types.
7. Adequate organ function as defined in Table 6.

Table 6 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 9.5 g/dL (patients that required transfusion or growth factor need to demonstrate stable haemoglobin for 7 days of 9.5 g/dL)
Platelets	≥ 100 X 10^9/L
PT/INR and PTT	≤ 1.5 X ULN
Hepatic	
Total bilirubin	≤ 1.5 x X ULN (isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome)
ALT and AST	≤2.5 × ULN
Renal	
Creatinine OR Calculated creatinine clearance [calculated by Cockcroft Gault formula[1]] OR 24-hour urine creatinine clearance [1]	≤1.5 X ULN ≥ 50 mL/min ≥ 50 mL/min
Cardiac	
Ejection fraction	≥ Lower limit of normal (LLN) by Echocardiogram (ECHO) (minimum of 50%)
Troponin (T)	≤ ULN
Potassium	≥LLN and ≤ULN
Magnesium	≥LLN
Thyroid	
Thyroid stimulating hormone (TSH)[2]	≥LLN and ≤ULN
Reproductive/Endocrine	
Testosterone	<50ng/dL (only for subjects with CRPC)

1. See Appendix 2 for Cockcroft Gault formula
2. If TSH is abnormal, but free T3 and/or free T4 are normal, then the subject may still be considered eligible for enrolment.

8. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
9. A female subject is eligible to participate if she is of:
    - Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) >40 MIU/ml and estradiol <40 pg/ml (<140 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use

one of the contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

- Child-bearing potential and agrees to use one of the contraception methods (described in Section 9.1) from the time of the screening pregnancy test until 7 months after the last dose of study medication.
- Negative serum pregnancy test ≤ 7 days prior to first study drug dose, for women of childbearing potential.
- Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for 5 half-lives of GSK525762 or at least 28 days (whichever is longer) following the last dose of study treatment.

10. Male subjects with a female partner of childbearing potential must agree to use one of the methods of contraception specified in Section 9.2. This method must be used from the time of the first dose of study medication until 16 weeks after the last dose of study medication.
11. Male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 16 weeks following the last dose of study medication.

4.2.1.1. Specific Eligibility Criteria for Part 2 CRPC Expansion Cohort

Subjects must meet all of the following additional inclusion criteria in order to be considered eligible for this cohort:

12. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma, surgically castrated or continuously medically castrated (for ≥8 weeks prior to pre-screening)
13. Persistent disease with evidence of disease progression following standard therapy(ies) including prior treatment with androgen/androgen receptor directed therapy, including enzalutamide and/or abiraterone
14. Ongoing androgen deprivation therapy with a serum testosterone level <1.7 nmol/L or <50 ng/dL [Scher, 2008]
15. Prostate-Specific Antigen (PSA) levels ≥2.0 ng/mL [Scher , 2008]

NOTE: If PSA level has been obtained within 14 days of Screening, this test does not need to be repeated and the result previously obtained may be used for the Screening value.

4.2.1.2. Specific Eligibility Criteria for Part 2 GIST Cohort

16. Histopathologically confirmed diagnosis of advanced (metastatic and/or unresectable) GIST.
17. Subjects must have had failure of at least imatinib as therapy for advanced disease due to progression. There is no limit on the number of prior TKI therapies.

4.2.2. 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.

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

1. Primary malignancy of the central nervous system, or malignancies related to Human Immunodeficiency Virus (HIV) or solid organ transplant. History of known HIV. History of known Hepatitis B surface antigen or positive Hepatitis C antibody (confirmed by RIBA).
2. Prior treatments usage as defined:
    a. Use of an investigational anti-cancer drug within 14 days or 5 half-lives, whichever is longer, prior to the first dose of the study medication. Note that an investigational drug is defined as a drug without an approved oncologic indication.
    b. Any therapy related toxicities must also have resolved to Grade 1 or less.
    c. Chemotherapy, radiotherapy, anti-neoplastic antibody or targeted therapy or immunotherapy within 14 days, major surgery within 28 days (or 42 days for prior nitrosoureas or mitomycin C) prior to the first dose of the study medication.
    d. Anti-androgen (e.g., bicalutamide) therapies for prostate cancer must be stopped 4 weeks prior to enrollment. Second line hormone therapies such as enzalutamide, abiraterone, or orteronel should be stopped 2 weeks prior to enrollment. Subjects with prostate cancer should remain on luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.
3. Current use of anticoagulants (e.g., warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of GSK525762. Low dose (prophylactic) low molecular weight heparin (LMWH) is permitted. In addition, INR must be monitored in accordance with local institutional practices.
4. Current use of a prohibited medication or requires any of these medications during treatment with the investigational drugs (details will be available in Section 8.2). This includes excluding current medications known or suspected to be associated QT

prolongation and strong inducers or inhibitors of CYP3A4. In addition, any subject who may require a QT prolonging medication while on trial should not be enrolled.

5. Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) except for cases where NSAIDs provide benefit over other analgesics or high dose aspirin (allowed up to 100 mg PO daily). Details are available in Section 8.2.
6. Evidence of severe or uncontrolled systemic diseases (e.g., unstable or uncompensated respiratory, hepatic, renal, cardiac disease, or clinically significant bleeding episodes). Any serious and/or unstable pre-existing medical (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures, in the opinion of the Investigator.
7. Symptomatic or untreated 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 >1months, 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. Subject treated with gamma knife the can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications/stable. In addition, subjects treated or currently taking enzyme-inducing anticonvulsant (EIAC) are allowed on study.
8. Cardiac abnormalities as evidenced by any of the following:
   - History or current untreated clinically significant uncontrolled arrhythmias.
   - Clinically significant conduction abnormalities or arrhythmias or subjects with Bundle Branch Block
   - Presence of cardiac pacemaker
   - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
   - History of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting within the past 3 months.
9. Any of the following EKG findings:
   - Baseline QTcF interval ≥450 msec
   - Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
10. GSK525762 is a benzodiazepine class molecule. Any serious known immediate or delayed hypersensitivity reaction(s) to GSK525762 or idiosyncrasy to drugs chemically related to the investigational drug.
11. Hemoptysis > 1 teaspoon in 24 hours within the last 28 days.
12. Subjects with a history of known bleeding disorder(s) or history of clinically significant hemorrhage (e.g., GI, neurologic) within the past 6 months.

13. Besylate Sub-Study only: unable or unwilling to eat the FDA recommended high-fat high-calorie breakfast (two eggs fried in butter, two strips of bacon, 4 oz. of hash brown potatoes and 8 oz of whole milk) within the recommended 30 minutes.

4.2.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently dosed with study treatment.

4.2.4. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.2.4.1. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable adverse event, including meeting stopping criteria for liver chemistry defined in Appendix 3 or for hematologic and other non-hematologic toxicity. After disease progression, subjects may be allowed to continue treatment with study drug if the Investigator strongly believes, and the Sponsor Medical Monitor concurs, that the subject could continue to receive benefit (for example in cases of an isolated new lesion, with the majority of the disease still under control).

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
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

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

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

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 (End of Treatment) as specified in Time and Events Tables.

All subjects who permanently discontinue study treatment without disease progression will be followed for progression according to the protocol schedule until:

- progression

- death, or
- subject has been followed for 2 years after stopping treatment.

All subjects who permanently discontinue study treatment for any reason will be followed for survival and new anti-cancer therapy [including radiotherapy] every 6 months until death or until the subject has been followed for 2 years. Reporting of any pregnancies in female subjects and/or female partners of male subjects will also be collected until 7 months after the last dose of study drug. If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).

4.2.4.2. Subject and Study Completion

In Part 1, a subject will be considered to have completed the study if:

- they complete screening assessments, the 28-day DLT observation period, and the end-of-treatment follow-up visit,
- they progress or die while receiving study treatment, or
- are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

In Part 2, a subject will be considered to have completed the study if:

- they progressed or die while receiving study treatment, or
- are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study may be considered completed for purposes of a final analysis when 70% of subjects enrolled at part 2 have progressed or died. If available, subjects continuing on treatment at the time of final analysis may be offered the option to continue in a rollover trial.

5. TIME AND EVENTS TABLES

Table 7 Time and Events: Part 1

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																									
Demography		X																									
Medical history		X																									
Disease characteristics		X																									
Cardiology evaluation		X																									
Prior therapy		X																									
Register subject		X																									
TREATMENT PHASE																											
Study Drug																											
Dispense study drug[a]	Refer to SPM for further details.		X							X							X		X		X		X		X		
Review compliance										X							X		X		X	X	X		X		
Safety																											
Pregnancy test[b]/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine	X	X																		X		X		X		X

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																					Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
	or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.																										
Physical Exam		X	X							X							X				X	X	X		X		X
ECOG PS		X	X							X							X		X		X	X	X		X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X	X				X		X					X		X		X		X	X	X		X		X
Pain		X	X	X				X		X					X		X		X		X	X	X		X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X		X		X
Chest x-ray		X																									
Pulmonary function test		X																									
Adverse events		*SAEs collected continuously from signing of informed consent; AEs collected continuously from time of first dose*																									
Concomitant medications		*Continuous from signing of informed consent*																									
Laboratory assessments: For details please see following tables																											
Tests		X	X	X				X		X					X		X		X		X	X	X	X	X	X	X
Cardiac Monitoring																											
Echocardiogram	Within 35 days of first dose	X													X						X		X			X	X
12-lead ECGs	For timing of triplicate ECGs on	X	O	O	O		O			X			O		X		X	O	X		X	X	O		X		X

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
(Triplicate)	O[c] days, see Table 9, Table 10, Table 11, Table 12 and Table 13. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30msec from baseline.																										
Efficacy																											
CT/MRI Scans[d]	SCR assessment within 28 days of first dose. Target lesions to be identified at SCR and followed.	X																			X		X			X	X
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation. EOT sample should be collected at time of progression where feasible. Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy[e].	X															One post-dose sample collected anytime between W3D1-W4D1 (4-6h post-dose).										X
PET scan[d]	Optional during rapid dose escalation; required during 3+3	X																			X		X				

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																					Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
	dose escalation. SCR assessment within 28 days of first dose.																										
Castrate-Resistant Prostate Cancer Assessments																											
PSA	PSA to be collected in line with PCWG2 guidelines. Levels may be checked more frequently if appropriate.	X																					X			X	
Neuroblastoma Assessments																											
CT/MRI	One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening Assessment within 28 days of first dose can be used as screening assessment.	X																					X			X	
MIBG scan[f]		X																					X			X	
FDG-PET		X																					X			X	
^{99}Tc scintigraphy for bone scan		X																					X			X	
Bilateral bone marrow aspirates and biopsy		X																					X			X	
Urine HVA, VMA, dopamine		X	X																		X		X		X		
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																											
PK and biomarker samples[c]	Fasting requirements apply for PK samples on W1D1 and W3D4.		X	X			X						X					X					X			X	

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																					Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
Samples for mRNA[c]			X	X														X									X
LPS blood sample	Not required with BID dosing schedule.		X																								
PK Urine samples	These are optional as of Amendment 9.		X															X									
Optional Saliva and Sample	Not collected with BID dosing schedule.		X															X									
Blood samples for circulating exploratory biomarkers (cfDNA, etc.)	EOT circulating biomarker blood samples to be collected with lab assessments.	X																	X								X
Pharmacogenomics (PGx)																											
PGx sample	Blood sample should be collected after screening (preferably on D1) if informed consent has been obtained for Genetic research.		X																								
FOLLOW-UP PHASE																											
Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.																											

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																				Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	D1	

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; FLC=free light chain; HVA=homovanillic acid; LPS=lipopolysaccharide; MIBG=meta-iodo-benzyl-guanidine; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; VMA= vanillylmandelic acid; W=week; PT=Prothrombin Time; INR=International Normalized Ratio; aPTT=Activated partial thromboplastin time; WNL=Within normal limits

a. Suggested timing of study medication dispensing; may be altered at the discretion of the Investigator or designee, based on availability and visit schedule.

b. Not required for women of non-childbearing potential, as defined in Section 4.2, Inclusion Criterion 9.

c. Some of these samples will be optional as of Amendment 9; please see Table 11, Table 12 and Table 13 for further details.

d. Per RECIST 1.1 baseline (within 28 days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter, scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate. Disease assessments should be performed no less than 4 weeks (28 days) after first dose and from previous on-treatment scan.

e. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the GSK Medical Monitor after subject recovery.

f. Subjects with neuroblastoma will have MIBG and bone marrow biopsies after week 24 as clinical indicated to confirm complete remission.

Table 8 Time and Events: Part 1 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	Refer to Section 6.1.2 for visit windows.											Q4 and Q8W Initiated from Week 9		EOT[a]
			W1			W2		W3	W4	W5	W7	W9	W11	q4W	q8W	
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP	For Troponin: all time points, including unscheduled, collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X	X		X			X	X
Hematology		X	X		X	X	X	X	X	X	X	X	X	X		X
Clinical chemistry		X	X		X			X		X	X	X		X		X
Pancreatic		X	X		X			X		X	X	X		X		X
Coagulation		X	X		X			X		X	X	X	X	X		X
Factor VII Assay	Also perform if PT, INR or aPTT are ≥1.5XULN, or in case of bleeding event	X						X		X						
Creatine phosphokinase		X	X		X			X		X	X	X		X		X
Liver chemistry		X	X		X			X		X	X	X	X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X			X		X	X	X		X		X
c-peptide and 1,5 AG	Will be performed at central lab if not available at local lab	X	X							X		X			X	
HbA1c		X	X					X	X	X		X			X	
Fasting lipids		X	X							X		X			X	X
Thyroid monitoring	TSH, free T3, free T4 at SCR and W1. If TSH is abnormal at W1D1, continue monitoring TSH, free T3 and free T4 going forward at time points indicated in this Table and at any time	X	X							X		X			X	X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**Refer to Section 6.1.2 for visit windows.**											**Q4 and Q8W Initiated from Week 9**		**EOT[a]**
			W1			**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**q4W**	**q8W**	
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
	when clinically appropriate.															
Urinalysis		X	X							X		X			X	X
Pregnancy test[b], females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X							X		X		X		X
Testosterone, males	Complete and free testosterone at SCR; free testosterone thereafter	X	X							X		X		X		X
CK, CK-MB	Pre-dose and 12-18 h post-dose		X	*as clinically appropriate*												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X														

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

a. EOT circulating biomarker blood samples to be collected with lab assessments.

b. Not required for women of non-childbearing potential, as defined in Section 4.2, Inclusion Criterion 9.

Table 9 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1 (fasting requirements apply)										W1D5		W2D4 + 1 day			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ±2h** [a]	**24h ±2h**	**48h ±2h** [b, d]	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**
12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optional Saliva Sample	X			X	X	X	X									
Urine PK sampling (Part 1 only)[c]	X	0-2h			2-24h											
mRNA whole blood sample	X				X	X	X	X	X	X						
LPS whole blood sample	X	X	X	X	X	X										

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment and acute phase protein assessment at pre-dose, 2, 4, 8, 12 and 24 hr post-dose. The frequency of sampling may be changed based on data from the first few subjects assessed.

a. PK blood samples collected after-hours may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

b. 48h PK sample to be collected prior to dosing on W1D3

c. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

d. W1D1 48h assessments (ECG, PK and mRNA) are optional.

Table 10 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed**) (fasting requirements apply)**										**W9D1 ±4 days** (if dose has been reduced or escalated, +4 to +7 days**)**			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ±2h** [a]	**24h ±2h** [b]	**48h ±2h** [b, d]	**pre dose**	**0.5-2h**	**4 - 8h**	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine PK sampling (Part 1 only)[c]		0-2h			2-24h									
mRNA whole blood sample	X					X	X							X

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment and acute phase protein assessment at pre-dose and at 2, 4, 8, 12 and 24 hr post-dose. The frequency of sampling may be changed based on data from the first few subjects assessed.

a. PK blood samples collected after-hours may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

b. 24h and 48h PK samples to be collected prior to dosing on those days

c. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

d. W3D4 48h assessments (ECG, PK and mRNA) are optional.

Table 11 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1

	W1D1																W1D2 and W1D3 (relative to W1D1 Morning Dose)		W1D5 ECG and PK samples after Morning Dose only	
	Morning Dose (fasting requirements apply)								Evening Dose (relative to W1D1 Morning Dose)											
	pre dose	0H	15 min ±5m	30 min ±5m	1h ±5m	2h ±10 m	4h ±15 m	8h ±1h	pre dose (12h-15m)[d]	12h [d]	15 min(12.25h) ± 5m [d]	30 min (12.5h) ±5m [d]	1h (13h) ±5m [d]	2h (14h) ±10 m [d]	4h (16h) ±15 m [d]	8h (20h) ±1h [d]	12 h (24h) ±1h [d]	36 h (48h) (pre-dose) ±1h [d]	30 min ±5m	3h ±15 m
Administer/dose Study Medication		X								X								X		
12-lead ECG, in triplicate[a]	X					X	X	X	X					X	X	X	X	X	X	X
PK and protein biomarker sample [b]	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Urine PK sampling [c]	X	0-2h				2-12h														
mRNA whole blood sample	X					X	X	X[d]		X				X	X	X	X	X		

The frequency of sampling may be changed based on data from the first few subjects assessed.

a. Triplicate ECGs should be collected 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.

b. PK blood samples collected overnight may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

c. Urine samples for quantitative analysis of GSK525762 are optional as of Amendment 9.

d. These assessments are optional as of Amendment 9.

Table 12 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 2 and Week 3

	W2D4 + 1 day ECG and PK samples after Morning Dose only				W3D4 +2 days															W3D5 and W3D6 (relative to W3D4 Morning Dose)	
					Morning Dose (fasting requirements apply)								Evening Dose (relative to W3D4 Morning Dose)								
	pre dose (Prior to Dosing)	30m ± 5m	3h ± 15m	8 h ±1h	pre dose	0h	15m ±5m	30m ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	pre dose	12h	15m ±5m (12.25m) [d]	30m ±5m [d]	1h (13h) ±5m [d]	2h (14h) ±10m [d]	4h (16h) ±15m [d]	8h (20h) ±1h [d]	12h (24h) ±1h (pre dose) [d]	36h (48h) ±1h (pre dose) [d]
Administer Study Medication	X					X								X							X	X
12-lead ECG, in triplicate [a]	X	X	X	X	X					X	X	X	X		X	X	X	X	X	X	X	X
PK and protein biomarker sample [b]	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Urine PK sampling [c]						0-2h				2-12h												
mRNA whole blood sample					X					X	X											

The frequency of sampling may be changed based on data from the first few subjects assessed.

a. Triplicate ECGs should be collected 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.

b. PK blood samples collected overnight may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

c. Urine samples for quantitative analysis of GSK525762 are optional as of Amendment 9.

d. These assessments (ECG, PK and mRNA) are optional as of Amendment 9.

Table 13 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 9

	W9D1 ±4 days ECG and PK samples after Morning Dose only			EOT
	Pre-dose	0.5-2h	4 - 8h	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	
PK and protein biomarker sample	X	X	X	
mRNA whole blood sample				X

Table 14 Time and Events: Part 2

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.									Q4, Q8 and Q12 Initiated from Week 13			EOT
			W1	W2	W3	W4	W5	W7	W9	W11	W13	q4W	q8W	q12W	
			D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X													
Demography		X													
Medical history		X													
Disease characteristics		X													
Cardiology evaluation		X													
Prior therapy		X													
Register subject		X													
TREATMENT PHASE															

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
Study Drug															
Dispense study drug[a]	Refer to SPM for further details.		X	X	X	X	X		X		X	X			
Review compliance				X	X	X	X		X		X	X	X	X	X
Safety															
Pregnancy test[b]/testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X	X				X		X		X	X			X
Physical exam		X	X	X	X	X	X		X		X	X			X
ECOG		X	X	X	X	X	X		X		X	X			X
Vital Signs and Pain Assessments		X	X	X	X	X	X		X		X	X			X
Weight and height	Height at SCR only	X	X				X		X		X	X			X
Chest x-ray		X													
Pulmonary function test		X													
Adverse events		*SAEs collected continuously from signing of informed consent; AEs collected continuously from time of first dose*													
Concomitant medications		*continuous from signing of informed consent*													
Laboratory assessments: For details please see Table 15															
Tests		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Castrate-Resistant Prostate Cancer Assessments															
PSA		X	X	X	X	X	X		X		X	X			X
Complete		X	X	X	X	X	X		X		X	X			X

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
testosterone															
Cardiac Monitoring															
ECHO	If Baseline ECHO within 35 days of first dose, the Week 1 Day 1 ECHO is only required if clinically appropriate.	X	X optional			X			X		X		X		X
12-lead ECGs (Single)	ECGs prior to dosing. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30 msec from baseline.	X	X	X	X	X	X		X		X		X		X
Efficacy															
Lesion assessments		X							X				X		X
CT scan or MRI [c]	Scans within 28 days of first dose may be used as screening assessment. Additional bone scans and brain scans not required unless clinically indicated.	X							X				X		X
PET scan (FDG or fluoride) [c]	Scans within 28 days of first dose may be used as screening assessment. Follow up scans conducted as clinically appropriate.	X													
PK															
PK	Three samples to be collected each sampling day: During first 4 weeks collect a pre-dose		X			X			X				X		

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
	within 60 minutes prior to dose, a single draw between 0.5-2h post-dose, and a single draw between 4-8h post-dose (fasting requirements apply).Thereafter only a Pre-dose and 0.5 hour post-dose sample are collected. NOTE: If dose level is adjusted, additional PK sampling may be requested.														
Blood samples for circulating exploratory biomarkers (cfDNA, etc)	Baseline sample collected pre-dose on W1D1 EOT circulating biomarker blood samples to be collected with lab assessments.		X			X									X
Translational Research															
PGx sample	Blood sample should be collected after screening (preferably on W1D1) if informed consent has been obtained for Genetic research.		X												
Tumor Sample	PK samples should be collected within 1 hour of on-treatment biopsy. EOT biopsy should be collected at time of disease progression where feasible. Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy[d].	X			One post-dose sample collected anytime between W3D1-W4D1 (4-6h post-dose)[e]										X

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
FOLLOW-UP PHASE															
Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.															

Abbreviations: CK=creatine kinase; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; q4W=every 4 weeks; q8W=every 8weeks; SCR=Screening; Wk=week; PT=Prothrombin Time; INR=International Normalized Ratio; aPTT=Activated partial thromboplastin time; WNL=Within normal limits

a. Suggested timing of study medication dispensing; may be altered at the discretion of the Investigator or designee, based on availability and visit schedule.

b. Not required for women of non-childbearing potential, as defined in Section 4.2, Inclusion Criterion 9.

c. Per RECIST 1.1 baseline (within 28 days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter, scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate. Disease assessments should be performed no less than 4 weeks (28 days) after first dose and from previous on-treatment scan.

d. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the GSK Medical Monitor after subject recovery.

e. Timing may be further optimized based on tumor type and emerging data.

Table 15 Time and Events: Part 2 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	Notes	SCR	W1		W2		W3	W4	W5	W7	W9	W11	W13	Q4, Q8 and Q12W Initiated from Week 13			EOT [b]
			D1	D4 [a]	D1	D4 [a]	D1	D1	D1	D1	D1	D1	D1	q4W D1	q8W D1	q12W D1	
Troponin, NT-proBNP	1 sample for local lab (troponin I or T), 1 sample for central lab (troponin T)	X	X		X		X	X	X		X		X		X		
Hematology		X	X		X		X	X	X	X	X	X	X	X			X
Clinical chemistry		X	X		X		X	X	X		X		X	X			X
Pancreatic		X	X		X		X	X	X		X		X	X			X
Coagulation		X	X		X		X	X	X	X	X	X	X	X			X
Factor VII Assay	Also perform if PT, INR or aPTT are ≥1.5XULN, or in case of bleeding event	X					X		X								
Liver chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X			X
Creatine phosphokinase		X	X					X	X		X		X		X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X		X	X	X		X		X	X			X
c-peptide and 1,5 AG	Will be performed at	X	X						X		X				X		

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	**Notes**	**SCR**	**W1**		**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**W13**	**Q4, Q8 and Q12W Initiated from Week 13**			**EOT** [b]
			D1	**D4** [a]	**D1**	**D4** [a]	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**q4W** **D1**	**q8W** **D1**	**q12W** **D1**	
	central lab if not available at local lab																
HbA1c		X	X								X				X		
Fasting lipids		X	X				X		X		X		X		X		X
Urinalysis		X	X						X		X		X			X	X
Thyroid monitoring	TSH, free T3, free T4 at SCR and W1. If TSH is abnormal W1D1, continue monitoring TSH, free T3 and free T4 going forward at time points indicated in this Table and at any time when clinically appropriate.	X	X						X		X		X		X		X
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X															

Abbreviations: D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; q12W=every 12 weeks; SCR=Screening Visit; W=week; ULN=Upper limit of normal

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	**Notes**	**SCR**	**W1**		**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**W13**	**Q4, Q8 and Q12W Initiated from Week 13**			**EOT** [b]
			D1	**D4** [a]	**D1**	**D4** [a]	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**q4W** **D1**	**q8W** **D1**	**q12W** **D1**	

a. Optional Visits, should be conducted when additional monitoring of laboratory values is clinically appropriate.

b. EOT circulating biomarker blood samples to be collected with lab assessments.

Table 16 Time and Events: Besylate Sub-Study

Besylate Sub-Study Assessments	**Notes**	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W7**	**W9**	**Q4 and Q8W Initiated from Week 9**		**EOT**
			D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**q4W** **D1**	**q8W** **D1**	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X					X		X		Continuous dosing starting W2D5												
Review subject	Diary not required when dosed in																X	X	X	X	X	X	X	X	X	

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	q4W	q8W	
diary	clinic.																									
Safety																										
Pregnancy test/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X							X							X		X		X	X	X	X		X
Pain		X	X							X							X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test		X																								
Adverse events		*SAEs collected continuously from signing of informed consent. AEs collected continuously from first dose.*																								
Concomitant medications		*Continuous from signing of informed consent*																								
Laboratory assessments: For details please see corresponding days in Table 8																										
Tests		X	X							X							X		X		X	X	X	X	X	X
Cardiac Monitoring																										
Echocardiogram	Within 35 days of first dose	X																			X		X		X	X
12-lead ECGs (Triplicate)	For timing of triplicate ECGs on O days, see Table 19and Table 20.	X	O		X					X		X					X		X	X	X	X	O	X		X

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	q4W D1	q8W D1	
	Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30msec from baseline.																									
Holter monitoring	At least 24 h, on dosing days start at least 60 min pre-dose.	X																	X							
Efficacy																										
CT/MRI Scans	SCR assessment within 35 days of first dose. Target lesions to be identified at SCR and followed.	X																			X		X		X	X
PET scan	SCR assessment within 35 days of first dose.	X																			X		X			
Neuroblastoma Assessments																										
CT/MRI	One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening assessment within 35 days of first dose	X																					X		X	
MIBG scan[a]		X																					X		X	
FDG-PET		X																					X		X	
^{99}Tc scintigraphy for bone scan		X																					X		X	
Bilateral bone marrow aspirates and biopsy		X																					X		X	
Urine HVA, VMA, dopamine		X	X																		X		X	X		
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																										
PK samples			X	X	X	X				X	X	X	X								X		X		X	

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	q4W D1	q8W D1	
Pharmacogenomics (PGx)																										
PGx sample			X																							
FOLLOW-UP PHASE																										
Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.																										

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; FLC=free light chain; HVA=homovanillic acid; LPS=lipopolysaccharide; MIBG=meta-iodo-benzyl-guanidine; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; VMA= vanillylmandelic acid; W=week

a. Subjects with neuroblastoma will have MIBG and bone marrow biopsies after week 24 as clinical indicated to confirm complete remission.

Table 17 Time and Events: Besylate Sub-Study Pharmacokinetics Sampling, Week 1 and Week 2

	W1D1, W1D3, W2D1 and W2D3											
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**1.5h ± 5m**	**2h ±10m**	**3h ±15m**	**4h ±15m**	**6h ±15mn**	**8h ±30 mn**	**24h ±2h**	**48h ±2h [a]**
12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 30 min PK draws and within 15 minutes prior to the other PK draws serial ECGs only W1D1	X		X	X		X	X	X	X	X	X	X
PK sample	X	X	X	X	X	X	X	X	X	X	X	X

a. On W1D3 and W2D3, the 48 hour sample has to be taken prior to GSK525762 dosing.

Table 18 Time and Events: Besylate Sub-Study Pharmacokinetics Sampling, Week 5 and Week 9

	W5				**W9D1 ±4 days** (if dose has been escalated, +4 to +7 days)		
	Pre-dose	**30 min ±5m**	**3h ±15m**	**8h ±30m**	**Pre-dose**	**0.5-2h**	**4 - 8h**
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	X	X	X	X
PK sample	X	X	X	X	X	X	X

6. STUDY ASSESSMENTS AND PROCEDURES

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

Refer to the Time and Events Tables for the timing of all assessments (Section 5).

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.

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.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

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

6.1. Study Visits

6.1.1. Assessments

See Time and Events Tables for details on the specific assessments.

6.1.2. Visit Windows

Screening (baseline to pre-dose): All assessments should be completed within 14 days prior to first dose, except for those specified in T&E tables (e.g. CT, MRI, ECHO). Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1. In Part 2, testing by the central laboratory for NMC diagnosis must be completed within 3 months prior to signing the main consent (no other treatments may have been received after the central diagnosis through study enrollment).

Part 1 only - Week 1: Based on subject and clinic schedule, Week 1 Day 3 assessments can be ± 1 day.

Part 1 only - Week 2 to Week 3: Based on subject and clinic schedule, assessments can be +3 days.

Part 1 only - Week 3 to Week 4: Based on subject and clinic schedule, assessments can be +3 days.

Part 2 only – Week 1 through Week 3: assessments can be +/- 2 days, with the exception of W1D1 assessments, which must occur on W1D1.

Part 1 and Part 2 – Visits between Week 4 to Week 9 (inclusive): Visits can be scheduled ±3 days.

Part 1 and Part 2 - Visits after Week 9 until Week 52: After the first disease assessment has been completed then the visits can be scheduled ± 5 days.

Part 1 and Part 2 - Visits after Week 52: Visits can be scheduled ± 7 days.

Discontinuation/End of Treatment visit – should be within 14 days from last dose of study drug. If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of adverse events.

Besylate Sub-Study – +1 day window is allowed as long as there are at least 48 hours between the single doses.

6.2. Baseline Assessment for NMC Subjects

For NMC subjects in Part 1, a diagnosis of NMC based on a positive IHC test and/or detection of NUT gene translocation as determined by FISH at screening will be required. In Part 2, a diagnosis of NMC based on a positive IHC test performed at a central laboratory will be required. A ≥20% nuclei staining cut off will be applied for a positive diagnosis as a subset of germ cell tumors (from testis and ovary) weakly stain for the NUT protein (5% maximal nuclei staining, PPD , personal communication). In rare instances, where a subject's tumor previously tested positive for NMC by other methods, and a false negative by central laboratory is suspected due to poor quality and/or heterogeneity of the tissue, retesting may be considered on a case-by-case basis in consultation with GSK Medical Monitor. If the retest by the central laboratory is positive for NMC, the subject may be considered eligible for enrollment.

In Part 2, fluorescence in situ hybridization (FISH) or next generation sequencing (NGS) may be undertaken retrospectively to characterize the NUT gene fusion partner and to support exploratory analysis of differential outcomes based on the NUT fusion partner.

6.3. Baseline Assessment for Non-NMC Subjects

Subjects diagnosed with SCLC, CRC, NB, CRPC, TNBC, ER+BC or NSCLC [based on standard diagnostic criteria, such as histology, cytology (including bone marrow evaluation)] or serological criteria (such as serum PSA) will be considered eligible for Part 1 of the study. In instances where a solid tumor subject's MYCN amplification status is known, then that subject will be considered eligible. N-Myc copy number gain of ≥5 will be considered positive for MYCN amplification. N-Myc testing may be performed using any method. Subjects diagnosed with SCLC, CRPC, TNBC, ER+BC or GIST will be eligible for Part 2 of the study.

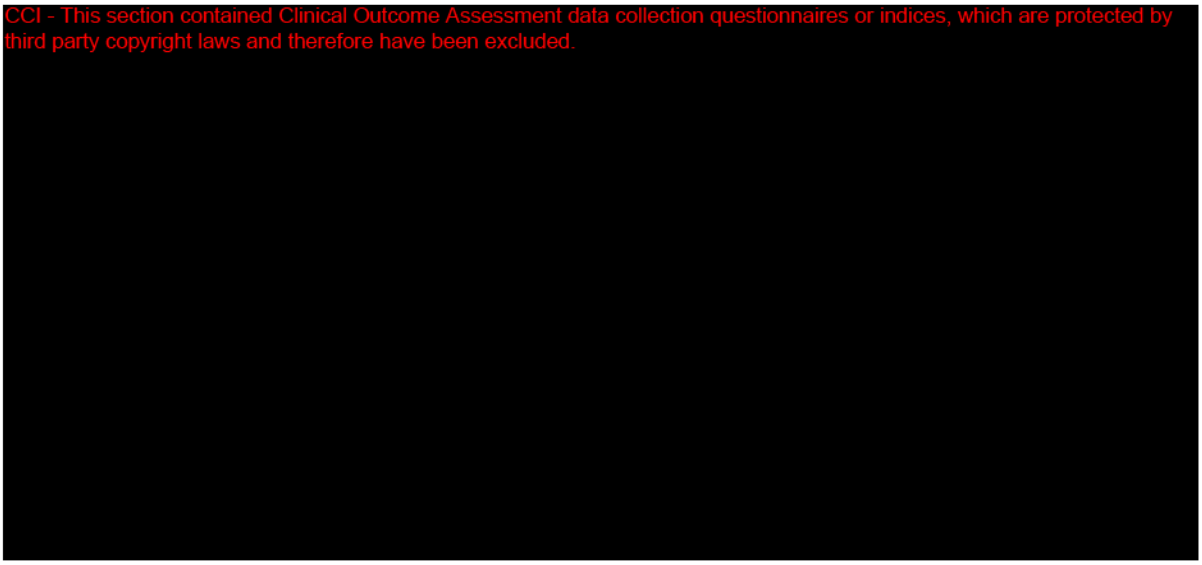
6.4. Safety

6.4.1. Physical Examinations

A routine physical examination will be performed by a qualified physician or designee according to local practice. Height and weight will also be measured and recorded. Height only needs to be measured at baseline.

Cardiovascular medical history/risk factors will also be assessed at baseline.

6.4.2. ECOG



6.4.3. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiration, temperature. The vital signs will be measured after resting for at least 5 minutes in a supine or semi-recumbent position. Pain will be assessed using a visual analog scale (Appendix 4).

6.4.4. Echocardiogram (ECHO)

For all subjects, ECHOs will be performed at screening and at assessment times as outlined in Section 5. ECHOs should be evaluated and compared to baseline by the same reader.

ECHO data will be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying ECHO scans are provided in the SPM.

6.4.5. Safety Electrocardiograms

Safety ECGs will be performed at the time points specified in Time and Events Tables using a standard 12-lead ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF intervals. Details will be provided in the SPM. In Part

1, the investigator will review the ECG data manually, and should not rely solely on the automatic readings of the equipment, when making decisions regarding dosing of subjects.

- During Part 1, a triplicate 12-lead ECG should be performed at Screening and at all other time points. Triplicate ECGs should be done for all time points on Serial Pharmacokinetic sampling days.
- During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Time and Events Tables. Standard 12-lead ECGs (Safety ECGs) will be performed as part of the real-time assessment of subjects and may not be included in the primary QT analysis. Safety ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

If a subject meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QTc interval ≥ 500 msec OR interval increase from baseline ≥ 60 msec: IP will be discontinued unless the benefits of therapy outweigh the risk of rechallenge in the opinion of the Investigator, the GSK Medical Monitor, as well as the GSK medical governance. In this situation, rechallenge may be permitted (see Table 24 for rechallenge guidelines).

NOTE: QT interval duration criteria should be based on the average QTc value of triplicate electrocardiograms (ECGs) to include 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 discontinued.

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

- For eligibility and withdrawal, QTcF will be used for all subjects.
- For purposes of data analysis, QTcF will be used.

Baseline results are defined by the nearest timepoint prior to first dose. For this trial, when triplicate ECGs are indicated at baseline, the baseline QTcF value is determined by the mean of the triplicate W1D1 pre-dose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate ECG results would be used.

Abnormal ECGs should be evaluated manually prior to final decision making. ECG data may be transferred and reviewed by an independent central reviewer.

6.4.6. Clinical Laboratory Assessments

All protocol required safety laboratory assessments, as defined in Table 19, are performed at the institution's local laboratory. All non-safety assessments (example: pharmacokinetic samples, biopsy, translational samples) will be assessed by a central laboratory. Please refer to the Study Procedures Manual (SPM) for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Some laboratory assessments can vary throughout the day such as testosterone. It is recommended but not mandated that laboratory assessments are collected at approximately the same time on each clinic day. If abnormal testosterone levels are observed, repeat measurements should occur at the approximate baseline timing to ensure this is a trend and not a single outlying event.

Table 19 Clinical Laboratory Tests

Serum Chemistry			
Blood urea nitrogen	Magnesium	aspartate aminotransferase	Total and direct bilirubin
Sodium	Potassium		Uric acid
Creatinine	Chloride	alanine aminotransferase	Albumin
Fasting Glucose	Total carbon dioxide	alkaline phosphatase	Total protein
Creatine phosphokinase	Ionized calcium	gamma-glutamyltransferase	Total calcium
Hematology			
Platelet count	*Automated White Blood Cell*		
Red blood cell count	*Differential:*		
White blood cell count (absolute)	Neutrophils (absolute)		
Hemoglobin	Lymphocytes (absolute)		
	Monocytes (absolute)		
	Eosinophils (absolute)		
	Basophils (absolute)		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other Tests			
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)			
Factor VII Assay			
Pancreatic markers (amylase and lipase)			
Fasting Lipid panel (triglycerides and total cholesterol, LDL, HDL)			
C-Peptide			
Troponin (I or T at local laboratory, Troponin T at central laboratory]			
Insulin			
Hemoglobin A1C			
1,5 –Anhydroglucitol (1,5 AG)			
NT-proBNP			
Thyroid-stimulating hormone (TSH)			
Free Thyroxine 3 (Free T3)			
Free Thyroxine 4 (Free T4)			
Creatine kinase (CK)			
Creatine Kinase-MB (CK-MB)			
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose and as indicated in the Time and Events tables for CRPC subjects)			
Pregnancy test for females (serum at screening, Urine or serum post-dose)			
Cytokine samples (collected as part of PK sample for plasma cytokines)			

Subjects should be instructed to fast (no food and only water allowed) for 10 hours prior to any fasting laboratory assessments (example: fasting glucose, fasting lipid panel, etc).

Abnormal laboratory results that are considered by the investigator to be clinically significant should be recorded on the eCRF as AEs. In addition, these clinically significant abnormal laboratory results should be followed until the abnormality resolves or is determined to be stable.

6.4.6.1. Troponin

Two samples for troponin will be collected at each time-point as outlined in Time and Events Tables. Troponin T will be assessed at a central laboratory as a means of consistent evaluation across all subjects. A second sample will be assessed at a local laboratory for purposes of subject management. Whenever possible, troponin T will be assayed by the local laboratory. However, either troponin I or troponin T may be assessed at a local laboratory. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study.

6.4.6.2. Clinical Laboratory Assessments Required Prior to Scheduled Surgeries

Subjects must have a platelet count of $\geq$75,000/mm^3 and a PT, INR and aPTT that are within normal limits within 48 hours prior to the post-dose biopsy and any scheduled surgical procedures.

6.5. Efficacy

6.5.1. Disease Assessment

Tumor response will be assessed as outlined in Time and Event Tables by the investigator using RECIST 1.1 (Appendix 6) or the Prostate Cancer Working Group 2 (PCWG2) guidelines [Scher, 2008] and documented in the eCRF as: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). For subjects with NB the appropriate tests and criteria will be followed (See Time and Events Tables, Appendix 6). See the SPM for additional instructions.

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects for central storage which may be transferred to a central independent imaging center. This includes baseline scans and all scans performed during the course of the study. GSK may request an independent review of scans. See SPM for additional details.

6.6. Pharmacokinetics

6.6.1. Blood Sample Collection

Blood samples to enable quantification of GSK525762 in plasma will be collected at the time points indicated in Time and Events Tables. The actual date and time of each blood

sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK sample collection, processing, storage and shipping procedures are provided in the Study Procedures Manual (SPM).

6.6.2. Plasma Sample Analysis

Plasma analysis will be performed under the management of Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics (DMPK), GlaxoSmithKline. Concentrations of GSK525762 will be determined in plasma samples using the currently approved analytical methodology. In addition, selected metabolites of GSK525762 may also be quantified using approved analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline.

In addition, plasma may be analyzed qualitatively for other circulating compound-related material and the results will be reported under a separate DMPK protocol.

6.6.3. Urine Collection

Urine samples for quantitative analysis of GSK525762 may be collected at the time points noted in the Time and Events Tables for Part 1 of the study (these samples are optional as of Amendment 9).

Selected urine samples may be analyzed qualitatively and/or quantitatively for GSK525762 metabolites and the results will be reported under a separate DMPK protocol.

Details of urine sample collection, processing, storage and shipping procedures are provided in the SPM.

6.6.4. Caffeine, Alcohol, and Tobacco

During serial PK sampling days (as outlined in Section 5), subjects will abstain from ingesting alcohol, tobacco products, caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and/or pharmacodynamic sample during each session.

6.6.5. Activity

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

6.7. Pharmacodynamics

6.7.1. Rationale for ^{18}FDG-PET

The inclusion of ^{18}F-FDG PET is based on the limited past experience with this modality of imaging in NUT Midline Carcinoma. In an small study (n=1) conducted at the Dana Farber Cancer Institute, an intolerable dose of Vorinostat demonstrated marked reduction

in glucose uptake in a 28 day period, which correlated with a smaller reduction in tumor volume by CT. On this basis, it would appear that at least in this case NMC is highly metabolically active, and thus glucose uptake may be a sensitive surrogate marker of tumor inhibition.

6.7.2. Assessments for PET

During the dose escalation phase in Part 1, ^{18}F-FDG PET assessments will be optional until the standard 3+3 design is implemented. At this point, the sites will be required to perform ^{18}F-FDG PET assessments for all NMC subjects and other solid tumors as appropriate.

During Part 2, PET (FDG or fluoride) scans should be performed at baseline, with follow up scans conducted as clinically appropriate (as outlined in the T&E Table 16). Additional details will be provided in the SPM.

Additional analysis may be conducted by an independent central reviewer. Instructions for submission of data are provided in the SPM.

6.8. Translational Research

Blood and/or tumor tissue specimens will be collected at various times throughout the study in order to support research aimed at identifying indicators of sensitivity/resistance to GSK525762, understanding the biological effect of GSK525762 and BET inhibition, and also to support diagnostic assay development for NMC.

Toward that end the successful collection of quality tumor specimens will be critical to furthering our understanding of BET biology and identifying the best way to treat patients with a BET inhibitor. Specifically, the evaluation of responders, responders at relapse, and non-responders for gene mutation status and/or pathway activation may lead to the discovery of potential new diagnostic markers or novel combinations. Similarly, pre- and post-dose tumor specimens will be evaluated for markers of target engagement, tumor response, and/or evaluated for changes in gene expression; thus supporting identification of a biologically effective dose and furthering our mechanistic understanding of BET inhibition in these settings.

The biopsies will be assessed for transcripts or proteins that reflect BET target engagement and/or tumor biology (For NMC, markers of cell proliferation and/or cell differentiation (e.g., Ki67 and cytokeratin [Schwartz, 2011]) will be analyzed. Biopsies may also be assessed for Deoxyribonucleic acid (DNA), Ribonucleic acid (RNA) or proteins which may be potential predictors of sensitivity or resistance to BET inhibition based on emerging data.

6.8.1. Tumor Tissue Collection

NMC patients in Part 1 will be required to submit a fresh or archival tumor specimen for retrospective diagnostic confirmation. NMC patients in Part 2 will be required to submit a fresh or archival tumor specimen to the central laboratory for diagnosis. Due to the timely need to determine NMC status by NUT IHC testing, a pre-screen informed

consent may be offered to expedite obtaining the tissue in Part 2. These specimens may also be evaluated retrospectively for exploratory research as described above.

All non-NMC patients will also be asked to submit an archival tumor specimen for retrospective testing for potential markers of sensitivity and/or resistance, e.g., N-Myc amplification; however, this will not be an eligibility requirement.

During the accelerated dose escalation phase (Part 1), fresh pre- and post-dose biopsy collections will be optional until the standard 3+3 design is implemented. During the 3+3 dose escalation phase in Part 1, and during Part 2, pre- and post-treatment biopsies are collected as outlined in the Time and Events Tables and are mandatory. Archival tissue may be accepted as a pre-treatment specimen if the subject is treatment naïve. For subjects in Part 1 and 2, if tumor tissue is not accessible, discussion with the GSK medical monitor is required.

Subjects must have a platelet count of $\geq$75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy. If study medication is held prior to the post-dose biopsy, dosing must be re-started and subjects should receive 4 consecutive days of dosing prior to collection of the biopsy. Specific timing of post-dose sample collection is defined in the T&E table. See Study Procedures Manual (SPM) and central lab manual for additional details.

6.8.2. Whole blood LPS-induced IL-6, Plasma Cytokines, and Plasma Protein Biomarkers

6.8.2.1. LPS-induced (Stimulated) Whole Blood Ex Vivo

GSK525762 has consistently shown inhibition of LPS induced IL-6 across different human cell populations and in different species. The action of the compound is through inhibition of the assembly of transcriptional complexes required to express the protein. Pre-clinical studies demonstrate that blood concentration of drug correlates to the degree of inhibition of LPS induced IL-6 in ex vivo whole blood samples. Therefore, this biomarker will be used as an indication of pharmacology and will be aligned with PK sampling. Since inhibition of BET family proteins is known to inhibit a range of pro-inflammatory mediators and acute phase proteins, a number of additional proteins (46) will also be measured from these ex vivo samples.

6.8.2.2. Systemic (Unstimulated) Plasma for Cytokines, Chemokines, and Acute Phase Proteins

The set of analytes identical to that used in the whole blood ex vivo assay (including for example, MCP-1, MIP1-β IL-8) will also be measured in plasma samples taken during PK sampling. This will assess systemic inflammatory response in the subject using biomarkers such as pro-inflammatory cytokines and acute phase proteins and correlate the systemic response to drug with that in stimulated and unstimulated blood. These biomarkers are expected to change over days rather than hours, based on the plasma half lives and pre-clinical data, such that sampling will also be performed after repeat dosing.

6.8.2.3. Whole Blood mRNA

GSK525762 has been shown to modulate the expression of a number of different genes in unstimulated whole blood between 1 h and 6 h. The mRNA levels of 31 such genes form a 'signature' panel which will also be used as a biomarker of engagement of pharmacology and will be measured using mRNA isolated from whole blood. The modulation of a number of these genes will also be measured as changes in systemic proteins as well as in the analysis of the ex vivo assay blood samples (e.g. CCL2 and IL-8) thus relating mRNA and protein expression with drug concentration. Other translational research studies, such as transcriptomics profiling, will also be performed using whole blood mRNA from selected patients.

Until preliminary subject data are generated for these biomarkers, it will be necessary to monitor frequently. Please refer to the Time and Events Tables for specific details on timing of samples. Further details regarding the sampling procedure and how to process the blood samples will be provided in the SPM.

6.8.3. Biomarker Blood Sample Timing and Schedule

A change in frequency of blood biomarker sampling times may be implemented based on emerging data. This would be determined during dose escalation decision meetings and communicated to the sites in the meeting minutes for implementation.

6.8.4. Exploratory Safety Biomarker Blood Samples

Unscheduled biomarker sample(s) may be collected based on emerging safety. One to three samples may be collected in a day to address specific safety concerns. Each sample would be up to 10mL of whole blood to look at cytokines, gene signature (mRNA) or other plasma proteins. The timing of the samples will be based on emerging safety data and would be discussed and determined by GSK medical monitor and study team review.

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

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 6.9.1 and Section 6.9.2.

6.9.1. 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).

"Lack of efficacy" or "failure of expected pharmacological action" per se is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or 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.

6.9.2. Definition of a SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or 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 are as follows:

- All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct) (or ALT ≥3xULN and INR>1.5, if INR 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 unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury

- Any new primary cancers
- Significant Cardiac dysfunction
- Grade 4 laboratory abnormalities (not disease related)
- Drug related hepatobiliary event leading to permanent discontinuation of study treatment

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

Any abnormal laboratory findings (e.g., hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, that are judged by the investigator to be

clinically significant are to be recorded as an AE or SAE, in accordance with the definitions provided. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

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.

6.9.4. Time Period and Frequency of Detecting AEs and SAEs

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

AEs will be collected from the time the first dose of study treatment is administered until 28 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 6.9.5.

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 28 days the investigator may report any adverse event that they believe possibly related to study treatment.

6.9.5. Prompt Reporting of SAEs and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in Table 20 once the investigator determines the event meets the protocol definition for that event.

Table 20 Reporting of SAEs and Other Events to GSK

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy Notification Form	24 hours	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT≥3xULN and bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]
ALT≥5xULN; ALT≥3xULN with symptoms of liver injury or hypersensitivity **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and biliribin <2xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

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

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

6.9.6. Regulatory reporting requirements for SAEs

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

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

regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

6.10. Pregnancy

6.10.1. Time period for collecting pregnancy information

Reporting of any pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until 7 months after the last dose of study drug.

6.10.2. Action to be taken if pregnancy occurs

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 6.9.5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

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

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

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

Procedures for pregnancy report will be located in the SPM.

6.11. Pharmacogenetics

An important objective of the clinical study is 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 host DNA from blood will be analysed to determine their relationship with response (safety, tolerability, pharmacokinetics, and efficacy) to treatment with GSK525762.

Information regarding pharmacogenetic research is included in Appendix 1. In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency also approve the PGx assessments (i.e., approval of Appendix 1), unless otherwise indicated. Where permitted by regulatory authorities, 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 are not approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. STUDY TREATMENTS

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

7.1. GSK525762 Investigational Product Dosage/Administration

GSK525762 Tablets will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. An amorphous, free-base formulation of GSK525762 will be used in Part 1 (Table 21) and a crystalline, besylate formulation (Table 22) will be introduced in the besylate sub-study in Part 1 (US sites only) and the Part 2 expansion cohorts. After completion of the besylate sub-study and introduction of besylate material for Part 2, remaining subjects ongoing in Part 1 were required to change from the amorphous free-base formulation to the besylate formulation (at the equivalent dose) based on the amorphous supply availability.

Under normal conditions of handling and administration, investigational product 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.

Table 21 GSK525762 Amorphous Free-base Investigational Product Dosage/Administration

Investigational Product			
Product name:	GSK525762 Amorphous Free Base Tablets[1]		
Unit dose strength(s)/Dosage level(s):	1mg	10mg	30mg
Dosage form	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK
Physical description:	white to off-white, round, biconvex tablets with no markings, uncoated tablet		
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings		
Dosing instructions:	Dose with 240mL water. No food or antacids for at least 1h before and 2h after dosing. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)		
1. Amorphous formulation is no longer available as of Amendment 9			

Table 22 GSK525762 Besylate Investigational Product Dosage/Administration

Investigational Product				
Product name:	GSK525762 Besylate Tablets			13C-GSK525762 Stable isotope powder for oral solution[1]
Unit dose strength(s)/Dosage level(s):	5mg	25mg	50mg[1]	Low dose
Dosage form	Tablet	Tablet	Tablet	Powder for oral solution
Manufacturer	GSK	GSK	GSK	GSK
Physical description:	White to slightly colored round, biconvex tablets with no markings, film-coated tablet		White to slightly colored , oval, biconvex tablets with no markings, film-coated tablet	White to slightly colored powder
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			Administer orally as a single dose with GSK525762 Tablets (besylate Sub-Study for Treatment A2, B and C)
Dosing instructions:	Dose with 240mL water and should be taken at approximately the same time each day. May be taken with or without food.. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Dissolve powder in 20 mL of water with bicarbonate buffer and administered with GSK525762 tablets (Besylate Sub-Study, Treatment A2, B and C)
1. Formulation is no longer available as of Amendment 9				

7.2. Handling and Storage of Study Treatment

GSK525762 Tablets must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK525762 Tablets will be limited to the investigator and authorized site staff. GSK525762 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK525762 tablets.

GSK525762 Amorphous Free-base Tablets are to be stored at up to 30°C (86°F) and protected from light and moisture.

GSK525762 Besylate Tablets are to be stored at up to 30°C (86°F) and protected from moisture.

Sample accountability, return or destruction per institutions' guidelines will be address in the SPM.

7.3. Meals and Dietary Restrictions

During Part 1, subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects will be asked to fast for an additional two hours. On serial PK sampling days (Week 1, Day 1 and Week 3, Day 4), subjects should fast overnight (i.e., at least 8 hours). These fasting requirements have been implemented in the protocol and informed consents to minimize pharmacokinetic variability.

During Besylate Sub-Study, subjects will be asked to fast overnight (at least 8 hours) and continue fasting for 4 hours post-dose administration except for the fed administration where subject will be requested to ingest a high-fat high-calorie meal within 30 minutes prior to administration (FDA, 2002).

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose. Should a twice daily regimen be required, additional consideration will be paid to fasting requirements once the escalation period is past.

In Part 2, based on the results of the besylate sub-study showing a lack of effect of a high-fat high-calorie breakfast on the overall exposure (i.e. AUC) to GSK525762 administered as besylate coated tablets, the fasting requirement is being lifted, except on Serial PK sampling days in Part 2 (Week 1 and Week 4). On these days, subjects should fast overnight (i.e., at least 8 hours). After dosing, subjects will be asked to fast for an additional two hours. These fasting requirements have been implemented in the protocol and informed consents to minimize PK variability.

Fasting will consist of avoiding the oral ingestion of calorie – containing products; however, ingestion of water is permitted.

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment until the last dose of study drug.

7.4. Treatment Assignment

This is an open-labeled study.

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Subjects in Besylate Sub-Study will be assigned to a treatment

sequence (see Table 4) in accordance with the randomization schedule generated by Discovery Biometrics, using a validated software.

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

7.5. 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 investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

7.6. Treatment Compliance

At each visit, an evaluation of subject compliance with taken medication will be performed. The investigator will make every effort to bring non-compliant subjects into compliance.

Compliance with GSK525762 will be assessed through querying the subject during the site visits and documented in the source documents and CRF.

A record of the number of GSK525762 tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

7.7. Dose Modifications

7.7.1. Dose and Safety Management Guidelines

The following dose modification criteria should provide guidance for, but not act as a replacement for sound clinical judgment. The investigator should use clinical judgment to determine which drug may be contributing to the toxicity necessitating dose adjustment, and make the appropriate change for that drug. Further details are provided in the Appendix 3.

Dose reductions for individual subjects may be required, based on toxicity observed during the study. Table 24 describes the guidance for dose level reductions. All dose reductions should be discussed with the GSK Medical Monitor.

Table 23 Guidance for GSK525762 Dose Reduction Levels

Current GSK525762 Dose (Total daily dose)	If subject requires a dose level reduction; new dose:

40 mg	No further dose reduction allowed
50 mg	40 mg
60 mg	50 mg
75 mg or 80 mg	60 mg

Table 24 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 (platelets <LLN to ≥75,000/mm^3) & Grade 2 (platelets <75,000 to ≥50,000/mm^3)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary.
	Grade 3 (platelets <50,000 to ≥25,000/mm^3)	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC twice a week and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at another lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur to the same level following a second rechallange, drug will be discontinued.
	Grade 4 (platelets <25,000/mm^3), or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC twice a week and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be held until platelet count recovers to Grade 2 (≥50,000/mm^3). For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		be permanently discontinued. If platelet count does not recover to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 may be continued at the current/reduced dose after discussion with the medical monitor. If platelet count does not recover to ≥25,000/mm^3 (Grade 3) within 7 days, GSK525762 should be permanently discontinued.
QTcF	If >30 msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	(1) Continue current dose of GSK525762 (2) Supplement electrolytes, particularly potassium and magnesium, to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L (3) Discontinue any concomitant medications with potential for QTcF prolongation. (4) Consider 24 hour or longer telemetry monitoring if clinically indicated.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. (1) Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L (2) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (3) Discontinue any concomitant medications with potential for QTcF prolongation. (4) Consider telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (1) QTcF reduced to <450 msec, (2) Potassium and magnesium levels are within institutional normal range, (3) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		Monitor), (4) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be performed for two weeks, and then next assessment at 4 weeks post-dose. a. If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN	Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin within 24-48 hours or as soon as possible. For asymptomatic subjects with repeat troponin values >ULN, hold study medication(s), refer to a cardiologist and contact the GSK Medical Monitor. If the repeat value is within the normal range, the subject may continue study medication with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. If the subject is symptomatic or the troponin level approaches the threshold for MI according to local lab parameters, the study medication must be withdrawn and the subject will be referred immediately to a cardiologist for appropriate medical care.
LVEF	Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN)	Temporarily discontinue investigational drugs(s) and repeat evaluation of LVEF within 2 weeks. If LVEF recovers (defined as $\geq$LLN and absolute decrease $\leq$10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		then per protocol specifications. If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution, whichever is longer.
	Grade 3 or 4	Permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution.
Liver	• ALT ≥5X ULN, OR • ALT ≥3X ULN plus either bilirubin ≥ 2X ULN (>35% direct bilirubin, bilirubin fractionation required) or INR >1.5 without evidence of biliary obstruction or progressive disease, OR • ALT ≥3X ULN with symptoms of liver injury or hypersensitivity[a]	Refer to Section 14.3 (Appendix 3) for liver chemistry stopping criteria, treatment algorithms, reporting and follow-up of suspected liver events. Discontinue study medication(s) and notify the GSK Medical Monitor.
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE version 4.0 Grade 1-5)	Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)	Monitor fasting and preprandial glucose. If persistent over 2 repeats over 3-4 weeks, consult Diabetologist and consider starting metformin.
	Any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)	Hold investigational product(s) and instruct subject to notify investigator immediately. Monitor for ketoacidosis as clinically indicated. If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist. Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	Hold investigational product(s). Provide sugar containing liquids and monitor monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes, may restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.
Diarrhea	Grade 1	Initiate supportive care including loperamide.
	Grade 2	Initiate supportive care including loperamide. Consider temporary discontinuation of study medications and discuss with GSK Medical Monitor.
	Grade 3 or 4	Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. Withhold study drug until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis May restart study treatment one dose level lower.
Mucositis	Grade 1-2	Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
	Grade 3-4	Above, plus systemic opiate administration as needed. Consider IV hydration and hospital admission as appropriate. For mucositis >Grade 3, hold GSK525762 until mucositis is <Grade 1 and resume the same dose of GSK525762. If mucositis >Grade 3 recurs, hold GSK525762 until mucositis is <Grade 1, then reduce GSK525762 one dose level. If mucositis >Grade 3 recurs a third time at reduced dose, hold GSK525762 until mucositis resolved to <Grade 1, then reduce GSK525762 one dose level (if possible) or discontinue permanently.
Pneumonitis	Grade 1	**For all grades obtain high resolution chest CT if possible.** Consider evaluation by pulmonologist. Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). If any decline is observed in O_2 saturation, hold study drug, repeat chest x-ray to determine if progression of pneumonitis has occurred and consult pulmonologist.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Grade 2	Must be evaluated by pulmonologist. Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to wnl. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL). Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated. Hold investigational drug(s) until recovery to ≤Grade 1, then reduce dose by at least 25%. Discontinue investigational drug(s) if no recovery to ≤Grade 1 within 4 weeks.
	Grade 3 and 4	Discontinue investigational drug(s). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to wnl. Bronchoscopy with biopsy and/or BAL is recommended. Consider treatment with corticosteroids in the appropriate clinical setting and in consultation with the pulmonologist (1-2 mg/kg of prednisone [or equivalent] IV once daily) if infectious origin is ruled out. Taper over 4-6 weeks

*Note: Baseline results are defined by the nearest timepoint prior to first dose. For this trial the Baseline QTcF value is determined by the mean of the triplicate W1D1 pre-dose QTcF results (when triplicate ECGs are indicated). If these results are not available, then the mean QTcF of the screening triplicate ECG results are considered baseline.

a. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia.

7.7.2. Dose Adjustments for Toxicity

Table 25 Guidance for Dose Adjustment for Toxicity [Except those listed in Table 24]

Worst Grade	GSK525762
1	No change in dose.
2	For drug-related Grade 2 toxicities, continue dosing with no change or may consider holding for up to 1 week for toxicity to be < Grade 2. Continue at the same dose (dose reduction is required if the Grade 2 toxicity is considered a DLT).

Worst Grade	GSK525762
3	Hold dose until toxicity is ≤ Grade 1*, then restart with no change for 1st episode. Reduce by one dose level with 2nd episode if recovery to ≤Grade 1 within 21 days. If no recovery to ≤Grade 1 after a 21 day delay in the 2nd episode, subject should be permanently discontinued.
4	Off protocol therapy. In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the patient is receiving benefit then the following criteria should be implemented: hold until toxicity is ≤Grade 1*, then restart with one dose level lower. If the same Grade 4 toxicity recurs, study drug will be permanently discontinued.

*Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for rash, alopecia, etc. Exceptions to ≤ drug-related Grade 1, 2, 3 requirements would be quickly reversible (<48 hours) laboratory abnormality (example: electrolyte changes).

Dose escalation decisions will take into account all available data, including pharmacokinetics data and the safety profile of prior cohorts, and will occur following review of these data by the investigator(s), GSK medical monitor, pharmacokineticist, and statistician. The decision and rationale will be documented in written format and distributed to the investigator(s), GSK medical monitor, pharmacokineticist, and statistician.

The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate [safety, pharmacokinetic and/or pharmacodynamic] findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the Screening Visit until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations during the study will be recorded in the eCRF. The minimum requirement is that drug name, route of administration, dose and frequency of dosing, along with start and stop dates of administration should be recorded. Additionally, a complete list of all prior 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.

8.1. Permitted Medications and Non-Drug Therapies

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

institutional guidelines. The only caveat is that subjects should not receive those medications listed as prohibited in Section 8.2.

Bisphosphonates will be allowed if subjects have been on a stable dose for at least three months.

Supportive measures including erythropoietin, blood transfusions, and hematopoietic colony stimulating factors for treatment of cytopenias are permitted. Erythropoiesis-stimulating agents and colony-stimulating factors like filgrastim and pegfilgrastim may be used as clinically indicated.

Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

8.2. Prohibited Medications and Non-Drug Therapies

8.2.1. Prohibited Medications

Subjects should not receive other anti-cancer therapy [including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormonal therapy (other than leuprolide or other GnRH agonists), surgery or tumor embolization] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. Note, palliative radiation and/or surgical intervention may be permitted (for example to address pain management) and should be discussed with the GSK medical monitor prior to invention to determine appropriate dosing and schedule.

Subjects may continue to use aspirin, but doses are not allowed to be greater than 100 mg per day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution, including concomitant use of proton pump inhibitors.Subjects taking enzyme-inducing antiepileptic agents or other potent inhibitors or inducers of CYP3A4 enzymes should be transitioned to another agent at least 14 days (or 5 half-lives, whichever is longer) prior to the first dose of study agents.

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

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (administered per the prescribing information) and ondansetron (at a maximum oral dose of 8 mg TID) are the only allowed drugs in this class (i.e. dolasetron and granisetron are not permitted).

Co-administration of the medications listed in Table 26 are prohibited for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until

discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of amiodarone, which is prohibited beginning 6 months prior to screening through discontinuation from the study; however, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines). If a prohibited medication is required for single use (such as for a procedure) while study treatment(s) is held, the GSK Medical Monitor can approve such use.

Table 26 Drugs with a Risk of Torsades de Pointes that are Prohibited[1]

Amiodarone	Dronedarone	Moxifloxacin
Anagrelide	Droperidol	Papaverine
Azithromycin	Erythromycin	Pentamidine
Chloroquine	Escitalopram	Pimozide
Chlorpromazine	Flecainide	Procainamide
Cilostazol	Fluconazole	Propofol
Ciprofloxacin	Halofantrine	Quinidine
Citalopram	Haloperidol	Roxithromycin
Clarithromycin	Ibogaine	Sevoflurane
Cocaine	Ibutilide	Sotalol
Disopyramide	Levofloxacin	Sulpiride
Dofetilide	Levomepromazine	Sultopride
Domperidone	Levosulpiride	Terlipressin
Donepezil	Methadone	Thioridazine

Data Source: crediblemeds.org revision date 09 January 2017.

1. The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

8.2.2. Cautionary Medications

Subjects should minimize the use of medications which contain acetaminophen. Subjects should be informed of alternative medications.

Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes **are to be used with EXTREME CAUTION** beginning **14** days prior to the first dose of study drug until discontinuation from the study. These medications include (but are not limited to):

Table 27 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution[1]

Alfuzosin	Foscarnet	Perphenazine
Apomorphine	Gemifloxacin	Pipamperone
Aripiprazole	Hydrocodone ER	Promethazine
Artenimole+piperaquine	Iloperidone	Rilpivirine
Asenapine	Imipramine	Risperidone
Atomoxetine	Isradipine	Saquinavir
Bedaquiline	Leuprolide	Sertindole
Buprenorphine	Lithium	Solifenacin
Clomipramine	Melperone	Tacrolimus
Clozapine	Mifepristone	Telavancin
Cyamemazine	Mirabegron	Telithromycin
Degarelix	Mirtazapine	Tetrabenazine
Delamanid	Moexipril/ hydrochlorothiazide	Tiapride
Desipramine	Nicardipine	Tizanidine
Dexmedetomidine	Norfloxacin	Tolterodine
Efavirenz	Nortriptyline	Trimipramine
Ezogabine	Ofloxacin	Tropisetron
Famotidine	Oxytocin	Vardenafil
Felbamate	Paliperidone	Venlafaxine
Fingolimod	Pasireotide	Zotepine
Flupentixol	Perflutren lipid microspheres	

Data Source: crediblemeds.org revision date 09 January 2017

1. The above table is not exhaustive and these drugs are defined by the online version at the time of screening of the subject

After starting cautionary medications such as in Table 27, it is recommended that ECGs are implemented daily until the steady state. If there are abnormalities, implement additional cardiotoxicity monitoring as addressed in Table 24, Section 7.7.

GSK525762 is a moderate CYP3A4 inducer. Medications that have a narrow therapeutic index and that are substrates of CYP3A4 should be administered with caution, as their metabolism may be affected by co-administration with GSK525762 and result in decreased exposure. These include alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline.

GSK525762 is a substrate for breast cancer resistance protein (BCRP) and P-glycoprotein (Pgp) transporters. Therefore, potent inhibitors of these transporters, such as cyclosporine, tacrolimus, or ketoconazole, should be avoided.

GSK525762 in as inhibitor of organic anion transporter 1A1 (OAT1) and organic anion transporter 3 (OAT3) in vitro. Substrates of these transporters include agents such as methotrexate, penicillin G, and indomethacin. While co-administration of these agents with GSK525762 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Higher doses of oral steroids can cause enzyme induction. As such, oral steroids should be used with caution (and discussed with the GSK Medical Monitor). NOTE: Topical or inhaled steroids are permitted.

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

8.3. Treatment after Discontinuation of Study Treatment or Withdrawal from/Completion of Study

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

Refer to Section 4.2.4.1 and Section 5 for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinue from study treatment.

8.4. Treatment of Study Treatment Overdose

In the event of a study drug overdose (defined as administration of more than the protocol-specified dose), the investigator should contact the GSK Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities.

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

A plasma or urine sample for PK analysis may be requested by the GSK Medical Monitor on a case-by-case basis. This plasma or urine sample should be collected as soon as possible, but within 3 days from the date of the last dose of on-study dosing.

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

9. LIFESTYLE REQUIREMENTS (CONTRACEPTION)

9.1. Female Subjects

Female subjects of childbearing potential must not become pregnant during the trial and for 7 months after stopping study medication 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%

- Non-hormonal intrauterine device (IUD) or intrauterine system (IUS) 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.

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.

All hormonal means of birth control such as oral, injectable, dermal, subdermal or topical contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

9.2. Male Subjects

This list does not apply to male subjects with a female partner of child bearing potential who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment and until 16 weeks after the last dose of study drug(s).

- Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview, **OR**
- Condom use PLUS partner use of a highly effective contraceptive (≤1% rate of failure per year) such as intrauterine device or system, or hormonal birth control such as contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches.

Male subjects whose partners are or become pregnant must continue to use condoms for 16 weeks after after the last dose of study medication. Male subjects should be advised not to donate sperm while on study and for 16 weeks after the last dose of study medication.

10. DATA MANAGEMENT

Subject data will be collected using defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

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

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1. Sample Size Assumptions

11.1.1. Part 1

The total number of subjects to be enrolled into Part 1will depend on the number of dose escalations required to establish the maximum tolerated dose of GSK525762; they are not driven by statistical considerations. To complete Part 1, it is estimated that 90 to 110 evaluable subjects will be enrolled.

Doses to be studied in Part 1 will be guided by calculating the posterior probability that the DLT rate falls within an acceptable range for each subsequent dose after each dose cohort observation period. The N-CRM method will be used to calculate posterior probabilities utilizing a pre-specified prior distribution.

11.1.2. Besylate Sub-Study

At least 8 and up to 12 US subjects will participate in Besylate Sub-Study.

Approximately 12 subjects will participate in the assessment to get at least 8 evaluable patients completing. A subject is considered a completer if they have PK assessments from all treatment periods.

Based on a within-subject coefficient of variance for AUC of 50%, a correlation of 0.95 between the enriched (liquid dose of GSK525762 added) and non-enriched PK, and 8 subjects completing in Besylate Sub-Study, it is estimated that the half-width of the 90% CI for the ratio of the geometric means (besylate salt tablet compared to the amorphous free-base tablet) will be approximately 0.20. Hence, if the ratio estimate is equal to 1, the 90% CI will be 0.80 to 1.25.

11.1.3. Part 2

The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with NMC, SCLC, CRPC, TNBC, ER+BC and GIST.

- For NMC, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 20% relative to a 5% response rate suggesting no activity

- For CRPC and SCLC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR; for CRPC subjects, defined as a percentage of subjects have PSA50 response) of 30% relative to a 10% response rate suggesting no activity.

- For TNBC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 25% relative to a 10% response rate suggesting no activity.

- For ER+BC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 30% relative to a 15% response rate suggesting no activity.

- For GIST, efficacy is defined as a disease control rate (defined as a percentage of subjects that have achieved a CR or PR or SD that has lasted at least 16 weeks) of 40% relative to a 15% disease control rate suggesting no activity.

Bayesian statistics will be employed to calculate the predictive probability that the response rate is greater than the historic response rate at interim analyses using a weak/non-informative prior. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior distribution is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior distribution and the observed data. A very weak prior Beta distribution with a mean response rate equal to the target response rate is assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows:

Let p denote the response rate, the number of responses in the current n subjects, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the prior distribution and the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.

In the following case, 30% is the target response rate.

$$p \sim \text{Beta}\ (0.03 + x,\ 0.07 + n\text{-}x) \text{ with the posterior mean } (0.03+ x)/(0.07 + n).$$

Futility analysis for each disease cohort will begin when response data is available for at least 10 subjects. Each disease cohort may be stopped early for futility if the predictive probability of success (response rate ≥ historical response rate) is less than 1%. Futility stopping rules are defined for each cohort in Section 3.2.7.

The following table describes for each disease cohort the null and alternative hypotheses that will be tested, maximum sample size and design characteristics. Each maximum sample size was calculated to ensure that at least 80% power and a maximum type 1 error rate of 10% is maintained.

	Null Hypothesis (H0) RR	Alternative Hypothesis (Target) (Ha) RR	Maximum Sample Size	Probability of stopping early for futility if H0 is true	Average Sample Size if H0 is true	Actual Type I Error Rate (%)	Actual Power (%)
NMC	5%	20%	**25**	**0.891**	**14**	**8.8**	**80.2**
CRPC	10%	30%	**22**	**0.860**	**16**	**6.0**	**82.5**
TNBC	10%	25%	37	0.876	23	6.4	81.7
ER+BC	15%	30%	37	0.855	25	8.7	80.3
SCLC	10%	30%	22	0.860	16	6.0	82.5
GIST	15%	40%	25	0.895	14	5.9	88

11.1.4. Sensitivity Analysis

No sample size sensitivity analysis was performed.

11.1.5. Sample Size Re-estimation

No sample size re-estimation will be performed.

11.1.6. Subset Analysis for NMC Population

An exploratory review for NMC molecular subtype (e.g. NUT-BRD3, NUT-BRD4, and NUT-NSD3) will be conducted.

11.2. Analysis Populations

All Treated Subjects (Safety and Clinical Activity) Population: This will consist of all subjects that received at least one dose of study treatment. Safety and clinical activity data will be evaluated based on this population.

The PK Population: This will consist of those subjects in All Subjects Population and for whom a PK sample is obtained and analyzed.

Pharmacodynamic Population: The PD Population is defined as subjects in the All Treated Subjects Population for whom a tumor biopsy or tissue was obtained and analysed for biomarkers.

More details of the analysis populations will be specified in RAP.

11.3. Data Analysis Considerations

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the 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.

11.3.1. Interim Analysis

An interim analysis of the key parameters may be carried-out before the conclusion of the study. Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).

The study will not utilize an Independent Data Monitoring Committee (IDMC).

11.3.2. Final Analyses

Final analysis on Part 1 may be conducted when

- Part 1 is completed
- or at least 70% of subjects enrolled in every dose group at Part 1 are completed or progressed or died.

Final analyses will be carried-out following the DBF (data base frozen) after all the data queries has been resolved .

11.3.3. Analysis Datasets

The construction of analysis data sets will be performed in accordance with all applicable GlaxoSmithKline standards and procedures.

11.3.4. Withdrawal

Reason for subject withdrawal will be listed.

11.3.5. Missing Data

Missing data will not be imputed. Where appropriate, available data will be summarized over specified intervals (e.g., from start of treatment until withdrawal from study) using suitable summary statistics.

11.3.6. Derived and Transformed Data

The PK parameters, AUC, Cmax, and terminal half-life will be log-transformed prior to analysis.

11.3.7. Assessment Windows

Safety assessments that occur prior to the administration of study drug will be considered screening assessments. Safety assessments that occur after dosing has begun will be considered as having occurred while on treatment.

Disease assessments will be distinguished as belonging to either screening, continued therapy or post-study phases of the study.

11.3.8. Other Issues

Data from participating centers will be pooled by tumor cohort prior to analysis. It is anticipated that subject accrual may be limited across centers and summaries of data by center would likely not be informative. Therefore, these summaries will not be provided.

Demographic and baseline characteristics will be summarized.

For PK analyses, assay values below the quantitative limit (BQL) will be handled as described in the GSK Creatine phosphokinase (CPK)/M&S PK Methods.

There will be no adjustments for multiplicity.

11.4. Efficacy Analyses

11.4.1. Primary Analysis

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data will be summarized by dose level.

The primary aim of Part 2 is to demonstrate clinically meaningful response rates in each of the disease cohorts separately.

Overall response rate is defined as the percentage of subjects who achieved CR or PR among subjects who received at least one dose of treatment. Overall response rate and the associated 2-sided 95% exact confidence limits will be provided separately for each disease cohort.

PSA 50 Response rate (RR) is defined as the response rate that a PSA reduction from baseline ≥50% is observed at 12 weeks and beyond (must be confirmed by a second value). RR will be reported for CRPC cohort along with the exact 95% confidence

interval. Waterfall plots will be presented that show the maximum percentage of change in PSA reduction from baseline.

Disease Control Rate (DCR) is defined as the percentage of subjects who achieved CR, PR or SD (defined as ≥ 16 weeks in duration) among subjects who received at least one dose of treatment. Disease control rate and the associated 2-sided 95% exact confidence limits will be provided separately for GIST cohort.

11.4.2. Secondary Analyses

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. For the analysis of overall survival (OS), the last date of known contact will be used for those subjects who have not died at the time of analysis; such subjects will be considered censored. Further details on rules for censoring will be provided in the RAP. Sensitivity analyses of PFS and further details on censoring rules will be provided in the RAP. Progression free survival (PFS) and overall survival (OS) will be summarized using Kaplan-Meier method.

The duration of response is defined for the subject or subjects with a confirmed CR or PR, as the time from the first documented evidence of a CR or PR until the first documented disease progression or death due to any cause. Censoring rules for duration of response will be outlined in detail in the RAP.

Time to Response is defined, for subjects with a confirmed CR or PR, as the time from first dose to the first documented evidence of CR or PR.

If sample size permits, duration of response and time to response will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a confirmed complete or partial tumor response will be included. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP.

11.5. Safety Analyses

Safety endpoints are described in Section 2.

The All Subject population will consist of all subjects receiving at least one dose of study drug and will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

A listing by subject including treatment administered, and compliance, will be generated with dates and times of treatment administered. The number of subjects exposed to study drug will be tabulated for Part 1 (for each dose cohort) and Part 2.

Adverse events will be coded and grouped by system organ class (SOC) and preferred (coded) term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) system for adverse event coding. AEs will be graded according to the National Cancer

Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4. All AEs will be listed. A summary of the number and percent of subjects reporting each AE at least once will be produced for all AEs, for drug-related AEs and for SAEs for Part 1 (for each dose cohort) and Part 2. A listing of those AEs identified as dose-limiting toxicities will also be produced for each dose cohort. A listing showing the relationship of AE verbatim text to group terms and body systems will also be produced. A listing of withdrawals due to AEs will be provided. Deaths and SAEs will be listed should they occur.

Clinical laboratory evaluations will be performed on the days specified in the Time and Events Tables. Clinical chemistry, coagulation, hematology and urinalysis values and change from baseline values will be listed for each subject and flagged high or low relative to their normal ranges, where applicable. The toxicity grade for laboratory data will be calculated using NCI CTCAE Version 4. The lab data will then be summarized according to the subject's baseline grade and maximum grade for each cycle of therapy. A listing of subjects with potentially clinically important lab abnormalities will also be produced. A summary of lab values and change from (baseline) may be done for Part 1 (for each dose cohort) and Part 2.

Vital signs and ECG data will be listed and summarized for Part 1(for each dose cohort) and Part 2. Changes from baseline will be included in the listings and summary.

ECOG Performance Status assessments will be listed and summarized for Part 1 (for each dose cohort) and Part 2.

All other relevant safety data will be listed and summarized according to the GSK IDSL standards as well.

All data will be listed. Further details will be provided in the RAP.

11.5.1. Extent of Exposure

Extent of exposure of GSK525762 will depend on tolerability of the subjects to the doses administered and the course of their disease. The number of subjects exposed to GSK525762 will be summarized for each dose level administered.

11.5.2. Adverse Events

Adverse events (AEs) will be coded using the standard GlaxoSmithKline Medical Dictionary for Regulatory Activities (MedDRA) and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 4.0).

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

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

AEs of special interest will be outlined in the RAP.

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

11.5.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled assessment according to NCI CTCAE grade (version 4.0). The proportion of values lying outside the reference range will also be presented for laboratory tests that are not graded because there are no associated NCI CTCAE criteria. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e. no visit windows will be applied). Unscheduled data will be included in "overall" and "any post-screening" summaries which will capture a worst case across all scheduled and unscheduled visits post first dose of study treatment. Further details will be provided in the RAP.

11.6. Pharmacokinetic Analyses

11.6.1. Pharmacokinetic Parameters

PK analyses will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Plasma GSK525762 and relevant metabolites, as appropriate, concentration-time data from dose escalation (Part 1) will be analyzed by non-compartmental methods with WinNonlin.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC(0-t) and AUC(0-∞) Week1 Day1 only) and apparent terminal phase half-life ($t_{½}$). Trough concentration ($C\tau$) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined. The ratio of AUC(0-τ) on Week 3 / AUC(0-∞) on Week 1 will be calculated to assess time invariance. GSK525762 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

11.6.2. Statistical analysis of pharmacokinetic parameters

Statistical analyses of the PK parameters data will be conducted by Discovery Biometrics, GSK. Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) pharmacokinetic parameters values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters (if applicable)) by dose cohort and age group will be reported.

Dose proportionality

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) from Part 1 will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data), dose proportionality of AUC and Cmax for GSK525762 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

Separate models will be evaluated for amorphous tablet and besylate salt.

Relative bioavailability of the besylate salt tablet to the amorphous tablet (Besylate Sub-Study)

Based on the US FDA guidance on relative bioavailability studies, two formulations will be considered bioequivalent if the 90% CI of the ratio for Cmax and AUC, based on log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on the dose amount impact of a deviation from bioequivalence with the besylate salt will be based on the magnitude of the change.

Food effect with besylate salt tablet (Besylate Sub-Study)

Pharmacokinetic (PK) parameters AUC(0-∞), and Cmax will be loge-transformed and analyzed using a mixed-effects model with and without food will be analyzed separately with fixed-effect terms for fed status (fed or fasted), and subject as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between fed and in fasted state. The point estimates and their associated 90% CIs were then backtransformed to provide point estimates and 90% CIs for the ratios of fed/fasted. Non-parametric methods such as the Hodges and Lehmann estimator will be used to estimate the median differences between the fed treatments and the fasted state treatments for tmax. An associated 90% CI for the median differences will be constructed.

Based on the US FDA guidance on food-effect bioavailability studies, the absence of a food-effect will be established if the 90% CI of the ratio for Cmax and AUC, based on log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on the clinical significance of the effect of food will be based on the magnitude of the change and our understanding of the exposure-clinical response relationship.

For the evaluation of food effect, tmax at fed and fasted status will be presented by subject and dose cohort in tabular and graphical form.

11.6.3. Population Pharmacokinetic Analysis

Plasma concentration-time data from parts 1 and 2 will be combined and may be combined with data from other studies and further analyzed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (absorption rate, Ka, apparent clearance, CL/F and volume of distribution, V/F) and summary exposure measures (Cmax, AUC and Cav = AUC/τ) and identify important covariates (e.g., age, weight, or disease related covariates).

11.7. Pharmacokinetic/Pharmacodynamic Analyses

Observed (Part 1) or predicted concentrations (Part 2) will be combined with safety and efficacy pharmacodynamic measures of interest to examine potential exposure response relationships.

The relationship between QTcF and concentration expressed as Cmax, Cav, and/or instantaneous time-matched concentration will be evaluated. A linear or non-linear mixed effects analysis of the relationship between QTcF adjusted for baseline and – concentration with a possible incorporation of time will be evaluated as a means of estimating QTcF effect in lieu of a thorough QT study.

Other quantitative safety parameters and biomarkers of interest will be plotted graphically against summary exposure measures (eg; Cmax, Ctrough, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PKPD parameters of interest; 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 [RAP].

11.8. Translational Research Analyses

Exploratory analysis may be performed to examine potential relationships between anticancer activity and changes in markers of BET target inhibition 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.

11.9. Pharmacogenetic Analyses

The results of pharmacogenetic research investigations will 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 pharmacogenetic research and analyses are found in Appendix 1 and will be addressed in the RAP.

12. STUDY CONDUCT CONSIDERATIONS

12.1. Posting of Information on Clinicaltrials.gov

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

12.2. 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 ICH Good Clinical Practice (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 Good Clinical Practice (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)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

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

Written informed consent must be obtained from each subject, or from a guardian if the subject is less than 18 years of age, prior to participation in the study.

12.3. Urgent Safety Measures

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

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

12.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, 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 CRF 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.

12.5. Quality Assurance

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

12.6. Study and Site Closure

The end of the study date is defined as last subject last visit (contact).

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

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

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

GSK may close sites which fail to recruit within a predefined timeframe, as defined within the Study Procedures Manual.

12.7. 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.

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

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

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

12.9. Safety Review

12.9.1. Dose Escalation Decisions

Dose escalation decisions will take into account all available data, including pharmacokinetics data and the safety profile of prior cohorts, and will occur following review of these data by the investigator(s), GSK medical monitor, clinical development scientist(s), pharmacokineticist, safety review team, and statistician. The decision and

rationale will be documented in written format and distributed to the investigator(s), GSK medical monitor, pharmacokineticist, safety review team and statistician.

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14. APPENDICES

14.1. Appendix 1 : Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (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:

PGx Associations with Safety Events

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002]	HLA-B (Human Leukocyte Antigen B)	Carriage of the HLA-B*5701 variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective HLA-B*5701 screening and exclusion of HLA-B*5701 positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective HLA-B*5701 screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. HLA-B*5701 screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010]	HLA-B*1502	Independent studies indicated that patients carrying HLA-B*1502 are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis and that this marker is prevalent in some populations, particularly with Asian ancestry. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that screening is justified in patients with ancestry in populations in which HLA-B*1502 may be present.

Drug	Disease	Gene	Outcome
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008]	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 patient without this variation, raising the risk of certain side-effects, that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who are homozygous for UGT1A1*28 allele are at increased risk of neutropenia A genetic blood test (Invader UGT1A1 molecular 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 samples, even when no a priori hypothesis has been identified, 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 GSK525762.

Pharmacogenetic 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 GSK525762. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK525762 that may be attributable to genetic variations of subjects, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics and/or pharmacodynamics of study treatment,
- Safety and/or tolerability, and
- Efficacy.

Study Population

Any subject who is enrolled in the clinical study can participate 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 (~10mL) 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 labelled (or "coded") with a study specific number that can be traced or linked back to the subject 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 GSK525762 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 GSK525762.

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 should instruct the participant that their PGx sample will be discarded. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or mechanism pathways, drug metabolizing enzymes, or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants and treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to GSK525762. 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) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

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 the PGx research results in the clinical study report or may publish the results in scientific journals.

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 that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. 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.

14.2. Appendix 2 : Cockcroft-Gault Formula

The Cockcroft-Gault formula is a commonly-used surrogate marker for actual creatinine clearance (CrCl) and employs creatinine measurements and a subject's weight (kg) to predict the clearance.

If the subject is obese *(>30% over ideal body weight*), use ideal body weight in calculation of estimate CrCl.

If the subject is *below ideal body weight*, use actual body weight in calculation of estimate CrCl.

Cockcroft-Gault Formula for serum creatinine in mmol/L

CrCl (mL/min)=	Q X (140-age [years]) X actual body weight (kg)[a] / 48816 X serum creatinine (mmol/L)
Q=0.85 for females Q=1.0 for males	
OR	
a. Calculation of Ideal Body Weight Using the Devine Formula [Devine, 1974]	
Male subjects:	
	50.0 kg + (2.3 kg X each inch over 5 feet) or 50.0 kg + (0.906 kg X each cm over 152.4 cm)
Female subjects:	
	45.5 kg + (2.3 kg X each inch over 5 feet) or 45.5 kg + (0.906 kg X each cm over 152.4 cm) 4 cm)

Cockcroft-Gault Formula for serum creatinine in mg/dL

CrCl (mL/min)=	Q X (140-age [years]) X actual body weight (kg)[a] / 72 X serum creatinine (mg/dL)
Q=0.85 for females Q=1.0 for males	

For example:

For a male subject with actual body weight = 90.0 kg and height = 68 inches, the calculation would be as follows:

Ideal body weight= 50.0 + (2.3) (68-60) = 68.4 kg

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

14.3. Appendix 3: Liver Events

14.3.1. Liver Safety Stopping Criteria and Required Actions and Follow Up Assessments

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Table 28 Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Section 14.3.2) • If restart/rechallenge is **not granted**, permanently discontinue study treatment and	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the

may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high pressure liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Table 29 Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
• ALT ≥3xULN **but** <5xULN **and** • bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline[1] • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

1. For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

14.3.2. Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

14.3.2.1. Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable

liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.

- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.

- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.

- GSK to be notified of any adverse events, as per Section 6.9.

14.3.2.2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK, or designee, to be notified of any adverse events, as per Section 6.9.

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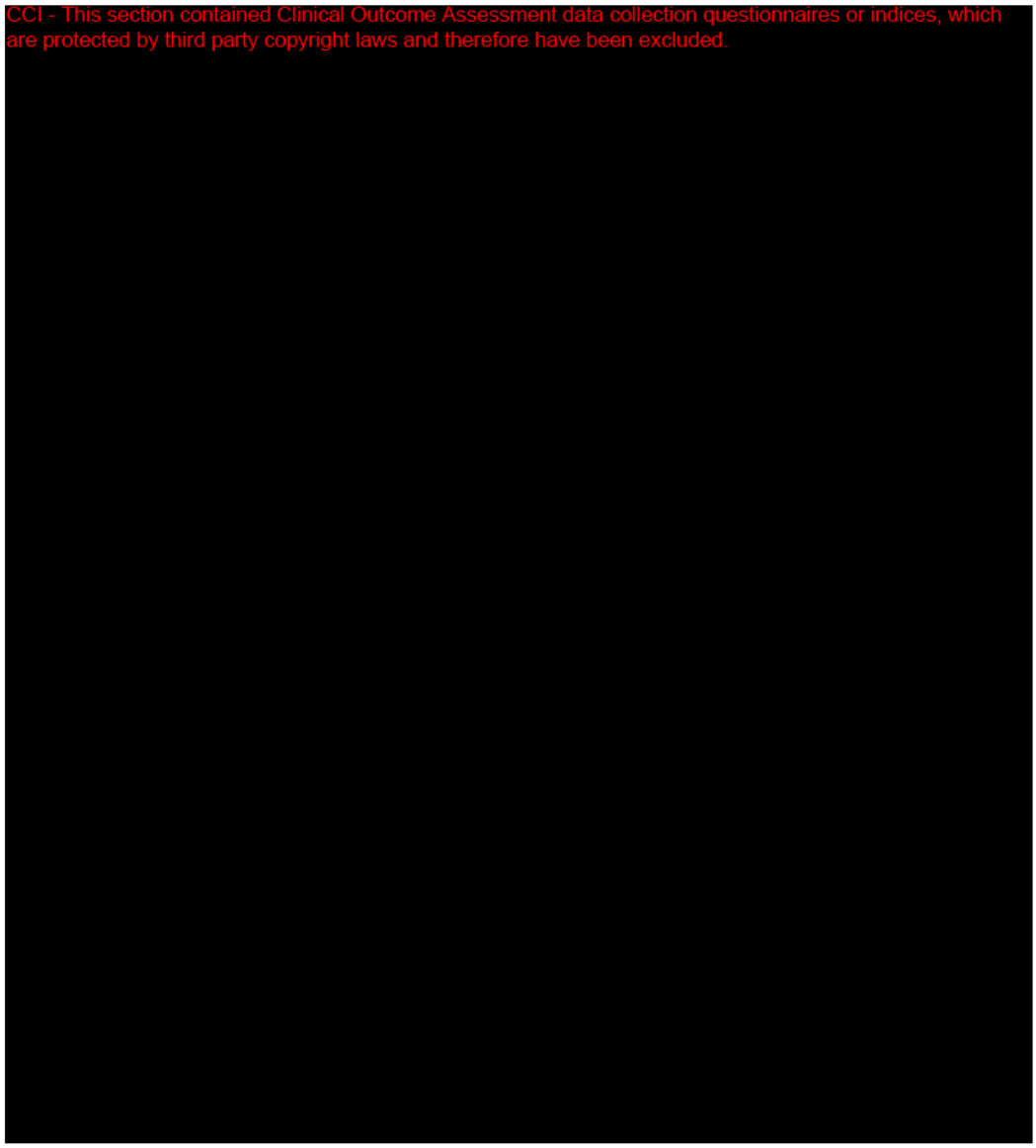
14.4. Appendix 4: Pain Assessment

Wong–Baker Faces Pain Rating Scale (page 1 of 1)



14.5. Appendix 5: RECIST 1.1

I. Efficacy Assessment

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Chung, 2010; Eisenhauer, 2009].

See the Time and Events Tables for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of ±14 days is permitted to allow for flexible scheduling.

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions, brain scan and bone scan. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required except for brain scan and bone scans. Brain and Bone scans should be performed as clinically indicated.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (e.g. evaluations must occur at each protocol scheduled timepoint regardless of unscheduled assessments).

A baseline bone scan is required for all subjects. For subjects without bone disease at baseline, subsequent bone scans should only be performed as clinically indicated (e.g. presentation of bone pain). For subjects with bone disease at baseline, a bone scan is required as clinically indicated. In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed within the timeframe of 1 week prior to the first of images showing CR to 4 weeks after the next protocol specified assessment.

A baseline brain scan is required for all subjects. For subjects without CNS disease at baseline, subsequent brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression). For subjects with CNS disease at baseline, a brain scan is required as clinically indicated. In addition, in order to confirm a CR in a subject with brain disease at baseline, a brain scan must be performed 1 week prior to the 1st set of images showing CR to 4 weeks after the next protocol specified assessment.

Ia. Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days of randomizations.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.

- Pathological lymph nodes with <15mm and but ≥10mm short axis are considered non measurable.
- Pathological lymph nodes with ≥15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, FDG-PET scans or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Ib. Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required

anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/callipers to measure the size of the lesion, is required. [Chung, 2010; Eisenhauer, 2009].

CT and MRI: Contrast enhanced CT with 5mm contiguous slices is recommended. 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. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Chung, 2010; Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Chung, 2010; Eisenhauer, 2009].

Brain Scan: Baseline brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Bone Scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (i.e.X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Ic. Follow-up Assessments for Subjects Permanently Discontinued from Study Treatment

Refer to Section 4.2.4.1 and the Time and Events Tables found in the protocol for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanently discontinue from study treatment

Id. Assessment of Subject Completion

If the last radiographic assessment was more than 8 weeks prior to withdrawal from study and progressive disease has not been documented, a disease assessment should be obtained at the time of withdrawal from study.

II. Guidelines for Evaluation of Disease

IIa. Measurable and Non-measurable Definitions

Measurable lesion:

A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥ 20 mm).
- ≥10 mm calliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Chung, 2010; Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.

III. Response Criteria

IIIa. 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 <10mm 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.

IIIb. 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 ≥ 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 timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

IIIc. 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.

IIId. Evaluation of overall response

The table below 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.

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.
- The dosing schedule, dosing interruptions and design (see Time and Events Tables) should be considered when assessing tumor response. Thus, subjects with PD before the Week 9 visit, but without rapid clinical deterioration, may continue planned dosing schedule to allow detection of antitumor response. It is recommended that subjects who experience investigator-determined PD at the Week 9 visit, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.
- During Part 1 or Part 2, is recommended that subjects who experience investigator-determined PD at any time, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.

IIIe. 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 investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 4 weeks.
- 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.

IIIf. Confirmation Criteria (recommended):

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

IIIg. Independent Review

Disease progression and response evaluations will be collected centrally during the study and may be reviewed or analyzed by an independent central reviewer. Details will be provided in the SPM.

14.6. Appendix 6: Response Criteria for Neuroblastoma

Response Criteria for Neuroblastoma Patients with Measurable Disease (using CT or MRI as per RECIST)

Follow standard RECIST criteria.

Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of 123I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

The following criteria will be used to report MIBG response:

Complete response: Complete resolution of all MIBG positive lesions

Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions

Stable disease: No change in MIBG scan in number of positive lesions

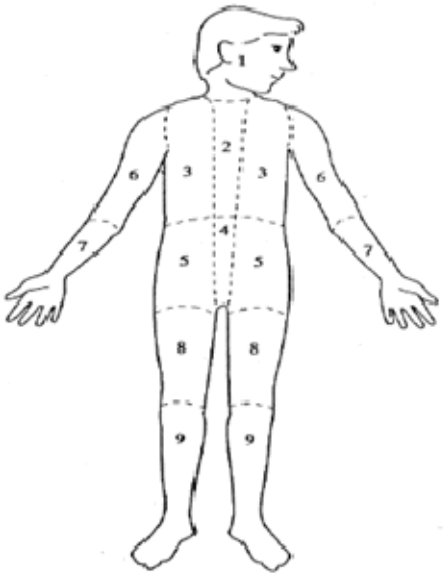
Progressive disease: Development of new MIBG positive lesions

The response of MIBG lesions will be assessed o using the Curie scale as outlined below.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan. In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. Complete response: all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a Complete Response.
2. Partial response: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. Stable disease: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. Progressive disease: New lesions on MIBG scan.

Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

Bone Marrow Involvement

Bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

14.7. Appendix 7: NYHA Functional Classification System for Heart Failure

The New York Heart Association (NYHA) Functional Classification [NYHA, 1994] provides a simple way of classifying the extent of heart failure. It places subjects in one of four 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.

14.8. Appendix 8: Country Specific Requirements

14.8.1. Investigational Product Label

14.8.2. Medical Devices Used in the Study

14.9. Appendix 9: Protocol Amendment Changes

AMENDMENT 1

Protocol Amendment 1 applies to all site(s) participating in the conduct of the study

Amendment 1 summary:

Amendment No.1: Amendment 1 applies to all study sites. Modifications include updated medical monitoring information due to a personnel change on the GSK team. In addition, the following review of the protocol by the FDA, the following changes are made: For Part 1, the starting dose of GSK525762 is reduced from 5 mg/day to 2 mg/day. Cardiac troponin T level assessments are required as a part of the inclusion criteria and thereafter. An observation of CTCAE Grade 2 drug related toxicity, including grade 2 troponin T elevation, in one subject will end accelerated dose titration in Part 1. Subjects with a history of gastrointestinal bleeding or active bleeding (positive guaiac fecal occult blood monitoring) will be excluded. In addition, wording for dose escalation decisions has been modified to state that no more than a 2-fold increase in dose will occur between successive cohorts. A staggered dosing approach will be implemented in the 3+3 dosing design to minimize potential for toxicity in multiple subjects. Alternative dosing regimens will not be implemented without consultation with FDA and a protocol amendment. For Part 2 of the trial, stopping rules based on lack of efficacy and the futility rule have been modified. Additionally the disease assessment scans may be reviewed retrospectively by an independent radiologist. Finally, multiple Time and Event Tables have been revised for consistency across Part 1 and Part 2 of the protocol.

List of Specific Changes

Rationale Change 1:

The sponsor and medical monitoring information has been updated based on internal GSK team personnel changes.

PREVIOUS TEXT, Section Sponsor/Medical Monitor Information

SPONSOR SIGNATORY:

Jamie Freeman, MD, PhD VP, Cancer Research, Early Development GlaxoSmithKline Oncology	**Date**

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD MD	PPD			GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4340 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD	PPD			709 Swedeland Road UW2230, King of Prussia, PA 19406-2711 USA PPD

REVISED TEXT, Section Sponsor/Medical Monitor Information

SPONSOR SIGNATORY:

Vijay G Peddareddigari, MD

Date

~~Jamie Freeman, MD, PhD~~
Associate Medical Director, ~~VP,~~
Cancer Epigenetics, Oncology Research & Development
~~Research, Early Development~~
GlaxoSmithKline Oncology

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD , MD	PPD			GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4340 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD ~~, MD, PhD~~ PPD , MD, PhD	PPD			~~709 Swedeland Road UW2230, King of Prussia, PA 19406-2711 USA~~ PPD GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 1-1450 Collegeville, PA 19426, USA PPD

Rationale Change 2:

Based on FDA recommendation, the starting dose of GSK525762 will be lowered from 5 mg to 2 mg once daily. This change reflects use of 0.3 mg/kg as the highest non-severe toxic dose (HNSTD) in the dog based on the effect on QT prolongation. ICH S9 guidelines now predict the dog as the most sensitive species and 1/6 HNSTD translates to a 1.7 mg starting dose in humans (assuming a 70 kg adult and adult surface area of 1.7 m^2). This calculated starting dose has been rounded to 2 mg.

PREVIOUS TEXT, Section Protocol Synopsis

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN: Starting dose will be 5 mg, orally (tablets), once a day.

REVISED TEXT, Section Protocol Synopsis

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN: Starting dose will be ~~5~~ 2 mg, orally (tablets), once a day.

PREVIOUS TEXT, Section 1.2.2.2 Starting dose

Based on tolerability, the HNSTD was defined as 1mg/kg in the dog. 1/6 dog HNSTD is 3.33 mg/m^2 which translates to a starting dose in man of 5.7 mg, assuming a 70 kg adult and adult surface area of 1.7 m^2.

REVISED TEXT, Section 1.2.2.2 Starting dose

Based on tolerability and QT prolongation ~~tolerability~~, the HNSTD was defined as 0.3~~1~~mg/kg in the dog. 1/6 dog HNSTD is 1~~3.33~~ mg/m^2 which translates to a starting dose in man of 1.7~~5.7~~ mg (rounded to a starting dose of 2 mg based on tablet strength), assuming a 70 kg adult and adult surface area of 1.7 m^2.

PREVIOUS TEXT. Section 1.2.2.2 Starting dose

Taking all four approaches into consideration, a starting dose of 5 mg is proposed. This dose will provide a suitable safety margin to the QTc prolongation observed on repeat dosing in the dog (given that a 10 mg clinical dose is equivalent to 6 mg/m^2, and has been shown to be equivalent to the QTc NOEL in the dog 4 week study).

REVISED TEXT, Section 1.2.2.2 Starting dose

Taking all four approaches into consideration, a starting dose of ~~5~~2 mg is proposed. This dose will provide a ~~suitable~~5-fold safety margin to the QTc prolongation observed on repeat dosing in the dog (given that a 10 mg clinical dose is equivalent to 6 mg/m^2, and has been shown to be equivalent to the HNSTD and QTc NOEL in the dog 4 week study).

PREVIOUS TEXT, Section 1.2.2.2 Starting Dose, Table 1

Table 1 Predicted Safety Cover for proposed 5mg starting dose (data from most sensitive NOAEL/NOEL from 4 week toxicology studies)

Clinical starting dose Dose (5 mg)	AUC (ng.hr/ml) 424	Free AUC (ng.hr/ml) 93	Cmax (ng/ml) 21	Free Cmax (ng/ml) 4.6
Cardiotoxicity				
QTc from single dose*	43.6x (NOEL)	51.6x (NOEL)	156.2x (NOEL)	184.6x (NOEL)
QTc on repeat dosing	1.8x (NOEL) 5.0x (LOEL)	2.2x (NOEL) 5.9x (LOEL)	5.1x (NOEL) 15.2x (LOEL)	6.0x (NOEL) 18.0x (LOEL)
Troponin	No cover		No cover	

Clinical starting dose Dose (5 mg)	AUC (ng.hr/ml) 424	Free AUC (ng.hr/ml) 93	Cmax (ng/ml) 21	Free Cmax (ng/ml) 4.6
Gastrointestinal toxicity				
In life changes	0.4x (NOAEL) 4.4x (LOAEL)		3.8x (NOAEL) 56.3x (LOAEL)	
Microscopic changes	5.0x (NOAEL) 21.0x (LOAEL)		15.2x (NOAEL) 62.4x (LOAEL)	
Haematopoietic toxicity	0.8x (NOAEL) 4.4x (LOAEL)		6.8x (NOAEL) 56.3x (LOAEL)	
Lymphoid toxicity	4.4x (NOAEL) 29.0x (LOAEL)		56.3x (NOAEL) 156.7x (LOAEL)	
Testicular toxicity	No cover		No cover	

NO(A)EL = No observed (adverse) effect level
LO(A)EL = Lowest observed (adverse) effect level
*Calculated from single dose GLP dog CV study

REVISED TEXT, Section 1.2.2.2 Starting Dose, Table 1

Table 1 Predicted Safety Cover for proposed 2~~5~~mg starting dose (data from most sensitive NOAEL/NOEL from 4 week toxicology studies)

Clinical starting dose **Dose** (2~~5~~ mg)	AUC (ng.hr/ml) 170~~424~~	Free AUC (ng.hr/ml) 37~~93~~	Cmax (ng/ml) 8.4~~21~~	Free Cmax (ng/ml) 1.85~~4.6~~
Cardiotoxicity				
QTc from single dose*	109.1~~43.6~~x (NOEL)	128.9~~51.6~~x (NOEL)	390.5~~156.2~~x (NOEL)	461.5~~184.6~~x (NOEL)
QTc on repeat dosing	4.6~~1.8~~x (NOEL) 12.4~~5.0~~x (LOEL)	5.4~~2.2~~x (NOEL) 14.74~~5.9~~x (LOEL)	12.7~~5.1~~x (NOEL) 38.0~~15.2~~x (LOEL)	15.0~~6.0~~x (NOEL) 45.0~~18.0~~x (LOEL)
Troponin	No cover		No cover	

Clinical starting dose **Dose** (25 mg)	AUC (ng.hr/ml) 170424	Free AUC (ng.hr/ml) 3793	Cmax (ng/ml) 8.421	Free Cmax (ng/ml) 1.854.6
Gastrointestinal toxicity				
In life changes	1.00.4x (NOAEL) 11.04.4x (LOAEL)		9.63.8x (NOAEL) 140.756.3x (LOAEL)	
Microscopic changes	12.45.0x (NOAEL) 52.521.0x (LOAEL)		38.015.2x (NOAEL) 156.062.4x (LOAEL)	
Hepatic toxicity (single rat)	11.0x (NOAEL) 72.5x (LOAEL)		140.7x (NOAEL) 391.7x (LOAEL)	
Hematopoietic toxicity	1.90.8x (NOAEL) 11.04.4x (LOAEL)		17.1 6.8x (NOAEL) 140.756.3x (LOAEL)	
Lymphoid toxicity	11.04.4x (NOAEL) 72.529.0x (LOAEL)		140.756.3x (NOAEL) 391.7156.7x (LOAEL)	
Hemolysis (rat specific)	11.0x (NOAEL) 72.5x (LOAEL)		140.7x (NOAEL) 391.7x (LOAEL)	
Clotting effects	12.4x (NOAEL) 52.5x (LOAEL)		38.0x (NOAEL) 156.0x (LOAEL)	
Pancreatic toxicity (male rat specific)	74.4x (NOAEL) 391.7x (LOAEL)		8.6x (NOAEL) 72.5x (LOAEL)	

Clinical starting dose **Dose** (25 mg)	AUC (ng.hr/ml) 170424	Free AUC (ng.hr/ml) 3793	Cmax (ng/ml) 8.421	Free Cmax (ng/ml) 1.854.6
Pulmonary effects (rat specific)	1.9x (NOEL) 11.0x (LOEL)		17.1x (NOEL) 140.7x (LOEL)	
Testicular toxicity	No cover		No cover	

NO(A)EL = No observed (adverse) effect level
LO(A)EL = Lowest observed (adverse) effect level
*Calculated from single dose GLP dog CV study

PREVIOUS TEXT, Section 1.3 Risk Assessment

Cardiovascular. Although there were minimal effects of GSK525762 on hERG current density or trafficking in HEK-293 cells or on ECG rhythms or arrhythmias in the ex vivo rabbit wedge assay, QT and QTc prolongation (maximum 41 milliseconds at 3 mg/kg for 12 days) was seen in dogs after a single oral dose of 30 mg/kg or repeat dosing at t 1 mg/kg/day in 4 week toxicology studies. Some evidence of adaptation was observed in the 4 week dog study. QTc prolongation observed at the early timepoints (Day 5-13) in dogs given 1 mg/kg had returned to baseline by the end of the study. No effect was seen in the dog at 0.3 mg/kg (6 mg/m^2) where exposure is estimated to be approximately equivalent to that achieved by a 10 mg dose in humans if 100% bioavailability is assumed. However, the proposed starting dose in this FTIH BET115521 study is 5 mg.

Reproductive:
Exposures associated with reproductive toxicity in male dogs overlap with the proposed 5 mg starting dose in this FTIH study.

REVISED TEXT, Section 1.3 Risk Assessment

Cardiovascular. Although there were minimal effects of GSK525762 on hERG current density or trafficking in HEK-293 cells or on ECG rhythms or arrhythmias in the ex vivo rabbit wedge assay, QT and QTc prolongation (maximum 41 milliseconds at 3 mg/kg for 12 days) was were seen in dogs after a single oral dose of 30 mg/kg or repeat dosing at ≥t 1 mg/kg/day (maximum increase was 41 milliseconds following 12 doses of 3 mg/kg/day) in 4 week toxicology studies. Some evidence of adaptation was observed in the 4 week dog study. QTc prolongation observed at the early timepoints (Day 5-13) in dogs given 1 mg/kg had returned to baseline by the end of the study. No effect was seen in the dog at 0.3 mg/kg (6 mg/m^2) where exposure is estimated to be approximately equivalent to that achieved by a 10 mg dose in humans if 100% bioavailability is assumed. HoweverThis represents a 5-fold safety margin over the proposed starting dose of 2 mg in this First Time in Human (FTIH) BET115521 study is 5 mg.

Reproductive:
Exposures associated with reproductive toxicity in male dogs overlap with the proposed 25 mg starting dose in this FTIH study.

PREVIOUS TEXT, Section 3.2.1.1, Accelerated Dose Titration

An accelerated dose titration schema with one subject per dose level will be used initially to minimize suboptimal drug exposures. Sequential subjects will follow an accelerated dose escalation as described in below (see Table 3). Accelerated dose titration will continue until DLT has occurred. This may occur with a doubling of dose until one of the subjects experiences a DLT or the second subject experiences a ≥ Grade 2 drug-related adverse event as determined by CTCAE v. 4.0 (Table 3). See Alternative dosing Section 3.2.1.4.

Table 3 Dose Escalation Procedures

Dose Level	**Change in Dose**
Dose Level -1	Lower doses may be used if Dose Level 1 is not tolerated. This may be achieved by reducing the dose or by alternate dosing (e.g. every other day)
Dose Level 1	Starting Dose at 5 mg once daily
Subsequent dose levels	Increase by ≤2-fold (one or fewer subjects with ≥ Grade 2 drug related toxicity AND no subjects with any DLTs in first 6 weeks of treatment)
End of Accelerated Titration Phase	Begin 3+3 Dose Escalation Phase (2 or more subjects with ≥ Grade 2 drug related toxicity or one or more subjects with DLT in first 6 weeks of treatment)

REVISED TEXT, Section 3.2.1.1, Accelerated Dose Titration

An accelerated dose titration schema with one subject per dose level will be used initially to minimize suboptimal drug exposures~~. Sequential subjects will follow an accelerated dose escalation as described in below~~. Accelerated dose titration will continue until a ≥ Grade 2 drug-related adverse event ~~or a DLT~~ is observed in one subject (see Table 3). This would end the accelerated dose escalation and would lead to the enrollment of a total of 3 subjects initially at this dose level. ~~This may occur with a doubling of dose until one of the subjects experiences a DLT or the second subject experiences a ≥ Grade 2 drug-related adverse event as determined by CTCAE v. 4.0 (Table 3). See Alternative dosing Section 3.2.1.6.~~ Subsequent subjects will follow a 3+3 dose escalation schema as described below (see Table 4). If no more than one DLT is observed in these 3 subjects then an additional 3 subjects will be added as described in Table 4 (3+3 Dose Escalation Decision Process). If two or more DLTs are observed at any dose level, the MTD will have been exceeded.

Table3. Accelerated Dose Escalation Procedures

Table 3 Dose Escalation Procedures

Dose Level	**Change in Dose**
Dose Level -1	Lower doses may be used if Dose Level 1 is not tolerated. This may be achieved by reducing the dose or by alternate dosing (e.g. every other day)
Dose Level 1	Starting Dose at 2~~5~~ mg once daily
Subsequent dose levels	Increase by ≤2-fold (~~one or fewer subjects with~~ No subjects with ≥ Grade 2 drug related toxicity AND no subjects with any DLTs in first 6 weeks of treatment)
End of Accelerated Titration Phase	Begin 3+3 Dose Escalation Phase (~~2 or more subjects with~~ 1 subject with any ≥ Grade 2 drug related toxicity ~~or one or more subjects with DLT~~ in the first 6 weeks of treatment)

Rationale Change 3

Eligibility for the BET115521 study will be restricted to subjects with NMC. Additional tumor types may be added in future protocol amendments based on scientific rationale and emerging preclinical data coupled with the emerging safety profile developed within the NMC population in the BET115521 study.

PREVIOUS TEXT, Section 3.2.1, Part 1 Single Dose and Repeat Dose Escalation in NMC

Additional tumor types may be added to Part 1 cohort based on emerging and compelling preclinical efficacy data and acceptable clinical safety data from the ongoing study (approval is required by Sponsor and subject to approval by GSK Global Safety Board).

REVISED TEXT, Section 3.2.1, Part 1 Single Dose and Repeat Dose Escalation in NMC

~~Additional tumor types may be added to Part 1 cohort based on emerging and compelling preclinical efficacy data and acceptable clinical safety data from the ongoing study (approval is required by Sponsor and subject to approval by GSK Global Safety Board).~~

PREVIOUS TEXT, Section 3.2.4, Part 2 Expansion Cohort(s)

Additional tumor types may be added to Part 2 cohort expansion based on emerging and compelling preclinical efficacy data and acceptable clinical safety data from the ongoing study (approval is required by Sponsor and subject to approval by GSK Global Safety Board).

REVISED TEXT, Section 3.2.4, Part 2 Expansion Cohort(s)

~~Additional tumor types may be added to Part 2 cohort expansion based on emerging and compelling preclinical efficacy data and acceptable clinical safety data from the ongoing study (approval is required by Sponsor and subject to approval by GSK Global Safety Board).~~

PREVIOUS TEXT, Section 4.2.1 Inclusion Criteria

3. Diagnosis of NUT Midline Carcinoma (based on IHC or FISH) for NUT fusion protein or transcript (irrespective of the NUT fusion partner). Subjects may be treatment naïve or have had prior therapy.

Additional tumor types may be added to the dose escalation Part 1 and tested in Part 2 cohort expansion based on emerging and compelling preclinical efficacy data and acceptable clinical safety data from the ongoing study (approval is required by Sponsor and subject to approval by GSK Global Safety Board).

REVISED TEXT, Section 4.2.1 Inclusion Criteria

3. Diagnosis of NUT Midline Carcinoma based on IHC or FISH) for NUT fusion protein or transcript (irrespective of the NUT fusion partner). Subjects may be treatment naïve or have had prior therapy.

~~Additional tumor types may be added to the dose escalation Part 1 and tested in Part 2 cohort expansion based on emerging and compelling preclinical efficacy data and acceptable clinical safety data from the ongoing study (approval is required by Sponsor and subject to approval by GSK Global Safety Board).~~

Rationale Change 4

A dose escalation schema has been included to describe Accelerated Dose escalation transition to a traditional 3+3 design. In addition, a staggered dosing approach will be implemented to minimize the risk of exceeding the maximum tolerated dose in multiple subjects. New wording has been added that any alternative dosing regimens will not be implemented without consultation with FDA and a protocol amendment. Finally, the timing of intra-subject dose escalation has been modified to lengthen the time period before a subject can dose escalate.

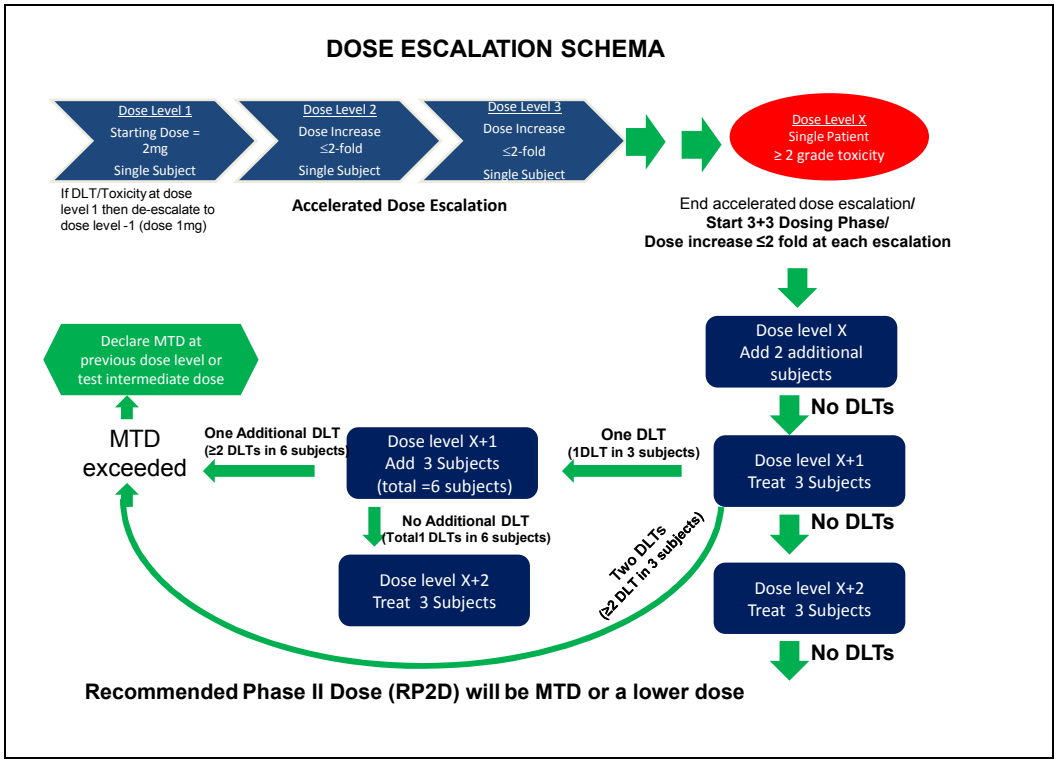
PREVIOUS TEXT, Section 3.2.1.1 Accelerated Dose Titration

3+3 Dose Escalation Decision Process

Number of subjects at given dose level with DLT	Action
0 out of 3 subjects	Escalate to next dose level
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	Escalate to the next dose level (Increase by ≤2-fold)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort. This will be the start of Part 2 where Cohorts may dose up to 20 subjects.

NEW TEXT, Section 3.2.1.1 Accelerated Dose Titration

Figure 2 Dose Escalation Schema



PREVIOUS TEXT, Section 3.2.1.2 Dose Escalation Rules (3+3 Design)

A standard 3+3 design will be implemented when one of the subject experiences a DLT or two or more of the subjects in the Accelerated Dose Escalation experience a ≥ Grade 2 drug related adverse event as determined by CTCAE v. 4.0 as illustrated in Table 3. At this point, two additional subjects will be added to this dosing level for a total of at least 3

subjects at this dosing level. If no more than one subject experiences a DLT from among these 3 subjects, then this dosing level cohort will expand to a total of 6 subjects. If two subjects experience a DLT while the cohort is expanding (recruiting), then no additional subjects would enter the cohort. Dose escalation decisions as shown in Dose Escalation Decision Process

Once a standard 3+3 dose escalation design is implemented the subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects.

As noted in Table 4, the escalation to the next dose level will not increase greater than 2 fold from the previous dose level.

Table 4. Once MTD or biologically active dose (example: clinical response) is reached, additional cohorts may be explored with a lower dose or alternative dosing schedules to optimize the pharmacokinetic, safety and tolerability profile (see Section 3.2.1.5).

REVISION TEXT, Section 3.2.1.2 Dose Escalation Rules (3+3 Design)

A standard 3+3 design will be implemented when one ~~of the~~ subject experiences ~~a DLT or two or more of the subjects in the Accelerated Dose Escalation experience~~ a ≥ Grade 2 drug related adverse event in the Accelerated Dose Escalation as determined by CTCAE v. 4.0 as illustrated in Table 3 or a DLT as illustrated in Table 3. ~~At this point, two additional subjects will be added to this dosing level for a total of at least 3 subjects at this dosing level. If no more than one subject experiences a DLT from among these 3 subjects, then this dosing level cohort will expand to a total of 6 subjects. If two subjects experience a DLT while the cohort is expanding (recruiting), then no additional subjects would enter the cohort. Dose escalation decisions as shown in Dose Escalation~~ Decision Process

Once a standard 3+3 dose escalation design is implemented the subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects.

As noted in Table 4, the escalation to the next dose level will not increase greater than 2 fold from the previous dose level.

Table 4~~. Once MTD or biologically active dose (example: clinical response) is reached, additional cohorts may be explored with a lower dose or alternative dosing schedules to optimize the pharmacokinetic, safety and tolerability profile (see Section 3.2.1.5).~~At this point, two additional subjects will be added to this dosing level for a total of at least 3 subjects at this dosing level, if no DLT are observed in any of the 3 patients then the dosing will proceed to the next higher dose level (≤ 2 fold increase in dose). If no more than one subject experiences a DLT from among these 3 subjects, then this dosing level cohort will expand to a total of 6 subjects. If two subjects experience a DLT while the cohort is expanding (recruiting), then no additional subjects would enter the cohort. Dose escalation decisions as shown in Table 4. Once MTD or biologically active dose (example: clinical response) is reached, additional cohorts may be explored with a lower dose or alternative dosing schedules to optimize the pharmacokinetic, safety and tolerability profile (see Section 3.2.1.5).

NEW TEXT, Section 3.2.1.4 Dose Escalation Decision Process

Once a standard 3+3 dose escalation design is implemented the subjects will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the maximum tolerated dose in multiple subjects.

As noted in Table 4, the escalation to the next dose level will not increase greater than 2 fold from the previous dose level.

Table 4. 3+3 Dose Escalation Decision Process

Number of subjects at given dose level with DLT	**Action**
0 out of 3 subjects	Escalate to next dose level
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	Escalate to the next dose level (Increase by ≤2-fold)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort. ~~This will be the start of Part 2 where Cohorts may dose up to 20 subjects.~~

NEW TEXT, 3.2.1.5 Alteration of Schedule

Alternative dosing regimens may be implemented after a protocol amendment.

PREVIOUS TEXT, 3.2.1.6 Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that:

- The subject has not experienced any Grade 2 or higher drug related toxicity during the first 5 weeks of investigational therapy.

REVISED TEXT, 3.2.1.6 Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that:

- The subject has not experienced any Grade 2 or higher drug related toxicity during the first 6 ~~5~~ weeks of investigational therapy.

Rationale Change 5

CTCAE grade 2 drug related toxicity including grade 2 cardiac troponin T elevation in one subject would end the Accelerated Dose Escalation phase.

PREVIOUS TEXT, Section 3.1, Study Design/Schematic

- An accelerated dose titration will be employed with one subject per dose level until the first instance of a dose limiting toxicity (DLT) or a second instance of Grade 2 toxicity occurs. Thereafter, subjects will be enrolled in a standard 3+3 design. The frequency and schedule of dosing may be adjusted based on emerging safety and PK data.

REVISED TEXT, Section 3.1, Study Design/Schematic

- An accelerated dose titration will be employed with one subject per dose level until the first instance of a ~~dose limiting toxicity (DLT) or a second instance of~~ Grade 2 drug related toxicity occurs. Thereafter, subjects will be enrolled in a standard 3+3 design. ~~. The frequency and schedule of dosing may be adjusted based on emerging safety and PK data.~~

Rationale Change 6

Troponin T assessment will be required in the inclusion criteria and for dose limiting toxicity (DLT) determination. At some sites, troponin T is not available and a central laboratory has been established. Therefore, troponin (I or T) checked locally and troponin T levels will be analyzed centrally to provide consistent monitoring of troponin T across the study. This will allow the sites a real-time monitoring for cardiac toxicity and provide consistent monitoring of troponin T across the study. In addition, the dose limiting toxicity definition has been clarified to exclude fatigue and mucosis which are common non-drug related events associated with disease.

PREVIOUS TEXT, Section 3.2.2. Dose Limiting Toxicity (DLT)

- Drug related Grade 3 or 4 non-hematologic toxicity (including QTc) as described in the Common Terminology Criteria for Adverse Events v 4.0 (excluding abnormalities of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (see criteria below). In addition, the DLT exceptions include: rash, diarrhea, nausea, and vomiting that do respond to standard medical care within 72 hours or for electrolyte disturbances within 24 hours).
- Troponin (I or T) > institutional ULN and > 10% coefficient of variance (CV) for the assay, measured on two separate occasion within 24 hours in order to confirm elevation, and with other clinical signs, symptoms, laboratory tests consistent with cardiac toxicity.

REVISED TEXT, Section 3.2.2. Dose Limiting Toxicity (DLT)

- Drug related Grade 3 or 4 non-hematologic toxicity (including QTc) as described in the Common Terminology Criteria for Adverse Events v 4.0 (excluding abnormalities of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (see criteria below). In addition, the DLT exceptions include: rash, fatigue, mucosis, diarrhea, nausea, and vomiting that do respond to standard medical care within 72 hours or for electrolyte disturbances within 24 hours).

- ~~Troponin (I or T) > institutional ULN and > 10% coefficient of variance (CV) for the assay, measured on two separate occasion within 24 hours in order to confirm elevation, and with other clinical signs, symptoms, laboratory tests consistent with cardiac toxicity.~~ Grade 2 Troponin T elevation (central laboratory >ULN), measured on two separate occasions within 48 hours in order to confirm elevation and with other clinical signs, symptoms, laboratory tests consistent with cardiac toxicity. (In the event a troponin T (central laboratory assessment) is not performed or a laboratory error occurs, considerations for a DLT criteria will involve review of two separate local troponin (I or T) assays done with in 48 hours at a local investigator site. Troponin I or T elevations greater than the upper limit of normal, and > 10% coefficient of variance (CV) for that assay will be considered as a grade 2 elevation).

Rationale Change 7

The inclusion and exclusion criteria have been clarified to address Troponin assessments for Troponin T only. In addition, additional clarifications regarding bleeding criteria have been modified. The HbA1C has been clarified to apply to Part 1and Part 2. Subjects with a history of or active gastrointestinal bleeding will be excluded from the study.

- **NEW TEXT, Abbreviations**

EIAC	Enzyme-inducing anticonvulsant
HbA1C	hemoglobin A1C

PREVIOUS TEXT, Section 4.2.1, Inclusion Criteria

5. All prior treatment- related toxicities must be CTCAE (Version 4.0) ≤ Grade 1 (except alopecia) at the time of treatment allocation [NCI-CTCAE, 2009], **and** stable for 4 weeks or longer at the time of screening evaluation.

7. Adequate organ function as defined in Table 5.

Table 5 Definitions for Adequate Organ Function

System	Laboratory Values
Metabolic	
Fasting Serum Glucose	<126 mg/dL
Cardiac	
Ejection fraction	≥ LLN by ECHO (minimum of 50%)
Troponin (I or T)	≤ULN
Potassium	≥LLN and ≤ULN
Magnesium	≥LLN

REVISED TEXT, Section 4.2.1, Inclusion Criteria

5. All prior treatment- related toxicities must be CTCAE (Version 4.0) ≤ Grade 1 (except alopecia) at the time of treatment allocation [NCI-CTCAE, 2009]~~, **and** stable for 4 weeks or longer at the time of screening evaluation~~.

7. Adequate organ function as defined in Table 5.

Table 5 Definitions for Adequate Organ Function

System	Laboratory Values
Metabolic	
Fasting Serum Glucose	<126 mg/dL
HbA1C	normal
Cardiac	
Ejection fraction	≥ LLN by ECHO (minimum of 50%)
Troponin (I or T)	≤ULN
Potassium	≥LLN and ≤ULN
Magnesium	≥LLN
Gastrointestinal	
Guaiac fecal occult blood test	Negative

PREVIOUS TEXT, Section 4.2.2. Exclusion Criteria

6. Symptomatic or untreated 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 >1months months, 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 patient treated with gamma knife the can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications/stable. In addition, subjects treated or currently taken EIAC are allowed on study.

7. **Part 1**: Based on normal HbA1C subjects would be allowed study entry.

9. Any of the following ECG findings:

- Baseline QTcF interval ≥450 msec
- Any clinically significant ECG assessments should be reviewed prior to study entry.

11. Pulmonary hemoptysis > 1 teaspoon in 24 hours within the last 14 days.

REVISED and NEW TEXT, Section 4.2.2. Exclusion Criteria

6. Symptomatic or untreated 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~~months~~ months, 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 patient treated with gamma knife the can be enrolled 2 weeks post-procedure as long as there are no post-procedure complications/stable. In addition, subjects treated or currently tak~~en~~ing enzyme-inducing anticonvulsant (EIAC) are allowed on study.

~~7. **Part 1**: Based on normal HbA1C subjects would be allowed study entry.~~

9. Any of the following EKG findings:

- Baseline QTcF interval ≥450 msec
- Any clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.

10 ~~11~~. Pulmonary hemoptysis > 1 teaspoon in 24 hours within the last 28 ~~14~~ days.

11. History of major gastrointestinal bleeding within the last 6 months. Any evidence of active gastrointestinal bleeding. (positive guaiac fecal occult blood test) excludes the subject.

Rationale Change 8

The Time and Events tables are modified to ensure consistency of timings and to correct errors that occurred during publishing. In addition, guaiac fecal occult blood testing has been added to the assessments to check for any evidence of gastrointestinal bleeding.

Section 5.0, Time and Events

PREVIOUS TEXT, Table 6: Part 1 – Baseline through Week 6

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																				
Assessments for **Baseline to Week 7**	**Screen[1]**	**W 1, D1**	**W 1, D2**	**W2, D1**	**W 2, D2**	**W2, D3**	**W2, D4 and D5**	**W 3, D 1**	**W 3, D2**	**W 3, D3**	**W 3, D4**	**W 3 , D 5**	**W 3, D6 and D7**	**W 4, D1**	**W 4 , D 2**	**W 4, D3**	**W 4 , D 4**	**W4, D5**	**W 4 , D 6**	**W 4, D 7**	**W 5 , D 1**	**W 6 , D 1**
Females: Pregnancy Test [2] Males: Testosterone [2]	X	X												X								X
Vital Signs (BP, T, Heart Rate, Resp)	X	X	X	X			X	X				X		X						X	X	X
Height and Weight [4]	X	X		X										X						X	X	X
Hematology, Clinical Chemistry, Pancreatic, Coagulation	X	X	X	X			X	X				X		X						X	X	X
Creatine phosphokinase	X	X	X				X					X								X	X	X
Fasting Blood Glucose;c-peptide; Insulin; and 1,5AG [5]	X	X	X	X			X	X				X		X						X	X	X
Fasting Lipid Panel, hA1C	X	X	X	X			X	X				X		X						X	X	X
Urinalysis	X	X		X				X						X							X	X
Thyroid monitoring [6]	X	X		X				X						X							X	X

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																				
Assessments for **Baseline to Week 7**	**Screen[1]**	**W 1, D1**	**W 1, D2**	**W2, D1**	**W 2,** **D2**	**W2, D3**	**W2, D4 and D5**	**W 3, D 1**	**W 3, D2**	**W 3, D3**	**W 3, D4**	**W 3 , D 5**	**W 3, D6 an d D7**	**W 4, D1**	**W 4 , D 2**	**W 4, D3**	**W 4 , D 4**	**W4, D5**	**W 4 , D 6**	**W 4, D 7**	**W 5 , D 1**	**W 6 , D 1**
HBsAg and hepatitis C antibody[7]	X																				X	X
ECHO	X												X									
Troponin and NT-proBNP [9]	X	X[8]	X[8]				X						X							X	X	X
CK and CK-MB (12-18 hrs post dose and as clinically indicated)		X																				
12-lead ECG [10,11]	X	X	X	X	X[10]	X	X	X	X[10]	X	X[10]	X	X	X	X[10]	X	X[10]	X[10]	X	X	X	X
Telemetry [10] (starts at least 60mins pre-dose and capture at least 48hrs post-dose)	X	48 hrs [9]																				
Response [16]	X																					
PK Blood Sampling (See Table 9)		X	X	X															X	X	X	

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																				
Assessments for **Baseline to Week 7**	**Screen[1]**	**W 1, D1**	**W 1, D2**	**W2, D1**	**W 2,** **D2**	**W2, D3**	**W2, D4 and D5**	**W 3, D 1**	**W 3, D2**	**W 3, D3**	**W 3, D4**	**W 3 , D 5**	**W 3, D6** **an d D7**	**W 4, D1**	**W 4 , D 2**	**W 4, D3**	**W 4 , D 4**	**W4, D5**	**W 4 , D 6**	**W 4, D 7**	**W 5 , D 1**	**W 6 , D 1**
PK Urine Sampling (See Table 11)		X	X	X															X	X	X	
LPS Blood sample (See Table 10)		X																				
Plasma Sample for Protein Biomarkers (See Table 10)	X	X	X	X			X	X					X	X						X		
PD Whole Blood sampling (mRNA sampling) (See Table 10)	X	X																				

Footnote 9: Troponin will be performed at the local (troponin I or T) and central lab (troponin I). Note, on Day 1 and Day 2 only the local lab assessments for troponin will be collected three times in 24 hours. Central lab assessments for troponin will only collected once on Day 1 and Day 2. Any unscheduled troponin assessments will be collected in duplicate for central and local assessments.

Footnote 11. W2 D2, W3 D2, W3 D4, W4 D2, W4 D4, W4 D5 are optional but if there is >30msec increase in QTcF the optional ECG days going forward become mandatory. On days when timing of ECGs are not specified in the Table 9 (Example: W2 D3, W3 D5, W4 D7) these assessments should be taken prior to dosing.

Footnote 12. Drug dispensing: From Day 1 to Wk 6, subjects may be dispensed drug at the clinic or provided drug for home dosing. The drug should be ingested in the morning at 8am ± 2 hours.

REVISED TEXT, Table 6 Time and Events: Part 1 – Baseline to Week 6

Table 6 Time and Events: Part 1 – Baseline to Week 6 ~~7~~(Continued)

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																				
Assessments for Baseline to Week 7	**Screen[1]**	**W1, D1**	**W1, D2**	**W1, D3**	**W2, D1**	**W2, D2**	**W2, D3**	**W2, D4 and D5**	**W3, D1**	**W3, D2**	**W3, D3**	**W3, D4**	**W3, D5**	**W3, D6 and D7**	**W4, D1**	**W4, D2**	**W4, D3**	**W4, D4**	**W4, D5**	**W4, D6**	**W4, D7**	**W5, D1**	**W6, D1**
Females: Pregnancy Test [2] Males: Testosterone [2]	X	X													X								~~X~~
Vital Signs (BP, T, Heart Rate, Resp) and Pain Assessment	X	X	X		X			X	X				X		X					X	~~X~~	X	X
Height and Weight [4]	X	X			X										X					X	~~X~~	X	~~X~~
Hematology, Clinical Chemistry, Pancreatic, Coagulation	X	X	X		X			X	X				X		X					X	~~X~~	X	~~X~~
Creatine phosphokinase	X	X	X					X					X							X	~~X~~	X	~~X~~
Fasting Blood Glucose;c-peptide; Insulin; and 1,5AG [5]	X	X	X		X			X	X				X		X					X	~~X~~	X	~~X~~

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																				
Assessments for Baseline to Week 7	**Screen[1]**	**W1, D1**	**W1, D2**	**W1, D3**	**W2, D1**	**W2, D2**	**W2, D3**	**W2, D4 and D5**	**W3, D1**	**W3, D2**	**W3, D3**	**W3, D4**	**W3, D5**	**W3, D6 and D7**	**W4, D1**	**W4, D2**	**W4, D3**	**W4, D4**	**W4, D5**	**W4, D6**	**W4, D7**	**W5, D1**	**W6, D1**
Fasting Lipid Panel~~, hA1C~~	X	X	X		X			X	X				X		X					X	~~X~~	X	~~X~~
hA1C	X	X																					
Guaiac fecal occult blood test	X														X								
Urinalysis	X	X			~~X~~				~~X~~						~~X~~							~~X~~	~~X~~
Thyroid monitoring [6]	X	X			X				X						X							~~X~~	~~X~~
HBsAg and hepatitis C antibody[7]	X																					~~X~~	~~X~~
ECHO	X													~~X~~	X								
Troponin and NT-proBNP [9]	X	X[8,9]	X[8,9]					X						~~X~~	X					X	~~X~~	X	X
CK and CK-MB (12-18 hrs post dose and as clinically indicated)		X																					

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																					
Assessments for Baseline to Week 7	**Screen[1]**	**W1, D1**	**W1, D2**	**W1, D3**	**W2, D1**	**W2, D2**	**W2, D3**	**W2, D4 and D5**	**W3, D1**	**W3, D2**	**W3, D3**	**W3, D4**	**W3, D5**	**W3, D6 and D7**	**W4, D1**	**W4, D2**	**W4, D3**	**W4, D4**	**W4, D5**	**W4, D6**	**W4, D7**	**W5, D1**	**W6, D1**
~~12-lead ECG [10,11]~~	~~X~~	~~X~~	~~X~~		~~X~~	~~X[10]~~	~~X~~	~~X~~	~~X~~	~~X [10]~~	~~X~~	~~X [10]~~	~~X~~	~~X~~		~~X [10]~~	~~X~~	~~X [10]~~	~~X[10]~~	~~X~~	~~X~~	~~X~~	~~X~~
Triplet ECGs at pre-treatment[10]	**X[10]**		**X[10]**	**X**	**X**	X[11]	**X**	**X**	**X**	**X**	X [11]	**X**	**X**	**X**	**X**	X [11]	**X**	X [11]	X[11]	**X**	**X**	**X**	**X**
Primary PK day Triplet ECGs (see Table 9 for more details, ECG timings pre-treatment, 0.5hr, 1hr, 2hr, 4hr, 8hr) [11]		**X**																					
Telemetry [10] (starts at least 60mins pre-dose and capture at least 48hrs post-dose)	X	48 hr~~[9]~~ [10]																					
~~Response [16]~~	~~X~~																						

Time and Events: Table 6		**Part 1 – Baseline through Week 6**																						
Assessments for **Baseline to Week 7**	**Screen[1]**	**W1, D1**	**W1, D2**	**W1, D3**		**W2, D1**	**W2, D2**	**W2, D3**	**W2, D4 and D5**	**W3, D1**	**W3, D2**	**W3, D3**	**W3, D4**	**W3, D5**	**W3, D6 and D7**	**W4, D1**	**W4, D2**	**W4, D3**	**W4, D4**	**W4, D5**	**W4, D6**	**W4, D7**	**W5, D1**	**W6, D1**
PK Blood Sampling (See Table ~~8~~ 9)		X		X	X	~~X~~															X	X	X	
PK Urine Sampling (See Table ~~10~~ 11)		X		~~X~~		~~X~~															X	~~X~~	~~X~~	
LPS Blood sample (See Table ~~10~~ 9)		X		X																	X	X	X	
Plasma Sample for Protein Biomarkers (See Table ~~10~~ 9)	X	X		X	X	X			X	X					X	X					~~X~~	X	X	
PD Whole Blood sampling (mRNA sampling) (See Table ~~10~~ 9)	X	X		X	X																			

Footnote 9. Troponin will be performed at the local (troponin I or T) and central lab (troponin ~~I~~T). Note, on Day 1 and Day 2 only the local lab assessments for troponin will be collected three times in 24 hours. Central lab assessments for troponin will only collected once on Day 1 and Day 2. Any unscheduled troponin assessments will be collected in duplicate for central and local assessments.

Footnote 11. W2 D2, W3 D2, W3 D4, W4 D2, W4 D4, W4 D5 are optional ~~but if~~ unless there is a >30msec increase in QTcF in which case the optional ECG days going forward become mandatory. ~~On days when timing of ECGs are not specified in the~~ See Table 9 for more specific details on timing of ECGs on PK sampling days. ~~(Example: W2 D3, W3 D5, W4 D7) these assessments should be taken prior to dosing.~~

Footnote 12. Drug dispensing: From Day 1 to Wk 6, subjects may be dispensed drug at the clinic or provided drug for home dosing. The drug should be ingested in the morning at approximately the same time everyday. ~~8am ± 2 hours~~. Subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects should fast for an additional two hours.

PREVIOUS TEXT, Time and Events: Table 7 Part 1 – Week 8 until End-of-Study

Time and Events: Table 7	**Week 10 to Week 48**										**Monthly Visit**	**Every other month**	**Every three months [1]**			
Part 1: **Assessments for** **Week 8 until End of study**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20,** **D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36,D1**	**W40,D1**	**W44,D1**	**Wk 48 onward** **Every 4 weeks Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 8weeks** **Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 12weeks** **Until** **Discharge/ progression [1]**	**Discharge / progression[2]**	**Follow-up [14]**	**End**
SAFETY																
Females: Pregnancy Test (serum or urine)	X	X	X	X	X	X	X	X	X	X	X			X		
Males: Testosterone (free)	X	X	X	X	X	X	X	X	X	X	X			X		
Physical Examination [3]	X	X	X	X	X	X	X	X	X	X	X			X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Week 10 to Week 48**										**Monthly Visit**	**Every other month**	**Every three months [1]**			
Part 1: **Assessments for** **Week 8 until End of study**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20,** **D1**	**W24,** **D1**	**W28,** **D1**	**W32,** **D1**	**W36,D1**	**W40,D1**	**W44,D1**	**Wk 48 onward** **Every 4 weeks Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 8weeks** **Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 12weeks** **Until** **Discharge/ progression [1]**	**Discharge / progression[2]**	**Follow-up [14]**	**End**
Vital Signs (BP, HR, T)	X	X	X	X	X	X	X	X	X	X	X			X		
Weight	X	X	X	X	X	X	X	X	X	X	X			X		
Hematology/Clinical Chemistry, Pancreatic	X	X	X	X	X	X	X	X	X	X	X			X		
Cytokine Samples	As clinically appropriate															
Coagulation	X	X	X	X	X	X	X	X	X	X		X		X		
Fasting Blood Glucose [4]	X	X	X	X	X	X	X	X	X	X	X			X		
Insulin and 1,5 AG [5]	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Week 10 to Week 48**										**Monthly Visit**	**Every other month**	**Every three months [1]**			
Part 1: **Assessments for** **Week 8 until End of study**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20,** **D1**	**W24,** **D1**	**W28,** **D1**	**W32,** **D1**	**W36,D1**	**W40,D1**	**W44,D1**	**Wk 48 onward** **Every 4 weeks Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 8weeks** **Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 12weeks** **Until** **Discharge/ progression [1]**	**Discharge / progression [2]**	**Follow-up [14]**	**End**
Fasting Lipid Panel, hA1C	X	X	X	X	X	X	X	X	X	X		X		X		
Thyroid monitoring [6]	X			X			X			X			X	X		
Urinalysis	X			X			X			X		X		X		
CARDIOTOXICITY MONITORING																
ECHO	X	X		X		X		X		X		X				
Troponin and NT-proBNP [8]	X	X		X		X		X		X		X				
12-lead ECG	X	X		X		X		X		X		X				

Time and Events: Table 7	**Week 10 to Week 48**										**Monthly Visit**	**Every other month**	**Every three months [1]**			
Part 1: **Assessments for** **Week 8 until End of study**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20,** **D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36,D1**	**W40,D1**	**W44,D1**	**Wk 48 onward** **Every 4 weeks Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 8weeks** **Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 12weeks** **Until** **Discharge/ progression [1]**	**Discharge / progression[2]**	**Follow-up [14]**	**End**
Holter Monitoring and telemetry	As clinically indicated															
STUDY DRUGS																
Dispense study drugs, assess compliance	X	X	X	X	X	X	X	X	X	X	X					
PK SAMPLING																
PK Blood Sampling (See Table 9)	X															
PK Urine Sampling (See Table 11)	X															

Time and Events: Table 7	**Week 10 to Week 48**										**Monthly Visit**	**Every other month**	**Every three months [1]**			
Part 1: **Assessments for** **Week 8 until End of study**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20,** **D1**	**W24,** **D1**	**W28,** **D1**	**W32,** **D1**	**W36,D1**	**W40,D1**	**W44,D1**	**Wk 48 onward** **Every 4 weeks Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 8weeks** **Until** **Discharge/ progression [1]**	**Wk 48 onward** **Every 12weeks** **Until** **Discharge/ progression [1]**	**Discharge / progression [2]**	**Follow-up [14]**	**End**
PD BLOOD SAMPLING																
LPS Blood sample																
Plasma Sample for Protein Biomarkers	X	X		X		X		X		X				X		
PD Whole Blood sampling (mRNA sampling)														X		

REVISED TEXT, Time and Events: Table 7 Part 1 – Week 7~~10~~ until End-of-Study

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Females: Pregnancy Test (serum or urine)	X	X	X	X	X	X	X	X	X	X	X	X			X		
Males: Testosterone (free)	X	X	X	X	X	X	X	X	X	X	X	X			X		
Physical Examination [3]	X	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X			X		
Vital Signs (BP, HR, T, Resp) and Pain Assessment	X	X	X	X	X	X	X	X	X	X	X	X			X		
Weight	X	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Hematology/Clinical Chemistry, Pancreatic	X	X	X	X	X	X	X	X	X	X	X	X			X		
Cytokine Samples	X	As clinically appropriate															
Guaiac fecal occult blood test	X		X		X	As clinically appropriate											

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Coagulation and Creatine phosphokinase	X	X	X	X	X	X	X	X	X	X	X		X		X		
Fasting Blood Glucose [4]	X	X	X	X	X	X	X	X	X	X	X	X			X		
C-peptide, Insulin and 1,5 AG [5]	X	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7, D1**	**W8, D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~ Every 4 weeks Until Discharge/ progression [1]**	**~~Wk 48 onward~~ Every 8weeks Until Discharge/ progression [1]**	**~~Wk 48 onward~~ Every 12weeks Until Discharge/ progression [1]**			
Fasting Lipid Panel~~, hA1C~~	X	~~X~~	X	X	X	X	X	X	X	X	X		X		X		
hA1C	X		X		X		X		X		X		X		X		
Thyroid monitoring [6]	X	~~X~~	X		X			X			X		~~X~~	X	X		
Urinalysis	X	X			X			X			X		X		X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
CARDIOTOXICITY MONITORING																	
ECHO	X	X	X		X		X		X		X		X		X		
Troponin and NT-proBNP [8]	X	X	X		X		X		X		X		X		X		
Triplet ECGs at pre-treatment	X		X	X	X	X	X	X	X	X	X		X		X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Primary PK day Triplet ECGs (see Table 9 for more details, ECG timing pre-treatment, 0.5hr, 1hr, 2hr, 4hr, 8hr)		X															

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
~~12-lead ECG~~		~~X~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		
Holter Monitoring ~~and telemetry~~	X	As clinically appropriate															
Telemetry	As clinically appropriate																

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
STUDY DRUGS																	
Dispense study drugs, assess compliance	X	X	X	X	X	X	X	X	X	X	X	X					
PK SAMPLING																	
PK Blood Sampling (See Table 9)		X															

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
PK Urine Sampling (See Table 11)		X															
PD BLOOD SAMPLING																	
LPS Blood sample																	

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [4]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Plasma Sample for Protein Biomarkers (Pre-dose)		X	X		X		X		X		X				X		
PD Whole Blood sampling (mRNA sampling)															X		

Footnote 8. Troponin will be performed at the local (troponin I or T) and central lab (troponin T ~~I~~).

Footnote 15. The drug should be ingested in the morning at approximately the same time every day. ~~8am ± 2 hours~~. Subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects should fast for an additional two hours.

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Females: Pregnancy Test (serum or urine)	X	X	X	X	X	X	X	X	X	X	X	X			X		
Males: Testosterone (free)	X	X	X	X	X	X	X	X	X	X	X	X			X		
Physical Examination [3]	X	X	X	X	X	X	X	X	X	X	X	X			X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Vital Signs (BP, HR, T, Resp) and Pain Assessment	X	X	X	X	X	X	X	X	X	X	X	X			X		
Weight	X	X	X	X	X	X	X	X	X	X	X	X			X		
Hematology/Clinical Chemistry, Pancreatic	X	X	X	X	X	X	X	X	X	X	X	X			X		
Cytokine Samples	X	As clinically appropriate															

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Guaiac fecal occult blood test	X		X		X	As clinically appropriate											
Coagulation and Creatine phosphokinase	X	X	X	X	X	X	X	X	X	X	X		X		X		
Fasting Blood Glucose [4]	X	X	X	X	X	X	X	X	X	X	X	X			X		
C-peptide, Insulin and 1,5 AG [5]	X	X	X	X	X	X	X	X	X	X	X	X			X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7, D1**	**W8, D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Fasting Lipid Panel~~, hA1C~~	X	~~X~~	X	X	X	X	X	X	X	X	X		X		X		
hA1C	X		X		X		X		X		X		X		X		
Thyroid monitoring [6]	X	~~X~~	X		X			X			X		~~X~~	X	X		
Urinalysis	X	X			X			X			X		X		X		
CARDIOTOXICITY MONITORING																	
ECHO	X	X	X		X		X		X		X		X		X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7, D1**	**W8, D1**	**W12, D1**	**W16, D1**	**W20, D1**	**W24, D1**	**W28, D1**	**W32, D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Troponin and NT-proBNP [8]	X	X	X		X		X		X		X		X		X		
Triplet ECGs at pre-treatment	X		X	X	X	X	X	X	X	X	X		X		X		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Primary PK day Triplet ECGs (see Table 9 for more details, ECG timing pre-treatment, 0.5hr, 1hr, 2hr, 4hr, 8hr)		X															
~~12-lead ECG~~		~~X~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		~~X~~		

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Holter Monitoring ~~and telemetry~~	X	As clinically appropriate															
Telemetry	As clinically appropriate																
STUDY DRUGS																	
Dispense study drugs, assess compliance	X	X	X	X	X	X	X	X	X	X	X	X					
PK SAMPLING																	

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
PK Blood Sampling (See Table 9)		X															
PK Urine Sampling (See Table 11)		X															
PD BLOOD SAMPLING																	
LPS Blood sample																	

Time and Events: Table 7	**Part 1 - Week 7 ~~10~~ to Week 48**											**Monthly Visit**	**Every other month**	**Every three months [1]**	**Discharge/ progression[2]**	**Follow-up [14]**	**End**
Part 1: **Assessments for** **Week 7 ~~8~~ until End of study**	**W7,** **D1**	**W8,** **D1**	**W12, D1**	**W16,** **D1**	**W20, D1**	**W24, D1**	**W28,** **D1**	**W32,** **D1**	**W36, D1**	**W40, D1**	**W44, D1**	**~~Wk 48 onward~~** **Every 4 weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 8weeks Until** **Discharge/ progression [1]**	**~~Wk 48 onward~~** **Every 12weeks Until** **Discharge/ progression [1]**			
Plasma Sample for Protein Biomarkers (Pre-dose)		X	X		X		X		X		X				X		
PD Whole Blood sampling (mRNA sampling)															X		

PREVIOUS TEXT, Time and Events Table 8 Part 2

Time and Events: Table 8		**Month 1** [1]						**Month 2**	**Month 3**	**Month 4**	**Monthly Visit**	**Every other month**	**Every three months**			
Part 2: Assessments	**Screening**	**W1 D1**	**W1 D3 or D4 or D5**	**W2 D1**	**W2 D3 or D4 or D5**	**W3 D1**	**W4 D1**	**W8, D1**	**W12, D1**	**W16, D1**	**Wk 20 onward Every 4 weeks until Discharge/ progression**[1]	**Wk 20 onward Every 8weeks until Discharge/ progression**[1]	**Wk 20 onward Every 12weeks until Discharge/ progression**[1]	**Discharge / progression**[1]	**Follow-up** [2]	**End**
Fasting Lipid Panel, hA1C	X	X						X	X	X	X			X		
Urinalysis	X	X						X	X	X		X	X	X		
ECHO	X	X					X	X	X	X		X				
Troponin and NT-proBNP [11]	X	X		X		X	X	X	X	X	X	X		X		
12-lead ECG	X			X		X	X	X	X	X	X	X		X		
Holter Monitoring							X									
PK Urine Sampling (See Table 11)				X				X								
Disease characteristics	X															

Footnote 11. Troponin will be performed at the local (troponin I or T) and central lab (troponin T~~I~~).

REVISED TEXT, Time and Events Table 8 - Part 2

Time and Events: Table 8 – Part 2																
Time and Events: Table 8		**Month 1** [1]						**Month 2**	**Month 3**	**Month 4**	**Monthly Visit**	**Every other month**	**Every three months**			
Part 2: Assessments	**Screening**	**W1 D1**	**W1 D3 or D4 or D5**	**W2 D1**	**W2 D3 or D4 or D5**	**W3 D1**	**W4 D1**	**W8, D1**	**W12, D1**	**W16, D1**	~~**Wk 20 onward**~~ **Every 4 weeks until Discharge/ progression**[1]	~~**Wk 20 onward**~~ **Every 8weeks until Discharge/ progression**[1]	~~**Wk 20 onward**~~ **Every 12weeks until Discharge/ progression**[1]	**Discharge/ progression**[1]	**Follow-up** [2]	**End**
Fasting Lipid Panel~~, hA1C~~	X	X						X	X	X	X			X		
~~hA1C~~	~~X~~	~~X~~						~~X~~	~~X~~	~~X~~		~~X~~		X		
Urinalysis	X	X						X	X	X		~~X~~	X	X		
ECHO	X	X					X	X	X	X		X		X		
Troponin and NT-proBNP 11	X	X		X		X	X	X	X	X	X	X		X		
12-lead ECG	X			X		X	X	X	X	X	X	X		X		
Holter Monitoring	X						X	As clinically indiciated								
Telemetry (24hr monitoring)	X			As clinically indicated												

Time and Events: Table 8 – Part 2																
Time and Events: Table 8		**Month 1** [1]						**Month 2**	**Month 3**	**Month 4**	**Monthly Visit**	**Every other month**	**Every three months**			
Part 2: **Assessments**	**Screening**	**W1 D1**	**W1 D3 or D4 or D5**	**W2 D1**	**W2 D3 or D4 or D5**	**W3 D1**	**W4 D1**	**W8, D1**	**W12, D1**	**W16, D1**	~~**Wk 20 onward**~~ **Every 4 weeks until Discharge/ progression**[1]	~~**Wk 20 onward**~~ **Every 8weeks until Discharge/ progression**[1]	~~**Wk 20 onward**~~ **Every 12weeks until Discharge/ progression**[1]	**Discharge/ progression**[1]	**Follow-up** [2]	**End**
~~PK Urine Sampling~~ ~~(See Table 11)~~				~~X~~				~~X~~								
Disease characteristics	X															

Footnote 11. Troponin will be performed at the local (troponin I or T) and central lab (troponin TI~~T~~).

Footnote 18. The drug should be ingested in the morning at approximately the same time every day. ~~8am ± 2 hours~~. Subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects should fast for an additional two hours.

PREVIOUS TEXT, Table 9 Time and Events for Pharmacokinetics Part 1

Table 9: Time and Events Table for Pharmacokinetics Part 1							
Plasma Pharmacokinetics (PK)	**Within 60 minutes prior to dose**	**Baseline**			**Timings Post Dose**		
		0hr	**PK 0.5 hr ±5 mins**	**PK 1hr ±5 mins**	**PK 2hr ± 10 mins**	**PK 4hr ± 15 mins**	**PK 8hr ± 15 mins**
Week 1 Day 1 PK Sample	X		X	X	X	X	X
Week 1 Day 1 Urine Sample (see Table 10)		Urine sample 0-2hrs				Urine sample 2-24hrs	
Week 1 Day 1 Safety Labs (see Table 8)	X						
Week 1 Day 1 LPS blood samples (whole blood transcriptional panel)[1]	X				X	X	X
Week 1 Day 1 PD Whole Blood sampling (mRNA sampling)	X				X	X	X
Week 1 Day 1 ECG (triplicate readings 5 mins apart +/10 mins of PK sample) [1]	X				X	X	X
Week 1 Day 1 Investigational Product dose		X					
Week 1 Day 2 PK Sample (this sample is 24hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 2 LPS blood samples (this sample is 24hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 2 PD Whole Blood sampling (mRNA sampling) (this sample is 24hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 3 PK Sample (this sample is 48hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 3 PD Whole Blood sampling (mRNA sampling) (this sample is 48hr ±- 1hr after Wk1 D1 dose)	X						
Week 4 Day 6 PK sample	X		X	X	X	X	X
Week 4 Day 6 LPS blood samples (whole blood transcriptional panel)[1]					X	X	X
Week 4 Day 7 PK Sample (this sample is 24hr ± 1hr after Wk4 D6 dose)	X						
Week 4 Day 7 LPS blood samples (whole blood transcriptional panel)[1]					X	X	X
Week 5, Day 1 PK Sample (this sample is 48hr ±- 1hr after Wk4 D6 dose)	X						

Table 9: Time and Events Table for Pharmacokinetics Part 1							
Plasma Pharmacokinetics (PK)	**Within 60 minutes prior to dose**	**Baseline**			**Timings Post Dose**		
		0hr	**PK 0.5 hr ±5 mins**	**PK 1hr ±5 mins**	**PK 2hr ± 10 mins**	**PK 4hr ± 15 mins**	**PK 8hr ± 15 mins**
Safety Labs	X						
ECG (triplicate readings 5 mins apart +/10 of PK sample)	X		X	X	X	X	X
Investigational Product dose		X					
Week 8 Day 1	X		Single draw between 0.5-2 hr			Single draw between 4-8 hr	
Safety Labs	X						
ECG (triplicate readings 5 mins apart +/10 of PK sample)	X		between 0.5-2 hr			between 4-8 hr	
Investigational Product dose		X					

Footnote 1: LPS and PD whole blood timing may be adjusted based on pharmacokinetic profile observed in the patient cohorts. The timing adjustment may shift to be closer to Tmax. For example, LPS samples could be 1hr ± 5 mins, 2hr ±-10mins and 4 hrs ± 15 mins. The shift in timing would be determined during a dose escalation meeting or safety review meeting and circulated in the minutes to the investigators to address the new timings.

REVISED TEXT, Table 9 Time and Events: Pharmacokinetics and Biomarker Sampling for Part 1

Table 9: Time and Events Table for Pharmacokinetics and Biomarker Sampling for Part 1							
Plasma Pharmacokinetics (PK) and Biomarker Sampling	**Within 60 minutes prior to dose**	**Baseline**			**Timings Post Dose**		
		0hr	**PK 0.5 hr ±5 mins**	**PK 1hr ±5 mins**	**PK 2hr ± 10 mins**	**PK 4hr ± 15 mins**	**PK 8hr ± 15 mins**
Screening visit: Plasma Sample for Protein Biomarkers (collect at anytime at screening visit as no dose is given)	X (collect at anytime during screening visit)						
Screening visit: PD Whole Blood sampling (mRNA sampling) (collect at anytime at screening visit as no dose is given)	X (collect at anytime during screening visit)						
Week 1 Day 1 ECG (triplicate readings 5 mins apart +/10 mins of PK sample) [1,3]	X		X	X	X	X	X
Week 1 Day 1 PK Urine Sample (see Table 11 ~~10~~)		Urine sample 0-2hrs				Urine sample 2-24hrs	
~~**Week 1 Day 1** Safety Labs (see Table 8)~~	~~X~~						
Week 1 Day 1 Plasma Sample for Protein Biomarkers	X						
Week 1 Day 1 LPS blood samples (whole blood transcriptional panel)[1]	X				X	X	X
Week 1 Day 1 PD Whole Blood sampling (mRNA sampling)	X				X	X	X
Week 1 Day 1 PK Sample	X		X	X	X	X	X
Week 1 Day 1 Investigational Product dose		X					
Week 1 Day 2 PK Sample (this sample is 24hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 2 Plasma Sample for Protein Biomarkers	X						
Week 1 Day 2 LPS blood samples (this sample is 24hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 2 PD Whole Blood sampling (mRNA sampling) (this sample is 24hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 3 Plasma Sample for Protein Biomarkers (this sample is 48hr ± 1hr after Wk1 D1 dose)	X						
Week 1 Day 3 PK Sample (this sample is 48hr ± 1hr after Wk1 D1 dose)	X						

Table 9: Time and Events Table for Pharmacokinetics and Biomarker Sampling for Part 1							
Plasma Pharmacokinetics (PK) and Biomarker Sampling	**Within 60 minutes prior to dose**	**Baseline**			**Timings Post Dose**		
		0hr	**PK 0.5 hr ±5 mins**	**PK 1hr ±5 mins**	**PK 2hr ± 10 mins**	**PK 4hr ± 15 mins**	**PK 8hr ± 15 mins**
Week 1 Day 3 PD Whole Blood sampling (mRNA sampling) (this sample is 48hr ±- 1hr after Wk1 D1 dose)	X						
Week 2 Days 1, 4, and 5 Plasma Sample for Protein Biomarkers **Week 3 Days 1, 6 and 7** Plasma Sample for Protein Biomarkers **Week 4 Day 1** Plasma Sample for Protein Biomarkers	X						
Week 4 Day 6 ECG (triplicate readings 5 mins apart +/10 of PK sample)[3]	X		X	X	X	X	X
Week 4 Day 6 PK sample	X		X	X	X	X	X
~~**Week 4 Day 6** Safety Labs (see Table 8)~~	~~X~~						
Week 4 Day 6 Plasma Sample for Protein Biomarkers	X						
Week 4 Day 6 LPS blood samples (whole blood transcriptional panel)[3]					X	X	X
Week 4 Day 6 Investigational Product dose		X					
Week 4 Day 7 PK Sample (this sample is 24hr ± 1hr after Wk4 D6 dose)	X						
Week 4 Day 7 Plasma Sample for Protein Biomarkers	X						
Week 4 Day 7 LPS blood samples (whole blood transcriptional panel)[1]	X				~~X~~	~~X~~	~~X~~
Week 5, Day 1 PK Sample (this sample is 48hr ±- 1hr after Wk4 D6 dose)	X						
Week 5 Day 1 Plasma Sample for Protein Biomarkers (this sample is 48hr ±- 1hr after Wk4 D6 dose)	X						
Week 8 Day 1 PK Blood Sample	X		Single draw between 0.5-2 hr			Single draw between 4-8 hr	

Table 9: Time and Events Table for Pharmacokinetics and Biomarker Sampling for Part 1							
Plasma Pharmacokinetics (PK) and Biomarker Sampling	**Within 60 minutes prior to dose**	**Baseline**			**Timings Post Dose**		
		0hr	**PK 0.5 hr ±5 mins**	**PK 1hr ±5 mins**	**PK 2hr ± 10 mins**	**PK 4hr ± 15 mins**	**PK 8hr ± 15 mins**
Week 1 Day 1 PK Urine Sample (see Table 11 ~~10~~)	X	Urine sample 0-2hrs				Urine sample 2-24hrs	
~~Safety Labs (see Table 8)~~	~~X~~						
Week 8 Day 1 ECG (triplicate readings 5 mins apart +/10 of PK sample)[3]	X		between 0.5-2 hr			between 4-8 hr	
Week 8 Day 1 Investigational Product dose		X					

Footnote 1: LPS and PD whole blood timing may be adjusted based on pharmacokinetic profile observed in the patient cohorts. The timing adjustment may shift to be closer to Tmax. For example, LPS samples could be 1hr ± 5 mins, 2hr ±-10mins and 4 hrs ± 15 mins. The shift in timing would be determined during a dose escalation meeting or safety review meeting and circulated in the minutes to the investigators to address the new timings.

Footnote 2: PK sampling should be completed within 10mins following ECGs in a consistent manner from visit to visit.

PREVIOUS TEXT, Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling for Part 2

Time and Events Table 10, Part 2		**Baseline**	**Timings Post Dose**				
	Within 60 minutes prior to dose	**0hr**	**PK 0.5 Hr**	**PK 1hr**	**PK 2hr**	**PK 4hr**	**PK 8hr**
Week 2, Day 1 PK Sample	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Week 2 Day 1 LPS blood samples (whole blood transcriptional panel)[1]	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Week 2 Day 1 Plasma Sample for Protein Biomarkers	X						
Week 2 Day 1 PD Whole Blood sampling (mRNA sampling)	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Safety Labs (see Table 6.)	X						
Investigational Product dose		X					
Week 8, Day 1 PK Sample	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Safety Labs (see Table 6.)	X						
Investigational Product dose		X					

PREVIOUS TEXT, Table 10

PREVIOUS TEXT, Table 10 Time and Events: Pharmacokinetics for Part 2

Tiem and Events Table 10, Part 2		**Baseline**	**Timings Post Dose**				
	Within 60 minutes prior to dose	**0hr**	**PK 0.5 Hr**	**PK 1hr**	**PK 2hr**	**PK 4hr**	**PK 8hr**
Week 2, Day 1 PK Sample	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Week 2 Day 1 LPS blood samples (whole blood transcriptional panel)[1]	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Week 2 Day 1 Plasma Sample for Protein Biomarkers	X						
Week 2 Day 1 PD Whole Blood sampling (mRNA sampling)	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Safety Labs (See Table 6)	X						
Investigational Product dose		X					
Week 8, Day 1 PK Sample	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Safety Labs (See Table 6)	X						
Investigational Product dose		X					

REVISED TEXT, Table 10 Time and Events: Pharmacokinetics and Biomarkers Sampling for Part 2

Table 10 Time and Events: Pharmacokinetics and Biomarker Sampling for Part 2							
~~**Tiem and Events Table 10, Part 2**~~		**Baseline**	**Timings Post Dose**				
Time and Events	**Within 60 minutes prior to dose**	**0hr**	**PK 0.5 Hr**	**PK 1hr**	**PK 2hr**	**PK 4hr**	**PK 8hr**
Week 2, Day 1 PK Sample	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Week 2 Day 1 LPS blood samples (whole blood transcriptional panel)[1]	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Week 2 Day 1 Plasma Sample for Protein Biomarkers	X						
Week 2 Day 1 PD Whole Blood sampling (mRNA sampling)	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Safety blood sampling[1] ~~Safety Labs (see Table 6~~)	X						
Investigational Product dose		X					
Week 8, Day 1 PK Sample	X		Single draw Between 0.5-2hr			Single draw Between 4-8hr	
Safety blood sampling[1] ~~Safety Labs (see Table 6~~)	X						
Investigational Product dose		X					

Footnote 1: The term "safety blood sampling" references any non-PK or non-biomarker sampling. Example of "safety blood sampling" includes blood sampling for haematology, clinical chemistry, pancreatic, coagulation, etc.

Rationale Change 9

This section was modified for consistency with the Time and Event tables in Section 5.

PREVIOUS TEXT, Section 6.2.3 Vitals

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, temperature and pain using a numerical rating scale from 0 to 10 [De Conno, 1994]. The vital signs will be measured after resting for at least 5 minutes in a supine or semi-recumbent position. On days where vital signs are measured multiple times, temperature does not need to be repeated, unless clinically indicated.

REVISED TEXT, Section 6.2.3 Vitals

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiration, temperature and pain using a numerical rating scale from 0 to 10 [De Conno, 1994]. The vital signs will be measured after resting for at least 5 minutes in a supine or semi-recumbent position. ~~On days where vital signs are measured multiple times, temperature does not need to be repeated, unless clinically indicated.~~

PREVIOUS TEXT, Section 6.2.8 Clinical Laboratory Assessments:

Other Tests
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)
Pancreatic markers (amylase and lipase)
Fasting Lipid panel (triglycerides and total cholesterol, LDL, HDL)
C-Peptide
Troponin (I or T at local laboratory, Troponin I at central laboratory]
Insulin Hemoglobin A1C 1,5 –Anhydroglucitol (1,5 AG) NT-proBNP Thyroid-stimulating hormone (TSH) Free Thyroxine 3 (Free T3) Free Thyroxine 4 (Free T4) Creatine kinase (CK) Creatine Kinase-MB (CK-MB)
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose)
Pregnancy test for females (serum at screening, Urine or serum post dose) Cytokine samples (TNF-alpha,IL-1,IL-6, IL-10)

REVISED TEXT. Section 6.2.8 Clinical Laboratory Assessments:

Other Tests
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)
Pancreatic markers (amylase and lipase)
Fasting Lipid panel (triglycerides and total cholesterol, LDL, HDL)
C-Peptide
Troponin (I or T at local laboratory, Troponin T at central laboratory)
Insulin Hemoglobin A1C 1,5 –Anhydroglucitol (1,5 AG) NT-proBNP Thyroid-stimulating hormone (TSH) Free Thyroxine 3 (Free T3) Free Thyroxine 4 (Free T4) Creatine kinase (CK) Creatine Kinase-MB (CK-MB)
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose)
Pregnancy test for females (serum at screening, Urine or serum post dose) Cytokine samples (TNF-alpha,IL-1,IL-6, IL-10) Guaiac fecal occult blood

PREVIOUS TEXT, Section 6.2.9:

Troponin I will be assessed at a central laboratory as a means of consistent evaluation across all subjects. A second sample will be assessed at a local laboratory for purposes of subject management (e.g., enrolment criteria). Whenever possible, troponin I will be assayed by the local laboratory. However, either troponin I or troponin T may be assessed at a local laboratory.

REVISED TEXT, Section 6.2.9:

Troponin ~~I~~T will be assessed at a central laboratory as a means of consistent evaluation across all subjects. A second sample will be assessed at a local laboratory for purposes of subject management ~~(e.g., enrolment criteria)~~. Whenever possible, troponin ~~I~~T will be assayed by the local laboratory. However, either troponin I or troponin T may be assessed at a local laboratory.

NEW TEXT, Section 7.3:

These fasting requirements have been implemented in the protocol and informed consents to minimize pharmacokinetic variability.

Rationale Change 10

The BET115512 study data may potentially be utilized for registration purposes. Therefore, the disease assessment imaging will be gathered for potential central review.

NEW TEXT, Section 6.3, Efficacy

6.3 Efficacy

6.3.1 Disease Assessment

Tumor response will be assessed as outlined in Time and Event Schedule by the investigator using RECIST 1.1 and documented in the eCRF as: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR) (See Appendix 4). See the SPM for additional instructions.

GSK requires sites to provide electronic copies (upload digital images or images on CD) of scans for all subjects for central storage which may be transferred to a central independent imaging center. This includes baseline scans and all scans performed during the course of the study. GSK may request an independent review of scans. See SPM for additional details.

PREVIOUS TEXT, Section 14.4 Appendix 4: RECIST 1.1:

Disease progression and response evaluations may be reviewed and analyzed by an independent reviewer or central review. Details will be provided in the SPM.

REVISED TEXT, Section 14.4 Appendix 4: RECIST 1.1:

Disease progression and response evaluations will be collected centrally during the study and may be reviewed ~~and~~ or analyzed by an independent ~~reviewer or~~ central reviewer. Details will be provided in the SPM.

Rationale Change 11

The Material Safety Data Sheet (MSDS) classifies GSK525762 as an oral toxicity Category 4, Reproductive Hazard. Additional instructions have been provided to the site staff regarding handling and exposure to GSK525762.

NEW TEXT, Section 7.2 Handling and Storage of Study Treatment, new second paragraph

Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK525762 tablets.

Rationale Change 12

Dose adjustments table has been clarified for drug related toxicity. Clinically manageable laboratory abnormalities activities would not implement a dosing delay or adjustment.

PREVIOUS TEXT, Section 7.7.1. Dose Adjustments for Toxicity- Table 17

Worst Grade	**GSK525762**
1	No change in dose
2	Decrease by one dose level for LFT changes. For other Grade 2 toxicities, continue dosing with no change
3	Hold dose for one week intervals until ≤Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.
4	Off protocol therapy In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the patient is receiving benefit then the following criteria should be implemented: hold dose for one week intervals until <Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy

*Note: Exceptions to ≤Grade 1 requirement may be made for Rash, alopecia, etc.

REVISED TEXT, Section 7.7.1. Dose Adjustments for Toxicity- Table 17

Toxicity

Worst Grade	GSK525762
1	No change in dose
2	Decrease by one dose level for LFT changes. For other drug – related Grade 2 toxicities, continue dosing with no change
3	Hold dose for one week intervals until ≤ drug – related Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.
4	Off protocol therapy In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the patient is receiving benefit then the following criteria should be implemented: hold dose for one week intervals until < drug – related Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy

*Note: Exceptions to ≤drug – related Grade 1 requirement may be made for Rash, alopecia, etc. Exceptions to ≤ drug – related Grade 1, 2, 3 requirements would be quickly reversible (≤48 hours) laboratory abnormality (example: electrolyte changes).

Rationale Change 13

Additional clarification has been provided regarding the analysis populations. FDA recommended including an exploratory analysis to assess safety and activity in the NUT-variant subset. In addition, clarification regarding the stopping rule for futility has been provided.

NEW TEXT, Section 11.1.5 Subset Analysis for NMC Population

An exploratory review for NMC molecular subtype (e.g. NUT-BRD3, NUT-BRD4 and NUT-variant) will be conducted.

Section 11.2, Stopping Rule for Futility (Interim Analysis)

PREVIOUS TEXT, Section 11.2, Stopping Rule for Futility (Interim Analysis)

An interim analysis will be conducted by a GSK statistician for this study in order to assess futility. Assessing for futility will involve: (1) safety review and (2) efficacy.

Safety Review: If a dose limiting toxicity has been observed in 4/20 subjects within the first 6 weeks then further analysis and data review may occur. Additional discussions between investigator(s) and GSK Medical Monitor will occur to determine if subjects receiving benefit and if potential alterations in schedule or regimen may need to be implemented to address the observed toxicity being observed in the specific cohort or tumor type.

Efficacy: If zero responses are observed among the 20 subjects at interim, then in conjunction with a thorough review of additional data, that cohort may be closed for further enrollment. If one or more subjects respond, then an additional 20 subjects may be enrolled to more accurately define the true response rate.

REVISED TEXT, Section 11.2, Stopping Rule for Futility (Interim Analysis)

An interim analysis will be conducted for Part 2 of this study in order ~~by a GSK statistician for this study in order~~ to assess futility after response data are available for the first 20 subjects based on the overall best response rate. ~~Assessing for futility will involve: (1) safety review and (2) efficacy.~~ If 0 responses are observed, then Part 2 of trial will be terminated with no further enrollment.

~~**Safety Review:** If a dose limiting toxicity has been observed in 4/20 subjects within the first 6 weeks then further analysis and data review may occur. Additional discussions between investigator(s) and GSK Medical Monitor will occur to determine if subjects receiving benefit and if potential alterations in schedule or regimen may need to be implemented to address the observed toxicity being observed in the specific cohort or tumor type.~~

~~**Efficacy:** If zero responses are observed among the 20 subjects at interim, then in conjunction with a thorough review of additional data, that cohort may be closed for further enrollment. If one or more subjects respond, then an additional 20 subjects may be enrolled to more accurately define the true response rate.~~

If at least 1 response occurs then an additional 20 subjects with NMC may be enrolled. Emerging safety data will also be reviewed. Safety data will be reviewed on an ongoing basis and after the first 20 patients to ensure the safety profile supports continued enrolment. If there is sufficient sample size an exploratory analysis will be undertaken to evaluate whether response rates differ between between molecular subtypes (e.g. NUT-BRD3, NUT-BRD4, NUT-variant).

NEW TEXT

Efficacy Review:
If there is sufficient sample size an exploratory analysis will be undertaken to evaluate whether response rates differ between molecular subtypes (e.g. NUT BRD3, NUT BRD4, variant).

PREVIOUS TEXT, Section 11.3 Analysis Populations

All Subjects (Safety and Clinical Activity) Population: This will consist of all subjects that received at least one dose of study treatment. Safety and clinical activity data will be evaluated based on this population.

Evaluable population: Any subject who received 75% of planned drug dosing by the first planned disease assessment. All subjects should have appropriate confirmatory scans at least 4 weeks subsequently.

The PK Population: This will consist of those subjects in All Subjects Population and for whom a PK sample is obtained and analyzed.

REVISED TEXT, Section 11.3 Analysis Populations

All Subjects (Safety and Clinical Activity) Population: This will consist of all subjects that received at least one dose of study treatment. Safety and clinical activity data will be evaluated based on this population.

~~Evaluable population: Any subject who received 75% of planned drug dosing by the first planned disease assessment. All subjects should have appropriate confirmatory scans at least 4 weeks subsequently.~~

The PK Population: This will consist of those subjects in All Subjects Population and for whom a PK sample is obtained and analyzed.

Assay Validation Population: Due to the rarity of NMC disease, 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 IHC and/or FISH. Data from this population may be used for future validation of the assay.

PREVIOUS TEXT, Section 11.5.1 Primary Analysis

The primary analysis will be based on the 'All Subject Population'. A secondary analysis wil be based on the 'Evaluable Population' which consists of all subjects who received at least 75% of planned dosing of drug by the first planned disease assessment.

REVISED TEXT, Section 11.5.1 Primary Analysis

~~The primary analysis will be based on the 'All Subject Population'. A secondary analysis wil be based on the 'Evaluable Population' which consists of all subjects who received at least 75% of planned dosing of drug by the first planned disease assessment.~~

Rationale Change 14

The clinical benefit rate has been revised from disease assessment at week 4 to week 8 to be consistent with the Time and Event Tables in Section 5.

PREVIOUS TEXT, 11.5.2. Secondary Analyses

The Clinical Benefit rate is defined as the percentage of subjects with a confirmed complete response (CR), partial response (PR) or stable disease lasting at least 4 weeks. Exact methods for calculated confidence intervals will be in the RAP.

REVISED TEXT, 11.5.2. Secondary Analyses

The Clinical Benefit rate is defined as the percentage of subjects with a confirmed complete response (CR), partial response (PR) or stable disease lasting at least 8 ~~4~~ weeks. Exact methods for calculated confidence intervals will be in the RAP.

AMENDMENT 02

Protocol Amendment 02 applies to all site(s) participating in the conduct of the study

Amendment 02 Summary of Substantial Changes:

Section 1, Introduction

Streamlined / reorganized text (Section 1.1, Background)

Added data on additional tumor cell lines (Section 1.2, Study Population Rationale)

Updated table on predicted safety cover for proposed 2 mg starting dose (Section 1.3, Dose Rationale)

Updated Risk Assessment (Section 1.5) in line with current asset language

Section 2, Objectives & Endpoints

Revised Text (strikethrough=deleted text; bold=new text):

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 **in subjects 16 years or older** • **To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 12 to ≤15 years old** • To evaluate the clinical activity of GSK525762 ~~in subjects with NUT Midline Carcinoma (~~NMC).
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD **in subjects 16 years or older** • **AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 12 to ≤15 years old.** • Assess overall response rate (RR) by RECIST 1.1 **in NMC**
Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory. • The primary goal of Part 2 is to demonstrate a clinically meaningful response rate of 20% in NMC relative to a 5% response rate suggesting no activity. This will be conducted by testing the null hypothesis that P0≤0.050 versus the alternative that P1≥0.200, assuming the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20.

Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the **pharmacokinetics** (PK) of GSK525762 **in subjects 16 years or older.** • **To characterize the pharmacokinetics (PK) of GSK525762 in subjects 12 to ≤15 years old** • To evaluate cardiac safety, including the potential for ~~QTc~~**QTcF**, of GSK525762 ~~in subjects with NUT Midline Carcinoma (NMC)~~ and to assess PK/~~QTc~~**QTcF** relationship. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival~~of subjects with NUT Midline Carcinoma (NMC).~~ • **To evaluate systemic and ex-vivo on-target BET inhibitory effects**
Endpoints	• PK parameter values for GSK525762 following single and repeat-dose oral administration **in subjects 16 years or older** • ~~Changes in cardiac safety including QTc~~ **PK parameter values for GSK525762** following single and repeat-dose oral administration ~~GSK525762.~~ **in subjects 12 to ≤15 years old** • ~~Changes from baseline and PK / biomarker response relationship in markers of BET pharmacology LPS induced IL-6 in whole blood.~~ • **Changes in cardiac safety including QTcF following single and repeat-dose oral administration GSK525762.** • Progression free survival (PFS), clinical benefit rate (CBR), time to response, duration of response, overall survival (OS), and exploratory analysis for antitumor response by various imaging modalities.

Exploratory (Objectives and Endpoints only)	
Objectives	• To evaluate the PD effect of GSK525762 on NMC biopsies **tumor biology** • **Correlation of GSK525762 exposure to changes in PD markers in tumor and/or surrogate tissue** • **To identify potential indicators of sensitivity or response to GSK525762** • ~~To evaluate exploratory markers of BET inhibition.~~ • ~~To evaluate the exposure response (PK/PD) relationship between GSK525762 PK and exploratory markers of BET inhibition and PD effects on NMC tumor biopsies.~~

Exploratory (Objectives and Endpoints only)	
Endpoints	~~• Tumor Biopsy: The samples will be evaluated for alterations in BRD-NUT by IHC and FISH for BRD4- NUT and changes in morphology and immunophenotype consistent with differentiation. Additionally, protein and mRNA expression of Keratin and other differentiation markers will be analyzed.~~ ~~• If sufficient tumor sample is remaining, gene expression of Brd4-NUT, Brd3-NUT and other "signature" markers of pathway inhibition may be evaluated in pre and postdose treated samples.~~ ~~• Changes from baseline and PK / biomarker response relationship in markers of BET pharmacology (serum amyloid A (SAA), haptoglobin, PK/PD parameter values for exposure response (by RECIST and ^{18}FDG-PET [if data allows]) relationship between GSK525762 and QTc, troponin and tumor response following single and repeat-dose oral administration.~~ • **Dose related changes in markers of cell proliferation and/or cell differentiation in tumor and/or surrogate tissue** • **Dose related changes in transcription of genes and/or changes in expression of proteins regulated by BRD proteins in tumor and/or surrogate tissue** • **PK/PD parameter values for exposure response (by RECIST and 18FDG-PET [if data allows]) relationship between GSK525762 and QTcF, troponin and tumor response following single and repeat-dose oral administration.** • **Changes from baseline and dose/response relationship in ex vivo LPS induced cytokines including IL-6 in whole blood and in systemic cytokines including IL-6** •

Section 3, Investigational Plan

Added language for MM, SCLC, CRC, NB and MYCN driving solid tumors (including NSCLC with MYCN amplification) (Section 3.1, Study Design/Schematic; Section 3.2.5, Part 2 Expansion Cohorts)

Added inclusion of pediatric subjects 12 - ≤15 years old to Part 1B, pediatric dose expansion and to Part 2

Changed text throughout to reflect proposed modified dosing regimen (Week 1 - dose on Day 1, off drug on Day 2, dose on Days 3, 4 and 5, off drug on Days 6 and 7; Week 2 – dose on Days 1 through 5, off drug Days 6 and 7; Week 3 – start daily doing).

Added language (for subjects who agree) regarding mandatory collection of tumor tissue in Part 1 if, after reaching the MTD and dosing at least 12 subjects, adequate tumor tissue (N=10 subjects) has not been collected.

Added language in the Intra-Subject Dose Escalation (Section 3.2.2.5) to allow for dose escalation in a subjects in Part 1, if after 8 weeks of dosing, no additional subjects have been identified.

Section 4, Study Population

Modified inclusion criteria to allow for enrolment of subjects with SCLC, CRC, NB, MM and other solid tumors with MYCN amplification (e.g., NSCLC)

Modified inclusion criteria to allow subjects 16 and older into adult cohort and subjects 12 to ≤15 years old to pediatric cohort

Removed metabolic criteria for inclusion in study

Allowed for treatment after disease progression (under specific circumstances where subject will benefit from treatment) (Section 4.2.4.1)

Section 5, Time and Events Table

Tables reformatted and changes made in line with proposed changes to protocol execution/study population(s)

Section 6, Study Procedures

Added language (for subjects who agree) regarding mandatory collection of tumor tissue in Part 1 if, after reaching the MTD and dosing at least 12 subjects, adequate tumor tissue (N=10 subjects) has not been collected.

Plasma protein biomarker language changed to include IL-6, haptoglobin and CRP (after single and repeat dosing)

Section 7, Study Treatments

Added text to describe/allow for administration of study medication via enteral feeding tube

Section 8, Concomitant Medications and Non-Drug Therapies

Text added to restrict antacids for at least one hour before and 2 hours after dosing.

Specified high-dose steroids as a cautionary medication.

AMENDMENT 03

Protocol Changes for Amendment 3 (04-FEB-2014) from the Protocol Amendment 2 (29-AUG-2012)

Where the Amendment Applies

Protocol Amendment 03 applies to all site(s) participating in the conduct of the study.

General Protocol Changes

The NMC PD Expansion Cohort was added to the protocol to evaluate the pharmacodynamic effects of GSK525762 across the predicted efficacious dose range at doses that have been previously cleared during 3+3 dose escalation. The collection of ECGs, PK samples and liver chemistry were clarified or corrected. Changes are noted below with ~~strikethrough~~ to identify deleted text and **bold underlining** to identify new or replacement text.

List of Changes

Previous Text:

Author:

PPD	Global Clinical Operational Sciences, USA Global Clinical Safety & Pharmacovigilance, USA Oncology Biomarkers, USA Clinical Pharmacology Modeling & Simulation, UK Global Clinical Operational Sciences, USA Exploratory Development Science, PTS, UK Biotransformation and Drug Disposition, PTS, UK Clinical Pharmacology Modeling & Simulation, USA Quantitative Sciences-Genetics, USA Oncology Biomarkers, USA SA Pathology, PTS, UK Global Clinical Safety & Pharmacovigilance, USA EpiNova DPU, UK Cancer Research, Epigenetics Management, USA Discovery Biometrics, Immuno Inflammation, UK Biology, Epigenetics Management, USA Statistics, Oncology TA Group, USA

Revised Text:

Author:

PPD	~~Global Clinical Operational Sciences, USA~~ ~~Global Clinical Safety & Pharmacovigilance, USA~~ **Oncology Biomarkers, USA** ~~Clinical Pharmacology Modeling & Simulation, UK~~ ~~Global Clinical Operational Sciences, USA~~ ~~Exploratory Development Science, PTS, UK~~ Biotransformation and Drug Disposition, PTS, UK **Cancer Research Epigenetics Management, USA** Clinical Pharmacology Modeling & Simulation, USA **Global Clinical Operational Sciences, USA** **Global Clinical Operational Sciences, USA** ~~Quantitative Sciences Genetics, USA~~ ~~Oncology Biomarkers, USA~~ SA Pathology, PTS, UK **Global Clinical Safety & Pharmacovigilance, USA** ~~Global Clinical Safety & Pharmacovigilance, USA~~ EpiNova DPU, UK ~~Cancer Research, Epigenetics Management, USA~~ **Global Clinical Safety & Pharmacovigilance, USA** ~~Discovery Biometrics, Immuno Inflammation, UK~~ Biology, Epigenetics Management, USA Statistics, Oncology TA Group, USA

Previous Text:

Sponsor Signatory: **Signature:** **Date:**

Klaus Edvardsen, MD
VP, Cancer Research

Revised Text:

SPONSOR SIGNATORY:

Christopher Carpenter, MD, PhD
VP, DPU-Head Cancer Epigenetics

Date

~~Klaus Edvardsen, MD~~
~~VP, Cancer Research~~
Previous Text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD , MD	PPD			GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4340 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD , MD	PPD			GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 1450 Collegeville, PA 19426, USA PPD

Revised Text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD **MD, PhD**	PPD			**GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA**
Secondary Medical Monitor	PPD **MD, PhD**	PPD			**GlaxoSmithKline 1250 South Collegeville Road Mailstop UP 4410 Collegeville, PA 19426, USA** PPD
~~Primary Medical Monitor~~	PPD ~~MD~~	PPD			~~GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4340 Collegeville, PA 19426, USA~~ PPD
~~Secondary Medical Monitor~~	PPD ~~MD~~	PPD			~~GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 1450 Collegeville, PA 19426, USA~~ PPD

Rationale for Change:

The authors, sponsor signature, and medical monitoring information were updated based on internal personnel changes to the GSK team.

Previous Text:

- **STUDY DESIGN AND DURATION**: This study is divided into 2 parts; Part 1 of the study is a dose escalation phase to select the recommended dose for Part 2 based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma, small cell lung cancer, colorectal cancer, neuroblastomaand any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, withdrawal of consent, or commercial supply of GSK525762 becomes available to the subject. An expansion cohort is planned to further explore clinical activity at the MTD in NMC (Part 2). Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There is serial pharmacokinetic (PK) sampling for this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Blood samples will be collected for analysis of protein biomarkers (cytokines and acute phase proteins) and mRNA. LPS induction of cytokines in whole blood will be assessed. In addition, pre-treatment and post-treatment tumor samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Revised Text:

- **STUDY DESIGN AND DURATION**: This study is divided into 2 parts; Part 1**A** of the study is a dose escalation phase to select the recommended dose for Part 2 based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma, small cell lung cancer, colorectal cancer, neuroblastoma and any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. **Subjects with NMC will also be enrolled in a pharmacodynamic dose expansion cohort during Part 1A.** Subjects may continue treatment in the study until disease progression, unacceptable toxicity, **or** withdrawal of consent**.** ~~or commercial supply of GSK525762 becomes available to the subject.~~ **Once the MTD is determined in adult subjects, Part 1B will be opened to enroll pediatric subjects 12 to ≤15 years of age with solid tumors to determine the MTD in pediatric subjects. Dose escalation in Part 1B will begin at 25% of the adult MTD and dose escalation will follow a 3+3 design. Pediatric subjects 12 to ≤ 15 years old may be enrolled in Part 2 once the MTD has been determined in Part 1B.** An expansion cohort is planned to further explore clinical activity at the MTD in NMC (Part 2). Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There is **extensive** ~~serial~~ pharmacokinetic (PK) sampling **in Part 1 and limited PK sampling in Part 2** for this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. Blood samples will be collected for analysis of protein biomarkers (cytokines and acute phase proteins) and mRNA. LPS induction of cytokines in whole blood will be assessed. In addition, pre-treatment and post-treatment tumor samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Rationale for Change:

The study design was updated with the addition of the NMC PD Expansion Cohort to evaluate the pharmacodynamic effects of GSK525762 at doses that have been cleared during 3+3 dose escalation during Part 1A. The study design was also clarified in this section to reference the pediatric cohort in Part1B. The duration of exposure on the study was updated in accordance with the Commission Directive 2005/28/EC such that availability of commercial drug supply was not included in duration of treatment on study. The collection of PK during Part 1 and Part were clarified.

Previous Text in Section 1.5 Risk Assessment:

Reproductive: In 4-week toxicology studies, bilateral sperm retention, germ cell degeneration and tubular vacuolization, and depletion of testicular germinal epithelium occurred in male dogs receiving ≥ 0.3 mg/kg and male rats receiving ≥ 10mg/kg doses of GSK525762. Exposures associated with reproductive toxicity in male dogs overlap with the proposed 5 mg starting dose in this FTIH study. In the BET11521 study, specific contraceptive guidelines and precautions for males and females are provided in the protocol. In addition, subjects will be informed of potential reproductive risks and precautions in the informed consent.

Potential drug-drug interactions based on nonclinical studies: There is low potential for GSK525762 to induce or inhibit cytochrome P450 (CYP) enzymes or to inhibit Pgp or BCRP. Use of concurrent drugs with potential to prolonged QTcF will be used with extreme caution or prohibited (as outlined in Section 7.1 of the protocol). Regarding drugs for hyperemesis, palonosetron and ondansetron at a maximum dose of 8 mg TID will be the only allowed serotonin 5-HT3 receptor antagonist drugs.

Revised Text in Section 1.5 Risk Assessment:

Reproductive: In 4-week toxicology studies, bilateral sperm retention, germ cell degeneration and tubular vacuolization, and depletion of testicular germinal epithelium occurred in male dogs receiving ≥ 0.3 mg/kg and male rats receiving ≥ 10mg/kg doses of GSK525762. Exposures associated with reproductive toxicity in male dogs overlap with the proposed 5 mg starting dose in this FTIH study. In the BET11521 study, specific contraceptive guidelines and precautions for males and females are provided in the protocol**. In addition, the informed consent will include potential reproductive risks and precautions in addition to recommendations for the preservation of reproductive capacity**. ~~In addition, subjects will be informed of potential reproductive risks and precautions in the informed consent.~~

Potential drug-drug interactions based on nonclinical studies: There is low potential for GSK525762 to induce or inhibit cytochrome P450 (CYP) enzymes or to inhibit Pgp or BCRP. Use of concurrent drugs with potential to prolonged QTcF will be used with extreme caution or prohibited (as outlined in Section 7.1 of the protocol). Regarding drugs for hyperemesis, palonosetron **(administered per the prescribing information)** and ondansetron **(**at a maximum **oral** dose of 8 mg TID**)** will be the only allowed serotonin 5-HT3 receptor antagonist drugs.

Rational for change:

Additional text was added to emphasize the recommendations for the preservation of reproductive capacity included in the informed consent. The guidance of potential drug-drug interactions and allowance of serotonin 5-HT3 receptor antagonist drugs were clarified.

Previous Text:

3.1 Study Design/Schematic

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

This is an open-label, single and repeat dose, 2-part study to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily orally. (Part 1A) will be conducted in adult subjects with NMC, small cell lung cancer (SCLC), colorectal cancer (CRC), neuroblastoma (NB), MYCN driven solid tumors [including non-small cell lung cancer (NSCLC) with MYCN amplification]. Once the MTD is determined in adult subjects, a pediatric cohort of subjects 12 to ≤15 years of age with solid tumors will be opened (Part 1B) to evaluate MTD in this age group. An expansion cohort (Part 2) is planned to further explore clinical activity of GSK525762 in subjects with NMC as shown in Figure 1. The expansion cohort will enroll both adult (16 years old and above) and pediatric (12 to ≤15 years) subjects at their appropriate R2PD doses.

In Part 1A, an accelerated dose titration will be employed with one subject per dose level until the first instance of a Grade 2 drug related toxicity occurs. Thereafter, subjects will be enrolled in a standard 3+3 design.

After the MTD has been determined in Part 1A, Part 1B and Part 2 will be opened. Dose titration in the pediatric subjects in Part 1B will start at 25% of the MTD determined in Part 1A and will follow a standard 3+3 design. Pediatric subjects will be entered to Part 2 upon completion of Part 1B.

In both Parts 1 and 2, all subjects will be evaluated for systemic and ex-vivo on-target BET inhibitory effects in blood. In addition, pre-treatment and post-treatment tumor samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Revised Text:

3.1 Study Design/Schematic

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

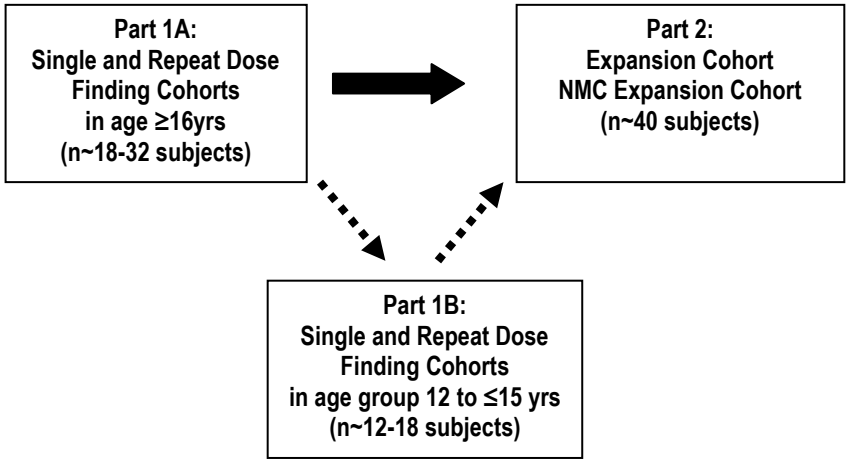
This is an open-label, single and repeat dose, 2-part study to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily orally. (Part 1A) will be conducted in adult subjects with NMC small cell lung cancer (SCLC), colorectal cancer (CRC), neuroblastoma (NB), MYCN driven solid tumors [including non-small cell lung cancer (NSCLC) with MYCN amplification]. **During the dose escalation of Part 1A, additional subjects with NMC will be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamic effects of GSK525762 at lower doses that have been previously cleared during dose escalation. This will enable collection of pharmacodynamic data across the predicted efficacious dose range and contribute to the evaluation of a biologically efficacious dose.** Once the ~~MTD~~ **RP2D** is determined in adult subjects, ~~a~~ **Part 1B will be opened to enroll** pediatric ~~cohort of~~ subjects 12 to ≤15 years of age with solid tumors ~~will be opened (Part 1B)~~ to **determine the** ~~MTD~~ **RP2D** in this age group. **Dose escalation in Part 1B will begin at 25% of the adult MTD and dose escalation will follow a 3+3 design.** An expansion cohort (Part 2) is planned to further explore clinical activity of GSK525762 in subjects with NMC as shown in Figure 1. The expansion cohort will enroll both adult (16 years old and above) and pediatric (12 to ≤15 years) subjects at their appropriate R2PD doses.

Rationale for Change:

The study design was updated with the addition of the NMC PD Expansion Cohort to evaluate the pharmacodynamic effects of GSK525762 at doses that have been cleared during 3+3 dose escalation during Part 1A.

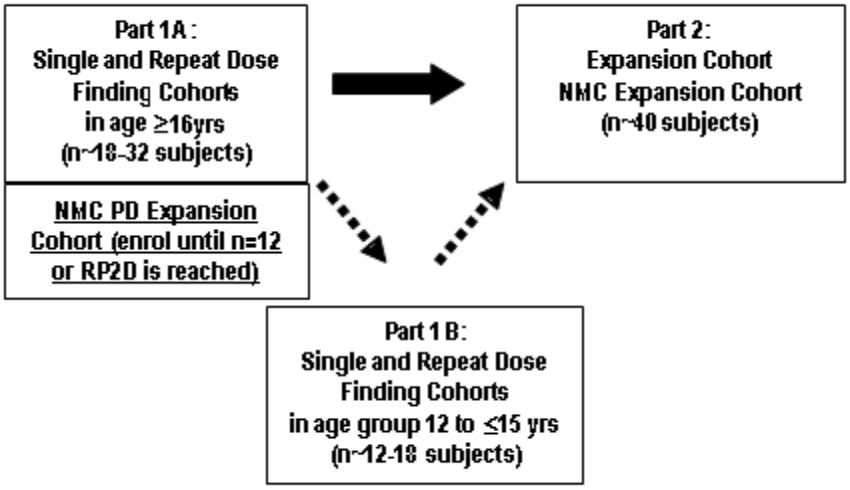
Previous Text:

Figure 1. Study Schema



Revised Text:

Figure 1. Study Schema



Rationale for Change:

Figure 1 was updated to include the NMC PD Expansion Cohort.

Previous Text:

3.2.1 Part 1 Dose Escalation

Part 1A will start with an accelerated dose escalation schema in subjects ≥16 years old with one subject per dose level. Accelerated dose titration will stop once a single Grade 2 or higher drug-related adverse event is observed in one subject, at which point a standard 3+3 dose escalation design will be implemented to define the MTD. The details of these 2 dose escalation strategies are in Figure 2.

Part 1B will be initiated after the MTD is reached in Part 1A and will start at 25% of the MTD determined in Part 1A. Part 1B will follow a standard 3+3 design.

Revised Text:

3.2.1 Part 1 Dose Escalation

Part 1A will start with an accelerated dose escalation schema in subjects ≥16 years old with one subject per dose level. Accelerated dose titration will stop once a single Grade 2 or higher drug-related adverse event is observed in one subject, at which point a standard 3+3 dose escalation design will be implemented to define the MTD. The details of these 2 dose escalation strategies are in Figure 2.

Part 1B will be initiated after the MTD is reached in Part 1A and will start at 25% of the MTD determined in Part 1A. Part 1B will follow a standard 3+3 design.

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the predicted dose from the Neuenschwander-Continuous Reassessment Method (N-CRM) design [Neuenschwander Neuenschwander**, 2009]. N-CRM design is a type of Bayesian adaptive dose escalation scheme. The method is fully adaptive and makes use of all the Dose Limiting Toxicity (DLT) information available at the time of each dose assignment. The DLT information of all subjects enrolled in the trial are used to update the dose-toxicity relationship and provide supportive information in addition to 3+3 design in the next escalation/de-escalation decision.**

Rationale for Change:

Dose escalation follows the 3+3 design and the protocol was updated to clarify that dose escalation decisions includes evaluation of all safety data from prior dose cohorts, PK/PD data, and supportive information that results from the CRM.

Previous Text:

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	Dose ECG,Tele,Holter	ECG,Tele	Dose ECG	Dose	Dose ECG,Holter	ECG	ECG
Week 2	Dose ECG	Dose	Dose	Dose	Dose ECG,Holter	ECG	ECG
Week 3	Dose ECG	Dose	Dose	Dose ECG	Dose	Dose	Dose
Week 4	Dose ECG,Holter	Dose	Dose	Dose ECG	Dose	Dose	Dose

Revised Text:

Table 2. Dosing Schedule and Cardiac Monitoring for Part 1A and Part 1B

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	Dose ECG,Tele,Holter	ECG,Tele	Dose ECG	Dose	Dose ECG,Holter	ECG	ECG
Week 2	Dose ECG	Dose	Dose	Dose ECG	Dose ~~ECG~~ Holter	ECG	ECG
Week 3	Dose ECG	Dose	Dose	Dose ECG	Dose	Dose	Dose
Week 4	Dose ECG,Holter	Dose	Dose	Dose ECG	Dose	Dose	Dose

Rationale:

Corrections were made to clarify that ECGs are to be collected on Week 2 Day 4 and not Week 2 Day 5.

Previous Text:

3.2.2.6 Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced any Grade 2 or higher drug related toxicity during the first 4 weeks of investigational therapy in the accelerated dose escalation phase or a DLT in the 3+3 dose escalation phase and contingent upon one of the following:

- If additional subject(s) have been enrolled at a higher dose in the dose escalation phase and at least one subject has completed 4 weeks of dosing on that regimen without a DLT, and after review of all safety data and approval by a GSK Medical Monitor, a subject on a lower dose level may be increased up to the highest dose

level tested. In this case the subject may begin daily dosing at the higher dose level as it will have already been demonstrated to be tolerable.

- If no further subjects have been identified for a subsequent higher dose level and after a subject has completed 4 weeks of dosing on that regimen without a DLT, that subject may be escalated to the next higher dose level after an additional 4 weeks of dosing (total of 8 weeks of dosing), review of all safety data and approval by a GSK Medical Monitor. In this case the subject must follow the staggered dosing schedule outlined in Table 2, as he/she will be the first subject exposed to the higher dose.

Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

Revised Text:

3.2.2.6 Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that the subject has not experienced any Grade 2 or higher drug related toxicity during the first 4 weeks of investigational therapy in the accelerated dose escalation phase or a DLT in the 3+3 dose escalation phase and contingent upon one of the following:

- If additional subject(s) have been enrolled at a higher dose in the dose escalation phase and at least one subject has completed 4 weeks of dosing on that regimen without a DLT, and after review of all safety data and approval by a GSK Medical Monitor, a subject on a lower dose level may be increased up to the highest dose level tested. In this case the subject may begin daily dosing at the higher dose level as it will have already been demonstrated to be tolerable.
- If no further subjects have been identified for a subsequent higher dose level and after a subject has completed 4 weeks of dosing on that regimen without a DLT, that subject may be escalated to the next higher dose level after an additional 4 weeks of dosing (total of 8 weeks of dosing), review of all safety data and approval by a GSK Medical Monitor. In this case the subject must follow the staggered dosing schedule outlined in Table 2, as he/she will be the first subject exposed to the higher dose.

Subjects approved for intra-subject dose escalation will require additional limited PK sampling at the higher dose (pre-dose, 0.5, 3 and 6-8 hours), as determined by GSK Clinical Pharmacology. Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

Rationale for Change:

Subjects who are approved for intra-subject dose escalation will require PK sampling at the higher approved dose in order to evaluate PK parameters at the higher dose level.

Additional Text:

3.2.5 Part 1 NMC Pharmacodynamic Expansion Cohort

In the event there are no available enrollment slots during 3+3 dose escalation, eligible subjects with NMC (Section 6.2) may be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamics of GSK525762 at doses that have previously been cleared during 3+3 dose escalation. Three subjects with NMC will be allowed to enroll at the last cleared dose level only if subjects with NMC or other solid tumor types (Section 4.2.1 Inclusion Criteria) have already enrolled in 3+3 dose escalation. Enrollment in the PD Expansion Cohort will continue until either 12 subjects with NMC are enrolled in the PD Expansion Cohort, or until the RP2D is determined in Part 1A, whichever occurs first. Eligibility criteria for subjects diagnosed with NMC to enroll in this cohort are described in Section 4.2 (Part 1A). Biopsy collection will be mandatory as described in Section 3.2.2.4, unless a waiver is granted by the GSK medical monitor. ^{18}FDG-PET will be required for all subjects in this cohort.

Subjects in the PD Dose Expansion Cohort will start with same staggered dosing during the first two weeks as described in Section 3.2.2 (Table 2); subjects will begin continuous dosing in Week 3. Extensive monitoring for cardiac safety signals will be performed as required in Part 1A, with triplicate 12-lead ECGs, 48-hour telemetry, and 24-hour Holter monitoring to be performed on the days indicated in Table 2. All safety and PK evaluations will be performed as outlined in the Time and Events Tables for Part 1A (Section 5). Safety data from subjects in the NMC PD Expansion Cohort will be reviewed on an ongoing basis by the GSK medical monitor, GSK Safety Review Team, and investigators for consideration during 3+3 dose escalation decisions.

Subjects will be eligible for intra-subject dose escalation to a higher approved dose as described in Section 3.2.2.6, upon completion of the 4 week observation period, tumor biopsy collection, and approval by the investigator and GSK medical monitor in consultation with the GSK study team. Subjects approved for intra-subject dose escalation will require additional limited PK sampling (pre-dose, 0.5, 3 and 6-8 hours) at the higher dose, as determined by GSK Clinical Pharmacology. Subjects may continue on daily administration of GSK525762 until permanent discontinuation or completion of the study as described in Section 4.2.3.

Rationale for additional text:

The study design was updated with the addition of the NMC PD Expansion Cohort to evaluate the pharmacodynamics of GSK525762 at doses that have been cleared during 3+3 dose escalation during Part 1A.

Previous Text:

4.2 Inclusion Criteria

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

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

1. Part 1A: Male or female 16 years or older, at the time of signing the informed consent.

   Part 1B: Male or female 12 years to ≤15 years, at the time of signing the informed consent

   Part 2: Male or female 16 years or older, at the time of signing the informed consent. After completion of Part 1B, male or female 12 years to ≤15 years, at the time of signing the informed consent.

2. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. If the subject is less than 18 years old, an Assent form and Consent form (replacing “you will” with “your child will” will be required).

Revised Text:

4.2 Inclusion Criteria

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

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

1. Part 1A: Male or female 16 years or older, at the time of signing the informed consent.

   Part 1B: Male or female 12 years to ≤15 years, at the time of signing the informed consent

Part 2: Male or female 16 years or older, at the time of signing the informed consent. After completion of Part 1B, male or female 12 years ~~to ≤15 years~~, at the time of signing the informed consent.

2. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form. If the subject is less than 18 years old, an Assent form and **parental/guardian** Consent form (replacing "you will" with "your child will" will be required).

Rationale for Change:

A clarification was made to the age requirement in Part 2 and emphasis was added for the parental/guardian Consent Form.

Previous Text: Table 8 Time and Events: Part 1

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X	X	X			X	X	X	X	X			Daily									
Review subject diary	Diary not required when dosed in clinic.									X							X		X		X	X	X	X		
Safety																										
Pregnancy test/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X	X				X		X					X		X		X		X	X	X	X		X

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Pain		X	X	X				X		X					X		X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test		X																								
Adverse events		*continuous from signing of informed consent*																								
Concomitant medications		*continuous from signing of informed consent*																								
Laboratory assessments: For details please see following tables																										
Tests		X	X	X				X		X					X		X				X	X	X	X	X	X
Cardiac Monitoring																										
Echocardiogram	Within 35 days of first dose	X													X						X		X		X	X
12-lead ECGs	SCR ECGs within 35 days of first dose. For timing of ECGs on O days, see Table 10 and Table 11. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O	O	X		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min pre-dose.	X	X				X							X					X				X			
Telemetry	Start at least 60 min predose and for at least 48 h.		X	X																						
Efficacy																										
CT/MRI Scans	SCR assessment within 35 days of first dose. Target lesions to be identified at SCR and followed.	X																					X		X	X
Tumor sample	Optional during rapid dose escalation;	X				One postdose sample between W1D4 and W9D1, timing optimized based on																				X

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
	required during 3+3 dose escalation					tumor type and emerging data																				
PET scan	Optional during rapid dose escalation; required during 3+3 dose escalation	X																					X			
Neuroblastoma Assessments																										
CT/MRI	One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening assessment within 35 days of first dose	X																					X		X	
MIBG scan		X																					X		X	
FDG-PET		X																					X		X	
^{99}Tc scintigraphy for bone scan		X																					X		X	
Bilateral bone marrow aspirates and biopsy		X																					X		X	
Urine HVA, VMA, dopamine		X	X																		X		X	X		
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																										
PK and biomarker			X	X			X						X					X					X			

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
samples																										
Samples for mRNA		X	X	X														X								X
LPS blood sample			X																							
PK Urine samples			X															X								
Pharmacogenomics (PGx)																										
PGx sample			X																							
FOLLOW-UP PHASE																										

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; FLC=free light chain; HVA=homovanillic acid; LPS=lipopolysaccharide; MIBG=meta-iodo-benzyl-guanidine; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; VMA= vanillylmandelic acid; W=week

Revised Text: Table 8 Time and Events: Part 1

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X	X	X			X	X	X	X	X			Daily									
Review subject diary	Diary not required when dosed in clinic.									X							X		X		X	X	X	X		
Safety																										
Pregnancy test/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X	X				X		X					X		X		X		X	X	X	X		X
Pain		X	X	X				X		X					X		X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test		X																								
Adverse events		*continuous from signing of informed consent*																								
Concomitant		*continuous from signing of informed consent*																								

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
medications																										
Laboratory assessments: For details please see following tables																										
Tests		X	X	X				X		X					X		X				X	X	X	X	X	X
Cardiac Monitoring																										
Echocardiogram	Within 35 days of first dose	X													X						X		X		X	X
12-lead ECGs **(Triplicate)**	**Triplicate** SCR ECGs within 35 days of first dose. For timing of **triplicate** ECGs on O days, see Table 10 and Table 11. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O	O	X		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X	X				X							X					X				X			
Telemetry	Start at least 60 min predose and for at least 48 h.		X	X																						
Efficacy																										
CT/MRI Scans	SCR assessment within 35 days of first dose. Target lesions to be identified at SCR and followed.	X																					X		X	X
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation	X	One postdose sample between W1D4 and W9D1, timing optimized based on tumor type and emerging data																							X
PET scan	Optional during rapid dose escalation; required during 3+3 dose escalation	X																					X			

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Neuroblastoma Assessments																										
CT/MRI	One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening assessment within 35 days of first dose	X																					X		X	
MIBG scan[a]		X																					X		X	
FDG-PET		X																					X		X	
^{99}Tc scintigraphy for bone scan		X																					X		X	
Bilateral bone marrow aspirates and biopsy		X																					X		X	
Urine HVA, VMA, dopamine		X	X																		X		X	X		
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																										
PK and biomarker samples			X	X			X						X					X					X			
Samples for mRNA		X	X	X														X								X
LPS blood sample			X																							
PK Urine samples			X															X								
Pharmacogenomics (PGx)																										
PGx sample			X																							

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
FOLLOW-UP PHASE																										

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.
Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; FLC=free light chain; HVA=homovanillic acid; LPS=lipopolysaccharide; MIBG=meta-iodo-benzyl-guanidine; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; VMA= vanillylmandelic acid; W=week

a. **Subjects with neuroblastoma will have MIBG and bone marrow biopsies after week 24 as clinical indicated to confirm complete remission.**

Rationale for Change:

Corrections were made to the Table 8 to clarify that triplicate ECGs are collected during Part 1 and MIBG scan for subjects with neuroblastoma.

Previous Text: Table 9 Time and Events: Part 1 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	W1			W2		W3	W5	W7	W9	q4W	q8W	EOT
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP-9	W1D1, W1D2: local lab sample 3X/24h; central lab sample 1X/24h. Unscheduled collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X		X		X	X
Hematology		X	X		X			X	X	X	X	X		X
Clinical chemistry		X	X		X			X	X	X	X	X		X
Pancreatic		X	X		X			X	X	X	X	X		X
Coagulation		X	X		X			X	X	X	X	X		X
Creatine phosphokinase		X	X		X			X	X	X	X	X		X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**W1**			**W2**		**W3**	**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Liver chemistry		X	X		X			X	X		X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X			X	X	X	X	X		X
c-peptide and 1,5 AG	Will be performed at central lab if not available at local lab	X	X						X		X		X	
HbA1c		X	X					X	X		X		X	
Fasting lipids		X	X						X		X		X	X
Thyroid monitoring	TSH, free T3, free T4. If TSH is abnormal W1D1, monitor TSH, free T3 and free T4 going forward	X	X						X		X		X	X
Urinalysis		X	X						X		X		X	X
Guaiac fecal occult blood		X							X		X		X	
Pregnancy test, females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X						X		X	X		X
Testosterone, males	Complete and free testosterone at SCR; free testosterone thereafter	X	X						X		X	X		X
CK, CK-MB	Predose and 12-18 h post dose		X	*as clinically appropriate*										
Safety Cytokines		X	*as clinically appropriate following fever*											
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X												

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

Revised Text:

Table 9 Time and Events: Part 1 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**W1**			**W2**		**W3**	**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Troponin, NT-proBNP-9	W1D1, W1D2: local lab sample 3X/24h; central lab sample 1X/24h. Unscheduled collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X		X		X	X
Hematology		X	X		X			X	X	X	X	X		X
Clinical chemistry		X	X		X			X	X	X	X	X		X
Pancreatic		X	X		X			X	X	X	X	X		X
Coagulation		X	X		X			X	X	X	X	X		X
Creatine phosphokinase		X	X		X			X	X	X	X	X		X
Liver chemistry		X	X		X			X	X	**X**	X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X			X	X	X	X	X		X
c-peptide and 1,5 AG	Will be performed at central lab if not available at local lab	X	X						X		X		X	
HbA1c		X	X					X	X		X		X	
Fasting lipids		X	X						X		X		X	X
Thyroid monitoring	TSH, free T3, free T4. If TSH is abnormal W1D1, monitor TSH, free T3 and free T4 going forward	X	X						X		X		X	X
Urinalysis		X	X						X		X		X	X
Guaiac fecal occult blood		X							X		X		X	
Pregnancy test, females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X						X		X	X		X
Testosterone, males	Complete and free testosterone at SCR; free testosterone thereafter	X	X						X		X	X		X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**W1**			**W2**		**W3**	**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
CK, CK-MB	Predose and 12-18 h post dose		X	*as clinically appropriate*										
Safety Cytokines	**This is collected as part of the Predose PK sample and is sent to GSK DMPK.**	X	*as clinically appropriate following fever*											
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X												

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

Rationale for Change:

A correction was added to clarify that liver chemistry is collected at Week 7 Day 1.

Previous Text:

Table 10 Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1										**W1D5**		**W2D4 + 1 day**			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±2h**	**24h ±2h**	**33h ±3h**	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**
12-lead ECG, in triplicate, 5 minutes apart and within 10 min of PK draw	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sampling (Part 1A only)	X	0-2h			2-24h											

	W1D1										W1D5		W2D4 + 1 day			
	pre dose	15 min ± 5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	16h ±2h	24h ±2h	33h ±3h	30 min ±5m	3h ±15m	pre dose	30 min ±5m	3h ±15m	8h ±1h
mRNA whole blood sample	X				X	X	X		X	X						
LPS whole blood sample	X	X	X	X	X	X										

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment (pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr) and acute phase protein assessment at pre-dose and at 2,4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

Revised Text:

Table 10 Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1										W1D5		W2D4 + 1 day			
	pre dose	15 min ± 5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	16h ±2h	24h ±2h	33h ±3h	30 min ±5m	3h ±15m	pre dose	30 min ±5m	3h ±15m	8h ±1h
12-lead ECG, in triplicate, 5 minutes apart and within 10 **minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws** ~~min of PK draw~~	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	W1D1										**W1D5**		**W2D4 + 1 day**			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±2h**	**24h ±2h**	**33h ±3h**	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**
Urine PK sampling (Part 1A only)[a]	X	0-2h			2-24h											
mRNA whole blood sample	X				X	X	X		X	X						
LPS whole blood sample	X	X	X	X	X	X										

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment (pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr) and acute phase protein assessment at pre-dose and at 2,4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

a. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

Rationale for Change:

Flexibility was added to allow for the collection of blood samples for PK analysis at the earlier time points indicated. Urine samples are not required from the NMC PD Expansion Cohort for quantitative metabolite analysis of GSK525762 since samples will be collected in the 3+3 dose escalation.

Previous Text:

Table 11 Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days										**W9D1 ±4 days** (if dose has been escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±2h**	**24h ±1h**	**48h ±1h**	**pre dose**	**0.5-2h**	**4 - 8h**	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min of PK draw	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine PK sampling (Part 1A only)		0-2h			2-24h									
mRNA whole blood sample	X													X
LPS whole blood sample														

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment at pre-dose and at 2, 4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

Revised Text: Table 11 Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days										**W9D1 ±4 days** (if dose has been escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**16h ±4h**	**24h ±1h**	**48h ±1h**	**pre dose**	**0.5-2h**	**4 - 8h**	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min **prior** ~~of~~ **to the 15 min and 30 min** ~~of~~ **PK draws and within 15 minutes prior to the other** PK draw**s**	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine PK sampling (Part 1A only)[a]		0-2h			2-24h									
mRNA whole blood sample	X													X
LPS whole blood sample														

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment at pre-dose and at 2, 4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

a. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

Rationale for Change:

The window for collecting blood for PK and performing ECGs at the 16 hour time point was extended from 16h ± 2h to 16 ± 4h to allow for more flexibility in collecting samples at this timepoint. Urine samples are not required from the NMC PD Expansion Cohort for quantitative metabolite analysis of GSK525762 since samples will be collected in the 3+3 dose escalation.

Previous Text: **Table 12 Time and Events: Part 2**

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	q4W D1	q8W D1	EOT
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X										
Demography		X										
Medical history		X										
Disease characteristics		X										
Cardiology evaluation		X										
Prior therapy		X										
Register subject		X										
TREATMENT PHASE												
Study Drug												
Dispense study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X	X	X	X	X	X	X	X		
Review compliance	Not required when dosed in clinic.			X	X	X	X					
Safety												
Pregnancy test/testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X					X	X	X	X		X
Physical exam		X	X	X	X	X	X	X	X	X		X
ECOG		X	X	X	X	X	X	X	X	X		X
Vital Signs		X	X	X	X	X	X	X	X	X		X
Weight and height	Height at SCR only	X	X				X	X	X	X		X
Chest x-ray		X										
Pulmonary function test		X										
Adverse events		*continuous from signing of informed consent*										
Concomitant medications		*continuous from signing of informed consent*										
Laboratory assessments: For details please see following tables												
Tests			X	X		X	X	X	X	X	X	
Cardiac Monitoring												
ECHO	Within 35 days of first dose	X	X			X	X	X	X		X	X

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	q4W D1	q8W D1	EOT
12-lead ECGs (triplicate)	Screening ECGs within 35 days of first dose. Triplicate ECGs prior to dosing. If QTcF increase >30msec, ECGs daily through W2.	X	X	X	X	X	X	X	X		X	X
Holter monitoring	At least 24 h, on dosing days start predose.	X	X			X						
Telemetry	Starting predose and for at least 48 h.		X									
Efficacy												
Lesion assessments		X						X			X	X
Tumor sample		X	One postdose sample, between W1D4 and W9D1, timing optimized based on emerging data									
PET scan		X										
PK and PD												
PK and protein biomarker samples	Three samples to be collected each sampling day for each type of analysis: Predose within 60 minutes prior to dose, single draw between 0.5-2h postdose, single draw between 4-8h postdose. Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment.		X					X				
Blood samples for mRNA			X					X				X
LPS blood sample			X					X				
PGx												
PGx sample			X									
FOLLOW-UP PHASE												

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.

Abbreviations: CK=creatine kinase; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; q4W=every 4 weeks; q8W=every 8weeks; SCR=Screening; Wk=week

Revised Text: **Table 12 Time and Events: Part 2**

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	q4W D1	q8W D1	EOT
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X										
Demography		X										
Medical history		X										
Disease characteristics		X										
Cardiology evaluation		X										
Prior therapy		X										
Register subject		X										
TREATMENT PHASE												
Study Drug												
Dispense study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X	X	X	X	X	X	X	X		
Review compliance	Not required when dosed in clinic.			X	X	X	X					
Safety												
Pregnancy test/testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X					X	X	X	X		X
Physical exam		X	X	X	X	X	X	X	X	X		X
ECOG		X	X	X	X	X	X	X	X	X		X
Vital Signs		X	X	X	X	X	X	X	X	X		X
Weight and height	Height at SCR only	X	X				X	X	X	X		X
Chest x-ray		X										
Pulmonary function test		X										
Adverse events		*continuous from signing of informed consent*										
Concomitant medications		*continuous from signing of informed consent*										
Laboratory assessments: For details please see following tables												
Tests			X	X		X	X	X	X	X	X	
Cardiac Monitoring												
ECHO	Within 35 days of first dose	X	X			X	X	X	X		X	X

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	q4W D1	q8W D1	EOT
12-lead ECGs (~~triplicate~~ Single)	Screening ECGs within 35 days of first dose. ~~Triplicate~~ECGs prior to dosing. If QTcF increase >30msec, ECGs daily through W2.	X	X	X	X	X	X	X	X		X	X
Holter monitoring	At least 24 h, on dosing days start predose.	X	X			X						
Telemetry	Starting predose and for at least 48 h.		X									
Efficacy												
Lesion assessments		X						X			X	X
Tumor sample		X	One postdose sample, between W1D4 and W9D1, timing optimized based on emerging data									
PET scan		X										
PK and PD												
PK and protein biomarker samples	Three samples to be collected each sampling day for each type of analysis: Predose within 60 minutes prior to dose, single draw between 0.5-2h postdose, single draw between 4-8h postdose. Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment.		X			**X**		X				
Blood samples for mRNA			X					X				X
LPS blood sample			X					X				
PGx												
PGx sample			X									
FOLLOW-UP PHASE												

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.

Abbreviations: CK=creatine kinase; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; q4W=every 4 weeks; q8W=every 8weeks; SCR=Screening; Wk=week

Rationale for Change:

Corrections were made to clarify that single ECGs are collected in Part 2 and PK collection on Week 4 Day 1 to coincide with Holter monitoring.

Previous Text:

6.6.3 Urine Collection

Urine samples for quantitative analysis of GSK525762 will be collected over 24 hours in two samples (sample collected 0-2hr and second sample collected 2-24hr) immediately following dosing on Week 1 Day 1 and in Week 3. Urine samples will be collected in subjects in Part 1A once the 3+3 dose escalation has been reached. Additional sampling may be instituted based on emerging data.

Revised Text:

6.6.3 Urine Collection

Urine samples for quantitative analysis of GSK525762 will be collected over 24 hours in two samples (sample collected 0-2hr and second sample collected 2-24hr) immediately following dosing on Week 1 Day 1 and in Week 3. Urine samples will be collected in subjects in Part 1A once the 3+3 dose escalation has been reached. Additional sampling may be instituted based on emerging data. **Urine collection will not be required in the PD Expansion Cohort.**

Rationale for Change:

Urine samples are not required from the NMC PD Expansion Cohort for quantitative metabolite analysis of GSK525762 since samples will be collected in the 3+3 dose escalation.

Previous Text:

6.4.5 Safety Electrocardiograms

Safety ECGs will be performed at the time points specified in Time and Events using a standard 12-lead ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF intervals. Details will be provided in the SPM. In Part 1, the investigator will review the ECG data manually, and should not rely solely on the automatic readings of the equipment, when making decisions regarding dosing of subjects.

- During Part 1, a single 12-lead ECG should be performed at Screening and at all other time points that are not associated with a Serial Pharmacokinetic sampling day. Triplicate ECGs should be done for all time points on Serial Pharmacokinetic sampling days.

Standard 12-lead ECGs (Safety ECGs) will be performed as part of the real-time assessment of subjects and may not be included in the primary QT analysis. Safety ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

In addition to the Safety ECGs performed during the study, continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired while subjects are at the site. Dual snap electrodes will be utilized to enable simultaneous collection of Holter and safety ECG data.

All ECGs must include QTcF measurements. Those values greater than 480 msec as calculated by the machine must be confirmed manually using Fridericia's formula given below:

- The Fridericia's formula is: QTcF=QT x (1/[RR/1000])1/3
- If there are any clinically significant abnormalities including but not limited to a QTcF >480 msec, confirm with two additional ECGs taken at least 5 minutes apart.
- During Part 1, a single 12-lead ECG should be performed at screening and at all other time points that are not associated with a serial pharmacokinetic sampling day. Triplicate ECGs should be done for all time points on serial pharmacokinetic sampling days. During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Time and Events Tables.

Revised Text:

6.4.5 Safety Electrocardiograms

Safety ECGs will be performed at the time points specified in Time and Events using a standard 12-lead ECG machine that automatically calculates the HR and measures PR, QRS, QT and QTcF intervals. Details will be provided in the SPM. In Part 1, the investigator will review the ECG data manually, and should not rely solely on the automatic readings of the equipment, when making decisions regarding dosing of subjects.

- During Part 1, a ~~single~~ **triplicate** 12-lead ECG should be performed at Screening and at all other time points. ~~that are not associated with a Serial Pharmacokinetic sampling day.~~ Triplicate ECGs should be done for all time points on Serial Pharmacokinetic sampling days. **During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Time and Events Tables.**

Standard 12-lead ECGs (Safety ECGs) will be performed as part of the real-time assessment of subjects and may not be included in the primary QT analysis. Safety ECGs should be reviewed by the investigator on an ongoing basis for safety purposes. The dosing for each new week in the first cycle should not begin until the safety ECG has been reviewed and no significant abnormalities have been detected

In addition to the Safety ECGs performed during the study, continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired while subjects are at the site. Dual snap electrodes will be utilized to enable simultaneous collection of Holter and safety ECG data.

All ECGs must include QTcF measurements. Those values greater than 480 msec as calculated by the machine must be confirmed manually using Fridericia's formula given below:

- The Fridericia's formula is: QTcF=QT x (1/[RR/1000])1/3
- If there are any clinically significant abnormalities including but not limited to a QTcF >480 msec, confirm with two additional ECGs taken at least 5 minutes apart.
- ~~During Part 1, a single 12-lead ECG should be performed at screening and at all other time points that are not associated with a serial pharmacokinetic sampling day. Triplicate ECGs should be done for all time points on serial pharmacokinetic sampling days. During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Time and Events Tables.~~

Rationale for changes:

Corrections were made to clarify that triplicate ECGs are collected in Part 1 and single ECGs are collected in Part 2.

Previous Text:

If a subject vomits within four hours after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.

Revised Text:

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose. ~~If a subject vomits within four hours after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.~~

Rationale for Change:

The instructions for subjects who vomit after taking study drug was corrected to reflect the dosing instructions in Table 17.

Other Changes:

The protocol was updated to change EKG to ECG for consistency.

AMENDMENT 04

Protocol Changes for Amendment 4 (06-OCT-2014) from the Protocol Amendment 3 (04-FEB-2014)

Protocol Amendment 4 applies to all site(s) participating in the conduct of the study

Amendment 04 summary: Amendment 04 includes the addition of subjects with the following solid tumor types: castration-resistant prostate cancer (CRPC), triple negative breast cancer (TNBC) estrogen receptor positive breast cancer (ER positive), and non-small cell lung cancer (NSCLC). Multiple myeloma (MM), a haematological malignancy previously included in the trial, is now removed from this trial as it is included in a separate trial open for hematologic malignancies with dose escalation to better define the benefit/risk balance. Additional details of twice daily (BID) dosing during dose escalation have been included. A Besylate Sub-Study has been added to determine the relative bioavailability (BA), food effect, and dose proportionality of the besylate formulation of GSK525762 at or near the MTD. An update to inclusion criteria has been made to allow subjects with evaluable disease to be enrolled in the NMC PD cohort. An updated imaging schedule for NMC subjects has been included.
Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

List of Specific Changes

Title Page

Added Text:

<u>Description</u>

<u>This is an open-label, single and repeat dose, multicenter, 2 part study to determine the MTD and the recommended Phase 2 dose (RP2D) for GSK525762 given orally once or twice daily. Part 1 will be conducted in subjects with NMC and other solid tumors in adult subjects (Part 1A) and pediatric subjects (Part 1B). Expansion cohorts (Part 2) are planned to further explore the clinical activity of GSK525762 in subjects with NMC and other specific solid tumors based on emerging data.</u>

Subject

Revised Text:

Oncology, GSK525762, BET ~~inhibitor~~<u>Inhibitor</u>, NUT Midline Carcinoma, NMC<u>,</u>
<u>Bromodomain Inhibitor, BRD3, BRD4.</u>

Authors

Revised Text:

PPD

Oncology Biomarkers, USA
Biology, Epigenetics Management, USA
Global Formulation Development, PTS, USA
Biotransformation and Drug Disposition, PTS, UK
Molecular Medicine Unit, USA
Cancer Research Epigenetics Management, USA
Clinical Pharmacology Modeling & Simulation, USA
Global Clinical Operational Sciences, USA
Global Clinical Operational Sciences, USA
Cancer Research Epigenetics, USA
SA Pathology, PTS, UK
Global Clinical Safety & Pharmacovigilance, USA
EpiNova DPU, UK
Global Clinical Safety & Pharmacovigilance, USA
PPD Biology, Epigenetics Management, USA
Statistics, Oncology TA Group, USA

Sponsor/medical monitor Information Page

Rationale for Change: The sponsor and medical monitoring information has been updated based on internal GSK team personnel changes.

Medical Monitor and Sponsor Contact Information

Revised Text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD , MD, PhD	PPD			GlaxoSmithKline 1250 South Collegeville Road, ~~UP4210~~ UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD	PPD			GlaxoSmithKline 1250 South Collegeville Road Mailstop UP 4410 Collegeville, PA 19426, USA PPD

Section PROTOCOL SYNOPSIS

Objectives and Endpoints

Rationale for Change: Primary Objectives and Endpoints were updated to include goals of the besylate sub-study and reference to BID dosing.

Revised Text:

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older <u>following QD and/or BID dosing schedules</u>. • To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 12 to ≤15 years old • To evaluate the clinical activity of GSK525762 in NMC • <u>To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets</u>.
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 16 years or older • AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 12 to ≤15 years old. • Assess overall response rate (RR) by RECIST 1.1 in NMC • <u>PK parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet.</u>

Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • To characterize the pharmacokinetics (PK) of GSK525762 in subjects 12 to ≤15 years old • To evaluate cardiac safety, including the potential for QTcF, of GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival • To evaluate systemic and ex vivo on-target BET inhibitory effects

Study Design And Duration

Rationale for Change: The study design was updated to include"recommended phase 2 dose (RP2D)" in addition to recommended dose for Part 2" to better summarize the long-term goal of determining the MTD which will aim to expand beyond Part 2 of the trial.

The study design was also updated to include the additional tumor types allowed with this amendment and multiple myeloma subjects were removed. The rationale for including additional solid tumors is included as part of the overall Study Population Rationale (Section 1.2). Multiple myeloma subjects will now be excluded from further enrolment in this solid tumor trial, as there is now a separate phase 1 dose escalation trial open in for hematologic malignancies to better define the benefit/risk balance. It has been difficult to enrol MM patients to this trial (1 out of 18 subjects over 2 years) and the higher doses already reached with solid tumors pose additional risk to MM patients.

Revised Text:

This study is divided into 2 parts:

- Part 1A of the study is a dose escalation phase to determine the maximum tolerated dose (MTD) and select ~~the~~ a recommended dose for Part 2 or a recommended Phase 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma (NMC), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, ~~multiple myeloma~~ and any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects with NMC will also be enrolled in a pharmacodynamic dose expansion cohort during Part 1A.

Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. ~~Once the MTD is determined in adult subjects,~~

- Part 1A besylate sub-study will explore the relative bioavailability, food effect and dose proportionality of besylate formulation. The sub-study will be conducted in subjects eligible for Part 1A at the MTD or a dose near the MTD or RP2D. This will be an open-label, randomized, single dose, four period, cross over sub-study to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as besylate tablets.
- Part 1B will be opened to enroll pediatric subjects 12 to ≤15 years of age with solid tumors to determine the MTD in pediatric subjects. Dose escalation in Part 1B will begin at 25% of the adult MTD and dose escalation will follow a 3+3 design. Pediatric subjects 12 to ≤ 15 years old may be enrolled in Part 2 once the MTD has been determined in Part 1B. ~~An~~
- Part 2 is an expansion cohort ~~is~~ planned to further explore clinical activity at the MTD in NMC ~~(Part 2)~~ subjects.
- Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

Subject Sample

Rationale for Change: Overall subject numbers were increased to account for the subjects in the besylate sub-study.

Revised Text:

Approximately 70-~~90~~100 subjects worldwide.

Section 1.2. Study Population Rationale

Rationale for Change:Updated various references and resources to reflect most current publication. Updated study population rationale section to include recent preclinical and other emerging data for inclusion of select solid tumor types. Multiple myeloma was removed from this section.

Revised Text, Section 1.2.1. NUT midline carcinoma

Paragraph 1:

NMCs are invariably lethal and despite aggressive chemotherapeutic regimens, subjects have a median life expectancy of only 6.7 months (N=63 patients) [Bauer, 2012, ~~personal communication~~ PPD].

Revised Text, Section 1.2.2

1.2.2. Other ~~solid tumors~~ tumor types

Recently published data as well as data generated internally at GSK and by collaborators have demonstrated the potential application of BRD extra-terminal (BET) inhibitors in tumor types other than NMC, including ~~multiple myeloma (MM),~~ small cell lung cancer (SCLC), ~~colorectal cancer (CRC)~~non-small cell lung cancer (NSCLC), colorectal cancer (CRC), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC); estrogen receptor positive (ER positive) breast cancer, neuroblastoma (NB), acute leukemias, and other N-Myc driven tumors. Studies in leukemia and MM have shown that small molecule inhibition of BET protein binding to chromatin can directly block both c-Myc expression and its downstream transcriptional functions, resulting in significant anti-tumor effects [Delmore, 2011; Mertz, 2011]. Myc family proteins play a central role in the regulation of gene expression and cell cycle control. Their enhanced expression has been implicated in all aspects of tumor cell biology [Adhikary, 2005].

Based on the preclinical findings within GSK, subjects with ~~the multiple myeloma,~~ small cell lung cancer, ~~colorectal~~non-small cell lung cancer (NSCLC), colorectal cancer, castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, neuroblastoma, and N-Myc amplified solid tumors will be enrolled to the dose finding part of the study.

~~***Multiple Myeloma***~~

~~Recent publications demonstrated silencing of c-Myc expression by BET inhibitors in MM [Delmore, 2011], Burkitt's lymphoma, and acute myeloid leukemia [Mertz, 2011].~~

~~A high percentage of MM lines (62%, 13/21) are sensitive to GSK525762, most of which are Myc driven. Relapsed refractory myeloma patients will be eligible for the dose escalation part of the study. Given the sensitivity of a majority of MM lines tested and that most were Myc driven, a selection marker will not be used for entry into the dose escalation part of the study. However, data will be collected retrospectively from available tissues in order to identify potential predictive biomarkers.~~

Small Cell Lung Cancer

GSK525762 was found to inhibit growth ~~of the great majority of all SCLC lines tested, with 33 of 37 lines possessing gIC_{50} < 10 µM. In order to identify the more sensitive cell lines, the criterion for GSK525762 sensitivity was defined as gIC_{100} (concentration resulting in net cell death) < 10 µM. By this definition, 38% (14/37) of SCLC lines are~~

~~more sensitive~~ in a subset of SCLC cell lines, with 46% (18 of 39) of cell lines possessing a gIC_{50} < 1 µM. It was confirmed in several of the cell lines that apoptosis (assessed by caspase cleavage) is induced at concentrations above the gIC_{100}. ~~In the 14 most sensitive cell lines, the median gIC_{50} = 0.53 µM and the median gIC_{100} = 2.2 µM. For comparison, GSK525762 has been tested in two cultured lines from NUT-midline carcinoma with an average gIC_{50} = 0.12 µM and average gIC_{100} = 0.32 µM~~ Additionally, significant tumor growth inhibition was observed in a subset of cell line and patient-derived subcutaneous xenograft models of SCLC.

No correlation between status of c-Myc or L-Myc and sensitivity was found. N-Myc amplified cell lines were found to be sensitive, though the low number (N=2) of lines tested with this amplification does not allow for a firm conclusion to be drawn. Although no predictive marker of GSK525762 sensitivity in SCLC has been identified and considering the high percentage of cell lines that are sensitive, we would enroll all relapsed refractory SCLC patients in the dose escalation part of the study while collecting data retrospectively on potential predictive biomarkers from the available tissues.

Non-Small Cell Lung Cancer

GSK525762 inhibited cell growth in a high percentage of NSCLC cell lines, with 73% (19/26) of cell lines tested exhibiting a gIC_{50} <1µM. Median gIC_{50} across the NSCLC cell line panel was 0.61µM. MYCN amplified cell lines were among the most sensitive NSCLC cell lines to GSK525762, with a median gIC_{50} of 0.17µM and gIC_{100} of 3.6µM (n=4). A subset of NSCLC cell lines, including the MYCN-amplified lines, exhibited a cytotoxic response to GSK525762. Given the broad sensitivity of NSCLC cell lines to GSK525762, a selection marker will not be used for entry into the dose escalation part of the study.

Colorectal Cancer

In colorectal cell lines, initial data using the same criterion of sensitivity indicates that GSK525762 ~~is cytotoxic~~ inhibits growth in a high percentage of lines tested (~~54%, 7/13~~58%, 25/43 with ~~gIC_{100} < 10 µM). In the 7 sensitive cell lines, the median~~ gIC_{50} = ~~0.18 µM and the median gIC_{100} = 2.2 µM. Also, GSK525762 was found to be sensitive in KRAS-mutant colorectal lines, as 5/7 sensitive lines possess this mutation~~ < 1 µM). No markers of sensitivity in these lines has been identified yet and, as with SCLC, we recommend dosing of all relapsed refractory CRC without a selection marker in an initial clinical trial.

Neuroblastoma

~~All~~ NB cell lines are sensitive to GSK525762, with 83% of cell lines tested ~~to date (n = 6) were found to be sensitive to GSK525762, with an average~~ (15/18) exhibiting a gIC_{50} ~~= 0.43 µM (n=6) and average gIC_{100} = 2.3 µM (n=4). The agent is sensitive in *MYCN*-amplified lines, as 3 of the 4 lines~~ < 1µM. Median gIC_{50} across the NB cell line panel was 0.48µM, with a subset of cell lines exhibiting a cytotoxic response to GSK525762. The agent is sensitive in *MYCN* amplified cell lines, as 10 of the 15 sensitive cell lines possess the copy number increase. As with MM, ~~CRC, and~~ SCLC, ~~subjects with NB may be eligible without regard to N-myc status .~~

~~***N-Myc amplified solid tumors***~~

~~N-Myc driven solid tumors from different sources have shown to be sensitive to GSK525762. GSK525762 was tested in a panel of~~ NSCLC ~~lines~~, and ~~N-Myc amplification was found to be~~ CRC, a selection marker ~~of sensitivity. One hundred percent (5/5) of N-Myc amplified lines were highly sensitive while only 8.3% (1/12) of non N-Myc amplified lines were highly sensitive. GSK525762 possesses a median gIC50 = 0.37 µM (n=5), gIC100 = 4.7 µM (n=4), in N-Myc amplified cell lines~~ will not be used in NB patients for entry into the dose escalation part of the study.

Castration-Resistant Prostate Cancer

A subset of protate cancer cell lines were found to be sensitive to GSK525762, with 57% (4/7) of cell lines exhibiting a gIC_{50} <1µM. Apoptosis was observed in a subset of prostate cancer cell lines as measured by poly ADP ribose polymerase (PARP) cleavage and accumulation of cells in sub-G1 phase of cell cycle. Prostate cancer lines cell lines, including models of CRPC, with high androgen receptor (AR) and high c-Myc protein expression were found to be the most sensitive (lowest gIC_{50}) to GSK525762A. Consistent with in vitro observations, significant tumor growth inhibition was observed in a subcutaneous patient-derived xenograft model of CRPC expressing high levels of AR and MYC. In contrast, no significant inhibition of tumor growth was observed in a second model expressing low levels of AR and MYC. Given the limited availability of pre-clinical prostate models and the broad sensitivity of prostate cancer cell lines to GSK525762, we recommend that no selection marker be used for entry into the dose escalation part of the study.

Triple Negative and ER-positive Breast Cancer

A subset of breast cancer cell lines representing the ER-positive and triple negative sub-types were found to be sensitive to GSK525762, with 55% (17/31) cell lines tested exhibiting a gIC_{50} < 1µM. Median gIC_{50} across the breast cancer cell line panel was 980nM, with a subset of cell lines exhibiting a cytotoxic response to GSK525762.

The activity observed with GSK525762 in ER+ breast cancer cell lines is consistent with data reported in two recent publications using the tool BET inhibitor JQ1 [Feng Q, 2014; Nagarajan, 2014]. Given the broad activity of BET inhibitors across the ER+ and triple negative subtypes, we recommend that no selection marker be used for entry into the dose escalation part of the study for ER-positive and TNBC patients.

N-Myc amplified solid tumors

A large majority of N-Myc amplified cell lines from various tumor types, including SCLC, NSCLC, and neuroblastoma, are highly sensitive to GSK525762. Across the three tumor types, 16 of 19 (84%) *MYCN*-amplified cell lines possess a gIC_{50} < 1µM, and 11 of 19 (58%) exhibit a cytotoxic response to GSK525762. Expression of *MYCN* was suppressed by GSK525762 in SCLC and NB cell lines, which is consistent with published reports [Puissant 2013; Wyce 2013].

Given the high percentage of responsive cell lines in ~~multiple myeloma,~~ small cell lung cancer, non-small cell lung cancer, colorectal, castration-resistant prostate cancer, triple-negative breast cancer, ER-positive breast cancer, and neuroblastoma it is appropriate to include refractory patients who have failed prior treatments regimens into the dose escalation phase of this study where this medicine may prolong survival. In addition subjects with any solid tumor that demonstrates N-~~myc amplification (e.g., NSCLC with N-~~Myc amplification~~)~~ will be eligible for the dose escalation phase of the study.

Section 1.3 Dose Rationale

Rationale for Change: Updated with clinical pharmaocokinetic data from subjects enrolled to date on ongoing trial to support continuation of dose escalation in effort to determine MTD. Also included rationale for BID dosing supported by preclinical and clinical pharmaocokinetic and pharmacodynamic data.

Revised Text, Section 1.3.1

1.3.1 Human ~~Pharmacokinetic extrapolation~~ Pharmacokinetics

Whole blood human clearance was predicted from three species (mouse, rat and dog) using simple power-law allometry (in the absence of detectable in vitro metabolism) to be 2.8 ml/min/kg. Volume of distribution was predicted from Gastroplus to be 2.6 L/kg and half-life 10 hours (GlaxoSmithKline Document Number 2010N108204_00, 2011). As the in vitro blood to plasma ration was 0.86, a 70 kg adult therefore has predicted total clearance of 10.1 L/hr and a total plasma volume of distribution of 157 L. Bioavailability is predicted to be high given GSK525762 is a Bio-pharmaceutics Classification System (BCS) Class 1 molecule, and assumed to fall in the range 50-100%.

As of 23-July-2014, the pharmacokinetics of GSK525762 has been evaluated in 19 subjects following single and repeated daily administration of 2 mg to 60 mg of GSK525762. The summary statistics of the preliminary PK parameters are summarized in Table 1 and Table 2 after single and repeat daily oral administration, respectively. GSK525762 pharmacokinetics are characterized by a rapid absorption with maximum concentration occurring mostly within the first hour after dosing. GSK525762 is eliminated rapidly with an average terminal phase half-life of 3 to 7 hours, leading to a lack of accumulation following once daily oral administration. Following single oral administration and repeated once daily administration of 2 mg to 60 mg of GSK525762, C_{max} and AUC tended to increase in a dose proportional fashion.

Table 1 Summary Statistics of GSK525762 Preliminary PK Parameters Following a Single Oral Administration of GSK525762 in Study BET115521

Parameters	Unit	2 mg N=3	4 mg N=4	8 mg N=1	16 mg N=3	30 mg N=4	60 mg N=4
Cmax	ng/mL	51.0 (41%)	70.4 (29%)	120	176 (37%)	604 (30%)	940 (31%)
tmax	h	0.5 (0.5 - 0.6)	1.2 (0.5 - 2.0)	1.1	2.0	2.0 (0.97 - 2.0)	1.0 (0.5 - 2.0)
AUC	ng.h/mL	172 (42%)	361 (35%)	434	884 (40%)	4420 (63%)	3720 (57%)
$t_{1/2z}$	h	3.3 (103%)	5.1 (36%)	2.95	6.9 (46%)	6.4 (37%)	6.1 (49%)

Note: Data are presented as geometric mean (CV%) for all parameters except for tmax where the median (min-max) are presented. If N=1, individual data are presented. Cmax is the maximum concentration observed at time tmax. AUC is the area under the concentration-time curve from 0 to infinity. T1/2 is the terminal phase half-life.

Table 2 Summary Statistics of GSK525762 Preliminary PK Parameters Following Repeat Daily Oral Administration of GSK525762 in Study BET115521

Parameters	Unit	2 mg N=1	4 mg N=2	8 mg N=1	16 mg N=3	30 mg N=4	60 mg N=2
Cmax	ng/mL	52	47.6 ; 59.9	103	138 (25%)	603 (17%)	602; 736
tmax	h	1.0	1.0 ; 4.0	0.5	1.5	0.9 (0.32 - 4.0)	1.0 ; 1.0
AUCτ	ng.h/mL	160	225 ; 497	330	674 (21%)	3150 (55%)	2010; 5290
$t_{1/2z}$	h	4.27	3.69 ; 4.46	4.92	3.6 (7.8%)	5.2 (26%)	2.5; 4.9
Cmax Week 3 / Cmax Week 1	--	1.42	0.968 ; 0.609	0.857	0.780 (12%)	0.998 (24%)	1.01; 1.23
AUCτ Week 3 / AUC Week 1	--	1.38	0.900 ; 1.64	0.759	0.774 (20%)	0.724 (12%)	0.898; 0.712
AUCτ week 3 / AUCt Week 1	--	1.39	0.904 ; 1.67	0.763	0.792 (20%)	0.799 (11%)	0.902; 0.778

Note: Data are presented as geometric mean (CV%) for all parameters except for tmax where the median (min-max) are presented. If N=1 or 2, individual data are presented. Cmax is the maximum concentration observed at time tmax. AUCτ is the area under the concentration-time curve from 0 to 24 hours, the end of the dosing interval. T1/2 is the terminal phase half-life.

Added Text:

1.3.5. BID Dose Cohort

1.3.5.1. Preclinical Rationale

Pre-clinical pharmacokinetic and pharmacodynamic data suggests a potential benefit of a BID dosing regimen compared to QD dosing. In mice, GSK525762 has a short half-life of about 1.5 hours. Single dose pharmacodynamic experiments were performed in three SCLC and one CRC mouse xenograft model. Dose-dependent changes in gene expression were observed in all models at early time points post-dose; however, expression returned to pre-treatment levels within 8-12 hours. Additionally, in a subcutaneous multiple myeloma cell line xenograft study, c-Myc protein levels were significantly reduced 2 and 5 hours post-dose, and returned to baseline by 8 hours.The transient effects on gene expression observed in these studies with QD dosing highlights the potential benefit of BID dosing by extending the duration of gene silencing within a 24 hour period.

QD and BID dosing have been further explored in efficacy studies in the above-mentioned SCLC and CRC xenograft models. In a subcutaneous, patient-derived model of SCLC, BID dosing at 12.5mg/kg resulted in improved tumor growth inhibition compared to 25 mg/kg QD (74% versus 60%, respectively). Improved efficacy with BID dosing was also observed in the cell line xenograft model of CRC. BID dosing at 12.5mg/kg resulted in 48% tumor growth inhibition, whereas 25mg/kg QD dosing resulted in 34% inhibition. In a third model, a cell line xenograft of SCLC, there was no significant difference in tumor growth inhibition resulting from 12.5mg/kg BID versus 25mg/kg QD dosing. Thus, we observed equivalent or improved efficacy with BID dosing in all xenograft models tested.

1.3.5.2. Clinical Rationale

Based on the pharmacokinetics of GSK525762 observed to date, with the short half-life of about 5 hours, it is predicted that even 100 mg QD doses would result in the trough concentrations falling below the average in vitro IC50 (0.08 uM to 1.3 uM) for the tumor types selected for this study. Dividing the daily dose into two doses administered about 12 hours apart would maintain the concentrations above the lower in vitro IC50 for doses around 30 mg BID.

1.3.6. Doses for Besylate Bioavailability/Food Effect/Dose Proportionality Sub-Study

A dose at or near the maximum tolerated dose or the recommended Phase 2 dose will be used to evaluate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet, as this dose would be the dose level used in Part 2.

As GSK525762 is a compound with high solubility but low permeability, it is expected that administration with food will have no effect or possibly a negative effect on its absorption [Gu, 2007] Pharm Res 2007, and a dose at or near the MTD or RP2D will be used to evaluate the effect of food on the relative BA of GSK525762 administered as the besylate salt tablet.

In addition, to evaluate the dose proportionality of the PK of GSK525762 after fasted administration as besylate salt tablet, a lower dose of half to one-third of the MTD or RP2D will be evaluated.

Section 1.4 Rationale for Study and Endpoints

Rationale for Change: Updated this section to include additional solid tumors and the besylate sub-study and to removemultiple myeloma.

Study schema was replaced to provide additional clarification and to include the Besylate sub-study. A separate schema was included to illustrate the besylate sub-study.

Revised Text:

Safety and efficacy (RR) 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 of once daily and/or twice daily dosing. The pharmacodynamic assessments will further support the recommended Phase II doses (RP2D) and expand the understanding regarding mechanism of action. The response rate hurdle of 20% in NMC was determined based on 3 parameters: NMC is a rare population, there is currently no standard of care therapy for NMC, and NMC carries a poor prognosis (median survival of ~~9.5~~6.7 months ~~[French, 2010]~~ [Bauer, 2012]).

Given the poor prognosis and high unmet medical need of NMC, as well as in other tumor types such as relapsed/refractory SCLC, NSCLC, CRC, MM, ~~NB~~CRPC, TN and ER+ BC, NB and N-Myc amplified tumors and the exceptional drug-to-target alignment of GSK525762, a combined Phase I/II study (BET115521) is proposed. The BET115521 study comprises an accelerated dose titration (Part 1), which will include subjects with NMC and other tumor types that are predicted to be responsive to GSK525762, to determine a maximum tolerated dose (MTD). The besylate sub-study will be an open-label, randomized, single dose, four period, crossover sub-study to investigate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet at a dose at or near the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate salt tablet at or near the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate salt tablets. Results of the besylate sub-study will enable the use of the besylate salt tablet formulation later in this study and provide recommendation around the need for fasting status when administering GSK525762.

The recommended phase II dose (RP2D) of GSK525762 with possible adjustment based on the relative bioavailability of the besylate salt formulation, will be studied in the cohort expansion (Part 2) to determine efficacy, safety and tolerability in NMC patients.

Section 1.5. Risk Assessment

Rationale for Change: Minor updates for clarification are included in this section. The risk assessment was also updated to include reproductive risks based on emerging preclinical data.

Revised Text:

Paragraph 1:

~~However, toxicology~~Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK525762 are gastrointestinal, cardiovascular, pancreatic, hematologic and reproductive (see Clinical Investigational Brochure, Section 3.4).

*Paragraph 7 (**Telemetry**)*:

Continuous telemetric in-patient monitoring for potential adverse arrhythmias will be performed for at least 48 hours from the ~~start~~administration of ~~each~~ the first dose.

Paragraph 8 Heading:

Holter Monitoring and Serum Markers

*Paragraph 11 (**Cytokines**)*:

In vitro incubation of human whole blood for 24 hours with GSK525762 resulted in a time and concentration-dependent induction of IL-1β. The maximum effect was variable between donors (34 to 3986 pg/mL, mean 1238 pg/mL from 16 donors); however, the concentration required to drive this effect was consistent across the donors (pEC_{50} 6.0, 0.42ug/mL). This effect was not observed in whole blood from other species (rat and dog) or in preparations of human PBMCs or neutrophils. ~~A human Cmax of 0.42 ug/mL would only be anticipated above the preclinical MTD (human doses 75-100 mg). Parity at Cmax for the EC20 from the most sensitive donor in these studies (pEC20 6.16, 0.29 ug/mL) is predicted to correspond to ~ 50 mg of a dose in humans.~~ Special note is made for the occurrence of fever which could be symptomatic of cytokine level elevation during dosing of the compound (see protocol Section 7.7, Table 28 "Fever"), and close monitoring of cytokine levels will be instigated at this point.

Added Text:

Preliminary rat embryo fetal development

GSK525762 at 0, 1, 3, 10, or 30 mg/kg/day (total dose; doses expressed as parent compound) was given orally by gavage BID (doses given 6 hours apart) to pregnant rats on Days 0 through 17 post-coitus. Dose-dependent maternal toxicity (reduced body weight gain and reduced food consumption) was evident at ≥10 mg/kg/day. Embryo-fetal toxicity was evident as both pre-implantation loss and increased fetal resorptions leading to complete loss of litters at 30 mg/kg/day, and dose-dependent increased fetal resorptions at doses ≥1 mg/kg/day. Developmental toxicity was evident as decreased fetal weights at 10 mg/kg/day and fetal malformations and/or variations at all doses

(membranous ventricular septal defects in the heart ≥1 mg/kg/day; great vessel, heart, kidney, ovary, uterus, and ureter malformations and/or variations at 10 mg/kg/day). The AUC0-t and Cmax at 1 mg/kg/day (the lowest dose tested) in non-mated female rats after 5 doses were 54 ng.h/mL and 18 ng/mL, respectively.

Section 2. Objectives, Endpoints, Hypotheses

Rationale for Change: Primary Objectives and Endpoints were updated to include goals of the besylate sub-study and reference to BID dosing.

Revised Text:

2. OBJECTIVES, ENDPOINTS, HYPOTHESES FOLLOWING QD AND/OR BID DOSING SCHEDULES

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 12 to ≤15 years old • To evaluate the clinical activity of GSK525762 in NMC • To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 16 years or older • AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 12 to ≤15 years old. • Assess overall response rate (RR) by RECIST 1.1 in NMC • PK parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet.

Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • To characterize the pharmacokinetics (PK) of GSK525762 in subjects 12 to ≤15 years old • To evaluate cardiac safety, including the potential for QTcF, of GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival • To evaluate systemic and ex vivo on-target BET inhibitory effects

Section 3.1. Study Design/Schematic

Rationale for Change: Updated this section to include additional solid tumors and the besylate sub-study and to removemultiple myeloma.

Revised Text:

Paragraph 2:

This is an open-label, single and repeat dose, 2-part study to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily orally. Twice daily dosing may also be explored upon evaluation of safety, PK, and PD data from once-daily dosing. ~~(~~Part 1A~~)~~ will be conducted in adult subjects with NMC, ~~multiple myeloma (MM),~~ small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and MYCN driven solid tumors ~~[including non-small cell lung cancer (NSCLC) with MYCN amplification]~~. During the dose escalation of Part 1A, additional subjects with NMC will be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamic effects of GSK525762 at lower doses that have been previously cleared during dose escalation. This will enable collection of pharmacodynamic data across the predicted efficacious dose range and contribute to the evaluation of a biologically efficacious dose. ~~Once the RP2D is determined in adult subjects, Part 1B will be opened to enroll pediatric subjects 12 to ≤15 years of age with solid tumors to determine the RP2D in this age group~~. Once the RP2D is determined in Part 1A, a besylate sub-study will be opened to approximately 10 subjects to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet at the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet at the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate tablet. This sub-

study will also use a stable isotope of GSK525762 in order to reduce the variability in the measurement of drug exposure caused by day-to-day biologic variations. After Part 1A is complete and the relative BA of the formulation for Part 2 is confirmed, an ~~Dose escalation in Part 1B will begin at 25% of the adult MTD and dose escalation will follow a 3+3 design. An~~ expansion cohort (Part 2) is planned to further explore clinical activity of GSK525762 in subjects with NMC as shown in Figure 1. The expansion cohort will enroll both adult (16 years old and above) and pediatric (12 to ≤15 years) subjects at their appropriate R2PD doses. After the MTD is determined in adult subjects, Part 1B is planned for enrollment of pediatric subjects 12 to ≤15 years of age with solid tumors to determine the RP2D in this age group. Dose escalation in Part 1B will begin at 25% of the adult MTD and dose escalation will follow a 3+3 design.

Paragraph 4:

After the MTD has been determined in Part 1A, and the besylate sub-study has completed, Part 1B and Part 2 will be opened. Dose titration in the pediatric subjects in Part 1B will start at 25% of the MTD determined in Part 1A and will follow a standard 3+3 design. Pediatric subjects 12 to 15 years of age will be ~~entered~~ allowed to enroll in Part 2 ~~upon completion of~~ once the MTD has been determined in Part 1B.

Figure 1 Study Schema (Deleted)

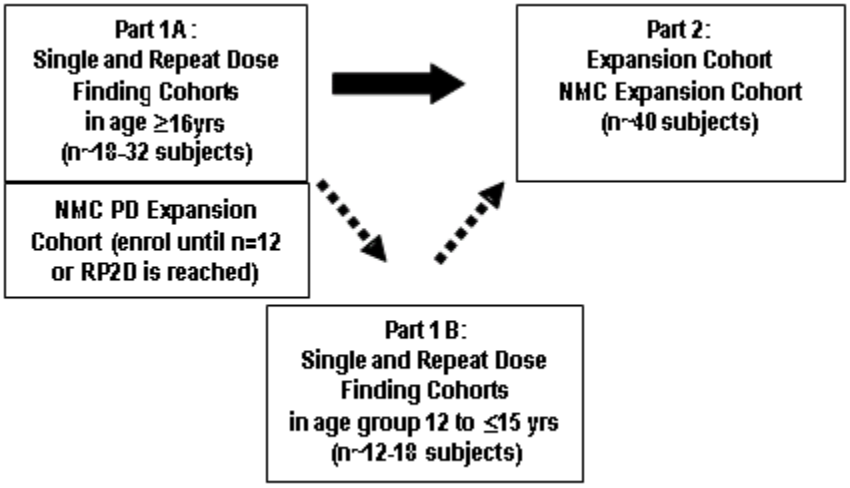
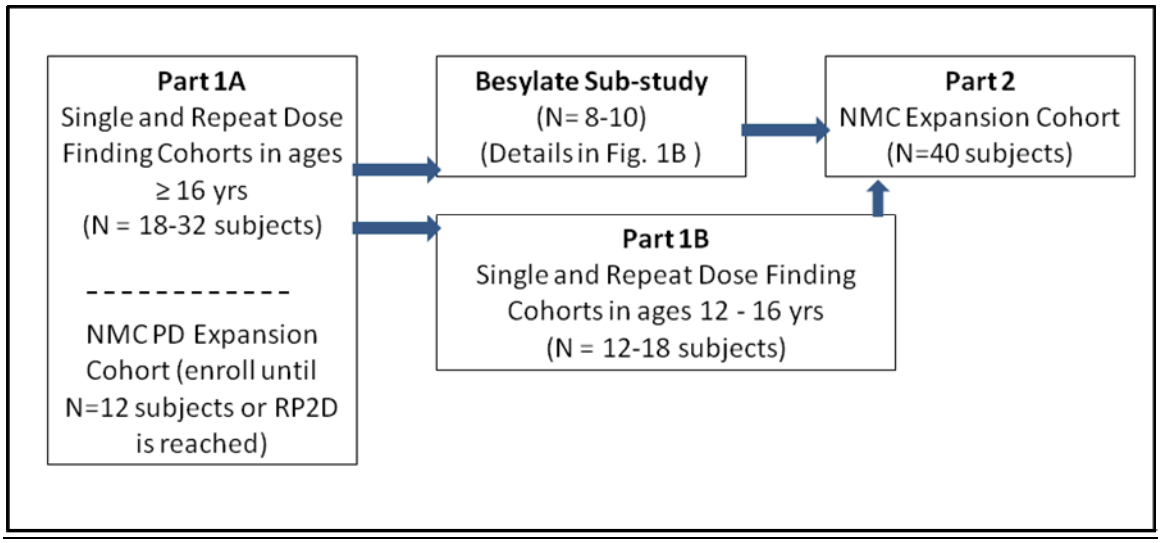
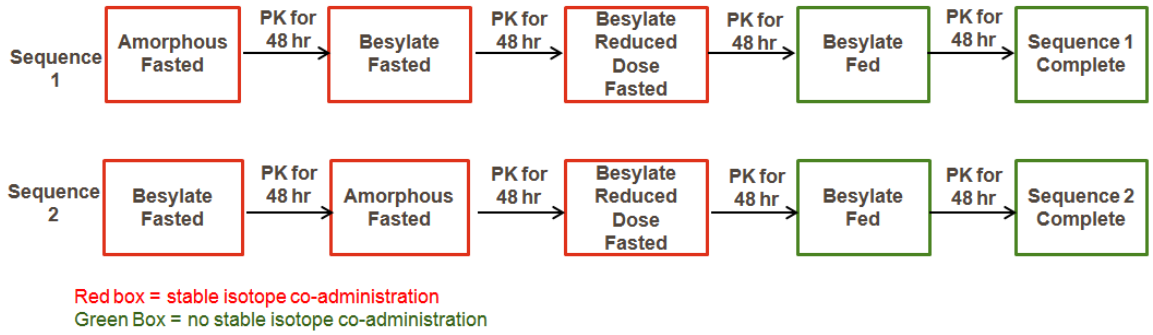


Figure 1 Study Schema (Replaced)

Part 1 and 2



B. Besylate Sub-Study (N=8 to 10 subjects)



After completion of either sequence all subjects enrolled in the sub-study will be allowed to continue in the study with a continuous once daily schedule.

Section 3.2.1. Part 1 Dose Escalation

Rationale for Change: An upper dosing limit of 200mg per day was included for consistency. The trial exploring GSK525762 in hematologic malignancies has an upper limit for daily dose administration.

Added Text:

Dose escalation will continue until an MTD is determined or until a dose of 200mg per day is reached.

Section 3.2.2. Dose Escalation and Schedule

Rationale for Change: This section was updated to include details for twice daily dosing.

Added footnote *(Section 3.2.2.1, Table 5 Accelerated Dose Escalation Procedures in Part 1A):*

NOTE: Route/Administration/Duration: Oral QD or BID (specific dosing instructions will be provided to each subject).

Revised Text:

3.2.2.6. BID Dosing Cohort

BID dosing~~, may also be explored. This approach~~ will be ~~considered if~~explored, based on the ~~safety and PK data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule. If a shorter recovery period is used, the~~ short half life. The initial dose level ~~will be ≤50% of the highest completed dose level (at or below MTD) with the initial schedule~~for BID will be 20mg BID or "x"mg BID (where 2x is equivalent to the last once daily dose cleared for dose escalation in Part 1A) – whichever is lower. Dosing will be separated by approximately 12 hours (± 1 hr). Escalation can then proceed as described using the 3 + 3 dose escalation. ~~Alternative schedules with intense supportive care~~Additional blood samples will be collected for PK, PD, and safety as described in Table 11.

Subjects may need to undergo dose modification(s) to manage toxicities. A dose adjustment (e.g., BID dose level with a minimum 25% reduction in total daily dosing or QD at the same or lower dose level) may ~~also~~ be explored after consultation with GSK Medical Monitor. The investigator should use clinical judgment to determine whether the dosing scheduling may be contributing to any potential toxicity necessitating dose adjustment, and make the appropriate change after consultation with the GSK Medical Monitor.

Section 3.2.5

Rationale for Change: This section was updated with language to clarify that NMC subjects with non-measurable disease per RECIST 1.1 may still be considered for enrolment.

Revised Text:

3.2.5. Part 1A

3.2.5.1. NMC Pharmacodynamic Expansion Cohort (*Paragraph 1*)

In the event there are no available enrollment slots during 3+3 dose escalation, eligible subjects with NMC (Section 6.2) may be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamics of GSK525762 at doses that have previously been cleared during 3+3 dose escalation. Three subjects with NMC will be allowed to enroll at the last cleared dose level only if subjects with NMC or other solid tumor types (Section 4.2.1 Inclusion Criteria) have already enrolled in 3+3 dose escalation. Enrollment in the PD Expansion Cohort will continue until either 12 subjects with NMC are enrolled in the PD Expansion Cohort, or until the RP2D is determined in Part 1A,

whichever occurs first. Eligibility criteria for subjects diagnosed with NMC to enroll in this cohort are described in Section 4.2 (Part 1A). NMC subjects with non-measurable disease by RECIST 1.1 but clinically evaluable for progression or response may be considered for enrollment after discussion with the GSK Medical Monitor. Biopsy collection will be mandatory as described in Section 3.2.2.4, unless a waiver is granted by the GSK medical monitor. ^{18}FDG-PET will be required for all subjects in this cohort

New Section added (Section 3.2.6)

Rationale for Change: This section was included to provide details for the besylate sub-study.

Added Text:

3.2.6. Bioavailability, Food Effect, and Dose Proportionality Besylate Sub-Study

Part 1A will include a besylate sub-study that will be an open-label, randomized, single dose, four period, cross over study to investigate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet at or near the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate salt tablet at or near the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate salt tablets. GSK525762 dosing will be separated by at least 48 hours. Up to 12 subjects may be enrolled in besylate sub-study. A subject requiring dose reduction or discontinuation from study before completion of the Besylate Sub-Study will be replaced by a new enrollment. All subjects enrolled to the Besylate Sub-Study, on completion of their participation in this segment of the study, will continue on a daily dosing schedule till disease progression or discontinuation due to investigational agent related toxicity or withdrawal of informed consent.

The high-fat (approximately 50% of the total caloric content of the meal), high-calorie meal (approximately 800 to 1000 calories) will be the representative example given by the 2002 US FDA guidance [FDA,2002]. It includes the following: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk.

In order to reduce variability in measurement of drug exposure caused by day-to-day biologic variation, a small (<10% of total dose) liquid dose of GSK525762, a stable, non-radioactive 13C isotope labeled version of GSK525762 besylate salt, will be coadministered orally with each fasted treatment in besylate sub-study to serve as an internal standard for quantitation purposes (Refer to Section 7.1 for additional information). Use of this stable isotope approach will allow better characterization of the impact of the besylate salt and dose on GSK525762 bioavailability, if any (Parr, 2012).

Table 9 Besylate Sub-Study Study Design: BA, Food Effect and Dose Proportionality Evaluation

Besylate Sub-Study: Single Dose PK Evaluation					
Sample Size	Sequence	Period 1 (Week 1 Day 1)	Period 2 (Week 1 Day 3)	Period 1 (Week 2 Day 1)	Period 4 (Week 2 Day 3)
6	1	Treatment A	Treatment B	Treatment C	Treatment D
6	2	Treatment B	Treatment A	Treatment C	Treatment D
Treatment A: RP2D (or MTD) amorphous free-base tablet + low dose stable isotope in solution, fasted administration Treatment B: RP2D (or MTD) besylate tablet + low dose stable isotope in solution, fasted administration Treatment C: half to one-third of RP2D (or MTD) besylate tablet + low dose stable isotope in solution, fasted administration Treatment D: RP2D (or MTD) besylate tablet, fed administration with FDA recommended high fat breakfast					

Section 4.1. Number of Subjects

Rationale for change: The overall subject numberswere increased to include subjects enrolled in besylate sub-study.

Added Text:

Paragraph 1:

The besylate sub-study will enroll approximately 12 evaluable subjects.

Section 4.2.1. Inclusion Criteria

Rationale for change: Additional solid tumors were added to inclusion criteria and multiple myeloma was removed. Language was included to allow enrolment of NMC patients with non-measurable disease at a previously cleared dose level. And Table 10 was updated to reflect adequate organ function values appropriate for CRPC subjects.

Revised Text:

Paragraph 1:

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential. Additional details regarding the enrollment and registration process for this study can be found in the Study Procedures Manual.

Paragraph 2:

A subject will be eligible for inclusion in this study only if all of the following criteria apply and after consultation with GSK:

Inclusion Criteria No. 3 Bullet Point "2":

- SCLC, CRC, NB, TNBC, ER positive BC, CRPC, NSCLC, ~~MM (subjects with history of allotransplant are excluded)~~ and any other solid tumor ~~(e.g., NSCLC)~~ which has been confirmed by clinical testing to be MYCN amplified (~~amplified is~~ defined as a MYCN gene copy number gain of ≥5). Subjects should have tumor progression after receiving at least one prior standard/approved chemotherapy, or where there is no approved therapy, or where standard therapy is refused.

Inclusion Criteria No. 4:

Subjects with solid tumors, with the exception of CRPC, must demonstrate measurable disease, per RECIST v1.1. NOTE: Subjects with NMC that do not meet the RECIST v1.1 criteria for measurable disease, but have evaluable disease may be considered for enrollment in the NMC PD Cohort at the previously cleared dose level.

Inclusion Criteria No. 7 :

Adequate organ function added for Reproductive/Endocrine System in Table 10.

Table 10 Definitions for Adequate Organ Function

Added Rows:

Reproductive/Endocrine	
Testosterone	<50ng/dL (only for subjects with CRPC)

Deleted footnote:

~~For MM subjects, calculated creatinine clearance criteria is <2.5mg/dL or 14-hour urine creatinine clearance of ≥ 30 mL/min~~

Section 4.2.2. Exclusion Criteria

Rationale for change: Exclusion criteria updated to define acceptable prior treatment usage for CRPC subjects, and also a new exclusion criteria was added for subjects enrolling in besylate sub-study.

Added Text, bullet point "e" for Exclusion Criteria no. 2:

e. Anti-androgen (e.g., bicalutamide) therapies for prostate cancer must be stopped 4 weeks prior to enrollment. Second line hormone therapies such as enzalutamide, abiraterone, or orteronel should be stopped 2 weeks prior to enrollement. Subjects with prostate cancer should remain on luteinizing hormone releasing hormone (LHRH) agonists or antagonists. Subjects with prostate cancer may also remain on low-dose prednisone or prednisolone (up to 10 mg/day) and still be eligible for this study.

Added Text, Exclusion Criteria no. 12:

12. Besylate Sub-Study only: unable or unwilling to eat the FDA recommended high-fat high-calorie breakfast (two eggs fried in butter, two strips of bacon, 4 oz. of hash brown potatoes and 8 oz of whole milk) within the recommended 30 minutes.

Section 5. TIME AND EVENTS TABLES

Rationale for change: The time and events tables were modified to ensure consistency of timings, correct previous errors, to include new assessments for CRPC and to remove assessments specific for multiple myeloma subjects. New tables were added for the BID dosing and the besylate sub-study. A summary of assessments added and removed are included below.

Table 11 Time and Events: Part 1

Assessments added:

Laboratory assessments Tests at visit W4D1

CT/MRI Scans and PET Scan at visit W5D1

Castrate-Resistant Prostate Cancer Assessments (Vitamin D3 and PTH; Urinalysis,Urine microscopy and UPC; Urine electrolytes; PSA) at Screening visit

PK and biomarker samples at visit q8WD1

Blood samples for circulating exploratory biomarkers (cfDNA, etc) at Screening, W4D1 and EOT visits.

Assessments removed:

Multiple Myeloma (MM) Assessments

Revised Text under the Notes column of Neuroblastoma Assessments:

One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening ~~a~~Assessment within 35 days of first dose can be used as screening assessment.

Table 12 Time and Events: Part 1 Laboratory Assessments

W4D1 Visit added to the table.

Assessments added: Troponin, NT-proBNP-9 at W4D1 visit, Hematology at W2D1 and W4D1 visits, HbA1c at W4D1 visit

Revised Tables:

Table 13 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1										**W1D5**		**W2D4 + 1 day**			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**~~16h ±2h~~ 12h ±1h**	**24h ~~±2h~~1h**	**~~33h~~48h ~~±3h~~1h**	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**
mRNA whole blood sample	X				X	X	X	X	X	X						

Table 14 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days										**W9D1 ±4 days** (if dose has been escalated, +4 to +7 days) **EOT**			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**~~16h ±4h~~ 12h ±1h**	**24h ±1h**	**48h ±1h**	**pre dose**	**0.5-2h**	**4 - 8h**	
mRNA whole blood sample	X					X	X							X
~~LPS whole blood sample~~														

New Tables Added:

Table 15 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1

	W1D1																W1D2 and W1D3 (relative to W1D1 Morning Dose)		W1D5 ECG and PK samples after Morning Dose only	
	Morning Dose								Evening Dose											
	pre dose	0H	15 min ±5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	pre dose (12h-15m)	12h	15 min(12.25h) ± 5m	30 min (12.5h) ±5m	1h (13h) ±5m	2h (14h) ±10m	4h (16h) ±15m	8h (20h) ±1h	12 h (24h) ±1h	36 h (48h) (pre-dose) ±1h	30 min ±5m	3h ±15m
Dose		X								X								X		
12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Urine PK sampling (Part 1A only)[a]	X	0-2h				2-12h														

	W1D1																**W1D2 and W1D3 (relative to W1D1 Morning Dose)**		**W1D5 ECG and PK samples after Morning Dose only**	
	Morning Dose								**Evening Dose**											
	pre dose	**0H**	**15 min ±5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**pre dose (12h-15m)**	**12h**	**15 min(12.25h) ± 5m**	**30 min (12.5h) ±5m**	**1h (13h) ±5m**	**2h (14h) ±10m**	**4h (16h) ±15m**	**8h (20h) ±1h**	**12 h (24h) ±1h**	**36 h (48h) (pre-dose) ±1h**	**30 min ±5m**	**3h ±15m**
mRNA whole blood sample	X					X	X	X		X				X	X	X	X	X		

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment (pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr) and acute phase protein assessment at pre-dose and at 2,4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

a. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

Table 16 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 2 and Week 3

	W2D4 + 1 day ECG and PK samples after Morning Dose only				W3D4 ±2 days																W3D5 and W3D6 (relative to W3D4 Morning Dose)	
					Morning Dose								Evening Dose (For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)									
	pre dose (Prior to Dosing)	30m ± 5m	3h ± 15m	8 h ±5m	pre dose	0h	15m ±5m	30m ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h	pre dose	12h	15m ±5m (12.25m)	30m ±5m	1h (13h) ±10m	2h (14h) ±15m	4h (16h) ±15m	8h (20h) ±1h	12h (24h) ±1h (pre dose)	36h (48h) ±1h (pre dose)
Dose	X					X								X							X	X
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sampling					X	0-2h				2-12h												

	W2D4 + 1 day ECG and PK samples after Morning Dose only				**W3D4 ±2 days**															**W3D5 and W3D6 (relative to W3D4 Morning Dose)**	
					Morning Dose								**Evening Dose** **(For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)**									
	pre dose (Prior to Dosing)	**30m ± 5m**	**3h ± 15m**	**8 h ±5m**	**pre dose**	**0h**	**15m ±5m**	**30m ±5m**	**1h ±10m**	**2h ±15m**	**4h ±15m**	**8h ±1h**	**pre dose**	**12h**	**15m ±5m (12.25m)**	**30m ±5m**	**1h (13h) ±10m**	**2h (14h) ±15m**	**4h (16h) ±15m**	**8h (20h) ±1h**	**12h (24h) ±1h (pre dose)**	**36h (48h) ±1h (pre dose)**
(Part 1A only)[a]																						
mRNA whole blood sample				X						X	X											

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment at pre-dose and at 2, 4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

a. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort

Table 17 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 9

	W9D1 ±4 days ECG and PK samples after Morning Dose only			**EOT**
	pre dose	**0.5-2h**	**4 - 8h**	
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	
PK and protein biomarker sample	X	X	X	
mRNA whole blood sample	X			X

Table 18 Time and Events: Part 2

Assessments added:

Blood samples for circulating exploratory biomarkers (cfDNA, etc) at Screening, W4D1 and EOT visits.

Revised Text under the Notes column of 12-lead ECGs (Single) Assessments:

~~Screening ECGs within 35 days of first dose.~~ ECGs prior to dosing. If QTcF increase >30msec, ECGs daily through W2.

New Tables Added:

Table 20 Time and Events: Besylate Sub-Study

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X		X					X		X					Continuous dosing starting W2D5									
Review subject diary	Diary not required when dosed in clinic.																X	X	X	X	X	X	X	X	X	
Safety																										
Pregnancy test/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X		X		X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X							X							X		X		X	X	X	X		X

Besylate Sub-Study Assessments	**Notes**	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W7**	**W9**	**q4W**	**q8W**	**EOT**
			D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	
Pain		X	X							X							X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test		X																								
Adverse events		*SAEs collected continuously from signing of informed consent. AEs collected continuously from first dose.*																								
Concomitant medications		*continuous from signing of informed consent*																								
Laboratory assessments: For details please see following tables																										
Tests		X	X							X							X				X	X	X	X	X	X
Cardiac Monitoring																										
Echocardiogram	Within 35 days of first dose	X																			X		X		X	X
12-lead ECGs (Triplicate)	Triplicate SCR ECGs within 35 days of first dose. For timing of triplicate ECGs on O days, see Table 11 and Table 12. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O		X					X		X					X		X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X	X																X				X			
Telemetry (Potentially will be removed for Besylate Sub-Study based on emerging data from Part 1)	Start at least 60 min predose and for at least 48 h.	X	X																							
Efficacy																										
CT/MRI Scans	SCR assessment within 35 days of	X																					X		X	X

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
	first dose. Target lesions to be identified at SCR and followed.																									
PET scan		X																					X			
Neuroblastoma Assessments																										
CT/MRI	One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening assessment within 35 days of first dose	X																					X		X	
MIBG scan[a]		X																					X		X	
FDG-PET		X																					X		X	
^{99}Tc scintigraphy for bone scan		X																					X		X	
Bilateral bone marrow aspirates and biopsy		X																					X		X	
Urine HVA, VMA, dopamine		X	X																		X		X	X		
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																										
PK samples			X	X	X	X				X	X	X	X								X		X			
Pharmacogenomics (PGx)																										
PGx sample			X																							
FOLLOW-UP PHASE																										

Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; FLC=free light chain; HVA=homovanillic acid; LPS=lipopolysaccharide; MIBG=meta-iodo-benzyl-guanidine; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; VMA= vanillylmandelic acid; W=week

a. Subjects with neuroblastoma will have MIBG and bone marrow biopsies after week 24 as clinical indicated to confirm complete remission.

Table 21 Time and Events: Besylate Sub-Study Pharmacokinetics Sampling, Week 1 and Week 2

		W1D1, W1D3, W2D1 and W2D3										
	pre dose	15 min ± 5m	30 min ±5m	1h ±5m	1.5h ± 5m	2h ±10m	3h ±15m	4h ±15m	6h ±15mn	8h ±30 mn	24h ±2h	48h ±2h [a]
12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 30 min PK draws and within 15 minutes prior to the other PK draws serial ECGs only W1D1	X		X	X		X	X	X	X	X	X	X
PK sample	X	X	X	X	X	X	X	X	X	X	X	X

a. On W1D3 and W2D3, the 48 hour sample has to be taken prior to GSK525762 dosing.

Table 22 Time and Events: Besylate Sub-StudyPharmacokinetics Sampling, Week 5 and Week 9

	W5				W9D1 ±4 days (if dose has been escalated, +4 to +7 days)		
	Pre dose	30 min ±5m	3h ±15m	8h ±30m	pre dose	0.5-2h	4 - 8h
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws	X	X	X	X	X	X	X
PK sample	X	X	X	X	X	X	X

Section 6.1.2. Visit Windows

Rationale for change: A window for visits in the besylate sub-study was included.

Added Text, Paragraph 9:

Besylate Sub-Study - +1 day window is allowed as long as there are at least 48 hours between the single doses.

Section 6.2. Baseline Assessment for NMC Subjects

Rationale for change: Clarification was included for baseline assessments for NMC subjects.

Revised Text, Paragraph 2:

Further retrospective ~~FISH~~ testing will be undertaken for all enrolled NMC subjects in order to ~~identify~~ characterize the ~~BRD3 or BRD~~ ~~4~~NUT gene fusion partner and to support exploratory analysis of differential outcomes based on the NUT fusion partner. ~~The cut-off for FISH positivity has not been robustly established but will be assessed during development.~~ The IHC and FISH analyses will be performed at a central laboratory.

Section 6.3. Baseline Assessment for Non-NMC Subjects

Rationale for change(s): Additional tumor types were added and MM removed from this section.

Revised Text, Paragraph 1:

Subjects diagnosed with SCLC, CRC, NB, CRPC, TNBC, ER+BC or NSCLC ~~or MM~~ [based on standard diagnostic criteria, such as histology, cytology (including bone marrow evaluation)] or serological criteria (such as serum M-protein) will be considered eligible for Part 1 of the study. In instances where a solid tumor subject's MYCN amplification status is known, then that subject will be considered eligible. N-Myc copy number gain of ≥5 will be considered positive for MYCN amplification. N-Myc testing may be performed using any method.

Table 23 QT Withdrawal Criteria

Rationale for change: Lowered QTcF withdrawal upper limit from 500 to 480 to be consistent with GSK QT withdrawal criteria.Removed reference to subjects with underlying bundle branch block, as these subjects are exluded from trial. Baseline QT results was defined.

Revised Text:

If QTcF > ~~500~~480 msec, or uncorrected QT > 600 msec (Grade 3 or 4), or any change from *baseline of ≥60 msec even if not exceeding ~~500~~480 msec, (all measurements based on an averaged manual overread of three ECGs over at least 15 minutes) permanently discontinue study medications and notify the GSK Medical Monitor. ~~For subjects with underlying bundle branch block, follow the criteria below:~~* Baseline results are defined by the nearest timepoint prior to first dose. For this trial the Baseline QTcF value is determined by the mean of the triplicate W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate ECG results would be used.	
~~**Baseline QTcF value with bundle branch block**~~	~~**Discontinuation QTcF with bundle branch block**~~
~~<450 msec~~	~~>500 msec~~
~~450-480 msec~~	~~≥530 msec~~

Section 6.4.7. Telemetry

Rationale for change: Flexible language to allow removal of telemetry requirement after all data is collected up to MTD and analyzed for QT safety and reviewed by our safety board was included.

Revised Text:

~~To~~In Part 1 to complement real-time ECG ~~assessements~~ assessments, monitoring for potential adverse arrhythmias will be conducted utilizing continuous telemetry ~~will be performed~~monitoring as outlined in the Time and Events Tables for at least 48 hours from the start of dose. If clinically indicated, telemetry may be extended past 48 hours. Participating sites will have trained staff capable of monitoring and responding in real time to any potential cardiac adverse event detected by telemetry. In addition, emergency resuscitation equipment including appropriate pharmacological agents will also be immediately accessible.

At the end of Part 1, an analysis of data collected on the QT interval up to, and including, the MTD expansion will be carried out. If the analysis by the GSK Cardiac Safety Panel of internal and external experts indicates that telemetry is no longer required for monitoring the QT interval, then the study can progress to the next stage without telemetry.

Removal of the telemetry requirement will be conveyed to the sites in the first instance through a separate document (or "note to file") that will note - i) a summary of the analysis, and ii) the decision to proceed without telemetry monitoring in the next stage of this study. This will allow the sites to submit the necessary documentation to the IECs/IRBs for approval and to start the next stage of this study without telemetry. However, this process will be permitted only if there are no other cardiac monitoring changes to be implemented. If additional cardiac monitoring changes are required, a protocol amendment will be necessary before the next stage of the study can start.

Table 24 Clinical Laboratory Tests

Rationale for change: Clarification was provided for safety cytokine sample collection at screening.

Revised Text:

Pregnancy test for females (serum at screening, Urine or serum post dose)Cytokine samples (collected as part of Predose PK sample for plasma cytokines; may also be performed as clinically appropriate following fever) Guaiac fecal occult blood

Section 6.5.1. Disease Assessment

Rationale for change: Disease assessment updated to include PCWG2 guidelines for CRPC subjects.

Revised Text, **Paragraph 1:**

Tumor response will be assessed as outlined in Time and Event Schedule by the investigator using RECIST 1.1 (Appendix 4) or the Prostate Cancer Working Group 2 (PCWG2) guidelines and documented in the eCRF as: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR). For subjects with ~~MM or~~ NB the appropriate tests and criteria will be followed (See Time and Events Schedule, Appendix 5 ~~and Appendix 6~~). See the SPM for additional instructions.

Section 6.6.3. Urine Collection

Rationale for change: Pooled urine sample collection timepoints was adjusted to reflect sample collections for both QD and BID dosing cohorts.

Revised Text, Paragraph 1:

Urine samples for quantitative analysis of GSK525762 will be collected over ~~24~~a dosing interval hours in two samples (sample collected 0-2hr and second sample collected 2-~~24hr~~end of dosing interval hr) immediately following dosing on Week 1 Day 1 and in Week 3. Urine samples will be collected in subjects in Part 1A (with the exclusion of besylate sub-study) once the 3+3 dose escalation has been reached. Additional sampling may be instituted based on emerging data.

Section 6.8. Translational Research

Rationale for change: Minor updates were made to this section to clarify that pre- and post-treatment biopsy collections are mandated during the 3+3 design (when there is accessible tumor tissue).

Revised Text, Paragraph 2 and 3:

NMC patients will be required to submit a fresh or archival tumor specimen for diagnosis or diagnostic confirmation. These archival specimens may also be evaluated retrospectively for exploratory research. ~~Selected~~ During the 3+3 design NMC patients

will also be required to supply fresh pre and post-treatment biopsies to test for relevant markers of tumor PD and/or biological effect and to support identification of a biologically effective dose.

Non-NMC patients will also be asked to submit an archival tumor specimen for retrospective testing for potential markers of sensitivity and/or resistance, eg. N-Myc amplification; however this will not be an eligibility requirement. Furthermore, as for NMC patients, ~~selected~~during the 3+3 design non-NMC patients will be required to supply fresh pre and post-treatment biopsies for tumor PD.

Section 6.8.1. Tumor Tissue Collection

Rationale for change: This section was updated to reflect exploratory analysis planned and to remove reference to multiple myeloma.

Revised Text, Paragraph 5:

The biopsies will be assessed for transcripts or proteins that reflect BET target engagement and/or tumor biology ~~(e.g., c-Myc protein level changes in multiple myeloma; changes in expression of genes important in SCLC tumorigenesis such as CCND1, SRC, NMYC and MLKL; changes in NMYC expression and protein in neuroblastoma).~~ For NMC, markers of cell proliferation and/or cell differentiation (e.g., Ki67 and cytokeratin [Schwartz, 2011]) will be analyzed. Biopsies may also be assessed for DNA, RNA or proteins which may be potential predictors of sensitivity or resistance to BET inhibition based on emerging data.

Section 6.8.2.3. Whole Blood mRNA

Rationale for change: This section was updated to reflect current exploratory analysis planned for mRNA samples.

Revised Text, Paragraph 1:

GSK525762 has been shown to modulate the expression of a number of different genes in unstimulated whole blood between 1 h and 6 h. The mRNA levels of 31 such genes form a 'signature' panel which will also be used as a biomarker of engagement of pharmacology~~. A~~ and will be measured using mRNA isolated from whole blood. The modulation of a number of these genes will also be measured as changes in systemic proteins as well as in the ~~analytes from~~ analysis of the ex vivo assay blood samples (e.g. CCL2 and IL-8) thus relating mRNA and protein expression with drug concentration. Other translational research studies, such as transcriptomics profiling, will also be performed using whole blood mRNA from selected patients.

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Rationale for change: This section was updated to include the besylate formulation

Revised Text:

Paragraph 1:

GSK525762 Tablets will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. Two investigational drug formulations will be introduced in Part 1. An amorphous, free-base formulation of GSK525762 will be used in Part 1 (Table 26) and a crystalline, besylate formulation (Table 27) will be introduced in the besylate sub-study in Part 1A and the Part 2 NMC expansion cohort.

Table 26:

Table 26 GSK525762 Amorphous Free-base Investigational Product Dosage/Administration

Investigational Product				
Product name:	GSK525762 AmorphousFree Base Tablets			
Unit dose strength(s)/Dosage level(s):	1mg	10mg	30mg	*100mg
Dosage form	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	GSK
Physical description:	white to off-white, round, biconvex tablets with no markings, uncoated tablet			white to off-white, capsule shaped, biconvex tablets with no markings, uncoated tablet
Route/ Administration/ Duration:	**Oral~~; OD~~;** see Time and Event Tables for schedule and administration timings			
Dosing instructions:	Dose with 240mL water and should be taken between 7 am and 10 am. No food or antacids for at least 1h before and 2h after dosing. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			

*100 mg tablets were never supplied to the sites/clinics.

Added Text:

Table 27 GSK525762 Besylate Investigational Product Dosage/Administration

Investigational Product				
Product name:	GSK525762 Besylate Tablets			13C-GSK525762 Stable isotope powder for oral solution
Unit dose strength(s)/Dosage level(s):	5mg	25mg	50mg	Low dose
Dosage form	Tablet	Tablet	Tablet	Powder for oral solution
Manufacturer	GSK	GSK	GSK	GSK
Physical description:	White to off-white, round, biconvex tablets with no markings, film-coated tablet		White to off-white, oval, biconvex tablets with no markings, film-coated tablet	White to off-white powder
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			Administer orally as a single dose with GSK525762 Tablets (besylate Sub-Study for Treatment A, B and C)
Dosing instructions:	Dose with 240mL water and should be taken between 7 am and 10 am. No food or antacids for at least 1h before and 2h after dosing. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			Dissolve powder in 10 mL of water with bicarbonate buffer and administered with GSK525762 tablets (Besylate Sub-Study, Treatment A, B and C)

Section 7.1.1. Preparation of GSK525762 Tablets for Administration via Enteral Feeding Tube

Rationale for change: Minor updates were included to provide clarification on GSK525762 as a dosing solution.

Revised Text, Paragraph 2:

The dose compounding should be performed only by pharmacy or appropriately trained personnel (please refer to Pharmacy Manual). A GSK525762 dosing solution is to be prepared by allowing GSK525762 tablets to disintegrate in 50 mL sterile water~~.~~ ~~GSK525762 tablets contain inert insoluble excipients that will remain in suspension. The contents will be mixed to ensure that complete dispersion is achieved.~~ All contents will be transferred into a syringe for administration via feeding tube. The compounding vessel

should be rinsed and the syringe and feeding tube flushed with further additions of sterile water. Total water volume will be 255 mL.

Section 7.2. Handling and Storage of Study Treatment

Rationale for change: Additional storage instructions for study treatment were included.

Revised Text, Paragraph 3:

GSK525762 Tablets are to be stored at up to 30°C (86°F~~).~~) and protected from light and moisture.

Section 7.3. Meals and Dietary Restrictions

Rationale for change: Instructions for meals and dietary restrictions were updated with information for besylate sub-study.

Revised Text, Paragraph 1:

Subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects will be asked to fast for an additional two hours. These fasting requirements have been implemented in the protocol and informed consents to minimize pharmacokinetic variability. During Besyalte Sub-Study, subjects will be asked to fast overnight (at least 8 hours) and continue fasting for 4 hours post dose administration except for the fed administration where subject will be requested to ingest a high-fat high-calorie meal within 30 minutes prior to administration (FDA 2002).

Section 7.4. Treatment Assignment

Rationale for change: Updates to this section were included to clarify the randomization schedule for the besylate sub-study.

Revised Text, Paragraph 2:

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study. Subjects in Besylate Sub-Study will be assigned to a treatment sequence (see Table 9) in accordance with the randomization schedule generated by Discovery Biometrics, using a validated software.

Section 7.7.1. Dose and Safety Management Guidelines,

Rationale for change: Updates were included in the Dose Adjustment/Stopping Criteria for QTc (to clarify “baseline”) and to provide additional guidance for thrombocytopenia (previouslynot includedin this section).

Revised Text:

Table 28 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2 (platelet count above 50,000)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelet count between 25,000-50,000)	After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider reduced daily dosing or dosing on alternate days). Monitor CBC at least twice a week, more frequently if necessary
	Grade 4 (platelet count below 25,000)	Temporarily interrupt study medication and monitor CBC every 2-3 days. If platelet counts recover to Grade 3 and is steady for at least 2 CBC reads at least 3days apart, or rising, discuss with medical monitor resuming treatment at the same or adjusted dose (see Grade 3) based on sound clinical judgement.
QTcF	QT monitoring: If >30msec and ≤60 msec change from baseline* occurs.	Management Guidelines for QTcF: Continue dosing and follow activities. Manually calculate QTcF to reconfirm clinically significant prolongation. Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4mol/L (2) Maintain serum magnesium levels 0.85 mmol/L Discontinue any concomitant medications with potential for QTcF prolongation. Consider 24 hour or longer telemetry monitoring if clinically indicated.
~~QTcF~~	~~QT monitoring:~~ ~~If >30msec and ≤60 msec change from baseline occurs.~~	~~Management Guidelines for QTcF:~~ ~~Continue dosing and follow activities.~~ ~~Manually calculate QTcF to reconfirm clinically significant prolongation.~~ ~~Supplement electrolytes, particularly potassium and magnesium, to recommended levels:~~ ~~(1) Maintain serum potassium > 4mol/L~~ ~~(2) Maintain serum magnesium levels 0.85 mmol/L~~ ~~Discontinue any concomitant medications with potential for QTcF prolongation.~~ ~~Consider 24 hour or longer telemetry monitoring if clinically indicated.~~ Grade 1 or 2 Temporarily discontinue study medications and review the following activities:

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Grade 1 or 2 During telemetry monitoring if a Grade 1-2: If >60msec change from baseline* and not exceeding 480 msec for QTcF (Averaged manual overread of three ECGs over at least 15 minutes)	Manual calculate QTcF to reconfirm clinically significant prolongation. Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4mol/L (2) Maintain serum magnesium levels 0.85 mmol/L Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia Discontinue any concomitant medications with potential for QTcF prolongation. Consider telemetry monitoring if clinically indicated. May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor. Permanently discontinue study medications and notify the GSK Medical Monitor. If the subject is variable around 480 msec assessments may be repeated. This subject may consider restarting study treatment at a reduced dose or dose level pre-event based on discussions with GSK Medical Monitor, Investigator and cardiologist.
	QTcF>480 msec (Averaged manual overread of three ECGs over at least 15 minutes) If QTcF > 60 msec over baseline* value AND QTcF>480 msec (Averaged manual overread of three ECGs over at least 15 minutes)	• QTcF Rechallenge Procedures: Do not rechallenge with study treatment unless under the following conditions: (1) QTcF event reduced to Grade ≤1, (2) potassium and magnesium levels are within

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		institutional normal range, (3) a favorable risk/benefit profile, (4) approval by the internal GSK Medical Monitor, (5) IRB approval, and (6) the subject is re-consented regarding the possible increase risk of QTcF prolongation. If approval for re-treatment is granted, the subject must be re-consented (with a separate informed consent specific to QTcF prolongation). • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: • Evaluation by cardiologist. • Weekly assessments for QTcF should be monitored weekly for two weeks, and then next assessment at 4 weeks post-dose. If QTcF results have not resolved to baseline then continue every 4-5 weeks until resolution.

* Baseline results are defined by the nearest timepoint prior to first dose. For this trial the Baseline QTcF value is determined by the mean of the triplicate W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate ECG results are considered baseline.

Section 7.7.2. Dose Adjustments for Toxicity, Table 29

Rationale for change: Revised Dose Adjustment for Toxicity to include specific guidance for thrombocytopenia.

Revised Title:

Table 29 Guidance for Dose Adjustment for Toxicity

Revised Footnote:

*Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for Rash, alopecia, etc. Exceptions to ≤ drug-related Grade 1, 2, 3 requirements would be quickly reversible (<48 hours) laboratory abnormality (example: electrolyte changes). In the case of thrombocytopenia, a subject may be considered for restarting study treatment if a resolution from Grade 4 to Grade 3 is experienced and after discussion with GSK medical monitor. See guidance in Table 28 above.

Table 31 Drugs with a Risk of Torsades de Pointes that are Prohibited

Rationale for change: Updated source for drugs with a risk of Torsades de Pointes that are prohibited.

Added row:

Levofloxacin	Levaquin

Table Footnote revised:

Data Source: ~~www.QTdrugs~~crediblemeds.org ~~(revised 25-Mar-2008)~~

Section 11.1. Sample Size Assumptions

Rationale for change:

Revised Text: Updates were made to sample size assumptions to include rationale for sample size for besylate sub-study.

Section 11.1.1. Part 1

The total number of subjects to be enrolled into Part ~~1~~1A and Part 1B will depend on the number of dose escalations required to establish the maximum tolerated dose of GSK525762; they are not driven by statistical considerations. To complete Part 1, it is estimated that ~~30~~50 to ~~50~~70 evaluable subjects will be enrolled.

Section 11.1.2. Part 1A Besylate Sub-Study

At least 8 and up to 12 subjects will participate in Besylate Sub-Study.

Approximately 12 subjects will participate in the assessment to get at least 8 evaluable patients completing. A subject is considered a completer if they have PK assessments from all treatment periods.

Based on a within-subject coefficient of variance for AUC of 50%, a correlation of 0.95 between the enriched (liquid dose of GSK525762 added) and non-enriched PK, and 8 subjects completing in Besylate Sub-Study, it is estimated that the half-width of the 90% CI for the ratio of the geometric means (besylate salt tablet compared to the amorphous free-base tablet) will be approximately 0.20. Hence, if the ratio estimate is equal to 1, the 90% CI will be 0.80 to 1.25.

Section 11.1.6. Subset Analysis for NMC Population

An exploratory review for NMC molecular subtype (e.g. NUT-BRD3, NUT-BRD4, and NUT-~~other~~NSD3) will be conducted.

Section 11.3. Analysis Populations

Rationale for change: This section was updated to further define subjects included in the PD population.

Revised Text:

Paragraph 1

All Treated Subjects (Safety and Clinical Activity) Population: This will consist of all subjects that received at least one dose of study treatment. Safety and clinical activity data will be evaluated based on this population.

Paragraph 3

~~**Assay Validation**~~ **Pharmacodynamic Population:** ~~Due to the rarity of NMC disease, the Assay Validation population~~ The PD Population is defined as ~~all~~ subjects ~~who were consented, screened~~ in the All Treated Subjects Population for ~~the study (regardless if the subject met eligibility requirements for study enrollment) and whose~~ whom a tumor biopsy or tissue was ~~assayed by IHC and/or FISH. Data from this population may be used for future validation of the assay~~ obtained and analysed for biomarkers

Section 11.7. Pharmacokinetic Analyses

Rationale for change: This section was updated to further define subjects included in the PK population and to include plans for analyses for the besylate sub-study.

Revised Text:

11.7.1. Pharmacokinetic Parameters

PK analyses will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Plasma GSK525762 concentration-time data from dose escalation (Part 1) will be analyzed by non-compartmental methods with WinNonlin.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC(0-t) and AUC(0-∞) Week1 Day1 only) and apparent terminal phase half-life ($t_{½}$). Trough concentration ($C\tau$) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined. The ratio of AUC(0-τ) on Week 3 AUC(0-τ) / Week 1 AUC(0-τ) will be calculated to assess time invariance. GSK525762 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

11.7.2. Statistical analysis of pharmacokinetic parameters

Statistical analyses of the PK parameters data will be conducted by Discovery Biometrics, GSK. Plasma concentration-time data will be listed by dose, age group, and summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) pharmacokinetic parameters values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters (if applicable)) by dose cohort and age group will be reported.

Dose proportionality

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) from Part 1 will be plotted as a function of the dose administered. If more than 2 dose cohorts are required to reach MTD (or the recommended dose based on available safety, PK and response data), dose proportionality of AUC and Cmax for GSK525762 following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be assessed graphically and using the power model ~~(details will be provided in the Reporting and Analysis Plan [RAP]).~~ as described below:

log (pharmacokinetic parameter) = a + b * log(dose)

where a is the intercept and b is the slope.

The power model will be fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. Both the intercept and slope will be fitted as fixed effects. If there is sufficient data, the model may also be fit with the intercept and/or slope as random effects depending on the ability of the model to converge and on estimation of variance-covariance matrix. The mean slope and corresponding 90% confidence interval will be estimated from the power model.

Separate models will be evaluated for amorphous tablet and besylate salt.

Relative bioavailability of the besylate salt tablet to the amorphous tablet (Besylate Sub-Study)

Based on the US FDA guidance on relative bioavailability studies, two formulations will be considered bioequivalent if the 90% CI of the ratio for Cmax and AUC, based on

log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on

the dose amount impact of a deviation from bioequivalence with the besylate salt will be based on the magnitude of the change.

Food effect with besylate salt tablet (Besylate Sub-Study)

Pharmacokinetic (PK) parameters AUC(0-∞), and Cmax will be loge-transformed and analyzed using a mixed-effects model with and without food will be analyzed separately with fixed-effect terms for fed status (fed or fasted), and subject as a random effect. Point estimates and their associated 90% CIs will be constructed for the differences between fed and in fasted state. The point estimates and their associated 90% CIs were then backtransformed to provide point estimates and 90% CIs for the ratios of fed/fasted. Non-parametric methods such as the Hodges and Lehmann estimator will be used to estimate the median differences between the fed treatments and the fasted state treatments for tmax. An associated 90% CI for the median differences will be constructed.

Based on the US FDA guidance on food-effect bioavailability studies, the absence of a food-effect will be established if the 90% CI of the ratio for Cmax and AUC, based on log-transformed data, is within the 80 to 125% equivalence limit. Recommendation on the clinical significance of the effect of food will be based on the magnitude of the change and our understanding of the exposure-clinical response relationship.

For the evaluation of food effect, tmax at fed and fasted status will be presented by subject and dose cohort in tabular and graphical form.

Section 11.7.3. Population Pharmacokinetic Analysis

Section 11.8. Pharmacokinetic/Pharmacodynamic Analyses

Rationale for change: Minor updates were included to further clarify plans for PK/PD analyses.

Revised Text, Paragraph 2, 3 and 4:

The relationship between QTcF and concentration expressed as Cmax, Cav, and/or instantaneous time-matched concentration will be ~~plotted graphically.~~evaluated. A linear or non-linear mixed effects analysis of the ~~slope of the~~ relationship between QTcF adjusted for baseline and –concentration ~~responses adjusting for baseline~~ with a possible incorporation of time will be evaluated as a means of estimating QTcF effect in lieu of a thorough QT study.

Other quantitative safety parameters and biomarkers of interest ~~including changes in tropinin, insulin and blood glucose levels~~ will be plotted graphically against summary exposure measures (eg; Cmax, Ctrough, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PKPD parameters of interest; slope, baseline (E0), ~~location~~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, ~~will~~ 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 [RAP].

Section 12.9.1. Dose Escalation Decisions

Rationale for change: Minor updates made to this section to further define the internal GSK team involved in dose escalation decisions.

Revised Text:

Dose escalation decisions will take into account all available data, including pharmacokinetics data and the safety profile of prior cohorts, and will occur following review of these data by the investigator(s), GSK medical monitor, clinical development scientist(s), pharmacokineticist, safety review team, and statistician. The decision and rationale will be documented in written format and distributed to the investigator(s), GSK medical monitor, pharmacokineticist, safety review team and statistician.

Section 13. REFERENCES

Rationale for change(s): The reference section was updated to reflect new/revised references used throughout the protocol amendment.

Added references:

Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB, Lüer SC et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clin Cancer Res. 2012;18(20):5773-9

FDA Guidance for industry: Food-effect bioavailability and fed bioequivalence studies. CDER 2002

Feng Q, Zhang Z, Shea MJ, Creighton CJ, Coarfa C, Hilsenbeck SG, et al. An epigenomic approach to therapy for tamoxifen-resistant breast cancer. Cell Res 2014;24:809-19.

Parr A., Gupta, M., Montague, T., and Hoke, F. Re-introduction of a Novel Approach to the Use of Stable Isotopes in Pharmacokinetic studies. The AAPS Journal 2012, 14:639-645.

C-H Gu, H Li, J Levons, K Lentz, R Gandhi, K Raghavan, and R Smith. Predicting effect of food on extent of drug absorption based on physicochemical properties. Pharm Res 2007 24:1118 – 1130)

Nagarajan, S, Hossan, T, Alawi, M, et al. Bromodomain Protein BRD4 Is Required for Estrogen Receptor-Dependent Enhancer Activation and Gene Transcription. Cell Reports 8, 460–469, July 24, 2014

Puissant A, Frumm SM, Alexe G, Bassil CF, Qi J, Chanthery YH, et al. Targeting MYCN in Neuroblastoma by BET Bromodomain Inhibition. Cancer Discov 2013.

Wyce A, Ganji G, Smitheman KN, Chung CW, Korenchuk S, Bai Y, et al. BET inhibition silences expression of MYCN and BCL2 and induces cytotoxicity in neuroblastoma tumor models. PLoS One 2013;8:e72967.

Section 14.6 Appendix 6: Response Criteria for Multiple Myeloma

Rationale for change: The response criteria for MM subjects was removed due to removal of MM subjects for enrolment in the trial.

Deleted Text:

~~**Section 14.6 Appendix 6: Response Criteria for Multiple Myeloma**~~

~~**Consensus Recommendations for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Workshop Consensus Panel**~~

~~**Response Criteria**~~

~~**sCR (stringent complete response):**~~

~~Complete response as defined below plus:~~

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

~~**CR (complete response):**~~

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

~~**VGPR (very good partial response):**~~

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

~~**PR (partial response):**~~

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

~~MR (minimal response):~~

- ~~≥25% but ≤49% reduction of serum M-protein and reduction in 24 hour urinary M-protein by 50% to 89%, AND~~
- ~~If present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required.~~
- ~~No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).~~

~~SD (stable disease):~~

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

~~PD (progressive disease):~~

~~Requires any one or more of the following~~

- ~~Increase of ≥ 25% from lowest response value in any one or more of the following:~~
  - ~~serum M-component (absolute increase must be ≥ 0.5 g/dl), or~~
  - ~~urine M-component (absolute increase must be ≥ 200 mg/24h), or~~
  - ~~the difference between involved and uninvolved free light chain levels (absolute increase must be > 10mg/dl): only for patients without measurable serum and urine M-protein levels, or~~
  - ~~bone marrow plasma cell percentage (the absolute % must be ≥10%) only for patients without measurable serum and urine M-protein levels and without measurable disease by FLC level~~
  - ~~definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas~~
  - ~~development of hypercalcemia (corrected calcium > 11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder~~

~~a. All response categories (CR, sCR, VGPR, PR,MR and PD) require two consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, MR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.~~

~~b. Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.~~

~~c. Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels;~~

~~"25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.~~

~~References~~

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

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

AMENDMENT 05

Protocol Changes for Amendment 5 (DD-MMM-YYYY) from the Protocol Amendment 4 (06-OCT-2014)

Protocol Amendment 5 applies to all site(s) participating in the conduct of the study

Amendment 05 summary: Amendment 05 includes the following additional expansion cohorts for Part 2 of the trial: castration-resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive breast cancer (ER positive) and small cell lung cancer (SCLC). An update was included regarding the Besylate Sub-Study to clarify that this sub-study would only be conducted at centers in the United States. The pediatric cohort in Part 1B was removed for further evaluation in a separate study. An update to the QTc management guidelines has been included.

General Protocol Changes

Part 1B has been removed. Reference to Part1A and/or Part1B has been changed to Part 1 wherever applicable throughout the protocol.

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

List of Specific Changes

TITLE PAGE

Rationale for Change: Part 1B has been removed. Reference to Part1A and/or Part1B has been changed to Part 1.

Revised Text:

Description: This is an open-label, single and repeat dose, multicenter, 2 part study to determine the MTD and the recommended Phase 2 dose (RP2D) for GSK525762 given orally once or twice daily. Part 1 will be conducted in subjects with NMC and other solid tumors in adult subjects (Part ~~1A) and pediatric subjects (Part 1B).~~<u>1).</u> Expansion cohorts (Part 2) are planned to further explore the clinical activity of GSK525762 in subjects with NMC and other specific solid tumors based on emerging data.

Section ABBREVIATIONS

Abbreviations added

<u>LCNEC</u>	<u>Large cell neuroendocrine carcinoma tumor</u>
<u>PSA</u>	<u>Prostate-Specific Antigen</u>

Section PROTOCOL SYNOPSIS

Objectives, Endpoints, Hypotheses

Rationale for Change: This section was updated to remove objectives, endpoints or hypotheses related to the pediatric subjects and the hypothesis section was updated to include or the additional tumor types in Part 2 included with this amendment.

Revised Text:

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • ~~To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 12 to ≤15 years old~~ • To evaluate the clinical activity of GSK525762 in NMC and other solid tumors. • To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 16 years or older • ~~AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 12 to ≤15 years old.~~ • Assess overall response rate (RR) by RECIST 1.1 in NMC and other solid tumors. • PK parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet
Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory. • The primary goal of Part 2 is to demonstrate a clinically meaningful response ~~rate of 20% in~~ , defined as follows: • NMC ~~relative to a 5% response rate suggesting no activity. This~~: this will be ~~conducted~~determined by testing the null hypothesis that ~~P0≤0.050 versus~~ the ~~alternative that P1≥0.200, assuming~~response rate is ≤5%, with about 80% power when the ~~maximum~~true response rate is 20%.

Primary	
	• SCLC and CRPC: this will be determined by testing the null hypothesis that the response rate ~~for an ineffective drug~~ is ~~0.05 and~~≤10%, with about 80% power when the ~~minimum~~true response rate ~~for an effective drug is 0.20.~~ is 30%. • ER+BC: this will be determined by testing the null hypothesis that the response rate is ≤15%, with about 80% power when the true response rate is 30%. • TNBC:this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 25%.

Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • ~~To characterize the pharmacokinetics (PK) of GSK525762 in subjects 12 to ≤15 years old~~ • To evaluate cardiac safety, including the potential for QTcF~~, of~~ changes with GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival. • ~~To evaluate systemic and ex vivo on target BET inhibitory effects.~~
Endpoints	• PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 16 years or older • ~~PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 12 to ≤15 years old~~ • Changes in cardiac safety including QTcF following single and repeat-dose oral administration GSK525762. • Progression free survival (PFS), time to response, duration of response, overall survival (OS), and exploratory analysis for antitumor response by various imaging modalities.

Exploratory (Objectives and Endpoints only)	
Objectives	• To evaluate the effect of GSK525762 on tumor biology • Correlation of GSK525762 exposure to changes in PD markers in tumor and/or surrogate tissue • To identify potential indicators of sensitivity or response to GSK525762. • <u>To evaluate systemic and ex vivo on-target BET inhibitory effects.</u>
Endpoints	• Dose related changes in markers of cell proliferation and/or cell differentiation in tumor and/or surrogate tissue • Dose related changes in transcription of genes and/or changes in expression of proteins regulated by BRD proteins in tumor and/or surrogate tissue • PK/PD parameter values for exposure response (by RECIST and ^{18}FDG-PET [if data allows]) relationship between GSK525762 <u>exposure</u> and QTcF, troponin and tumor response following single and repeat-dose oral administration. • Changes from baseline and dose/response relationship in ex vivo LPS induced cytokines including IL-6 in whole blood and systemic cytokines including IL-6.

Study Design And Duration:

Rationale for Change: This section was updated to include the additional expansion cohorts for Part 2 (CRPC, TNBC, ER positive and SCLC), to clarify that the sub-study would be conducted in the US only and remove reference of the pediatric cohort (Part 1B).

Revised Text:

This study is divided into 2 parts:

- Part ~~1A~~1 of the study is a dose escalation phase to determine the maximum tolerated dose (MTD) and select a recommended dose for Part 2 or a recommended Phase 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with NUT midline carcinoma (NMC), small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and any other MYCN-amplified solid tumor will be enrolled in the dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects with NMC will also be enrolled in a pharmacodynamic dose expansion cohort during Part ~~1A~~1. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent.
- Part ~~1A~~ 1 besylate sub-study will explore the relative bioavailability, food effect and dose proportionality of besylate formulation. The sub-study will be conducted <u>at active centers in the United States</u> in subjects eligible for Part

~~1A~~1 at the MTD or a dose near the MTD or RP2D. This will be an open-label, randomized, single dose, four period, cross over sub-study to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as besylate tablets.

- ~~Part 1B will be opened to enroll pediatric subjects 12 to ≤15 years of age with solid tumors to determine the MTD in pediatric subjects. Dose escalation in Part 1B will begin at 25% of the adult MTD and dose escalation will follow a 3+3 design. Pediatric subjects 12 to ≤ 15 years old may be enrolled in Part 2 once the MTD has been determined in Part 1B.~~
- Part 2 is an expansion cohort planned to further explore clinical activity at the MTD in NMC, SCLC, CRPC, and TN and ER positive BC subjects
- Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

Subject Sample

Rationale for Change: The overall subject numbers were increased to accommodate enrolment into additional expansion cohorts added to Part 2 (CRPC, TNBC, ER+BC and SCLC).

Revised Text:

~~Approximately 70-100 subjects worldwide.~~Worldwide approximately 60 subjects will be enrolled in Part 1, and approximately 150 subjects will be enrolled in Part 2.

Pharmacokinetic/Pharmacodynamic Measurements:

Rationale for Change: Minor updates were made to this section to provide further clarification on planned cytokine testing.

Revised Text:

There is extensive pharmacokinetic (PK) sampling in Part 1 and limited PK sampling in Part 2 for this study. Single safety PK blood draws may be collected for subjects with severe adverse events ~~or~~ adverse events of concern. Blood samples will be collected for analysis of protein biomarkers (cytokines and acute phase proteins) and mRNA. Ex-vivo LPS induction of cytokines in whole blood will be assessed. In addition, pre-treatment and post-treatment tumor samples will also be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Data Analysis

Rationale for Change: Minor updates were made to this section to clarify and reflect that futility assessments would be conducted for each expansion cohort, now that additional cohorts have been added to Part 2.

Revised Text:

Subject demographic and safety data will be collected on electronic case report forms (eCRFs). All data will be pooled and descriptive safety analyses summarized and listed by cohort at study conclusion. Part 2 of the study is powered to test overall Response Rate (RR). A futility assessment will be conducted after data are available from the first ~~20~~10 subjects in each expansion cohort in Part 2.

Section 1.2.1. NUT midline carcinoma

Rationale for Change: Updates were made to this section based on emerging data.

Revised Text

Paragraph 5:

NMC is extremely rare ~~(fewer than 100 cases have been identified globally to date), and~~with approximately 20 cases being reported in the United States annually, however due to misdiagnosis or underdiagnosis, the exact incidence and frequency of NMC are not well established (http://www.nmcregistry.org/). NMC may affect subjects of all ages (age range 0-78 yrs). The only known long-term survivor had a complete tumor resection. Therefore, patients with this rare tumor have a significant unmet medical need for more effective therapy.

Section 1.2.2 Other tumor types

Rationale for Change: Updates were made to this section based on emerging data.

Revised Text

Non-Small Cell Lung Cancer

GSK525762 inhibited cell growth in a ~~high percentage~~subset of NSCLC cell lines, with ~~73% (19/26~~46% (33/72) of cell lines tested exhibiting a gIC_{50} <1µM. Median gIC_{50} across the NSCLC cell line panel was ~~0.61µM~~1.1µM. MYCN amplified cell lines and large cell neuroendocrine carcinoma (LCNEC) cell lines were among the most sensitive ~~NSCLC cell lines~~ to GSK525762, with a median gIC_{50} of 0.17µM and ~~gIC_{100} of 3.6µM~~ 0.24µM (n=4~~).~~ for each sub-type). A subset of NSCLC cell lines, including ~~the~~ MYCN-amplified and LCNEC lines, exhibited a cytotoxic response to GSK525762. Given the broad sensitivity of NSCLC cell lines to GSK525762, a selection marker will not be used for entry into the dose escalation part of the study.

Section 1.3.1 Human Pharmacokinetics

Rationale for Change: Updates were made to this section based on emerging data.

Revised Text

Whole blood human clearance was predicted from three species (mouse, rat and dog) using simple power-law allometry (in the absence of detectable in vitro metabolism) to be 2.8 ml/min/kg. Volume of distribution was predicted from Gastroplus to be 2.6 L/kg and half-life 10 hours (GlaxoSmithKline Document Number 2010N108204_00, 2011). As the in vitro blood to plasma ration was 0.86, a 70 kg adult therefore ~~has~~had a predicted total clearance of 10.1 L/hr and a total plasma volume of distribution of 157 L. ~~Bioavailability is predicted to be high given GSK525762 is a Bio-pharmaceutics Classification System (BCS) Class 1 molecule, and assumed to fall in the range 50-100%~~.

As ~~of 23-July-2014~~of 06-February-2015, the pharmacokinetics of GSK525762 has been evaluated in ~~19~~23 subjects following single and repeated daily administration of 2 mg to 60 mg of GSK525762 in the BET115521 trial. The summary statistics of the preliminary PK parameters are summarized in Table 1 and Table 2 after single and repeat daily oral

administration, respectively. GSK525762 pharmacokinetics are characterized by a rapid absorption with maximum concentration occurring mostly within the first hour after dosing. GSK525762 is eliminated rapidly with an average terminal phase half-life of 3 to 7 hours, leading to a lack of accumulation following once daily oral administration. Following single oral administration and repeated once daily administration of 2 mg to 60 mg of GSK525762, C_{max} and AUC tended to increase in a dose proportional fashion with a full overlap for individual AUC between 30 and 60 mg cohorts.

Table 1 Summary Statistics of GSK525762 Preliminary PK Parameters Following a Single Oral Administration of GSK525762 in Study BET115521

Parameters	Unit	2 mg N=3	4 mg N=4	8 mg N=1	16 mg N=3	30 mg N=4	60 mg N=48
Cmax	ng/mL	51.0 (41%)	70.4 (29%)	120	176 (37%)	604 (30%)	~~940 (31~~871 (25%)
tmax	h	0.5 (0.5 - 0.6)	1.2 (0.5 - 2.0)	1.1	2.0	2.0 (0.97 - 2.0)	1.0 (0.5 - ~~2~~4.0)
AUC	ng.h/mL	172 (42%)	361 (35%)	434	884 (40%)	4420 (63%)	~~3720 (574~~330 (46%)
$t_{1/2z}$	h	3.3 (103%)	5.1 (36%)	2.95	6.9 (46%)	6.4 (37%)	~~6.1 (49~~5.7 (36%)

Table 2 Summary Statistics of GSK525762 Preliminary PK Parameters Following Repeat Daily Oral Administration of GSK525762 in Study BET115521

Parameters	Unit	2 mg N=1	4 mg N=2	8 mg N=1	16 mg N=3	30 mg N=4	60 mg N=~~2~~6
Cmax	ng/mL	52	47.6 ; 59.9	103	138 (25%)	603 (17%)	~~602;~~ ~~736~~634 (53%)
tmax	h	1.0	1.0 ; 4.0	0.5	1.5	0.9 (0.32 - 4.0)	1.0 ; ~~1.~~(0.50 - 2.0)
AUC_τ	ng.h/mL	160	225 ; 497	330	674 (21%)	3150 (55%)	~~2010;~~ ~~5290~~1.0 (0.50 - 2.0)
$t_{1/2z}$	h	4.27	3.69 ; 4.46	4.92	3.6 (7.8%)	5.2 (26%)	~~2.5;~~ ~~4.9~~3.48 (32%)
Cmax Week 3 / Cmax Week 1	--	1.42	0.968 ; 0.609	0.857	0.780 (12%)	0.998 (24%)	1.~~01;~~ ~~1.23~~00 (21%)
~~**AUC_τ Week 3 / AUC Week 1**~~	~~--~~	~~1.38~~	~~0.900 ; 1.64~~	~~0.759~~	~~0.774 (20%)~~	~~0.724 (12%)~~	~~0.898; 0.712~~

Parameters	Unit	2 mg N=1	4 mg N=2	8 mg N=1	16 mg N=3	30 mg N=4	60 mg N=26
AUC_τ week 3 / AUCt Week 1	--	1.39	0.904 ; 1.67	0.763	0.792 (20%)	0.799 (11%)	0.902; 0.778758 (12%)

Section 1.3.6. Doses for Besylate Bioavailability/Food Effect/Dose Proportionality Sub-Study

Revised Text

A dose at or near the maximum tolerated dose or the recommended Phase 2 dose will be used to evaluate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet~~, as this dose would be the dose level used in Part 2~~.

Section 1.4. Rationale for Study and Endpoints

Rationale for Change: This section was updated to clarify that the besylate sub-study will only be conducted in the US.

Revised Text

Paragraph 2:

Given the poor prognosis and high unmet medical need of NMC, as well as in other tumor types such as relapsed/refractory SCLC, NSCLC,CRC, MM, CRPC, TN and ER+ BC, NB and N-Myc amplified tumors and the exceptional drug-to-target alignment of GSK525762, a combined Phase I/II study (BET115521) is proposed. The BET115521 study comprises an accelerated dose titration (Part 1), which will include subjects with NMC and other tumor types that are predicted to be responsive to GSK525762, to determine a maximum tolerated dose (MTD). The besylate sub-study will be an open-label, randomized, single dose, four period, crossover sub-study to investigate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet at a dose at or near the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate salt tablet at or near the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate salt tablets. Results of the besylate sub-study will enable the use of the besylate salt tablet formulation later in this study and provide recommendation around the need for fasting status when administering GSK525762. The besylate sub-study will be conducted at centers in the United States.

Section 2 Objectives, Endpoints, Hypotheses following QD and/or BID dosing schedules

Rationale for Change: This section was updated to remove objectives, endpoints or hypotheses related to the pediatric subjects and the hypothesis section was updated to include or the additional tumor types in Part 2 included with this amendment.

Revised Text

Primary	
Objective	• To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • ~~To determine the safety, tolerability and maximum tolerated dose (MTD) of GSK525762 in subjects 12 to ≤15 years old~~ • To evaluate the clinical activity of GSK525762 in NMC and other solid tumors. • To evaluate, after single dose administration, the relative bioavailability of the GSK525762 besylate tablet compared to the amorphous free-base tablet, the effect of high-fat high-calorie meal on the bioavailability of the besylate tablet and the dose proportionality of two doses of GSK525762 administered as the besylate tablets.
Endpoints	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 16 years or older • ~~AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECG, cardiotoxicity, gastrointestinal, etc) to determine the MTD in subjects 12 to ≤15 years old.~~ • Assess overall response rate (RR) by RECIST 1.1 in NMC and other solid tumors. • PK parameter values for GSK525762 following single oral administration as amorphous free-base or besylate tablet

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.
	• The primary goal of Part 2 is to demonstrate a clinically meaningful response ~~rate of 20% in~~ , defined as follows:
	  • NMC ~~relative to a 5% response rate suggesting no activity. This~~: this will be ~~conducted~~determined by testing the null hypothesis that ~~P0≤0.050 versus~~ the ~~alternative that P1≥0.200, assuming~~response rate is ≤5%, with about 80% power when the ~~maximum~~true response rate is 20%.
	  • SCLC and CRPC: this will be determined by testing the null hypothesis that

Primary	
	the response rate ~~for an ineffective drug~~ is ~~0.05 and~~≤10%, with about 80% power when the ~~minimum~~true response rate ~~for an effective drug is 0.20.~~ is 30%. • ER+BC: this will be determined by testing the null hypothesis that the response rate is ≤15%, with about 80% power when the true response rate is 30%. • TNBC:this will be determined by testing the null hypothesis that the response rate is ≤10%, with about 80% power when the true response rate is 25%.

Secondary (Objectives and Endpoints only)	
Objectives	• To characterize the pharmacokinetics (PK) of GSK525762 in subjects 16 years or older following QD and/or BID dosing schedules. • ~~To characterize the pharmacokinetics (PK) of GSK525762 in subjects 12 to ≤15 years old~~ • To evaluate cardiac safety, including the potential for QTcF~~, of~~ changes with GSK525762 and to assess PK/QTcF relationship following QD and/or BID dosing schedules. • To evaluate the exposure response (pharmacokinetic/pharmacodynamic [PK/PD]) relationship between GSK525762 and safety and efficacy parameters following QD and/or BID dosing schedules. • To evaluate the effect of treatment with GSK525762 on tumor growth and survival. • ~~To evaluate systemic and ex vivo on-target BET inhibitory effects.~~
Endpoints	• PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 16 years or older • ~~PK parameter values for GSK525762 following single and repeat-dose oral administration in subjects 12 to ≤15 years old~~ • Changes in cardiac safety including QTcF following single and repeat-dose oral administration GSK525762. • Progression free survival (PFS), time to response, duration of response, overall survival (OS), and exploratory analysis for antitumor response by various imaging modalities.

Exploratory (Objectives and Endpoints only)	
Objectives	• To evaluate the effect of GSK525762 on tumor biology • Correlation of GSK525762 exposure to changes in PD markers in tumor and/or surrogate tissue • To identify potential indicators of sensitivity or response to GSK525762. • <u>To evaluate systemic and ex vivo on-target BET inhibitory effects.</u>
Endpoints	• Dose related changes in markers of cell proliferation and/or cell differentiation in tumor and/or surrogate tissue • Dose related changes in transcription of genes and/or changes in expression of proteins regulated by BRD proteins in tumor and/or surrogate tissue • PK/PD parameter values for exposure response (by RECIST and ^{18}FDG-PET [if data allows]) relationship between GSK525762 <u>exposure</u> and QTcF, troponin and tumor response following single and repeat-dose oral administration. • Changes from baseline and dose/response relationship in ex vivo LPS induced cytokines including IL-6 in whole blood and systemic cytokines including IL-6.

Section 3.1. Study Design/Schematic

Rationale for Change: This section was updated to include the additional expansion cohorts for Part 2 (CRPC, TNBC, ER positive and SCLC), to clarify that the sub-study would be conducted in the US only and remove reference of the pediatric cohort (Part 1B).

Revised Text

Paragraph 2

This is an open-label, single and repeat dose, 2-part study to determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily orally. Twice daily dosing may also be explored upon evaluation of safety, PK, and PD data from once-daily dosing. Part ~~1A~~1 will be conducted in adult subjects with NMC, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), neuroblastoma (NB), castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, and MYCN driven solid tumors. During the dose escalation of Part ~~1A~~1, additional subjects with NMC will be enrolled in a Pharmacodynamic (PD) Expansion Cohort to evaluate the pharmacodynamic effects of GSK525762 at lower doses that have been previously cleared during dose escalation. This will enable collection of pharmacodynamic data across the predicted efficacious dose range and contribute to the evaluation of a biologically efficacious dose. ~~Once the RP2D is determined in Part 1A, a besylate~~ A sub-study will be opened to approximately 10 subjects <u>in the United States</u> to investigate the relative bioavailability of the besylate tablet compared to the amorphous free-base tablet at the MTD or RP2D, the effect of high-fat high-calorie meal on the

bioavailability of the besylate tablet at the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate tablet. This sub-study will also use a stable isotope of GSK525762 in order to reduce the variability in the measurement of drug exposure caused by day-to-day biologic variations. ~~After Part 1A is complete and the relative BA of the formulation for Part 2 is confirmed, an e~~Expansion cohorts (Part 2) ~~is~~ are planned to further explore clinical activity of GSK525762 in subjects with NMC, SCLC, CRPC, TNBC and ER+BC as shown in Figure 1. The expansion cohorts will enroll ~~both~~ adult (16 years old and above) ~~and pediatric (12 to ≤15 years)~~ subjects at ~~their~~the appropriate R2PD ~~doses. After the MTD is determined in adult subjects, Part 1B is planned for enrollment of pediatric subjects 12 to ≤15 years of age with solid tumors to determine the RP2D in this age group. Dose escalation in Part 1B will begin at 25% of the adult MTD and~~ dose ~~escalation will follow a 3+3 design.~~ .

Paragraph 4 and 5

After the MTD has been determined in Part ~~1A, and the besylate sub-study has completed~~1, Part ~~1B and Part~~ 2 will be opened~~. Dose titration in the pediatric subjects in Part 1B will start at 25% of the MTD determined in Part 1A and will follow a standard 3+3 design. Pediatric subjects 12 to 15 years of age~~ for the SCLC, TNBC, ER+BC and CRPC expansion cohorts. The NMC expansion cohort will be ~~allowed to enroll in Part 2 once the MTD has been determined in~~Part 1B.opened with the pivotal besylate tablet after results from the besylate study are available.

In ~~both~~ Part~~s~~ 1 ~~and 2~~, all subjects will be evaluated for systemic and ex-vivo on-target BET inhibitory effects in blood. In addition, pre-treatment and post-treatment tumor samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Figure 1 Study Schema

A. Part 1 and 2

Revised figure to reflect removal of Part 1B (pediatric cohort), to clarify that the sub-study would be conducted in the US only and to update number of subjects planned to be enrolled

B. Besylate Sub-Study (N=~~8~~up to ~~10~~12 subjects in the United States)

After completion of either sequence all subjects enrolled in the sub-study will be allowed to continue in the study with a continuous ~~once~~ daily schedule.

Section 3.2.1 Part 1 Dose Escalation

Rationale for Change: This section was updated to remove reference of the pediatric cohort (Part 1B).

Revised Text

Paragraph 2 and 3

~~Part 1B will be initiated after the MTD is reached in Part 1A and will start at 25% of the MTD determined in Part 1A. Part 1B will follow a standard 3+3 design.~~

In the accelerated dose escalation cohorts and the 3+3 dose escalation cohorts, the dose will be escalated based on all available data, including PK data and the safety profile of prior cohorts, as well as the ~~predicted~~recommended dose from the Neuenschwander-Continuous Reassessment Method (N-CRM) design [Neuenschwander, 2009].

Figure 2 Dose Escalation Schema

Revised figure to reflect removal of Part 1B (pediatric cohort)

Section 3.2.2.2 3+3 Dose Escalation in Part ~~1A~~1

Rationale for Change: Minor updates were made to this section to provide additional clarification on the NMC PD cohort.

Revised Text

Paragraph 2

Once the MTD is reached, up to 12 additional subjects may be enrolled at the MTD to further evaluate safety and ~~obtain~~ tumor ~~tissue for~~ PD ~~biomarkers~~. Up to an additional 6 subjects may be enrolled at any dose level below the MTD to order to obtain additional ~~tumor tissue (tumor biopsies would be required; see additional details in Section 6.8.1).~~dose/response information related to tumor PD. Additional cohorts (with daily exposure not exceeding QD MTD exposure) may also be initiated to explore alternative dosing schedules to optimize the PK, safety and tolerability profile (see Section3.2.2.4). The enrolment of additional subjects as described could be in parallel with Part 2 enrolment.

Deleted Section 3.2.2.3 3+3 Dose Escalation in Part 1B

Rationale for Change: This section was updated to remove reference of the pediatric cohort (Part 1B).

Deleted Text

~~**Section 3.2.2.3 3+3 Dose Escalation in Part 1B**~~

~~Once MTD in declared in adult patients (age ≥16yrs), a pediatric cohort of subjects 12 to ≤15 yrs old will be opened. The starting dose for this cohort will be 25% of the adult MTD and dose escalation will follow a 3+3 design (Table 7 and Table 8). Each dose escalation will ≤2-fold increase over the dose of the prior cohort. Once MTD is reached, up to 6 additional patients may be enrolled at the MTD dose and each of 2 dose levels below the MTD to obtain additional safety and PK data and tissue for PD analysis if necessary.~~

Table 7 Dose escalation procedures in Part 1B

Dose Level	Change in Dose
Dose Level -1	Lower doses may be used if Dose Level 1 is not tolerated. This may be achieved by reducing the dose or by alternate dosing (e.g. every other day)
Dose Level 1 (25% of adult MTD)	Begin 3+3 Dose Escalation Phase
Dose Level 2	Increase by ≤2 fold (No subjects with any DLTs in first 4 weeks of treatment)
Subsequent dose levels	Continue 3+3 Dose Escalation

Table 8 Dose Escalation Decision Process in Part 1B

Number of subjects at given dose level with DLT	Action
0 out of 3 subjects	Escalate to next dose level
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	Escalate to the next dose level (Increase by ≤2 fold)
2 or more subjects in a dosing cohort (up to 6 subjects)	Maximum tolerated dose has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort.

Section 3.2.3 Dose Limiting Toxicity (DLT)

Rationale for Change: This section was updated for consistency with CTCAE guidelines.

Revised Text

1st Bullet Point:

- Neutropenia:

  - Grade 4 neutropenia lasting ≥~~5days~~7days.

  - Febrile neutropenia: ~~ANC<500/mm^3 and fever ≥38.5°C which persists > 48~~as defined by CTCAE version 4.0 lasting for >24 hours despite adequate treatment ~~with antibiotics and/or antifungal/antiviral agents~~.

7th Bullet Point:

- ALT ≥~~>~~3x ULN + bilirubin ≥2xULN (>35% direct) or ALT between 3-5 X ULN with bilirubin < 2xULN but with hepatitis symptoms or rash or ALT ≥~~>~~5xULN.

Section 3.2.6 Bioavailability, Food Effect, and Dose Proportionality Besylate Sub-Study

Rationale for Change: This section was updated to clarify that the sub-study would be conducted in the US only.

Revised Text

Paragraph 1

Part ~~1A~~1 will include a besylate sub-study that will be an open-label, randomized, single dose, four period, cross over study to investigate the relative bioavailability of the besylate salt tablet compared to the amorphous free-base tablet at or near the MTD or RP2D, the effect of high-fat high-calorie meal on the bioavailability of the besylate salt tablet at or near the MTD or RP2D and the dose proportionality of two doses of GSK525762 administered as besylate salt tablets. GSK525762 dosing will be separated by at least 48 hours. Up to 12 subjects in the United States may be enrolled in besylate sub-study.

Table 7 (Besylate Sub-Study Design: BA, Food Effect and Dose Proportionality Evaluation)

Sample Size	Sequence	Period 1 (Week 1 Day 1)	Period 2 (Week 1 Day 3)	Period ~~1~~3 (Week 2 Day 1)	Period 4 (Week 2 Day 3)

Section 3.2.7 Part 2 Expansion Cohort

Rationale for Change: The overall enrolment numbers were updated to accommodate enrolment of additional subjects into the supplementary expansion cohorts now included with this amendment. This section also includes information on the predictive probability design and the futility assessments planned for each cohort in Part 2.

Revised Text

~~Up to 40~~Approximately 150 subjects with NMC ~~may,~~ SCLC, CRPC, TNBC and ER+BC will be enrolled in ~~an~~ expansion cohort at the RP2D (appropriate to each age group) to gather more safety data and to further assess anti-tumor activity. ~~Pediatric subjects 12 to ≤15 years old may be enrolled in Part 2 once the MTD has been determined in Part 1B.~~

Subjects in Part 2 will start with a continuous daily dosing schedule unless safety, PK or PD data necessitate a different dosing schedule. The final dose and regimen for Part 2 will be decided upon completion of dose escalation in Part ~~1A and Part 1B for the respective age groups~~1.

~~For purposes of assessing activity, it will be assumed that the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20. Futility assessment will be conducted after data are available from the first 20 subjects. Safety from all prior subjects, will be reviewed along with this response data (and PK/PD and biomarker data when available) for consideration regarding expansion cohorts.~~

The statistical design and number of subjects to be enrolled in a cohort is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. The predictive probability design allows for evaluation of stopping rules after each subject once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. Final decisions on stopping enrollment will depend on the totality of the data collected.

For NMC, once 10 subjects have been enrolled into the expansion cohort to examine safety and efficacy, if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of 40 subjects in this cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 3 Diagram of Stopping Rules for NMC Cohort Expansion

	Number of Responses			
Number of Subjects	**0**	**1**	**2**	**3**
10				
11				
12				

	Number of Responses			
Number of Subjects	**0**	**1**	**2**	**3**
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				

Figure 3: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 10% or less (the futility criterion) and the study will be stopped.

For SCLC and CRPC, once 10 subjects have been enrolled in the cohort to examine safety and efficacy, if 0 responses are observed in either cohort, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4. A maximum of 22 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 4 Diagram of Stopping Rules for SCLC and CRPC Cohort Expansion

	Number of Responses				
Number of Subjects	**0**	**1**	**2**	**3**	**4**
10					
11					
12					
13					
14					
15					
16					

	Number of Responses				
17					
18					
19					
20					
21					
22					

Figure 4 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

For TNBC, once 10 subjects have been enrolled in the cohort to examine safety and efficacy, if 0 responses are observed in the cohort, Part 2 of the trial may be terminated with no further enrolment in this cohort. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 5. A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 5 Diagram of Stopping Rules for TNBC Cohort Expansion

	Number of Responses						
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							

	Number of Responses						
26							
27							
28							
29							
30							
31							
32							
33							
34							
35							
36							
37							

Figure 5 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

For ER+BC, once 10 subjects have been enrolled in each cohort to examine safety and efficacy, if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 6. A maximum of 37 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Figure 6 Diagram of Stopping Rules for ER+BC Cohort Expansion

	Number of Responses								
Number of Subjects	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
10									
11									
12									
13									
14									
15									
16									
17									
18									
19									

	Number of Responses								
20									
21									
22									
23									
24									
25									
26									
27									
28									
29									
30									
31									
32									
33									
34									
35									
36									
37									

Figure 6 Legend: The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study will be stopped.

Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified. Plasma samples for pharmacokinetic evaluation will be collected in all subjects. Plasma samples and tumor biopsies will be collected pre- and post-treatment for the pharmacodynamic evaluation.

Section 4.1 Number of Subjects

Rationale for Change: Overall enrolment numbers were updated in this section.

Revised Text

Paragraph 1:

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) and schedule(s) of GSK525762 for further study. To complete Part ~~1A and Part 1B~~1, it is estimated 30 to ~~50~~ 60 evaluable subjects will be enrolled. The besylate sub-study will enroll approximately 10 to 12 evaluable subjects in the United States only. Part 2 will enroll approximately ~~40 NMC~~150 subjects.

Section 4.2.1 Inclusion Criteria

Rationale for Change: This section was updated to clarify tumor types eligible for enrolment in Part 1 and Part 2 and remove reference of the pediatric cohort (Part 1B). Part 2 specific exclusion criteria were added for CRPC subjects.

Revised Text:

Bullet Point 1:

~~Part 1A:~~ Male or female 16 years or older, at the time of signing the informed consent.

~~Part 1B: Male or female 12 years to ≤15 years, at the time of signing the informed consent~~

~~Part 2: Male or female 16 years or older, at the time of signing the informed consent. After completion of Part 1B, male or female ≥12 years, at the time of signing the informed consent.~~

Bullet Point 3:

Diagnosis of one of the following:

- Part 1 Only:
  - NUT Midline Carcinoma based on ectopic expression of NUT protein as determined by IHC and/or detection of NUT gene translocation as determined by FISH. Subjects may be treatment naïve or have had prior therapy.
  - SCLC, CRC, NB, TNBC, ER positive BC, CRPC, NSCLC, and any other solid tumor which has been confirmed by clinical testing to be MYCN amplified (defined as a MYCN gene copy number gain of ≥5). Subjects should have tumor progression after receiving at least one prior standard/approved chemotherapy, or where there is no approved therapy, or where standard therapy is refused.
- ~~Pediatric solid tumors in Part 1B must have progressed after receiving at least one prior standard/approved chemotherapy, or where there is no approved therapy, or where standard therapy is refused, may be enrolled.~~
- Part 2 Only:
  - NUT Midline Carcinoma as diagnosed by the Central Laboratory. Subjects may be treatment naïve or have had prior therapy.
  - SCLC, CRPC, TNBC and ER+BC

Bullet Point 4:

Subjects with solid tumors, with the exception of CRPC, must demonstrate measurable disease, per RECIST v1.1. NOTE: Subjects with NMC that do not meet the RECIST v1.1 criteria for measurable disease, but have evaluable disease may be considered for enrollment ~~in the NMC PD Cohort at the previously cleared dose level.~~ after discussion with the GSK medical monitor.

Bullet Point 7 (Table 8):

Rationale for Change: The requirement for stool guaiac testing (fecal occult blood testing) was eliminated after discussion with the clinical and safety teams to achieve alignment across all GSK BET inhibitor protocols. Any recent evidence of overt gastrointestinal bleeding will remain exclusionary.

Revised Text:

System	Laboratory Values
~~Gastrointestinal~~	
~~Guaiac fecal occult blood test~~	~~Negative~~

Footnote no. 3 added for TSH: If TSH is abnormal, but free T3 and/or free T4 are normal, then the subject may still be considered eligible for enrolment.

Added Text

4.2.1.1.1 Specific Eligibility Criteria for Part 2 CRPC Expansion Cohort

Subjects must meet all of the following additional inclusion criteria in order to be considered eligible for this cohort:

11. Histologically or cytologically confirmed diagnosis of prostate adenocarcinoma, surgically castrated or continuously medically castrated (for ≥8 weeks prior to pre-screening)
12. Persistent disease with evidence of disease progression following standard therapy(ies) including prior treatment with androgen/androgen receptor directed therapy, including enzalutamide and/or abiraterone
13. Ongoing androgen deprivation therapy with a serum testosterone level <1.7 nmol/L or <50 ng/dL [Scher, 2008]
14. PSA levels ≥2.0 ng/mL [Scher, 2008]

    NOTE: If PSA level has been obtained within 14 days of Screening, this test does not need to be repeated and the result previously obtained may be used for the Screening value.

Section 4.2.2 Exclusion Criteria

Rationale for Change: Minor change made for clarification. The requirement for stool guaiac testing (fecal occult blood testing) was eliminated after discussion with the clinical and safety teams to achieve alignment across all GSK BET inhibitor protocols. Any recent evidence of overt gastrointestinal bleeding will remain exclusionary.

Revised Text:

Bullet Point 10:

~~Pulmonary hemoptysis~~ Hemoptysis > 1 teaspoon in 24 hours within the last 28 days

Bullet Point 11:

History of major gastrointestinal bleeding within the last 6 months. Any evidence of active gastrointestinal bleeding ~~(positive guaiac fecal occult blood test)~~ excludes the subject.

Section 5. TIME AND EVENTS TABLES

Rationale for changes: The time and events tables were modified to ensure consistency of timings, correct previous errors, and to include new assessments for CRPC in Part 2.
The requirement for stool guaiac testing (fecal occult blood testing) was eliminated after discussion with the clinical and safety teams to achieve alignment across all GSK BET inhibitor protocols. Any recent evidence of overt gastrointestinal bleeding will remain exclusionary.

Table 9 Time and Events: Part 1

Assessments Removed

- Pharmacogenomics (PGx): Blood samples for circulating exploratory biomarkers (cfDNA, etc)
- Castrate-Resistant Prostate Cancer Assessments: Vitamin D3 and PTH, Urinalysis Urine microscopy UPC, Urine electrolytes
- Pharmacokinetics (PK) and Pharmacodynamics (PD): Samples for mRNA at Screening Visit

Footnote added to CT/MRI Scans (Efficacy): Per RECIST 1.1 baseline (within 35 days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate.

Revised Text

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Safety																										
Adverse events		*SAEs collected continuously~~continuous~~ from signing of informed consent; AEs collected continuously from time of first dose*																								
Efficacy																										
CT/MRI Scans[a]	SCR assessment within ~~35~~ 28 days of first dose. Target lesions to be identified at SCR and followed.	X																				X		X		X	X
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation. EOT sample should be collected at time of progression where feasible.	X	All Tumor Types: One postdose sample ~~between W1D4 and W9D1, timing~~collected anytime betweenW2D1-D5 or W3D1 (2-4h post-dose). Timing may be further optimized based on tumor type and emerging data.																							X
Castrate-Resistant Prostate Cancer Assessments																										
PSA	PSA to be collected in line with PCWG2 guidelines. Levels may be checked more frequently if appropriate.	X																					X		X	

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Pharmacokinetics (PK) and Pharmacodynamics (PD)																										
Optional Saliva and/or Sweat Sample	A saliva and/or sweat sample may be requested on serial PK sampling days. Additional collection details will be provided in the SPM.		X															X								

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	q4W	q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Blood samples for circulating exploratory biomarkers (cfDNA, etc)		X																	X							X

Table 10 Time and Events: Part 1 Laboratory Assessments

Revised Notes for Troponin, NT-proBNP-9:

For Troponin: W1D1, W1D2: local lab sample 3X/24h; central lab sample 1X/24h. All other timepoints, including unscheduled ~~Unscheduled~~ collect 2 samples: 1 for local, 1 for central lab

Assessment Removed:

Guaiac fecal occult blood.
Hematology at q8W D1 Visit.

Table 11 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

Revised Text

	W1D1										W1D5		W2D4 + 1 day			
	pre dose	15 min ± 5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	12h ~~±1h~~2h	24h ~~±1h~~2h	48h ~~±1h~~2h [a]	30 min ±5m	3h ±15m	pre dose	30 min ±5m	3h ±15m	8h ±1h
Urine PK sampling (Part ~~1A~~1 only)[ab]	X	0-2h			2-24h											

Footnote added to W1D1 48h ±2h Time point: 48h PK sample to be collected prior to dosing on W1D3

Table 12 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

Revised Text

	W3D4 + 2 days									**W9D1 ±4 days** (if dose has been escalated, +4 to +7 days) ~~**EOT**~~			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ~~±1h~~2h**	**24h ±1h2h** [a]	**48h ±1h2h** [a]	**pre dose**	**0.5-2h**	**4 - 8h**	
Urine PK sampling (Part ~~1A~~1 only)~~ab~~		0-2h			2-24h									

Footnote added to W3D4 + 2 days 24h ±2h and 48h ±2h Time points: 24h and 48h PK samples to be collected prior to dosing on those days

Table 13 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1

Revised Text

	W1D1																W1D2 and W1D3 (relative to W1D1 Morning Dose)		W1D5 ECG and PK samples after Morning Dose only	
	Morning Dose								Evening Dose											
	pre dose	0H	15 min ±5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	pre dose (12h-15m)	12h	15 min(12.25h) ± 5m	30 min (12.5h) ±5m	1h (13h) ±5m	2h (14h) ±10m	4h (16h) ±15m	8h (20h) ±1h	12 h (24h) ±1h	36 h (48h) (pre-dose) ±1h	30 min ±5m	3h ±15m
~~12-lead ECG, in triplicate, 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.~~12-lead ECG, in triplicate[a]	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
PK and protein biomarker sample[b]	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Urine PK sampling~~(Part 1A only)~~[a,c]	X	0-2h				2-12h														

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment (pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr) and acute phase protein assessment at pre-dose and at 2,4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

	W1D1																W1D2 and W1D3 (relative to W1D1 Morning Dose)		W1D5 ECG and PK samples after Morning Dose only	
	Morning Dose								Evening Dose											
	pre dose	0H	15 min ±5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	pre dose (12h-15m)	12h	15 min(12.25h) ± 5m	30 min (12.5h) ±5m	1h (13h) ±5m	2h (14h) ±10m	4h (16h) ±15m	8h (20h) ±1h	12 h (24h) ±1h	36 h (48h) (pre-dose) ±1h	30 min ±5m	3h ±15m

a. Triplicate ECGs should be collected 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.

b. PK blood samples collected overnight may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

c. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

Table 14 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 2 and Week 3

Revised Text

	W2D4 + 1 day ECG and PK samples after Morning Dose only				**W3D4~~±~~+2 days**															**W3D5 and W3D6 (relative to W3D4 Morning Dose)**	
					Morning Dose								**Evening Dose** **(For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)**									
	pre dose (Prior to Dosing)	**30m ± 5m**	**3h ± 15m**	**8 h ±5m**	**pre dose**	**0h**	**15m ±5m**	**30m ±5m**	**1h ~~±5m 10m~~**	**2h ~~±10m 15m~~**	**4h ±15m**	**8h ±1h**	**pre dose**	**12h**	**15m ±5m (12.25m)**	**30m ±5m**	**1h (13h) ~~±5m 10m~~**	**2h (14h) ~~±10m 15m~~**	**4h (16h) ±15m**	**8h (20h) ±1h**	**12h (24h) ±1h (pre dose)**	**36h (48h) ±1h (pre dose)**
12-lead ECG, in triplicate~~, 5 minutes apart and within 10 min prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws~~[a]	X	X	X	X	X	~~X~~	X	X	X	X	X	X	X	~~X~~	X	X	X	X	X	X	X	X
PK and protein biomarker sample[b]	X	X	X	X	X	~~X~~	X	X	X	X	X	X	X	~~X~~	X	X	X	X	X	X	X	X	X
Urine PK sampling					X	0-2h				2-12h												

	W2D4 + 1 day ECG and PK samples after Morning Dose only				**W3D4±+2 days**															**W3D5 and W3D6 (relative to W3D4 Morning Dose)**	
					Morning Dose								**Evening Dose** **(For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)**									
	pre dose (Prior to Dosing)	**30m ± 5m**	**3h ± 15m**	**8 h ±5m**	**pre dose**	**0h**	**15m ±5m**	**30m ±5m**	**1h ±5m ~~10m~~**	**2h ±10m ~~15m~~**	**4h ±15m**	**8h ±1h**	**pre dose**	**12h**	**15m ±5m (12.25m)**	**30m ±5m**	**1h (13h) ±5m ~~10m~~**	**2h (14h) ±10m ~~15m~~**	**4h (16h) ±15m**	**8h (20h) ±1h**	**12h (24h) ±1h (pre dose)**	**36h (48h) ±1h (pre dose)**
~~(Part 1A only)~~[ac]																						
mRNA whole blood sample				~~X~~	X					~~X~~	X	X										

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment at pre-dose and at 2, 4, 8 and 24 hr post-dose. The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.

a. Triplicate ECGs should be collected 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.

b. PK blood samples collected overnight may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

c. Urine samples for quantitative analysis of GSK525762 are not required in the NMC PD Expansion Cohort.

Table 16 Time and Events: Part 2

Assessments Added: Castrate-Resistant Prostate Cancer Assessments (PSA and Serum testosterone) at SCR W1 D1, W2 D1, W3 D1, W4 D1, W5 D1, W9 D1, W13 D1, q4W D1 and EOT Visits

Assessments Removed: LPS blood sample, Blood samples for mRNA

Revised Text

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	q4W D1	q8W D1	EOT
Safety												
Adverse events		*SAEs collected continuously~~continuous~~ from signing of informed consent; AEs collected continuously from time of first dose*										
Efficacy												
~~Tumor sample~~		~~X~~	~~One postdose sample between W1D4 and W9D1, timing optimized based on emerging data~~									
~~PET~~CT scan or MRI	Scans within 28 days of first dose may be used as screening assessment. Additional bone scans and brain scans not required unless clinically indicated.	X						X			X	X
PK ~~and PD~~												
PK ~~and protein biomarker samples~~	Three samples to be collected each sampling day for each type of analysis: Predose within 60 minutes prior to dose, single draw between 0.5-2h postdose, single draw between 4-8h postdose. Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment.		X			X		X				
Blood samples for circulating exploratory biomarkers (cfDNA, etc)		X				X						X

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	q4W D1	q8W D1	EOT
Safety												
Adverse events		*SAEs collected continuously~~continuous~~ from signing of informed consent; AEs collected continuously from time of first dose*										
~~PGx~~ Translational Research												
PGx sample			X									
Tumor Sample	EOT biopsy should be collected at time of disease progression where feasible	X	All Tumor Types: One postdose sample collected anytime betweenW2D1-D5 or W3D1 (2-4h post-dose). Timing may be further optimized based on tumor type and emerging data									X

Table 18 Time and Events: Besylate Sub-Study

Assessment Added: PK samples at q8W D1 Visit, CT/MRI Scans and PET Scan (Efficacy) at W5D1 Visit

Section 6.1.2. Visit Windows

Revised Text

Paragraph 1

Screening (baseline to pre-dose): All assessments should be completed within ~~35~~ 14 days prior to ~~screening~~first dose, except for those specified in T&E table (e.g. CT, MRI, ECHO) . Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within 72 hours of first dose do not need to be repeated on Day 1.

Section 6.2 Baseline Assessment for NMC Subjects

Rationale for Change: Minor updates were made to this section to include mention of NGS for potential NMC diagnosis.

Revised Text

For NMC subjects, a diagnosis of NMC based on a positive IHC test at screening will be required. A ≥20% nuclei staining cut off will be applied for a positive diagnosis as a subset of germ cell tumors (from testis and ovary) weakly stain for the NUT protein (5% maximal nuclei staining, PPD , personal communication). Fluorescence in-situ hybridization (FISH) testing or next generation sequencing (NGS) will be undertaken prospectively to provide confirmation of borderline IHC staining (nuclear staining ≥1% and <20%) and retrospectively ~~to confirm NUT gene translocation in all positive IHC cases.~~

~~Further retrospective testing will be undertaken for all enrolled NMC subjects in order to~~ characterize the NUT gene fusion partner and to support exploratory analysis of differential outcomes based on the NUT fusion partner. The IHC and FISH or NGS analyses will be performed at a central laboratory.

Section 6.3 Baseline Assessment for Non-NMC Subjects

Rationale for Change: Minor updates made to this section to correct previous errors and to remove any reference to pediatric cohort.

Revised Text

Subjects diagnosed with SCLC, CRC, NB, CRPC, TNBC, ER+BC or NSCLC [based on standard diagnostic criteria, such as histology, cytology (including bone marrow evaluation)] or serological criteria (such as serum ~~M-protein~~PSA) will be considered eligible for Part 1 of the study. In instances where a solid tumor subject's MYCN amplification status is known, then that subject will be considered eligible. N-Myc copy number gain of ≥5 will be considered positive for MYCN amplification. N-Myc testing may be performed using any method.

~~Subjects with pediatric solid tumors enrolled in Part 1B must have diagnosis confirmed by standard criteria as appropriate for their tumor.~~

Section 6.4.5 Safety Electrocardiograms

Rationale for Change: This section was updated to ensure consistency with new QTc management guidelines.

Revised Text

Paragraph 2 onwards:

~~In addition to the Safety ECGs performed during the study, continuous 12-lead Holter ECGs (obtained via a Holter monitor) will be acquired while subjects are at the site. Dual snap electrodes will be utilized to enable simultaneous collection of Holter and safety ECG data.~~

~~All ECGs must include QTcF measurements. Those values greater than 480 msec as calculated by the machine must be confirmed manually using Fridericia's formula given below:~~

- ~~The Fridericia's formula is: QTcF=QT x (1/[RR/1000])1/3~~
- ~~If there are any clinically significant abnormalities including but not limited to a QTcF >480 msec, confirm with two additional ECGs taken at least 5 minutes apart.~~

Table 23 QT Withdrawal Criteria

~~If QTcF > 480 msec, or uncorrected QT > 600 msec (Grade 3 or 4), or any change from *baseline of ≥60 msec even if not exceeding 480 msec, (all measurements based on an averaged manual overread of three ECGs over at least 15 minutes) permanently discontinue study medications and notify the GSK Medical Monitor.~~ ~~* Baseline results are defined by the nearest timepoint prior to first dose. For this trial the Baseline QTcF value is determined by the mean of the triplicate W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate ECG results would be used.~~

If a subject meets the corrected QT (QTc) interval duration criteria below, study treatment(s) will be withheld.

- QTc interval ≥ 500 msec OR interval increase from baseline ≥ 60 msec: IP will be discontinued unless the benefits of therapy outweigh the risk of

rechallenge in the opinion of the Investigator, the GSK Medical Monitor, as well as the GSK medical governance. In this situation, rechallenge may be permitted (see Table 25 for rechallenge guidelines).

NOTE: QT interval duration criteria should be based on the average QTc value of triplicate electrocardiograms (ECGs) to include 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 discontinued.

The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF).

- For eligibility and withdrawal, QTcF will be used for all subjects.
- For purposes of data analysis, QTcF will be used.

Baseline results are defined by the nearest timepoint prior to first dose. For this trial the Baseline QTcF value is determined by the mean of the triplicate W1D1 predose QTcF results. If these results are not available, then the mean QTcF of the screening triplicate ECG results would be used.

Abnormal ECGs should be evaluated manually prior to final decision making. ECG data may be transferred and reviewed by an independent central reviewer. ~~Instructions for submission of qualifying ECHOs scans are provided in the SPM.~~

Table 21 Clinical Laboratory Tests

Rationale for Change: The requirement for stool guaiac testing (fecal occult blood testing) was eliminated after discussion with the clinical and safety teams to achieve alignment across all GSK BET inhibitor protocols. Any recent evidence of overt gastrointestinal bleeding will remain exclusionary.

Deleted Text

~~Guaiac fecal occult blood~~

Section 6.6.3. Urine Collection

Revised Text

Paragraph 1

Urine samples for quantitative analysis of GSK525762 will be collected at pre-dose and over a dosing interval ~~hours in two samples (sample collected 0-2hr and second sample collected 2-end of dosing intervalhr)~~ immediately following dosing on Week 1 Day 1 and in Week 3. Urine samples will be collected in subjects in Part ~~1A~~1 (with the exclusion of besylate sub-study) once the 3+3 dose escalation has been reached. Additional sampling may be instituted based on emerging data.

Section 6.8 Translational Research

Rationale for Change: This section was revised and reworded to provide additional rationale, details and clarification on the translational research strategy for this study.

Revised Text

Blood and/or tumor tissue specimens will be collected at various times throughout the study in order to support research aimed at identifying indicators of sensitivity/resistance to GSK525762 ~~and~~, understanding the biological effect of GSK525762 and BET inhibition, and also to support diagnostic assay development for NMC.

Toward that end the successful collection of quality tumor specimens will be critical to furthering our understanding of BET biology and indentifying the best way to treat patients with a BET inhibitor. Specifically, the evaluation of responders, responders at relapse, and non-responders for gene mutation status and/or pathway activation may lead to the discovery of potential new diagnostic markers or novel combinations. Similarly, pre- and post-dose tumor specimens will be evaluated for markers of target engagement, tumor response, and/or evaluated for changes in gene expression; thus supporting identification of a biologically effective dose and furthering our mechanistic understanding of BET inhibition in these settings.

The biopsies will be assessed for transcripts or proteins that reflect BET target engagement and/or tumor biology (For NMC, markers of cell proliferation and/or cell differentiation (e.g., Ki67 and cytokeratin [Schwartz, 2011]) will be analyzed. Biopsies may also be assessed for DNA, RNA or proteins which may be potential predictors of sensitivity or resistance to BET inhibition based on emerging data.

6.8.1 Tumor Tissue Collection

NMC patients will be required to submit a fresh or archival tumor specimen for diagnosis or diagnostic confirmation. These archival specimens may also be evaluated retrospectively for exploratory research~~. During the 3+3 design NMC patients will also be required to supply fresh pre and post-treatment biopsies to test for relevant markers of tumor PD and/or biological effect and to support identification of a biologically effective dose~~. as described above.

~~Non~~All non-NMC patients will also be asked to submit an archival tumor specimen for retrospective testing for potential markers of sensitivity and/or resistance, eg. N-Myc amplification; however this will not be an eligibility requirement. ~~Furthermore, as for NMC patients, during the 3+3 design non-NMC patients will be required to supply fresh pre and post-treatment biopsies for tumor PD.~~

During the accelerated dose escalation phase (Part 1), fresh pre- and post-dose biopsy collections will be optional until the standard 3+3 design is implemented. During the 3+3 dose escalation phase in Part 1, and during Part 2, pre- and post-treatment biopsies are mandatory. For subjects in Part 1 and 2, if tumor tissue is not accessible, discussion with the GSK medical monitor is required.

Archival tissue may be accepted as a pre-treatment specimen if the subject is treatment naïve. Specific timing of post-treatment sample collection is defined in the T&E table. See Study Procedures Manual (SPM) and central lab manual for additional details.

~~Blood samples collected at time points described in the Time and Events tables for PK and PD testing will be required for all subjects.~~

~~6.8.1 Tumor Tissue Collection~~

~~During the accelerated dose escalation phase (Part 1A), biopsy assessments will be optional until the standard 3+3 design is implemented. Once the 3+3 design is implemented in Part 1A, sites will be required to obtain pre- and post-treatment biopsies (when tumor tissue is accessible).~~

~~Up to 6 additional subjects per dose level may be enrolled and required to consent to pre and post treatment biopsies during the 3+3 dose escalation, for a maximum of 9 subjects per cohort until MTD is reached. Up to12 additional subjects may be enrolled and required to consent to pre and post treatment biopsies at the MTD for a maximum of 18 subjects (tumor tissue may be collected from one or more histological subtypes). Additional biopsy patients will help determine biologically effective dose(s) and provide additional safety data. The goal is to obtain evaluable tissue biopsies from approximately 8-10 subjects at MTD and 4-6 subjects at lower dose levels. This may occur in-stream before reaching MTD based upon adverse events or response profile. The tumor types appropriate for biopsy and pharmacodynamic evaluation may be restricted to a few specific tumor types/subtypes based on emerging pre-clinical data. Depending upon the emerging safety profile, Part 2 of the study may begin after enrollment of 6 subjects at the MTD or after determination of a biologically effective dose. Tumor biopsies will be optional for subjects below age 16 in either Part 1B or Part 2.~~

~~Archival tissue may be accepted as a pre-treatment specimen if the subject is treatment naïve. Specific timing of post-treatment sample collection will be based upon tumor type and emergent data. See Study Procedures Manual (SPM) for details.~~

~~For subjects with accessible tumor and who have signed the appropriate consent form the procedure will consist of approximately 3 core needle biopsies of the same accessible target tumor at the designated pre and post treatment time points. Where feasible,~~

~~biopsies are requested at time of progression. Further details regarding the biopsy procedure and how to process the tumor samples will be provided in the SPM.~~

~~The biopsies will be assessed for transcripts or proteins that reflect BET target engagement and/or tumor biology (For NMC, markers of cell proliferation and/or cell differentiation (e.g., Ki67 and cytokeratin [Schwartz, 2011]) will be analyzed. Biopsies may also be assessed for DNA, RNA or proteins which may be potential predictors of sensitivity or resistance to BET inhibition based on emerging data.~~

Section 6.9.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Rationale for Change: This section was updated to provide additional clarification regarding reporting of AEs for lab abnormalities.

Revised Text

Paragraph 1

Any abnormal laboratory ~~test results (~~findings (e.g., 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~~ that are judged by the investigator 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. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Section 7.1 GSK525762 Investigational Product Dosage/Administration

Rationale for Change: This section was updated to provide clarity on which formulations were being used for which part of the trial.

Revised Text

Paragraph 1:

GSK525762 Tablets will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. ~~Two investigational drug formulations will be introduced in Part 1.~~ An amorphous, free-base formulation of GSK525762 will be used in Part 1 (Table 23) and a crystalline, besylate formulation (Table ~~27~~24) will be introduced in the besylate sub-study in Part ~~1A~~1 (US sites only) and the Part 2 ~~NMC~~ expansion ~~cohort~~cohorts.

Table 23 (GSK525762 Amorphous Free-base Investigational Product Dosage/Administration):

Removed details of 100 mg tablet

Table 24 (GSK525762 Besylate Investigational Product Dosage/Administration)

Investigational Product			
Product name:	GSK525762 Besylate Tablets		13C-GSK525762 Stable isotope powder for oral solution
Physical description:	White to ~~off-white,~~slightly colored round, biconvex tablets with no markings, film-coated tablet	White to ~~off-white~~slightly colored , oval, biconvex tablets with no markings, film-coated tablet	White to ~~off-white~~slightly colored powder

Investigational Product		
Dosing instructions:	Dose with 240mL water and should be taken between 7 am and 10 am. No food or antacids for at least 1h before and 2h after dosing. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)	Dissolve powder in ~~10~~20 mL of water with bicarbonate buffer and administered with GSK525762 tablets (Besylate Sub-Study, Treatment A, B and C)

Section 7.7.1 Dose and Safety Management Guidelines

Rationale for Change: The QTc management guidelines were updated to reflect new guidelines.

Revised Text

Table 25 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
QTcF	~~• QT monitoring:~~ • If >30msec and ~~≤~~≤60 msec change from baseline~~* occurs.~~ ~~Grade 1 or 2 During telemetry monitoring if a Grade 1-2: If >60msec change from baseline* and not exceeding 480 msec for QTcF (Averaged~~ AND manual ~~overread~~QTcF <500 (average of three ECGs over at least 15 minutes)	~~Management Guidelines for QTcF:~~ • Continue ~~dosing and follow activities.~~ current dose of GSK525762 ~~Manually calculate QTcF to reconfirm clinically significant prolongation.~~ • Supplement electrolytes, particularly potassium and magnesium, to recommended levels: (1) Maintain serum potassium > 4mol/L (2) Maintain serum magnesium levels ≥0.85 mmol/L • Discontinue any concomitant medications with potential for QTcF prolongation. Consider 24 hour or longer telemetry monitoring if clinically indicated. ~~Grade 1 or 2 Temporarily discontinue study medications and review the following activities:~~ ~~Manual calculate QTcF to reconfirm clinically significant prolongation.~~ ~~Supplement electrolytes, particularly potassium and magnesium, to recommended levels:~~ ~~(1) Maintain serum potassium > 4mol/L~~ ~~(2) Maintain serum magnesium levels 0.85 mmol/L~~ ~~(1) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia~~ ~~(2) Discontinue any concomitant medications with potential for QTcF prolongation.~~ ~~(3) Consider telemetry monitoring if clinically indicated.~~ ~~May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical~~

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		~~Monitor.~~ ~~Permanently discontinue study medications and notify the GSK Medical Monitor.~~ ~~If the subject is variable around 480 msec assessments may be repeated. This subject may consider restarting study treatment at a reduced dose or dose level pre-event based on discussions with GSK Medical Monitor, Investigator and cardiologist.~~
	If ≥ 60 msec change from baseline occurs OR QTcF~~>480 msec (Averaged manual overread~~ ≥500 (average of three ECGs over at least 15 minutes) ~~If QTcF > 60 msec over baseline* value AND QTcF>480 msec (Averaged manual overread of three ECGs over at least 15 minutes)~~	• Discontinue GSK525762 and notify the GSK Medical Monitor. (4) Supplement electrolytes to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L (5) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (6) Discontinue any concomitant medications with potential for QTcF prolongation. (7) Consider telemetry monitoring if clinically indicated. • This subject may consider restarting study treatment at a previous dose level if the following criteria for QTcF rechallenge are met : • QTcF Rechallenge Procedures: Do not rechallenge with study treatment unless under the following conditions: (1) QTcF event reduced to ~~Grade ≤1~~<450 msec, (2) potassium and magnesium levels are within institutional normal range, ~~(3)~~ a favorable risk/benefit profile (3) ~~(4) approval by~~ (in the ~~internal~~ medical judgement of the Investigator and the GSK Medical Monitor), (4) ~~(5) IRB~~ approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval~~, and~~ d. ~~(6) the~~ Head Unit Physician approval (5) Institutional IRB (or equivalent) approval, and (6) The subject is re-consented regarding the possible ~~increase~~increased risk of ~~QTcF~~QTc prolongation. • If approval for re-~~treatment~~challenge is granted, the subject must be re-consented (with a separate informed consent specific to ~~QTcF~~QTc prolongation) • Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (1) Evaluation by cardiologist. (2) Weekly assessments for QTcF should be monitored

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		weekly for two weeks, and then next assessment at 4 weeks post-dose. (3) If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Liver	ALT ≥~~>~~5X ULN ALT≥ ~~>~~3X ULN and bilirubin ~~>~~≥/= 2X ULN (>35% direct bilirubin, bilirubin fractionation required) or INR >1.5 without evidence of biliary obstruction or progressive disease ALT ≥~~>~~3X ULN with the appearance hepatitis symptoms or rash	In the absence of known hepatic metastases, discontinue study medications, notify the GSK Medical Monitor, and refer to follow-up procedures outlined in Appendix 3, Section IIIa, Liver chemistry follow-up procedures. In the presence of known hepatic metastases, if there is evidence to suggest a drug induced effect, discontinue study medications, notify the GSK Medical Monitor, and refer to follow-up procedures outlined in Appendix 3, Section IIIa, Liver Chemistry Follow-Up Procedures.

Section 8.2.1 Cautionary Medications

Rationale for Change: The data source for Table 27 was updated in this section.

Revised Text

Table 27 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Generic Name	Brand Name
Amiodarone	Cordarone, Pacerone, Nexterone
Astemizole	Hismanal
Chlorpromazine	Thorazine, Largactil, Megaphen
Clarithromycin	Biaxin, Prevpac
Haloperidol	Haldol

*There may be situations when the subject is on study that Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines
Data Source: www.~~QTdrugs~~crediblemeds.org (revised ~~25~~02-Mar-~~2008~~2015)

Section 11.1 Sample Size Assumptions

Rationale for Change: Analysis and sample size updated for new tumor types included in Part 2 and additional information provided on rationale for sample size, futility and probability predictions.

Revised Text

11.1.1 Part 1

The total number of subjects to be enrolled into Part ~~1A and Part 1B will~~1will depend on the number of dose escalations required to establish the maximum tolerated dose of GSK525762; they are not driven by statistical considerations. To complete Part 1, it is estimated that 50 to 70 evaluable subjects will be enrolled.

~~11.1.2 Part 1A Besylate Sub-Study~~

Doses to be studied in Part 1 will be guided by calculating the posterior probability that the DLT rate falls within an acceptable range for each subsequent dose after each dose cohort observation period. The N-CRM method will be used to calculate posterior probabilities utilizing a pre-specified prior distribution.

11.1.2 Besylate Sub-Study

Paragraph 1:

At least 8 and up to 12 US subjects will participate in Besylate Sub-Study.

11.1.3 Part 2

~~Up~~The primary goal of Part 2 is to ~~40~~ evaluate disease-specific efficacy in subjects ~~in~~ with NMC, SCLC, CRPC, TNBC and ER+BC. .

- For NMC, efficacy is defined as a clinically meaningful response rate (defined as the ~~NMC expansion~~percentage of subjects that have achieved a CR or PR) of 20% relative to a 5% response rate suggesting no activity
- For CRPC and SCLC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 30% relative to a 10% response rate suggesting no activity.
- For TNBC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 25% relative to a 10% response rate suggesting no activity.
- For ER+BC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 30% relative to a 15% response rate suggesting no activity.

Bayesian statistics will be employed to calculate the predictive probability that the response rate is greater than the historic response rate at interim analyses using a weak/non-informative prior. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior distribution is defined to characterize the level of knowledge about a parameter before the data are collected. Once the data are collected, a posterior distribution is formed using the prior distribution and the observed data. A very weak prior Beta distribution with a mean response rate equal to the target response rate is

assumed. Thus, the posterior distribution for the response rate will be primarily driven by the data and can be derived as follows:

Let p denote the response rate, the number of responses in the current n subjects, x, follows a binomial distribution, Binomial (n, p). Taking the Bayesian method and combining the prior distribution and the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.

In the following case, 30% is the target response rate.

$$p \sim \text{Beta}(0.03 + x, 0.07 + n-x) \text{ with the posterior mean } (0.03+ x)/(0.07 + n).$$

Futility analysis for each disease cohort will begin when response data is available for at least 10 subjects. Each disease cohort may be ~~enrolled. With a sample size of approximately 40 subjects, the study will have 90% statistical power to test~~stopped early for futility if the predictive probability of success (response rate ≥ historical response rate) is less than 1%. Futility stopping rules are defined for each cohort in Section 3.2.7.

The following table describes for each disease cohort the null ~~hypothesis that overall Response Rate (RR) P0≤0.05 versus the~~ and alternative ~~that P1≥0.20 at actual alpha=0.05 (using a two-stage~~hypotheses that will be tested, maximum sample size and design~~, verified using Green Dahlberg two-stage design [, 1992].~~ characteristics. Each maximum sample size was calculated to ensure that at least 80% power and a maximum type 1 error rate of 10% is maintained.

	Null Hypothesis (H0) ORR	Alternative Hypothesis (Target) (Ha) ORR	Maximum Sample Size	Probability of stopping early for futility if H0 is true	Average Sample Size if H0 is true	Actual Type I Error Rate (%)	Actual Power (%)
NMC	5%	20%	**25**	**0.891**	**14**	**8.8**	**80.2**
CRPC	10%	30%	**22**	**0.860**	**16**	**6.0**	**82.5**
TNBC	10%	25%	37	0.876	23	6.4	81.7
ER+BC	15%	30%	37	0.855	25	8.7	80.3
SCLC	10%	30%	22	0.860	16	6.0	82.5

11.1.4 Sensitivity Analysis

~~A~~No sample size sensitivity analysis was performed ~~to assess the effect on power if the true response rate varies from the anticipated 20%.~~.

Table 32 Sample Size Sensitivity Analysis

~~True Response Rate~~	~~N1~~	~~N2~~	~~Overall Power~~
~~15%~~	~~20~~	~~20~~	~~69%~~
~~20%~~	~~20~~	~~20~~	~~90%~~
~~25%~~	~~20~~	~~20~~	~~98%~~
~~30%~~	~~20~~	~~20~~	~~99%~~

~~N1=Sample size at interim. N1+N2=Total sample size~~

Deleted Section 11.2 Stopping Rule for Futility (Interim Analysis)

Rationale for Change: This section was deleted as the stopping rule for futility is described in the previous sections and elsewhere in the protocol.

Deleted Text:

~~11.2 Stopping Rule for Futility (Interim Analysis)~~

~~An interim analysis will be conducted for Part 2 of this study in order to assess futility after response data are available for the first 20 subjects based on the overall best response rate. If 0 responses are observed, then Part 2 of trial will be terminated with no further enrolment.~~

~~If at least 1 response occurs then an additional 20 subjects with NMC may be enrolled. Emerging safety data will also be reviewed. Safety data will be reviewed on an ongoing basis and after the first 20 patients to ensure the safety profile supports continued enrolment. If there is sufficient sample size an exploratory analysis will be undertaken to evaluate whether response rates differ between molecular subtypes (e.g. NUT-BRD3, NUT-BRD4, NUT-variant).~~

~~There is a 1% probability of stopping for futility under the alternative hypothesis (i.e incorrectly stopping at the interim when in drug is efficacious) and a 36% probability of stopping for futility under the null hypothesis (i.e. correctly stopping at the interim when the drug is not efficacious).~~

~~At final analysis, if >=5 responses are observed then we reject the null hypothesis and accept the alternative hypothesis that there is at least a 20% response rate in NMC following dosing with GSK525762.~~

Section 11.4.1 Primary Analysis

Rationale for Change: The analysis section was updated to include additional tumor types in Part 2 now included with this protocol amendment.

Revised Text

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and response criteria. If the data warrant, the response data will be summarized by dose level.

The primary aim of Part 2 is to demonstrate ~~a~~ clinically meaningful response ~~rate~~rates in each of ~~20% relative to a 5% response rate suggesting no activity~~the disease cohorts separately.

~~The overall~~Overall response rate is defined as the percentage of subjects ~~with a confirmed complete response (~~who achieved CR~~)~~ or ~~a partial response (~~PR~~) at any time as per RECIST 1.1 criteria. Subjects with unknown or missing response will be treated as non responders, i.e., these~~ among subjects ~~will be included in the denominator when calculating the percentage. Exact methods for calculated~~who received at least one dose of treatment. Overall response rate and the associated 2-sided 95% exact confidence ~~intervals~~limits will be ~~in the RAP.~~

~~The number and types of responses, as outlined in RECIST 1.1, will be listed and summarized, as appropriate, for the NMC~~provided separately for each disease cohort ~~in Part 2.~~

~~NMC is an extremely rare cancer and there is no known response to chemotherapy. This cancer has an extremely poor survival rate of 6.7 months (median). Based on dialog between investigators and GSK, it is estimated that a RR of 20% would be the lowest threshold which is of clinical relevance. The study is based on the assumption that the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20. A futility assessment will be conducted after data is available from the first 20 subjects. If 0 responses are observed among the 20 subjects at interim, then in conjunction with a thorough review of additional data, that cohort may be closed for further enrollment. If one or more subjects respond, then an additional 20 subjects may be enrolled to more accurately define the true response rate.~~

~~At final analysis, if ≥ 5 responses are observed then the null hypothesis will be rejected and the alternative hypothesis that there is at least a 20% response rate in NMC following dosing with GSK525762 will be accepted~~.

Section 13 References

Rationale for Change: References were updated based on updates made throughout the protocol amendment.

Reference Deleted

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AMENDMENT 06

Protocol Changes for Amendment 6 (DD-MMM-YYYY) from the Protocol Amendment 5 (24-MAR-2015)

Protocol Amendment 6 applies to all site(s) participating in the conduct of the study

Amendment 06 summary: Amendment 6 includes updated guidance on contraception use based on emerging data from preclinical studies. Section 6.4.6 was updated to clarify how the Holter Monitoring data will be reviewed and analyzed. Additionally, updates were made throughout to correct minor inconsistencies and provide further clarification, specifically with the Time and Events Tables. Furthermore, the dosing schedule was updated from a staggered (1,3,5,7) dosing schedule in the first two weeks to a continuous daily dosing schedule. Finally, after an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 100 mg QD cohort available by May 15 2015, the 48-hour telemetry requirement has been removed for all parts of the study and the frequency of Holter Monitoring has been decreased in Part 1.

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

List of Specific Changes

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Rationale for Change: Updated to include back-up medical monitor's cell phone number.

Added Text:

After-hours contact number added for Secondary Medical Monitor

PROTOCOL SYNOPSIS

Rationale for Change: After an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 100 mg QD cohort available by May 15 2015, the 48-hour telemetry requirement was removed for all parts of the study and the frequency of Holter Monitoring was decreased in Part 1. There was no GSK525762 related QTc prolongation observed within the first 48 hours of treatment.Therefore the inpatient telemetry on W1D1 and W1D2 was discontinued. Although the presence of a slight delayed QT prolonging effect was noted, this did not lead to any marked prolongation (no individual subjects with delta >60ms or QTc >500ms). The frequency of Holter monitoring in Part 1 was also reduced from 6 timepoints to 4 timepoints, as the ECG time-points currently included in the required assessments provide adequate cardiac safety assessments of any potential QT-prolonging effect (including potential delayed effects). All Holter monitoring will continue to be reviewed at a central lab for arrhythmia assessment. The overnight stays previously mandated as part of the 48-hour in-patient telemetry will only be required on serial ECG/PK days at sites that are unable to collect after-hours PK timepoints as outpatient.

Revised Text:

SAFETY MEASUREMENTS: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. ~~Stringent~~ Ce~~a~~rdiac safety monitoring will be required, consisting of ~~at least 48 hours of telemetry following the first dose (overnight stays in research facility necessary)~~, 24 hours of Holter monitoring at Screening and in Week 1, ~~Week 2~~, and Week 4~~, and Week 9~~, and triplicate 12-lead ECGs prior to dosing on selected days and prior to drawing PK samples on serial PK sampling days (overnight stays in research facility may be necessary in Part 1~~).~~). Extensive laboratory testing includes, in addition to standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels, testing for troponin, c-peptide, 1,5 AG, HBA1c, and thyroid monitoring. Additional safety assessments may be necessary if a combination treatment regimen is administered to address specific safety concerns with the other agent(s) being administered.

Section 1.5 Risk Assessment

Rationale for Change: The Telemetry was removed from the Risk Assessment section after an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 100 mg QD cohort available by May 15 2015, the 48-hour telemetry requirement was removed for all parts of the study and the frequency of Holter Monitoring was decreased in Part 1. There was no GSK525762 related QTc prolongation observed within the first 48 hours of treatment. Therefore the inpatient telemetry on W1D1 and W1D2 was discontinued. Although the presence of a slight delayed QT prolonging effect was noted, this did not lead to any marked prolongation (no individual subjects with delta >60ms or QTc >500ms). The frequency of Holter monitoring in Part 1 was also reduced from 6 timepoints to 4 timepoints, as the ECG time-points currently included in the required assessments provide adequate cardiac safety assessments of any potential QT-prolonging effect (including potential delayed effects). All Holter monitoring will continue to be reviewed at a central lab for arrhythmia assessment.

The Reproductive Risk section was also updated after new findings related to GSK525762 in a rat female fertility study in which adverse reproductive findings in pregnant rats (maternal and embryo-fetal) were observed. This section was updated with a summary of those findings.

Revised Text:

Cardio-vascular: *(Paragraph 2)*

Given the risks of long QTc associated arrhythmias, and of compound associated cardiomyopathy, subjects will be monitored closely for changes in QTc with triplicate 12-lead ECG, Holter monitoring, ~~telemetry,~~ and for elevations in plasma Troponin. Inpatient 48-hour telemetry was originally required for all subjects following the first dose of study drug, as part of the cardiac monitoring. Evaluation of cardiac safety data from subjects treated up to the 100 mg QD cohort by the cut-off date of May 15, 2015 demonstrated no significant QTc prolongation after single and repeat dose administration. Therefore, the 48-hour telemetry requirement was removed and the frequency of Holter monitoring was reduced with Protocol Amendment 6.

Specific stopping criteria and management guidelines are provided for cardiac toxicities.

Deleted Text:

~~**Telemetry**~~

~~Continuous telemetric in-patient monitoring for potential adverse arrhythmias will be performed for at least 48 hours from the administration of the first dose. Thereafter, hospitalization and monitoring will be instituted if significant QTcF prolongation is detected for the immediate detection of any detected dysrhythmia. Participating sites will have trained staff capable of monitoring and responding in real time any potential cardiac adverse event detected by telemetry. In addition, trained personnel and emergency resuscitation equipment, including appropriate pharmacological agents, will also be immediately accessible.~~

Revised Text:

Reproductive and Developmental: In 4-week toxicology studies, bilateral sperm retention, germ cell degeneration and tubular vacuolization, and depletion of testicular germinal epithelium occurred in male dogs receiving ≥ 0.3 mg/kg and male rats receiving ≥ 10 mg/kg doses of GSK525762. Exposures associated with reproductive toxicity in male dogs overlap with the proposed 5 mg starting dose in this FTIH study.

~~Preliminary rat embryo fetal development~~

GSK525762 at 0, 1, 3, 10, or 30 mg/kg/day (total dose; doses expressed as parent compound) was given orally by gavage BID (doses given 6 hours apart) to pregnant rats on Days 0 through 17 post-coitus. Dose-dependent maternal toxicity (reduced body weight gain and reduced food consumption) was evident at ≥10 mg/kg/day. Embryo-fetal toxicity was evident as both pre-implantation loss and increased fetal resorptions leading to complete loss of litters at 30 mg/kg/day, and dose-dependent increased fetal resorptions at doses ≥1 mg/kg/day. Developmental toxicity was evident as decreased fetal weights at 10 mg/kg/day and fetal malformations and/or variations at all doses (membranous ventricular septal defects in the heart ≥1 mg/kg/day; great vessel, heart, kidney, ovary, uterus, and ureter malformations and/or variations at 10 mg/kg/day). The AUC0-t and Cmax at 1 mg/kg/day (the lowest dose tested) in non-mated female rats after 5 doses were 54 ng.h/mL and 18 ng/mL, respectively.

No ovarian histologic changes were observed in the 4 week toxicology studies, however female fertility (disrupted estrous cyclicity, delays to mating and/or reduced fertility index) was affected in rats given 30 mg/kg/day GSK525762 for 15 days prior to mating and 15 days prior to mating through to Day 6 post coitus (pc). Systemic exposure in rats was approximately 2-fold higher than current exposure in late stage cancer patients (at 60 mg/day). No fertility effects were observed when 30 mg/kg/day was given for 6 weeks followed by 6 weeks off-dose prior to mating.

Reproductive and developmental toxicity (decreased fetal body weight, fetal malformations or variations and / or pre- and post-implantation loss) occurred in rats given GSK525762 ≥ 1mg/kg/day from conception through gestation day 17 (of 21 days)

and when dosed at ≥10 mg/kg/day for 14 days and dosing stopped prior to mating or continued until Day 6 pc. Systemic exposure in rats was approximately 80-fold lower than current exposure in late stage cancer patients (at 60 mg/day). These results are consistent with observations that BRD2, BRD3, BRD4 and BRDT have crucial roles in reproduction and development [see the GSK 525762 IB [GlaxoSmithKline Document Number 2011N113741_03] for references.

Based on the findings in these reproductive and developmental toxicity studies in rats with GSK525762, there is a substantiated risk for adverse effects on embryofetal development and impacts on female fertility.

In the BET11521 study, specific contraceptive guidelines and precautions for males and females are provided in the protocol. In addition, the informed consent will include potential reproductive risks and precautions in addition to recommendations for the preservation of reproductive capacity.

Section 3.2.2. Dose Escalation and Schedule

Rationale for Change: The original staggered dosing schedule (1,3,5,7) was designed to include dosing breaks over the course of the first two weeks to monitor for any potential immediate toxicities before moving into continuous daily dosing in the third week. As included in the rationale for removal of 48-hour telemetry and reduction of holter monitoring frequency, after an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 100 mg QD cohort available by May 15 2015, evidence of a slight delayed QT prolonging effect was noted, however this did not lead to any marked prolongation and there were no individual subjects with delta >60ms or QTc >500ms.

In an effort to achieve an optimal dosing schedule and further explore alternate dosing schedules (i.e.; two weeks of dosing, followed by one week off study drug), the intermittent dosing was modified to allow subjects to begin continuous daily dosing on Day 1.

Revised Text:

~~A unique, staggered dosing schedule will be implemented to monitor for safety (Table 4). This approach allows repeat dosing in a step-wise fashion to detect changes in safety, such as cardiotoxicity. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data.~~

In Part 1, subjects will follow the dose schedule outlined in Table 4. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data.~~Specifically, in Week 1 subjects will receive a single dose of study drug on Day 1, rest on Day 2, receive study drug on Day 3, Day 4, and Day 5, and rest again on Day 6 and Day 7. In Week 2, subjects will receive study drug on Day 1 through Day 5, and rest Day 6 and Day 7. From Week 3 the subject will start daily dosing which will continue until study completion.~~

Extensive monitoring for cardiac safety signals will be performed, with triplicate 12-lead ECGs, ~~48-hour telemetry,~~ and 24-hour Holter monitoring to be performed on the days indicated in Table 4.

Subjects will be evaluated for dose limiting toxicities (DLTs) during the first 4 weeks of treatment (Section 3.2.3).

Table 4 Dosing Schedule and Cardiac Monitoring for Part 1

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG,~~Tele,Holter~~	ECG,~~Tele~~	ECG		ECG,Holter	ECG	ECG
Week 2	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG			ECG	~~Holter~~	ECG	ECG
Week 3	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG			ECG			
Week 4	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG,Holter			ECG			

Section 3.2.2.4. Alteration of Schedule

Rationale for Change: This section was updated to include a statement that PK sampling and other assessments may be modified if alternate dosing schedules are explored to reflect the new dosing schedule. This was to allow PK and/or other safety assessments to be collected during dosing days, and also to exempt subjects from having these assessments if they fell on a non-dosing day under a revised altered schedule.

Revised Text:

Alterations may be made to the schedule of administration and/or PK/PD sampling schedule based on the results of emerging PK and safety data.

Schedules that incorporate a recovery period may be explored (e.g. every other day or two weeks on treatment followed by one week off). This approach will be considered if the safety and PK data suggest that a therapeutic exposure cannot be achieved using the initial schedule without excessive toxicity. The starting dose for the alternate schedule will be the highest completed dose level (at or below MTD) with the initial schedule. Escalation can then proceed as described using 3 + 3 dose escalation. If alternative dosing schedules are explored, PK sampling times and other safety assessments may be modified to reflect the new dosing schedule.

Section 3.2.2.6. Intra-Subject Dose Escalation

Revised Text

Paragraph 1, Bullet point no 2:

If no further subjects have been identified for a subsequent higher dose level and after a subject has completed 4 weeks of dosing on that regimen without a DLT, that subject may be escalated to the next higher dose level after an additional 4 weeks of dosing (total of 8 weeks of dosing), review of all safety data and approval by a GSK Medical Monitor. In this case the subject must follow the ~~staggered~~ dosing/monitoring schedule for the first 4-weeks as outlined in Table 4, as he/she will be the first subject exposed to the higher dose.

Section 3.2.5.1. NMC Pharmacodynamic Expansion Cohort

Rationale for Change: The rationale for moving from a staggered dosing schedule to a continuous daily dosing schedule is explained above and all reference to staggered dosing was removed throughout the protocol.

Revised Text

Paragraph 2:

Subjects in the NMC PD Expansion Cohort will start with same ~~staggered~~ dosing schedule ~~during the first two weeks as~~ described in Section 3.2.2 (Table 4); ~~subjects will begin continuous dosing in Week 3~~. Extensive monitoring for cardiac safety signals will be performed as required in Part 1, with triplicate 12-lead ECGs, ~~48-hour telemetry,~~ and 24-hour Holter monitoring to be performed on the days indicated in Table 4. All safety and PK evaluations will be performed as outlined in the Time and Events Tables for Part 1 (Section 5). Safety data from subjects in the NMC PD Expansion Cohort will be reviewed on an ongoing basis by the GSK medical monitor, GSK Safety Review Team, and investigators for consideration during 3+3 dose escalation decisions.

Section 3.2.6. Bioavailability, Food Effect, and Dose Proportionality Besylate Sub-Study

Table 7 Besylate Sub-Study Design: BA, Food Effect and Dose Proportionality Evaluation:

Rationale for Change: Minor updates were made to this section to clarify treatment arm A as A2 to be consistent with the naming convention of this treatment arm in GSK's internal interactive voice response system for registration of subjects.

Revised Text: 'Treatment A' changed to 'Treatment A2' throughout the Table.

Section 3.2.7. Part 2 Expansion Cohort

Rationale for Change:

Revised Text This section was updated to clarify that during the futility assessment for individual cohorts in Part 2, if stopping criteria were met, further enrolment into that specific cohort would cease, but would not require stopping enrolment in other cohorts.

Paragraph 1:

Approximately 150 subjects with NMC, SCLC, CRPC, TNBC and ER+BC will be enrolled in expansion cohort at the RP2D ~~(appropriate to each age group)~~ to gather more safety data and to further assess anti-tumor activity.

Footnote for Figure 3, Figure 4, Figure 5 and Figure 6:

The shaded regions are the specific regions for stopping ~~the study~~enrollment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 10% or less (the futility criterion) and further enrollment ~~the study~~into this cohort will be stopped.

Section 4.2.1. Inclusion Criteria

Rationale for Change: Based on emerging data from pre-clinical fetal and embryo toxicity studies, the inclusion criteria specifying contraception requirements were updated to extend the length of time for contraception use for subjects. A summary of the findings from these preclinical studies may be found in the body of the protocol under Reproductive Risks in Section 1.5.

Revised Text

Inclusion criteria no 9, Bullet point no 2:

Child-bearing potential and agrees to use one of the contraception methods (described in Section 9.1) for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until ~~at least~~ 7 months~~4 weeks~~ after the last dose of study medication.

Inclusion criteria no 10:

Male subjects must agree to use one of the methods of contraception specified. This method must be used from the time of the first dose of study medication until ~~least~~ 16 weeks after the last dose of study medication. In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 7 days after stopping study medications.

Section 4.2.3.1. Permanent Discontinuation from Study Treatment

Rationale for Change: Minor updates were made to this section to further clarify the follow up phase and requirements.

Revised Text

Paragraphs 7 and 8:

All subjects who permanently discontinue study treatment without disease progression will be followed for progression according to the protocol schedule until:

~~New anti-cancer therapy is initiated~~

progression

death, or

subject has been followed for 2 years after stopping treatment.

All subjects who permanently discontinue study treatment will be followed for survival and new anti-cancer therapy [including radiotherapy] every 6 months until death or until the subject has been followed for 2 years. Reporting of any pregnancies in female subjects and/or female partners of male subjects will also be collected until 7 months after the last dose of study drug.- If subjects are unable or unwilling to attend clinic visits during follow-up, contact to assess survival may be made via another form of communication (e.g., telephone, email, etc.).

Section 5. TIME AND EVENTS TABLES

Rationale for Change: The time and events tables were modified to ensure consistency of timings, correct previous errors, provide additional clarifications and to include new updates based on removal of telemetry and revised holter monitoring schedule.

Table 9 Time and Events: Part 1

Revised Text:

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9 q4W	Q4 and Q8W Initiated from Week 9 q8W	EOT
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D 1	D 1	
TREATMENT PHASE																										
Study Drug																										
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Daily									
Cardiac Monitoring																										
12-lead ECGs (Triplicate)	~~Triplicate SCR ECGs within 35 days of first dose.~~ For timing of triplicate ECGs on O days, see Table 11 and Table 12. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O	O	O ~~X~~		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X	~~X~~				X							~~X~~					X				~~X~~			
~~Telemetry~~	~~Start at least 60 min predose and for at least 48 h.~~		~~X~~	~~X~~																						
Efficacy																										
CT/MRI Scans[a]	SCR assessment within ~~28~~35 days of first dose. Target lesions to be identified at SCR and followed.	X																			X		X		X	X

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9 q4W	Q4 and Q8W Initiated from Week 9 q8W	EOT
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D 1	D 1	
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation. EOT sample should be collected at time of progression where feasible.	X	All Tumor Types: One postdose sample collected anytime betweenW2D1-~~D5 or~~ W3D1 (2-4h post-dose). Timing may be further optimized based on tumor type and emerging data.																							X
PET scan	Optional during rapid dose escalation; required during 3+3 dose escalation. SCR assessment within 35 days of first dose.	X																			X		X			

Table 10 Time and Events: Part 1 Laboratory Assessments

Revised Text:

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	W1			W2		W3	W4	W5	W7	W9	Q4 and Q8W Initiated from Week 9 q4W	Q4 and Q8W Initiated from Week 9 q8W	EOT
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP-9	For Troponin: W1D1 &~~,~~ W1D2: local lab sample collect 3X/24h; central lab sample collect 1X/24h. All other timepoints, including unscheduled collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X	X		X		X	X

Table 11 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

Revised Footnote:

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment ~~(pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr)~~ and acute phase protein assessment at pre-dose~~, and at~~ 2, 4, 8, 12 and 24 hr post-dose. The frequency of sampling may be changed ~~(likely reduced)~~ based on data from the first few subjects assessed.

Footnote added for W1D1 12h ±2h Time point:

PK blood samples collected after-hours may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)

Table 12 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

Revised Footnote:

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment and acute phase protein assessment at pre-dose and at 2, 4, 8, 12 and 24 hr post-dose. The frequency of sampling may be changed ~~(likely reduced)~~ based on data from the first few subjects assessed.

Footnote added for W3D4 + 2 days 12h ±2h Time point:

PK blood samples collected after-hours may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H).

Table 13 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1

Revised Footnote:

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment ~~(pre-dose and at 15 min, 30 min, 1 hr, 2 hr, and 4hr)~~ and acute phase protein assessment for morning and evening dosing at pre-dose and at 2, 4, 8, 12 and 24 hr post-dose. The frequency of sampling may be changed ~~(likely reduced)~~ based on data from the first few subjects assessed.

Table 14 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 2 and Week 3

Assessments Removed:

Urine PK sampling at pre dose (Morning Dose) on W3D4 +2 days Visit

Revised Footnote:

Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment and acute phase protein assessment at pre-dose and at 2, 4, 8, 12 and 24 hr post-dose. The frequency of sampling may be changed ~~(likely reduced)~~ based on data from the first few subjects assessed.

Table 15 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 9

Assessments Removed:

mRNA whole blood sample at pre dose on W9D1 ±4 days Visit

Table 16 Time and Events: Part 2

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13: q4W D1	q8W D1	q12W D1	EOT
Laboratory assessments: For details please see Table 17													
Tests		X	X	X	X	X	X	X	X	X	X	X	X
Cardiac Monitoring													
~~Telemetry~~	~~Start predose and for at least 48 h.~~		~~X~~										
Efficacy													
CT scan or MRI	Scans within ~~28~~ 35 days of first dose may be used as screening assessment. Additional bone scans and brain scans not required unless clinically indicated.	X						X			X		X
PET scan	Scans within 35 days of first dose may be used as screening assessment.	X											
PK													
PK	Three samples to be collected each sampling day for each type of analysis: Predose within 60 minutes prior to dose, single draw between 0.5-2h postdose, single draw between 4-8h postdose. ~~Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for acute phase protein assessment.~~		X			X		X					
Translational Research													
Tumor Sample	EOT biopsy should be collected at time of disease progression where feasible	X	All Tumor Types: One postdose sample collected anytime betweenW2D1~~-D5 or~~ W3D1 (2-4h post-dose). Timing may be further optimized based on tumor type and emerging data										X

Table 17 Time and Events: Part 2 Laboratory Assessments

Revised Text:

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	**Notes**	**SCR**	**W1**		**W2**		**W3**	**W4**	**W5**	**W9**	**W13**	**Q4, Q8 and Q12W Initiated from Week 13**			**EOT**
			D1	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	**q4W**	**q8W**	**~~q~~Q12w**	
												D1	**D1**	**D1**	

Table 18 Time and Events: Besylate Sub-Study

Revised Text:

Besylate Sub-Study Assessments	**Notes**	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W7**	**W9**	**Q4 and Q8W Initiated from Week 9**		**EOT**
			D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**q4W**	**q8W**	
																								D1	**D1**	
Cardiac Monitoring																										
12-lead ECGs (Triplicate)	~~Triplicate SCR ECGs within 35 days of first dose.~~ For timing of triplicate ECGs on O days, see Table 11 and Table 12. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs daily through W2.	X	O		X					X		X					X		X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X	~~X~~																X				~~X~~			
~~Telemetry (Potentially will be removed for Besylate Sub-Study based on~~	~~Start at least 60 min predose and for at least 48 h.~~	~~X~~	~~X~~																							

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	q4W D 1	q8W D 1	
~~emerging data from Part 1)~~																										
Efficacy																										
PET scan	SCR assessment within 35 days of first dose.	X																			X		X			

Section 6.4.4. Echocardiogram (ECHO)

Rationale for Change: This section was updated to clarify that GSK is receiving all ECHOs, not just those with a >10% LVEF decrease from baseline.

Revised Text:

For all subjects, ECHOs will be performed at screening and at assessment times as outlined in Section 5. ECHOs should be evaluated and compared to baseline by the same reader. ~~Copies of all ECHO scans performed on subjects who experience an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF < LLN will be required by GSK for review.~~

ECHO data ~~may~~ will be transferred and reviewed by an independent cardiologist. Instructions for submission of qualifying ECHO scans are provided in the SPM.

Section 6.4.6. Holter Monitoring

Rationale for Change: This section was updated to reflect the actual analysis of the Holter Monitoring at the central cardiac monitoring lab and clarify that ECGs are not being extracted from the 24-hour holter; however arrhythmia assessments will continue at the central cardiac monitoring lab for the holter monitoring.

Revised Text

Paragraph 3, 4 and 5:

Analysis of intervals and morphology from the continuous digital ECG data will be acquired and stored electronically and manually over-read by an external central validated ECG laboratory. ~~Around each of the designated time points, 3 ECGs will be selected approximately 2 minutes apart.~~ In order to increase consistency of ECG interpretation, a limited number of central ECG over-readers will be used throughout the study. All ECGs for a given subject will be over-read by the same reader from the central validated ECG laboratory. The central reader will be blinded to subject identifiers (e.g., subject number, age, and sex), treatment assignment, and study day when Holter ~~ECGs~~ data ~~were~~ was collected. The final intervals and morphology analyses entered into the database will be those generated by the central ECG laboratory.

~~Baseline QT/QTcF values will be determined on Study Day -1 using time matched ECGs obtained from the Holter monitor at approximately the same time points as planned for: Week 1 Day 1 to 2; Week 2 Day 3 to 4, Week 3 Day 5 to 6 and Week 4 Day 7 to Week 5 Day 1. The mean from triplicate ECGs will be evaluated at each time point. For a given time point, the mean QTcF from 3 separate beats should be analyzed on each ECG. Analysis of Lead II will be conducted with V5 as back-up and one of the remaining precordial leads as an alternative when T waves are not well defined in Leads II or V5. QTcF for an individual beat will be calculated from the preceding RR interval since using the average heart rate (RR) intervals from the ECG could result in inaccurate QTcF calculations due to beat to beat variations in the RR intervals.~~

~~QT values should not be reported when the rhythm is other than sinus rhythm (sinus rhythm with normal respiratory variation is acceptable), and in intraventricular conduction delays (IVCD, QRS >120 msec). The other ECG information (including the rhythm and presence of IVCD) should be reported. The choice of the 3 consecutive beats to be measured should avoid ectopic beats and the first beat after an ectopic beat. If IVCD occur, these should be reported.~~

Section 6.4.7. Telemetry

Rationale for Change: The rationale for removing the 48-hour telemetry is explained above and all sections containing language around the original telemetry requirements were updated throughout the protocol.

Revised Text

~~In Part 1~~As part of the original cardiac monitoring plan, and to complement real-time ECG assessments, monitoring for potential adverse arrhythmias ~~will be~~was conducted utilizing continuous telemetry monitoring~~ as outlined in the Time and Events Tables for at least 48 hours from the start of dose. If clinically indicated, telemetry may be extended past 48 hours. Participating sites will have trained staff capable of monitoring and responding in real time to any potential cardiac adverse event detected by telemetry~~. In addition, emergency resuscitation equipment including appropriate pharmacological agents will also be immediately accessible throughout the study.

~~At the end of Part 1, an analysis of data collected on the QT interval up to, and including, the MTD expansion will be carried out. If the analysis by the GSK Cardiac Safety Panel of internal and external experts indicates that telemetry is no longer required for monitoring the QT interval, then the study can progress to the next stage without telemetry.~~ After internal QTc analysis and evaluation of cardiac safety data collected from subjects up to the 100 mg QD cohort by the cut-off date of May 15, 2015, ~~The GSK Cardiac Safety Panel approved the removal of~~ the 48-hour telemetry requirement was removed from all parts of the study in Protocol Amendment 6.

~~• Removal of the telemetry requirement will be conveyed to the sites in the first instance through a separate document (or "note to file") that will note – i) a summary of the analysis, and ii) the decision to proceed without telemetry monitoring in the next stage of this study. This will allow the sites to submit the necessary documentation to the IECs/IRBs for approval and to start the next stage of this study without telemetry. However, this process will be permitted only if there are no other cardiac monitoring changes to be implemented. If additional cardiac monitoring changes are required, a protocol amendment will be necessary before the next stage of the study can start.~~

Section 6.6.2. Plasma Sample Analysis

Rationale for Change: A statement was added in this section to further clarify planned analysis for plasma samples from subjects.

Revised Text

Paragraph 1:

Plasma analysis will be performed under the management of Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics (DMPK), GlaxoSmithKline. Concentrations of GSK525762 will be determined in plasma samples using the currently approved analytical methodology. In addition, selected metabolites of GSK525762 may also be quantified using approved analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline.

Section 6.6.3. Urine Collection

Rationale for Change: A statement was added in this section to further clarify planned analysis for plasma samples from subjects.

Revised Text

Paragraph 2:

Selected urine samples may be analyzed qualitatively and/or quantitatively for GSK525762 metabolites and the results will be reported under a separate DMPK protocol.

Section 6.10.1. Time period for collecting pregnancy information

Rationale for Change: The length of time for collecting information on any possible pregnancies after stopping study drug was extended to 7 months based on emerging data from the preclinical female fertility studies in rats. The summary of findings from these studies may be found in the Reproductive Risks section under Risk Assessment Section 1.5 of the protocol.

Revised Text

~~All pregnancies~~Reporting of any pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until ~~for 16 weeks~~7 months after the last dose of study drug.

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Rationale for Change: The morning dose of study medication (for subjects dosing once daily and twice daily) should be taken in the morning around the same time each dosing day. The time window was removed to allow additional flexibility. Further instructions on timing for dosing are included in the subject dosing diaries.

Revised Text

Table 23 GSK525762 Amorphous Free-base Investigational Product Dosage/Administration

Dosing instructions: Dose with 240mL water ~~and should be taken between 7 am and 10 am~~. No food or antacids for at least 1h before and 2h after dosing. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose)

Table 24 GSK525762 Besylate Investigational Product Dosage/Administration

'Treatment A' changed to 'Treatment A2' throughout the Table.

Section 7.7.1. Dose and Safety Management Guidelines

Rationale for Change: A minor change was made to the Management Guidelines for subjects with Pneumonitis to clarify that Medical Monitor approval is required prior to a subject restarting study treatment.

Revised Text

Table 25 Dose Adjustment/Stopping Safety Criteria:

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Pneumonitis	Grade 3 and 4	(Grade 3 and 4) Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to wnl. Bronchoscopy with biopsy and/or BAL is recommended. Consider corticosteroids if infective origin is ruled out. Taper as medically indicated. (Grade 3) Hold investigational drug(s) until recovery to < Grade 1. Discontinue investigational drug(s) if no recovery to <Grade 1 within 4 weeks. May consider restarting study treatment at a reduced dose after discussion with GSK Medical Monitor if there is clinical benefit. Grades 1-3: May consider restarting study treatment at a reduced dose or dose level pre-event ~~based on~~after discussion with GSK Medical Monitor. (Grade 4) Discontinue investigational drug(s)

Section 8.2.1. Cautionary Medications

Rationale for Change: This table was updated with the most recent list of drugs with a Risk of Torsades de Pointes which are permitted with extreme caution during the study.

Revised Text:

Table 27 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Generic Name	**Brand Name**
Amiodarone	Cordarone, Pacerone, Nexterone
Astemizole	Hismanal
Chlorpromazine	Thorazine, Largactil, Megaphen
~~Clarithromycin~~	~~Biaxin, Prevpac~~
Degarelix	Firmagon
~~Haloperidol~~Leuprolide	~~Haldol~~ Lupron
Tropisetron	Navoban and Setrovel

*There may be situations when the subject is on study that Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines
Data Source: www.crediblemeds.org (revised ~~02~~27-May~~r~~-2015)

Section 8.2.2. Potential Drug Interactions with GSK525762

Rationale for Change: This section was updated with emerging metabolite data from the ongoing clinical studies with GSK525762.

Revised Text

Paragraph 1:

The precise in vivo metabolic liability for GSK525762 has yet to be assessed. In vitro data suggests that GSK525762 is only metabolized by CYP3A4 and thus coadministration of inducers and inhibitors of CYP3A4 should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. ~~has a negligible turnover and~~ GSK525762 has low potential to inhibit the major human CYP isoforms (IC50's ≥ 33 μM) or major transporters. There is ~~with~~ no evidence for time dependent inhibition of CYP2D6 or CYP3A4. ~~These results suggest a low risk for therapeutic drug interactions although inducers and inhibitors of both CYP2D6 and CYP3A4 should be avoided during the course of the study where possible.~~ Potential interactions with other Cytochrome P450 metabolized drugs ~~or effects on transporters~~ have not been assessed.

Section 8.3. Prohibited Medications

Rationale for Change: This section was updated to include additional drugs that may impact the exposure of GSK525762 based on emerging metabolite data from the ongoing clinical studies with GSK525762.

Revised Text

Table 28 Drugs with a Risk of Torsades de Pointes that are Prohibited

Added a drug:

Generic Name	Brand Name
Clarithromycin	Biaxin, Prevpac

Section 9.1. Female Subjects

Rationale for Change: Based on emerging data from pre-clinical fetal and embryo toxicity studies, the inclusion criteria specifying contraception requirements were updated to extend the length of time for contraception use for subjects. A summary of the findings from these preclinical studies may be found in the body of the protocol under Reproductive Risks in Section 1.5. Double Barrier methods was also removed from Contraceptive Methods with a Failure Rate of ≤ 1% to align with the Clinical Trial Facilitation Group (CTFG)'s guidance related to contraception use in clinical trials which lists a combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) as an acceptable, but not a highly effective, birth control method.

Revised Text

Paragraph 1:

Female subjects of childbearing potential must not become pregnant during the trial and for 7 months after stopping study medication and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Paragraph 3:

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) 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 spermicidal agent (foam/gel/film/cream/suppository)~~

Section 9.2. Male Subjects

Rationale for Change: The additional guidance for condom use specific to males with a pregnant partner were included as there is not yet sufficient evidence to rule out the potential of 762 being transferred to a developing embryo or fetus via the semen.

Added Text:

In addition, male subjects whose partners are or become pregnant while on study medication must continue to use condoms for 7 days after stopping study medications.

Section 11.6.1. Pharmacokinetic Parameters

Rationale for Change: A minor change was made to this section to correct a previous error.

Revised Text

Paragraph 2:

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve (AUC(0-t) and AUC(0-∞) Week1 Day1 only) and apparent terminal phase half-life (t½). Trough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined. The ratio of AUC(0-τ) on Week 3 / AUC(0-∞) on Week 1 ~~AUC(0-τ) / Week 1 AUC(0-τ)~~ will be calculated to assess time invariance. GSK525762 concentrations will be determined in urine samples to determine urinary recovery of unchanged drug and renal clearance.

AMENDMENT 07

Protocol Changes for Amendment 7 (10-MAR-2016) from the Protocol Amendment 6 (19-JUN-2015)

Protocol Amendment 7 applies to all site(s) participating in the conduct of the study.

Amendment 07 summary:

Amendment 07 updates were made, to include the final dose and regimen for Part 2, which was determined to be 75 mg once daily based on emerging data from Part 1 and Besylate Sub-Study; to clarify that the besylate salt tablets will be the formulation used for subjects enrolled in Part 2 (and potentially for ongoing or newly enrolled subjects in Part 1); to update required number of subjects to be enrolled in the Part 1; to update the subject and study completion details; to update the Visit window for Discontinuation and End of Treatment; to update diagnosis criteria of NMC for Part 1 and 2 for NMC subjects; to update dosing, handling and storage instruction for GSK525762 Besylate tablet; to modify the meals and dietary restrictions based on the results of the besylate sub-study, the fasting requirement is being lifted, except on Serial PK sampling days in Part 2 (Week 1 and Week 4); to include the details about interim and final analysis. Additionally, following updates were in the time and event table, 12-lead ECGs monitoring for prolonged QTcF for Part 1 and 2 was updated, tumor sampling time point was updated for Part 1 and 2; optional Sweat PK sampling for Part1 was removed; optional saliva sampling for time points for part 1 was updated; pain assessments was included for Part 2; W1D1, ECHO was made optional for Part 2; and CT Scan, MRI and PET scan detail were updated for Part 2.

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

List of Specific Changes

PROTOCOL SYNOPSIS

Rationale for Change: This section was updated to increase the total number of subjects to be enrolled in the Part 1 based on actual recruitment.

Revised Text:

- **SUBJECT SAMPLE**: Worldwide approximately ~~60~~<u>90</u> subjects will be enrolled in Part 1, and approximately 150 subjects will be enrolled in Part 2.

Rationale for Change: The analyses sections were updated throughout the protocol to allow for the flexibility to conduct an interim analysis at some point during the study, prior to end of Part 2.

Revised Text:

DATA ANALYSIS: Subject demographic and safety data will be collected on electronic case report forms (eCRFs). All data will be pooled and descriptive safety analyses summarized and listed by cohort at ~~study~~ conclusion of Part 2 expansion cohorts. Additional analyses may occur between Part 1 and Part 2 and details will be included in the Reporting Analysis Plan (RAP). Part 2 of the study is powered to test overall Response Rate (RR). A futility assessment will be conducted after data are available from the first 10 subjects in each expansion cohort in Part 2.

Section 1.3.1. Human Pharmacokinetics

Rationale for Change: This section was updated to include reference to the latest Investigator Brochure, rather than include a summary of the pharmacokinetic data collected to date in this section, as study is ongoing and data is continuously emerging**.**

Revised Text:

Second paragraph

~~As of 06-February-2015, the pharmacokinetics of GSK525762 has been evaluated in 23 subjects following single and repeated daily administration of 2 mg to 60 mg of GSK525762 in the BET115521 trial. The summary statistics of the preliminary PK parameters are summarized in Table 1 and Table 2 after single and repeat daily oral administration, respectively.~~ Information on the pharmacokinetics of GSK525762 in humans can be found in the Investigator's Brochure (2011N113741_04). In summary, GSK525762 pharmacokinetics are characterized by a rapid absorption with maximum concentration occurring mostly within the first hour after dosing. GSK525762 is eliminated rapidly with an average terminal phase half-life of 3 to 7 hours, leading to a lack of accumulation following once daily oral administration. Following single oral administration and repeated once daily administration of 2 mg to ~~60~~100 mg of GSK525762, Maximum observed concentrations (C_{max}) and Area under concentration-time curve (AUC) tended to increase in a dose proportional fashion with a large~~full~~ overlap for individual AUC between 30, 60, 80 and 100 ~~and 60~~ mg cohorts.

~~Table 27 Summary Statistics of GSK525762 Preliminary PK Parameters Following a Single Oral Administration of GSK525762 in Study BET115521~~

~~Parameters~~	~~Unit~~	~~2 mg N=3~~	~~4 mg N=4~~	~~8 mg N=1~~	~~16 mg N=3~~	~~30 mg N=4~~	~~60 mg N=8~~
~~Cmax~~	~~ng/mL~~	~~51.0 (41%)~~	~~70.4 (29%)~~	~~120~~	~~176 (37%)~~	~~604 (30%)~~	~~871 (25%)~~
~~tmax~~	~~h~~	~~0.5 (0.5 - 0.6)~~	~~1.2 (0.5 - 2.0)~~	~~1.1~~	~~2.0~~	~~2.0 (0.97 - 2.0)~~	~~1.0 (0.5 - 4.0)~~
~~AUC~~	~~ng.h/mL~~	~~172 (42%)~~	~~361 (35%)~~	~~434~~	~~884 (40%)~~	~~4420 (63%)~~	~~4330 (46%)~~
~~$t_{1/2z}$~~	~~h~~	~~3.3 (103%)~~	~~5.1 (36%)~~	~~2.95~~	~~6.9 (46%)~~	~~6.4 (37%)~~	~~5.7 (36%)~~

Note: Data are presented as geometric mean (CV%) for all parameters except for tmax where the median (min-max) are presented. If N=1, individual data are presented. Cmax is the maximum concentration observed at time tmax. AUC is the area under the concentration-time curve from 0 to infinity. T1/2 is the terminal phase half-life.

Table 28 Summary Statistics of GSK525762 Preliminary PK Parameters Following Repeat Daily Oral Administration of GSK525762 in Study BET115521

Parameters	Unit	2 mg N=1	4 mg N=2	8 mg N=1	16 mg N=3	30 mg N=4	60 mg N=6
Cmax	ng/mL	52	47.6 ; 59.9	103	138 (25%)	603 (17%)	634 (53%)
tmax	h	1.0	1.0 ; 4.0	0.5	1.5	0.9 (0.32 - 4.0)	1.0 (0.50 - 2.0)
AUC_τ	ng.h/mL	160	225 ; 497	330	674 (21%)	3150 (55%)	1.0 (0.50 - 2.0)
$t_{1/2z}$	h	4.27	3.69 ; 4.46	4.92	3.6 (7.8%)	5.2 (26%)	3.48 (32%)
Cmax Week 3 / Cmax Week 1	--	1.42	0.968 ; 0.609	0.857	0.780 (12%)	0.998 (24%)	1.00 (21%)
AUC_τ week 3 / AUCt Week 1	--	1.39	0.904 ; 1.67	0.763	0.792 (20%)	0.799 (11%)	0.758 (12%)

Note: Data are presented as geometric mean (CV%) for all parameters except for tmax where the median (min-max) are presented. If N=1 or 2, individual data are presented. Cmax is the maximum concentration observed at time tmax. AUC_τ is the area under the concentration-time curve from 0 to 24 hours, the end of the dosing interval. T1/2 is the terminal phase half-life.

Section 3.2.2.2. 3+3 Dose Escalation in Part 1

Rationale for Change: Minor grammatical error corrected in this section.

Revised Text:

Second paragraph

Once the MTD is reached, up to 12 additional subjects may be enrolled at the MTD to further evaluate safety and tumor PD. Up to an additional 6 subjects may be enrolled at any dose level below the MTD int~~o~~ order to obtain additional dose/response information related to tumor PD. Additional cohorts (with daily exposure not exceeding QD MTD exposure) may also be initiated to explore alternative dosing schedules to optimize the PK, safety and tolerability profile (see Section 3.2.2.4). The enrolment of additional subjects as described could be in parallel with Part 2 enrolment.

Section 3.2.2.4. Alteration of Schedule

Rationale for Change: This section was updated to include the final dose and regimen for Part 2 and to allow for the introduction of the besylate tablets to Part 1 subjects based on emerging data from Part 1 and Besylate Sub-Study.

Revised Text:

New text added after second paragraph:

On completion of the besylate sub-study for relative bioavailabilty of besylate formulation in tablet form, and having determined a dose for Part 2, all subjects in Part 1 daily dosing cohorts and in Part 2 will be administered the besylate tablets at the recommended Part 2 dose of 75 mg once daily. Those subjects in Part 1 daily dosing cohort who were on amorphous tablet dosing before availability of besylate tablets, they will be switched to the equivalent besylate tablet dose and will have limited PK samples drawn after start on besylate tablets.

In Part 2, subjects approved to alter their current dose level with either a dose reduction or dose escalation may require additional limited PK sampling (pre-dose, 0.5, and 3 hours) at the new dose level, after 4-7 days at the adjusted dose level.

Section 3.2.2.6. Intra-Subject Dose Escalation

Rationale for Change: Minor clarification made in this section to clarify intra-subject dose escalation was relevant to Part 1 subjects only.

Revised Text:

Second paragraph

In Part 1, Subjects approved for intra-subject dose escalation will require additional limited PK sampling (pre-dose, 0.5, 3 and 6-8 hours) at the higher dose, as determined by GSK Clinical Pharmacology. Additional safety assessments such as insulin/glucose or cardiac monitoring may be specified at the time of dose escalation or schedule modification based on the safety profile in previous subjects at the higher dose level. Intra-subject dose escalations or schedule modification will be discussed with investigators and approved by the GSK Medical Monitor and safety monitoring required will be specified in writing.

Section 3.2.7. Part 2 Expansion Cohort

Rationale for Change: This section was updated to include the final dose and regimen for Part 2 based on emerging data from Part 1 and Besylate Sub-Study.

Additional text added to further clarify statistical design and observed response data that will guide futility assessments and further enrolment decisions for each expansion cohort in Part 2.

Revised Text:

First and second paragraph

Based on the analysis and evaluation of the safety profile and available pharmacodynamic, pharmacokinetic and efficacy data generated from all subjects enrolled in Part 1 as of January 28, 2016, including the analysis of subjects enrolled in the Besylate Sub-Study, the final dose and regimen for Part 2 is determined to be 75 mg once daily. The besylate salt tablets will be the formulation used for subjects enrolled in Part 2 (and potentially for ongoing or newly enrolled subjects in Part 1). Additional details and supporting information are provided under separate cover in a companion document and dose decision memo. Approximately 150 subjects with NMC, SCLC, CRPC, TNBC and ER+BC will be enrolled in expansion cohort at the RP2D to gather more safety data and to further assess anti-tumor activity.

Subjects in Part 2 will start with a continuous daily dosing schedule unless safety, PK or PD data necessitate a different dosing schedule. ~~The final dose and regimen for Part 2 will be decided upon completion of dose escalation in Part 1.~~

Third paragraph

For NMC, to test for 20% ORR relative to a 5% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look may be conducted once 10 evaluable subjects have been enrolled into the expansion cohort or treated at the same dose level to examine safety and efficacy; if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 3. A maximum of 25~~40~~ subjects in this cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Fourth paragraph

For SCLC and CRPC, to test for 30% ORR relative to a 10% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conducted once 10 evaluable subjects have been enrolled in ~~the~~ either cohort or treated at the same dose level to examine safety and efficacy, if 0 responses are observed in either cohort, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4. A maximum of 22 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Fifth paragraph

For TNBC, to test for 25% ORR relative to a 10% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conduced once 10 evaluable TNBC subjects have been enrolled in the cohort or treated at the same dose level to examine safety and efficacy, if 0 responses are observed in the cohort, Part 2 of the trial may be terminated with no further enrolment in this cohort. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 5. A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Sixth paragraph

For ER+BC, to test for 25% ORR relative to a 10% ORR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conduced once 10 evaluable ER+BC subjects have been enrolled in this ~~each~~ cohort or treated at the same dose level to examine safety and efficacy, if 0 responses are observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 6. A maximum of 37 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrollment decisions

Section 4.1. Number of Subjects

Rationale for Change: This section was updated to increase the total number of subjects to be enrolled in the Part 1 based on actual recruitment.

Revised Text:

First paragraph:

The number of dose levels and the level at which the MTD will be reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish a recommended dose(s) and schedule(s) of GSK525762 for further study. To complete Part 1, it is estimated ~~30~~60 to ~~60~~90 evaluable subjects will be enrolled. The besylate sub-study will enroll approximately 10 to 12 ~~evaluable~~ subjects in the United States only. Part 2 will enroll approximately 150 subjects.

Section 4.2.3.2. Subject and Study Completion

Rationale for Change: This section was updated to clarify the definition of a completed subject in the study.

Revised Text:

4.2.3.2. Subject and Study Completion

~~A subject will be considered to have completed the study 2 years after the last treatment or if the subject dies or is still in follow-up at the time the study is closed or terminated, whichever is sooner. Document the cause of death in the CRF. A subject will be considered to have withdrawn from the study if the subject has not died and is lost to follow-up, has withdrawn consent, or at the investigator's discretion is no longer being followed.~~

In Part 1, a subject will be considered to have completed the study if:

- they complete screening assessments, the 28-day DLT observation period, and the end-of-treatment follow-up visit,
- they progress or die while receiving study treatment, or
- are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

In Part 2, a subject will be considered to have completed the study if:

- they progressed or die while receiving study treatment, or
- are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. The End of Study eCRF should only be completed when a subject is no longer being followed. The study may be considered completed for purposes of a final analysis when 70% of subjects enrolled at part 2 have progressed or died. If available, subjects continuing on treatment at the time of final analysis may be offered the option to continue in a rollover trial.

Section 5. TIME AND EVENTS TABLES

Rationale for Change: The time and events tables were modified to correct previous errors and provide additional clarifications around timings and procedures as appropriate. No new procedures were added.

Revised Text:

Table 9 Time and Events: Part 1

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	q4W	q8W	
Cardiac Monitoring																										
12-lead ECGs (Triplicate)	For timing of triplicate ECGs on O days, see Table 11 and Table 12. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs ~~daily through W2.~~ should be repeated Q2-3 days until QTcF is within 30msec from baseline.	X	O	O	O		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Efficacy																										
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation. EOT sample should be collected at time of progression where feasible.	X				All Tumor Types: One postdose sample collected anytime betweenW2D1-W3D1 (4-6h ~~2-4h~~ post-dose). Timing may be further optimized based on tumor type and emerging data.																				X

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	q4W D 1	q8W D 1	
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																										
LPS blood sample	Not required with BID dosing schedule.		X																							
Optional Saliva and~~/or Sweat~~ Sample	A saliva ~~and/or sweat~~ sample may be requested on serial PK sampling days. Additional collection details will be provided in the SPM.		X															X								
Blood samples for circulating exploratory biomarkers (cfDNA, etc)	EOT circulating biomarker blood samples to be collected with lab assessments.	X																	X							X

Table 10 Time and Events: Part 1 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	W1			W2		W3	W4	W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT[a]
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	q4W D1	q8W D1	

Footnote added to EOT time point:

a. EOT circulating biomarker blood samples to be collected with lab assessments.

Table 11 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1										**W1D5**		**W2D4 + 1 day**			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ±2h** [a]	**24h ±2h**	**48h ±2h** [b,d]	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**
Optional Saliva Sample	X			X	X	X	X									

Footnote added to W1D1, 48h ±2h time point:

d. W1D1 48h assessments (ECG, PK and mRNA) are optional

Table 12 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed)										**W9D1 ±4 days** (if dose has been reduced or escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ±2h** [a]	**24h ±2h** [b]	**48h ±2h** [b,d]	**pre dose**	**0.5-2h**	**4 - 8h**	

Footnote added to W3D4 + 2 days, 48h ±2h time point:

d) W3D4 48h assessments (ECG, PK and mRNA) are optional.

Table 13 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1

	W1D1																W1D2 and W1D3 (relative to W1D1 Morning Dose)		W1D5 ECG and PK samples after Morning Dose only	
	Morning Dose								Evening Dose											
	pre dose	0H	15 min ±5m	30 min ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	pre dose (12h-15m)	12h	15 min(12.25h) ± 5m	30 min (12.5h) ±5m	1h (13h) ±5m	2h (14h) ±10m	4h (16h) ±15m	8h (20h) ±1h	12 h (24h) ±1h	36 h (48h) (pre-dose) ±1h[d]	30 min ±5m	3h ±15m

Footnote added to W1D2 and W1D3, 36 h (48h) (pre-dose) ±1h time point:

d) W1D1 48h assessments (ECG, PK and mRNA) are optional.

Table 14 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 2 and Week 3

	W2D4 + 1 day ECG and PK samples after Morning Dose only				W3D4 +2 days															W3D5 and W3D6 (relative to W3D4 Morning Dose)	
					Morning Dose								Evening Dose (For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)									
	pre dose (Prior to Dosing)	30m ± 5m	3h ± 15m	8 h ±1h~~5m~~	pre dose	0h	15m ±5m	30m ±5m	1h ±5m	2h ±10m	4h ±15m	8h ±1h	pre dose	12h	15m ±5m (12.25m)	30m ±5m	1h (13h) ±5m	2h (14h) ±10m	4h (16h) ±15m	8h (20h) ±1h	12h (24h) ±1h (pre dose)	36h (48h) ±1h (pre dose) [d]

Footnote added to W3D5 and W3D6 (relative to W3D4 Morning Dose), 36h (48h) ±1h (pre dose)time point:

d. W3D4 48h assessments (ECG, PK and mRNA) are optional.

Table 16 Time and Events: Part 2

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
						TREATMENT PHASE							
Study Drug													
Dispense study drug	Administer about same time of day. ~~No food or antacids 1h before and 2h after.~~		X	X	X	X	X	X	X	X			
Review compliance	Not required when dosed in clinic.			X	X	X	X	X	X	X	X	X	X
Safety													
Vital Signs and Pain Assessments		X	X	X	X	X	X	X	X	X			X
Cardiac Monitoring													
ECHO	If Baseline ECHO ~~W~~within 35 days of first dose, the Week 1 Day 1 ECHO is only required if clinically appropriate.	X	X optional			X	X	X	X		X		X
12-lead ECGs (Single)	ECGs prior to dosing. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30msec from baseline.~~daily through W2.~~	X	X	X	X	X	X	X	X		X		X
Efficacy													
CT scan or MRI[a, b]	Scans within 35 days of first dose may be used as screening assessment. Additional bone scans and brain scans not required unless clinically indicated.	X						X			X		X
PET scan (FDG or fluoride) [b, c]	Scans within 35 days of first dose may be used as screening assessment. Follow up scans conducted as clinically appropriate.	X											
PK													
PK	Three samples to be collected each sampling day ~~for each type of analysis: Predose~~ During first 4 weeks collect a predose within 60 minutes prior to dose,		X			X		X			X		

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13: q4W D1	q8W D1	q12W D1	EOT
	a single draw between 0.5-2h postdose, and a single draw between 4-8h postdose (fasting requirements apply).Thereafter only a Predose and 0.5hour post-dose sample are collected. NOTE: If dose level is adjusted, additional PK sampling may be requested.												
Blood samples for circulating exploratory biomarkers (cfDNA, etc)	Baseline sample collected pre-dose on W1D1. EOT circulating biomarker blood samples to be collected with lab assessments.	~~X~~	X			X							X
Translational Research													
PGx sample			X										
Tumor Sample	PK samples should be collected within 1hour of on-treatment biopsy. EOT biopsy should be collected at time of disease progression where feasible	X	All Tumor Types: One postdose sample collected anytime between W2D1- W3D1 (~~2-4h~~ 4-6h post-dose). Timing may be further optimized based on tumor type and emerging data										X
FOLLOW-UP PHASE													

Footnote added to CT scan/MRI and PET scan efficacy assessments:

a. Per RECIST 1.1 baseline (within 35 days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate.

b. PET scan (FDG or fluoride) required at baseline and follow up scans should be collected when clinically appropriate.

c. Disease assessments should be performed no less than 4 weeks (28 days) after first dose and after previous on-treatment scan.

Table 29 Time and Events: Part 2 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	Notes	SCR	W1		W2		W3	W4	W5	W9	W13	Q4, Q8 and Q12W Initiated from Week 13			EOT[b]
			D1	D4[a]	D1	D4[a]	D1	D1	D1	D1	D1	q4W D1	q8W D1	q12w D1	

Footnote added to W1D4, W2D4 and EOT Time point:

a. Optional Visits, should be conducted when additional monitoring of laboratory values is clinically appropriate

b. EOT circulating biomarker blood samples to be collected with lab assessments.

Table 30 Time and Events: Besylate Sub-Study

Besylate Sub-Study Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	q4W D1	q8W D1	
Laboratory assessments: For details please see corresponding days in Table 10																										
Tests		X	X							X							X		X		X	X	X	X	X	X
Cardiac Monitoring																										
12-lead ECGs (Triplicate)	For timing of triplicate ECGs on O days, see Table 19~~Table 11~~ and Table 20~~Table 12.~~ Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30msec from baseline. ~~ECGs daily through W2.~~	X	O		X					X		X					X		X	X	X	X	O	X		X

Section 6.1.2. Visit Windows

Rationale for Change: The EOT and Study Discontinuation section was updated to clarify timing of this visit.

Revised Text:

Eighth paragraph:

Discontinuation/End of Treatment visit: should be within 14 ~~to 28~~ days from last dose of study drug~~s~~. If a subject is unable to return to the clinic due to hospitalization, site staff~~s~~ are encouraged to telephone the subject for assessment of adverse events.

Section 6.2. Baseline Assessment for NMC Subjects

Rationale for Change: This section was updated to clarify acceptable and required diagnostic methods for NMC subjects.

Revised Text:

For NMC subjects, in Part 1 a diagnosis of NMC based on a positive IHC test and/or detection of NUT gene translocation as determined by FISH at screening will be required. In Part 2, a diagnosis of NMC based on a positive IHC test will be required. A ≥20% nuclei staining cut off will be applied for a positive diagnosis as a subset of germ cell tumors (from testis and ovary) weakly stain for the NUT protein (5% maximal nuclei staining, PPD , personal communication). ~~Fluorescence in situ hybridization (FISH) testing or next generation sequencing (NGS) will be undertaken prospectively to provide confirmation of borderline IHC staining (nuclear staining ≥1% and <20%) and retrospectively characterize the NUT gene fusion partner and to support exploratory analysis of differential outcomes based on the NUT fusion partner. The IHC and FISH or NGS analyses will be performed at a central laboratory.~~

Section 6.7.2. Assessments for PET

6.7.2. Assessments for ^{18}~~FDG~~-PET

Rationale for Change: This section was updated to provide additional guidance and clarification around the PET assessments for subjects in Part 1 and Part 2.

Revised Text:

First and second paragraph:

During the dose escalation phase in Part 1 ^{18}F-FDG PET assessments will be optional until the standard 3+3 design is implemented. At this point, the sites will be required to perform ^{18}F-FDG PET assessments for all NMC subjects and other solid tumors as appropriate.

~~At selected sites, subjects ^{18}F-FDG PET avid tumors are eligible for pre-dose and post-dose (baseline and on treatment) ^{18}F-FDG PET assessments. The initial assessment should be performed as close to Tmax as possible and pharmacokinetics sampling will be performed as outlined in Time and Events Table to pair with ^{18}F-FDG PET assessments. Additional scans may be performed at different timepoints based on emerging data during the study.~~

During Part 2 PET (FDG or fluoride) scans should be performed at baseline, with follow up scans conducted as clinically appropriate (as outlined in the T&E Table 16).

Section 6.8.1. Tumor Tissue Collection

Rationale for Change: Further clarification added to this section to the requirements for tumor tissue collection in Part 1 and Part 2.

Language was also included to allow for the introduction of a pre-screen consent to subjects in order to facilitate collection of tumor tissue.

Revised Text:

First paragraph:

NMC patients in Part 1 will be required to submit a fresh or archival tumor specimen for ~~diagnosis or~~ retrospective diagnostic confirmation. NMC patients in Part 2 will be required to submit a fresh or archival tumor specimen to the central laboratory during the 14 day screening period for diagnosis. Due to the timely need to determine NMC status by NUT IHC testing, a pre-screen informed consent may be offered to expedite obtaining the archival tissue in Part 2. These specimens may also be evaluated retrospectively for exploratory research as described above.

Third Paragraph:

During the accelerated dose escalation phase (Part 1), fresh pre- and post-dose biopsy collections will be optional until the standard 3+3 design is implemented. During the 3+3 dose escalation phase in Part 1, and during Part 2, pre- and post-treatment biopsies collected between W2D1 – W3D1 (4-6 hrs post-dose) are mandatory. For subjects in Part 1 and 2, if tumor tissue is not accessible, discussion with the GSK medical monitor is required.

Section 6.8.2.2. Systemic (Unstimulated) Plasma for Cytokines, Chemokines, and Acute Phase Proteins

Rationale for Change: A minor correction was made to the list of possible analytes being measured in plasma samples to change MIP1-α to MIP1-β.

Revised Text:

The set of analytes identical to that used in the whole blood ex vivo assay (including for example, MCP-1, MIP1-β~~α~~, IL-8) will also be measured in plasma samples taken during PK sampling and at the time of any Grade 2 fever or symptoms of a cytokine storm. This will assess systemic inflammatory response in the subject using biomarkers such as pro-inflammatory cytokines and acute phase proteins and correlate the systemic response to drug with that in stimulated and unstimulated blood. These biomarkers are expected to change over days rather than hours, based on the plasma half lives and pre-clinical data, such that sampling will also be performed after repeat dosing.

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Rationale for Change: This section was updated following results from the besylate sub-study, showing the besylate salt coated tablet is bioequivalent to the amorphous free-base uncoated tablet. In addition there is a lack of effect of a high-fat high-calorie breakfast on the overall exposure (i.e. AUC) to GSK525762 administered as besylate coated tablets while administration with food tended to slightly decrease Cmax. The fasting requirement is thus no longer necessary in subjects taking the besylate formulation in Part 2.

Therefore, language was added to allow for the introduction of the besylate tablets to Part 1 subjects. The dose administration section was also updated to allow study drug to be taken any time of day as long as taken at the same time each day (Part 1 and Part 2) and to be taken with or without food (Part 2 subjects only).

Revised Text:

First paragraph:

GSK525762 Tablets will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements. An amorphous, free-base formulation of GSK525762 will be used in Part 1 (Table 23) and a crystalline, besylate formulation (Table 24) will be introduced in the besylate sub-study in Part 1 (US sites only) and the Part 2 expansion cohorts. <u>After completion of the besylate sub-study and introduction of besylate material for Part 2, remaining subjects ongoing in Part 1 may be required to change from the amorphous free-base formulation to the besylate formulation (at the equivalent dose) based on the amorphous supply availability.</u>

Table 24:

Table 24 GSK525762 Besylate Investigational Product Dosage/Administration

Dosing instructions:	Dose with 240mL water and should be taken ~~between 7 am and 10 am~~ at approximately the same time each day. May be taken with or without food. ~~No food or antacids for at least 1h before and 2h after dosing.~~ (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)	Dissolve powder in 20 mL of water with bicarbonate buffer and administered with GSK525762 tablets (Besylate Sub-Study, Treatment A2, B and C)

Section 7.2. Handling and Storage of Study Treatment

Rationale for Change: Updated storage requirements were included in this section for the besylate tablets.

Revised Text:

Third and fourth paragraph:

GSK525762 Amorphous Free-base Tablets are to be stored at up to 30°C (86°F) and protected from light and moisture.

GSK525762 Besylate Tablets are to be stored at up to 30°C (86°F) and protected from moisture.

Section 7.3. Meals and Dietary Restrictions

Rationale for Change: This section was updated based on the results of the besylate sub-study showing a lack of effect of a high-fat high-calorie breakfast on the overall exposure (i.e. AUC) to GSK525762 administered as besylate coated tablets, to clarify that the fasting requirement is being lifted in Part 2; however, on Serial PK sampling days in Part 2 (Week 1 and Week 4) subjects will still be required to fast overnight (i.e., at least 8 hours).

Revised Text:

First three paragraph:

~~Subjects~~ During Part 1 subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects will be asked to fast for an additional two hours. These fasting requirements have been implemented in the protocol and informed consents to minimize pharmacokinetic variability. During ~~Besylte~~Besylate Sub-Study, subjects will be asked to fast overnight (at least 8 hours) and continue fasting for 4 hours post dose administration except for the fed administration where subject will be requested to ingest a high-fat high-calorie meal within 30 minutes prior to administration (FDA, 2002).

If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose. ~~Requirements for fasting before and after dosing may be modified based on emerging pharmacokinetic, pharmacodynamic, and safety data. Any change in fasting requirements will be communicated to each investigator and site staff in future protocol amendment.~~ Should a twice daily regimen be required, additional consideration will be paid to ~~this requirement~~ fasting requirements once the escalation period is past.

In Part 2 based on the results of the besylate sub-study showing a lack of effect of a high-fat high-calorie breakfast on the overall exposure (i.e. AUC) to GSK525762 administered as besylate coated tablets, the fasting requirement is being lifted , except on Serial PK sampling days in Part 2 (Week 1 and Week 4). On these days, subjects should fast overnight (i.e., at least 8 hours). After dosing, subjects will be asked to fast for an additional two hours. These fasting requirements have been implemented in the protocol and informed consents to minimize PK variability.

Section 8.2.1. Cautionary Medications

Rationale for Change: The data source for Table 27 was updated with latest revision date.

Revised Text:

Table 27 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Table Footnote revised:

Data Source: www.crediblemeds.org (revised 17~~27~~ Dec~~May~~ 2015)

Section 8.2.2. Potential Drug Interactions with GSK525762

Rationale for Change: This DDI section was updated based on emerging metabolite data.

Revised Text:

The precise in vivo metabolic liability for GSK525762 has yet to be assessed. In vitro data suggests that GSK525762 is only metabolized by CYP3A4 and thus coadministration of inducers and inhibitors of CYP3A4 should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. ~~GSK525762 has low potential to inhibit the major human CYP isoforms (IC50's ≥ 33 μM) or major transporters. There is no evidence for time dependent inhibition of CYP2D6 or CYP3A4.~~ GSK525762 is considered to have a low risk of causing clinically relevant perpetrator drug interactions with CYP3A4, CYP2B6 and CYP2C8 enzymes and/or PgP, BCRP, OATP1B3, OAT1, OCT2, MATE1, MATE2-K, BSEP or MRP2 transporters either via direct or metabolism-dependent inhibition.

GSK525762 was shown to be an inhibitor of OATP1B1 and OAT3 in vitro, however, the clinical impact of this inhibition is only deemed a concern for sensitive substrates of OATP1B1 or OAT3 (e.g. methotrexate).

Potential interactions with other Cytochrome P450 metabolized drugs have not been assessed.

Section 8.3. Prohibited Medications

Rationale for Change: This section was updated to clarify that only ORAL administration of palonosetron and ondansetron are allowed at 8 mg TID.

Revised Text:

Table 28 Drugs with a Risk of Torsades de Pointes that are Prohibited

Generic Name	Brand Name
Arsenic trioxide	Trisenox
Asenapine	Saphris,Sycrest
Bepridil	Vascor
Chloroquine	Aralen
Cisapride	Propulsid
Clarithromycin	Biaxin, Prevpac
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium
Droperidol	Inapsine
Erythromycin	Erythrocin, E.E.S.
Halofantrine	Halfan
Hydrocodone	Hysingla ER and Zohydro ER

Generic Name	Brand Name
Ibutilide	Corvert
Levofloxacin	Levaquin
Levomethadyl	Orlaam
Mesoridazine	Serentil
Methadone	Dolophine, Methadose
Pentamidine	Pentam, NebuPent
Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl, Procan
Quinidine	Quinaglute, Cardioquin
Sotalol	Betapace
Sparfloxacin	Zagam
Terfenadine	Seldane
Thioridazine	Mellaril

Data Source: crediblemeds.org

Last paragraph:

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class.

Section 8.4. Non-Drug Therapies

Rationale for Change: A minor error was corrected in this section.

Revised Text:

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the ~~transition~~ screening visit through the post-study follow-up visit.

NOTE: Subjects may receive palliative radiation treatment during this study.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit. Decaffeinated tea and coffee are permissible.

Section 11.1. Sample Size Assumptions

Rationale for Change: This section was updated to increase the total number of subjects to be enrolled in the Part 1 based on actual recruitment.

Revised Text:

First paragraph:

The total number of subjects to be enrolled into Part 1will depend on the number of dose escalations required to establish the maximum tolerated dose of GSK525762; they are not driven by statistical considerations. To complete Part 1, it is estimated that 6~~5~~0 to 9~~7~~0 evaluable subjects will be enrolled.

Section 11.2. Analysis Populations

Rationale for Change: The analyses sections were updated throughout the protocol to allow for the flexibility to conduct an interim analysis at some point during the study, prior to end of Part 2. This section was included to note that full details of the analysis populations will be included in the reporting and analysis plan (RAP).

Revised Text:

Last paragraph:

More details of the analysis populations will be specified in RAP.

Section 11.3. Data Analysis Considerations

Rationale for Change: The analyses sections were updated throughout the protocol to allow for the flexibility to conduct an interim analysis at some point during the study, prior to end of Part 2.

Revised Text:

New sub section added:

11.3.1. Interim Analysis

An interim analysis of the key parameters may be carried-out before the conclusion of the study. Full details of procedures and of the analyses planned at the interim analysis will be provided in the Reporting and Analysis Plan (RAP).

The study will not utilize an Independent Data Monitoring Committee (IDMC).

11.3.2. Final Analyses

Final analysis on Part 1 may be conducted when

- Part 1 is completed
- or at least 70% of subjects enrolled in every dose group at Part 1 are completed or progressed or died.

Final analyses will be carried-out following the DBF (data base frozen) after all the data

queries has been resolved .

Section 11.6.1. Pharmacokinetic Parameters

Rationale for Change: This section was updated to clarify that parent and metabolite data would both be analyzed as part of PK analysis.

Revised Text:

PK analyses will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Plasma GSK525762 and relevant metabolites, as appropriate, concentration-time data from dose escalation (Part 1) will be analyzed by non-compartmental methods with WinNonlin.

Section 11.6.3. Population Pharmacokinetic Analysis

Rationale for Change: This section was updated to clarify that PK data from other ongoing studies using GSK525762 may be taken into consideration when analyzing PK data from this study.

Revised Text:

Plasma concentration-time data from parts 1 and 2 will be combined and may be combined with data from other studies and further analyzed using a population approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (absorption rate, Ka, apparent clearance, CL/F and volume of distribution, V/F) and summary exposure measures (Cmax, AUC and Cav = AUC/τ) and identify important covariates (e.g., age, weight, or disease related covariates).

Section 13 References

Rationale for Change: Reference was added based on updates made in the protocol amendment.

Reference added:

GlaxoSmithKline Document Number 2011N113741_04. GSK525762 Investigator's Brochure, Version 20. March 2015.

AMENDMENT 08

Protocol Changes for Amendment 8 (02-DEC-2016) from the Protocol Amendment 7 (10-MAR-2016)

Protocol Amendment 8 applies to all site(s) participating in the conduct of the study.

Amendment 08 summary:

Amendment 8 includes changes as the result of the Dear Investigator Letter, dated 16 November 2016 which outlines the updated thrombocytopenia management guidelines, as outlined in the Dear Investigator Letter, dated 16 November 2016. This amendment also includes increased coagulation monitoring for Part 2 (added at W2D1, W3D1 and changed from q8W to q4W after Week 13), addition of Factor VII monitoring in Part 2 (at Screening, W3D1 and reflex testing if PT or INR are ≥1.5XULN) and addition of laboratory values required prior to performing the post-dose biopsy.

Changes are noted below with ~~strikethrough~~ to identify deleted text and underlining to identify new or replacement text. Revisions within tables will be displayed as text

List of Specific Changes

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

Rationale for change: The back-up medical monitor information has been updated based on GSK personnel changes.

Revised text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD MD, PhD	PPD			GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD				GlaxoSmithKline 1250 South Collegeville Road Mailstop UP 4410 Collegeville, PA 19426, USA PPD

NEW text added, ABBREVIATIONS

INR	International Normalized Ratio

Rationale for change: Addition of laboratory values required prior to performing the post-dose biopsy added to reduce the risk for bleeding after biopsy.

Section 5. Time and Events Tables

Table 7: Time and Events: Part 1

Revised text:

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	q4W D 1	q8W D 1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																								
Demography		X																								
Medical history		X																								
Disease characteristics		X																								
Cardiology evaluation		X																								
Prior therapy		X																								
Register subject		X																								
TREATMENT PHASE																										
Study Drug																										

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9 q4W	Q4 and Q8W Initiated from Week 9 q8W	EOT
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D 1	D 1	
Administer study drug	Administer about same time of day. No food or antacids 1h before and 2h after.		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Daily									
Review subject diary	Diary not required when dosed in clinic.									X							X		X		X	X	X	X		
Safety																										
Pregnancy test/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X	X		X
Physical exam		X	X							X							X				X	X	X	X		X
ECOG PS		X	X							X							X		X		X	X	X	X		X
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X	X				X		X					X		X		X		X	X	X	X		X
Pain		X	X	X				X		X					X		X		X		X	X	X	X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test		X																								
Adverse events		*SAEs collected continuously from signing of informed consent; AEs collected continuously from time of first dose*																								
Concomitant medications		*continuous from signing of informed consent*																								
Laboratory assessments: For details please see following tables																										
Tests		X	X	X				X		X					X		X		X		X	X	X	X	X	X
Cardiac Monitoring																										

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9 q4W	Q4 and Q8W Initiated from Week 9 q8W	EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Echocardiogram	Within 35 days of first dose	X													X						X		X		X	X
12-lead ECGs (Triplicate)	For timing of triplicate ECGs on O days, see Table 9 and Table 10. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30msec from baseline.	X	O	O	O		O	X	X	X			O		X	X	X	O	X	X	X	X	O	X		X
Holter monitoring	At least 24 h, on dosing days start at least 60 min predose.	X					X												X							
Efficacy																										
CT/MRI Scans[a]	SCR assessment within 35 days of first dose. Target lesions to be identified at SCR and followed.	X																			X		X		X	X
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation. EOT sample should be collected at time of progression where feasible. Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy.	X								All Tumor Types: One post-dose sample collected anytime between W2D1-W3D1 (4-6h post-dose). Timing may be further optimized based on tumor type and emerging data.															X
PET scan	Optional during rapid dose escalation; required during 3+3 dose escalation.	X																			X		X			

Part 1 Assessments	Notes	SCR	Week 1							Week 2							W3		W4		W5	W7	W9	Q4 and Q8W Initiated from Week 9		EOT
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	q4W D1	q8W D1	
	SCR assessment within 35 days of first dose.																									
Castrate-Resistant Prostate Cancer Assessments																										
PSA	PSA to be collected in line with PCWG2 guidelines. Levels may be checked more frequently if appropriate.	X																					X		X	

Table 14: Time and Events: Part 2

Revised text:

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X											
Demography		X											
Medical history		X											
Disease characteristics		X											
Cardiology evaluation		X											
Prior therapy		X											
Register subject		X											
TREATMENT PHASE													
Study Drug													
Dispense study drug	Administer about same time of day.		X	X	X	X	X	X	X	X			

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
Review compliance	Not required when dosed in clinic.			X	X	X	X	X	X	X	X	X	X
Safety													
Pregnancy test/testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X					X	X	X	X			X
Physical exam		X	X	X	X	X	X	X	X	X			X
ECOG		X	X	X	X	X	X	X	X	X			X
Vital Signs and Pain Assessments		X	X	X	X	X	X	X	X	X			X
Weight and height	Height at SCR only	X	X				X	X	X	X			X
Chest x-ray		X											
Pulmonary function test		X											
Adverse events			*SAEs collected continuously from signing of informed consent; AEs collected continuously from time of first dose*										
Concomitant medications			*continuous from signing of informed consent*										
Laboratory assessments: For details please see Table 15													
Tests		X	X	X	X	X	X	X	X	X	X	X	X
Castrate-Resistant Prostate Cancer Assessments													
PSA		X	X	X	X	X	X	X	X	X			X
Serum testosterone		X	X	X	X	X	X	X	X	X			X
Cardiac Monitoring													
ECHO	If Baseline ECHO within 35 days of first dose, the Week 1 Day 1 ECHO is only required if clinically appropriate.	X	X optional			X	X	X	X		X		X
12-lead ECGs (Single)	ECGs prior to dosing. If QTcF	X	X	X	X	X	X	X	X		X		X

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
	increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30msec from baseline.												
Holter monitoring	At least 24 h, on dosing days start predose.	X	X			X							
Efficacy													
Lesion assessments		X						X			X		X
CT scan or MRI [a, b]	Scans within 35 days of first dose may be used as screening assessment. Additional bone scans and brain scans not required unless clinically indicated.	X						X			X		X
PET scan (FDG or fluoride) [b, c]	Scans within 35 days of first dose may be used as screening assessment. Follow up scans conducted as clinically appropriate.	X											
PK													
PK	Three samples to be collected each sampling day: During first 4 weeks collect a predose within 60 minutes prior to dose, a single draw between 0.5-2h postdose, and a single draw between 4-8h postdose (fasting requirements apply).Thereafter only a Predose and 0.5hour post-dose sample are collected. NOTE: If dose level is adjusted, additional PK sampling may be requested.		X			X		X			X		
Blood samples for circulating exploratory	Baseline sample collected pre-dose on W1D1 EOT circulating biomarker		X			X							X

Part 2 Assessments	Notes	SCR	W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W9 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13: q4W D1	q8W D1	q12W D1	EOT
biomarkers (cfDNA, etc)	blood samples to be collected with lab assessments.												
Translational Research													
PGx sample			X										
Tumor Sample	PK samples should be collected within 1 hour of on-treatment biopsy. EOT biopsy should be collected at time of disease progression where feasible. Subjects must have a platelet count of ≥75,000/mm3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy.	X	All Tumor Types: One post-dose sample collected anytime between W2D1- W3D1 (4-6h post-dose). Timing may be further optimized based on tumor type and emerging data.										X
FOLLOW-UP PHASE													
Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.													

Abbreviations: CK=creatine kinase; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; q4W=every 4 weeks; q8W=every 8 weeks; SCR=Screening; Wk=week; PT=Prothrombin Time; INR=International Normalized Ratio; aPTT=Activated partial thromboplastin time; WNL=Within normal limits

a. Per RECIST 1.1 baseline (within 35 days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate.
b. PET scan (FDG or fluoride) required at baseline and follow up scans should be collected when clinically appropriate.
c. Disease assessments should be performed no less than 4 weeks (28 days) after first dose and from previous on-treatment scan.

Table 15: Time and Events: Part 2 Laboratory Assessments

Rationale for change: Increased frequency of coagulation monitoring and addition of Factor VII testing due to higher than expected number of haemorrhagic events observed with the use of GSK525762 in the BET115521 study. GSK is investigating the potential effects of GSK525762 on coagulation, including possible decrease in Factor VII activity.

Revised text:

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	Notes	SCR	W1		W2		W3	W4	W5	W9	W13	Q4, Q8 and Q12W Initiated from Week 13			EOT [b]
			D1	D4 [a]	D1	D4 [a]	D1	D1	D1	D1	D1	q4W D1	q8W D1	q12W D1	
Troponin, NT-proBNP-9	1 sample for local lab (troponin I or T), 1 sample for central lab (troponin T)	X	X		X		X	X	X	X	X		X		
Hematology		X	X		X		X	X	X	X	X	X			X
Clinical chemistry		X	X		X		X	X	X	X	X	X			X
Pancreatic		X	X		X		X	X	X	X	X	X			X
Coagulation		X	X		X		X	X	X	X	X	X	~~X~~		X
Factor VII Assay	Also perform if PT or INR are ≥1.5XULN	X					X								
Liver chemistry		X	X	X	X	X	X	X	X	X	X	X			X
Creatine phosphokinase		X	X					X	X	X	X		X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X		X	X	X	X	X	X			X
c-peptide and 1,5 AG	Will be performed at central lab if not available at local	X	X						X	X			X		

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	**Notes**	**SCR**	**W1**		**W2**		**W3**	**W4**	**W5**	**W9**	**W13**	**Q4, Q8 and Q12W Initiated from Week 13**			**EOT** [b]
			D1	**D4** [a]	**D1**	**D4** [a]	**D1**	**D1**	**D1**	**D1**	**D1**	**q4W** **D1**	**q8W** **D1**	**q12W** **D1**	
	lab														
HbA1c		X	X							X			X		
Fasting lipids		X	X				X		X	X	X		X		X
Urinalysis		X	X						X	X	X			X	X
Thyroid monitoring	TSH, free T3, free T4. If TSH is abnormal W1D1, monitor TSH, free T3 and free T4 going forward	X	X						X	X	X		X		X
Cytokines		X	*as clinically appropriate*												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X													

a. Optional Visits, should be conducted when additional monitoring of laboratory values is clinically appropriate.

b. EOT circulating biomarker blood samples to be collected with lab assessments.

Abbreviations: D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; q12W=every 12 weeks; SCR=Screening Visit; W=week; ULN=Upper limit of normal

Section 6.4.8 Clinical Laboratory Assessments
Table 19: Clinical Laboratory Tests

Rationale for change: Addition of Factor VII Assay testing, per updated Table 15: Time and Events: Part 2 Labortatory Assessments.

Revised Text

Other Tests Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen) Factor VII Assay Pancreatic markers (amylase and lipase) Fasting Lipid panel (triglycerides and total cholesterol, LDL, HDL) C-Peptide Troponin (I or T at local laboratory, Troponin T at central laboratory] Insulin Hemoglobin A1C 1,5 –Anhydroglucitol (1,5 AG) NT-proBNP Thyroid-stimulating hormone (TSH) Free Thyroxine 3 (Free T3) Free Thyroxine 4 (Free T4) Creatine kinase (CK) Creatine Kinase-MB (CK-MB) Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose) Pregnancy test for females (serum at screening, Urine or serum post dose)Cytokine samples (collected as part of Predose PK sample for plasma cytokines; may also be performed as clinically appropriate following fever)

Section 7.7.1 Dose and Safety Management Guidelines

Table 23 Dose Adjustment/Stopping Safety Criteria

Rationale for change: Due to the higher than expected number of haemorrhagic events observed with the use of GSK525762 in BET115521, many of which have occurred in the presence of moderate to severe thrombocytopenia, this section is being updated with more stringent guidelines for thrombocytopenia management

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 (platelets <LLN to ≥75,000/mm^3) & Grade 2 (platelets <75,000 to ≥50,000/mm^3) ~~Grade 1 & 2 (platelet count above 50,000)~~	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000 to ≥25,000/mm^3) ~~Grade 3 (platelet count between 25,000 50,000)~~	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC twice a week and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at the same

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		dose or at lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at a lower dose level, after discussion with the medical monitor. ~~After discussion with medical monitor and using sound clinical judgement, continue at same dose or adjust dose (e.g. consider reduced daily dosing or dosing on alternate days). Monitor CBC at least twice a week, more frequently if necessary~~
	Grade 4 (platelets <25,000/mm^3), or any moderate to severe bleeding accompanied by drug related thrombocytopenia ~~Grade 4 (platelet count below 25,000~~	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC twice a week and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 may be continued at the current/reduced dose after discussion with the medical monitor. ~~Temporarily interrupt study medication and monitor CBC every 2-3 days. If platelet counts recover to Grade 3 and is steady for at least 2 CBC reads at least 3days apart, or rising, discuss with medical monitor resuming treatment at the same or adjusted dose (see Grade 3) based on sound clinical judgement~~

AMENDMENT 09

Protocol Changes for Amendment 9 (24-FEB-2017) from the Protocol Amendment 8 (02-DEC-2016)

Protocol Amendment 9 applies to all site(s) participating in the conduct of the study.

Amendment 09 summary:

Amendment 9 applies to all global sites. Updates were made throughout the protocol to correct minor inconsistencies, spelling and typographical errors and provide further clarification. The following changes have been made based on comments from regulatory agencies during review of this protocol and other GSK525762 protocols: addition of exclusion criteria for exclusionary medications; updated exclusion of bleeding to include all history of bleeding and added known bleeding disorders; addition of laboratory monitoring required prior to surgeries, as described in Section 6.4.6.2 and Section 6.8.1; addition of guidance for dose reduction levels, as described in Section 7.7.1; updated dose adjustment/stopping safety criteria, as described in Table 24 and Table 25; updated prohibited medications in Section 8.2.1. In addition, other changes include: addition of a GIST cohort in Part 2, including background information, updated endpoints, overall Part 2 sample size, futility information, eligibility criteria and Section 11, Data Analysis and Statistical Considerations; updated Section 1.5 Risk Assessment to include current available data; removal of cytokines throughout protocol; updated sample size for MTD dose level in Part 1; update to contraception use in Inclusion 9 and 10 and clarifications in Section 9 Lifestyle Requirements; removal of Holter monitoring; changes to Part 1 time and events tables which includes removal of certain ECG time points, change from required to optional for urine PK samples and certain PK/ECG/biomarker tests (see Tables 12 to 14), addition of Factor VII assay testing, additional lab samples at Week 7 and Week 11, change in timing of on-treatment biopsy; changes to Part 2 time and events tables which includes additional lab samples at Week 7 and 11 and increase in Factor VII testing, addition of pregnancy/testosterone test at W1D1; change in timing of on-treatment biopsy and removal of an ECHO time point; change to the pregnancy reporting guidelines to 24 hours; addition of wording that subjects are to abstain from consuming certain fruits in Section 7.3; updates to Section 8, Concomitant Medications and Non-Drug Therapies to reorganize and update the prohibited, cautionary medication tables and drug interaction information; removal of fever and diarrhea information from Appendix 3. Additionally, Appendix 3 was updated with the current GSK Liver Event and follow-up information, but the liver event criteria did not change.

Version and document number changed for Investigator's Brochure, GlaxoSmithKline Document Number, 2011N113741_04, Version 4 to GlaxoSmithKline Document Number 2011N113741_05 Version 5 throughout the document.

NEW TEXT, Abbreviations

GIST	Gastrointestinal Stromal Tumor
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

List of Specific Changes

PROTOCOL SYNOPSIS

Objective & Endpoint

Primary endpoint, Point 2

Rationale for Change: Include PSA50 criteria and GIST endpoints with addition of GIST cohort.

Revised Text:

- Assess overall response rate (RR) usingby RECIST 1.1 in NMC and other solid tumors or PSA50 response rate using PCWG2 guidelines in CRPC or DCR (CR+PR+ SD ≥ 16 weeks in duration) in GIST.

Primary Hypothesis

Rationale for Change: Include GIST information with addition of GIST cohort.

Revised Text:

Gastrointestinal stromal tumor (GIST): this will be determined by testing the null hypothesis that the disease control rate is ≤15%, with about 80% power when the true disease control rate is 40%.

SUBJECT SAMPLE:

Rationale for Change: Update number of subjects to allow for additional subjects to be enrolled in Part 1 at the MTD and the addition of the GIST cohort in Part 2.

Revised Text:

Worldwide approximately 90 110 subjects will be enrolled in Part 1, and approximately 175 0 subjects will be enrolled in Part 2.

EFFICACY MEASUREMENTS:

Rationale for Change: Include PSA50 criteria and GIST endpoints with addition of GIST cohort.

Revised Text:

Response Rate (RR), Disease Control Rate (DCR), PSA50 response rate, Progression Free Survival (PFS) and Overall Survival (OS), time to response and duration of response.

SAFETY MEASUREMENTS:

Rationale for Change: After an internal evaluation of cardiac safety data collected from all subjects available by 20Dec2016, the Holter Monitoring was removed, as the ECG time-points currently included in the required assessments provide adequate cardiac safety assessments of any potential QT-prolonging effect (including potential delayed effects).

Revised Text:

Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events. Cardiac safety monitoring will be required, consisting of ~~24 hours of Holter monitoring at Screening and in Week 1 and Week 4, and~~ triplicate 12-lead ECGs in Part 1 prior to dosing on selected days and prior to drawing PK samples on serial PK sampling days (overnight stays in research facility may be necessary in Part 1).

Section 1. INTRODUCTION

Section 1.2.2 Other tumor types

Rationale for Change: Addition of GIST cohort and rational to support using a BET inhibitor in this tumor type.

Revised Text:

First paragraph first sentence:

acute leukemias, gastrointestinal stromal tumors (GIST), and other N-Myc driven tumors.

Second paragraph

Based on the preclinical findings within GSK and with collaborators, subjects with small cell lung cancer, non-small cell lung cancer (NSCLC), colorectal cancer, castration resistant prostate cancer (CRPC), triple negative breast cancer (TNBC), estrogen receptor positive (ER positive) breast cancer, neuroblastoma, and N-Myc amplified solid tumors will be enrolled to the dose finding part of the study. In addition, Part 2 expansion cohorts will enrol subjects with NMC, SCLC, CRPC, TNBC, ER+BC and GIST.

Last Paragraph, GIST (Gastrointestinal Stromal Tumor) point added

GIST (Gastrointestinal Stromal Tumor)

The super-enhancer profiling of sarcoma tumor samples and cell lines identified conserved super-enhancer program in GIST tumors. Some of the genes associated with super-enhancers in GIST tumors include well-established drivers, such as *KIT* and *PDGFRA*, but also potential novel targets, such as *ETV1* and *HAND1*. GIST-specific *KIT* super-enhancer regulating *KIT* gene activity is remarkably sensitive to bromodomain inhibition. KIT-dependent GIST cell lines have an IC50 to the prototypical bromodomain inhibitor, JQ1, ranging from 150 – 470nM (Matthew Hemming, personal communication, December 2016). Other bromodomain inhibitors, including GSK525762, demonstrate similar selective toxicity in KIT-dependent GIST cell lines. At the gene and protein expression levels, BET bromodomain inhibitors attenuate the expression of genes, associated with superenhancers, such as *KIT, ETV1* and *HAND1*, suggesting that BET proteins are required for the maintenance of GIST super-enhancer associated transcriptional program and are critical regulators of GIST growth and survival. In support of this mechanism, uncoupling *KIT* expression from its native super-enhancer leads to resistance to bromodomain inhibition. In KIT-dependent GIST cells, bromodomain inhibition shows synergistic toxicity with KIT-inhibition, further suggesting an independent and complimentary mechanism of action in GIST (Matthew Hemming, personal communication, December 2016). These evolving data have driven strong enthusiasm in developing bromodomain inhibitors in GIST.

Section 1.4. Rationale for Study and Endpoints

Rationale for Change: Addition of GIST cohort (second paragraph) and clarification of the tumor types included in Part 2 (third paragraph).

Revised Text:

Second paragraph first sentence

Given the poor prognosis and high unmet medical need of NMC, as well as in other tumor types such as relapsed/refractory SCLC, NSCLC, CRC, CRPC, TN and ER+ BC, GIST, NB and N-Myc amplified tumors and the exceptional drug-to-target alignment of GSK525762, a combined Phase I/II study (BET115521) is proposed.

Third paragraph first sentence

The recommended phase II dose (RP2D) of GSK525762 with possible adjustment based on the relative bioavailability of the besylate salt formulation, will be studied in the cohort expansion (Part 2) to determine efficacy, safety and tolerability in NMC ~~patients~~and other tumor types including SCLC, CRPC, TNBC, ER+BC and GIST.

Section 1.5. Risk Assessment

Rationale for Change: Risk assessment section changed to be in line with changes throughout the protocol (e.g. removal of Holter monitoring, will no longer collect cytokines in event of fever) and updated section with most current pre-clinical data.

Revised Text:

Gastrointestinal: *Second and Third Sentence*

Microscopic examination included degenerative changes in the esophagus, stomach, small and large intestine, including erosion or ulceration, mucosal congestion, hemorrhage and edema, crypt dilatation and focal inflammatory cell infiltration in the ~~28 day~~toxicology studies of up to 3 month duration~~y~~ in the dog and rat. Recovery was evident after a minimum of 3 weeks off dose.

Cardio-vascular:

First Paragraph first sentence

Although there were minimal effects of GSK525762 on current density and no effects on trafficking in HEK-293 cells or on ECG rhythms or arrhythmias in the *ex vivo* rabbit wedge assay, QT and QTc prolongation (maximum 41 milliseconds at 3 mg/kg for 12 days) was seen in dogs after a single oral dose of 30 mg/kg or repeat dosing at ≥1 mg/kg/day in ~~4 week~~ toxicology studies of up to 3 month duration.

First Paragraph fourth sentence

Increases in biomarkers of cardiac damage (cardiac troponin I and T, myosin light chain and NT-proANP) were also seen in the rat and cardiac troponin I in the dog.

Second Paragraph first sentence

Given the risks of long QTc associated arrhythmias, and of compound associated cardiomyopathy, subjects will be monitored closely for changes in QTc with triplicate 12-lead ECG~~, Holter monitoring,~~ and for elevations in plasma Troponin.

Second Paragraph fourth sentence

Therefore, the 48-hour telemetry requirement was removed and the frequency of Holter monitoring was reduced with Protocol Amendment 6 and upon further review of the totality of data, Holter monitoring was removed in Amendment 9.

Safety ECGs

First Paragraph second sentence

The mean from triplicate ECGs (when indicated) will be evaluated at each time point.

Subpoint Serum Markers

~~Holter Monitoring and~~ Serum Markers

Heading of subsection and first sentence

In addition to the Safety ECGs performed during the study, ~~continuous 12-lead Digital Holter ECGs will be acquired at baseline and at selected time points during therapy for accurate retrospective analysis of QTcF variation. Laboratory~~laboratory evaluations for cardiac troponins and electrolytes will be performed and NT-pro-brain natriuretic peptide (BNP) will be checked at baseline, regular intervals (as specified in the Time and Events tables of the protocol), and when clinically warranted during the study treatment.

Hematologic and lymphoid:

First Two Sentence

Lymphoid toxicity was observed in rats and dogs manifested by bone marrow hypo-cellularity and variable and inconsistent changes in ~~decreased~~ total white cell lymphocyte and decreased platelet counts. There were variable and inconsistent changes in multiple red blood cell parameters~~s~~ and reticulocytes in the periphery, and decreased organ weight, thymus, spleen, and lymph node hypocellularity.

Deleted text

~~**Cytokines:** In vitro incubation of human whole blood for 24 hours with GSK525762 resulted in a time and concentration-dependent induction of IL-1β. The maximum effect was variable between donors (34 to 3986 pg/mL, mean 1238 pg/mL from 16 donors); however, the concentration required to drive this effect was consistent across the donors (pEC50 6.0, 0.42ug/mL). This effect was not observed in whole blood from other species (rat and dog) or in preparations of human PBMCs or neutrophils. Special note is made for the occurrence of fever which could be symptomatic of cytokine level elevation during dosing of the compound (see protocol Section 7.7, Table 23"Fever"), and close monitoring of cytokine levels will be instigated at this point.~~

Pulmonary:

First paragraph first sentence

Aggregates of foamy macrophages in peri-bronchiolar areas were evident in rats given ≥10 mg/kg/day for 28 days.

First paragraph fourth sentence

This finding is unlikely to affect pulmonary function; no effects were observed in the 3 month studies in rats and dogs.~~however the effect of dosing beyond 4 weeks is unknown.~~

Hepatic Toxicity:

Non-adverse liver changes were observed in rats and dogs including increases in bilirubin levels and transient increases in AST in rats. Necrosis was observed in one rat at 30 mg/kg/day in the 4 week study. GSK525762 has been demonstrated to undergo bioactivation in vitro which indicates potential for idiosyncratic heptotoxicity. The precursor metabolite has been observed in clinical plasma samples.

The BET115521 protocol includes frequent monitoring of liver biochemistry along with stopping criteria for dose limiting toxicity (DLT), liver monitoring guidelines and management (see Section 3.2.3, Section 7.7.2, and Appendix 3).

Reproductive and Developmental:

First Paragraph first sentence

In ~~4-week~~ toxicology studies of up to 3 month duration, bilateral sperm retention, germ cell degeneration and tubular vacuolization, and depletion of testicular germinal epithelium occurred in male dogs receiving ≥ 0.~~3~~01 mg/kg and male rats receiving ≥ 10 mg/kg doses of GSK525762. Exposures associated with reproductive toxicity in male dogs overlap with the proposed 5 mg starting dose in this FTIH study.

First Paragraph third sentence

These changes were accompanied in rats and dogs by changes in sperm morphology, motility and number and hormonal changes (decreased testosterone and Inhibin B in rats and increased FSH in rats and dogs). Reduced prostate weight and secretory content was also evident in the rat. An effect on spermatogenesis is anticipated. Full or partial reversibility of the testicular effects was observed in the 3 month rat and dogs studies following a 17 week off dose period.

Section 2. OBJECTIVES, ENDPOINTS, HYPOTHESES FOLLOWING QD AND/OR BID DOSING SCHEDULES

Objective & Endpoint

Primary Endpoint Point 2

Rationale for Change: Include PSA50 criteria and GIST endpoints with addition of GIST cohort.

Revised Text:

- Assess overall response rate (RR) using RECIST 1.1 in NMC and other solid tumors or PSA50 response rate using PCWG2 guidelines in CRPC or DCR (CR+PR+ SD ≥ 16 weeks in duration) in GIST.

Primary Hypothesis

Rationale for Change: Include GIST information with addition of GIST cohort.

Revised Text:

GIST: this will be determined by testing the null hypothesis that the disease control rate is ≤15%, with about 80% power when the true disease control rate is 40%.

Section 3.1. Study Design/Schematic

Rationale for Change: Include GIST information and rationale.

Revised Text:

Second Paragraph Last sentence

Expansion cohorts (Part 2) are planned to further explore clinical activity of GSK525762 in subjects with NMC, SCLC, CRPC, TNBC, ~~and~~ ER+BC and GIST as shown in Figure 1.

Fouth Paragraph Third sentence

The GIST expansion cohort is being added in Amendment 9 due to pre-clinical evidence for bromodomain inhibition in GIST.

Section 3.2.2. Dose Escalation and Schedule

Rationale for Change: Simplification of section due to removal of Holter monitoring.

Revised Text:

First Paragraph Onwards

In Part 1, subjects will ~~follow the dose schedule outlined in Table 2~~dose once or twice daily, depending on the cohort. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data.

~~Extensive m~~Monitoring for cardiac safety signals will be performed, with triplicate 12-lead ECGs~~, and 24-hour Holter monitoring~~ to be performed on the days indicated in ~~Table 2~~the Time and Events Table.

Subjects will be evaluated for dose limiting toxicities (DLTs) during the first 4 weeks of treatment (Section 3.2.3).

~~**Table 2 Dosing Schedule and Cardiac Monitoring for Part 1**~~

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG	ECG	ECG		ECG,Holter	ECG	ECG
Week 2	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG			ECG		ECG	ECG
Week 3	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG			ECG			
Week 4	Dose	Dose	Dose	Dose	Dose	Dose	Dose
	ECG,Holter			ECG			

Section 3.2.2.2. 3+3 Dose Escalation in Part 1

Rationale for Change: Increase the number of subjects that may be treated at the MTD to gather additional data at the MTD for Part 1.

Revised Text:

Second Paragraph First sentence

Once the MTD is reached, up to ~~12~~ 20 additional subjects may be enrolled at the MTD to further evaluate safety and tumor PD.

Section 3.2.2.4. Alteration of Schedule

Rationale for Change: Additional PK samples may not be required in all cases and timing will be on a case-by-case basis, depending on the subject's current dose level and time on treatment.

Revised Text:

Fourth Paragraph

In Part 2, subjects approved to alter their current dose level with either a dose reduction or dose escalation may require additional limited PK sampling, after discussion with the GSK Medical Monitor. ~~(pre-dose, 0.5, and 3 hours) at the new dose level, after 4-7 days at the adjusted dose level.~~

Section 3.2.2.6. Intra-Subject Dose Escalation

Rationale for Change: Update to account for removal of Table 2.

Revised Text:

Bullet point 2 Second Sentence

In this case the subject must follow the dosing/monitoring schedule for the first 4-weeks as outlined in ~~Table2~~the Time and Events Tables, as he/she will be the first subject exposed to the higher dose.

Section 3.2.5.1. NMC Pharmacodynamic Expansion Cohort

Rationale for Change: Update to account for removal of Table 2 and Holter monitoring.

Revised Text:

Second Paragraph First sentence

Subjects in the NMC PD Expansion Cohort will start with same dosing schedule described in Section 3.2.2 ~~(Table 2);~~ ~~Extensive m~~Monitoring for cardiac safety signals will be performed as required in Part 1~~,~~ with triplicate 12-lead ECGs ~~, and 24-hour Holter monitoring~~ to be performed on the days indicated in ~~Table 2~~the Time and Events Table.

Section 3.2.7. Part 2 Expansion Cohort

Rationale for Change: Addition of GIST cohort and related futility information.

Revised Text:

First Paragraph Last sentence

Approximately 1~~5~~70 subjects with NMC, SCLC, CRPC, TNBC, ~~and~~ ER+BC and GIST will be enrolled in expansion cohort at the RP2D to gather more safety data and to further assess anti-tumor activity.

Below Figure 6 Table 6

For GIST, to test for 40% DCR relative to a 15% DCR suggesting no activity with 0.1 type I error and 80% power, first interim look maybe conducted once 8 evaluable GIST subjects have been enrolled in this cohort or treated at the same dose level to examine safety and efficacy, if 0 confirmed response or SD with at least 16 weeks is observed, further enrolment into this cohort may be terminated. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Table 5. A maximum of 25 subjects will be enrolled at the RP2D. All available data will be considered in making enrollment decisions.

Table 5 Decision Making Criteria for Futility of GIST

Number of Evaluable Subjects	≤ This Number of Confirmed Responses/SD to Stop Early for Futility	Probability of continuing enrolling when DCR=0.4	Probability of continuing enrolling when DCR=0.15
8	0	0.0000	0.7275
9	0	0.0000	0.7275
10	1	0.0000	0.4496
11	1	0.0000	0.4496
12	1	0.0000	0.4496
13	1	0.0000	0.4496
14	2	0.0000	0.3087
15	2	0.0000	0.3087
16	2	0.0000	0.3087
17	2	0.0000	0.3087
18	3	0.0000	0.2215
19	3	0.0000	0.2215
20	3	0.0000	0.2215
21	4	0.0000	0.1532
22	4	0.0000	0.1532
23	4	0.0000	0.1532
24	5	0.0000	0.1047
25	6	0.0585	0.0000

Section 4.1. Number of Subjects

Rationale for Change: Update number of subjects to allow for additional subjects to be enrolled in Part 1 at the MTD and the addition of the GIST cohort in Part 2 (first paragraph) and clarification to include all tumor types in Part 2 (third paragraph).

Revised Text:

First Paragraph Third and Fourth sentence

To complete Part 1, it is estimated ~~60~~ 90 to ~~90~~110 evaluable subjects will be enrolled. The besylate sub-study will enroll approximately 10 to 12 subjects in the United States only. Part 2 will enroll approximately 17~~5~~0 subjects.

Third Paragraph

If subjects discontinue the study before completing Week 8 during Part 2, additional subjects may be enrolled at the discretion of the Sponsor in consultation with the investigator to ensure adequate population for determination of response within NMC and other expansion cohorts.

Section 4.2.1. Inclusion Criteria

Rationale for Change: Include GIST as tumor type for Part 2. Update the adequate organ function table (Table 6) to clarify the footnotes. Update the contraception language based on GSK guidelines.

Revised Text:

Inclusion Criteria No. 3, Part 2 Only: Bullet Point "2":

SCLC, CRPC, TNBC, ~~and~~ ER+BC and GIST

Inclusion Criteria No. 7,

Table 6 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥ 1.5 X 10^9/L
Hemoglobin	≥ 9.5 g/dL (patients that required transfusion or growth factor need to demonstrate stable haemoglobin for 7 days of 9.5 g/dL)
Platelets	≥ 100 X 10^9/L
PT/INR and PTT ~~3~~	≤ 1.5 X ULN
Hepatic	
Total bilirubin	≤ 1.5 x X ULN (isolated bilirubin >1.5 X ULN is acceptable if bilirubin is fractionated and direct bilirubin <35% or subject has a diagnosis of Gilbert's syndrome)
ALT and AST	≤2.5 × ULN
Renal	
Creatinine OR Calculated creatinine clearance [calculated by Cockcroft Gault formula~~1, 2~~]	≤1.5 X ULN ≥ 50 mL/min
OR 24-hour urine creatinine clearance~~2~~	≥ 50 mL/min
Cardiac	
Ejection fraction	≥ Lower limit of normal (LLN) by Echocardiogram (ECHO) (minimum of 50%)
Troponin (T)	≤ ULN
Potassium	≥LLN and ≤ULN
Magnesium	≥LLN
Thyroid	
Thyroid stimulating hormone (TSH)~~2~~	≥LLN and ≤ULN
Reproductive/Endocrine	
Testosterone	<50ng/dL (only for subjects with CRPC)

1. See Appendix 2 for Cockcroft Gault formula

~~2. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2~~

2~~3~~. If TSH is abnormal, but free T3 and/or free T4 are normal, then the subject may still be considered eligible for enrolment.

Inclusion Criteria No. 9, Bullet Point "2":

Child-bearing potential and agrees to use one of the contraception methods (described in Section 9.1) ~~for an appropriate period of time (as determined by the product label or investigator)~~from the time of the screening pregnancy test ~~prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception~~ until 7 months after the last dose of study medication.

Inclusion Criteria No. 9, Bullet Point "3":

Negative serum pregnancy test ≤ 7 days prior to first study drug dose, for women of childbearing potential.

Inclusion Criteria No. 10 modified and splitted to add criteria No.11

10. Male subjects with a female partner of childbearing potential must agree to use one of the methods of contraception specified in Section 9.2. This method must be used from the time of the first dose of study medication until 16 weeks after the last dose of study medication. ~~In addition, m~~

11. Male subjects whose partners are or become pregnant while on study medication must continue to use condoms for ~~7 days~~16 weeks following the last dose of~~after stopping~~ study medication~~s~~.

Section 4.2.1. Inclusion Criteria

Rationale for Change: Include GIST-specific criteria for eligibility.

Revised Text:

New sub section added

4.2.1.2. Specific Eligibility Criteria for Part 2 GIST Cohort

16. Histopathologically confirmed diagnosis of advanced (metastatic and/or unresectable) GIST.

17. Subjects must have had failure of at least imatinib as therapy for advanced disease due to progression. There is no limit on the number of prior TKI therapies.

4.2.2. Exclusion Criteria

Rationale for Change: Simplificaiton of criterion 2. Futher clarification in criteria 4 and 8. Addition of criterion 5 and expand criterion 12 to further minimize the risk of bleeding.

Revised Text:

Exclusion Criteria No. 2

2. Prior treatments usage as defined:

a. Use of an investigational anti-cancer drug within 14 days or 5 half-lives, whichever is longer, prior to the first dose of the ~~investigational products~~ study medication. Note that an investigational drug is defined as a drug without an approved oncologic indication.

~~b. A minimum of 14 days between termination of the investigational drug and administration of GSK525762.~~

~~c.~~b. Any therapy related toxicities must also have resolved to Grade 1 or less. ~~Note that an investigational drug is defined as a drug without an approved oncologic indication.~~

~~d.~~c. Chemotherapy, radiotherapy, anti-neoplastic antibody or targeted therapy or immunotherapy within 14 days, major surgery within 28 days (or 42 days for prior nitrosoureas or mitomycin C) prior to the first dose of the ~~investigational product~~study medication.

Exclusion Criteria No. 4

Current use of a prohibited medication or requires any of these medications during treatment with the investigational drugs (details will be available in Section ~~8.3~~8.2). This includes excluding current medications known or suspected to be associated QT prolongation and strong inducers or inhibitors of CYP3A4. In addition, any subject who may require a QT prolonging medication while on trial should not be enrolled.

Exclusion Criteria No. 5

Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) except for cases where NSAIDs provide benefit over other analgesics or high dose aspirin (allowed up to 100 mg PO daily). Details are available in Section 8.2.

Exclusion Criteria No. 8 Bullet point 2

Clinically significant conduction abnormalities or arrhythmias or~~,~~ subjects with Bundle Branch Block.

Exclusion Criteria No.12

~~History of major gastrointestinal bleeding within the last 6 months. Any evidence of active gastrointestinal bleeding excludes the subject.~~ Subjects with a history of known bleeding disorder(s) or history of clinically significant hemorrhage (e.g., GI, neurologic) within the past 6 months.

Section 4.2. Eligibility Criteria

Rationale for Change: Addition of definition of a screen failure.

Revised Text:

New sub section added:

Section 4.2.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently dosed with study treatment.

Section 4.2.4.1. Permanent Discontinuation from Study Treatment

Rationale for Change: Clarify that assessments occur at the End of Treatment visit for subjects who discontinue to clarify that all subjects should be followed for survival and new anti-cancer therapy.

Revised Text:

Sixth Paragraph

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment ~~follow-up~~ (End of Treatment) as specified in Time and Events Tables.

Eight Paragraph first sentence

All subjects who permanently discontinue study treatment for any reason will be followed for survival and new anti-cancer therapy [including radiotherapy] every 6 months until death or until the subject has been followed for 2 years.

5. TIME AND EVENTS TABLES

Rationale for Change: Table 7: Clarification to dispensing of study medication, reduction of ECGs and removal Holter monitoring. Scans should be completed within 28 days of first dose to align with other sections of the protocol. Addition of labs at W11D1 to increase frequency of monitoring. Urine PK samples are now optional. Saliva samples should not be collected for subjects in BID cohorts. Post-dose biopsy moved out to W3-W4 and language added so that subjects who require a dose interruption due to laboratory requirements may still undergo a biopsy at a later point. Additional minor clarifications throughout. Table 8: Removal of triplicate troponin collection, additional safety labs added at W11D1, addition of Factor VII testing, removal of cytokine collection and other minor clarifications. Table 9 and 10: Clarification when fasting requirements apply. Table 11 and 12: Many samples are now optional. Table 14: Additional lab monitoring at W7D1 and W11D1, clarification to dispensing of study medication, removal of Holter monitoring, update to timeframe for scans prior to first dose, additional pregnancy test for woman of childbearing potential at W1D1, change in timing of post-dose tumor biopsy and other minor clarifications throughout. Table 15: Additional safety labs at W7D1 and W11D1, additional Factor VII testing at W5D1 and reflex if aPTT is abnormal or with a bleeding event, removal of cytokine collection and other minor clarifications.

Revised Text:

Table 7 Time and Events: Part 1

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	D1	
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X																									
Demography		X																									
Medical history		X																									
Disease characteristics		X																									

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
Cardiology evaluation		X																									
Prior therapy		X																									
Register subject		X																									
TREATMENT PHASE																											
Study Drug																											
Dispense study drug[a]	Refer to SPM for further details ~~Administer about same time of day. No food or antacids 1h before and 2h after.~~		X							X							X		X		X		X		X		
Review ~~subject diary~~ compliance	~~Diary not required when dosed in clinic.~~									X							X		X		X	X	X		X		
Safety																											
Pregnancy test [b]/ testosterone	**Females**: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. **Males**: complete and free testosterone at SCR; free testosterone thereafter.	X	X																		X		X		X		X
Physical Exam		X	X							X							X				X	X	X		X		X
ECOG PS		X	X							X							X		X		X	X	X		X		X

Part 1 Assessments	**Notes**	**SCR**	**Refer to Section 6.1.2 for visit windows.**																						**Q4 and Q8W Initiated from Week 9**		**EOT**
			Week 1							**Week 2**							**W3**		**W4**		**W5**	**W7**	**W9**	**W11**	**q4W**	**q8W**	
			D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Vital Signs	SBP, DBP, heart rate, respiratory rate, temp	X	X	X				X		X					X		X		X		X	X	X		X		X
Pain		X	X	X				X		X					X		X		X		X	X	X		X		X
Weight and height	Height at SCR only	X	X							X							X		X		X	X	X		X		X
Chest x-ray		X																									
Pulmonary function test		X																									
Adverse events		*SAEs collected continuously from signing of informed consent; AEs collected continuously from time of first dose*																									
Concomitant medications		*Continuous from signing of informed consent*																									
Laboratory assessments: For details please see following tables																											
Tests		X	X	X				X		X					X		X		X		X	X	X	X	X	X	X
Cardiac Monitoring																											
Echocardiogram	Within 35 days of first dose	X													X						X		X			X	X
12-lead ECGs (Triplicate)	For timing of triplicate ECGs on Oc days, see ~~Table 10 and Table 11~~ Tables 9 through 13. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within	X	O	O	O		O	~~X~~	~~X~~	X			O		X	~~X~~	X	O	X	~~X~~	X	X	O		X		X

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	D1	
	30msec from baseline.																										
~~Holter monitoring~~	~~At least 24 h, on dosing days start at least 60 min predose.~~	~~X~~					~~X~~												~~X~~								
Efficacy																											
CT/MRI Scans[d,a]	SCR assessment within 28~~35~~ days of first dose. Target lesions to be identified at SCR and followed.	X																			X		X			X	X
Tumor sample	Optional during rapid dose escalation; required during 3+3 dose escalation. EOT sample should be collected at time of progression where feasible. Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy[e].	X															One post-dose sample collected anytime between W3D1-W4D1 (4-6h post-dose).										X
PET scan[d]	Optional during rapid dose escalation; required during 3+3 dose escalation. SCR assessment within 28~~35~~ days of first dose.	X																			X		X				
Castrate-Resistant Prostate Cancer Assessments																											
PSA	PSA to be collected in line with PCWG2 guidelines.	X																					X			X	

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
	Levels may be checked more frequently if appropriate.																										
Neuroblastoma Assessments																											
CT/MRI	One or more tests should be used as appropriate for disease. The same modalities utilized at screening should be used throughout study. Screening Assessment within 28 ~~35~~ days of first dose can be used as screening assessment.	X																X				X			X	
MIBG scan[f,b]		X																X				X			X	
FDG-PET		X																X				X			X	
^{99}Tc scintigraphy for bone scan		X																X				X			X	
Bilateral bone marrow aspirates and biopsy		X																X				X			X	
Urine HVA, VMA, dopamine		X	X																	X		X		X		
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																											
PK and biomarker samples[c]	Fasting requirements apply for PK samples on W1D1 and W3D4.		X	X			X						X					X					X		X	
Samples for mRNA[c]			X	X														X								X
LPS blood sample	Not required with BID dosing schedule.		X																								
PK Urine samples	These are optional as of Amendment 9.		X															X									
Optional Saliva and Sample	~~A saliva sample may be requested on serial PK~~		X															X									

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																						Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4 W	q8 W	
			D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 4	D 1	D 4	D 1	D 1	D 1	D1	D 1	D 1	
	~~sampling days. Additional collection details will be provided in the SPM .~~ Not collected with BID dosing schedule.																										
Blood samples for circulating exploratory biomarkers (cfDNA, etc)	EOT circulating biomarker blood samples to be collected with lab assessments.	X																	X								X
Pharmacogenomics (PGx)																											
PGx sample	Blood sample should be collected after screening (preferably on D1) if informed consent has been obtained for Genetic research.		X																								
FOLLOW-UP PHASE																											
Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.																											

Part 1 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.																				Q4 and Q8W Initiated from Week 9		EOT
			Week 1							Week 2							W3		W4		W5	W7	W9	W11	q4W	q8W	
			D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	D1	

Abbreviations: CK=creatine kinase; CRP=c-reactive protein; D=day; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; FLC=free light chain; HVA=homovanillic acid; LPS=lipopolysaccharide; MIBG=meta-iodo-benzyl-guanidine; q4W=every 4 weeks; q8W=every 8weeks; SBP=systolic blood pressure; SCR=Screening; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis; VMA= vanillylmandelic acid; W=week; PT=Prothrombin Time; INR=International Normalized Ratio; aPTT=Activated partial thromboplastin time; WNL=Within normal limits

a. Suggested timing of study medication dispensing; may be altered at the discretion of the Investigator or designee, based on availability and visit schedule.

b. Not required for women of non-childbearing potential, as defined in Section 4.2, Inclusion Criterion 9.

c. Some of these samples will be optional as of Amendment 9; please see Tables 12-14 for further details.

d. Per RECIST 1.1 baseline (within 28 ~~35~~ days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter, scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate. Disease assessments should be performed no less than 4 weeks (28 days) after first dose and from previous on-treatment scan.

e. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the GSK Medical Monitor after subject recovery.

f. Subjects with neuroblastoma will have MIBG and bone marrow biopsies after week 24 as clinical indicated to confirm complete remission.

Table 8 Time and Events: Part 1 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	Notes	SCR	Refer to Section 6.1.2 for visit windows.										Q4 and Q8W Initiated from Week 9		EOT[a]
			W1			W2		W3	W4	W5	W7	W9	W11	q4W	q8W	
			D1	D2	D6	D1	D6	D1	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT-proBNP ~~9~~	For Troponin. ~~: W1D1 & W1D2: local lab sample collect 3X/24h; central lab sample collect 1X/24h~~. All ~~other~~ timepoints, including unscheduled, collect 2 samples: 1 for local, 1 for central lab	X	X	X	X	X	X	X	X	X		X			X	X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**Refer to Section 6.1.2 for visit windows.**											**Q4 and Q8W Initiated from Week 9**		**EOT[a]**
			W1			**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**q4W**	**q8W**	
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Hematology		X	X		X	X	X	X	X	X	X	X	X	X		X
Clinical chemistry		X	X		X			X		X	X	X		X		X
Pancreatic		X	X		X			X		X	X	X		X		X
Coagulation		X	X		X			X		X	X	X	X	X		X
Factor VII Assay	Also perform if PT, INR or aPTT are ≥1.5XULN, or in case of bleeding event	X						X		X						
Creatine phosphokinase		X	X		X			X		X	X	X		X		X
Liver chemistry		X	X		X			X		X	X	X	X	X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X			X		X	X	X		X		X
c-peptide and 1,5 AG	Will be performed at central lab if not available at local lab	X	X							X		X			X	
HbA1c		X	X					X	X	X		X			X	
Fasting lipids		X	X							X		X			X	X
Thyroid monitoring	TSH, free T3, free T4 at SCR and W1. If TSH is abnormal at W1D1, continue monitoring TSH, free T3 and free T4 going forward at time points indicated in this Table and at any time when clinically appropriate.	X	X							X		X			X	X
Urinalysis		X	X							X		X			X	X
Pregnancy test[b], females	Serum pregnancy test within 7 days of first dose; urine or serum test thereafter	X	X							X		X		X		X
Testosterone, males	Complete and free testosterone	X	X							X		X		X		X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 72h of first dose.	**Notes**	**SCR**	**Refer to Section 6.1.2 for visit windows.**											**Q4 and Q8W Initiated from Week 9**		**EOT**[a]
			W1			**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**q4W**	**q8W**	
			D1	**D2**	**D6**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
	at SCR; free testosterone thereafter															
CK, CK-MB	Predose and 12-18 h post dose		X	*as clinically appropriate*												
~~Safety Cytokines~~	~~This is collected as part of the Predose PK sample and is sent to GSK DMPK.~~	~~X~~		~~*as clinically appropriate following fever*~~												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X														

C=cycle; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; SCR=Screening; W=week

a. EOT circulating biomarker blood samples to be collected with lab assessments.

b. Not required for women of non-childbearing potential, as defined in Section 4.2, Inclusion Criterion 9.

Table 9 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1 and Week 2

	W1D1 (fasting requirements apply)										**W1D5**		**W2D4 + 1 day**			
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ±2h**[a]	**24h ±2h**	**48h ±2h**[b, d]	**30 min ±5m**	**3h ±15m**	**pre dose**	**30 min ±5m**	**3h ±15m**	**8h ±1h**

Table 10 QD Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 3 and Week 9

	W3D4 + 2 days (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed) **(fasting requirements apply)**									**W9D1 ±4 days** (if dose has been reduced or escalated, +4 to +7 days)			**EOT**
	pre dose	**15 min ± 5m**	**30 min ±5m**	**1h ±5m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**12h ±2h**[a]	**24h ±2h**[b]	**48h ±2h**[b, d]	**pre dose**	**0.5-2h**	**4 - 8h**	

Table 11 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 1

	W1D1																**W1D2 and W1D3 (relative to W1D1 Morning Dose)**		**W1D5 ECG and PK samples after Morning Dose only**	
	Morning Dose (fasting requirements apply)								**Evening Dose (relative to W1D1 Morning Dose)**											
	pre dose	**0 H**	**15 min ±5 m**	**30 min ±5 m**	**1h ±5 m**	**2h ±10 m**	**4h ±15 m**	**8h ±1 h**	**pre dose (12h-15m) d**	**12 h d**	**15 min(12.25 h) ± 5m d**	**30 min (12.5h) ±5m d**	**1h (13h) ±5m d**	**2h (14h) ±10 m d**	**4h (16h) ±15 m d**	**8h (20h) ±1h d**	**12 h (24h) ±1h d**	**36 h (48h) (pre-dose) ±1h d**	**30 min ±5 m**	**3h ±15 m**
~~Dose~~Administer/dose Study Medication		X								X								X		
12-lead ECG, in triplicate[a]	X		~~X~~	~~X~~	~~X~~	X	X	X	X		~~X~~	~~X~~	~~X~~	X	X	X	X	X	X	X
PK and protein biomarker sample [b]	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Urine PK sampling [c]	X	0-2h				2-12h														
mRNA whole blood sample	X					X	X	X[d]		X				X	X	X	X	X		

~~Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment and acute phase protein assessment for morning and evening dosing at pre-dose and at 2, 4, 8, 12 and 24 hr post dose.~~ The frequency of sampling may be changed based on data from the first few subjects assessed.

a. Triplicate ECGs should be collected 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.

b. PK blood samples collected overnight may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)
c. Urine samples for quantitative analysis of GSK525762 are ~~not required in the NMC PD Expansion Cohort~~optional as of Amendment 9.
d. ~~W1D1 48h assessments (ECG, PK and mRNA)~~These assessments ~~(ECG, PK and mRNA)~~ are optional as of Amendment 9.

Table 12 BID Dosing Time and Events: Part 1 Pharmacokinetics and Biomarker Sampling, Week 2 and Week 3

	W2D4 + 1 day ECG and PK samples after Morning Dose only				**W3D4 +2 days**																**W3D5 and W3D6 (relative to W3D4 Morning Dose)**	
					Morning Dose (fasting requirements apply)								**Evening Dose (relative to W3D4 Morning Dose) ~~(For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)~~**											
	pre dose (Prior to Dosing)	**30m ± 5m**	**3h ± 15m**	**8 h ±1 h**	**pre dose**	**0h**	**15m ±5 m**	**30m ±5 m**	**1h ±5 m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**pre dose**	**12h**	**15m ±5m (12.25m) [d]**	**30m ±5 m [d]**	**1h (13h) ±5m [d]**	**2h (14h) ±10m [d]**	**4h (16h) ±15m [d]**	**8h (20h) ±1h [d]**	**12h (24h) ±1h (pre dose) [d]**	**36h (48h) ±1h (pre dose) [d]**
~~Dose~~ Administer Study Medication	X					X								X							X	X
12-lead ECG, in triplicate [a]	X	X	X	X	X		~~X~~	~~X~~	~~X~~	X	X	X	X		X	X	X	X	X	X	X	X
PK and protein biomarker sample [b]	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Urine PK sampling [c]						0-2h				2-12h												
mRNA whole blood					X					X	X	~~X~~										

	W2D4 + 1 day ECG and PK samples after Morning Dose only				**W3D4 +2 days**																**W3D5 and W3D6 (relative to W3D4 Morning Dose)**	
					Morning Dose (fasting requirements apply)								**Evening Dose (relative to W3D4 Morning Dose) ~~(For W3D4 subjects that are not staying overnight after the evening dose, the 15min – 8h PK/ECG timepoints are optional)~~**											
	pre dose (Prior to Dosing)	**30m ± 5m**	**3h ± 15m**	**8 h ±1 h**	**pre dose**	**0h**	**15m ±5 m**	**30m ±5 m**	**1h ±5 m**	**2h ±10m**	**4h ±15m**	**8h ±1h**	**pre dose**	**12h**	**15m ±5m (12.25m) [d]**	**30m ±5 m [d]**	**1h (13h) ±5m [d]**	**2h (14h) ±10m [d]**	**4h (16h) ±15m [d]**	**8h (20h) ±1h [d]**	**12h (24h) ±1h (pre dose) [d]**	**36h (48h) ±1h (pre dose) [d]**
sample																						

~~Plasma samples will be divided at the GSK DMPK facility where bioanalysis of PK is performed and shipped to a vendor for systemic cytokine assessment and acute phase protein assessment at pre-dose and at 2, 4, 8, 12 and 24 hr post-dose.~~ The frequency of sampling may be changed based on data from the first few subjects assessed.

a. Triplicate ECGs should be collected 5 minutes apart and within 10 minutes prior to the 15 min and 30 min PK draws and within 15 minutes prior to the other PK draws.
b. PK blood samples collected overnight may be kept refrigerated at 4ºC in the event the PK lab is closed overnight (stable up to 12H)
c. Urine samples for quantitative analysis of GSK525762 are optional as of Amendment 9~~not required in the NMC PD Expansion Cohort.~~
d. ~~W3D4 48h~~These assessments (ECG, PK and mRNA) are optional as of Amendment 9.

Table 14 Time and Events: Part 2

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
Informed consent	Unless otherwise noted, screening assessments to be completed within 14 days of first dose.	X													
Demography		X													
Medical history		X													
Disease characteristics		X													
Cardiology evaluation		X													
Prior therapy		X													
Register subject		X													
TREATMENT PHASE															
Study Drug															
Dispense study drug[a]	Refer to SPM for further details. ~~Administer about same time of day.~~		X	X	X	X	X		X		X	X			
Review compliance	~~Not required when dosed in clinic.~~			X	X	X	X		X		X	X	X	X	X
Safety															
Pregnancy test[b]/testosterone	Females: serum pregnancy test within 7 days of first dose; urine or serum test thereafter. Males: complete and free testosterone at SCR; free testosterone thereafter.	X	X				X		X		X	X			X
Physical exam		X	X	X	X	X	X		X		X	X			X
ECOG		X	X	X	X	X	X		X		X	X			X
Vital Signs and Pain Assessments		X	X	X	X	X	X		X		X	X			X
Weight and height	Height at SCR only	X	X				X		X		X	X			X
Chest x-ray		X													

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
Pulmonary function test		X													
Adverse events		*SAEs collected continuously from signing of informed consent; AEs collected continuously from time of first dose*													
Concomitant medications		*continuous from signing of informed consent*													
Laboratory assessments: For details please see Table 15															
Tests		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Castrate-Resistant Prostate Cancer Assessments															
PSA		X	X	X	X	X	X		X		X	X			X
~~Serum~~ Complete testosterone		X	X	X	X	X	X		X		X	X			X
Cardiac Monitoring															
ECHO	If Baseline ECHO within 35 days of first dose, the Week 1 Day 1 ECHO is only required if clinically appropriate.	X	X optional			~~X~~			X		X		X		X
12-lead ECGs (Single)	ECGs prior to dosing. If QTcF increase >30msec, ECGs should be repeated Q2-3 days until QTcF is within 30 msec from baseline.	X	X	X	X	X	X		X		X		X		X
~~Holter monitoring~~	~~At least 24 h; on dosing days start predose~~	~~X~~	~~X~~			~~X~~									
Efficacy															
Lesion assessments		X							X				X		X
CT scan or MRI ~~c,a,b~~	Scans within 28~~35~~ days of first dose may be used as screening assessment. Additional bone scans and brain scans not	X							X				X		X

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.									Q4, Q8 and Q12 Initiated from Week 13			EOT
			W1	W2	W3	W4	W5	W7	W9	W11	W13	q4W	q8W	q12W	
			D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	
	required unless clinically indicated.														
PET scan (FDG or fluoride) ~~[b, c]~~	Scans within 28~~35~~ days of first dose may be used as screening assessment. Follow up scans conducted as clinically appropriate.	X													
PK															
PK	Three samples to be collected each sampling day: During first 4 weeks collect a predose within 60 minutes prior to dose, a single draw between 0.5-2h postdose, and a single draw between 4-8h postdose (fasting requirements apply).Thereafter only a Predose and 0.5 hour post-dose sample are collected. NOTE: If dose level is adjusted, additional PK sampling may be requested.		X			X			X				X		
Blood samples for circulating exploratory biomarkers (cfDNA, etc)	Baseline sample collected pre-dose on W1D1 EOT circulating biomarker blood samples to be collected with lab assessments.		X			X									X
Translational Research															
PGx sample	Blood sample should be collected after screening (preferably on W1D1) if informed consent has been		X												

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows. W1 D1	W2 D1	W3 D1	W4 D1	W5 D1	W7 D1	W9 D1	W11 D1	W13 D1	Q4, Q8 and Q12 Initiated from Week 13 q4W D1	q8W D1	q12W D1	EOT
	obtained for Genetic research.														
Tumor Sample	PK samples should be collected within 1 hour of on-treatment biopsy. EOT biopsy should be collected at time of disease progression where feasible. Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy[e].	X			One post-dose sample collected anytime between W3D1-W4D1 (4-6h post-dose)[f]										X
FOLLOW-UP PHASE															
Follow-up contact by clinic visit or other means (telephone contact, email, etc) for survival status and anticancer therapy every 6 months. Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death. Individual subjects will be considered to have completed the study 2 years after their last treatment or upon death, whichever is sooner. Document the cause of death. For the study, the Follow-up Phase ends after a minimum of 70% of subjects have died or 5 years after the last subject is enrolled in Phase 2.															

Abbreviations: CK=creatine kinase; D=day; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=End-of-Treatment; q4W=every 4 weeks; q8W=every 8weeks; SCR=Screening; Wk=week; PT=Prothrombin Time; INR=International Normalized Ratio; aPTT=Activated partial thromboplastin time; WNL=Within normal limits

a. Suggested timing of study medication dispensing; may be altered at the discretion of the Investigator or designee, based on availability and visit schedule.
b. Not required for women of non-childbearing potential, as defined in Section 4.2, Inclusion Criterion 9.
~~a.~~c. Per RECIST 1.1 baseline (within 28~~35~~ days of first dose) bone scans and brain scans are to be conducted for all subjects. Thereafter, scans should be conducted as clinically indicated. Subjects undergoing baseline full body PET/CT and/or brain MRI will not require these additional scans, unless clinically appropriate. Disease assessments should be performed no less than 4 weeks (28 days) after first dose and from previous on-treatment scan.
~~b. PET scan (FDG or fluoride) required at baseline and follow up scans should be collected when clinically appropriate.~~
d. ~~Disease assessments should be performed no less than 4 weeks (28 days) after first dose and from previous on-treatment scan.~~
e. If the post-dose biopsy is not performed during this timeframe due to lab abnormalities or subject status, it should be performed at the next agreed upon visit with the GSK Medical Monitor after subject recovery.
~~c.~~f. Timing may be further optimized based on tumor type and emerging data.

Part 2 Assessments	Notes	SCR	Refer to Section 6.1.2 for visit windows.									Q4, Q8 and Q12 Initiated from Week 13			EOT
			W1	W2	W3	W4	W5	W7	W9	W11	W13	q4W	q8W	q12W	
			D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	D1	

Table 15 Time and Events: Part 2 Laboratory Assessments

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	Notes	SCR	W1		W2		W3	W4	W5	W7	W9	W11	W13	Q4, Q8 and Q12W Initiated from Week 13			EOT [b]
			D1	D4 [a]	D1	D4 [a]	D1	D1	D1	D1	D1	D1	D1	q4W D1	q8W D1	q12W D1	
Troponin, NT-proBNP~~9~~	1 sample for local lab (troponin I or T), 1 sample for central lab (troponin T)	X	X		X		X	X	X		X		X		X		
Hematology		X	X		X		X	X	X	X	X	X	X	X			X
Clinical chemistry		X	X		X		X	X	X		X		X	X			X
Pancreatic		X	X		X		X	X	X		X		X	X			X
Coagulation		X	X		X		X	X	X	X	X	X	X	X			X
Factor VII Assay	Also perform if PT, ~~or~~ INR or aPTT are ≥1.5XULN, or in case of bleeding event	X					X		X								
Liver chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X			X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	**Notes**	**SCR**	**W1**		**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**W13**	**Q4, Q8 and Q12W Initiated from Week 13**			**EOT** [b]
			D1	**D4** [a]	**D1**	**D4** [a]	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**q4W**	**q8W**	**q12W**	
Creatine phosphokinase		X	X					X	X		X		X		X		X
Fasting blood glucose and insulin	Will be performed at central lab if not available at local lab	X	X		X		X	X	X		X		X	X			X
c-peptide and 1,5 AG	Will be performed at central lab if not available at local lab	X	X						X		X				X		
HbA1c		X	X								X				X		
Fasting lipids		X	X				X		X		X		X		X		X
Urinalysis		X	X						X		X		X			X	X
Thyroid monitoring	TSH, free T3, free T4 at SCR and W1. If TSH is abnormal W1D1, continue monitoring TSH, free T3 and free T4 going forward at time points indicated in this Table and at any time when clinically appropriate.	X	X						X		X		X		X		X

NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 72h of first dose	**Notes**	**SCR**	**W1**		**W2**		**W3**	**W4**	**W5**	**W7**	**W9**	**W11**	**W13**	**Q4, Q8 and Q12W Initiated from Week 13**			**EOT** [b]
			D1	**D4** [a]	**D1**	**D4** [a]	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**q4W** **D1**	**q8W** **D1**	**q12W** **D1**	
~~Cytokines~~		~~X~~			~~*as clinically appropriate*~~												
HBsAg, HepC antibody	If hepatits C antibody positive, perform third generation immunoassay on same sample to confirm results	X															

Abbreviations: D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; q12W=every 12 weeks; SCR=Screening Visit; W=week; ULN=Upper limit of normal

a. Optional Visits, should be conducted when additional monitoring of laboratory values is clinically appropriate.

b. EOT circulating biomarker blood samples to be collected with lab assessments.

Section 6.1.2. Visit Windows

Rationale for Change: Additional guidance for window for NMC diagnostic testing and Part 2 visits. Clarification to windows for visits from Week 4 on.

Revised Text:

New text added

Screening (baseline to pre-dose):

First paragraph, Last sentence

In Part 2, testing by the central laboratory for NMC diagnosis must be completed within 3 months prior to signing the main consent (no other treatments may have been received after the central diagnosis through study enrollment).

Fifth, Sixth, Seventh and Eighth paragraphs

Part 2 only – Week 1 through Week 3: assessments can be +/- 2 days, with the exception of W1D1 assessments, which must occur on W1D1.

Part 1 and Part 2 – Visits between Week 4 to Week 9 (inclusive): ~~**Clinic**~~ Visits can be scheduled ±3 days

Part 1 and Part 2 - ~~Monthly~~ Visits after Week 9 until Week 52: After the first disease assessment has been completed then the ~~monthly clinic~~ visits can be scheduled ± 5 days.

Part 1 and Part 2 - ~~Monthly~~ Visits after Week 52: ~~clinic~~ Visits can be scheduled ± 7 days.

Section 6.2. Baseline Assessment for NMC Subjects

Rationale for Change: Additional guidance for NMC diagnostic testing in case of potential for false negative by central laboratory testing and addition of FISH testing which may take place retrospectively on NMC samples.

Revised Text:

For NMC subjects in Part 1, a diagnosis of NMC based on a positive IHC test and/or detection of NUT gene translocation as determined by FISH at screening will be required. In Part 2, a diagnosis of NMC based on a positive IHC test performed at a central laboratory will be required. A ≥20% nuclei staining cut off will be applied for a positive diagnosis as a subset of germ cell tumors (from testis and ovary) weakly stain for the NUT protein (5% maximal nuclei staining, PPD , personal communication). In rare instances, where a subject's tumor previously tested positive for NMC by other methods, and a false negative by central laboratory is suspected due to poor quality and/or heterogeneity of the tissue, retesting may be considered on a case-by-case basis in

consultation with GSK Medical Monitor. If the retest by the central laboratory is positive for NMC, the subject may be considered eligible for enrollment.

In Part 2, fluorescence in situ hybridization (FISH) or next generation sequencing (NGS) may be undertaken retrospectively to characterize the NUT gene fusion partner and to support exploratory analysis of differential outcomes based on the NUT fusion partner.

Section 6.3. Baseline Assessment for Non-NMC Subjects

Rationale for Change: Clarification of tumor types included in Part 2.

Revised Text:

Last sentence

Subjects diagnosed with SCLC, CRPC, TNBC, ER+BC or GIST will be eligible for Part 2 of the study.

Deleted Section 6.4.6. Holter Monitoring and 6.4.7. Telemetry

Rationale for Change: Holter monitoring is being removed in Amendment 9 and telemetry was removed in Amendment 6; text being removed from body of protocol to avoid confusion of required tests.

Deleted Text:

~~**Section 6.4.6. Holter Monitoring**~~

~~Digital Holter ECG data will be obtained from 12-lead continuous Holter monitoring device supplied by the Sponsor. ECG acquisition via the Holter monitoring device will be performed at planned time points indicated in the Time and Events and should be obtained prior to phlebotomy and vital sign time points. Collection of critical ECG data shortly after meals or during sleep should be avoided since QT prolongation occurs at these times and a change in the QT-RR relationship occurs during sleep. Meals should be administered according to the guidelines provided in Section 7.3 and in the SPM as meal and snack times will need to be adjusted accordingly on dosing and ECG sampling days.~~

~~Analysis of intervals and morphology from the continuous digital ECG data will be acquired and stored electronically and manually over-read by an external central validated ECG laboratory. In order to increase consistency of ECG interpretation, a limited number of central ECG over-readers will be used throughout the study. All ECGs for a given subject will be over-read by the same reader from the central validated ECG laboratory. The central reader will be blinded to subject identifiers (e.g., subject number, age, and sex), treatment assignment, and study day when Holter data was collected. The final intervals and morphology analyses entered into the database will be those generated by the central ECG laboratory.~~

~~**6.4.7. Telemetry**~~

~~As part of the original cardiac monitoring plan, and to complement real-time ECG assessments, monitoring for potential adverse arrhythmias was conducted utilizing continuous telemetry monitoring. In addition, emergency resuscitation equipment including appropriate pharmacological agents will also be immediately accessible throughout the study.~~

~~After internal QTc analysis and evaluation of cardiac safety data collected from subjects up to the 100 mg QD cohort by the cut-off date of May 15, 2015, the 48-hour telemetry requirement was removed from all parts of the study in Protocol Amendment 6.~~

Section 6.4.6. Clinical Laboratory Assessments

Rationale for Change: Clarification to testosterone testing and removal of cytokines being collected with fever.

Revised Text:

Table 19 Clinical Laboratory Tests

Other Tests
Testosterone for males (free and complete testosterone at prior to first dose, free testosterone after first dose and as indicated in the Time and Events tables for CRPC subjects) Pregnancy test for females (serum at screening, Urine or serum post dose) Cytokine samples (collected as part of ~~Predose~~ PK sample for plasma cytokines~~); may also be performed as clinically appropriate following fever)~~

Section 6.4.6.2 Added

Rationale for Change: Addition of laboratory testing prior to scheduled surgeries to minimize the risk of bleeding during or after surgery.

Revised Text:

6.4.6.2. Clinical Laboratory Assessments Required Prior to Scheduled Surgeries

Subjects must have a platelet count of ≥75,000/mm^3 and a PT, INR and aPTT that are within normal limits within 48 hours prior to the post-dose biopsy and any scheduled surgical procedures.

Section 6.5.1. Disease Assessment

Rationale for Change: Addition of reference to Prostate Working Group 2 guidelines.

Revised Text:

First Sentence

Tumor response will be assessed as outlined in Time and Event Schedule by the investigator using RECIST 1.1 (Appendix 6) or the Prostate Cancer Working Group 2 (PCWG2) guidelines [Scher, 2008] and documented in the eCRF as: progressive disease (PD), stable disease (SD), partial response (PR), and complete response (CR).

6.6.3. Urine Collection

Rationale for Change: Urine PK will no longer be required to be collected in this study.

Revised Text:

First paragraph

Urine samples for quantitative analysis of GSK525762 ~~will~~ may be collected ~~at pre-dose and over a dosing interval immediately following dosing on Week 1 Day 1 and in Week 3~~at the time points noted in the Time and Events Tables for Part 1 of the study (these samples are optional as of Amendment 9). ~~Urine samples will be collected in subjects in Part 1 (with the exclusion of besylate sub-study) once the 3+3 dose escalation has been reached. Additional sampling may be instituted based on emerging data.~~

Section 6.8.1. Tumor Tissue Collection

Rationale for Change: Removal of 14 day window for collection of tissue for NMC subjects in Part 2 for the diagnostic testing. Pre-screen consents will be allowed for archival or fresh tissue biopsy in Part 2 NMC subjects. Addition of language regarding the required laboratory values prior to post-dose biopsy.

Revised Text:

First paragraph second and third sentence

NMC patients in Part 2 will be required to submit a fresh or archival tumor specimen to the central laboratory ~~during the 14 day screening period~~ for diagnosis. Due to the timely need to determine NMC status by NUT IHC testing, a pre-screen informed consent may be offered to expedite obtaining the ~~archival~~ tissue in Part 2.

Third paragraph onwards

During the accelerated dose escalation phase (Part 1), fresh pre- and post-dose biopsy collections will be optional until the standard 3+3 design is implemented. During the 3+3 dose escalation phase in Part 1, and during Part 2, pre- and post-treatment biopsies are collected as outlined in~~collected between W2D1 – W3D1 (4-6 hrs post-dose)~~ the Time and Events Tables and are mandatory. Archival tissue may be accepted as a pre-treatment specimen if the subject is treatment naïve. For subjects in Part 1 and 2, if tumor tissue is not accessible, discussion with the GSK medical monitor is required.

~~Archival tissue may be accepted as a pre-treatment specimen if the subject is treatment naïve~~. Subjects must have a platelet count of $\geq$75,000/mm^3 and a PT, INR and aPTT that are WNL within 48 hours prior to the post-dose biopsy. If study medication is held prior to the post-dose biopsy, dosing must be re-started and subjects should receive 4 consecutive days of dosing prior to collection of the biopsy. Specific timing of post-~~treatment~~dose sample collection is defined in the T&E table. See Study Procedures Manual (SPM) and central lab manual for additional details.

Section 6.8.2.2. Systemic (Unstimulated) Plasma for Cytokines, Chemokines, and Acute Phase Proteins

Rationale for Change: Removal of collection of cytokines in case of fever.

Revised Text:

First sentence

The set of analytes identical to that used in the whole blood ex vivo assay (including for example, MCP-1, MIP1-β IL-8) will also be measured in plasma samples taken during PK sampling~~and at the time of any Grade 2 fever or symptoms of a cytokine storm.~~

Deleted section 6.9.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

Rationale for Change: Removal of section as there have been no pre-defined disease-related events.

Deleted Text:

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

~~6.9.6.~~ 6.9.5. Prompt Reporting of SAEs and Other Events to GSK

Rationale for Change: Updated pregnancy reporting timeframe to 24 hours, per GSK policy.

Revised Text:

Table 20~~20~~ Reporting of SAEs and Other Events to GSK

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	~~2 Weeks~~24 hours	Pregnancy Notification Form	~~2 Weeks~~24 hours	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT≥3xULN and bilirubin≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured)[3]	24 hours[1]	SAE data collection tool. Liver Event Case Report Form (CRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event CRF[2]

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT≥5xULN; ALT≥3xULN with ~~hepatitis or rash~~symptoms of liver injury or hypersensitivity **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT≥3xULN and <5xULN and biliribin <2xULN	24 hours[1]	Liver Event CRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

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

6.10.2. Action to be taken if pregnancy occurs

Revised Text:

First paragraph second sentence

The investigator will record pregnancy information on the appropriate form and submit it to GSK within ~~2 weeks~~24 hours of learning of a subject's pregnancy.

Third paragraph second sentence

Furthermore, any SAE occurring as a result of a post-study pregnancy and is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Section 6.9.5~~6.9.6~~.

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

Revised Text:

First paragraph second sentence

The investigator will record pregnancy information on the appropriate form and submit it to GSK within ~~2 weeks~~24 hours of learning of the partner's pregnancy.

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Footnote updated for Table 21 and 21

Rationale for Change: Clarify that amorphous product is no longer available and all study medication must be taken by mouth, as of Amendment 9.

Revised Text:

Table 22 footnote

1. Amorphous formulation is no longer available as of Amendment 9

Table 23 Footnote

1. Formulation is no longer available as of Amendment 9

Third paragraph onwards: Deleted text

~~Preparation of GSK525762 Tablets for Administration via Enteral Feeding Tube~~

~~Administration via enteral feeding tube is intended only for subjects who are unable to swallow and retain orally administered GSK525762 tablets as directed in Section 7.1.~~

~~The dose compounding should be performed only by pharmacy or appropriately trained personnel (please refer to Pharmacy Manual). A GSK525762 dosing solution is to be prepared by allowing GSK525762 tablets to disintegrate in 50 mL sterile water. All contents will be transferred into a syringe for administration via feeding tube. The compounding vessel should be rinsed and the syringe and feeding tube flushed with further additions of sterile water. Total water volume will be 255 mL.~~

~~GSK525762 dosing solutions may be stored in the syringe at up to 30°C (86°F) prior to administration. Dosing must be completed on the day of solution preparation.~~

Section 7.3. Meals and Dietary Restrictions

Rationale for Change: Clarification that subjects must fast prior to serial PK days. Addition of restriction from certain fruits and juices due to the potential for drug interactions with study medication.

Revised Text:

First paragraph

During Part 1, subjects will fast for at least one hour prior to each dose of study drug. After dosing, subjects will be asked to fast for an additional two hours. On serial PK sampling days (Week 1, Day 1 and Week 3, Day 4), subjects should fast overnight (i.e., at least 8 hours). These fasting requirements have been implemented in the protocol and informed consents to minimize pharmacokinetic variability.

Last paragraph

Subjects should abstain from consumption of Seville oranges, grapefruit, grapefruit hybrids or grapefruit juice and/or pomelos, exotic citrus fruits, from one day prior to the first dose of study treatment until the last dose of study drug.

7.7.1. Dose and Safety Management Guidelines

Rationale for Change: Added guidance for dose adjustment dose levels. Updated the management guidelines based on recent regulatory feedback and removed fever guidelines as there have been no occurrences clinically which warrant the need for such guidance.

New text added & Table 23 added

Revised Text:

Dose reductions for individual subjects may be required, based on toxicity observed during the study. Table 23 describes the guidance for dose level reductions. All dose reductions should be discussed with the GSK Medical Monitor.

Table 23 Guidance for GSK525762 Dose Reduction Levels

Current GSK525762 Dose (Total daily dose)	If subject requires a dose level reduction; new dose:
40 mg	No further dose reduction allowed
50 mg	40 mg
60 mg	50 mg
75 mg or 80 mg	60 mg

Table 2423 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 (platelets <LLN to ≥75,000/mm^3) & Grade 2 (platelets <75,000 to ≥50,000/mm^3)	Continue dosing at same dose level with weekly or more frequent monitoring as necessary.
	Grade 3 (platelets <50,000 to ≥25,000/mm^3)	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC twice a week and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤ Grade 2 AND aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted ~~at the same dose or~~ at a lower dose level, after discussion with the medical monitor.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		If safety lab abnormalities recur following rechallenge, drug may be discontinued or restarted at another lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur to the same level following a second rechallenge, drug will be discontinued.
	Grade 4 (platelets <25,000/mm^3), or any moderate to severe bleeding accompanied by drug related thrombocytopenia	Withhold GSK525762 and check aPTT, PT, and INR. Monitor CBC twice a week and coagulation studies twice a week until normal, or increase monitoring frequency if clinically indicated. Hold GSK525762 until thrombocytopenia has resolved to ≤Grade 2 **AND** aPTT, PT, and INR are all ≤ ULN. Drug may then be restarted at a lower dose level, after discussion with the medical monitor. If safety lab abnormalities recur following rechallenge, drug may be held until platelet count recovers to Grade 2 (≥50,000/mm^3). For subjects with moderate to severe bleeding requiring transfusion support, GSK525762 should be permanently discontinued. If platelet count does not recover to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 should be permanently discontinued. If platelet count recovers to ≥50,000/mm^3 (Grade 2) within 14 days, GSK525762 may be continued at the current/reduced dose after discussion with the medical monitor. If platelet count does not recover to ≥25,000/mm^3 (Grade 3) within 7 days, GSK525762 should be permanently discontinued.
QTcF	If >30 msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	(5) Continue current dose of GSK525762 (6) Supplement electrolytes, particularly potassium and magnesium, to recommended levels: a. Maintain serum potassium > 4mol/L b. Maintain serum magnesium levels >0.85 mmol/L (7) Discontinue any concomitant medications with potential for QTcF prolongation. (8) Consider 24 hour or longer telemetry monitoring if clinically indicated.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	Discontinue GSK525762 and notify the Medical Monitor. (5) Supplement electrolytes to recommended levels: c. Maintain serum potassium > 4mol/L d. Maintain serum magnesium levels >0.85 mmol/L (6) Rule out other potential etiologies for prolonged QTcF such as cardiac ischemia (7) Discontinue any concomitant medications with potential for QTcF prolongation. (8) Consider telemetry monitoring if clinically indicated. This subject may consider restarting study treatment at one dose level reduced if all of the following criteria for QTcF re-challenge are met. If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to QTc prolongation) (7) QTcF reduced to <450 msec, (8) Potassium and magnesium levels are within institutional normal range, (9) A favorable risk/benefit profile (in the medical judgement of the Investigator and the Medical Monitor), (10) Approval within GSK medical governance: a. agreement with SERM MD and PPL, b. review with Chair or co-Chair of the GSK QT panel, c. SERM VP and Clinical VP approval d. Head Unit Physician approval (11) Institutional IRB (or equivalent) approval, and (12) The subject is re-consented regarding the possible increased risk of QTc prolongation. Discontinuation procedures: If the subject is withdrawn due to QTcF event, the subject should complete the following activities post-dose: (3) Evaluation by cardiologist. (4) Weekly assessments for QTcF should be performed for two weeks, and then next assessment at 4 weeks post-dose. a. If QTcF results have not resolved to baseline by 4 weeks post-dose, then continue every 4-5 weeks until resolution
Troponin	Troponin level >ULN~~and >10% CV level.~~	Contact the subject immediately for evaluation of symptoms and to obtain ECG. Repeat troponin within 24-48 hours or as soon as possible.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		For asymptomatic subjects with repeat troponin values >ULN~~and >10% CV~~, hold study medication(s), refer to a cardiologist and contact the GSK Medical Monitor. If the repeat value is within the normal range, the subject may continue study medication with close follow-up for symptoms, ECG monitoring and further troponin measurements as clinically indicated. If the subject is symptomatic or the troponin level approaches the threshold for MI according to local lab parameters, the study medication must be withdrawn and the subject will be referred immediately to a cardiologist for appropriate medical care.~~May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.~~
LVEF	Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN)	Temporarily discontinue investigational drugs(s) and repeat evaluation of LVEF within 2 weeks If LVEF recovers (defined as ≥LLN and absolute decrease ≤10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK medical monitor, the subject may be restarted on investigational drug(s) at a reduced dose. Monitoring to be performed at 2 and 4 weeks after restarting investigational drug(s) and then per protocol specifications. If LVEF does not recover within 4 weeks, permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should continue to be monitored at 2 weeks, 4 weeks and every 4 weeks until 16 weeks or resolution<u>, whichever is longer.</u> ~~May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical.~~
	Grade 3 or 4	Permanently discontinue investigational drug(s). Evaluation by a cardiologist will be conducted. Ejection fraction should be monitored at 2 weeks, 4 weeks and then every 4 weeks until 16 weeks or resolution.
Liver	• ALT ≥5X ULN, OR • ALT ≥3X ULN ~~and~~<u>plus either</u> bilirubin <u>≥</u>~~>/=~~ 2X ULN (>35% direct bilirubin, bilirubin fractionation required) or	<u>Refer to Section14.3 (Appendix 3) for liver chemistry stopping criteria, treatment algorithms, reporting and follow-up of suspected liver events.</u> ~~In the absence of known hepatic metastases, d~~ <u>D</u>iscontinue study medication<u>(s) and</u> notify the GSK Medical Monitor~~,~~ ~~and refer to follow-up procedures outlined in~~

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	INR >1.5 without evidence of biliary obstruction or progressive disease, OR • ALT ≥3X ULN with ~~the appearance hepatitis symptoms or rash~~symptoms of liver injury or hypersensitivity[a]	~~Appendix 3, , Section IIIa, Liver chemistry follow-up procedures. In the presence of known hepatic metastases, if there is evidence to suggest a drug induced effect, discontinue study medications, notify the GSK Medical Monitor, and refer to follow-up procedures outlined in Appendix 3, Section IIIa, Liver Chemistry Follow-Up Procedures.~~
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE version 4.0 Grade 1-5)	Fasting blood glucose >150 mg/dL to 250 mg/dL (Mild hyperglycemia)~~(Mild) Fasting blood glucose >150 mg/dL~~	Monitor fasting and preprandial glucose. If persistent over 2 repeats over 3-4 weeks, consult Diabetologist and consider starting metformin.
	~~Fasting blood glucose <70 mg/dL OR a~~Any blood glucose >250 mg/dL (Moderate to Severe hyperglycemia)	Hold investigational product(s) and instruct subject to notify investigator immediately. ~~If a blood glucose >250 mg/dL is observed the subject should be m~~Monitor~~ed~~ for ketoacidosis as clinically indicated. If subject has evidence of ketoacidosis, initiate prompt therapy. Antihyperglycemic therapy with insulin is preferred. Consult Diabetologist/Endocrinologist .Careful monitoring should be performed to control for rebound hypoglycemia as effect of investigational product(s) resolve →~~Treatment should be undertaken with awareness that the action of insulin or other antihyperglycemic agents (e.g. sulfonylureas, biguanides, etc.) may be substantially blocked by the action of the study medication. The action of insulin or other antihyperglycemic agents should be restored as study medication is cleared. If an antihyperglycemic agent is administered, then the subject should be observed closely for rebound hypoglycemia as the study medication is cleared. Intravenous insulin treatment is recommended.~~ May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
	Fasting blood glucose <70 mg/dL (Moderate to Severe hypoglycemia)	Hold investigational product(s). Provide sugar containing liquids and monitor monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes, may restart study treatment one dose level lower if the hypoglycemia cannot be attributed to any other cause, and fasting blood sugar will be monitored on a daily basis until the blood glucose level is stabilized.
Diarrhea	Grade 1	Initiate supportive care including loperamide.
	Grade 2	Initiate supportive care including loperamide. Consider temporary discontinuation of study medications and discuss with GSK Medical Monitor.
	Grade 3 or 4	Above plus consider IV hydration, hospital admission and prophylactic antibiotics as appropriate. Withhold study drug until diarrhea has resolved to ≤Grade 1, continue diarrheal prophylaxis~~Consider temporary discontinuation of study medications and discuss with GSK Medical Monitor.~~ ~~Additional guidance is located in~~Appendix ~~3~~May restart study treatment ~~at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor~~.one dose level lower.
Mucositis	Grade 1-2	Encourage oral hygiene. Offer topical supportive anesthetics. Encourage adequate hydration.
	Grade 3-4	Above, plus systemic opiate administration as needed. Consider IV hydration and hospital admission as appropriate. For mucositis >Grade 3, hold GSK525762 until mucositis is <Grade 1 and resume the same dose of GSK525762. If mucositis >Grade 3 recurs, hold GSK525762 until mucositis is <Grade 1, then reduce GSK525762 one dose level. If mucositis >Grade 3 recurs a third time at reduced dose, hold GSK525762 until mucositis resolved to <Grade 1, then reduce GSK525762 one dose level (if possible) or discontinue permanently.~~May restart study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.~~
Pneumonitis	Grade 1	**For all grades obtain high resolution chest CT if possible.** Consider evaluation by pulmonologist. Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). ~~Repeat evaluations every 8-12 weeks until return to within normal limits. Continue investigational drug(s) at current dose(s).~~

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		If any decline is observed in O_2 saturation, hold study drug, repeat chest x-ray to determine if progression of pneumonitis has occurred and consult pulmonologist.
	Grade 2	~~Consider~~Must be evaluated~~ion~~ by pulmonologist. Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and weekly room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations every 8-12 weeks until return to wnl. Consider a bronchoscopy with biopsy and/or bronchoalveolar lavage. (BAL). Treat only if symptomatic. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated. Hold investigational drug(s) until recovery to ≤~~<~~Grade 1, then reduce dose by at least 25%. Discontinue investigational drug(s) if no recovery to ≤~~<~~Grade 1 within 4 weeks. ~~May consider escalation to pre-event dose after discussion with GSK Medical Monitor~~
	Grade 3 and 4	Discontinue investigational drug(s). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to wnl. Bronchoscopy with biopsy and/or BAL is recommended. Consider treatment with corticosteroids in the appropriate clinical setting and in consultation with the pulmonologist (1-2 mg/kg of prednisone [or equivalent] IV once daily) if infectious origin is ruled out. Taper over 4-6 weeks ~~(Grade 3) Hold investigational drug(s) until recovery to < Grade 1. Discontinue investigational drug(s) if no recovery to <Grade 1 within 4 weeks. May consider restarting study treatment at a reduced dose after discussion with GSK Medical Monitor if there is clinical benefit.~~ ~~Grades 1-3: May consider restarting study treatment at a reduced dose or dose level pre-event after discussion with GSK Medical Monitor.~~ ~~(Grade 4) Discontinue investigational drug(s)~~
~~Fever~~	~~Grade 1~~	~~(Grade 1)~~ ~~(1) Continue current dose(s) of study treatment(s)~~

Toxicity	Dose Adjustment/Stopping Criteria	Management Guidelines
		~~and monitor for change in severity.~~
	~~Grade 2~~	~~(Grade 2)~~ ~~(1) Consider temporary discontinuation of study medication and monitor for change in severity.~~ ~~(2) Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. Assess vital signs.~~ ~~(3) Collect Cytokine blood samples as outlined in the SPM. Collect blood culture and investigate viral infections as applicable.~~ ~~(4) May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor.~~
	~~Grade 3-4~~	~~Grade 3-4~~ ~~(1) Temporary discontinuation of study medication and monitor for change in severity.~~ ~~2) Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea.~~ ~~(3) Collect Cytokine blood samples as outlined in the SPM. Collect blood culture and investigate viral infections as applicable.~~ ~~(4) May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor~~

*Note: Baseline results are defined by the nearest timepoint prior to first dose. For this trial the Baseline QTcF value is determined by the mean of the triplicate W1D1 predose QTcF results (when triplicate ECGs are indicated). If these results are not available, then the mean QTcF of the screening triplicate ECG results are considered baseline.

a. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia.

Section 7.7.2 Dose Adjustments for ToxicityDose Adjustments for Toxicity

Rationale for Change: Updated based on regulatory feedback.

Revised Text:

Table 25~~24~~Guidance for Dose Adjustment for Toxicity [Except those listed in Table 24]

Worst Grade	**GSK525762**
1	No change in dose.

2	For drug-related Grade 2 toxicities, continue dosing with no change or may consider holding for up to 1 week for toxicity to be < Grade 2. Continue at the same dose (dose reduction is required if the Grade 2 toxicity is considered a DLT).
3	Hold dose ~~for one week intervals~~ until toxicity is ≤ Grade 1*, then restart with no change for 1st episode. . Reduce by one dose level with 2nd episode if recovery to ≤Grade 1 within 21 days. If no recovery to ≤Grade 1 after a 21 day delay in the 2nd episode, subject should be permanently discontinued. ~~drug-related Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.~~
4	Off protocol therapy In rare situations, based on discussion and written agreement between GSK medical monitor and investigator, if the patient is receiving benefit then the following criteria should be implemented: hold ~~dose for one week intervals~~ until toxicity is ≤Grade 1*, then restart with one dose level lower. If the same Grade 4 toxicity recurs, study drug will be permanently discontinued. ~~< drug-related Grade 2 then restart with no change for 1st episode. Utilize an alternative, less frequent schedule or reduce by one dose level with 2nd episode. If no recovery to ≤Grade 1* after a 21 day delay, patient should go off protocol therapy.~~

*Note: Exceptions to ≤ drug-related Grade 1 requirement may be made for rash, alopecia, etc. Exceptions to ≤ drug-related Grade 1, 2, 3 requirements would be quickly reversible (<48 hours) laboratory abnormality (example: electrolyte changes). ~~In the case of thrombocytopenia, a subject may be considered for restarting study treatment if a resolution from Grade 4 to Grade 3 is experienced and after discussion with GSK medical monitor. See guidance in Table 23 above.~~

Section 7.8 deleted

Rationale for Change: Events of Special Interest are defined in the RAP and may change during the study based on clinical data.

~~**7.8 Guidelines for Events of Special Interest and Dose Modifications**~~

~~The severity of adverse events will be graded utilizing the CTCAE v4. Additional details regarding fever, diarrhea, rash and liver toxicity are outlined in Appendix 3.~~

Section 8 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Rationale for Change: Section was updated and reorganized for clarity and ease of reading. The sections were also updated with most recent drug interaction data, including updating the prohibited and cautionary medication tables. The restriction for antacids around dosing was removed. Restriction of NSAIDs and aspirin use and guidance to minimize the use of acetaminophen were added to minimize the risk of bleeding.

Heading of Section 8.1 changed

Section 8.1. Permitted Medications and Non-Drug Therapies

Revised Text:

Fourth Paragraph

Drugs with a low risk of causing QTc prolongation (e.g., aprepitant) may be used without restriction.

Heading of Section 8.2. changed

8.2. Prohibited Medications and ~~Cautionary Medications~~Non-Drug Therapies

Inserted new subsection Section 8.2.1. Prohibited Medications

Section 8.2.1.Prohibited Medications

Subjects should not receive other anti-cancer therapy [including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormonal therapy (other than leuprolide or other GnRH agonists), surgery or tumor embolization] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. Note, palliative radiation and/or surgical intervention may be permitted (for example to address pain management) and should be discussed with the GSK medical monitor prior to invention to determine appropriate dosing and schedule.

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

Subjects may continue to use aspirin, but doses are not allowed to be greater than 100 mg per day. The use of non-steroidal anti-inflammatory drugs (NSAIDs) will be excluded, except for when NSAIDs will provide benefit over other analgesics and then to be used with caution, including concomitant use of proton pump inhibitors.

Subjects taking enzyme-inducing antiepileptic agents or other potent inhibitors or inducers of CYP3A4 enzymes should be transitioned to another agent at least 14 days (or 5 half-lives, whichever is longer) prior to the first dose of study agents.

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

~~Antacids should not be consumed for at least 1h before and 2h after administration of GSK525762.~~

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (administered per the prescribing information) and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class (i.e. dolasetron and granisetron are not permitted).

Co-administration of the medications listed in Table 26 are prohibited for 5 half-lives (or at least 14 days, whichever is longer) prior to the first dose of study drug until discontinuation from the study drug due to unacceptable risk of Torsades de Pointes (with the exception of amiodarone, which is prohibited beginning 6 months prior to screening through discontinuation from the study; however, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines). If a prohibited medication is required for single use (such as for a procedure) while study treatment(s) is held, the GSK Medical Monitor can approve such use.

Table 26 Drugs with a Risk of Torsades de Pointes that are Prohibited[1]

Amiodarone	Dronedarone	Moxifloxacin
Anagrelide	Droperidol	Papaverine
Azithromycin	Erythromycin	Pentamidine
Chloroquine	Escitalopram	Pimozide
Chlorpromazine	Flecainide	Procainamide
Cilostazol	Fluconazole	Propofol
Ciprofloxacin	Halofantrine	Quinidine
Citalopram	Haloperidol	Roxithromycin
Clarithromycin	Ibogaine	Sevoflurane
Cocaine	Ibutilide	Sotalol
Disopyramide	Levofloxacin	Sulpiride
Dofetilide	Levomepromazine	Sultopride
Domperidone	Levosulpiride	Terlipressin
Donepezil	Methadone	Thioridazine

Data Source: crediblemeds.org revision date 09 January 2017.

1. The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject

~~8.2.1.~~8.2.2. Cautionary Medications

Revised Text:

Subjects should minimize the use of medications which contain acetaminophen. Subjects should be informed of alternative medications.

~~If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class.~~

Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes **are to be used with EXTREME CAUTION** beginning **14** days prior to the first dose of study drug until discontinuation from the study. These medications include (but are not limited to):

Table 27~~25~~Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution[1]

~~**Generic Name**~~	~~**Brand Name**~~
~~Amiodarone~~	~~Cordarone, Pacerone, Nexterone~~
~~Astemizole~~	~~Hismanal~~
~~Chlorpromazine~~	~~Thorazine, Largactil, Megaphen~~
~~Degarelix~~	~~Firmagon~~
~~Leuprolide~~	~~Lupron~~
~~Tropisetron~~	~~Navoban and Setrovel~~

~~*There may be situations when the subject is on study that Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines~~

~~Data Source: www.crediblemeds.org (revised 17-Dec-2015)~~

Alfuzosin	Foscarnet	Perphenazine
Apomorphine	Gemifloxacin	Pipamperone
Aripiprazole	Hydrocodone ER	Promethazine
Artenimole+piperaquine	Iloperidone	Rilpivirine
Asenapine	Imipramine	Risperidone
Atomoxetine	Isradipine	Saquinavir
Bedaquiline	Leuprolide	Sertindole
Buprenorphine	Lithium	Solifenacin
Clomipramine	Melperone	Tacrolimus
Clozapine	Mifepristone	Telavancin
Cyamemazine	Mirabegron	Telithromycin
Degarelix	Mirtazapine	Tetrabenazine
Delamanid	Moexipril/ hydrochlorothiazide	Tiapride
Desipramine	Nicardipine	Tizanidine
Dexmedetomidine	Norfloxacin	Tolterodine
Efavirenz	Nortriptyline	Trimipramine
Ezogabine	Ofloxacin	Tropisetron
Famotidine	Oxytocin	Vardenafil
Felbamate	Paliperidone	Venlafaxine
Fingolimod	Pasireotide	Zotepine
Flupentixol	Perflutren lipid microspheres	

Data Source: crediblemeds.org revision date 09 January 2017

1. The above table is not exhaustive and these drugs are defined by the online version at the time of screening of the subject

After starting cautionary medications such as in Table 27~~Table 25~~, it is recommended that ECGs are implemented daily until the steady state. If there are abnormalities,

implement additional cardiotoxicity monitoring as addressed in Table 24~~Table 23~~, Section7.7.

GSK525762 is a moderate CYP3A4 inducer. Medications that have a narrow therapeutic index and that are substrates of CYP3A4 should be administered with caution, as their metabolism may be affected by co-administration with GSK525762 and result in decreased exposure. These include alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, and theophylline.

GSK525762 is a substrate for breast cancer resistance protein (BCRP) and P-glycoprotein (Pgp) transporters. Therefore, potent inhibitors of these transporters, such as cyclosporine, tacrolimus, or ketoconazole, should be avoided.

GSK525762 in as inhibitor of organic anion transporter 1A1 (OAT1) and organic anion transporter 3 (OAT3) in vitro. Substrates of these transporters include agents such as methotrexate, penicillin G, and indomethacin. While co-administration of these agents with GSK525762 is not prohibited, they should be used with caution and additional monitoring for adverse effects should be utilized.

Higher doses of oral steroids can cause enzyme induction. As such, oral steroids should be used with caution (and discussed with the GSK Medical Monitor). NOTE: Topical or inhaled steroids are permitted.

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

~~Section 8.2.2. Potential Drug Interactions with GSK525762~~

~~The precise in vivo metabolic liability for GSK525762 has yet to be assessed. In vitro data suggests that GSK525762 is only metabolized by CYP3A4 and thus coadministration of inducers and inhibitors of CYP3A4 should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762.GSK525762 is considered to have a low risk of causing clinically relevant perpetrator drug interactions with CYP3A4, CYP2B6 and CYP2C8 enzymes and/or PgP, BCRP, OATP1B3, OAT1, OCT2, MATE1, MATE2-K, BSEP or MRP2 transporters either via direct or metabolism-dependent inhibition.~~

~~GSK525762 was shown to be an inhibitor of OATP1B1 and OAT3 in vitro, however, the clinical impact of this inhibition is only deemed a concern for sensitive substrates of OATP1B1 or OAT3 (e.g. methotrexate).~~

~~Potential interactions with other Cytochrome P450 metabolized drugs have not been assessed.~~

~~Higher doses of oral steroids can cause enzyme induction. As such, oral steroids should be used with caution (and discussed with the GSK Medical Monitor). NOTE: Topical or inhaled steroids are permitted.~~

8.3. Prohibited Medications Subjects should not receive other anti-cancer therapy [including chemotherapy, radiation therapy, immunotherapy, biologic therapy, investigational therapy, hormonal therapy (other than leuprolide or other GnRH agonists), surgery or tumor embolization] while on treatment in this study. Other anti-cancer therapy should not be administered unless one of the following occurs: documented disease progression; unacceptable or unmanageable toxicity; subject is withdrawn from the study at the investigator's discretion or consent is withdrawn; or no further clinical benefit is anticipated which requires permanent discontinuation of study drug. Note, palliative radiation and/or surgical intervention may be permitted (for example to address pain management) and should be discussed with the GSK medical monitor prior to invention to determine appropriate dosing and schedule.

Co-administration of medications that are known to prolong the QT interval and have a risk of causing Torsades de Pointes are **PROHIBITED** for 5 half-lives of the drug prior to the first dose of study drug until discontinuation from the study drug with the exception of **amiodarone** which is prohibited beginning **6 months** prior to Screening through discontinuation from the study. (However, there may be situations when the subject is on study and Advanced Cardiac Life Support (ACLS) requires the use of amiodarone, which should be used as per local clinical guidelines). These medications include (but are not limited to):

Table 26 Drugs with a Risk of Torsades de Pointes that are Prohibited**Generic Name**	**Brand Name**
Arsenic trioxide	Trisenox
Asenapine	Saphris,Sycrest
Bepridil	Vascor
Chloroquine	Aralen
Cisapride	Propulsid
Clarithromycin	Biaxin, Prevpac
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium
Droperidol	Inapsine
Erythromycin	Erythrocin, E.E.S.
Halofantrine	Halfan
Hydrocodone	Hysingla ER and Zohydro ER
Ibutilide	Corvert
Levofloxacin	Levaquin
Levomethadyl	Orlaam
Mesoridazine	Serentil
Methadone	Dolophine, Methadose
Pentamidine	Pentam, NebuPent
Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl, Procan
Quinidine	Quinaglute, Cardioquin

Table 26 Drugs with a Risk of Torsades de Pointes that are Prohibited**Generic Name**	**Brand Name**
Sotalol	Betapace
Sparfloxacin	Zagam
Terfenadine	Seldane
Thioridazine	Mellaril

Data Source: crediblemeds.org

At time of screening, if a subject is currently receiving any of the listed prohibited medications/substances, the medication or substance must be discontinued for a period of **at least 14 days** prior to the administration of the first dose of study drug in order for the subject to meet study eligibility.

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron and ondansetron at a maximum oral dose of 8 mg TID are the only allowed drugs in this class.

8.4. Non-Drug Therapies

Non-drug anti-cancer therapies (e.g., radiation therapy, surgery, and/or tumor embolization) will not be permitted from the screening visit through the post-study follow-up visit.

NOTE: Subjects may receive palliative radiation treatment during this study.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit. Decaffeinated tea and coffee are permissible.

Herbal products include, but are not limited to:

- St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto , ginseng

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

9.1. Female Subjects

Rationale for Change: Clarification to section.

Revised Text:

First paragraph first sentence

Female subjects of childbearing potential must not become pregnant during the trial and for 7 months after stopping study medication and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of ≤<1%.

Contraceptive Methods with a Failure Rate of ≤ 1%

First bullet point

Non-hormonal ~~I~~intrauterine device (IUD) or intrauterine system (IUS) that meets the ≤~~<~~1% failure rate as stated in the product label

Last paragraph

All ~~H~~hormonal means of birth control such as oral, injectable, dermal, subdermal or topical contraceptives are NOT acceptable forms of birth control given that their efficacy has not been evaluated when given in combination with the investigational drugs.

Section 9.2. Male Subjects

Rationale for Change: Update to reflect current GSK guidance and to align with Inclusion criteria.

Revised Text:

First paragraph first sentence onwards

This list does not apply to male subjects with a female partner of child bearing potential who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment and until 16 weeks after the last dose of study drug(s).

Vasectomy with documentation of azoospermia. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview, **OR**

Condom use ~~plus~~PLUS partner use of a highly effective contraceptive (≤1% rate of failure per year) such as ~~occlusive cap (diaphragm or cervical/vault cap)~~ intrauterine device or system, or hormonal birth control such as contraceptive subdermal implant, combined estrogen and progestogen oral contraceptive, injectable progestogen, contraceptive vaginal ring, or percutaneous contraceptive patches~~. plus spermicidal agent (foam/gel/film/cream/suppository), or intrauterine device.~~ **~~OR~~**

~~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~~

In addition, mMale subjects whose partners are or become pregnant~~while on study medication~~ must continue to use condoms for ~~7 days~~16 weeks after ~~stopping~~ after the last dose of study medications. Male subjects should be advised not to donate sperm while on study and for 16 weeks after the last dose of study medication.

Section 11.1.1. Part 1

Rationale for Change: Update number of subjects to allow for additional subjects to be enrolled in Part 1 at the MTD and the addition of the GIST cohort in Part 2.

Revised Text:

First paragraph second sentence

To complete Part 1, it is estimated that ~~60~~ 90 to ~~90~~ 110 evaluable subjects will be enrolled.

Section 11.1.3. Part 2

Rationale for Change: Addition of GIST cohort information and inclusion of PSA50 response for CRPC.

Revised Text:

First paragraph first sentence onwards

The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with NMC, SCLC, CRPC, TNBC, ~~and~~ ER+BC and GIST.

- For NMC, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR or PR) of 20% relative to a 5% response rate suggesting no activity

- For CRPC and SCLC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR; for CRPC subjects, defined as a percentage of subjects have PSA50 response) of 30% relative to a 10% response rate suggesting no activity.

- For TNBC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 25% relative to a 10% response rate suggesting no activity.

- For ER+BC, efficacy is defined as a clinically meaningful response rate (defined as a percentage of subjects that have achieved as CR or PR) of 30% relative to a 15% response rate suggesting no activity.

- For GIST, efficacy is defined as a disease control rate (defined as a percentage of subjects that have achieved a CR or PR or SD that has lasted at least 16 weeks) of 40% relative to a 15% disease control rate suggesting no activity.

In text Table

	Null Hypothesis (H0) ~~O~~RR	Alternative Hypothesis (Target) (Ha) ~~O~~RR	Maximum Sample Size	Probability of stopping early for futility if H0 is true	Average Sample Size if H0 is true	Actual Type I Error Rate (%)	Actual Power (%)
NMC	5%	20%	**25**	**0.891**	**14**	**8.8**	**80.2**
CRPC	10%	30%	**22**	**0.860**	**16**	**6.0**	**82.5**
TNBC	10%	25%	37	0.876	23	6.4	81.7
ER+BC	15%	30%	37	0.855	25	8.7	80.3
SCLC	10%	30%	22	0.860	16	6.0	82.5
GIST	15%	40%	25	0.895	14	5.9	88

Section 11.4.1. Primary Analysis

Rationale for Change: Addition of PSA50 response information for CRPC and GIST analysis information.

Revised Text:

Fourth paragraph onwards

PSA 50 Response rate (RR) is defined as the response rate that a PSA reduction from baseline ≥50% is observed at 12 weeks and beyond (must be confirmed by a second value). RR will be reported for CRPC cohort along with the exact 95% confidence interval. Waterfall plots will be presented that show the maximum percentage of change in PSA reduction from baseline.

Disease Control Rate (DCR) is defined as the percentage of subjects who achieved CR, PR or SD (defined as ≥ 16 weeks in duration) among subjects who received at least one dose of treatment. Disease control rate and the associated 2-sided 95% exact confidence limits will be provided separately for GIST cohort.

Section 14 APPENDICES

Heading of subsection 14.3 is modified Section

Rationale for Change: Fever and diarrhea guidelines were removed. Fever was removed as this has not been seen clinically and diarrhea was removed because guidance is presented in Table 24. The Liver Events section was then reorganized with updated tables and figures, though the stopping criteria have not changed.

Revised Text:

Section 14.3. Appendix 3: ~~Dose Adjustment/Stopping Criteria/Supportive Care~~Liver Events

Section 14.3.

Revised Text:

Subpoints I and II under section 14.3 is deleted

~~I.Fever~~

~~Safety monitoring cytokine blood samples may be collected (based on Table 23 of the protocol). These samples include (but not limited to) assessments for TNF-alpha, IL-1,IL-6, IL-10 as outlined in the SPM.~~

~~Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea.~~

~~II.Diarrhea~~

~~**General considerations for diarrhea management**~~

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

~~**For uncomplicated Grade 1 to 2 diarrhea** (i.e., mild to moderate and defined as CTCAE Grade 1-2 with no complicating signs or symptoms):~~

- ~~Dietary modifications: stop all lactose containing products and eat small meals. A BRAT (banana, rice, apples, toast) diet can be helpful.~~
- ~~Hydration: drink 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth)~~
- ~~Consider administration of standard dose of loperamide (subjects should have loperamide available in order to start at the first signs of diarrhea):~~
  - ~~Initial dose of 4 mg followed by 2 mg every four hours or after every unformed stool; maximum 16 mg/day.~~
  - ~~Continuation of loperamide is suggested until diarrhea free for 12 hours~~
- ~~Consider a temporary investigational drug dose interruption until symptoms have resolved to baseline or Grade 1. Re-treatment with GSK525762 may then be resumed at 100%. Please refer to for additional guidance.~~
- ~~If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every two hours; maximum 16 mg/day. Consider adding oral antibiotics.~~

- If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, start second-line agents (otreotide, budesonide or tincture of opium). Consider adding oral antibiotics.

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

- The subject must call the investigator immediately for any complicated severe diarrhea event.
- Discontinue GSK1120212 treatment and hold until symptoms resolve to Grade 1 or baseline. Consider re-starting therapy at a reduced dose.
- If loperamide has not been initiated, initiate loperamide immediately. Initial dose 4 mg followed by 2 mg every two hours or after every unformed stool; maximum 16 mg/day.
- For dehydration, use intravenous fluids as appropriate; if severe dehydration, administer octreotide.
- Administer antibiotics as needed (e.g., fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 to 4 neutropenia.
- Intervention should be continued until the subject is diarrhea free for at least 24 hours.
- Intervention may require hospitalization for subjects most at risk for life-threatening complications.

III.Hepatobiliary Events

Monitoring, Interruption, and Stopping Criteria for Hepatobiliary Events

Liver chemistry stopping criteria are defined as follows:

ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured)

*serum bilirubin fractionation should be performed if testing is available; if unavailable, withdraw subject (if ALT ≥3xULN and total bilirubin ≥2xULN) and measure urinary bilirubin via dipstick

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants

ALT ≥5xULN.

ALT ≥3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia)

ALT ≥3xULN persists for ≥ 4 weeks.

ALT ≥3xULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3xULN **and** < 5xULN **and** bilirubin < 2xULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment as long as they can be monitored weekly for 4 weeks.

Refer to the diagram in Figure 7 **for a visual presentation of the procedures listed below. When any of the liver chemistry stopping criteria is met, do the following:**

- **Immediately discontinue** subject from study treatment
- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 6.9.2 of the protocol), the SAE data collection tool will be completed separately with the relevant details
    - All events of ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).**
    - NOTE: if serum bilirubin fractionation is not immediately available, and if ALT≥ 3xULN and bilirubin ≥ 2xULN, discontinue subject from study treatment. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury
- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments as outlined below, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below
- For studies where survival or progression is an endpoint, follow-up for overall survival or progression is required following discontinuation from study treatment.
- Do not restart investigational product unless written approval is granted by GSK Medical Governance, whereupon the subject continues in the study after completion of the liver chemistry monitoring. See Section IIIc of Appendix 3 for drug restart/rechallenge process.

In addition, for subjects meeting liver stopping criterion 1:

- Make every reasonable attempt to have subjects return to clinic **within 24 hours** for repeat liver chemistries, liver event follow-up assessments (refer to Section IIIa of Appendix 3), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

~~For subjects meeting criteria 2-5:~~

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

Section 14.3.1

~~Section 14.3.1.IIIa.Liver Event Follow Up AssessmentsSafety Stopping Criteria and Required Actions and Follow Up Assessments~~

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Table 28 Phase I/II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN **and** cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained approximately 48h after last dose[5] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN

• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** (refer to Appendix7) • If restart/rechallenge is **not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments **MONITORING:** **For bilirubin or INR criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For All other criteria:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	• Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications • Record alcohol use on the liver event alcohol intake case report form **For bilirubin or INR criteria:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct high pressure liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN and INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study

treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Table 29 Phase I/II Oncology liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, **without** symptoms believed to be related to liver injury or hypersensitivity **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline[1] • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

1. For the purpose of these guidelines "baseline" refers to laboratory assessments performed closest and prior to first dose of study treatment

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

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

- ~~Viral hepatitis serology including:~~
  - ~~Hepatitis A Immunoglobulin M (IgM) antibody~~
  - ~~Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM)~~
  - ~~Hepatitis C RNA~~
  - ~~Cytomegalovirus IgM antibody~~
  - ~~Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)~~

- ~~Hepatitis E IgM antibody.~~

- ~~Blood sample for pharmacokinetic (PK) analysis, obtained within 2 days of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.~~

- ~~Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).~~

- ~~Fractionate bilirubin, if total bilirubin ≥2xULN.~~

- ~~Obtain complete blood count with differential to assess eosinophilia.~~

- ~~Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE form.~~

- ~~Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the Concomitant Medications CRF page.J~~

- ~~Record alcohol use on the Liver Event CRF page.~~

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

- ~~Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins)~~

- ~~Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).~~

- ~~Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody~~

- ~~Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease. The Liver Imaging and/or Liver Biopsy CRF pages are also to be completed if these tests are performed.~~

~~IIIb.Liver Chemistry Monitoring Criteria~~

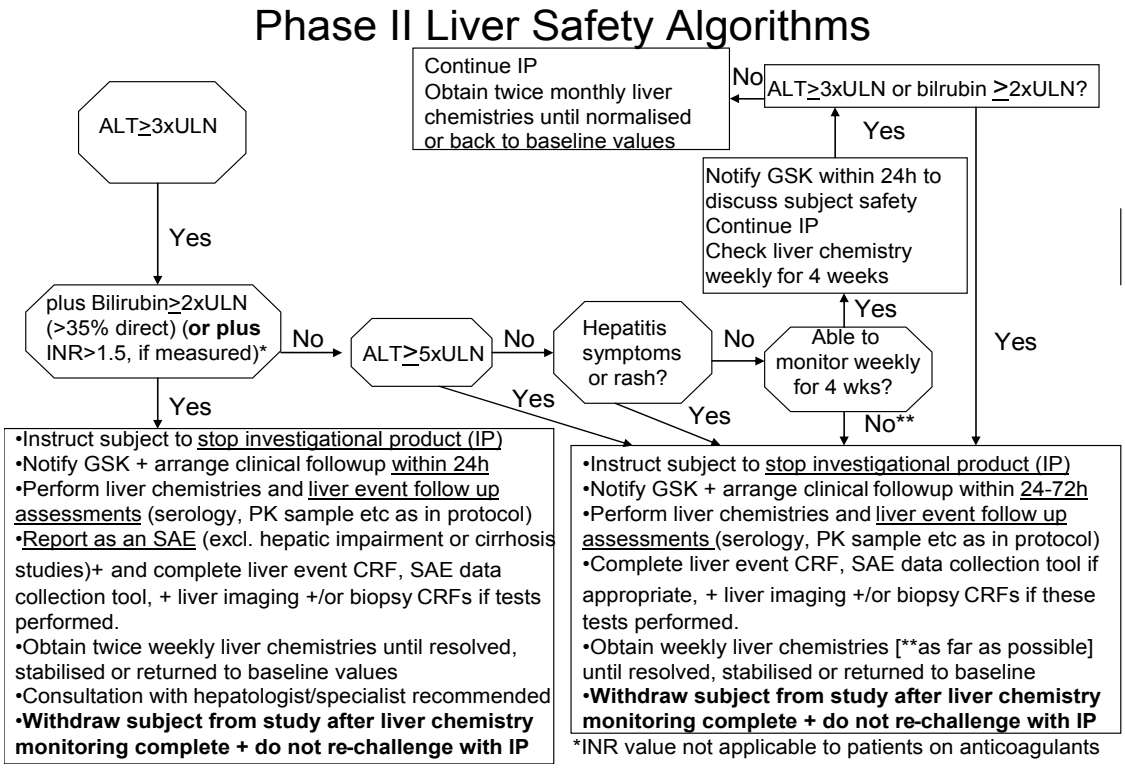
~~For subjects with ALT ≥3xULN **but** <5xULN **and** bilirubin <2xULN, without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks, the following actions should be taken:~~

- ~~Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety~~

- ~~Subject can continue study treatment if liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) can be monitored weekly for up to 4 weeks~~
- ~~If at any point these subjects meet the liver chemistry stopping criteria, immediately withdraw study treatment, perform additional testing and continue safety follow-up until liver chemistries resolve, stabilize or return to baseline values~~
- ~~If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.~~

~~Refer to Figure 7 for the algorithm of liver chemistry monitoring, stopping and follow up criteria.~~

~~Figure 7 Liver Safety Algorithms~~



14.3.2 ~~IIIc.~~Liver Safety Drug Restart Guidelines

If subject meets liver chemistry stopping criteria do not restart/rechallenge subject with study treatment unless:

- GSK Medical Governance approval **is granted** (as described below),
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the subject

If GSK Medical Governance approval to restart/rechallenge subject with study treatment **is not granted**, then subject must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments

14.3.2.1 Rechallenge Following Liver Stopping Events that are Possibly Related to Study Treatment

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andarde, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andarde, 2009]
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- subject currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a subject for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by GSK for rechallenge with study treatment can be considered where:

- Investigator requests consideration of rechallenge with study treatment for a subject who is receiving compelling benefit with study treatment that exceeds risk, and no effective alternative therapy is available.
- Ethics Committee or Institutional Review Board approval for rechallenge with study treatment must be obtained, as required.
- If the rechallenge is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the rechallenge with study treatment. Documentation of informed consent must be recorded in the study chart.

- Study treatment must be administered at the dose specified by GSK.
- Subjects approved by GSK Medical Governance for rechallenge with study treatment must return to the clinic twice a week for liver chemistry tests until stable liver chemistries have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, subject meets protocol-defined liver chemistry stopping criteria, study treatment should be permanently discontinued.
- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 6.9..

14.3.2.2. Restart Following Transient Resolving Liver Stopping Events NOT Related to Study Treatment

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by GSK for study treatment restart can be considered where:

- Investigator requests consideration for study treatment restart if liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <3xULN).
- Restart risk factors (e.g. fever, rash, eosinophilia, or hypersensitivity, alcoholic hepatitis, possible study treatment-induced liver injury or study treatment has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate) are reviewed and excluded
- Ethics Committee or Institutional Review Board approval of study treatment restart must be obtained, as required.
- If restart of study treatment is approved by GSK Medical Governance in writing, the subject must be provided with a clear description of the possible benefits and risks of study treatment administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study treatment restart. Documentation of informed consent must be recorded in the study chart.
- Study treatment must be administered at the dose specified by GSK.

- Subjects approved by GSK Medical Governance for restarting study treatment must return to the clinic once a week for liver chemistry tests until stable liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol.

- If after study treatment re-start, subject meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.

- Medical Monitor, and the Ethics Committee or Institutional Review Board as required, must be informed of the subject's outcome following study treatment restart.

- GSK, or designee, to be notified of any adverse events, as per Section 6.9.

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Saf.* 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. *Hepatol.* 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, et al. Drug-induced liver injury following positive drug rechallenge. *Regul Tox Pharm*. 2009;54:84-90.

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

~~Background Information on Drug Restart/Rechallenge~~

~~Following drug-induced liver injury,~~ **~~drug restart or rechallenge is associated with a 13% mortality across all drugs in prospective studies~~** ~~(Expert Opin Drug Saf 2009;8:709-714). Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity[1] with initial liver injury (e.g. fever, rash, eosinophilia), jaundice or bilirubin>2xULN or INR>1.5 suggesting severe liver injury, prior IP-related severe or fatal drug restart/rechallenge (Papay, 2009; Hunt, 2010) or evidence of drug-related preclinical liability / mitochondrial impairment (Hunt, 2010).~~

Drug Restart/Rechallenge Process (also see Figure8)

Principal Investigator (PI) requests consideration of drug restart for a subject receiving compelling benefit from a critical or life-saving drug, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment.

GSK Medical Monitor & Clinical Safety Physician to review the subject's restart/rechallenge risk factors & complete checklist (See Table below).

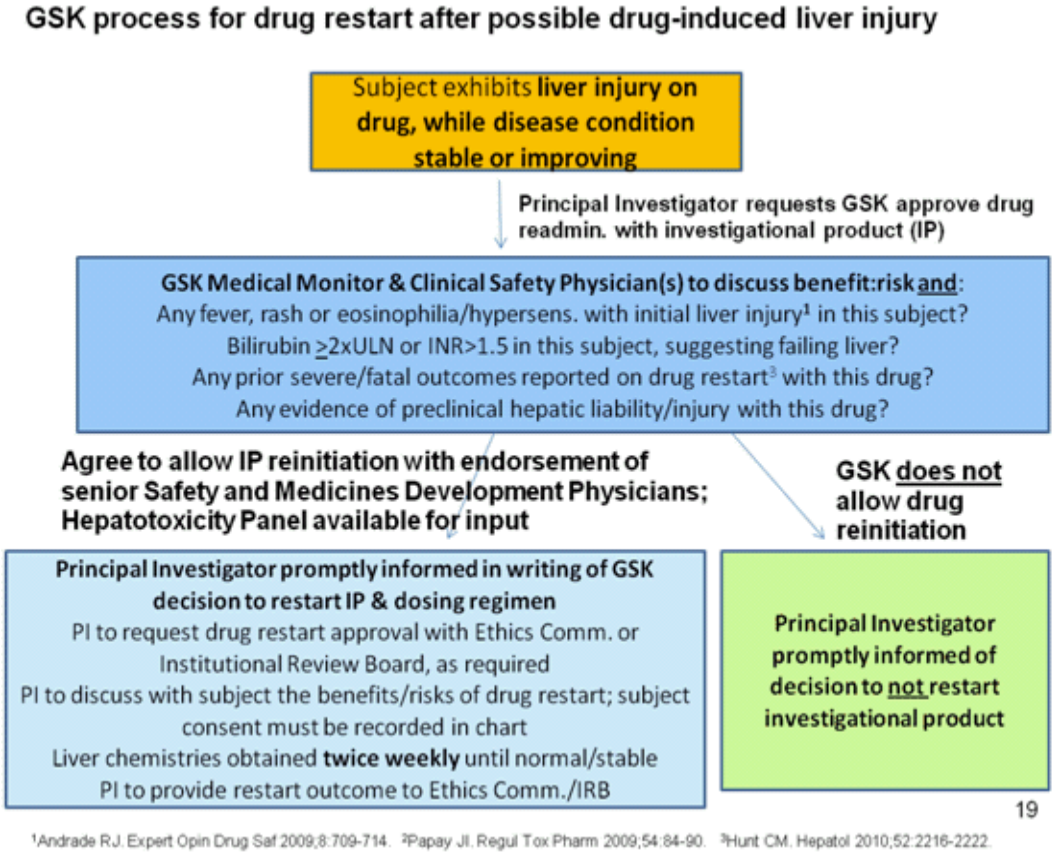
Checklist for drug restart/rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)		
	Yes	**No**
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**.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

If GSK provides written approval for restart/rechallenge following the above review, the Principal Investigator (PI) must ensure the following:

- The PI is to obtain Ethics Committee or Institutional Review Board review of drug reinitiation, as required.
- PI must discuss the possible benefits and risks of drug reinitiation with the subject.
- The subject must sign informed consent with a clear description of possible benefits and risks of drug administration, including recurrent liver injury or death. Consent specifically for the IP restart must be recorded in the study chart.

- ~~The drug must be reinitiated at GSK-approved dose(s).~~
- ~~Subjects approved by GSK for restart of IP must return to the clinic twice a week for liver chemistry tests until stable, liver chemistries have been demonstrated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.~~
- ~~The Ethics Committee or Institutional Review Board is to be informed of the subject's outcome, as required.~~
- ~~GSK is to be notified of any adverse events, as per Section 6.9 of the protocol.~~

~~Figure 8 Process for Drug Restart After Possible Drug-induced Liver Injury~~



Section 14.4.1. Appendix 5: RECIST 1.1

I. Efficacy Assessment

Rationale for Change: Text added to section that was previously missing for clarification.

Revised Text:

Fourth paragraph third sentence

In addition, in order to assign a response of CR in a subject with bone disease at baseline, a bone scan must be performed within the timeframe of 1 week prior to the first of images showing CR to 4 weeks after the next protocol specified assessment.

II. Guidelines for Evaluation of Disease

Non-Measurable only disease: The presence of only non-measurable lesions. ~~Note: non-measurable only disease is not allowed per protocol.~~

IIId. Evaluation of overall response

Note Bullet point 3

- The dosing schedule, dosing interruptions and design (see ~~Table 2of the protocol~~ Time and Events Tables) should be considered when assessing tumor response. Thus, subjects with PD before the Week 9 visit~~8~~, but without rapid clinical deterioration, may continue planned dosing schedule to allow detection of antitumor response. It is recommended that subjects who experience investigator-determined PD at the ~~w~~Week 9 visit~~8~~, at the discretion of the investigator, may receive additional tumor assessment before the initiation of alternative anticancer therapy.

Section 14.8 is added

Rationale for Change: Added in case of use for countries participating in study.

Added Text:

14.7. Appendix 8: Country Specific Requirements

14.7.1. Investigational Product Label

14.7.2. Medical Devices Used in the Study