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 relapsed, refractory hematologic malignancies

Compound Number: GSK525762

Development Phase: I/II

Effective Date: 15-MAR-2018

Protocol Amendment Number: BET116183/09

Authors:

PPD (Biology, Epigenetics Management, USA)
PPD (Statistics, Oncology TA Group, USA)
PPD (Biotransformation and Drug Disposition, PTS, UK)
PPD (Cancer Research Epigenetics Management, USA)
PPD (Clinical Pharmacology Modeling & Simulation, USA)
PPD (Global Clinical Safety & Pharmacovigilance, USA)
PPD (Global Clinical Operational Sciences, USA)
PPD (Precision Medicine and Diagnostics, USA)
PPD (Clinical Oncology, USA)
PPD (Pathology, PTS, UK)
PPD (Global Clinical Safety & Pharmacovigilance, USA)
PPD (Global Clinical Operational Sciences, USA)
PPD (Biology, Epigenetics Management, USA)

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N159121_00	2013-MAY-20	Original
2013N159121_01	2013-AUG-15	Amendment No. 01
Country Specific Protocol Amendment: At the request of the Medicines and Healthcare products Regulatory Agency, United Kingdom, the duration of exposure on the study was revised in accordance with the Commission Directive 2005/28/EC.		
2013N159121_02	2013-OCT-15	Amendment No.: 02
At the request of the Food and Drug Administration, United Stated, the dose limiting toxicity (DLT) in Section 3.2.3 was updated to require that it must clearly be established that an event is unrelated to treatment for the event to not be considered a DLT; the stopping rules related to safety were expanded in Section 11.4.1. Additional changes include the clarification of exploratory endpoints to assess metabolites, correction of exclusion criteria number 12, and clarification of the Time and Events Table, Dietary Restrictions, and the futility analysis of Part 2.		
2013N159121_03	2014-NOV-12	Amendment No. 03
The secondary objectives of Part 1 were updated to include evaluation of the clinical activity of GSK525762 (response rate and overall survival). Additional details for twice daily (BID) dosing during dose escalation included. Eligibility criteria refined: • Clarification of eligibility for subjects with AML (Part 1 and 2). • Platelets count eligibility criteria were specified for each group of hematological malignancies separately. • Exemption of exclusion due to prior allogeneic stem cell transplant added DLT for hematological toxicities clarified and dose reduction algorithm for thrombocytopenia added. Study statistic amended for part 2 (AML expansion cohort): hypothesis and number of patients. Data from ongoing preclinical and clinical research added. Time point of collection for samples for disease and efficacy assessments refined. List of baseline assessments for each indication added. Minor clarifications, reformatting of tables and typographical errors are also addressed in this amendment.		
2013N159121_04	2015-APR-06	Amendment No. 04
An update to the QTc management guidelines and enhanced guidance for management and dose modifications for thrombocytopenia, specifically for subjects with AML, has been added. Separation of cohorts in Part 1 was included to determine MTD/RP2D separately in AML, MM, NHL cohorts. Eligibility criteria were refined to account for new platelet		

management guidelines. Eligibility regarding prior allogeneic stem cell transplant and CNS disease were simplified. Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2. PD assessments have been removed from Part 2 and tumor biopsies were added in Part 2 for translational research. The 100 mg dose strength was removed due to a change in manufacturing. Minor clarifications, reformatting of tables and typographical errors were also addressed in this amendment.		
2013N159121_05	2015-JUN-25	Amendment No. 05
Amendment 5 includes updated inclusion criteria and guidance on contraception use based on emerging data from embryo-fetal development preclinical studies of. Minor clarifications were made regarding the Echo and Holter monitoring requirements and the list of medications with risk for Torsades de Pointes and prohibited medications were updated. The AML response criteria were updated with modified Cheson 2003 guidelines. Futhermore, the dosing schedule was updated to a continuous daily dosing schedule. Finally, after an internal QTc analysis and evaluation of cardiac safety data collected from all subjects in the BET115521 study up to and including the 100mg QD cohort available by 15 May 2015, the 48-hour telemetry requirement has been removed for all parts of the study and the frequency of Holter Monitoring was decreased in Part 1. Minor clarifications, reformatting of tables and typographical errors were also addressed in this amendment.		
2013N159121_06	2015-JUL-08	Re-published Amendment No. 05
Protocol amendment 5 was re-published to correct an error in the first sentence of the Revision Chronology, dated 2015-JUN-25. The text has been revised to: Amendment 5 includes updated inclusion criteria and guidance on contraception use based on emerging data from preclinical studies of embryo-fetal development.		
2013N159121_07	2016-MAR-15	Amendment No. 06
Amendment 6 includes an update to introduce the crystalline besylate formulation within Part 1 and Part 2 of the study. The meals and dietary restrictions for the crystalline besylate formulation were added. Minor clarifications, reformatting of tables and typographical errors were also addressed in this amendment.		
2013N159121_08	2016-JUN-23	Amendment No. 07
Study design was amended to include collection of additional safety data of GSK525762 BID dosing (exploratory cohort) after determination of maximum tolerated dose with QD dose and to evaluate the preliminary efficacy of GSK525762 BID dosing. The secondary objectives of Part 1 were updated to include evaluation of clinical efficacy of GSK525762 (overall response rate). The endpoints for secondary objective of Part 2 (determination of clinical activity of GSK525762) was updated to include TTP, DOR, PFS for MM and NHL. Eligibility criteria were clarified for MM and NHL for both Part 1 and 2. Risk associated with drug interaction was updated. Permanent discontinuation from study treatment section was updated. Time and events tables were also updated in		

line with study design modifications. Whole section of urine collection was removed. Tables of cautionary medications, prohibited medications and drugs affecting PK of GSK525762 were updated. Interim analysis was included for part 1. Minor clarifications, formatting and typographical errors were also addressed in this amendment.		
2013N159121_09	2017-FEB-14	Amendment No. 8
The study population for the AML cohort in Part 2 was amended from a population of subjects with AML to a population of subjects with relapsed or refractory myelodysplastic syndrome (MDS) or hypoproliferative AML that has arisen from an antecedent MDS. The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new population. The safety assessments were updated to be in line with the Investigator Brochure. The dose limiting toxicity criteria were modified to remove the specific criteria for leukemia. The time and events tables were updated to reduce the cardiac monitoring (ecg, holter and troponin), remove mRNA and cytokine collection, add a Pain Assessment, addition of an exploratory translational research blood draw and to add Factor VII assay collection. The disease related events/outcomes section was removed and the pregnancy reporting timeframe was reduced to 24 hours. Fever was removed from the dose adjusting/stopping safety criteria. Aspirin and non-steroidal-anti-inflammatory drugs (NSAIDs) were added to the Cautionary medications. Response Criteria for MDS was added as an Appendix. Minor clarifications, formatting and typographical errors were also addressed in this amendment.		
2013N159121_10	2018-MAR-15	Amendment No. 9
The study population for the NHL cohort in Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL). The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2. Eligibility criteria for all populations were updated (ECOG, cardiac safety). The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile, and BID dosing was removed. Medications affecting QT prolongation were re-categorized from prohibited to cautionary. Liver chemistry monitoring, interruption stopping and follow-up criteria were updated as per latest criteria. Response Criteria for CTCL was added as an Appendix, and a QOL questionnaire (SKINDEX-29) was added. Minor clarifications, formatting and typographical errors were also addressed in this amendment.		

SPONSOR SIGNATORY

PPD

15 Mar 2018

Li Yan, MD, PhD Date

Vice President, Head Unit Physician

Oncology R&D

PPD

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

Medical Monitor and Sponsor Contact Information:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD MD, PhD	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD, MD, PhD	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Sponsor Registered Address:

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

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

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) # IND119332

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number BET116183

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

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

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

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF TABLES

PAGE

LIST OF FIGURES

PAGE

LIST OF ABBREVIATIONS

1,5 AG	1,5-Anhydroglucitol
ACLS	Advanced Cardiac Life Support
AE	Adverse Event
ALC	Absolute lymphocyte count
ALL	Acute Lymphoblastic Leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (SGPT)
AML	Acute Myeloid Leukemia
AMM	Agnogenic Myeloid Metaplasia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BAL	Bronchoalveolar lavage
BCL	B-Cell Leukemia
BCRP	Breast Cancer Resistance Protein
BET	Bromodomain and extra-terminal
BID	Bis in die - Twice daily
BM	Bone marrow
BNP	B-type Natriuretic Peptide
BP	Blood pressure
BQL	Below the quantitative limit
BRD	Bromodomain
Cav	Average observed concentration
CBC	Complete blood count
CD4	Cluster of differentiation
CK	Creatine kinase
CKD-Epi	Chronic Kidney Disease Epidemiology Collaborative
CK-MB	Creatine kinase-MB (isozyme)
CL	Clearance
CL/F	Apparent clearance following oral administration
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CML	Chronic Myeloid Leukemia
CML-BP	Chronic Myelogenous Leukemia in Blast Phase
CMML	Chronic MyeloMonocytic Leukaemia
CNS	Central nervous system
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine phosphokinase

CPMS	Clinical Pharmacokinetics Modelling & Simulation
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRp	As per CR but platelet count <100 x 109/L
CRP	C reactive protein
CRu	Complete Response/Unconfirmed
CT	Computerized Tomography
CTCL	Cutaneous T cell lymphoma
Cτ	Pre-dose (trough) concentration at the end of a dosing interval
D	Day
DBP	Diastolic blood pressure
DHEA	Dehydroepiandrosterone
DHL	Double hit lymphoma
DILI	Drug induced liver injury
dL	Deciliter
DLBCL	Diffuse large B cell lymphoma
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organization of Research and Treatment of Cancer
EOT	End of treatment
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FLC	Free light chain (assay)
FLIPI	Follicular Lymphoma International Prognostic Index
FSH	Follicle Stimulating Hormone
Fu	Fraction unbound
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMCSF	Granulocyte-macrophage colony-stimulating factor
GSK	GlaxoSmithKline
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol

HepC	Hepatitis C
hERG	Human ether à go-go-related gene (encoding the alpha subunit of the potassium ion channel Kv11.1)
HIV	Human Immunodeficiency Virus
HNSTD	Highest non-severely toxic dose
hr	Hour(s)
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
Ig	Immunoglobulin
IL	Interleukin
IMWG	International Myeloma Working Group
IND	Investigational New Drug
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
ISCL	International Society for Cutaneous Lymphomas
ISS	International Staging System
IUD	Intrauterine device
IUS	Intrauterine system
IVRS	Interactive voice response system
Kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	Mycosis fungoides
µL	Microliter
mg	Milligrams
Mins	Minute(s)
mL	Milliliter
MLL	Mixed-Lineage, Leukemia
MM	Multiple Myeloma
mmHg	Millimeter of mercury
mmol	Millimole
MPN	Myeloproliferative neoplasms
MR	Minimal Response
MRI	Magnetic Resonance Imaging

mRNA	Messenger Ribonucleic acid
MSDS	Material Safety Data Sheet
msec	Milliseconds
mSWAT	Modified severity weighted assessment tool
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
N-CRM	Neuenschwander continual reassessment method
NHL	Non-Hodgkin's Lymphoma
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NT-proBNP	N-terminal pro–B-Type natriuretic peptide
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
ORR	Overall Response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
pcALCL	Primary cutaneous anaplastic large cell lymphoma
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression Free Survival
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PI	Primary Investigator
PK	Pharmacokinetic
PR	Partial response
PS	Performance status
PT	Prothrombin time/ Preferred (coded) term
PTT	Partial thromboplastin time
QD	quaque die - Once daily
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
Ro	Observed accumulation ratio
RP2D	Recommended Part 2 Dose
RR	Time interval from the onset of one QRS complex to the onset of the next QRS complex
SAE	Serious adverse event(s)
SBP	Systolic blood pressure
SCLC	Small cell lung cancer
sCR	Stringent complete response

SCR	Screening Visit
SD	Stable disease/ Standard deviation
SOC	System Organ Class
SPD	Sum of products of the diameters
SPEP	Serum protein electrophoresis
SPM	Study Procedures Manual
SRT	Safety Review Team
SS	Sézary syndrome
STD 10	10% mortality over the duration of the study
T0	Time of transplant
t1/2	Apparent terminal half-life
Tmax	Time of maximum concentration
TNF	Tumor Necrosis Factor
TNMB	Tumor-node-metastasis-blood
TSH	Thyroid stimulating hormone
TTP	Time to Progression
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
USA	United States
V/F	Volume of distribution
VGPR	Very good partial response
W	Week
WBC	White blood cells
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

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 relapsed, refractory hematologic malignancies
- **PROTOCOL NO.:** BET116183
- **U.S. IND NO.:** IND119332
- **EudraCT NO:** 2013-000445-39
- **CLINICAL PHASE:** I/II
- **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 Part 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with select relapsed refractory hematological malignancies (acute myeloid leukemia [AML], non-Hodgkin's Lymphoma [NHL] and multiple myeloma [MM]), will be enrolled in once daily (QD) cohorts until a maximum tolerated dose (MTD) is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Part 2 will explore clinical activity at the MTD or RP2D; separate expansion cohorts will be planned for myeloid malignancies (high-risk myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML] that has evolved from an antecedent MDS, hereafter referred as the "myeloid cohort"), and cutaneous T-cell lymphomas (mycosis fungoides [MF], Sézary syndrome [SS], primary cutaneous anaplastic large cell lymphoma [pcALCL], and large cell transformation of underlying MF/SS; hereafter referred as the "cutaneous T cell lymphoma [CTCL] cohort").
- **STUDY RATIONALE:** Current data from GSK525762 preclinical development indicate a potential to inhibit the BET family of bromodomain (BRD) proteins and that this inhibition may have clinical utility in the treatment of various tumors, including hematological malignancies. Relapsed and/or refractory hematological malignancies such as MDS, AML, NHL, and MM have an overall poor outlook. This is the first study of this agent to be conducted in subjects with these relapsed and/or refractory hematological malignancies with few or no conventional treatment options that could be expected to provide any lasting benefit. Dose escalation initially focused on AML, NHL (without consideration to histologic subtype), and MM, based on preclinical data. Emerging clinical data demonstrated delayed response in AML subjects, many of whom had evidence of antecedent MDS. In the NHL cohort, more robust clinical efficacy was observed in subjects with CTCL compared to other NHL subtypes. As a result of these observations, dose expansion (Part 2) was modified to evaluate MDS and CTCL instead of AML and unselected NHL, respectively.

- **OBJECTIVES AND ENDPOINTS:**

Part 1:

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) administration, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with acute myeloid leukemia (AML), multiple myeloma (MM), or non-Hodgkin's lymphoma (NHL).	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	• To evaluate clinical efficacy following QD administration in subjects with AML, MM, and NHL.	• Objective response rate (ORR), as measured by standard response criteria
	• To characterize the Pharmacokinetic (PK) of GSK525762, and relevant metabolites, as applicable, after single- and repeat-dose administration.	• PK parameters for GSK525762 and relevant metabolites, as applicable, following single- and repeat-dose administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
Exploratory	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters.	• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC, following single and repeat-dose oral administration of GSK525762)
	• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic response.	• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.

Part 1 Objectives		Part 1 Endpoints
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	• Assess objective response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.
	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical samples.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response.

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

Part 2:

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort").	• For MDS cohort: ORR (defined as the percentage of subjects achieving Complete Response [CR], marrow CR, CRp [as per CR but platelet count <100 x 10^9/L], CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR],) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in CTCL	• For CTCL: ORR4; defined as the percentage of subjects that have achieved a CR or PR, per global response criteria and the modified severity weighted assessment tool (mSWAT), lasting more than 4 months
Secondary	• To evaluate the effect of GSK525762 on disease-related symptoms, as reported by subjects (CTCL cohort only)	• For CTCL: measure the effects of skin disease based on quality of life questionaire Skindex-29
	• To characterize the PK of GSK525762, and relevant metabolites, as applicable, in 2 disease-specific cohorts of subjects with MDS/AML, or CTCL after repeat-dose administration.	• Population PK parameters for GSK525762, and relevant metabolites, as applicable, such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the safety and tolerability of RP2D of GSK525762 in 2 disease-specific cohorts of subjects with	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory

Part 2 Objectives		Part 2 Endpoints
	MDS/AML, or CTCL.	parameters, vital signs, and cardiac parameters) at RP2D.
	• To determine the clinical activity of GSK525762 in 2 disease-specific cohorts of subjects with MDS/AML, or CTCL.	• Duration of response (DOR, time from onset of response to earlier date of disease progression or death due to any cause) for MDS/AML and CTCL • Progression free survival (PFS, time from the treatment start date to earlier date of disease progression or death due to any cause) for MDS/AMLand CTCL. • Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML, and CTCL
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical samples.
	• To evaluate the exposure response relationship between GSK525762 and safety/efficacy parameters in 2 disease-specific cohorts of subjects with MDS/AML, or CTCL.	• Relationship between GSK525762 exposure markers and safety and efficacy parameters.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response; Leukemic Stem Cell studies; PDX model studies and other translational medicine studies.

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • Myelodysplastic syndrome and transformed MDS: A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with MDS/AML. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.30, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • CTCL: A response rate, lasting more than 4 months, of 40% relative to a 20% response rate suggesting no activity in subjects with CTCL. This will be conducted by testing the null hypothesis that P0≤0.20 versus the alternative that P1≥0.40, assuming the maximum response rate for an ineffective drug is 0.20 and the minimum response rate for an effective drug is 0.40.

- **STUDY DURATION:** Duration of study will depend on recruitment rates, and timing of subjects' duration on study (withdrawal rates due to toxicity or progression).

- **SUBJECT SAMPLE:** Up to 138 subjects worldwide

- **INCLUSION/EXCLUSION CRITERIA:**

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 and after consultation with GlaxoSmithKline (GSK):

1. Written informed consent provided.
2. Males and females 18 years old or older.
3. Subjects must have a diagnosis of one of the following hematologic malignancies, which has relapsed or been refractory to treatment as follows:
    - (Part 1 only): Subjects with AML are eligible if they
        - have relapsed and/or refractory disease, *OR*
        - are ≥65 years of age and not candidates for or have refused standard chemotherapy.
    - (Part 2 only): Subjects with MDS/AML (myeloid cohort) are eligible if they:
        - Have high-risk (defined as intermediate [INT]-2 or higher by International Prognostic Scoring System [IPSS] criteria, or high/very high by IPSS-Revised [IPSS-R] criteria) MDS that has relapsed after or been refractory to prior therapy with hypomethylating agent, *OR*
        - Have AML that has arisen from an antecedent MDS (irrespective of IPSS/IPSS-R score; subjects without a documented history of antecedent MDS/ myeloproliferative neoplasms (MPN) must have AML with myelodysplasia-related changes or recurrent cytogenetic abnormalities per World Health Organization [WHO] criteria)
            - Subjects with secondary AML must have progressed despite, or failed to respond to, prior therapy with hypomethylating agent, *AND*
            - Subjects must have hypoproliferative disease, defined as either:
                - A peripheral white blood cell count of less than 20,000 cells/µL in the absence of leukoreducing therapy (e.g., hydroxyurea, leukapheresis), *OR*
                - At least one bone marrow biopsy obtained within 28 days of first dose of GSK525762 must demonstrate a marrow blast percentage of no more than 30%

                  Note: If marrow blasts exceed 30% on any biopsy within 28 days of first dose of GSK525762, enrolment will only be permitted after discussion with the medical monitor

- (Part 1): Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination
- (Part 1 only): Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20)
- (Part 2 only): Subjects will be eligible for enrolment into the CTCL cohort if they:
    - Have histologically- or cytology-proven diagnosis of CTCL (MF, SS, pcALCL, or large cell transformation of underlying MF/SS) that has failed to respond to, or progressed despite, at least one prior systemic therapy

4. Subjects with a prior history of stem cell transplant (autologous and/or allogeneic) are allowed if
    - At least 3 months have elapsed from the time of transplant, *and*
    - the subject has recovered from transplant-associated toxicities prior to the first dose of GSK525762*, and*
    - For subjects with a prior history of allogeneic transplant,
        - the subject has been off systemic immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids) for at least 1 month prior to the first dose of GSK525762. Topical steroids are permitted
        - there are no signs or symptoms of graft versus host disease, other than Grade 1 skin involvement
5. Eastern Cooperative Oncology Group (ECOG) performance status of:

- ≤1 for all Part 1 Cohorts (AML, MM, and NHL)
- ≤2 for all Part 2 cohorts (MDS/AML and CTCL)

6. Subject must be stable enough to be expected to complete dosing through the DLT observation period as assessed by the investigator.
7. 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.
8. 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 MlU/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 defined in protocol 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 enrolment. For most forms of HRT, at least two to four 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 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 after the last dose of study medication.
- Negative serum pregnancy test ≤7 days prior to first study drug dose.
- 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.

9. Male subjects with a female partner of childbearing potential or who is pregnant must agree to use one of the methods of contraception specified in Section 9.1. 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, male subjects whose partners are or become pregnant must use/continue to use condoms until 16 weeks after last dose of study medication.
10. Adequate organ system functions (at both screening and where applicable pre first dose) as defined in below.
11. Ability to comply with dietary and tobacco/alcohol abstinence requirements.

Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Hemoglobin (only for myeloma and lymphoma)	≥8.0 g/dL
Coagulation assays (prothrombin time/ international normalized ratio [PT/INR] and activated partial thromboplastin time [aPTT] [1]	≤1.2 X upper limit of normal (ULN)
Platelets (for subjects with lymphoma) Platelets (for subjects with MM) Platelets (for subjects with acute leukemia)	≥75,000 (transfusion independent) ≥50,000 (transfusion independent) ≥10,000 (transfusions permitted to bring platelet count to >10,000)
Hepatic	
Total bilirubin	≤1.5 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)
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	≤2.5 X ULN
Renal	
Creatinine[3] OR Calculated creatinine clearance [calculated by Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method [2, 3]] OR 24-hour urine creatinine clearance [3]	≤1.5 X ULN ≥50 mL/min ≥50 mL/min
Cardiac	
Ejection fraction	≥Lower limit of normal (LLN) by echocardiogram (ECHO) (minimum of 50%) or Multi Gated Acquisition (MUGA) scan
Troponin (T)	≤ULN
Thyroid	
Thyroid stimulating hormone (TSH) [4]	≥LLN and ≤ULN

1. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2
2. For MM subjects, adequate renal function is defined as serum creatinine ≤2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ≥30 mL/min
3. If TSH is abnormal but free T3 and or Free T4 are normal, then the subject can be enrolled.

Exclusion Criteria

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

1. Haematological malignancy associated with human immunodeficiency virus (HIV) infection or solid organ transplant or positive Hepatitis B Antigen or positive Hepatitis C antibody at screening or within 3 months prior to first dose (subjects with positive Hepatitis C antibody may be enrolled, provided that the confirmatory test [e.g., Hepatitis C Virus [HCV] Ribonucleic acid [RNA] polymerase chain reaction [PCR] is negative).
2. History or concurrent malignancy of solid tumours, except for below.

   Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible. Subjects with second malignancies that are indolent or definitively treated may be enrolled even if less than 5 years have elapsed since treatment. Consult the GSK Medical Monitor if unsure whether second malignancies meet requirements specified above.

3. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization).

   Note: the following are allowed:

   Hydroxyurea for proliferative disease

   Corticosteroids (topical and/or systemic)

   Use of hematopoetic growth factors is permitted at the discretion of the investigator according to published guidelines (e.g., National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), etc.).

   Note: the following are NOT allowed:

   Investigational anti-cancer drug within 2 weeks prior to the first dose of GSK525762.

   Major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK525762.

   Chemotherapy regimens with delayed toxicity within the last 4 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.

   Nitrosourea or mitomycin C within the last 6 weeks.

4. Evidence of severe or uncontrolled infection.
5. Use of anticoagulants (e.g., warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of GSK525762. Low dose (prophylactic) anticoagulants (e.g., low molecular weight heparin (LMWH) or oral anticoagulants) is permitted.

In addition, INR must be monitored in accordance with local institutional practices, as appropriate.

6. Current use of a prohibited medication or planned use of a prohibited medication during treatment with GSK525762.
7. 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.
8. Symptomatic or untreated central nervous system (CNS) disease,
   - Subjects with a history of CNS disease (leukemia, lymphoma or myeloma) are permitted to enrol if they have previously received appropriate therapy and CNS remission has been documented.
   - Subject with primary CNS lymphoma (defined as isolated CNS lymphoma without systemic involvement) are excluded from study.
9. Cardiac abnormalities as evidenced by any of the following:
   - History or current clinically significant conduction abnormalities, uncontrolled arrhythmias or hypertension.
   - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA).
   - Recent history (within the past 3 months) of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting.
10. Any of the following electrocardiogram (ECG) findings or assessments including:
    - Baseline QTcF interval ≥480 msec.
    - Clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
11. 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.
12. Evidence of hemoptysis within the last 7 days.
13. History of major gastrointestinal bleeding within the last 3 months or any evidence of active gastrointestinal bleeding.
14. Presence of gastrointestinal disease that would significantly affect compound absorption.

- **DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**: Starting dose will be 5 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 e.g. intermittent dosing may be required to manage toxicities and may be considered based on investigator assessment and after consultation with GSK without requiring a protocol amendment.
- **PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS**: There will be serial blood sampling for PK and pharmacodynamics (in some subjects) measurements in Part 1 of this study and more limited PK sampling in Part 2 of this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. In addition, pre-treatment and post-treatment tumor tissue samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.
- **EFFICACY MEASUREMENTS**: ORR, PFS and OS in AML, MDS, MM, and CTCL; time to progression (TTP) and duration of response in MM and CTCL. Rate of objective response lasting at least 4 months (ORR4) in CTCL
- **SAFETY MEASUREMENTS**: Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events will be performed. Cardiac safety monitoring will be required, consisting of 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). Laboratory testing includes, in addition to standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels, testing for troponin, N-terminal prohormone B-type Natriuretic Peptide (NT pro-BNP), c-peptide, 1,5-Anhydroglucitol (1, 5 AG), Hemoglobin A1c (HbA1c), and thyroid monitoring. Additional safety assessments may be necessary based on emerging data.
- **STATISICAL 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; details will be included in the Reporting Analysis Plan (RAP). Part 2 of the study is designed to evaluate preliminary efficacy. Futility assessment will be conducted on an ongoing basis, starting with a minimum of 10 treated subjects assessed for response. The assessments are based on the predictive probability of success if the enrolment continues to the maximum of 32 subjects in the MDS cohort and 37 subjects in the CTCL cohort respectively. Subjects enrolled in Part 1, at the Part 2 dose, for diseases under study in Part 2, will be included in Part 2 analysis.

1. INTRODUCTION

1.1. Background

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 facilitates the localisation of transcriptional complexes to specific genes, thereby regulating epigenetically controlled processes including gene transcription and Messenger Ribonucleic acid (mRNA) elongation. The BRD and extra-terminal (BET) family of BRD proteins includes the BRD2, BRD3, BRD4 and BRDT [testes] proteins.

The investigational agent GSK525762 is a potent inhibitor of the BET family of proteins and prevents the binding required for macromolecular complex assembly and the subsequent transcriptional response [Nicodeme, 2010].

GSK525762 inhibits growth in a broad spectrum of human hematological cancer cell lines and solid cancer cell lines. In cell line sensitivity studies, GSK525762 consistently exhibits broad anti-proliferative activity and induces cytotoxicity in the majority of these tumour derived cell lines including Acute Myeloid Leukemia (AML), Chronic Myeloid Leukemia (CML), Acute Lymphoblastic Leukemia (ALL), B- Cell Leukemia (BCL), Multiple Myeloma (MM), and non-Hodgkin's Lymphoma (NHL). GSK525762 is orally active *in vivo* in both solid and haematological xenograft tumour models of disease, and exhibits tumour growth inhibition and a significant survival advantage compared to vehicle treated animals in a MM mouse model [GSK525762 IB, GlaxoSmithKline Document Number 2011N113741_06].

Recent published data studying another BET inhibitor [Dawson, 2011] have also shown therapeutic promise in pre-clinical models of hematologic malignancies and further support extending clinical evaluation of this novel therapeutic agent in a broad spectrum of hematological malignancies.

Parallel to study BET116183, GSK525762 is being investigated in solid tumors (GlaxoSmithKline [GSK] Study BET115521, NCT# NCT01587703)

1.2. Study Population Rationale

Myelodysplastic syndromes (MDS) and AML are related neoplasms of myeloid cells characterized by an excess of immature myeloblasts in the bone marrow, as well as ineffective hematopoiesis leading to peripheral cytopenias. MDS and AML exist along a spectrum defined by the percentage of marrow blasts, with > 20% delineating the boundary between the two diseases. While AML may arise *de novo,* it may also evolve from an antecedent myelodysplasia or myeloproliferative syndrome. Both AML and MDS are increasingly defined by genetic characteristics, with cytogenetic abnormalities and mutations in genes involved in RNA splicing and epigenetic regulation frequently observed in MDS as well as AML that transformed from MDS. The only approved therapies for MDS are the hypomethylating agents 5-azacitidine and decitabine; these agents are frequently used in patients with AML who are not suitable candidates for aggressive induction chemotherapy (e.g., as a consequence of advanced age or other

comorbidity). To date, there are no second-line agents for subjects who did not respond to or who have progressed despite hypomethylating agent therapy, and overall survival for patients who have failed prior therapy is typically measured in months (Prebet, 2011; Sekeres, 2014; Jabbour, 2010).

Non-Hodgkin's lymphomas are a family of more than sixty malignancies arising from abnormal lymphoid, histiocytoid, or dendritic cell development (Swerdlow, 2016). They constitute a spectrum of diseases that may be focal or systemic, indolent or aggressive, based on the underlying cell of origin and other biological factors. Therapy is customized for each patient based on the disease subtype and location and typically involves radiation, systemic therapy, or both. Recently, targeted systemic therapies have emerged and have been approved based on promising response data. However, NHL is an incurable disease for most patients and thus new approaches are necessary in the face of inexorable progression and relapse.

Cutaneous T-cell lymphomas are a family of NHLs characterized by skin infiltration by cluster of differentiation 4 (CD4)-positive T-cells. These diseases are characterized by erythroderma and/or tumor-phase growths on the skin, as well as intense pruritis as a consequence of upregulation of multiple pro-inflammatory cytokines [Ahern, 2012]. Targeted systemic therapies remain the cornerstone of treatment for many patients, including those with limited-stage disease, both to control the disease itself as well as to reduce the overall symptomatic burden [Whittaker, 2016]. Recently, a role for BRD4 in the expression of lymphoma-associated genes has been demonstrated (Kohnken, 2017), making BET inhibition a rational approach for treatment of cutaneous T cell lymphoma (CTCL).

Multiple myeloma is a neoplastic proliferation of plasma cells. In almost all cases, myeloma is incurable; though novel therapies have emerged in the past decade and a half, most patients with multiple myeloma will die from their disease. Thus, new therapies are necessary.

Relapsed and/or refractory hematological malignancies such as AML, MDS, NHL, and MM have an overall poor outlook. These subjects are appropriate for clinical trials with new agents such as the BET inhibitor GSK525762. Preclinical studies have shown that small molecule based inhibition of BET protein binding to chromatin downregulates oncogene expression (e.g., down regulation of MYC oncogene expression and its downstream transcriptional functions) in several hematological cancer cell lines. This down regulation results in significant anti-tumour activity both *in vitro* and in animal models of disease [Delmore, 2011; Mertz, 2011]. Down-regulation of c-Myc protein expression has been reported upon exposure to GSK525762 in MM MM1S cells [Delmore, 2011], Burkitt's Lymphoma Raji cells and LP-1 myeloma cells [Mertz, 2011].

Consistent with the published literature, GSK525762 inhibits proliferation and induces a cytotoxic response in cell lines across a wide range of hematological tumour types (Table 1).

Table 1 Hematological cancer cell line sensitivity to GSK525762, 3-day growth-death assay

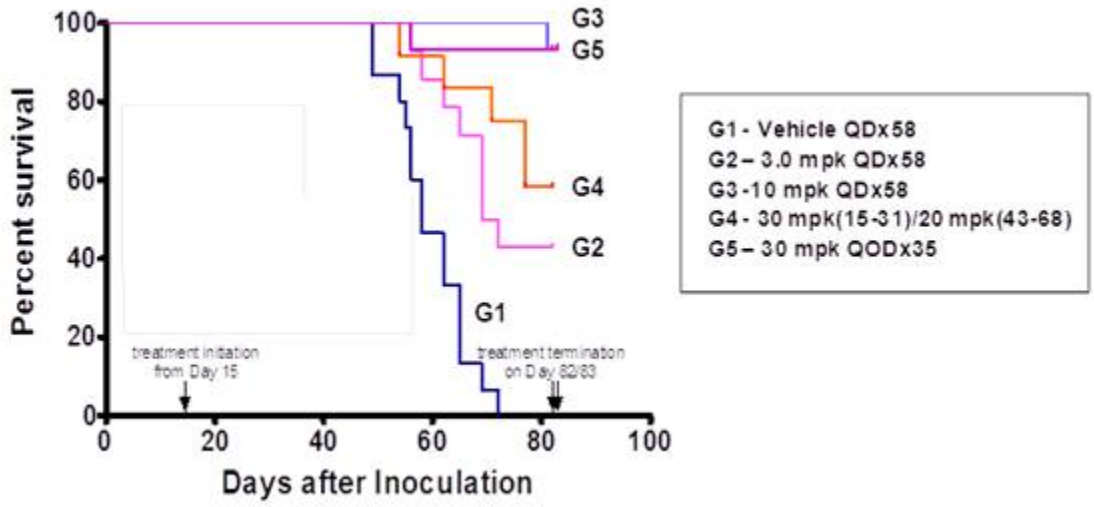
Cell Line Tumor Type	% Sensitive Lines[a]	Total Lines Tested	Median gIC_{50} (µM)
ALL	100	4	0.29
AML	96	25	0.10
Burkitt	50	8	1.2
CML	100	4	0.32
CTCL	100	3	0.22
DLBCL	90	29	0.17
Erythroleukemia	100	2	0.38
FL	100	4	0.06
MCL	80	5	0.80
MM	100	12	0.06

a. Cell lines defined as sensitive to GSK525762 if the gIC_{50} <1.0 µM.

Abbreviations: ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; CML = Chronic myeloid leukemia; CTCL = Cutaneous T cell lymphoma; DLBCL = Diffuse large B cell lymphoma; FL = Follicular lymphoma; gIC_{50} = Growth IC_{50}, 6-day assay; MCL = Mantle cell lymphoma; MM = Multiple myeloma.

Ninety-one percent of hematological cancer cell lines tested (87/96) are sensitive to GSK525762, exhibiting growth IC50 (gIC50) values below 1.0µM. Some of the most sensitive hematological cancer cell types include FL (median gIC50= 60 nM), MM (median gIC50= 60 nM), AML (median gIC50= 100 nM), and DLBCL (median gIC50= 170 nM). Additionally, oral dosing of GSK525762 results in tumour growth inhibition and improved survival in a myeloma mouse xenograft model (OPM-2) of disease (Figure 1). Consistent with published reports, down-regulation of c-Myc protein expression was observed in OPM-2 xenografts following a single dose of GSK525762 or daily administration for up to 11 days.

Figure 1 Survival of Multiple Myeloma (OPM-2) bearing mice



These preclinical data highlight the potential of GSK525762 to provide benefit to subjects with relapsed and/or refractory hematological malignancies where significant unmet need still exists [GSK525762 IB, GlaxoSmithKline Document Number 2011N113741_06].

1.3. Dose Rationale

1.3.1. QD Dose Cohort

1.3.1.1. Starting Dose Calculations

The proposed starting dose for this clinical study in subjects with hematologic malignancies is 5 mg once daily (QD) based on the following, assuming a 70 kg adult with a body surface area of 1.7 m^2. The dose of 5 mg daily was based on preclinical considerations described Section 1.3.1.1.1, preliminary human pharmacokinetics (PK; Section 1.3.1.1.2), clinical consideration including the aggressive nature of the relapsed and/or refractory tumor (Section 1.3.1.1.3), and the desire to minimise sub-therapeutic exposures. This starting dose is different from the ongoing solid tumor study (GSK Study BET115521, NCT# NCT01587703) in which the starting dose was 2 mg daily (see Section 1.3.1.1.3).

1.3.1.1.1. Preclinical Considerations

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

1. One tenth of the rat STD (Severely Toxic Dose) 10 as per International Conference on Harmonization (ICH) S9 guidance (based on dose):
   a. Based on the observed morbidity levels in the 30 mg/kg dose group following 1 month of dosing, the Rat STD10 was defined as 30 mg/kg. One tenth of the rat STD10 as per the ICH S9 guidance is 18 mg/m^2 (this dose is also not severely toxic to dogs) which results in a starting human dose of 30 mg daily.
   b. Assuming that 30 mg/kg may not be tolerated for dosing periods greater than 1 month without significant morbidity, a conservative Rat STD10 was defined as 10 mg/kg. One tenth of the rat STD10 is 6 mg/m^2 (this dose is also not severely toxic to dogs) which results in a starting human dose of 10.2 mg daily.
2. One sixth of the dog Highest Non Severely Toxic Dose (HNSTD) as per ICH S9 guidance (based on dose):
   a. Based on tolerability, the HNSTD was defined as 1 mg/kg in the dog. One sixth of the dog HNSTD is 3.33 mg/m2 which translates to a starting dose in man of 5.7 mg.
   b. Based on feedback from the Food and Drug Administration (FDA), QTc prolongation was taken into consideration when defining the HNSTD. The revised HNSTD was defined as 0.3 mg/kg in the dog. One sixth of the dog HNSTD is 1 mg/m^2, which translates to a starting dose in man of 1.7 mg that was rounded to 2 mg, based on tablet strength.

1.3.1.1.2. Human Pharmacokinetics and Equivalent Exposure for NOEL for QTc prolongation

Average plasma systemic exposure in dogs at the repeat dose that resulted in QTc prolongation No observable effect level (NOEL) (0.3 mg/kg) was as follows: Area under concentration-time curve (AUC) - 642 ng.hr/mL total and 167 ng.hr/mL free; Maximum observed concentration (Cmax) - 80 ng/mL total and 20.8 ng/ml free (fraction unbound [Fu] in plasma is 26%). Extrapolating the free AUC to humans, the dose required for parity is given by Dose = AUC x Clearance (CL)/Fu, where Fu is fraction unbound in plasma in humans (18.6%). The average clearance observed in the 2 first subjects in BET115521 who received 2 mg was 9.7 L/hr, a value similar to the value predicted from animal data using allometric scaling. Using the above expression, the predicted starting dose would be 167 ng.hr/mL x 9.70 (L/hr)/0.186 = 8.7 mg.

Based on the Cmax observed in the two subjects who received a single 2 mg dose of GSK525762, the predicted free drug Cmax is about 50.4 ng/mL for a 8.7 mg dose. This predicted free Cmax is higher than the observed free Cmax in dogs (27.8 ng/mL) at QTc NOEL. This does not impact the proposed starting dose using exposure at the NOEL for QTc prolongation as the preclinically observed QTc prolongation is not consistent with a direct hERG blockade (i.e., free Cmax levels). Taking this into consideration, the human dose which matches the average free exposure that did not result in QTc prolongation (QTc NOEL) in the dog is 9 mg daily.

PK information obtained up to January 2017 is available in the Investigator's Brochure Section 5.2.

1.3.1.1.3. Clinical Considerations

Relapsed and/or refractory hematologic malignancies have an aggressive and rapidly progressive course and patients with leukemia are unlikely to remain stable even for 3 week for the Dose Limiting Toxicity (DLT) assessment to be done. Therefore there is a need to minimise the number of patients exposed to sub-therapeutic doses without compromising safety. The 5 mg starting dose provides adequate safety margins for toxicities that can be clinically monitored and are largely reversible (excluding testicular long-term effects on male and female reproductive function, which is being evaluated), while minimizing the number of patients with aggressive hematologic cancers exposed to predicted sub-therapeutic doses. Moreover, the starting dose of 2 mg daily in the solid tumor trial (BET115521) has been successfully cleared. Taking all the above into consideration and the extensive clinical monitoring for QT prolongation, a starting dose of 5 mg QD is planned.

1.3.1.2. Predicted therapeutic dose range

Cell lines of hematological origin were generally more sensitive than the cell lines of other solid tumor origins, namely small cell lung cancer (SCLC) and Colorectal cancer (CRC) cells. The more sensitive cell lines had growth IC50 (gIC50) values as low as 50-100 nM. The potential therapeutic dose for GSK525762 in humans was derived using available preclinical PK, data from *in vitro* cell lines of hematological origin, and efficacy data from OPM-2 multiple myeloma tumour xenograft studies. Based on

modeling, maximal efficacy of GSK525762 may require ≥50% target inhibition. The predicted human effective daily dose is likely to be in the range of 25 to 100 mg assuming 50 to 100% oral bioavailability.

1.3.2. Dose escalation steps

Human PK predictions suggest that exceeding the systemic exposure of the preclinical 4 week maximum tolerated dose (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 amenable to clinical monitoring and are largely reversible (excluding testicular effects). A stringent safety monitoring and evaluation process will be implemented and therefore semi-semi-log (≤2-fold) dose escalation above the preclinical MTD, conditional on acceptable safety and tolerability, is permitted until the clinical MTD is established.

The MTD of GSK525762 may be different for AML/MDS, NHL, and MM. To fully evaluate this, each dose escalation step will be evaluated separately for the three disease types. Parallel cohorts will commence upon termination of accelerated dose titration (Section 3.2.1.2) and follow the 3 + 3 design described in Section 3.2.1.3.

1.4. Rationale for Study and Endpoints

Safety and efficacy (Response Rate) are being assessed to address the primary objectives of the study. The safety assessments along with PK will be important for determining the MTD. The pharmacodynamic assessments will further support the recommended Phase II doses (RP2D) and expand the understanding regarding mechanism of action.

The BET116183 study has 2 parts. Part 1 is a dose finding study, which will include subjects with hematologic malignancies to determine an MTD. Part 2 is a cohort expansion, which will study the RP2D of GSK525762 to determine preliminary efficacy, safety and tolerability in three separate cohorts of subjects with myeloid neoplasms (myelodysplastic syndrome [MDS] or MDS that has transformed to AML), and CTCL.

Originally, Part 2 of the study was designed to evaluate preliminary clinical efficacy in relapsed or refractory AML, MM, and NHL. However, after an evaluation of data from the Part 1 AML cohort, the following observations prompted changes to the Part 2 cohort; clinical responses were observed at doses of 60 mg and above, these responses occurred in subjects whose disease harbored complex karyotype and recurrent mutations in TP53 and in proteins that regulate gene expression, suggesting that these subjects had an antecedent MDS that transformed to AML. Furthermore, most subjects with AML discontinued GSK525762 early in the course of their treatment as a consequence of their underlying AML or disease complications. Responses tended to be delayed (at the four week mark or later, with many requiring more than 10 weeks to manifest). Thus, most subjects were not remaining on study for long enough to achieve benefit. In order to maximize time on-study, Part 2 was updated to enroll subjects with a more slowly-progressing disease that maintained many of the clinical characteristics of the AML responses that were observed in Part 1 (i.e., MDS and MDS that has transformed to AML with a low burden of disease).

The original study design included a dose expansion in non-Hodgkin's lymphoma, enrolling subjects regardless of histological subtype. Furthermore, this cohort enrolled subjects with double- and triple-hit lymphoma (i.e., B-cell lymphomas with rearrangement and/or overexpression of myc and BCL2 and/or BCL6) in an exploratory sub-cohort. However, interim analysis of the Part 1 data demonstrated limited activity in both B-cell lymphomas in general as well as double/triple hit lymphomas. Responses, including very deep, durable responses, were achieved in subjects with CTCL and other T-cell lymphomas of the skin. Therefore, Part 2 of the study was amended to restrict enrollment to these diseases, for which emerging clinical data suggested a reasonable rate of benefit.

1.5. Benefit: Risk Assessment

The investigational agent GSK525762 is a potent inhibitor of the BET family of proteins that prevents BET binding to acetylated histone tails required for macromolecular complex assembly and the subsequent transcriptional response of many oncogenes [Nicodeme, 2010]. GSK525762 inhibits growth in a broad spectrum of human hematological and solid cancer cell lines. In cell line sensitivity studies, GSK525762 consistently exhibits broad antiproliferative activity and induces cytotoxicity in the majority of these tumor derived cell lines including AML, CML, ALL, NHL, and MM.

GSK525762 is orally active *in vivo* in both solid and hematological xenograft tumor models of disease, and exhibits tumor growth inhibition and a significant survival advantage compared to vehicle treated animals in a MM mouse model. Recent published data studying BET inhibitors [Dawson, 2011] have also shown therapeutic promise in pre-clinical animal models of hematologic malignancies. Considering the overall poor outlook of patients with relapsed and/or refractory hematological malignancy and the therapeutic promise of GSK525762, clinical evaluation of this novel therapeutic agent in a broad spectrum of hematological malignancies is justified.

1.5.1. Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK525762 can be found in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2011N113741_06]. Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK525762 are gastrointestinal, cardiovascular, pancreatic, hematologic and reproductive (see the GSK525762 IB [GlaxoSmithKline Document Number 2011N113741_06]). The following Section outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal	Gastrointestinal effects contributed to the definition of severely toxic repeat dose in both rats and dogs. 30 mg/kg (rat) and 3 mg/kg (dog). In life findings included reduced body weight gain / body weight loss, reduced food consumption, abnormal faeces. Microscopic evidence of erosions or ulcerations with inflammation in multiple locations throughout the Gastrointestinal (GI) tract. Recovery after 3 weeks off dose.	Informed Consent Form (ICF) includes the risk of gastrointestinal effects. Protocol includes medical history, physical examination (including weight) and clinical laboratory assessments to assess toxicity in the GI tract. Subjects with a history of gastrointestinal bleeding in the past 3 months (Section 4.2) or active bleeding will be excluded. Protocol also includes specific dose adjustment/stopping safety criteria for diarrhea and mucositis.
Lymphoid / Hematologic	Lymphoid / hematologic toxicity was observed in rats and dogs and the effects contributed to the definition of severely toxic repeat dose in rats (30 mg/kg). The effects manifested as hypocellularity in bone marrow, thymus, spleen and lymph nodes; decreased spleen and thymic weight; mild hemolysis; variable and inconsistent changes in white cell /lymphocyte count, multiple red blood cells parameters and reticulocyte counts. Minimal bone marrow hypocellularity was still evident in male rats previously given 30/20 mg/kg/day for 13 weeks following a 17 week off dose period. Changes relating to coagulation were evident in both rats (considered non-adverse) and dogs (considered adverse at 3 mg/kg/day). These included a reduction in platelet counts (54%) and an increase in activated partial thromboplastin time (aPTT; 1.38X). Full recovery of aPTT and a compensatory increase in platelet counts in dogs (1.27X) was evident following the 3 week off-dose period.	ICF includes the risk of lymphoid / hematologic toxicity. Protocol includes laboratory assessments (complete blood count [CBC] and coagulation factors [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], exclusion criteria if there is evidence of clinically significant bleeding episodes, monitoring for bruising/infection and dose stopping/modifications criteria. 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 the subject's PT/PTT meet entry criteria.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** (up to 20%; 41 msec in dog) Can occur or persists after drug is cleared from plasma; general trend to increase on repeat dosing; no potentiation beyond day13 in 28 day toxicology study in dogs. Reversible on cessation of dosing; not potentiated on subsequent dosing following a 7 day dosing holiday. No significant arrhythmias were detected in preclinical studies. No clear link to human ether à go-go-related gene (hERG) binding or trafficking. No evidence of heart accumulation of GSK525762. Mechanism & risk for Torsades de Pointe is unclear. A review of all available data as of November 2017 (representing 271 subjects dosed up to 100 mg in the BET115521 solid tumor study and up to 120 mg in the BET116183 heme malignancy study) demonstrated a clinically negligible effect on QT in humans. **Blood pressure (BP**) Variable changes in blood pressure following a single dose (≥1 mg/kg in dogs and 60 mg/kg in rats); no effects were observed in the 7 day repeat dose dog CV study; increase in mean BP up to 11 mmHg; decrease in mean BP up to 13 mmHg. **QA interval** (indirect measure of cardiac contractility). Decreased QA interval at single non-tolerated doses in dog (no effect seen in rats); up to 10 msec. No effects were observed in the 7 day repeat dose dog CV study; No echocardiography changes in the 28 day dog toxicology study.	Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK] and creatine kinase-MB [CK-MB]), cardiac monitoring (electrocardiograms [ECGs], and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management cardiac events. Drugs with a risk of QT prolongation must be used with caution, (refer to Section 8.2). Given the risks of long QTc associated arrhythmias, and of compound associated cardiomyopathy, subjects will be monitored closely for changes in QTc with 12-lead ECG, 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 and including 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 5 and removed in Protocol Amendment 8 following additional analysis of all available data by the cut off of 10-Jun-2016. Specific stopping criteria and management guidelines are

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		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
Cardiovascular - Troponin	Elevations in cardiac biomarkers relative to 4 week Good Laboratory Practice (GLP) toxicology study control group in: • Cardiac troponin I (up to 15X in rat and 4.7X in dog) • Cardiac troponin T (up to 8.9X in rat) • Myosin light chain III (up to 4.8X in rat) • NT-proANP (up to 1.54X in rat) Changes were reversible and there was no evidence of compound related myocardial histopathological changes in either species after up to 3 months of dosing.	Protocol includes troponin monitoring (local laboratory monitoring for troponin I or T based on availability and troponin T at central laboratory) and dose stopping/modifications criteria for the management of cardiac toxicity. .
Reproductive	GSK525762 has shown adverse degenerative effects on testes in rats, rabbits and dogs, with no observed adverse effect level (NOAEL) in rabbits. 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 has shown effects on female fertility (disrupted estrous cyclicity, delays to mating and/or reduced fertility index), embryo-fetal toxicity and embryofetal developmental (decreased fetal body weight, fetal malformations or variations and / or pre- and	ICF includes the risk of damage to reproductive organs such as testes or ovaries. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and complete) for male subjects. ICF includes the potential risk of reproductive effects. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	post-implantation loss). A NOAEL has yet to be determined. There is a substantiated risk for adverse effects on embryofetal development and impacts on female fertility.	
Pancreatic	A male rat-specific pancreatic change (islet cell fibrosis / fibroplasias and peri-islet haemorrhage, pigmented macrophages and inflammation) was observed at a dose of 30 mg/kg/day in the 4 week study only. No effects were observed in the 3 month toxicology studies. Following the 3 week off-dose period, these changes were decreased in incidence and/or severity. An unrelated pancreatic lesion (acinar cell apoptosis, vacuolation and/or degranulation) was present in female dogs given 3 mg/kg/day.	ICF includes the risk of pancreatic effects. Protocol includes laboratory assessments (glucose -serum and urine, insulin and 1,5-Anhydroglucitol (1,5-AG), c-petide, Hemoglobin A1c (HbA1c), amylase, lipase) as appropriate and monitoring for signs of gastric distress, abdominal pain, and clinical signs of malabsorption. Protocol also includes dose stopping/modifications criteria for the management of hypo/hyperglycemia.
Liver/Gallbladder	Non-adverse liver changes were observed in preclinical toxicology studies including increases in bilirubin levels and transient increases in AST in rats. Hepatocellular necrosis was observed in a single rat at a non-tolerated dose (30 mg/kg/day). 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.	ICF includes the risk of hepatic/gallbladder effects. Protocol includes hepatic eligibility criteria, laboratory assessments during the study, dose stopping/modifications criteria for the management hepatic events.
Lung effects	Aggregates of foamy macrophages in peribronchiolar 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 finding is unlikely to affect pulmonary function. No effects were observed in the 3 month toxicology studies. For more information, see the GSK 525762 IB [GlaxoSmithKline Document Number 2011N113741_06].	ICF includes the risk of lung effects.
Kidney	Eosinophilic inclusions and/or tubular basophilia were observed in the kidneys of rats in preclinical toxicology studies up to 3 months dosing. These changes were	Protocol includes renal monitoring including urinalysis (assessment for protein) and creatinine.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	considered non-adverse.	
Effect on Teeth	Effects (disruption of dentin formation) on incisors (teeth that continually grow in rodents) were evident in male rats given ≥10 mg/kg/day GSK525762 and both male and female rats at 30 mg/kg/day in the 13 week study, which resulted in pale and broken teeth during the in-life phase of the study from Week 8. These microscopic effects were lower in severity and incidence after a minimum of 3 week off dose period. No effects were observed in molar teeth (non-growing).	Unlikely to affect adults.
Drug Interactions	GSK525762 is a substrate for CYP3A4 enzymes, and for P-gp and breast cancer resistance protein (BCRP) transporters. GSK525762 clearance is virtually solely via CYP3A4. There is evidence of potential auto-induction after repeat dosing in clinical studies since reduction in parent exposures (~25% at lower doses to ≥60% at doses ≥60 mg, mainly in BET115521 study) have been observed. There is low potential for GSK525762 to inhibit cytochrome P450 (CYP) enzymes or to inhibit P-gp or BCRP based on in vitro data. GSK525762 was shown to be an inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1) and organic anion transporter 3 (OAT3) in vitro. GSK525762 was shown to be a moderate inducer of CYP3A4 in a human hepatocyte induction study.	Use of concomitant medications, herbal medicines and fruit juices that are strong or moderate CYP3A4 inhibitors or inducers should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. Potent inhibitors of breast cancer resistance protein (BCRP) and P-glycoprotein transporters, such as cyclosporine, tacrolimus, or ketoconazole, should be avoided. Use of concomitant medications that are sensitive substrates of OATP1B1 and OAT3 should be done with caution. 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.

1.5.2. Benefit Assessment

Study BET116183 is an open-label, dose escalation study and the first study of this agent to be conducted in subjects with hematological malignancies that have not responded to or have relapsed following standard therapy. GSK525762 has promising preclinical activity in the hematological cell lines, however it is unknown whether GSK525762 will have clinical efficacy in subjects with hematological malignancies, thus any potential beneficial effect for an individual subject attributable to GSK525762 is unknown. Data obtained in Study BET116183 may assist in progressing the knowledge base on advanced hematological malignancies and their treatment, or help identify individuals more likely to benefit or have side-effects from GSK525762. Study participants may benefit from the medical tests and screening performed during the study.

1.5.3. Overall Benefit: Risk Conclusion

Current data from GSK525762 preclinical development indicate a potential to inhibit the BET family of BRD proteins and that this inhibition may have clinical utility in the treatment of various tumors, including hematological malignancies. Taking into account the measures taken to minimise risk to subjects participating in the Phase I clinical trials, the potential risks identified in association with GSK525762 are justified by the anticipated benefits that may be afforded to subjects with the previously mentioned tumor types that have been shown in preclinical models to respond to GSK525762.

1.6. Communication Plan for Safety Evaluation

This phase I/II study is intended to enroll subjects at two or more sites. Safety data will be closely monitored and reviewed by the GSK medical monitor, and/or clinical scientist(s), responsible for all studies of GSK525762 (e.g., the BET115521 solid tumor study). There will be 2 way communication between the local participating sites and the GSK clinical team via email, fax and phone. The GSK team will review all safety data throughout the study, and safety findings from all studies with GSK525762 will be discussed with investigators from all participating sites on a monthly basis and appropriate action will be taken. Urgent safety information will be shared with all the participating sites at the earliest possible time after the data becomes available. Emerging safety and tolerability data from the currently ongoing phase I study in solid tumors will also be communicated to the participating investigators in this study as appropriate at the monthly meeting, or sooner if necessary.

2. OBJECTIVES, ENDPOINTS, HYPOTHESES

Part 1

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) administration, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with acute myeloid leukemia (AML), multiple myeloma (MM), or non-Hodgkin's lymphoma (NHL).	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	• To evaluate clinical efficacy following QD administration in subjects with AML, MM, and NHL.	• Objective response rate (ORR), as measured by standard response criteria
	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration.	• GSK525762 PK parameters following single- (Day 1) and repeat-dose (Day 15) administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
Exploratory	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters.	• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC), following single and repeat-dose oral administration of GSK525762
	• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic response.	• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by Bromodomain [BRD] proteins) in tumor tissue and/or peripheral blood samples.
	• To evaluate the relationship	• Assess objective response rate (ORR)

Part 1 Objectives		Part 1 Endpoints
	between GSK525762 dose and exposure with clinical activity of GSK525762	according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.
	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical l samples.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response.

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort").	• For MDS Cohort: ORR (defined as the percentage of subjects achieving Complete Response (CR), Marrow CR, CRp [as per CR but platelet count <100 x 10^9/L], CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR] per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in CTCL.	• For CTCL: ORR4; defined as the percentage of subjects that have achieved a CR or PR, per global response criteria and the modified severity weighted assessment tool (mSWAT), lasting more than 4 months
Secondary	• To evaluate the effect of GSK525762 on disease-related symptoms, as reported by subjects (CTCL cohort only)	• For CTCL: measure the effects of skin disease based on quality of life questionaire Skindex-29
	• To characterize the PK of GSK525762 in 3 disease specific cohorts of subjects with MDS/AML, or CTCL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the safety and	• AEs, SAEs, dose reductions or delays,

Part 2 Objectives		Part 2 Endpoints
	tolerability of RP2D of GSK525762 in 2 disease-specific cohorts of subjects with MDS/AML, or CTCL.	withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	• To determine the clinical activity of GSK525762 in2 disease-specific cohorts of subjects with MDS/AML, or CTCL.	• Progression free survival (PFS, time from treatment start date to disease progression or death due to any cause, whichever is earlier) for MDS/AML, andCTCL. Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML, and CTCL. • Duration of response (DOR, time from onset of response to disease progression or death due to any cause, whichever is earlier in responders) for MDS/AML, and CTCL • Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML, and CTCL
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical samples.
	• To evaluate the exposure response relationship between GSK525762 and safety/efficacy parameters in 2 disease-specific cohorts of subjects with MDS/AML, orCTCL.	• Relationship between GSK525762 exposure markers and safety and efficacy parameters.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response; Leukemic stem cell studies; PDX model studies and other translational medicine studies.

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • Myelodysplastic syndrome and transformed MDS (myeloid cohort): A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with MDS/AML. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.300, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • CTCL: A response rate, lasting more than 4 months, of 40% relative to a 20% response rate suggesting no activity in subjects with CTCL. This will be conducted by testing the null hypothesis that P0≤0.20 versus the alternative that P1≥0.40, assuming the maximum response rate for an ineffective drug is 0.20 and the minimum response rate for an effective drug is 0.40.

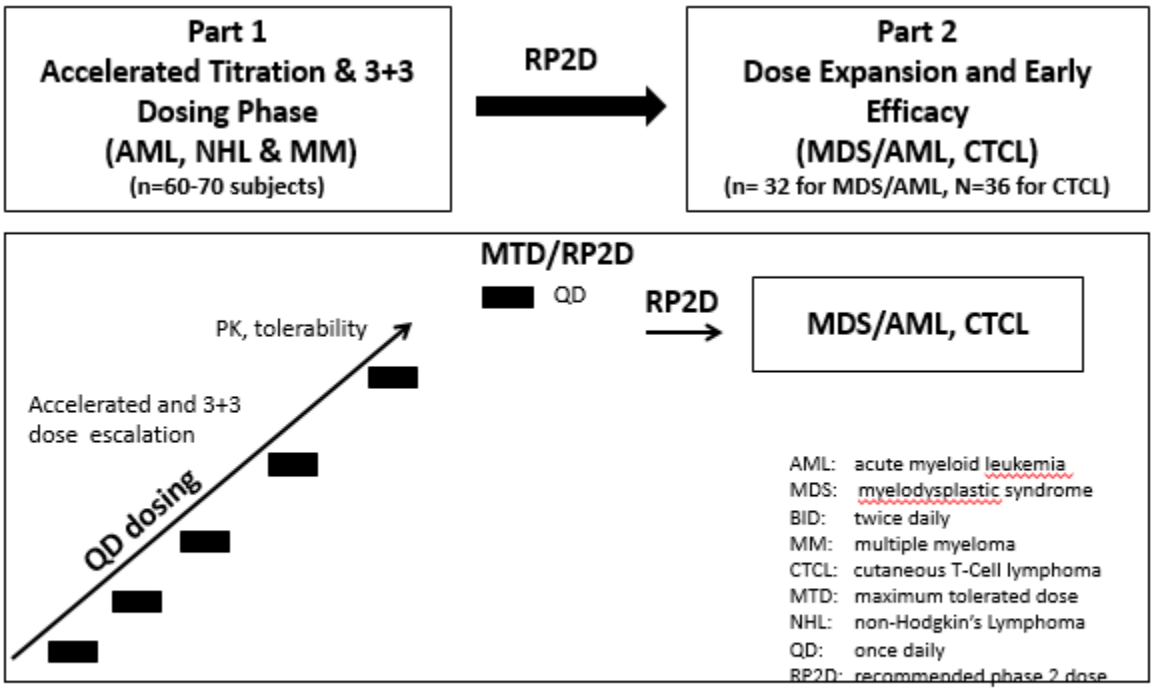
3. INVESTIGATIONAL PLAN

3.1. Study Design/Schematic

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Section 5 Time and Events Tables are essential.

This is an open-label repeat dose, multicenter, 2-part study to determine the MTD in subjects with myeloid malignancies, multiple myeloma, and non-Hodgkin's Lymphoma, and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily (QD) orally. Part 1 will be conducted in adult subjects with relapsed and/or refractory myeloid malignancies, multiple myeloma, and non-Hodgkin's lymphomas. Part 2 will be conducted in adult subjects with relapsed and/or refractory myeloid malignancies and cutaneous T-cell lymphoma (Figure 2).

Figure 2 Study Schema



Objective: To evaluate and define safety and tolerability in heme tumors with continuous (and intermittent dosing) Starting dose of 5 mg
Dose escalation window 3 weeks
Evaluate preliminary efficacy in AML or select AML subtypes

In both Parts 1 and 2, subjects may be evaluated for systemic BET inhibitory effects in blood (whole blood transcriptional). A subset of subjects in Part 1 may also be evaluated for plasma cytokine profiling.. In addition, pre-treatment and post-treatment bone marrow, skin, whole blood for PBMC isolation or lymph node samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

All study treatment(s) including investigational product will be referred to as 'study treatment(s)' for ease of presentation throughout the protocol. For EU regulatory purposes, the term 'investigational product' will only be used in Section 7 when describing the GSK compound under investigation.

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

3.2. Discussion of Design

3.2.1. Part 1: Dose Escalation

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 non-hematological toxicity, (except for

a pre-specified Grade 3 non-serious non-hematological drug related adverse event that would allow continuation of accelerated dose escalation; Section 3.2.1.6). During accelerated dose titration, there will be a single cohort comprised of all eligible subjects; parallel cohorts will not be evaluated during this stage.

Thereafter, subjects will be enrolled in a standard 3+3 design. Separate dose escalation cohorts will be opened for subjects with AML, NHL, and MM.

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 Neuenschwander continual 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 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 200 mg per day is reached. After the MTD has been determined in Part 1 for each disease type, then the Part 2 dose expansion cohorts will be opened for that disease type.

Due to the potentially different MTD in subjects with myeloid neoplasms, NHL, and MM (Section 1.3.2), each dose escalation step will be evaluated separately for the three disease types.

3.2.1.1. Dose Escalation and Schedule

A staggered dosing schedule will be implemented to monitor for safety including any delayed toxicity. This approach allows repeat dosing in a step-wise fashion to detect changes in safety, such as cardiotoxicity. Based on a low risk of drug accumulation and the aggressive nature of relapsed and/or refractory hematologic malignancies, a three week period will be used for DLT monitoring and dose escalation decision making. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data and without requiring a protocol amendment.

Extensive monitoring for cardiac safety signals will be performed including 12-lead ECG on the days indicated in the Time and Events Table.

3.2.1.2. 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 and continuing until one subject experiences ≥Grade 2 drug related non-hematological toxicity, or DLT (except for pre-specified Grade 3 non-serious non-hematological drug related adverse event, see Section 3.2.2) (Table 2). Once this occurs, the accelerated dose escalation will terminate, and subjects will be enrolled in one of three disease-specific cohorts (AML, MM, or NHL) under a standard 3+3 design (Section 3.2.1.3).

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 5 mg once daily
Subsequent dose levels	Increase by ≤2-fold after a subject clears the previous dose cohort (No subjects with ≥Grade 2 drug related toxicity AND no subjects with any DLTs in first 3 weeks of treatment)
End of Accelerated Titration Phase	Begin 3+3 Dose Escalation Phase (1 subject ≥Grade 2 drug related non-hematological toxicity in the first 3 weeks of treatment) or ≥ Grade 3 drug related specific toxicity)
NOTE: Route/Administration/Duration: Oral QD (specific dosing instructions will be provided to each subject)	

3.2.1.3. 3 + 3 Dose Escalation in Part 1

Due to the potentially different MTDs in myeloid neoplasms, MM, and NHL, dose escalation will be evaluated in three separate cohorts divided by disease subtype. These cohorts will be evaluated in parallel with each other, and DLT/MTD determination will be made separately for each cohort.

Upon termination of accelerated dose titration, two additional subjects with the final disease type will be enrolled, for a total of three subjects with that disease type at that dose level. Three additional subjects with each of the two other disease subtypes will also be enrolled at that dose level, for a total of nine subjects at each dose level.

Subjects unable to receive at least 75% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

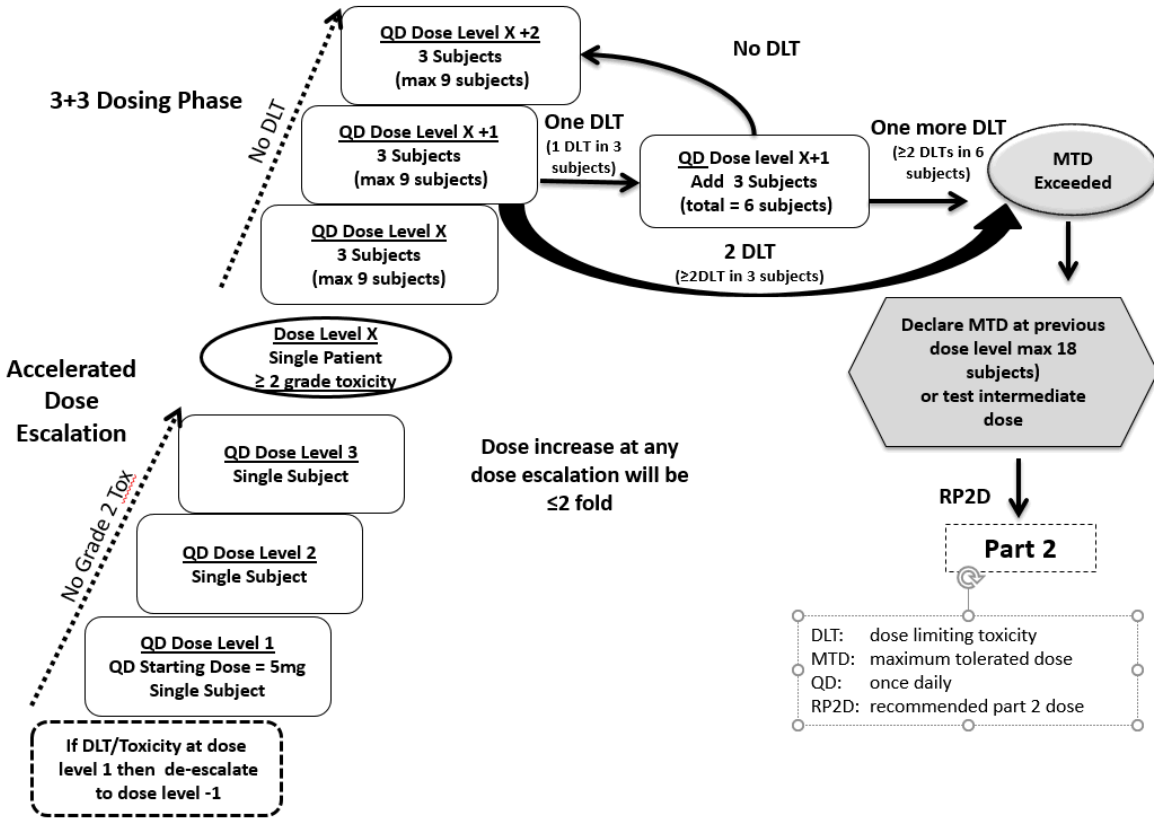
For each cohort, if no DLTs are observed in any of the 3 subjects, then dosing will proceed to the next higher dose level (≤2fold increase in dose). Subjects within each cohort will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the MTD in multiple subjects. Each disease cohort may initiate dosing independent of the other two (i.e., subjects with different diseases may start therapy <3days apart, but subjects with the same disease must be separated by at least three days). Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. If 2 or more DLTs in 6 subjects are observed at any dose level, the MTD will have been exceeded (Table 3).

Table 3 3 + 3 Dose Escalation Design

Number of Subjects with DLT in a Cohort	Action
0 out of 3 subjects	Escalate to the next dose level with increase ≤100% if there have been less than 2 subjects with ≥ Grade 2 toxicity and no DLTs (first 3 weeks of treatment in any cohort) Escalate to next dose level with an increase of ≤50% if, in the first 3 weeks of any cohort, there have been: - two or more subjects with ≥ Grade 2 toxicity
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 with an increase of ≤50%
2 or more subjects in a dosing cohort (up to 6 subjects)	MTD has been exceeded. Either evaluate an intermediate dose lower than current dose or expand a prior cohort up to 15 subjects

Once the MTD is reached and RP2D is determined, up to 12 additional subjects within each cohort may be enrolled at the MTD to evaluate safety, additional PK, and obtain clinical samples for pharmacodynamic biomarkers. Additional subjects may be enrolled at the MTD, and at least 1 dose level below MTD, to confirm if the MTD is appropriate for AML, MM and NHL subjects. Up to an additional 6 subjects may be enrolled at any dose level below the MTD in order to obtain additional clinical specimens for pharmacodynamic biomarkers to better understand the dose/exposure/pharmacodynamic relationship. Additional cohorts (with daily exposure not exceeding MTD exposure) may also be initiated to explore alternative dosing schedules to optimize the PK, safety and tolerability profile. The enrolment of additional subjects as described could be in parallel with Part 2 enrolment. Although DLT will not be based on the additional subjects enrolled into the study to further evaluate safety, PK, to obtain tumor tissue for biomarkers, data from these additional subjects will be considered in defining final MTD and RP2D (Figure 3).

Figure 3 Dose Escalation Schema (Part 1)



3.2.1.4. Alteration of Schedule

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

Schedules that incorporate a recovery period may be explored (e.g., 2 weeks on, 1 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.

Subjects may need to undergo dose modification(s) to manage toxicities. A dose adjustment may be made after consultation with the 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.

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 at least 7 days at the adjusted dose level.

3.2.1.5. Intra-Subject Dose Escalation

Intra-subject dose escalations may be considered on a case-by-case basis, provided that a higher dose level cohort (accelerated phase or 3+3 phase) has been cleared, and after review of all safety data and approval by a GSK Medical Monitor and discussion with the investigator. The subject on a lower dose level may be increased up to the highest dose level cleared. In this case, the subject may begin daily dosing at the higher dose level as it will have already been demonstrated to be tolerable and monitoring will be performed as described in the protocol.

Subjects approved for intra-subject dose escalation may require additional limited PK sampling (pre-dose, 0.5, 3 and 6-8 hours) at the higher dose, as determined by GSK Clinical Pharmacology, after at least 7 days at the adjusted dose level. Additional safety assessments 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.

3.2.1.6. Toxicity Leading to Termination of Accelerated Titration

The following events will result in an end to accelerated dose escalation:

- Any Grade 2 or higher adverse event (except drug related Grade 3 fatigue, asthenia, and nausea that respond to standard medical care within 48hrs, Grade 3 or higher electrolyte abnormalities unrelated to underlying malignancy and corrected in 48 hrs) that is considered related to the study medication and which do not improve with standard medical care within 48hrs. Disease related events such as abnormalities in hematologic parameters for acute leukemia will not be considered.
- Grade 2 QTcF prolongation (confirmed on triplicate ECGs by manual reading) Grade 2 alanine aminotransferase (ALT) increase (unless clearly attributed to the underlying disease).
- Any grade adverse events that are considered in the judgment of the investigator and GSK Medical Monitor to be serious and related to the drug and requiring addition of additional subjects to better understand the toxicity.

3.2.2. Dose Limiting Toxicity (DLT)

An event will be considered a DLT if it occurs within the first 3 weeks of treatment and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment. As described in Section 3.2.1.3, subjects unable to receive at least 75% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

- Prolonged myelosuppression, as follows:
  - For myeloma or lymphoma:

- Grade 4 neutropenia persisting for ≥7 days or febrile neutropenia not responding to treatment within 24h
- Grade 4 thrombocytopenia lasting more than 7 day and not responding to transfusions, or Grade 3 thrombocytopenia associated with bleeding (>10mL)

- Drug-related Grade 3 or 4 non-hematologic toxicity (including QTcF prolongation) as described in the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 [NCI, 2009] (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 or new electrolyte disturbance that do respond to standard medical care within 72 hours. Electrolyte disturbances associated with underlying malignancy are excluded.
- 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, and/or 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 criterion 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 will be considered as a Grade 2 elevation).
- Treatment delay of 14 days or greater due to unresolved drug-related toxicity (Treatment delays due to underlying malignancy are excluded).
- ALT ≥3xULN + bilirubin ≥2xULN (>35% direct) or ALT between 3-5xULN with bilirubin <2xULN but with hepatitis symptoms or rash or ALT ≥5xULN.

3.2.3. 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 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 Part 1 for that disease type. If necessary alternate schedules can be explored to determine additional biologically active doses even after a RP2D is defined.

3.2.4. Part 2: Disease Specific Expansion Cohorts

Up to 32 subjects with myelodysplastic syndrome and up to 37 subjects with CTCL (as defined in Section 4.2.1), may be enrolled in an expansion cohort at the RP2D. These will be conducted 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 or PK 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.

Plasma samples for PK evaluation will be collected in all subjects. The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored with the constraint of both Type I and Type II error rates. Clinical response will be defined per standard evaluation criteria (see Appendix 6, Appendix 7 and Appendix 8). Patient-reported outcome questionaire, Skindex 29 (Appendix 11) will be used to gauge the effects of treatment with GSK525762 on the quality of life and other subjective measures in subjects with CTCL.

For each cohort, the first interim analysis will be conducted after at least 10 subjects become evaluable (have had at least one-post baseline disease assessment, have progressed or died, or have discontinued from study treatment) in the MDS and CTCL cohorts respectively. The number of subjects may be increased up to a total of 32 for the MDS cohort and up to a total of 37 for the CTCL cohort, depending on the results observed; a separate decision will be made for each disease cohort. The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility, are indicated in Figure 4 and Figure 5. The methodology is based on the predictive probability of success if enrolment continues to maximum number of subjects for MDS and CTCL. Subjects enrolled in Part 1 with the same type of disease as Part 2, and treated at the RP2D, will be included in the Part 2 analysis. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

For MDS and CTCL cohorts: when 10 subjects are included in the first interim analysis, a single responder in a cohort will be adequate to pursue further enrolment. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4 and Figure 5. A maximum of 32 subjects with MDS and 37 subjects with CTCL will be enrolled at the RP2D. All available data will be considered in making enrolment decisions.

Figure 4 Diagram of Stopping Rules for MDS Cohort Expansion

	Number of Responders						
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							
26							
27							
28							
29							
30							
31							
32							

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 enrollment in these cohorts may be stopped.

Figure 5 Diagram of Stopping Rules for CTCL Cohort Expansion

Number of Subjects	0	1	2	3	4	5	6	7	8	9	10	11
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	■	■	■	■	■	■	■	■	■	■	■	■

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 enrollment in this cohort may be stopped.

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 60 to 70 evaluable (as described in Section 11) subjects will be enrolled. Part 2 will enroll up to 69 subjects (two disease-specific cohorts of 32 and 37 subjects, for the MDS and CTCL cohorts, respectively)

See Section 11.1 for sample size assumptions.

If a subject discontinues the study before completing Week 3 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 an adequate population for DLT and MTD evaluations.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events (AEs), and other pertinent information on the GSK study treatment that may impact subject eligibility is provided in the GSK525762 Investigator Brochure [GlaxoSmithKline Document Number 2011N113741_06].

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. Written informed consent provided.
2. Males and females 18 years old or older.
3. Subjects must have a diagnosis of one of the following hematologic malignancies, which has relapsed or been refractory to treatment as follows. (Part 1 only) Subjects with AML, are eligible if they
    - have relapsed and/or refractory disease, *OR*
    - are ≥65 years of age and not candidates for or have refused standard chemotherapy.
    - (Part 2 only): Subjects with MDS/AML are eligible if they:

- Have high-risk (defined as intermediate [INT]-2 or higher by International Prognostic Scoring System [IPSS] criteria [Greenberg], or high/very high by IPSS-Revised [IPSS-R] criteria [Greenberg]) MDS that has relapsed after or been refractory to prior therapy with hypomethylating agent, *OR*
- Have AML that has arisen from an antecedent MDS (irrespective of IPSS/IPSS-R score; subjects without a documented history of antecedent MDS/MPN must have AML with myelodysplasia-related changes or recurrent cytogenetic abnormalities per World Health Organization [WHO] criteria)
  - Subjects with secondary AML must have progressed despite, or failed to respond to, prior therapy with hypomethylating agent, *AND*
  - Subjects must have hypoproliferative disease, defined as either:
    - A peripheral white blood cell count of less than 20,000 cells/μL in the absence of leukoreducing therapy (e.g., hydroxyurea, leukapheresis), *OR*
    - At least one bone marrow biopsy obtained within 28 days of first dose of GSK525762 must demonstrate a marrow blast percentage of no more than 30%

      Note: If marrow blasts exceed 30% on any biopsy within 28 days of first dose, enrolment will only be permitted after discussion with the medical monitor

- (Part 1): Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination
- (Part 1 Only): Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20)
- (Part 2 only): Subjects will be eligible for enrolment into the CTCL cohort if they:
  - Have histologically- or cytology-proven diagnosis of CTCL (mycosis fungoides [MF], Sézary syndrome [SS], primary cutaneous anaplastic large cell lymphoma [pcALCL], or large cell transformation of underlying MF/SS) that has failed to respond to, or progressed despite, at least one prior systemic therapy

4. Subjects with a prior history of stem cell transplant (autologous and/or allogeneic) are allowed if:
   - At least 3 months has elapsed from the time of transplant *and*
   - the subject has recovered from transplant-associated toxicities prior to the first dose of GSK525762, *and*

- For subjects with a prior history of allogeneic transplant,
  - the subject has been off systemic immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids) for at least 1 month prior to the first dose of GSK525762. Topical steroids are permitted.
  - there are no signs or symptoms of graft versus host disease, other than Grade 1 skin involvement.

5. Eastern Cooperative Oncology Group (ECOG) performance status of:
   - ≤1 for all Part 1 Cohorts (AML, MM, and NHL)
   - ≤2 for all Part 2 cohorts (MDS/AML and CTCL)
6. Subject must be stable enough to be expected to complete dosing through the DLT observation period as assessed by the investigator.
7. 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.
8. 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 MlU/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 defined in protocol 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 enrolment. For most forms of HRT, at least two to four 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) 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 after the last dose of study medication.
- Negative serum pregnancy test ≤7 days prior to first study drug dose.
- 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.

9. Male subjects with a female partner of childbearing potential or a female partner who is pregnant must agree to use one of the methods of contraception specified in Section 9.1. 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, male subjects whose partners are or become pregnant must use/continue to use condoms until 16 weeks after last dose of study medication.
10. Adequate organ system functions (at both screening and where applicable pre first dose) as defined in Table 4.
11. Ability to comply with dietary and tobacco/alcohol abstinence requirements as defined in Section 9.2.

Table 4 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Hemoglobin (only for myeloma and lymphoma)	≥8.0 g/dL
Coagulation assays (prothrombin time/ international normalized ratio [PT/INR] and activated partial thromboplastin time [aPTT][1]	≤1.2 X upper limit of normal (ULN)
Platelets (for subjects with lymphoma) Platelets (for subjects with MM) Platelets (for subjects with acute leukemia)	≥75,000 (transfusion independent) ≥50,000 (transfusion independent) ≥10,000 (transfusions permitted to bring platelet count to >10,000)
Hepatic	
Total bilirubin	≤1.5 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)
Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	≤2.5 X ULN
Renal[3]	
Creatinine[3] OR Calculated creatinine clearance [calculated by Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method [2, 3]] OR 24-hour urine creatinine clearance [3]	≤1.5 X ULN ≥50 mL/min ≥50 mL/min
Cardiac	
Ejection fraction	≥Lower limit of normal (LLN) by echocardiogram (ECHO) (minimum of 50%) or Multi Gated Acquisition (MUGA) scan
Troponin (T)	≤ULN
Thyroid	
Thyroid stimulating hormone (TSH) [4]	≥LLN and ≤ULN

1. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2.
2. See Appendix 1 for CKD-Epi formula.
3. For MM subjects, adequate renal function is defined as serum creatinine ≤2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ≥ 30 mL/min.
4. If TSH is abnormal but free T3 and or Free T4 are normal, then the subject can be enrolled.

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. Haematological malignancy associated with human immunodeficiency virus (HIV) infection or solid organ transplant or positive Hepatitis B Antigen or positive Hepatitis C antibody at screening (subjects with positive Hepatitis C antibody may be enrolled, provided that the confirmatory test [e.g. Heptatitis C Virus Hepatitis C Virus [HCV] Ribonucleic acid [RNA] polymerase chain reaction [PCR] is negative).

2. History or concurrent malignancy of solid tumours, except for below.

   Exception: Subjects who have been disease-free for 5 years, or subjects with a history of completely resected non-melanoma skin cancer or successfully treated *in situ* carcinoma are eligible. Subjects with second malignancies that are indolent or definitively treated may be enrolled even if less than 5 years have elapsed since treatment. Consult the GSK Medical Monitor if unsure whether second malignancies meet requirements specified above.

3. Currently receiving cancer therapy (chemotherapy, radiation therapy, immuno-therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization).

   Note: the following are allowed:

   Hydroxyurea for proliferative disease

   Corticosteroids (topical and/or systemic)

   Use of hematopoetic growth factors is permitted at the discretion of the investigator according to published guidelines (e.g., National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), etc.).

   Note: the following are NOT allowed:

   Investigational anti-cancer drug within 2 weeks prior to the first dose of GSK525762

   Major surgery, radiotherapy, or immunotherapy within 4 weeks of GSK525762

   Chemotherapy regimens with delayed toxicity within the last 4 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.

   Nitrosourea or mitomycin C within the last 6 weeks

4. Evidence of severe or uncontrolled infection.
5. Use of anticoagulants (e.g., warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of GSK525762. Low dose (prophylactic) anticoagulants (e.g., low molecular weight heparin (LMWH) or oral anticoagulants) is permitted. In addition, INR must be monitored in accordance with local institutional practices, as appropriate.
6. Current use of a prohibited medication or planned use of a forbidden medication during treatment with GSK525762.
7. 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.
8. Symptomatic or untreated CNS disease,
   - Subjects with a history of CNS disease (leukemia, lymphoma or myeloma) are permitted to enrol if they have previously received appropriate therapy and CNS remission has been documented.
   - Subject with primary CNS lymphoma (defined as isolated CNS lymphoma without systemic involvement) are excluded from study.
9. Cardiac abnormalities as evidenced by any of the following:
   - History or current clinically significant conduction abnormalities, uncontrolled arrhythmias or hypertension.
   - History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association (NYHA) [Appendix 2].
   - Recent history (within the past 3 months) of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting.
10. Any of the following ECG findings or assessments including:
    - Baseline QTcF interval ≥480 msec
    - Clinically significant ECG assessments should be reviewed by the site cardiologist prior to study entry.
11. 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.
12. Evidence of hemoptysis within the last 7 days.
13. History of major gastrointestinal bleeding within the last 3 months or any evidence of active gastrointestinal bleeding excludes the subject (refer to Section 1.5).

14. Presence of gastrointestinal disease that would significantly affect compound absorption.

4.2.3. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

4.2.3.1. 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 in Appendix 4. 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, the subject is not experiencing serious toxicity, and there is no alternative treatment that could benefit the subject. For subjects with CTCL, in cases where the definition of progressive disease (PD) or relapse is met but the clinical impression is questionable, documentation for a period of at least 4 weeks is also recommended to avoid a subject being removed prematurely from the study.

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

- Substantial deviation(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- a dose delay of >14 days unless the investigator or GSK Medical Monitor agree that further treatment may benefit the subject
- intercurrent illness that prevents further administration of study treatment(s)
- 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 electronic case report form (eCRF). If a subject dies while on study, the cause of death should be recorded in the eCRF.

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

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

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in the Section 5 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 will be followed for survival and new anti-cancer therapy 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. Upon discontinuation, any samples previously collected for pharmacodynamic and/or translational research will be retained and tested as defined in the protocol, unless consent is specifically withdrawn.

4.2.3.2. Subject Completion

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

- they complete screening assessments, the 21-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 the subject is followed until death or the end of study.

Subjects who have not died, and are no longer being followed for survival are considered to have discontinued the study. 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. 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 in 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.

4.2.4. Treatment after the End of the Study

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

5. TIME AND EVENTS TABLES

This section consists of the Time and Events Table(s) and supplemental footnotes to describe assessment windows and sequencing of study-specific assessments and procedures

Table 5 Time and Events: Part 1

																		From W10		
Procedure (Notes)		**SCR**	**Week 1**						**Week 2**			**W3**	**W4**	**W5**	**W6**	**W7**	**W10**	**q3w**	**q6w**	**EOT**
			D1	**D2**	**D3**	**D5**	**D6**	**D7**	**D1**	**D6**	**D7**	**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[a]		X																		
Disease characteristics		X																		
Cardiology eval.		X																		
Prior therapy		X																		
Register subject		X																		
TREATMENT PHASE																				
Study Drug: For details see Table 8																				
Administer study drug (Administer about same time of day. No food or antacids 1h before and 2h after.)			Daily																	
Review subject diary (Not required when dosed in clinic.)									X			X	X	X		X	X	X		
Safety																				
Pregnancy test/ testosterone [b]		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
Vital Signs [c]/Pain Assessment		X	X			X			X			X	X	X		X	X	X		X
Height and weight (Height at Scr only)		X	X			X			X			X	X	X		X	X	X		X
Chest x-ray		X																		
Adverse events		AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.4)																		
Concomitant medications		continuous from signing of informed consent																		
Laboratory assessments: For details please see Table 6																				
Tests		X	X	X		X			X	X		X	X	X	X	X	X	X	X	X

Procedure (Notes)	SCR	Week 1						Week 2			W3	W4	W5	W6	W7	W10	q3W	q6w	EOT
		D1	D2	D3	D5	D6	D7	D1	D6	D7	D1	D1	D1	D1	D1	D1	D1	D1	
Cardiac Monitoring																			
ECHO or MUGA (Within 35 days of first dose)	X								X				X			X		X	X
12-lead ECGs [e]	X	O			O			X		O		X	X		O	X	X		X
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see Table 8																			
PK Blood samples for GSK525762		X	X[k]	X[h]	X				X	X	X[k]				X			X[f]	
PD Tumor Sample	X[g]			X[h]															
Translational Research [i]																			
Pharmacogenomics (PGx) sample		X																	
Blood sample for exploratory translational research	X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression or when patient is discontinued from study/end of treatment[j]																	
Tumor biopsy at progression																			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 (as described in Table 7). 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.																			

a. Medical, surgical, alcohol, tobacco and treatment history, including date (month and year) of first diagnosis, histology, and current sites of disease, will be taken as part of the medical history and disease status.

b. 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. Pregnancy testing not required for females of non-childbearing potential as defined in Section 4.2.1.

c. Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate and temperature

d. 12-lead ECGs : Screening ECGs within 14 days of first dose. For timing of ECGs on "O" days, see Table 8 for QD. Otherwise, ECGs at approximately same time of day, and prior to dosing.

e. For subjects on study longer than 12 weeks, collect a pre-dose PK sample q6W. Reduce to q12w after 12 months on study.

f. Pretreatment biopsy for pharmacodynamic tumor sample must be performed within 14 days of first dose.

g. During 3+3 dose escalation, pharmacodynamic tumor sample collection will be mandatory unless infeasible to collect, and approval is obtained by the GSK medical monitor. Subjects with MM will have bone marrow aspirates collected on W1 D3 within 3-6 hours after the dose. Subjects with AML will have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on W1 D3 within 3-6 hours after the dose. Subjects with NHL will have a tissue biopsy (lymph node or other affected organ/region) collected on W1D3 within 3-6 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on

emerging data. For operational reasons sampling can be delayed by up to 2 days as long as the hours post-dose for collection remain as described. A PK sample will need to be obtained within 1 hour of the tissue sampling. See Table 7 disease specific assessments for details).

h. Refer to Section 6.6 for details on Translational Research and Appendix 5 for details on PGx Research.
i. Refer to Table 7 Disease Specific Assessments for timepoints.
j. Assessment only completed for Part 1 QD subjects

Abbreviations: ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; ECOG PS=Eastern Cooperative Oncology Group Performance Status; MUGA=multi-gated acquisition scan; PGx=Pharmacogenetics; COPD=Chronic obstructive pulmonary disease; SPM=Study Procedures Manual; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 6 Time and Events: Part 1 Laboratory Assessments

														q3w and q6w Initiated from Wk 10		
NB: Collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 24h of first dose.		SCR	W1			W2		W3	W4	W5	W6	W7	W10	q3W	q6W	EOT
Assessment	**Notes**		D1	D2	D5	D1	D6	D1	D1	D1	D1	D1	D1	D1	D1	
Troponin, NT pro-BNP	Troponin: Collect 2 samples: 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		X	X
Hematology	Increase frequency as medically indicated	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
Factor VII Assay	In addition to scheduled timepoints, perform if PT or INR or aPTT are ≥1.5XULN, or in case of bleeding event	X						X		X						
Creatine phosphor-kinase		X	X	X	X	X	X	X	X				X		X	X
CK-MB	CK-MB at predose and 12-18 h post dose take on W1D1, and as clinically appropriate.	X	X													
Liver chemistry		X	X	X	X	X	X	X	X			X	X	X		X
LDH		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; performed at baseline and repeated if necessary during the study.	X														
HbA1c	Performed at baseline and repeated if necessary during the study.	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

														q3w and q6w Initiated from Wk 10		
NB: Collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 24h of first dose.		**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Assessment	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
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
HBsAg, HepC antibody	If hepatitis C antibody positive, a confirmatory study (e.g., HCV RNA PCR) should be performed as per local standard	X														

Abbreviations: 1,5 AG=1,5-Anhydroglucitol, NT-pro BNP=N-ternimal prohormone B-type Natriuretic Peptide; C=cycle; CK-MB=Creatine Kinase – MB (isoform); LDH=Lactate dehydrogenase; TSH=Thyroid stimulating hormone; HBsAg = Hepatitis B surface Antigen; HepC=Hepatitis C; HCV Hepatitis C Virus; RNA=Ribonucleic acid; PCR=polymerase chain reaction; D=day; EOT=End of Treatment Visit; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 7 Disease Specific Assessments

Multiple Myeloma (MM) Assessments (Part 1)								
						q3w and q6w Initiated from Wk 10		
Procedure	Notes	SCR	W4 D1	W7 D1	W10 D1	q3W D1	q6W D1	EOT
Disease Characteristics	Including cytogenetics as appropriate	X						
Total Protein, CRP, β2 microglobulin		X	X	X	X	X		
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM;	X	X	X	X		X	
UPEP	Only required if paraprotein is present in urine	X	X		X		X	
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X	X		X	X		
Blood sample for exploratory translational research	A blood sample for exploratory translational research should be collected at EOT and/or date of progression and at timepoints as indicated	X	X		X		X	X
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X			X			
Response assessment	Every 6 weeks after wk4; Response criteria in Appendix 6		X		X		X	X

NHL Assessments (Part 1)										
							q3w and q6w Initiated from Wk 10			
Procedure	**Notes**	**SCR**	**W4**		**W7**	**W10**	**q3W**	**q6W**	**q12W**	**EOT**
			D1		**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history[a] immunophenotypes, cytogenetics and prognostic markers [b]		X								
β2-microglobulin		X	X							
B Symptoms		X	X		X	X	X			
Lymph node and organ exam		X	X		X	X	X			
Bone marrow/tissue biopsy [c]		X			X					
Blood sample for exploratory translational research		X			X			Wk 16, wk 24, then q12wks		X[g]
CT Scan [d]		X			X			Wk 16, wk 24, then q12wks		X
PET Scan [d, e]		X			X					
Response evaluation [f]					X			Wk 16, wk 24, then q12wks		X

a. Including date of first diagnosis, disease stage, and complete history of diagnostic results and therapies.
b. Examples of prognostic markers may include: ALC, FLIPI-1, FLIPI-2 (includes β2-microglobulin), FcR gamma 3A.
c. A sample will be required at screening only if clinically appropriate for the lymphoma subtype AND an appropriate previous sample is available. A follow-up bone marrow biopsy will be performed no later than 8 weeks following CR (as judged by investigator) in accordance with the response guidelines (Appendix 7) if a subject had involvement of the BM at the start of the study.
d. Baseline/Screening Computerized Tomography (CT) and PET scans may be obtained within 35 days of first dose Follow-up CT scans at week 7 wk 16, wk 24 and then every 12 weeks.
e. Positron emission tomography (PET) or PET/CT scan if clinically indicated (e.g., confirmation of CR for Diffuse large B-cell lymphoma).
f. Evaluation of response for lymphoma at week 7, week 16, week 24 and then every 12 weeks. Assessments are described in Appendix 7 : Response Criteria for Lymphoma.
g. A blood sample for exploratory translational research should be collected at EOT and/or date of progression

CTCL Assessments (Part 2)						
	SCR	**W3**	**W7**	**W10**	**W16 and beyond**	**EOT**
Procedure		**D1**	**D1**	**D1**		
Disease characteristics, including history[a] and current staging	X					
Skin assessment (e.g., medical photography)	X		X		Wk 16, wk 24, then q12wks	X
Cross-sectional imaging[b]	X		X		Wk 16, wk 24, then q12wks	X
Quantitative evaluation of disease in blood (e.g., flow cytometry)	X		X		Wk 16, wk 24, then q12wks	X
Gobal response scoring[c]	X		X		Wk 16, wk 24, then q12wks	X
Skindex 29 (Quality of life/symptom assessment)	X	X	X	X	Wk 16, wk 24, then q12wks	X
Tissue biopsy[d]	X	X				X
Blood sample for exploratory translational research[e]	X	X	X		Wk 16, wk 24, then q12wks	X

a. Including date of first diagnosis, disease stage, and history of prior therapies
b. CT, PET/CT, or magnetic resonance imaging (MRI) may be used, as per standard practice
c. Global response score (refer to Appendix 10 for full description) takes into account status of disease as measured by assessment of skin, lymph nodes, viscera, and blood. Any response or PR should be confirmed by repeat assessment no sooner than 4 weeks after the assessment demonstrating response.
d. Punch biopsy of affected skin lesion should be performed at times indicated for translational research. Pre- and post-dose biopsies should be collected from the same lesion. The W3D1 biopsy should be collected within 3-6 hours after the dose
e. Blood samples should be collected within 3-6 hours after the dose

MDS and Leukaemia Assessments (Part 1 and Part 2)											
									q3w and q6w Initiated from Wk 10		
Procedure	Notes	SCR	Week 2 D1	W3 D1	Wk4 D1	W5 D1	W7 D1	W10 D1	q3W D1	q6W D1	EOT
Disease characteristics, including history, immuno-phenotype, cytogenetics and molecular studies as appropriate and History [a]		X									
Lymph node and spleen assessment	Only as appropriate	X			X		X	X	X		X
Response Assessment[b]					X			X		X	X
Blood sample for exploratory translational research		X			X			X		X	X[f]
Transfusion History [c]		X	X	X	X	X	X	X	X		
Bleeding History		X	X	X	X	X	X	X	X		
Hematology [d, e]		X	X	X	X	X	X	X	X		

a. Including date of diagnosis and complete history of diagnostic results and therapies.
b. Bone marrow biopsy/aspirate should be obtained for response assessment at the timepoints indicated. Subjects without marrow involvement may be assessed by other means (e.g., medical photography for leukemia cutis) after discussion with the medical monitor, provided that the same method is used for all assessments of that subject. Response criteria for AML are described in Appendix 8; response criteria for MDS are described in Appendix 9. For subjects with AML, a peripheral blood sample can be taken at baseline if a bone marrow sample cannot be collected. Subjects should be off cytokine support (granulocyte colony-stimulating factor [GCSF] or granulocyte-macrophage colony-stimulating factor [GMCSF]) for a minimum of 7 days before obtaining bone marrow to document remission.
c. Platelet and blood transfusions to be assessed at designated visits and summarized per unit on a weekly cumulative basis.
d. Hematology includes complete blood count (CBC) with white blood cell count differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes) and platelets; hemoglobin, hematocrit, red blood cell count. A CBC with differential and platelets, hemoglobin and hematocrit may be performed daily during in-patient care; once subject is discharged, assessments to continue weekly until disease response assessment. This is collected at baseline/screening;, then weekly. Platelet count achievement of 20,000/mL for 3 days is entered into the eCRF and the date of platelet count achievement of 100,000/mL is entered into the eCRF.
e. A blood cell smear to measure peripheral blood blasts.
f. A blood sample for exploratory translational research should be collected at EOT and/or date of progression

Table 8 Time and Events: Part 1 Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling

	W1D1									W1D2		W1D5		
Procedure / time after dose	**pre dose**	**0h**	**15 min ± 5m**	**30 min ±5m**	**1h ±10m**	**2h ±15m**	**4h ±15m**	**8h ±1h**	**12h ±2h**	**24h ±1h**	**0h**	**0h**	**2h ±15m**	**4h ±15m**
Dose		X									X	X		
12-lead ECG [a]	X					X	X						X	X
PK sample for GSK525762 [b]	X		X	X	X	X	X	X	X	X [b]			X	X

	W2D6	**W2D7** (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed**)**								**W3D1**		**W7D1 ±4 days [c]**			
Procedure / time after dose	**pre dose**	**pre dose**	**0h**	**15 min ± 5m**	**30 min ±5m**	**1h ±10m**	**2h ±15m**	**4h ±15m**	**8h ±1h**	**12h ±2h**	**24h ±1h**	**0h**	**pre dose**	**0h**	**0.5-2h**	**4 - 8h**
Dose			X									X		X		
12-lead ECG		X					X	X					X		X	X
PK sample for GSK525762	X	X		X	X	X	X	X	X	X	Xb		X		X	X

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

a. A single ECG should be collected at each timepoint, within 10 min prior to PK draw.

b. Sample to be obtained before dosing on Week 1, Day 2 or Week 3 Day 1

c. If dose was escalated, the W7D1 visit may be performed +4 to +7 days.

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Table 9 Time and Events: Part 2 Expansion Cohort

Part 2 Procedure (Notes)		SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles (q3w and q6w Initiated from Wk 10)		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			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[a]		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.)			Continuous daily dosing (unless safety, PK or pharmacodynamic data necessitate a different dosing schedule), see Section 3.2.4						X		
Review compliance (Not required when dosed in clinic.)				X	X	X	X	X	X	X	X
Safety											
Pregnancy test/testosterone[b]		X	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
Vital Signs[c]/Pain Assessment		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									
Adverse events		AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.4)									
Concomitant medications		continuous from signing of informed consent									
Laboratory assessments: For details please see Table 10											

Part 2 Procedure (Notes)		**SCR**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
			W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
			D1	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Tests		X	X	X	X	X	X	X	X	X	X
Cardiac Monitoring											
ECHO or MUGA (Within 35 days of first dose).		X				X	X	X		X	X
12-lead ECGs [d]		X	X	X	X	X	X	X	X		X
PK and Blood pharmacodynamics											
PK Blood samples[f]	Three samples to be collected each sampling day: During the first 3 weeks collect a predose (within 60 minutes prior to dose), a single draw between 0.5 to 2 h postdose, and a single draw between 4-8h postdose (fasting requirements apply). Thereafter W7 and Q6W only a predose and 0.5 hour post dose sample are collected. PK sampling may be discontinued after 6 months on study		X		X		X			X	
Translational Research											
PGx sample			X								
Tumor sample (e.g., bone marrow biopsy, skin punch biopsy, or peripheral blood collection [only for subjects with circulating disease])		X [e]			X [f] (CTCL only)	X [f] (MDS/AML only)					X[g]
Blood samples for exploratory translational research		X			X[f](CTCL only)	X [f] (MDS/AML only)	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression or when patient is discontinued from study/end of treatment				
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 (as described in Table 7). 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.											

a. Medical, surgical, alcohol, tobacco and treatment history, including date (month and year) of first diagnosis, histology, and current sites of disease, will be taken as part of the medical history and disease status
b. 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. Pregnancy testing not required for females of non-childbearing potential as defined in Section 4.2.1
c. Vital signs include SBP, DBP, heart rate, respiratory rate and temperature
d. Screening ECGs within 35 days of first dose. ECGs prior to dosing. If QTcF increase >30msec, ECGs should be repeated every 2-3 days until the QTcF is within 30 msec of baseline.
e. Pretreatment biopsy for tumor sample must be performed within 14 days of first dose.
f. Subjects with MDS/AML should have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on W4 D1 within 3-6 hours after the dose. Subjects with CTCL will have a punch biopsy of the skin and blood sample collected on W3D1 within 3-6 hours after the dose. Any additional blood samples should be collected within 3-6 hours post-dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as **the hours post-dose for collection remain as described**. **A PK sample will need to be obtained within 1 hour of the tissue sampling**. For CTCL subjects the 4-8 hour PK sample required to be drawn can be utilized as the sample that is required after tissue sampling. See Table 7 disease specific assessments for details).
g. Tumor samples for translational research are requested at end of treatment for subjects with progressive disease.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; PK=Pharmacokinetics; PGx=Pharmacogenetics; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; Wk=week

Table 10 Time and Events: Part 2 Laboratory Assessments

***NB*: Collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 24h of first dose. (Notes)**		**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles q3w and q6w Initiated from Wk 10**		
		W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
	SCR	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**EOT**
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 [a]	X X [a]	X [a]	X [a]	X [a]	X	X		X
Clinical chemistry	X	X	X	X	X	X	X	X		X
Pancreatic	X	X		X	X	X	X	X		X
Coagulation	X	X		X	X	X	X		X	X
Factor VII Assay[b]	X			X		X				
Liver chemistry	X	X	X	X	X	X	X	X		X
LDH	X	X	X	X	X	X	X	X		X
Creatine phosphokinase	X	X			X	X	X		X	X
Fasting blood glucose, c-peptide, insulin, 1,5 AG (Will be performed at central lab if not available at local lab)	X	X			X	X			X	X
HbA1c	X	X			X	X			X	
Fasting lipids	X	X			X	X			X	X
Urinalysis	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
HBsAg, HepC antibody (If hepatitis C antibody positive, a confirmatory study [e.g., HCV RNA PCR] should be performed as per local standard)	X									

a. Assess platelet count as clinically appropriate but at minimum twice weekly for weeks 1 and 2; weekly for weeks 3 to 8.

b. In addition to scheduled timepoints, perform if PT or INR or aPTT are ≥1.5XULN, or in case of bleeding event

Abbreviations: NT-proBNP=N-terminal pro–B-type Natriuretic Peptide; 1,5 AG=1,5-Anhydroglucitol; Hb=Hemoglobin; TSH=Thyroid Stimulating Hormone; HBsAg = Hepatitis B surface Antigen HepC=Hepatitis C; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; q12W=every 12 weeks; SCR=Screening Visit; W=week

6. STUDY ASSESSMENTS AND PROCEDURES

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

Refer to the timing of each assessment in the Section 5 Time and Events Tables. The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for the assessments.

The change in timing or addition of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. Detailed procedures for obtaining each assessment are provided in the SPM).

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.

6.1. Study Visits

6.1.1. Assessments

See the Section 5 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 screening unless otherwise noted in the Section 5 Time and Events Tables. Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within 24 hours of first dose do not need to be repeated on Day 1.

Visits during Week 1: Based on subject and clinic schedule, Week 1 Day 5 assessments can be ± 1 day.

Visits between Week 2 through Week 3 (inclusive): Based on subject and clinic schedule, assessments can be +3 days.

Visits between Week 4 through Week 9 (inclusive): Clinic visits can be scheduled ±4 days.

Every 3-week and 6-week visits from Week 10 through Week 48 Clinic visits can be scheduled ± 7 days.

After Week 48: Every 3-week visits are no longer required, based on clinical judgment. Every 6-week clinic visits must include safety assessments from the "q3w" column in the Time and Events Table and can be scheduled ± 7 days. Response assessments may be scheduled ± 7 days.

Discontinuation visit: should be within 14 days from last dose of study drugs. 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.

Discontinuation Survival Follow Up Visit: can be scheduled ± 7 days

6.2. Baseline Assessment

Subjects diagnosed with refractory hematological malignancy (MM, NHL (excepting CTCL), CTCL, MDS and/or AML), will be assessed at baseline for general disease characteristics as noted in Section 6.2.1 and tumor type specific measures as noted in Section 6.2.2, Section 6.2.3 Section 6.2.4, and Section 6.2.5, respectively.

Baseline is defined as the assessment closest to first dose, (i.e., Week [W] 1 Day [D] 1 assessment) or screening if SCR sample collected within 24h of first dose.

6.2.1. Baseline assessment for all Subjects

- Primary tumor type (immunophenotyping and histology if applicable)
- History of other tumor types/medical history
- Date of initial diagnosis of primary tumor type
- Date of relapse/progression

6.2.2. Baseline assessment for Subjects with MDS/AML

- WHO classification
- FAB classification (AML only)
- Cytogenetics
- IPSS/IPSS-R classification (MDS only)

6.2.3. Baseline assessment for Subjects with NHL (excepting CTCL)

- Ann Arbor staging at initial diagnosis and screening
- Number of sites with extranodal involvement at initial diagnosis
- Follicular Lymphoma International Prognostic Index (FLIPI) 1 and 2

- FCgR3a genotype and other cytogenetics/molecular analysis applicable such as antigen gene receptor rearrangements, BCL2 rearrangements and translocations.
- Fluorescence *in situ* hybridization (FISH), cytogenetics/molecular analysis, and/or IHC for MYC, BCL2, and/or BCL6 (only required to enrol in double- and triple-hit lymphoma sub-cohort)

6.2.4. Baseline assessment for Subjects with CTCL

- Modified International Society for Cutaneous Lymphomas (ISCL)/ European Organization of Research and Treatment of Cancer (EORTC) stage at initial diagnosis and screening (Appendix 10, Table 22)
- Quality of life assessment (Skindex-29 [refer to Appendix 11])

6.2.5. Baseline assessment for Subjects with myeloma

- International staging system (ISS) stage at initial diagnosis and screening
- Type (active or smoldering)
- Presence of plasmacytoma
- Cytogenetics
- Presence of extramedullary disease
- Laboratory assessment: Total protein, paraprotein, C reactive protein (CRP) and β2-microglobulin; for secretory MM: serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), IgG, IgA, IgM, free light chain (FLC) assay

6.3. Safety Evaluations

Planned time points for all safety assessments are provided in the Section 5 Time and Events Tables.

6.3.1. Physical Examinations

A complete 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 by the Investigator. Additional assessment by a cardiologist may be required at the discretion of the Investigator and/or Medical Monitor [prior to enrolment/first dose] if any cardiovascular risk factors or ECG/laboratory abnormalities are identified."

6.3.2. ECOG performance status

The performance status assessment is based on the ECOG scale [Oken, 1982].

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

6.3.3. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiration, and 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 (see Appendix 12).

6.3.4. Left ventricular ejection fraction (LVEF) Evaluation

For all subjects, evaluation of cardiac output will be performed at screening and at assessment times as outlined in Section 5. While ECHO is the preferred modality of imaging, MUGA scans may be accepted as an alternative. Subjects should have the same assessment modality performed at each time point listed in Section 5. When possible, ECHOs/MUGAs should be evaluated and compared to baseline by the same reader. All ECHO/MUGA data may be transferred and reviewed by an independent cardiologist.

6.3.5. Electrocardiograms

ECGs will be performed using a standard 12-lead ECG machine that automatically calculates the Heart Rate (HR) and measures PR, QRS, QT and QTcF intervals. 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.

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 ≥530 msec OR interval increase from baseline ≥60 msec: Investigational product (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 Section 7.7 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.

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

6.3.6. Clinical Laboratory Assessments

All protocol required safety laboratory assessments, as defined in Section 5, are performed at the institution's local laboratory. All non-safety assessments (e.g., PK samples, biopsy, translational samples) will be assessed by a central laboratory. 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 11 Clinical Laboratory Tests

Serum Chemistry			
Blood urea nitrogen	Magnesium	Aspartate aminotransferase (AST)	Total and direct bilirubin
Sodium	Potassium	Alanine aminotransferase (ALT)	Uric acid
Creatinine	Chloride	Alkaline phosphatase (ALP)	Albumin
Fasting Glucose	Calcium		Total protein
Lactate dehydrogenase	Ionized calcium		
Hematology			
Platelet count	*Automated White Blood Cell*		
Red blood cell count	*Differential:*		
White blood cell count (absolute)	Neutrophils (absolute)		
Blast count			
Hemoglobin	Lymphocytes (absolute)		
	Monocytes (absolute)		
	Eosinophils (absolute)		
	Basophils (absolute)		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood, and ketones by dipstick			
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, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)			
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)			
HBsAg, HepC antibody			
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)			
24-hour urine creatinine clearance (if needed)			

Subjects should be instructed to fast (no food and only water allowed) for 8 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. Laboratory results or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay, must be recorded as an associated AE or SAE. In addition, these clinically significant abnormal laboratory results should be followed until the abnormality resolves or is determined to be stable.

6.3.7. Troponin

Troponin T will be assessed at a central laboratory as a means of consistent evaluation across all subjects. A second troponin 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, troponin I may be assessed at a local laboratory if troponin T is not available. The same local laboratory test (troponin I or troponin T) should be used consistently for an individual subject throughout the study.

6.4. Efficacy

6.4.1. Disease Assessment

Response will be assessed as outlined in the Section 5 Time and Events Table 7 Table by the investigator using the appropriate criteria for MM, lymphoma, CTCL, AML, and MDS, as noted in Appendix 6, Appendix 7 Appendix 8, Appendix 9, and Appendix 10, respectively.

Subjects enrolled in Part 1 at RP2D and Part 2 are to be followed until death for assessment of overall survival (OS).

6.5. Pharmacokinetics

6.5.1. Blood Sample Collection

Blood samples to enable quantification of GSK525762, and relevant metabolites, as applicable, in plasma will be collected at the time points indicated in the Section 5 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.

6.5.2. 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.

6.5.3. Activity

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

6.6. Translational Research

Blood and or tumor tissue specimens will be collected at various times, throughout the study in order to support research aimed at understanding the biological effect of GSK525762 and BET inhibition as well as identifying indicators of sensitivity or resistance to GSK525762.

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. In certain settings such as myeloid malignancies, samples may be used to evaluate changes in leukemic stem cell populations or to generate PDX models.

The biopsies will be assessed for transcripts or proteins that reflect BET target engagement and/or tumor biology. Biopsies may also be assessed for deoxyribonucleic acid (DNA), RNA or proteins which may be potential predictors of sensitivity or resistance to BET inhibition based on emerging data.

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.

6.6.1. Tumor Specific Tissue Collection

The tissue collection and pharmacodynamic tests for Part 1 are disease specific and outlined below:

- For subjects with AML, changes in specific protein markers and/or mRNA expression signatures will be assessed in bone marrow and/or tumor cell-enriched PBMCs isolated from whole blood.
- For subjects with lymphomas, tissue biopsies will be required before and after treatment to evaluate changes in tumor-specific protein markers and/or gene expression signatures.
- For subjects with MM, bone marrow will be evaluated for changes in tumor-specific protein markers and/or gene expression signatures (for example, c-Myc).

The tissue collection to support translational and mechanistic research for Part 2 is also disease specific and is similar to that described above.

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.

6.6.2. Blood Sample Collection for Exploratory Translational Research

Blood samples collected at time points described below and in the Time and Events tables for PK and pharmacodynamic testing may be required for all subjects.

- Part 1 &2: At screening, date of bone marrow biopsy (Part 2 MDS cohort only), disease assessment (Table 7) and disease progression for isolating plasma for circulating biomarkers (eg, cfDNA) , PBMCs and neutrophils.

6.6.3. Unscheduled 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 10 mL 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.

6.7. 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 6.7.1 and Section 6.7.2, respectively.

6.7.1. 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.

6.7.2. Definition of a SAE

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

a. Results in death.

b. Is life-threatening.

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

c. Requires hospitalization or prolongation of existing hospitalization

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

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

d. Results in disability/incapacity, or

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

e. Is a congenital anomaly/birth defect.

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

g. Protocol-Specific SAEs 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 such as Grade 3 or higher decrease in LVEF and QTcF withdrawal criteria.
- Grade 4 laboratory abnormalities (not disease related).
- Drug related hepatobiliary event leading to permanent discontinuation of study treatment.

6.7.2.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thrombosis
- Deep Venous Thrombosis

- Revascularization

6.7.2.2. Death Events

In addition, all deaths, whether or not they are considered SAEs, will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded within one week of when the death is first reported.

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

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

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

Any new primary cancer must be reported as a SAE.

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

6.7.4. 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 6.7.6.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs (including laboratory abnormalities such as an increase in troponins) 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.

6.7.5. Method of Detecting AEs and SAEs

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

"How are you feeling?"

"Have you had any (other) medical problems since your last visit/contact?" "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

6.7.6. 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 12 once the investigator determines the event meets the protocol definition for that event.

Table 12 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 electronic Case Report Form (eCRF) and liver imaging and/or biopsy CRFs if applicable[2]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[2]
ALT≥5xULN; ALT≥3xULN with hepatitis or rash **or** 3xULN ≥4 weeks	24 hours[1]	Liver Event eCRF[2]	24 hours	Updated Liver Event eCRF[2]
ALT≥3xULN and <5xULN and bilirubin <2xULN	24 hours[1]	Liver Event eCRF does not need completing unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[2]		

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

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

6.7.7. 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)/ Ethics Committee (EC) and investigators.

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

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

6.8. Pregnancy

6.8.1. 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.

6.8.2. Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted 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 6.7.6. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

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

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to 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.

6.9. Pharmacogenetics

An important objective of the clinical study is pharmacogenetics (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 saliva sample taken for analysis. The presence/absence of genetic variations in selected candidate genes in DNA from saliva will be analysed to determine their relationship with response (safety, tolerability, PK, and efficacy) to treatment with GSK525762.

Information regarding PGx research is included in Appendix 5. The IRB/ EC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 5). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

6.10. Quality of Life/Patient-Reported Outcomes

Patient-reported outcome, Skindex 29 (refer to Appendix 11) will be used to gauge the effects of treatment with GSK525762 on the quality of life and other subjective measures in subjects with CTCL.

7. 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 (Table 13) and a crystalline, besylate formulation (Table 14) will be utilized.

In the BET115521 study, a sub-study was conducted to evaluate the PK characteristics of the new besylate formulation. This sub-study was an open-label, randomized, single dose, four period, cross over sub-study performed 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.

The sub-study results showed that 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.

Either amorphous or besylate tablets may be used in Part 1, based on the bioequivalence described above. During the DLT observation period, subjects will only receive one or the other formulation; any individual cohort will only enrol subjects receiving a single formulation type. Upon completion of the DLT observation window, subjects may be changed from amorphous to besylate tablets at the equivalent dose.

The besylate tablet will be utilized in Part 2.

Precaution will be taken to avoid direct contact with the study treatment.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 13 GSK525762 Amorphous Free Base Investigational Product Dosage/ Administration

Investigational Product			
Product name:	GSK525762 Amorphous Free Base Tablets		
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		
Route/ Administration/ Duration:	Oral; see the Section 5 Time and Events Tables for schedule and administration timings		
Dosing instructions:	Dose with 240 mL water and should be taken within a similar time frame each morning. No food or antacids for at least 1 h before and 2 h 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 14 GSK525762 Besylate Investigational Product Dosage/Administration

	Investigational Product			
Product name:		GSK525762 Besylate Tablets		
Unit dose strength(s)/Dosage level(s):	5mg	20mg	25mg	50mg
Dosage form	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	GSK
Physical description:	White to slightly colored, round, biconvex tablet.	Yellowish pink, round, biconvex tablet	White to slightly colored, round, biconvex tablet	White to slightly colored, oval shaped tablet
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings			
Dosing instructions for Part 1:	Dose with 240mL water and should be taken at the same time each day, preferably in the morning**. 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.)			
Dosing Instructions for Part 2	Dose with 240mL water and should be taken at the same time each day, preferably in the morning. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)			

7.2. Handling and Storage of Study Treatment

Handling

Precaution will be taken to avoid direct contact with the study treatment.

An 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

Adequate precautions must be taken to avoid direct contact with the IP. Limited exposure and precautionary action (example: wearing gloves, washing hands post exposure, etc.) should be taken by site staff dispensing GSK525762 tablets.

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

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

Storage

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.

7.3. Meals and Dietary Restrictions

Subjects enrolled under Part 1 will fast for at least one hour prior to each dose of study drug (amorphous free or besylate). No food or antacid should be taken for 2 hours after dosing. Subjects should not eat a heavy meal in the morning prior to the 1 hour washout before dosing to minimize potential risk for food interaction. On serial PK sampling 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.

If a subject vomits after taking study medication, 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 PK, pharmacodynamic and safety data. Any change in fasting requirements will be communicated to each investigator and site staff in a future protocol amendment. Should a twice daily regimen be required, additional consideration will be paid to this requirement once the escalation period is past.

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

Based on the results of the BET115521 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 for subjects in Part 2 only

except on Serial PK sampling days (Week 1 and Week 3) or days in which required for fasting blood draws. 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.

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.

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

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 eCRF.

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 eCRF.

7.7. Dose Modifications

7.7.1. Dose and Safety Management Guidelines

The following dose modification criteria in Table 15 should be used to provide guidance, 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.

Table 15 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	After discussion with medical monitor and using sound clinical judgement, continue at same dose or dose reduce to previously cleared dose level. Monitor CBC at least twice a week, or more frequently if clinically indicated.
	Grade 4 (platelets <25,000/mm^3) and/or any grade accompanied by severe bleeding related to thrombocytopenia	<u>For Lymphoma and Multiple Myeloma:</u> Interrupt study medication and monitor CBC every 2-3 days. 1. If platelet counts recover to Grade 2 and are steady for at least 2 CBC measurements at least 3 days apart, or rising, discuss with the medical monitor. Based on clinical judgement, resume treatment at the same or previously cleared lower dose. 2. Platelet transfusion is allowed based on institutional guidelines. If platelet transfusions are required, hold drug until platelet counts recover to Grade 2, and are steady for at least 2 CBC measurements at least 3 days apart, or rising. Using clinical judgement and after consultation with the medical monitor, consider resuming treatment at same or the previously cleared lower dose. 3. Discontinue treatment if drug has to be held for >14 days. For Acute Myeloid Leukemia and Myelodysplastic Syndrome - if platelet count <25,000/mm^3 but ≥10,000/mm^3: Use clinical judgement to institute more frequent monitoring as necessary. For Acute Myeloid Leukemia and Myelodysplastic Syndrome - if platelet count <10,000/mm^3 : 1. Continue treatment and start platelet transfusion as per institutional guidelines. After platelet transfusion, assess platelet level within a couple of hours of transfusion. Institute more frequent monitoring as clinically indicated. 2. If repeat platelet transfusions are not able to rescue platelet count to ≥10,000/mm^3 (or to ≥20,000/mm^{3}in case of accompanying fever, sepsis, or minor bleeding) in 2 days, then interrupt treatment. If subsequent transfusions are able to increase the platelet count within 14 days of interruption, consider restarting therapy at the same or previously cleared dose after discussing with the medical monitor and approval by GSK

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		medical governance. If transfusions are unable to increase the platelet count within 14 days of interruption, therapy will be discontinued. 3. Use of adjunctive therapies is permitted. 4. Use of hydroxyurea is permitted in the setting of increased blast counts in conjunction with decreased platelet counts.
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <530 (average of three ECGs over at least 15 minutes)	• Continue current dose of GSK525762 • 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.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥530 (average of three ECGs over at least 15 minutes)	• Discontinue GSK525762 and notify the GSK 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 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 <480 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 GSK Medical 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 (if

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		required), and (6) The subject is re-consented regarding the possible increased risk of QTc prolongation. • If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to 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 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
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. • May consider restarting study treatment at a reduced dose based on discussion with GSK Medical Monitor.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
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)	• Interrupt investigational drug(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.
	• 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 • 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	• Discontinue study medications, notify the GSK Medical Monitor, and refer to follow-up procedures outlined in protocol, 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 protocol Liver Chemistry Follow-Up Procedures (see Appendix 3).

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Hypo- and Hyperglycemia (for management purposes, refer to mild, moderate and severe intensity criteria; however for CRF reporting use NCI-CTCAE v4.0 [NCI, 2009] Grade 1-5)	• (Mild) Fasting blood glucose >150 mg/dL	• Monitor fasting and preprandial glucose.
	• (Moderate to Severe) Fasting blood glucose any blood glucose >250 mg/dL	• Hold investigational product and instruct subject to notify investigator immediately. • If a blood glucose >250 mg/dL is observed the subject should be monitored for ketoacidosis as clinically indicated. • If subject has evidence of ketoacidosis→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.
	• (Moderate to Severe) Fasting blood glucose <70 mg/dL	• (Moderate to Severe) Hold investigational product • Provide sugar containing liquids and monitor blood sugar closely. Check for insulin and c-peptide levels. After blood sugar normalizes • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor
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. Consider temporary discontinuation of study medications and discuss with GSK Medical Monitor. • May restart 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
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. • 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 (wnl). Continue investigational drug(s) at current dose(s).
	• Grade 2	• Consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and 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 infectious 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	• Permanently discontinue investigational drug • 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 normal. Bronchoscopy with biopsy and/or BAL is recommended. • Consider corticosteroids if infectious origin is ruled out. Taper as medically indicated.

*Baseline results are defined by the nearest time point prior to first dose. If W1D1 results are available, these are considered the baseline results. If screening occurred within 72h of fit dose, W1D1 samples are not needed and screening data are considered as baseline.

Abbreviations: GSK=GlaxoSmithKline; QTcF= QT duration corrected for heart rate by Fridericia's formula; ECG=Electrocardiogram; IRB=Institutional review board; EC=Ethics committee; ULN=Upper limit of normal; LLN=Lower limit of normal; LVEF= Left ventricular ejection fraction; ALT=Alanine Transferase; BAL=Bronchoalveolar lavage; DLCO=Diffusing Capacity of the Lung for Carbon Monoxide; IL=Interleukin

7.7.2. Dose Adjustments for Toxicity

Dose adjustments for toxicity, other than those described in Section 7.7.1, are indicated in Table 16.

Table 16 Dose Adjustment for Toxicity

Worst Grade	Action
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 ≤ 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, subject should go off protocol therapy.
4	Permanently discontinue study medication except if the event is considered non-serious and patient is likely to benefit by being on the study then hold dose for one week intervals until ≤ drug-related Grade 1 then restart after dose reduction by one dose level. If no recovery to ≤Grade 1* after a 21 day delay, subject 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). Abbreviations: DLT=Dose limiting toxicity.	

Dose escalation decisions will take into account all available data, including PK data and the safety profile of prior cohorts, relevant data from Study BET116183, 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, PK and/or pharmacodynamics] 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.

7.8. Guidelines for Events of Special Interest and Dose Modifications

The severity of adverse events will be graded utilizing the NCI-CTCAE v4.0 [NCI, 2009]. Additional details regarding diarrhea, rash and liver toxicity are outlined in Appendix 4.

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from signing informed consent until the end of the study (Final Study Visit). Any concomitant medication(s), including herbal preparations taken 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

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 leat 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.

8.2. Cautionary/Prohibited Medications

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 must not receive other anti-cancer therapy (including chemotherapy, immunotherapy, biologic therapy, or hormonal therapy, whether approved or investigational) while on treatment in this study. Short courses of steroids may be co-administered with permission from the GSK medical monitor.

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.

Aspirin may not be administered at doses that exceed 100 mg per day. Non-steroidal anti-inflammatory agents should be avoided except where they provide benefit over other analgesics; if administered, they should be used with caution and consideration should be given to co-administration with proton pump inhibitors.

Co-administration of medications that are associated with prolonged QT interval (please refer to crediblemeds.org for a complete list of these medications) is permitted as follows:

- If a subject is taking a QT-prolonging medication prior to first dose of GSK525762, then the subject may continue to take this medication without additional monitoring, so long as the baseline QTcF meets criteria as described in Section 4.2.2
- If a subject must initiate a QT-prolonging medication while receiving GSK525762, then additional ECG monitoring should be implemented, per local standard, until the QT-prolonging medication achieves therapeutic concentrations. Refer to Table 15 for QT management guidelines.

During Part 1, Antacids should not be consumed for at least 1h before and 2h after administration of GSK525762.

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

8.2.1. Drugs Potentially Affecting GSK525762 Pharmacokinetics or affected by GSK525762

In vitro data suggests that GSK525762 is only metabolized by CYP3A4 and thus coadministration of potent inducers and moderate or potent inhibitors of CYP3A4 should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. Note: any medication (including antibacterials, antifungals, or antivirals) which are necessary for the health, well-being, and standard clinical care of patients with hematologic malignancies are exempt from the restrictions below.

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.

8.3. 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, except as follows:

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. Irradiated/resected lesions should not subsequently be utilized as the sole lesion(s) for response assessment determination.

Subjects will abstain from using herbal preparations/medications throughout the study until the final study visit. Subjects enrolled in Part 1 of the study should abstain from coffee and tea from 24 hours prior to an extensive PK collection day (i.e. W1D1 and W2D7) until the end of PK collection on that day.

Herbal products include, but are not limited to:

- St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng, and marijuana.

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

Refer to Section 4.2.3 and Section 5 for follow-up assessment of subjects who are to be followed up for disease progression and/or survival after permanent discontinuation from study treatment.

8.5. 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
- closely monitor the subject for AEs/SAEs and laboratory abnormalities.
- obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study treatment if requested by the GSK Medical Monitor (determined on a case-by-case basis).
    - This plasma sample should be collected as soon as possible from the date of the last dose of on-study dosing.
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

9. LIFESTYLE REQUIREMENTS (CONTRACEPTION) AND/OR DIETARY RESTRICTIONS

9.1. Contraception

9.1.1. Female Subjects

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

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

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

Female subjects of childbearing potential must not become pregnant during the trial and for 7 months after stopping medications and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%.

Abstinence

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

Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the < 1% failure rate as stated in the product label
    - Note: Hormonal IUDs may only be used if the following criteria are met:
        - Male condoms are required AND
        - Subjects are informed of the potential for reduced systemic hormone levels from the IUD when taking GSK525762

- 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.

9.1.2. Male Subjects

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 (documentation of azoospermia)**, or**

  Condom use **PLUS** partner use of 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, **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.

Male subjects whose partners are pregnant, or whose partners become pregnant during participation in the study, must use condoms from the first dose of study medication and for 16 weeks after stopping study medication(s).

Male subjects should be advised not to donate sperm while on study and for 16 weeks after the last dose of study drug(s).”

9.2. Caffeine, Alcohol, and Tobacco

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 PK and or pharmacodynamic sample during each extensive PK session in Part 1.

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.

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

and audit trails, will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.

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

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently enrolled. Data for screen failures will be collected in source documentation at the site but will not be transmitted to GSK.

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1. Sample Size Assumptions

No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

11.1.1. Part I, Dose Escalation

The sample size in Part 1 is not driven by statistical considerations. The total number of subjects will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 60-70.

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.

Subjects in Part 1 treated at the RP2D may be included in the efficacy analysis as described in Section 11.6.1.

11.1.2. Part 2, Expansion Cohort

The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with MDS, and CTCL.

- For MDS, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, marrow CR, or PR) of 30% relative to a 10% response rate suggesting no activity. Historically, hypomethylating agent failure has conferred a poor prognosis, with a response rate to second-line therapy of 10% or less (Prebet, 2011). Investigational agents have demonstrated a response rate of approximately 30%, though no effects on overall survival have been reported (Seetharam, 2012; Kantarjian, 2010). Because of the high unmet medical need of relapsed/refractory MDS, and because no agent to date has exceeded the 30%

response rate published above, 30% was chosen as a realistic goal for subjects with MDS.

- For CTCL, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, or PR lasting more than 4 months) of 40% relative to a 20% response rate suggesting no activity. Multiple clinical studies with active and approved agents have demonstrated a response rate of 30-40% in a comparable patient population (Duvic, 2007; Piekarz, 2009; Whittaker, 2010). Therefore, a target response rate of 40% was chosen to represent the response rate of an active agent. Conversely, an agent with a response rate of 20% is unlikely to be developed further; this is approximately the response rate of placebo described in the denileukin difitox package insert [ONTAK package insert, 2008]. Therefore, 20% was chosen to represent the activity of a futile agent.

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 (e.g. Beta (0.03, 0.07)) 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.

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

Futility analysis for each disease cohort will begin when response data is available for at least 10 subjects treated at the RP2D in Part 1 and Part 2. 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 3.2.4.

For the MDS cohort, starting with a cohort of 10 subjects and allowing for a maximum sample size of 32 subjects at the RP2D with stopping guidelines as described in Section 3.2.4, this design will have a Type I Error (α) of 0.034 and 87% power. Futility analysis will be based on subjects who have at least one post-baseline disease assessment, have progressed or died, or have permanently discontinued from study treatment. The trial will be stopped early for futility if the predictive probability of success (that the response rate $\geq$ historical response rate) is less than 1%. If the true response rate is 10%, the average sample size is 20 and the probability of early termination for futility is 93%. If the true response rate is 30%, the average sample size is 31 subjects and the probability of early termination is 9%.

For the CTCL cohort, starting with a cohort of 10 subjects and allowing for a maximum sample size of 37 subjects at the RP2D with stopping guidelines as described in Section 3.2.4, this design will have a Type I Error (α) of 0.049 and 85.2% power. Futility analysis will be based on subjects who have at least one post-baseline disease assessment, have progressed or died, or have permanently discontinued from study treatment. The trial will be stopped early for futility if the predictive probability of success (that the response rate ≥ historical response rate) is less than 1%. If the true response rate is 20%, the average sample size is 23 and the probability of early termination for futility is 92%. If the true response rate is 40%, the average sample size is 36 subjects and the probability of early termination is 11%.

11.1.3. Sensitivity Analysis

No analysis of sample size sensitivity was performed.

11.1.4. Sample Size Re-estimation

No sample size re-estimation will be performed.

11.2. Analysis Populations

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

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

The PK Parameter Population: This will consist of those subjects in All Subjects Population for whom a PK parameter is available.

The Pharmacodynamic Population: This will consist of those subjects in All Subjects Population who contribute pharmacodynamic/biomarker samples.

More details of the analysis populations will be specified in reporting and analysis plan (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 Reporting and Analysis Plan (RAP). Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

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

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

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

Demographic and baseline characteristics will be summarized.

11.3.1. Analysis Datasets

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

11.3.2. Withdrawal

Reasons for subject withdrawal will be listed.

11.3.3. 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.

11.3.4. Derived and Transformed Data

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

11.3.5. 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.

11.3.6. 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 Clinical Pharmacokinetics Modelling & Simulation (CPMS) PK Methods.

There will be no adjustments for multiplicity.

11.4. Interim Analysis

Interim analysis on Part 1 may be conducted when

- Part1 is completed or
- All subjects enrolled in any or all of AML, MM, and NHL cohorts in Part 1 have had at least one post-baseline disease assessment or progressed or died or withdrawn from the study

For each disease type in Part 2, after at least 10 subjects in the MDS or cutaneous lymphoma cohorts become evaluable (have had at least one post baseline disease assessment, have progressed or died, or have permanently discontinued from study treatment) at the selected dose regimen for the Expansion Cohort, data will be reviewed for clinical benefit on an ongoing basis and the number of subjects with observed clinical benefit will be compared with the stopping guidelines provided in Section 3.2.4. For the CTCL cohort, subjects with CTCL in Part 1 treated at the RP2D will be included in this analysis of efficacy.

The study will not stop due to efficacy. The trial may continue to enrol the maximum planned sample size to provide a better an estimate on the distribution of the response rate in the target patient populations.

11.4.1. Other Stopping Criteria for Part 2

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics). Deaths, SAEs and Grade 3/4 adverse events will be carefully evaluated for causality.

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, and/or if deaths related to study drug are observed, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded. The final determination will be made by the Sponsor and investigators.

11.5. Final Analyses

Final primary analysis will occur when at least 70% of subjects are dead, have withdrawn consent, or are lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up, whichever is earlier.

The data will be listed and summarized mostly by doses. Separate analyses will be provided for Part 1 and in Part 2 where applicable. In some instances, analysis may also be generated based on the dose of GSK525762. Data from Part 1 and Part 2 may be combined for some analyses at the end of the trial, as appropriate. More detail on the data displays will be provided in the RAP.

Final OS analysis may be conducted when all subjects have completed the study.

11.6. Efficacy Analyses

11.6.1. Primary Analysis

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and response criteria described in the Section 5 Time and Events Table 7 for MM, lymphoma and/or leukemias, as noted in Appendix 6, Appendix 7 and Appendix 8, respectively. If the data warrant, the response data will be summarized by dose level. In addition, any subject in Part 1 treated at the RP2D may be included in the analysis of efficacy described below.

The primary aim of Part 2 is to detect a possibly clinically meaningful response rate in each of the disease cohorts separately. Each disease type (MDS and CTCL) will be evaluated separately.

Overall Response rate is defined as

- MDS: The percentage of subjects who achieved CR, marrow CR, or PR, as defined in Appendix 9. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided.

CTCL: ORR4 is defined as percentage of subjects who achieved a CR or PR lasting at least 4 months. Responses will be defined as per consensus guidelines [Olsen, 2011] using mSWAT criteria (Appendix 10). All subjects treated at RP2D with CTCL will be counted as the denominator. The estimate for ORR4 along with 95% exact confidence interval will be provided.

For subjects in the CTCL cohort, scans, photographs and raw flow cytometry used for response assessments may be requested for independent review. Further details regarding collection, storage, and transmission of these will be provided in the SRM

All subjects who received at least one dose of treatment will be included in the evaluation for response. Response rates and the associated 2-sided 95% exact confidence limits will be provided.

11.6.2. Secondary Analysis

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 Not Evaluable) 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 if data warrant.

The duration of response is defined for responders (subjects with CR, marrow CR, or PR for MDS cohort, or subjects with a CR or PR for CTCL cohort), as the time from the first documented evidence of response 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.

If sample size permits, duration of response will be summarized descriptively using Kaplan-Meier medians and quartiles. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP

OS along with 95% confidence intervals for leukemia subjects in Part 1, MDS subjects in Part 2, and MM subjects treated in Part 1 and cutaneous lymphoma subjects treated in Part 2, will be estimated using the Kaplan Meier method if data warrant. OS analysis for AML will exclude subjects with AML subtype M3. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis.

11.7. Safety Analyses

Safety endpoints are described in Section 2. The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a “worst-case” analysis. Complete details of the safety analyses will be provided in the RAP.

A listing by subject including treatment administered, and compliance, will be generated with dates and times of treatment administered.

All relevant safety data will be listed and summarized according to IDSL standards. The reporting and analysis plan will list the Integrated Data Standards Library (IDSL) templates for the displays. 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 for Part 1. 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 Section 5 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 the NCI-CTCAE v4.0 [NCI, 2009]. 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.

11.7.1. Extent of Exposure

Extent of exposure of GSK 525762 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 according to the duration of therapy.

11.7.2. Adverse Events

AEs will be coded and summarized by frequency and proportion of total subjects, 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 by the investigator according to the NCI-CTCAE v4.0 [NCI, 2009].

Events will be summarized by maximum toxicity grade for each initial dose level. Separate summaries will be given for all AEs, treatment-related AEs, serious AEs and AEs leading to discontinuation of study treatment.

If the AE is listed in the NCI-CTCAE v4.0 [NCI, 2009] table, the maximum grade will be summarized. Otherwise, the AEs will be summarized by maximum intensity.

AEs of special interest will be outlined in the RAP.

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

Dose-limiting toxicities (DLTs) will be listed for each subject and summarized by dose cohort according to IDSL standards.

11.7.3. Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE v4.0 [NCI, 2009] grade. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized using proportions. 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.

11.8. Pharmacokinetic Analyses

PK analyses will be the responsibility of GSK CPMS. Plasma GSK525762 and relevant metabolite(s), 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 pharmacology 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 from the ratio of AUC(0-τ) in Week 2 Day 7 / AUC(0-τ) in Week 1 Day 1. The ratio of AUC(0-τ) on Week 2 Day 7 / Week 1 Day 1 AUC(0-∞) will be calculated to assess time invariance. Plasma concentration-time data will be listed by dose, dosing regimen, and summarized using descriptive statistics (n, mean, standard deviation [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) PK 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 day, dose and dose regimen cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered and dosing regimen. If more than 2 dose cohorts are evaluated, dose proportionality of AUC and Cmax for GSK525762 will be assessed using the power model (details will be provided in the RAP).

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 PK parameters (absorption rate, Ka, apparent clearance, CL/F and volume of distribution, V/F) and summary exposure measures (Cmax, AUC and Average observed concentration (Cav) = AUC/τ) and identify important covariates (e.g., age, weight, or disease related covariates). This analysis may be reported separately.

11.9. Pharmacokinetic/Pharmacodynamic Analyses

Observed or predicted concentrations will be combined with safety, efficacy, and/or pharmacodynamic measures of interest to examine potential exposure response relationships.

The relationship between QTcF and concentration expressed as Cmax, Cav, and instantaneous time-matched concentration will be plotted graphically. A linear mixed effects analysis of the slope of the QTcF-concentration responses adjusting for baseline 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 troponin levels will be plotted graphically against summary exposure measures (e.g., Cmax, Cτ, and Cav). Where evidence of a signal is seen, linear and non-linear mixed effect models will be fitted to the data to estimate PK/pharmacodynamic parameters of interest; slope, baseline (E0), exposure producing 50% of the maximum effect (EC50), and maximum effect (Emax).

Overall efficacy data and overall tumor burden may be described using categorical/continuous models with summary exposure parameters (e.g., Cmax, Cτ, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the RAP. This analysis may be reported separately.

11.10. 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 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.

11.11. Pharmacogenetic Analyses

The results of PGx 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 PGx research and analyses are found in Appendix 5 and will be addressed in the PGx RAP.

11.12. Quality of Life Analyses

Skindex-29 inquires about how often during the previous four weeks the patient experienced the effect described in each item. It includes three domains: Emotional, Symptoms, and Functioning as well as an additional item about Treatment that is not scored. Details about the score derivation and analysis will be provided in the RAP. See Appendix 11 for more details.

12. STUDY CONDUCT CONSIDERATIONS

12.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on publicly available clinical trial registers 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 GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/ EC review and approval of study protocol and any subsequent amendments.

- Subject informed consent.
- Investigator reporting requirements.

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

Written informed consent must be obtained from each subject, prior to participation in the study.

12.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the Investigational Product (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 IRB/ EC 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 eCRF will serve as the source document.

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

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

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

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 will be defined as the date of the last visit of the last subject enrolled.

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

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

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

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 of Information on Publicly Available 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.

13. COUNTRY SPECIFIC

At the request of the Medicines and Healthcare products Regulatory Agency, Amendment 1 applies to study centres in the United Kingdom. Protocol amendment 1 removed “until commercial supply of GSK525762 becomes available” as a duration of exposure on the study in accordance with the Commission Directive 2005/28/EC. Modifications include an updated protocol synopsis as outlined in Section 15.14. The protocol amendment 1 may also apply to other countries if specifically requested.

14. REFERENCES

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. *Expert Opin Drug Safety* 2009; 8: 709–14.

Ahern K, Gilmore ES, Poligone B. Pruritus in cutaneous T-cell lymphoma: a review. *J Am Acad Dermatol*. 2012;67(4):760-768.

Cheson BD, Bennett JM, Kopecky KJ, et al.. International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003 Dec 15;21(24):4642-9.

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006; 8:419-426.

Cheson BD, Pfistner B, Juweid ME, et al.; International Harmonization Project on Lymphoma. Revised response criteria for malignantlymphoma. *J Clin Oncol*. 2007; 25(5): 579-86.

Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. *Expert Opin. Drug Saf*. 2010; 9: 15-21.

CredibleMeds. List of drugs with a risk of Torsades de Pointes. Available at: http://www.crediblemeds.org Accessed 02 March 2016

Dawson MA, Prinjha RK, Dittmann A, et al. Inhibition of BET recruitment to chromatin as an effective treatment for MLL-fusion leukaemia. *Nature*. 2011; 478: 529-533.

Delmore JE, Issa GC, Lemieux ME, et al. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. *Cell* 2011; 146: 904-17.

Devine BJ. Case Number 25 Gentamycin Therapy: Clinical Pharmacy Case Studies. *Drug Intel. Clin. Pharm*. 1974; 8: 650-55.

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

Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood*. 2007 Jan 1;109(1):31-39.

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

GlaxoSmithKline Document Number 2011N113741_06 Version 6. GSK525762 Investigator's Brochure. Report Date 06-Apr-2017.

Green SJ and Dahlberg S. Planned Versus Attained Design in Phase II Clinical Trials. *Stat Med.* 1992; 11: 853-62.

Greenberg P, C Cox, MM LeBeau, P Fenaux, P Morel, et al. *Blood 1997;*89*(6):2079-*2088

Greenberg PL, H Tuechler, J Schanz, G Sanz, G Garcia-Manero, et al. Blood 2012 120:2454-2465

Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002; 359(9312): 1121–2.

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: a systematic review. *Hepatology*. 2010; 2: 2216–22.

Innocenti F, Undevia SD, Iyer L, et al. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J *Clin Oncol.* 2004; 22: 1382-88.

Jabbour, Garcia-Manero, Batty, Shan, et al. Outcome of Patients with Myelodysplastic Syndrome after Failure of Decitabine Therapy. *Cancer*, 2010; 116(16): 3830-4.

James LP. Pharmacokinetics of Acetaminophen - Protein Adducts Liver Failure. *Drug Metab Disp*. 2009: 37: 1779-84.

Kantarjian H, Garcia-Manero G, O'Brien S, et al. Phase I clinical and pharmacokinetic study of oral sapacitabine in patients with acute leukemia and myelodysplastic syndrome. *J Clin Oncol*. 2010 Jan 10;28(2):285-91. Epub 2009 Nov 23.

Kohnken R, Wen J, Mundy-Bosse B, McConnell K, Keiter A, Grinshpun L, et al. Diminished microRNA-29b level is associated with BRD4-mediated activation of oncogenes in cutaneous T-cell lymphoma. *Blood*. 2017;131(7):771-781.

Kortuem KM, Zidich K, Schuster SR, Khan ML, Jimenez-Zepeda VH, Mikhael JR, et al. Activity of 129 single-agent drugs in 228 phase I and II clinical trials in multiple myeloma. *Clinical lymphoma, myeloma & leukemia.* 2014;14:284-90 e5.

Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. *Clinical Trials*. 2008; 5(2): 93-106.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI,, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

Liu CY, Chen PM, Chiou TJ, et al. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. *Cancer*. 2008; 112: 1932-40.

Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002; 359: 727-32.

Mertz JA. Targeting MYC dependence in cancer by inhibiting BET bromodomains. *Proc Natl Acad Sci* USA 2011; 108: 16669-74.

NCI-CTCAE (NCI Common Terminology Criteria for Adverse Events), Version 4.0, DCTD, NCI, NIH, DHHS, May 28, 2009.

Neuenschwander, B, Branson, M, and Gsponer, T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med.* 2009; 27: 2420–39.

Nicodeme E, Jeffrey K, et al. Suppression of inflammation by a synthetic histone mimic. *Nature.* 2010; 478: 1119-23.

NYHA. The Criteria Committee of the New York Heart Association (NYHA). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, Mass: Little, Brown & Co.; 1994; 253-56.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group, *Am. J. Clin. Oncol.* 1982; 5: 649-55.

Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneousT-cell lymphoma. *J Clin Oncol*. 2007;25: 3109-3115.

Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011;29(18):2598-2607.

ONTAK (denileukin diftitox) Product Information. October, 2008.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. *Regul Toxicol Pharmacol*. 2009; 54: 84–90.

Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol*. 2009;27(32):5410-5417.

Prebet T, Gore SD, Esterni B, Gardin C, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Aug 20;29(24):3322–7

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; 117:4691–95.

Seetharam M, Fan A, Tran M, Xu L, et al. Treatment of Higher Risk Myelodsplastic Syndrome Patients Unresponsive to Hypomethylating Agents with ON 01910.NA *Leukemia Research.* 2012; Jan; 36(1): 98–103.

Sekeres MA and Cutler C. How We Treat Higher-Risk Myelodysplastic Syndromes *Blood*. 2014; Feb 6;123(6):829-36.

Swerdlow, Campo, Pileri, et al. The 2016 revision of the World Health Organization Classification of Lymphoid Neoplasms. *Blood* 2016; 127(20):2375-2390.

Tefferi A. Chronic myeloid disorders: Classification and treatment overview. *Semin Hematol*. 2001; 38(1 Suppl 2): 1–4

Whittaker S, Hoppe R, Prince HM. How I treat mycosis fungoides and Sézary syndrome. *Blood*. 2016;127(25):3142-3153.

Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2010;28(29):4485-4491.

Wilke RA, Berg RL, Vidaillet HJ, et al. Impact of age, CYP2C9 genotype and concomitant medication on the rate of rise for prothrombin time during the first 30 days of warfarin therapy. *Clin Med Res*. 2005; 3(4): 207–13.

15. APPENDICES

15.1. Appendix 1: CKD-Epi Formula

The CKD-Epi method is a commonly-used surrogate marker for actual creatinine clearance (CrCl) and employs creatinine measurements and a subject's age and gender to predict the clearance.

Females, serum creatinine >62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-1.209} \times 0.993^{\text{age}}$

Females, serum creatinine ≤62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-0.329} \times 0.993^{\text{age}}$

Males, serum creatinine >80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-1.209} \times 0.993^{\text{age}}$

Males, serum creatinine ≤80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-0.411} \times 0.993^{\text{age}}$

[Levey, 2009]

15.2. Appendix 2: 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.

15.3. Appendix 3: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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	
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data colle`/ction tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants 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 participants weekly until liver chemistries resolve, stabilize or return to within baseline

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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 participants 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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) 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 participant'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 SRM.

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.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

Liver Safety Drug Restart Guidelines

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant 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 participant

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

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 (Andrade, 2009) with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- participant 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; Hunt, 2010)
- 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 participant 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 participant 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 participant 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 participant 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.
- Participants 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, participant 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 participant's outcome following study treatment rechallenge.
- GSK to be notified of any adverse events, as per Section 6.7.

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

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).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Section 7.7 will apply.
- There is no evidence of alcoholic hepatitis.
- 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 participant 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 participant 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.
- Participants 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, participant 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 participant's outcome following study treatment restart.
- GSK to be notified of any adverse events, as per Section 6.7.

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

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.

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.

15.4. Appendix 4: Dose Adjustment/Stopping Criteria/Supportive Care

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 NCI-CTCAE v4.0 [NCI, 2009] 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 Section 7.7.2 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 (octreotide, 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 GSK525762 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.

15.5. Appendix 5: 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 PK (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 analysis include:

PGx Associations with Safety Events

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002]	Human Leukocyte Antigen B (HLA-B*5701)	Individuals with HLA-B*5701 variant may be at increased risk for experiencing hypersensitivity to abacavir. Clinical assays are available for HLA-B*5701 but none has been validated. HLA-B*5701 screening would supplement but never replace abacavir clinical risk management strategies aimed at minimizing rare but serious outcomes associated with abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	HLA-B*1502	Independent studies indicated that patients carrying *HLA-B*1502* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
Warfarin	Cardiovascular [Wilke, 2005]	CYP2C9	SAEs experienced by some subjects on warfarin may be explained by variations in the CYP2C9 gene that influences the degree of anticoagulation achieved.
Irinotecan	Cancer [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 subject without this variation, raising the risk of certain side-effects. 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 saliva samples, 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

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

Study Population

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

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

Study Assessments and Procedures

A saliva sample will be collected for the PGx research using an Oragene DNA self collection tube. It is recommended that the saliva sample be taken at day 1, but may be taken at any time while the subject is participating in the clinical study after the subjects provided informed consent for the PGx research.

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 saliva 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 saliva 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 ICF.

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.

Pharmacogenetics Analyses

Specific genes sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying adverse events, and those linked to study disease and, thus, linked to drug response.

These candidate genes that may be investigated in this study include the following: the GSK Absorption, Distribution, Metabolism and Excretion genes. These play a central role in drug PK and pharmacodynamics. 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.

Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) located throughout the genome, often correlated with a candidate gene, may be studied to determine the. This approach is often employed when potential genetic effects are not well understood.

The results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. All endpoints of interest from all comparisons will be

descriptively and/or graphically summarized as appropriate to the data. In all cases, appropriate statistical methods will be used to analyze the genetic markers in the context of other clinical data. Statistical methods may include, but are not limited to Hardy-Weinberg Equilibrium testing, Comparison of Demographic and Baseline Characteristics by Genotype, Evaluation of Genotypic Effects, Evaluation of Treatment by Genotype and Gene-Gene Interaction, Linkage Disequilibrium, Multiple Comparison and Multiplicity and/or Power and Sample Size Considerations. A detailed description of the analyses to be conducted will be documented in the PGx RAP.

Informed Consent

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

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.

15.6. Appendix 6: Response Criteria for Multiple Myeloma

Consensus Recommendations [Rajkumar, 2011] **for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Working Group (IMWG) Consensus Panel**

Response Criteria [Durie, 2006]

sCR (stringent complete response):

Complete response as defined below plus:

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

CR (complete response):

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

VGPR (very good partial response):

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

PR (partial response):

- ≥ 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥ 90% or to < 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 Progressive Disease.

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 subjects without measurable serum and urine M-protein levels, or
  - bone marrow plasma cell percentage (the absolute % must be ≥10%) – only for subjects without measurable serum and urine M-protein levels and without measurable disease by FLC level.
  - definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
  - development of hypercalcemia (corrected calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.

All response categories (CR, sCR, VGPR, PR, MR and Progressive Disease) 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 Progressive Disease, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

Clarifications to IMWG criteria for coding Progressive Disease: Bone marrow criteria for Progressive Disease are to be used only in subjects 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.

15.7. Appendix 7: Response Criteria for Non-Hodgkin's Lymphoma (Part 1)

Non-Hodgkin's Lymphoma Response Criteria

This study employs response criteria from the International Workshop to standardize response criteria for Non-Hodgkin's Lymphomas [Cheson, 2007]. These criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression. To be assigned a status of PR, Complete Response/Unconfirmed (CRu) or CR, changes in tumor assessment must be confirmed by repeat studies performed at least four weeks after the criteria for response are first met. Because the criteria for Partial Response (PR) requires a decrease by ≥ 50% in sum of products of the diameters (SPD) in the six largest dominant nodes or nodal masses, six dominant nodes and/or nodal masses must be identified if > six involved nodes/nodal masses are present.

Complete Response

To be assigned a status of complete response, all changes must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for CR were met.

- Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease related B-symptoms if present prior to therapy, as well as normalization (normal limits of institutional labs) of those biochemical abnormalities (e.g., LDH) definitely attributed to NHL.
- All lymph nodes and nodal masses must have regressed to normal size. Nodes that were 1.1 to 1.5 cm in their greatest diameter prior to treatment must each have decreased to < 1.0 cm in their greatest diameter after treatment or by more than 75% in the sum of the products of the greatest perpendicular diameters (SPD) of all nodes initially measuring 1.1 to 1.5 cm. Nodes that were > 1.5 cm in their greatest diameter prior to therapy must have decreased to < 1.5 cm in the greatest diameter.
- The spleen, if considered to be enlarged before therapy on the basis of a scan, must have decreased in size and must not be palpable on physical examination. Any macroscopic nodules in any organs (i.e., splenic, hepatic) detectable on imaging studies should no longer be present. Similarly, other organs considered to be enlarged prior to therapy due to involvement of lymphoma (i.e., kidneys, liver, etc.) must have decreased in size.
- If the bone marrow was involved by lymphoma prior to treatment, the biopsy must be cleared. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in subject outcome.

Partial Response (PR)

To be assigned a status of partial response, all changes must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for PR were met.

- A decrease of > 50% in the SPD (sum of the products of the diameters) of the six largest (or less) dominant nodes or nodal masses.
- No increase in the size of the liver or the spleen. No unequivocal progression in any nonmeasurable or nondominant site.
- Splenic and hepatic nodules must regress by > 50% in SPD (sum of the products of the diameters).
- With the exception of splenic and hepatic nodules, involvement of other organs is considered nonmeasurable disease. However, all extra-nodal sites should be followed.
- Bone marrow assessment is not relevant for determination of a PR because it is assessable and not measurable disease.
- No new sites of disease.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease taking as reference the smallest SPD since the treatment started.

Progression

For subjects who have not responded or have achieved PR.

- Appearances of any new lesions/sites during or after therapy.
- Increase of ≥50% in the SPD from nadir measurement of any previously involved abnormal node or nodal mass.

Relapse

For subjects who have achieved CR or CRu.

- Appearance of any new lesions/sites during or after therapy.
- Increase of ≥50% in the SPD from nadir measurement of any previously involved dominant node >1.0 cm in its short axis.

Response Assessment

CT scans remain the standard for evaluation of nodal disease. Chest, abdominal, and pelvic CT scans should be done even if those areas were not initially involved because of the unpredictable pattern of relapse in NHL.

Confirmation Measurement/Duration of Response

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed at least four (4) weeks after the criteria for response are first met.

15.8. Appendix 8: Response Criteria for Acute Myeloid Leukaemia

[Modified Cheson, 2003]

Complete remission (CR): The subject must achieve a morphologic leukemia-free state (≤5% blasts) and have no evidence of extramedullary disease. The subject must be free of all symptoms related to leukemia, have an absolute neutrophil count ≥1 x 10^9/L and platelet count ≥100 x 10^9/L, and be transfusion independent.

CRp: Marrow response as per CR but platelet count <100 x 10^9/L.

CRi: Marrow response as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L.

Partial remission (PR): A decrease from baseline of at least 50% in the number of bone marrow blasts, to between 5% and 25% of the bone marrow aspirate.

No response: Subject does not meet criteria for CR, CRp, CRi, or PR.

Recurrence: Morphologic relapse, defined as the reappearance of peripheral blasts or increase in bone marrow blasts ≥ 5% not attributable to any other cause (e.g., infection, growth factor support, bone marrow regeneration)

15.9. Appendix 9: Response Criteria for Myelodysplastic Syndrome

[Cheson , 2006]

Complete remission (CR): Bone marrow ≤5% myeloblasts with normal maturation of all cell lines. Persistent dysplasia may be noted. The subject must have a haemoglobin concentration of ≥ 11 g/dL, an absolute neutrophil count ≥1 x 10^9/L, a platelet count ≥100 x 10^9/L, and have 0% blasts in the peripheral blood.

Marrow CR: Bone marrow ≤5% myeloblasts and decrease by ≥ 50% over pretreatment

Partial remission (PR): Bone marrow blasts decreased by ≥ 50% over pretreatment but still >5%. Cellularity and morphology not relevant

Stable disease: Failure to achieve at least PR, but no evidence of progression for > 8 weeks

Disease progression: For patients with:

- Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
- 5% - 10% blasts: ≥ 50% increase to > 10% blasts
- 10% - 20% blasts: ≥ 50% increase to > 20% blasts
- 20% - 30% blasts: ≥ 50% increase to > 30% blasts

AND

Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets, reduction in haemoglobin by ≥ 2 g/dL, transfusion dependence

Relapse after CR or PR: At least one of the following: return to pretreatment bone marrow blast percentage, decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets, reduction in haemoglobin concentration by ≥ 1.5 g/dL or transfusion dependence

15.10. Appendix 10: Staging and Response Criteria for CTCL (mSWAT method)

[Olsen, 2011]

15.10.1. Staging of Subjects with CTCL

Table 17 Modified ISCL/EORTC Revisions to the tumor-node-metastasis-blood (TNMB) Classification of MF/SS

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or National Cancer Institute (NCI) LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI

TNMB Stages	Description of TNMB
	LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

†Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.

‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Table 18 Modified ISCL/EORTC Revisions to the Staging of MF/SS

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

15.10.2. Response Assessment of Subjects with CTCL

Refer to Table 19, Table 20, Table 22, Table 23, and Table 24 for definitions of response in each category. All subjects achieving CR or PR should be confirmed by repeat assessment no sooner than 4 weeks after the prior assessment demonstrating response.

Table 19 Global Response Score

Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease	PD in any category			
Relapse	Recurrence disease in prior CR	Relapse in any category			

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.

Refer to Table 21 for definition of mSWAT

Table 20 Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.

*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides7), the response should be considered a partial response only.

†Whichever criterion occurs first.

Table 21 Modified Severity Weighted Assessment Tool (mSWAT)

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Table 22 Response in Lymph Nodes

Response	Definition
CR	All lymph nodes are now ≤1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

*Peripheral and central lymph nodes.

†Whichever criterion occurs first.

Table 23 Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or New organ involvement or Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

*Whichever criterion occurs first.

Table 24 Response in Blood

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/μL or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*As determined by absolute numbers of neoplastic cells/μL.

†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.

§Whichever occurs first.

15.11. Appendix 11: Patient Reported Outcomes Assessments for CTCL (Skindex-29)

15.11.1. US English Skindex-29

Note: please refer to the SPM for additional translations of Skindex-29

Skindex29
©MMChren,1996

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

Skindex29 - United States/English -Mapi

Skindex29
©MMChren,1996

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

Please turn to next page

Skindex29 - United States/English -Mapi.

Skindex29
©MMChren,1996

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

Skindex29 - United States/English -Mapi.

15.12. Appendix 12: Pain Assessment

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

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

Indications: Adults and children (> 3 years old) in all patient care settings.

Instructions:

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

Reference

Wong, D. and Whaley, L. (1986). Clinical handbook of pediatric nursing, ed., 2, p. 373. St. Louis: C.V. Mosby Company.

15.13. Appendix 13: Updated PK data from protocols BET115521 and BET116183

As of 11-August-2014, the pharmacokinetics of GSK525762 has been evaluated in 19 subjects in study BET115521 following single and repeated once daily administration of 2 mg to 60 mg of GSK525762 and in 2 subjects in study BET116183 following single and repeated once daily administration of 5 and 10 mg of GSK525762. The summary statistics of the preliminary PK parameters are summarized in Table 25 and Table 26 after single and repeat once 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 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 25 Summary Statistics of GSK525762 Preliminary PK Parameters Following a Single Oral Administration of GSK525762 in Study BET115521 and BET116183

Parameters	2 mg N=3	4 mg N=4	5 mg N=1	8 mg N=1	10 mg N=1	16 mg N=3	30 mg N=4	60 mg N=4
Cmax, ng/mL	51.0 (41%)	70.4 (29%)	90.6	120	117	176 (37%)	604 (30%)	940 (31%)
Tmax, h	0.5 (0.5 - 0.6)	1.2 (0.5 - 2.0)	0.62	1.1	2.0	2.0	2.0 (0.97 - 2.0)	1.0 (0.5 - 2.0)
AUC, ng.h/mL	172 (42%)	361 (35%)	467	434	1092	884 (40%)	4420 (63%)	3670 (54%)
$t_{1/2z}$, h	3.3 (103%)	5.1 (36%)	4.01	2.95	5.74	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. All data are from BET115521 study except for the 5 mg and 10 mg doses that were evaluated in BET116183 study.

Table 26 Summary Statistics of GSK525762 Preliminary PK Parameters Following Repeat Daily Oral Administration of GSK525762 in Study BET115521 and BET116183

Parameters	2 mg N=1	4 mg N=2	5 mg N=1	8 mg N=1	10 mg N=1	16 mg N=3	30 mg N=4	60 mg N=3
Cmax, ng/mL	52	47.6 ; 59.9	103	103	133	138 (25%)	603 (17%)	807 (36%)
Tmax, h	1.0	1.0 ; 4.0	0.5	0.5	0.5	1.5	0.9 (0.32 - 4.0)	1.0 (0.50 - 1.0)
AUC_τ, ng.h/mL	160	225 ; 497	511	330	911	674 (21%)	3150 (55%)	2910 (56%)
$t_{1/2z}$, h	4.27	3.69 ; 4.46	3.54	4.92	5.26	3.6 (7.8%)	5.2 (26%)	3.13 (40%)
Cmax Week 3 / Cmax Week 1	1.42	0.968 ; 0.609	1.14	0.857	1.14	0.780 (12%)	0.998 (24%)	1.12 (10%)
AUC_τ Week 3 / AUC Week 1	1.38	0.900 ; 1.64	1.10	0.759	0.834	0.774 (20%)	0.724 (12%)	0.779 (13%)
AUC_τ week 3 / AUCt Week 1	1.39	0.904 ; 1.67	1.11	0.763	0.890	0.792 (20%)	0.799 (11%)	0.807 (10%)

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. All data are from BET115521 study except for the 5 and 10 mg dose that were evaluated in BET116183 study.

15.14. Appendix 14: Protocol Changes for Amendment 1 (15-Aug-2013) from the Original Protocol (20-May-2013)

Where the Amendment Applies

Amendment 1 applies to study centres in the United Kingdom, and may also apply to other countries if specifically requested.

General Protocol Changes

The study duration has been modified at the request of the Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom. MHRA requested the removal of "until commercial supply of GSK525762 becomes available" as a duration of exposure in accordance with the Commission Directive 2005/28/EC. Changes are noted below with strikethrough of deleted words and an underlining of new language added to the amendment. In addition, the sponsor/medical monitor information page has updated information.

15.11.1 List of Changes

- **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 Part 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with relapsed refractory hematological malignancies 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, or withdrawal of consent ~~commercial supply of GSK525762 becomes available to the subject~~. An expansion cohort is planned in subjects with acute leukemias to further explore clinical activity at the MTD (Part 2).

  - **Updated 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	PPD	PPD	~~GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 4340 Collegeville, PA 19426, USA~~ PPD
Primary Medical Monitor	PPD MD	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 1450 Collegeville, PA 19426, USA PPD

15.15. Appendix 15: Protocol Changes for Amendment 2 (15-OCT-2013) from the Protocol Amendment 1 (15-AUG-2013)

Where the Amendment Applies

Amendment 2 applies to all study centres.

General Protocol Changes

At the request of the Food and Drug Administration, United Stated, the dose limiting toxicity (DLT) in Section 3.2.3 was updated to require that it must clearly be established that an event is unrelated to treatment for the event to not be considered a DLT; the stopping rules related to safety were expanded in Section 11.4.1. Additional changes include the clarification of exploratory endpoints to assess metabolites, correction of exclusion criteria number 12, and clarification of the Time and Events Table, Dietary Restrictions, and the futility analysis of Part 2. Changes are noted below with ~~strikethrough~~ to identify deleted text and **bold underlining** to identify new or replacement text.

15.12.1 List of Changes

Previous Text:

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD MD	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD , MD	PPD	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	PPD		**GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA** PPD
Secondary Medical Monitor	PPD **MD**	PPD	PPD		**GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA** PPD
~~Primary Medical Monitor~~	PPD ~~MD~~	PPD	PPD		~~GlaxoSmithKline 1250 South Collegeville Road, UP4210 Collegeville, PA 19426, USA~~ PPD
~~Secondary Medical Monitor~~	PPD ~~MD~~	PPD	PPD		~~GlaxoSmithKline 1250 South Collegeville Road, Mailstop UP 1450 Collegeville, PA 19426, USA~~ PPD

Rationale for Change:

- The Medical Monitor and contact information has been updated with changes in GSK staff.
- Previous Text:

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD), establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with relapsed and/or refractory hematologic malignancies.	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration.	○ GSK525762 PK parameters following single- (Day 1) and repeat-dose (Day 15) administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time

Part 1 Objectives		Part 1 Endpoints
		invariance and accumulation ratio.
	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters.	○ Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC, following single and repeat-dose oral administration of GSK525762
	• To evaluate the relationship between GSK525762 exposure and Pharmacodynamic (PD) response	○ Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by Bromodomain [BRD] proteins) in tumor tissue and/or peripheral blood samples.
Exploratory	○ To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 ○ To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762	• Pharmacogenomic (PGx) study using blood samples • Transcriptomics studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response

- Revised Text:

- **2. OBJECTIVES, ENDPOINTS, HYPOTHESIS**

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD), establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with relapsed and/or refractory hematologic malignancies.	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration.	○ GSK525762 PK parameters following single- (Day 1) and repeat-dose (Day 15) administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of

Part 1 Objectives		Part 1 Endpoints
		maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters.	○ Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC, following single and repeat-dose oral administration of GSK525762
	• To evaluate the relationship between GSK525762 exposure and Pharmacodynamic (PD) response	○ Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by Bromodomain [BRD] proteins) in tumor tissue and/or peripheral blood samples.
Exploratory	○ To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762	○ Pharmacogenomic (PGx) study using blood samples
	○ To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762	○ Transcriptomics studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response
	○ **To generate samples (data reported separately) with which to characterize the metabolic profile of GSK525762 after single and repeat-dosing (In the PK/PD expansion cohort only)**	○ **Samples to characterize the metabolites in plasma and/or urine**
	○ **To determine the amount of GSK525762 excreted in urine after oral single and repeat-dosing**	○ **Concentration of GSK575762 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time**

Rationale for Change:

The exploratory endpoints of Part 1 were clarified in Section 2 to include the collection and characterization of metabolites in plasma and urine that were described elsewhere in the protocol.

Previous Text:

Exclusion criteria

No evidence of pulmonary hemoptysis within the last 7 days.

Revised Text:

Exclusion criteria

~~No~~ **E**vidence of pulmonary hemoptysis within the last 7 days.

Rationale for Change:

Exclusion criteria was corrected in the synopsis and Section 4.2.2.

Previous Text (excerpt from Table in Section 1.5.1):

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** (up to 20%; 41 msec in dog) Can occur or persists after drug is cleared from plasma; general trend to increase on repeat dosing; no potentiation beyond day13 in 28 day toxicology study in dogs. Reversible on cessation of dosing; not potentiated on subsequent dosing following a 7 day dosing holiday. No significant arrhythmias were detected in preclinical studies. No clear link to human ether à go-go-related gene (hERG) binding or trafficking. No evidence of heart accumulation of GSK525762. Mechanism & risk for Torsades de Pointe is unclear. **Blood pressure (BP**) Variable changes in blood pressure following a single dose (no effects were observed in the 28 day toxicology studies); increase in mean BP up to 11 mmHg; decrease in mean BP up to 13 mmHg. **QA interval** (indirect measure of cardiac contractility). Increased QA interval at single non-tolerated doses; up to 10msec. No effects were observed in the 28 day toxicology studies).	ICF includes the risk of (fatal) arrhythmias Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK] and creatine kinase-MB [CK-MB]), cardiac monitoring (electrocardiograms [ECGs], Holter monitoring and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management cardiac events. Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 8.3). All subjects will receive their first doses of study medication (Week 1 Day 1) in the hospital

Revised Text:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** (up to 20%; 41 msec in dog) Can occur or persists after drug is cleared from plasma; general trend to increase on repeat dosing; no potentiation beyond day13 in 28 day toxicology study in dogs. Reversible on cessation of dosing; not potentiated on subsequent dosing following a 7 day dosing holiday. No significant arrhythmias were detected in preclinical studies. No clear link to human ether à go-go-related gene (hERG) binding or trafficking. No evidence of heart accumulation of GSK525762. Mechanism & risk for Torsades de Pointe is unclear. **Blood pressure (BP**) Variable changes in blood pressure following a single dose (no effects were observed in the 28 day toxicology studies); increase in mean BP up to 11 mmHg; decrease in mean BP up to 13 mmHg. **QA interval** (indirect measure of cardiac contractility). Increased QA interval at single non-tolerated doses; up to 10msec. No effects were observed in the 28 day toxicology studies).	ICF includes the risk of (fatal) arrhythmias Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK] and creatine kinase-MB [CK-MB]), cardiac monitoring (electrocardiograms [ECGs], Holter monitoring and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management cardiac events. Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 8.3). All subjects will receive their first doses of study medication (Week 1 Day 1 **and Week 1 Day 2**)

Rationale for Change:

The Mitigation Strategy in Section 1.5.1 Risk Assessment was updated to include the complete Study Day details for clarification.

Previous Text:

3.2.3 Dose Limiting Toxicity (DLT)

A dose-limiting toxicity (DLT) is defined as a clinically significant AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first 3 weeks after administration of the first dose that meets any of the following criteria:

Revised Text:

3.2.3 Dose Limiting Toxicity (DLT)

An event will be considered a DLT if it occurs within the first 3 weeks of treatment, and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment. ~~A dose-limiting toxicity (DLT) is defined as a clinically significant AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first 3 weeks after administration of the first dose that meets any of the following criteria:~~

Rationale for Change:

The text was updated to clarify criteria for a DLT.

Previous Text (Table 6, Table 9, Table 10 and Table 11):

Table 6 Time and Events: Part 1

Procedure (Notes)		SCR	Week 1							Week 2							W3		W4		W5	W7	W10	q3W	q6W	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	X	X	X	Daily									
Review subject 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
Vital Signs (SBP, DBP, heart rate, respiratory rate, temp.)		X	X				X			X							X		X		X	X	X	X		X
Height and weight (Height at SCR only)		X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test (As appropriate [subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation])		X																								
Adverse events		continuous from signing of informed consent																								

Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	
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																									
ECHO (Within 35 days of first dose)	X													X						X		X		X	X
12-lead ECGs (Screening ECGs within 14 days of first dose. Triplicate ECGs prior to dosing. For timing of 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 performed daily through W2.)	X	O	O			O	X		X			X		X	O	X	X	X	X	X	O	X	X		X
Holter monitoring (At least 24 h, on dosing days start predose.)	X	X				X									X			X				X			
Telemetry (Starting predose and for at least 48 h)		X	X																						
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																									
PK Blood samples		X	X			X						X		X	X	X					X			X[a]	
Blood samples for biomarkers (PD)	X	X	X												X										
Blood samples for plasma cytokines	X	X	X												X										
PK Urine samples (only for subjects in PK/PD expansion)	X																X								
PD Tumor Sample [b]	X[b,c]	Tissue and Timing to be based on tumor type and emerging data. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM.																							

Procedure (Notes)	SCR	Week 1							Week 2							W3		W4		W5	W7	W10	q3W	q6W	EOT
		D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Translational Research [d]																									
Pharmacogenomics (PGx) blood sample	X																								
Blood samples for circulating biomarkers (cfDNA etc.) collected at: screening; date of	X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression																							
Archival tumor tissue	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.																									

a. For subjects on study longer than 12 weeks, collect a pre-dose PK sample q6W.
b. PD tumor samples will be collected when feasible (see Table 8 disease specific assessments for details).
c. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.
d. Refer to Section 6.6 for details on Translational Research and Appendix 5 for details on PGx Research.

Abbreviations: ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PGx=Pharmacogenetics; COPD=Chronic obstructive pulmonary disease; SPM=Study Procedures Manual; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 9 Time and Events: Part 1 Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling, Week 1 and Week 2

	W1D1									W1D5	
Procedure	**pre dose**	**15 min ± 5m**	**30 min ±5m**	**1h ±10m**	**2h ±15m**	**4h ±15m**	**8h ±1h**	**12h ±2h**	**24h ±1h**	**30 min ±10m**	**3h ±30m**
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to PK draw	X	X	X	X	X	X	X	X	X	X	X
PK sample [a]	X	X	X	X	X	X	X	X	X [a]	X	X
Blood sample for biomarkers	X				X	X	X		X		
Plasma cytokine sample	X				X	X	X		X		
Urine PK sampling (Only at MTD or RP2D in 6 subjects)	X										

The frequency of sampling of plasma cytokines may be changed (likely reduced) based on data from the first few subjects assessed.

a. Pharmacokinetic sample to be obtained before dosing on Week 1, Day 2.

Table 10 Time and Events: Part 1 Serial Electrocardiograms and Pharmacokinetics, Week 3 and Week 7

	W2D7 + 2 days									W7D1 ±4 days (if dose was escalated, +4 to +7 days)		
Procedure	**pre dose**	**15 min ± 5m**	**30 min ±5m**	**1h ±10m**	**2h ±15m**	**4h ±15m**	**8h ±1h**	**12h ±2h**	**24h ±1h[a]**	**pre dose**	**0.5-2h**	**4 - 8h**
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to PK draw	X	X	X	X	X	X	X	X	X	X	X	X
PK sample	X	X	X	X	X	X	X	X	X	X	X	X
Urine PK sampling (Only at MTD in 6 subjects)		0-2h			2-24h							

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

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Table 11 Time and Events: Part 2

Part 2 Procedure	Notes	SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			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											
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		
Review compliance	Not required when dosed in clinic.			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
Vital Signs		X	X	X	X	X	X	X	X		X
Weight	Height at SCR	X	X			X	X	X	X		X

Part 2 Procedure	Notes	SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			D1	D1	D1	D1	D1	D1	D1	D1	
and height	only										
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	
Cardiac Monitoring											
ECHO	Within 35 days of first dose	X	X			X	X	X		X	X
12-lead ECGs (triplicate)	Screening ECGs within 35 days of first dose. Triplicate ECGs prior to dosing. If QTcF increase >30msec, ECGs performed daily through W2.	X	X	X	X	X	X	X	X		X
Holter monitoring	At least 24 h, on dosing days start predose.	X				X					
Tumor PD Assessment											
PD Tumor sample		X[a]	1 biopsy between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of tumor sample collection.								

Part 2 Procedure	Notes	SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			D1	D1	D1	D1	D1	D1	D1	D1	
PK and Blood PD											
PK Blood samples	Three samples to be collected each sampling day for each type of analysis: Predose within 60 minutes prior to dose, single draw between 2-4 h postdose, single draw between 6-8h postdose		X			X	X			X	
Blood sample for biomarker			X				X				X
Blood samples for plasma cytokines			X				X				
Translational Research											
PGx blood sample			X								
Blood samples for circulating biomarkers (cfDNA etc.)		X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression								
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.											

1. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; PD=Pharmacodynamics; PK=Pharmacokinetics; PGx=Pharmacogenetics; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; Wk=week

Revised Text:

Table 6 Time and Events: Part 1

Procedure (Notes)		SCR	Week 1							Week 2							W3		W4		W5	W7	W10	q3W	q6W	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	X	X	X	Daily									
Review subject 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
Vital Signs (SBP, DBP, heart rate, respiratory rate, temp.)		X	X				X			X							X		X		X	X	X	X		X
Height and weight (Height at SCR only)		X	X							X							X		X		X	X	X	X		X
Chest x-ray		X																								
Pulmonary function test (As appropriate [subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation])		X																								
Adverse events		continuous from signing of informed consent																								

Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	
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																									
ECHO (Within 35 days of first dose)	X													X						X		X		X	X
12-lead ECGs (Screening ECGs within 14 days of first dose. Triplicate ECGs prior to dosing. For timing of 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 performed daily through W2.)	X	O	O			O	X		X			X		X	O	X	X	X	X	X	O	X	X		X
Holter monitoring (At least 24 h, on dosing days start predose.)	X	X				X									X			X				X			
Telemetry (Starting predose and for at least 48 h)		X	X																						
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see following tables																									
PK Blood samples **for GSK525762**		X	X			X						X		X	X	X					X			X[a]	
PK blood samples for metabolite evaluation (only at MTD or RP2D in 6 subjects)		**X**	**X**											**X**	**X**										
Blood samples for biomarkers (PD)	~~X~~	X	X												X										**X**
Blood samples for plasma cytokines	~~X~~	X	X												X										
PK Urine samples (only **at MTD or RP2D in 6 subjects** ~~for subjects in PK/PD expansion~~)	X	**X**	**X**											**X**	**X**		~~X~~								
PD Tumor Sample [b]	X[b,c]	Tissue and Timing to be based on tumor type and emerging data. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM.																							

Procedure (Notes)	SCR	Week 1							Week 2							W3		W4		W5	W7	W10	q3W	q6W	EOT
		D1	D2	D3	D4	D5	D6	D7	D1	D2	D3	D4	D5	D6	D7	D1	D4	D1	D4	D1	D1	D1	D1	D1	
Translational Research [d]																									
Pharmacogenomics (PGx) blood sample	X																								
Blood samples for circulating biomarkers (cfDNA etc.) ~~collected at: screening; date of~~	X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression																							
Archival tumor tissue	X																								
Tumor biopsy at progression																									**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.																									

a. For subjects on study longer than 12 weeks, collect a pre-dose PK sample q6W.
b. PD tumor samples will be collected when feasible (see Table 8 disease specific assessments for details).
c. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.
d. Refer to Section 6.6 for details on Translational Research and Appendix 5 for details on PGx Research.

Abbreviations: ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PGx=Pharmacogenetics; COPD=Chronic obstructive pulmonary disease; SPM=Study Procedures Manual; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 9 Time and Events: Part 1 Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling, Week 1 ~~and Week 2~~

	W1D1 – W1D2									**W1D5**	
Procedure	**pre dose**	**15 min ± 5m**	**30 min ±5m**	**1h ±10m**	**2h ±15m**	**4h ±15m**	**8h ±1h**	**12h ±2h**	**24h ±1h**	**30 min ±10m**	**3h ±30m**
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to PK draw	X	X	X	X	X	X	X	X	X	X	X
PK sample for GSK525762[a]	X	X	X	X	X	X	X	X	X [a]	X	X
PK sample for metabolite (only at MTD or RP2D in 6 subjects)[a]	X	X	X	X	X	X	X	X	X [a]		
Blood sample for biomarkers (PD)	X[b]				X	X	X		X		
Plasma cytokine sample	X[b]				X	X	X		X		
Urine PK sampling (Only at MTD or RP2D in 6 subjects)	X	**0-2 h**				**2-24 h**					

The frequency of sampling of plasma cytokines may be changed (likely reduced) based on data from the first few subjects assessed.

b. Pharmacokinetic sample to be obtained before dosing on Week 1, Day 2.

c. May be collected **within 14 days prior to first dose.**

Table 10 Time and Events: Part 1 Serial Electrocardiograms and Pharmacokinetics, Week ~~3~~ 2 and Week 7

Procedure	W2D 4	W2D 6	W2D7 + 2 days									W7D1 ±4 days (if dose was escalated, +4 to +7 days)		
	pre dose	pre dose	pre dose	15 min ± 5m	30 min ±5 m	1h ±10 m	2h ±15 m	4h ±15 m	8h ±1 h	12h ±2 h	24h ±1 h	pre dose	0.5 -2h	4 - 8 h
12-lead ECG, in triplicate, 5 minutes apart and within 10 min prior to PK draw	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for biomarkers			X											
Blood samples for plasma cytokines			X											
Urine PK sampling (Only at MTD in 6 subjects)				0-2h			2-24h							

The frequency of sampling may be changed (likely reduced) based on data from the first few subjects assessed.
Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Table 11 Time and Events: Part 2

Part 2 Procedure	Notes	SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			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											
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		
Review compliance	Not required when dosed in clinic.			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
Vital Signs		X	X	X	X	X	X	X	X		X
Weight	Height at SCR	X	X			X	X	X	X		X

Part 2 Procedure	Notes	SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			D1	D1	D1	D1	D1	D1	D1	D1	
and height	only										
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	
Cardiac Monitoring											
ECHO	Within 35 days of first dose	X	X			X	X	X		X	X
12-lead ECGs ~~(triplicate)~~	Screening ECGs within 35 days of first dose. ~~Triplicate~~ ECGs prior to dosing. If QTcF increase >30msec, ECGs performed daily through W2.	X	X	X	X	X	X	X	X		X
Holter monitoring	At least 24 h, on dosing days start predose.	X				X					
Tumor PD Assessment											
PD Tumor sample		X[a]	1 biopsy between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of tumor sample collection.								

Part 2 Procedure	Notes	SCR	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1	W2	W3	W4	W7	W10	q3W	q6W	
			D1	D1	D1	D1	D1	D1	D1	D1	
PK and Blood PD											
PK Blood 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 to 2** ~~2-4~~ h postdose, single draw between **4** ~~6~~-8h postdose		X			X	X			X	
Blood sample for biomarker **(PD)**			X				X				X
Blood samples for plasma cytokines			X				X				
Translational Research											
PGx blood sample			X								
Blood samples for circulating biomarkers (cfDNA etc.)		X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression								
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.											

1. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; PD=Pharmacodynamics; PK=Pharmacokinetics; PGx=Pharmacogenetics; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; Wk=week

Rationale for Changes:

The Time and Events tables were updated to clarify pharmacodynamic and translational research sample collection in Table 6, Week 1 serial ECGs and sample collection in Table 9, blood sample collection for biomarkers in Table 10, and remove triplicate ECG in Table 11.

Previous Text:

6.3.5 Electrocardiograms

ECGs will be performed using a standard 12-lead ECG machine that automatically calculates the Heart Rate (HR) and measures PR, QRS, QT and QTcF intervals. 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 PK sampling day. Triplicate ECGs should be performed for all time points on Serial PK sampling days. During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Section 5 Time and Events Tables.

Revised Text:

6.3.5 Electrocardiograms

ECGs will be performed using a standard 12-lead ECG machine that automatically calculates the Heart Rate (HR) and measures PR, QRS, QT and QTcF intervals. 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, **triplicate** ~~a single~~ 12-lead ECG should be performed at ~~Screening and at~~ all ~~other~~ time points **indicated in the Section 5 Time and Events Tables** ~~that are not associated with a Serial PK sampling day. Triplicate ECGs should be performed for all time points on Serial PK sampling days.~~ During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Section 5 Time and Events Tables.

Rationale for Change:

The corrections were made for consistency with the Time and Events Table 5.

Previous Text:

6.6.2 Tumor Tissue Collection for PD Cohort

Subjects who consent to tumor PD assessments will also be required to provide pre- and post-treatment tumor specimens as appropriate in order to assess tumor PD response. The PD tests and tissue required are disease specific as outlined below.

- For subjects with leukemias, changes in specific protein markers and/or mRNA expression signatures will be assessed in bone marrow or tumor cell-enriched PBMCs isolated from whole blood.

- For subjects with lymphomas, lymph node biopsies (or bone marrow, if appropriate) samples will be required before and after treatment to evaluate changes in tumor-specific protein markers and/or gene expression signatures.
- For subjects with MM, bone marrow will be evaluated for changes in tumor-specific protein markers and/or gene expression signatures (for example, c-Myc).

Revised Text:

6.6.2 Tumor Tissue Collection for PD Cohort

Subjects who consent to tumor PD assessments will also be required to provide pre- and post-treatment tumor specimens as appropriate in order to assess tumor PD response. The PD tests and tissue required are disease specific as outlined below.

- For subjects with leukemias, changes in specific protein markers and/or mRNA expression signatures will be assessed in bone marrow **and/**or tumor cell-enriched PBMCs isolated from whole blood.
- For subjects with lymphomas, lymph node biopsies (or bone marrow, if appropriate) ~~samples~~ will be required before and after treatment to evaluate changes in tumor-specific protein markers and/or gene expression signatures.
- For subjects with MM, bone marrow will be evaluated for changes in tumor-specific protein markers and/or gene expression signatures (for example, c-Myc).

- Rationale for Change:

Section 6.6.2 was modified for clarification of sample collection.

Previous Text:

7.3 Meals and Dietary Restrictions

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 PK variability.

Revised Text:

7.3 Meals and Dietary Restrictions

Subjects will fast for at least one hour prior to each dose of study drug. **Subjects should not eat a heavy meal in the morning prior to the 1 hour washout before dosing to minimize potential risk for food interaction. On serial PK sampling 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.

Rationale for Change:

The change was made to minimize the potential food interactions with the study drug.

Previous Text:

11.1.2 Part 2, Expansion Cohort

The primary goal of Part 2 is to detect a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, PR or a morphologic leukemia-free state) of 20% in AML relative to a 5% response rate suggesting no activity.

Symbolically, the null hypothesis is:

H_0: $_{RR} \leq 5\%$

The alternative hypothesis is:

H_A:$_{RR} \geq 20\%$

Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥20% and ≥5% at interim and final analysis using a weak/non-informative prior.

To determine a maximal sample size for Part 2, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated. To test the hypotheses (RR=20% versus RR=5%) by Green-Dahlberg design, 40 subjects would be needed to minimize the Type I (< 5%) and Type II error rate (i.e., Power > 85%).

Using this sample size, a Bayesian design was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior 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 and the likelihood (i.e., the data). A very weak prior Beta (0.02, 0.08) with a mean response rate of 20% 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 and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.,

$$p \sim \text{Beta}(0.02 + x, 0.08 + n\text{-}x) \text{ with the posterior mean } (0.02+ x)/(0.\ 1 + n).$$

Starting with a cohort of 20 subjects and allowing for a maximum sample size of 40, this Bayesian design will have a type I error rate (α) of 5% and 89% power. For the interim analysis at N=20, if the predictive probability that the response rate ≥20% (H1) is small (i.e., less than 2% chance) or equivalent to observe one or no response in the first evaluable 20 subjects, the enrollment will be stopped due to futility. Otherwise, the enrolment will continue to the target sample size of 40. For the final analysis, if the

posterior probability that the response rate of >5% (H0) is large (i.e., greater than 95% chance), or equivalent to observe at least 5 responses in 40 subjects, sufficient statistical evidence has been provided in favor of declaring response rate >20%.

Revised Text:

11.1.2 Part 2, Expansion Cohort

The primary goal of Part 2 is to detect a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, PR or a morphologic leukemia-free state) of 20% in AML relative to a 5% response rate suggesting no activity.

Symbolically, the null hypothesis is:

H_0: $_{RR} \leq 5\%$

The alternative hypothesis is:

H_A:$_{RR} \geq 20\%$

Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥20% and ≥5% at interim and final analysis using a weak/non-informative prior.

To determine a maximal sample size for Part 2, a traditional, 2-stage Green-Dahlberg design [Green, 1992] was evaluated. To test the hypotheses (RR=20% versus RR=5%) by Green-Dahlberg design, 40 subjects would be needed to minimize the Type I (< 5%) and Type II error rate (i.e., Power > 85%).

Using this sample size, a Bayesian design was evaluated. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior 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 and the likelihood (i.e., the data). A very weak prior Beta (0.02, 0.08) with a mean response rate of 20% 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 and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.,

$$p \sim \text{Beta}(0.02 + x, 0.08 + n\text{-}x) \text{ with the posterior mean } (0.02+ x)/(0.\ 1 + n).$$

Starting with a cohort of 20 subjects and allowing for a maximum sample size of 40, this Bayesian design will have a type I error rate (α) of 5% and 89% power. For the interim analysis at N=20, if the predictive probability that the response rate ≥20% (H1) is small (i.e., less than 2% chance) or equivalent to observe one or no response in the first evaluable 20 subjects, the enrollment will be stopped due to futility. **Futility analysis**

will be based on subjects who have at least one post-baseline disease assessment. Otherwise, the enrolment will continue to the target sample size of 40. For the final analysis, if the posterior probability that the response rate of >5% (H0) is large (i.e., greater than 95% chance), or equivalent to observe at least 5 responses in 40 subjects, sufficient statistical evidence has been provided in favor of declaring response rate >20%.

Rationale for Change:

To clarify that futility analysis of response in the expansion cohort will require a population of subjects with at least one response assessment.

Previous Text:

11.1 Analysis Populations

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

Revised Text:

11.1 Analysis Populations

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

Rationale for Change:
The change was made for clarification of the analysis population.

Previous Text:

11.14.1 Other Stopping Criteria for Part 2

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics.

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded. The final determination will be made by the Sponsor and investigators.

Revised Text:

11.14.1 Other Stopping Criteria for Part 2

Safety will be reviewed on an ongoing basis by the Safety Review Team (SRT) which will be compromised of, at a minimum, a GSK medical monitor, GSK Global Safety representative, and GSK clinical study representative (including a representative from Biostatistics). **Deaths, SAEs and Grade 3/4 adverse events will be carefully evaluated for causality.**

If clinically significant adverse events or toxicities are observed in more than one third of the subjects, **and/or if deaths related to study drug are observed**, enrollment may be terminated and/or a lower-dose cohort may be opened or expanded. The final determination will be made by the Sponsor and investigators.

Rationale for Change:

The stopping criteria in Part 2 was updated to clarify that deaths related to study drug are included in the evaluation for stopping the study.

Previous Text:

15.4 Appendix 4: Dose Adjustment/Stopping Criteria/Supportive Care

Fever

Safety monitoring cytokine blood samples may be collected (based on Section 7.7.1 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.

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 NCI-CTCAE v4.0 [NCI, 2009] 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.

Revised Text:

15.4 Appendix 4: Dose Adjustment/Stopping Criteria/Supportive Care

Fever

Safety monitoring cytokine blood samples may be collected (based on Section 7.7.1 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.

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 NCI-CTCAE v4.0 [NCI, 2009] 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 Section 7.7.2 for additional guidance.

Rationale for Change:

Section 7.2.2 was added for reference to the guidance.

15.16. Appendix 16: Protocol Changes for Amendment 3 (12-NOV-2014) from the Protocol Amendment 2 (15-OCT-2013)

Where the Amendment Applies

Amendment 3 applies to all study centres.

General Protocol Changes

Amendment No. 3: The secondary objectives of Part 1 were updated to include evaluation of the clinical activity of GSK525762 (response rate and overall survival). Additional details of twice daily (BID) dosing during dose escalation were included. Eligibility criteria refined: 1) Clarification of eligibility for subjects with AML (Part 1 and 2). Platelets count eligibility criteria were specified for each group of hematological malignancies separately. 3) Exemption of exclusion due to prior allogeneic stem cell transplant added. DLT for hematological toxicities clarified and dose reduction algorithm for thrombocytopenia added. Study statistic amended for part 2 (AML expansion cohort): hypothesis and number of patients. Data from ongoing preclinical and clinical research added. Time point of collection for samples for disease and efficacy assessments refined. List of baseline assessments for each indication added. Minor clarifications, reformatting of tables and typographical errors are also addressed in this amendment.

15.13.1 List of Changes

Title Page

Rationale for Change: Clarification of indication, addition of twice daily dosing cohort to protocol

Revised Text (strikethrough=deleted text; underline=new text):

Description

This is an open-label repeat dose, multicenter, 2-part study to determine the MTD and the recommended Phase 2 dose (RP2D) for GSK525762 given in subjects with acute leukemia and multiple myeloma/non-Hodgkin's Lymphoma, once-daily orally and twice daily orally. Part 1 will be conducted in adult subjects with relapsed and/or refractory hematological malignancies. An expansion cohort (Part 2) is planned to further explore clinical activity of GSK525762 in subjects with specific subtypes of acute leukemias based on emerging data.

Title Page, Authors

Rationale for Change: The sponsor information were updated based on internal GSK team personnel changes.

Revised Text

PPD ~~Global Clinical Safety & Pharmacovigilance, USA~>

PPD Precision Medicine and Diagnostics, USA

PPD ~~Global Clinical Operational Sciences, USA~>

PPD Biology, Epigenetics Management, USA

PPD Global Clinical Safety & Pharmacovigilance, USA

PPD Global Formulation Development, PTS, USA

PPD Biotransformation and Drug Disposition, PTS, UK
PPD Molecular Medicine Unit, USA
PPD Cancer Research Epigenetics Management, USA
PPD Clinical Pharmacology Modeling & Simulation, USA
PPD ~~Cancer Research Epigenetics Management, USA~~
PPD Global Clinical Operational Sciences, USA
PPD Global Clinical Operational Sciences, USA
PPD ~~Quantitative Sciences Genetics, USA~~
PPD Clinical Oncology, USA
PPD Global Clinical Operational Sciences , UK
PPD SA Pathology, PTS, UK
PPD Global Clinical Safety & Pharmacovigilance, USA
PPD ~~Global Clinical Safety & Pharmacovigilance, USA~~
PPD EpiNova DPU, UK
PPD ~~Global Clinical Safety & Pharmacovigilance, USA~~
PPD
PPD Biology, Epigenetics Management, USA
PPD 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.

Revised Text:

Medical Monitor and Sponsor Contact Information

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD , MD, PhD	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, PhD	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road UP4410 Collegeville, PA 19426, USA PPD

Sponsor Registered Address:

Rationale for Change: Global Update of business address for GSK

Revised Text:

GlaxoSmithKline
~~Iron Bridge~~ Research & Development Limited
980 Great West Road
~~Stockley Park West, Uxbridge,~~
Brentford
Middlesex, ~~UB11 1BU,~~ TW8 9GS
UK

~~Telephone:~~ PPD

ABBREVIATIONS

Rationale for Change: Abbreviations added as part of the protocol amendment and clarification

Revised Text:

BID	*Bis in die* - Twice daily
N-CRM	Neuenschwander continual reassessment method
QD	*quaque die* - Once daily

TRADEMARK INFORMATION

Rationale for Change: Omission

Revised Text:

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
WinNonlin

PROTOCOL SYNOPSIS

Rationale for Change: Twice daily dosing will be assessed in a formal separate cohort. No formal MTD analysis in separate cohorts for the different indication will be conducted.

Revised 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 Part 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with relapsed refractory hematological malignancies will be enrolled in ~~the~~ once

daily (QD) and twice daily (BID) dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. An expansion cohort is planned in subjects with acute myeloid leukemias to further explore clinical activity at the MTD or RP2D (Part 2).

STUDY RATIONALE

Rationale for Change: Clarification of indication

Revised Text:

Current data from GSK525762 preclinical development indicate a potential to inhibit the BET family of BRD proteins and that this inhibition may have clinical utility in the treatment of various tumors, including hematological malignancies. Relapsed and/or refractory hematological malignancies such as Acute Myeloid Leukemia (AML), Adult Acute Lymphoblastic Leukemia (ALL), non-Hodgkin's Lymphoma (NHL), Multiple Myeloma (MM) and high-risk Myelodysplastic Syndromes (MDS) have an overall poor outlook. This is the first study of this agent to be conducted in subjects with these relapsed and/or refractory hematological malignancies for which no standard therapies are anticipated to result in a durable remission.

OBJECTIVES AND ENDPOINTS

Rationale for Change: Objectives and Endpoints were updated to reflect the addition of a BID dosing cohort; to clarify the target indications and to clarify specimens required and analysed for the exploratory research. Overall response rate and overall survival were added as secondary endpoints. The statistical hypothesis was updated in accordance with the changes.

Revised Text:

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) and/or twice daily (BID) dosing schedules, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with relapsed and/or refractory AML and other hematologic malignancies.	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration following QDand/or BID dosing schedules.	○ GSK525762 PK parameters following single- (Day 1) and repeat-dose (Day 15) administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters following QD and/or BID dosing schedules.	○ Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC, following single and repeat-dose oral administration of GSK525762
	• To evaluate the relationship between GSK525762 exposure and ~~P~~pharmacodynamic (PD) response following QD and/or BID dosing schedules.	○ Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by Bromodomain [BRD] proteins) in tumor tissue and/or peripheral blood samples.
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	○ Assess overall response rate (RR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma.

Part 1 Objectives		Part 1 Endpoints
Exploratory	○ To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD and/or BID dosing schedules.	○ Pharmacogenomic (PGx) study using blood or buccal samples
	○ To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	○ Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response
	○ To generate samples (data reported separately) with which to characterize the metabolic profile of GSK525762 after single and repeat-dosing (In the PK/PD expansion cohort only).	○ Samples to characterize the metabolites in plasma and/or urine
	○ To determine the amount of GSK525762 excreted in urine after oral single and repeat-dosing.	○ Concentration of GSK5~~7~~25762 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in relapsed or refractory acute myeloid leukemia (r/r AML).	• Objective response rate (% of subjects achieving Complete Response (CR), Partial Response (PR), CRp (as per CR but platelet count <100 x 10^9/L) or morphologic leukemia-free state) per response criteria.
Secondary	• To characterize the PK of GSK525762 in subjects with ~~relapse refractory hematology malignancies~~ r/r AML after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the exposure response (i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in ~~acute leukemia.~~ r/r AML.	○ PK/PD relationship between GSK525762 exposure markers and safety and efficacy parameters.
	• To evaluate the safety and tolerability of RP2D of GSK525762 in ~~acute leukemia~~ r/r AML.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.

Part 2 Objectives		Part 2 Endpoints
	• To evaluate the relationship between GSK525762 exposure and PD response in ~~acute leukemia~~ r/r AML.	○ Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	○ To determine the clinical activity of GSK525762 in r/r AML.	○ Overall survival (OS, the time from the treatment start date until death from any cause)
Exploratory	○ To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762	○ Pharmacogenomic (PGx) study using or buccal blood samples
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762	○ Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response; Leukemic Stem Cell studies; PDX model studies and other translational medicine studies

Hypothesis	○ The primary goal of Part 2 is to detect a clinically meaningful response rate of ~~20~~30% relative to a ~~5~~10% response rate suggesting no activity in subjects with acute leukemia. This will be conducted by testing the null hypothesis that P0≤0.~~05~~010 versus the alternative that P1≥0.~~20~~0 30, assuming the maximum response rate for an ineffective drug is 0.~~05~~10 and the minimum response rate for an effective drug is 0.~~20~~.3

Inclusion Criteria

Rationale for Change: Clarification of AML eligibility and that GSK should be consulted prior to enrolment. Platelet count eligibility criteria for MM was amended based on discussion with investigators and GSK to reflect standard of care. Mistake in Table reference was corrected.

Revised Text:

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 number 3: In Part 1, subjects must have relapsed and/or refractory hematologic malignancies (leukemias, myeloproliferative neoplasms, lymphomas, and myelomas) for which no standard therapies are available or anticipated to result in remission. ~~In Part 2, subjects must have a diagnosis of relapsed and/or refractory Acute Myeloid Leukemia (AML).~~

~~AML~~In Part 2, subjects must have Acute Myeloid Leukemia (AML).

Subjects with AML (Part 1 and Part 2), are eligible if they

○ have relapsed and/or refractory disease, *OR*

- are ≥65 years of age ~~who are~~and not candidates for or have refused standard chemotherapy.

Inclusion criteria number 10: Adequate organ system functions (at both screening and where applicable pre first dose) as defined in below.

Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Platelets (~~only~~ for subjects with lymphoma ~~or~~)	≥ 75,000
Platelets (for subjects with MM)	≥ 50,000 (transfusion independent)
Platelets (for subjects with acute leukemia)	No restrictions

For MM subjects, calculated creatinine clearance criteria is <2.5mg/dL or ~~14~~24-hour urine creatinine clearance of ≥ 30 mL/min

Exclusion Criteria

Rationale for Change: Clarification of exclusion criteria to allow participation of subjects where prior allogeneic stem cell transplantation does not impact the study data. Clarification of use of anticoagulants.

Revised Text:

Exclusion criteria number 4: Subjects with prior allogeneic stem cell transplant are excluded unless

- transplant was >60 days prior to study enrollment.
- subject has not taken immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) for at least 1 month
- no signs or symptoms of graft versus host disease other than Grade 1 skin involvement
- no active infection

Exclusion criteria number 5: ~~Current u~~Use of anticoagulants (e.g., warfarin, heparin) at therapeutic levels within ~~14~~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, as appropriate.

- **DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**

Rationale for Change: To include BID dosing cohort.

Revised Text:

Starting dose will be 5 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. BID dosing will be explored in a parallel cohort. Alternate dosing schedules ~~(Twice daily [BID] or~~e.g. intermittent dosing) may be ~~considered~~required to manage toxicities and may be considered based on investigator assessment and after consultation with GSK; and may be implemented if the safety, pharmacokinetic (PK), and

pharmacodynamic (PD) data suggest that a sufficient therapeutic exposure cannot be achieved using the ~~initial~~protocol schedule and after a protocol amendment.

- **PHARMACOKINETIC/PHARMACODYNAMIC, EFFICACY and SAFETY MEASUREMENTS:**
- **Rationale for Change:** Clarification that PK and PD sampling in Part 1 and Part 2 differ. Response assessment for haematologic malignancies differs by indication; therefore language was replaced with a broader term that encompasses all indications. Analyte name for safety measurement was clarified.
- **Revised Text:**
- There will be serial blood sampling for PK and PD measurements in Part 1 of this study and more limited PK sampling in Part 2 of this study. Single safety PK blood draws may be collected for subjects with severe adverse events or adverse events of concern. In addition, pre-treatment and post-treatment tumor tissue samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.
- ~~CR, PR, CRp or morphologic leukemia-free state~~ Type and duration of response in AML, MM and NHL.
- Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events will be performed. Stringent cardiac 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 and triplicate 12-lead ECGs prior to dosing on selected days and prior to drawing PK samples on serial PK sampling days. Laboratory testing includes, in addition to standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels, testing for troponin, N-terminal prohormone B-type Natriuretic Peptide (NT pro-BNP), c-peptide, 1,5-Anhydroglucitol (1, 5 AG), Hemoglobin A1c (HbA1c), and thyroid monitoring. Additional safety assessments may be necessary based on emerging data.
- **STATISTICAL ANALYSIS:**
- **Rationale for Change:** Clarification of when futility assessment will be conducted.
- **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 designed to evaluate preliminary efficacy. ~~A f~~Futility assessment will be conducted ~~after data are available from the first 20~~ on an ongoing basis, starting with a minimum of 10 treated subjects assessed for response. The assessments are based on the predicted probability of success with a maximum of 32 subjects treated and assessed for response. ~~subjects in Part 2.~~

Section 1.1. Background

Rationale for Change: Transparency of clinical development for the reader of the protocol.

Revised Text:

Paragraph 5:

Parallel to study BET116183, GSK525762 is being investigated in solid tumors (GSK Study BET115521, NCT# NCT01587703)

Section 1.2. Study Population Rationale

Rationale for Change: Availability of updated information.

Revised Text:

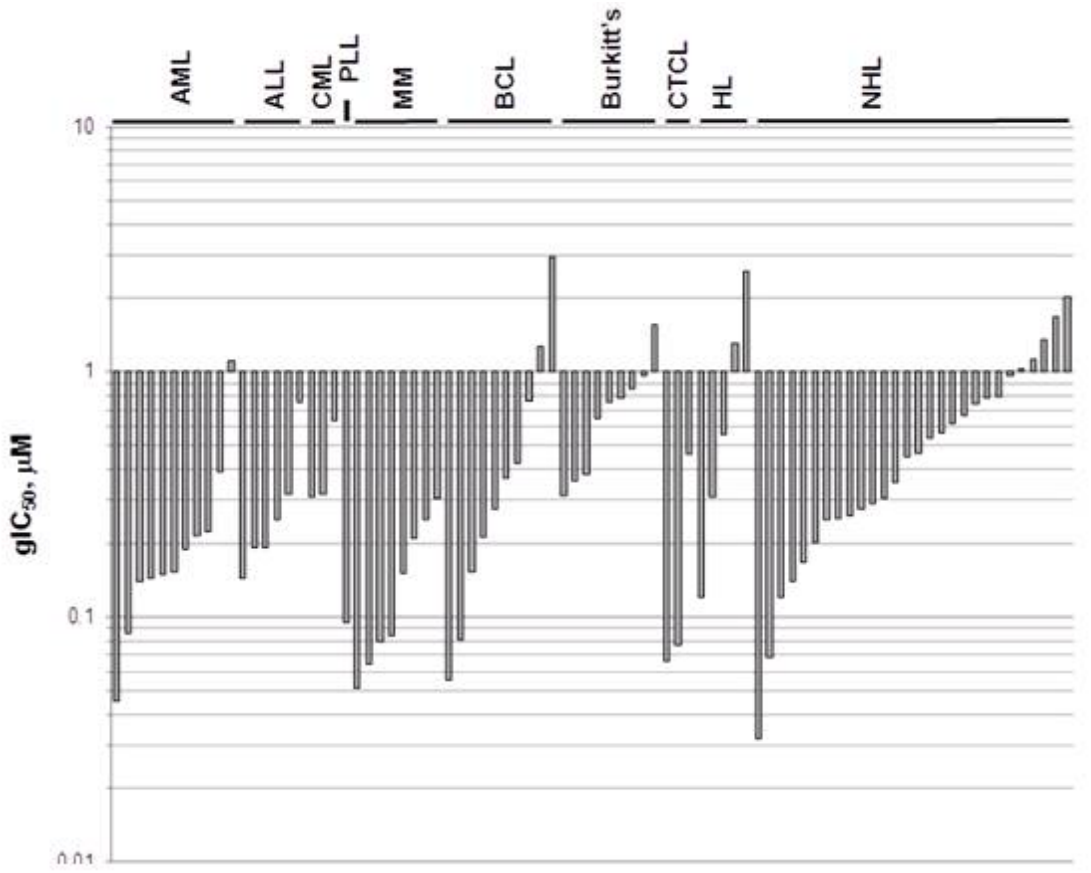
Paragraph 2, 3, 4:

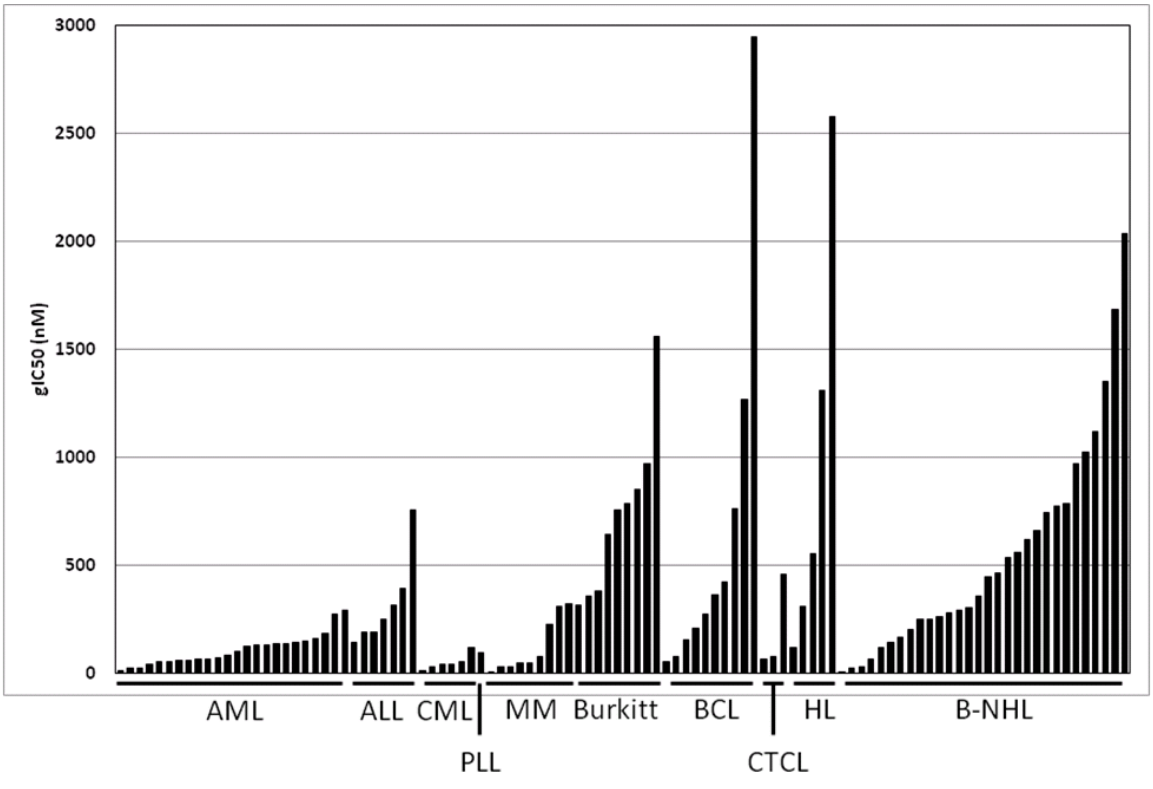
~~Eighty-seven percent of hematological cancer cell lines tested (73/84) are highly sensitive to GSK525762, with growth IC50 (gIC50) < 1.0 µM, and GSK525762 results in net cell death in 61% (51/84) of those cell lines. Some of the most sensitive hematological cancer cell types were derived from AML (median gIC50 = 0.15 µM), ALL (median gIC50 = 0.22 µM), MM (median gIC50 = 0.12 µM), and BCL (median gIC50 = 0.32 µM) [GSK525762 IB, GlaxoSmithKline Document Number 2011N113741_02].~~

Ninety percent of hematological cancer cell lines tested (94/104) are highly sensitive to GSK525762, exhibiting growth IC50 (gIC50) values below 1.0µM. Some of the most sensitive hematological cancer cell types include CML (median gIC50= 40 nM), MM (median gIC50= 49 nM), CTCL (median gIC50= 77 nM), and AML (median gIC50= 94 nM).

~~Oral~~Additionally, oral dosing of GSK525762 results in tumour growth inhibition and improved survival in ~~the~~a myeloma mouse xenograft model (OPM-2) of disease (Figure 2). Consistent with published reports, down-regulation of c-Myc protein expression was observed in OPM-2 xenografts following a single dose of GSK525762 or daily administration for up to 11 days.

Superseded and Updated Figure 1:





Section 1.3. Dose Rationale

Rationale for Change: A BID dosing cohort was added to the study. In alignment with that, information was added on BID dosing including the rationale for BID. To facilitate reading of the protocol, new paragraphs were added and all paragraph numbering was updated to implement a parallel paragraph structure for QD and BID dosing. Minor clarifications in the QD cohort section were added. New or updated information based on clinical or preclinical studies was added.

Revised Text:

Section 1.3.1. QD Dose Cohort

Section 1.3.1.1. Starting Dose Calculations

The proposed starting dose for this clinical study in subjects with hematologic malignancies is 5 mg once daily (QD) based on the following, assuming a 70 kg adult with a body surface area of 1.7 m^2. ~~This is different from the ongoing solid tumor study (BET115521) in which the starting dose was 2 mg daily. This dose level has been successfully cleared and a dose of 4 mg is currently being evaluated.~~ The dose of 5 mg daily was based on preclinical considerations described Section 1.3.1.1.1~~below,~~), preliminary human pharmacokinetics (PK; Section 1.3.1.1.2), clinical consideration ~~such as~~including the aggressive nature of the relapsed and/or refractory tumor (Section 1.3.1.1.3), and the desire to minimise sub-therapeutic exposures. This starting dose is different from the ongoing solid tumor study (GSK Study BET115521, NCT# NCT01587703) in which the starting dose was 2 mg daily (see Section 1.3.1.1.3)

Section 1.3.1.1.1. Preclinical Considerations

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

Section 1.3.1.1.2. Human ~~PK~~Pharmacokinetics and Equivalent Exposure for NOEL for QTc prolongation

Paragraph 3

Updated PK information obtained after first subject first dose is presented in Appendix 13 (Section 15.13)

Section 1.3.1.1.3 Clinical Considerations

Relapsed and/or refractory hematologic malignancies have an aggressive and rapidly progressive course and patients with leukemia are unlikely to remain stable even for 3 week for the Dose Limiting Toxicity (DLT) assessment to be done. Therefore there is a need to minimise the number of patients exposed to sub-therapeutic doses without compromising safety. The 5 mg starting dose provides adequate safety margins for toxicities that can be clinically monitored and are largely reversible (excluding testicular ~~effects~~long-term effects on male and female reproductive function, which is being evaluated), while minimizing the number of patients with aggressive hematologic cancers exposed to predicted sub-therapeutic doses. Moreover, the starting dose of 2 mg daily in

the solid tumor trial (BET115521) has been successfully cleared ~~and a dose of 4 mg daily is currently being explored.~~

Taking all the above into consideration and the extensive clinical monitoring for QT prolongation, a starting dose of 5 mg QD is planned.

~~**Starting Dose Based on Dose Level Cleared in the Solid Tumor Study**~~

~~The key safety findings from the ongoing solid tumor study (BET115521) will be shared with the investigators in this hematologic malignancies study (as described in Section). Currently, the dose level of 2 mg has been cleared. In the event a dose level of 4 mg or higher is cleared in the solid tumor study, and the next dose level to be tested is higher than 5 mg, then GSK would consider amending this protocol to start at the same dose that the solid tumor protocol is testing at that time.~~

Section 1.3.1.2. Predicted therapeutic dose range

Cell lines of hematological origin were generally more sensitive than the cell lines of other solid tumor origins, namely small cell lung cancer (SCLC) and Colorectal cancer (CRC) cells. The more sensitive cell lines had growth IC50 (gIC50) values as low as 50-100 nM. The potential therapeutic dose for GSK525762 in humans was derived using available preclinical PK, data from *in vitro* cell lines of hematological origin, and efficacy data from OPM-2 multiple myeloma tumour xenograft studies. Based on modeling, maximal efficacy of GSK525762 may require ≥ 50% target inhibition. The predicted human effective daily dose is likely to be ~~25 to 50 mg~~in the range of 25 to 100 mg assuming 50 to 100% oral bioavailability.

Section 1.3.2. BID Dose Cohort

Section 1.3.2.1. Preclinical Rationale for BID

Recent clinical and pre-clinical pharmacokinetic and pharmacodynamic data suggests a potential benefit of a twice daily (BID) dosing regimen compared to QD dosing [GSK525762 IB, GlaxoSmithKline Document Number 2011N113741_03]. 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 cell line 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.

QD and BID dosing have been further explored in a number of *in vivo* xenograft efficacy studies. 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 a 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 observe equivalent or improved efficacy with BID dosing in all xenograft models tested.

Section 1.3.2.2. Clinical Rationale for BID

Pharmacokinetics of GSK525762 has been evaluated in subjects for studies BET115521 and BET116183 following single and repeated daily administration of GSK525762 (Section 15.13).

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.

Based on the pharmacokinetics of GSK525762 observed to date, and evidence of a short half-life of about 5 hours, trough concentrations are predicted to be below the average in vitro IC50 (0.08 uM to 1.3 uM) for the tumor types selected for this study. Furthermore, based on the pharmacokinetics to date, it is predicted that even 100 mg QD doses would result in the trough concentrations below the average in vitro IC50. Dividing the daily dose into two doses administered about 12 hours apart would allow the trough concentration to be above the lower in vitro IC50 for doses around 30 mg BID.

Section 1.3.2.3. Starting Dose for BID

The maximum starting dose for BID will be 20 mg provided the 40 mg QD dose cohort has been cleared. A lower BID starting dose will be considered depending on emerging safety, PK, and PD data

Section 1.3.3. Dose escalation steps (QD and BID)

The MTD in subjects with leukemia may differ from the MTD in subjects with multiple myeloma and lymphoma therefore AML subjects will be enrolled initially to determine the MTD for AML. Once the 40 mg dose cohort is cleared in AML, the MTD determination of MM and NHL subjects will begin at the 40 mg dose level.

Section 1.4 Rationale for Study and Endpoints

Rationale for Change: Clarification

Revised Text:

Paragraph 2

The BET116183 study has 2 parts. Part 1 is a dose finding study, which will include subjects with relapsed refractory hematologic malignancies to determine an MTD. Part 2 is a cohort expansion, which will study the RP2D of GSK525762 to determine preliminary efficacy, safety and tolerability in subjects with ~~specific~~ acute myeloid leukemias.

Section 1.5.1. Risk Assessment

Rationale for Change: New information available.

Revised Text:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Reproductive	GSK525762 has shown adverse and potentially irreversible effects on testes in rats, rabbits and dogs, with no NOAEL in rabbits. An effect on spermatogenesis is anticipated. In definitive four-week oral toxicology studies, sperm retention and degenerative effects occurred in male dogs and rats. Degenerative changes were also observed in rabbits dosed dermally for 14 days. ~~GSK525762 has not been tested in reproductive toxicology studies but there is a theoretical risk that GSK525762 may also impact female reproductive organs (ovaries) and the development of an unborn baby (see the GSK 525762 IB [GlaxoSmithKline Document Number] for references~~ 2011N113741_02 In a dose range rat embryofetal development study, GSK525762 has been shown to impact fetal development at doses ≥1 mg/kg/day, including embryo-fetal toxicity, leading to a complete loss of litters at 30 mg/kg/day and developmental toxicity including fetal malformations at doses ≥1 mg/kg/day. These adverse reproductive effects occur in rats at systemic exposures approximately 3-fold below the exposure observed in patients given 2 mg/day on the ongoing dose escalation Phase 1 clinical trial BET115521. The findings from the dose-range reproductive toxicity study in rats with GSK525762 are consistent with literature reports that BRD2, BRD3, BRD4 and BRDT have crucial roles in reproductive function and embryofetal development (see the GSK 525762 IB [GlaxoSmithKline Document Number 2011N113741_03~~).~~ for references). Based on the findings in this reproductive toxicity study in rats with GSK525762, there is a substantiated risk for adverse effects on embryofetal development. There is a theoretical risk that GSK525762 may also impact female reproductive organs (ovaries).	ICF includes the risk of damage to reproductive organs such as testes or ovaries. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and complete) for male subjects. ICF includes the potential risk of reproductive effects. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	A rat female fertility study is ongoing to evaluate this risk.	

Section 1.5.2. Benefit Assessment

Rationale for Change: Clarification

Revised Text:

Study BET116183 is an open-label, dose escalation study and the first study of this agent to be conducted in subjects with relapsed and/or refractory hematological malignancies for which no standard therapies are anticipated to result in a durable remission. GSK525762 has promising preclinical activity in the hematological cell lines, however it is unknown whether GSK525762 will have clinical efficacy in subjects with hematological malignancies, thus any potential beneficial effect for an individual subject attributable to GSK525762 is unknown. Data obtained in Study BET116183 may assist in progressing the knowledge base on advanced hematological malignancies and their treatment, or help identify individuals more likely to benefit or have side-effects from GSK525762. Study participants may benefit from the medical tests and screening performed during the study

Section 1.6. Communication Plan for Safety Evaluation

Rationale for Change: Clarification of process and functions/people involved

Revised Text:

This phase I/II study is intended to enroll subjects at two or more sites. Safety ~~evaluations~~data will be closely monitored and reviewed by ~~a GSK Safety Review Team that includes~~ the GSK medical monitor, and/or clinical scientist(s), ~~and GSK safety physician~~ responsible for ~~both the BET116183 study and other ongoing clinical~~ all studies of GSK525762 (e.g., the BET115521 solid tumor study). There will be ~~a~~ 2 way communication between the local participating sites and the GSK clinical team via email, fax and phone. The GSK team will review all safety data throughout the study, and safety findings from all studies with GSK525762 will be discussed with investigators from all participating sites on a monthly basis and appropriate action will be taken. Urgent safety information will be shared with all the participating sites at the earliest possible time after the data becomes available. Emerging safety and tolerability data from the currently ongoing phase I study in solid tumors will also be communicated to the participating investigators in this study as appropriate at the monthly meeting, or sooner if necessary.

Section 2. OBJECTIVES, ENDPOINTS, HYPOTHESES

The same changes were implemented in Section 2 of the protocol as documented in the change section of the protocol synopsis under 'OBJECTIVES AND ENDPOINTS'

Section 3. Study Design/Schematic

Rationale for Change: Clarification of the study population and addition of a BID dosing cohort.

Revised Text:

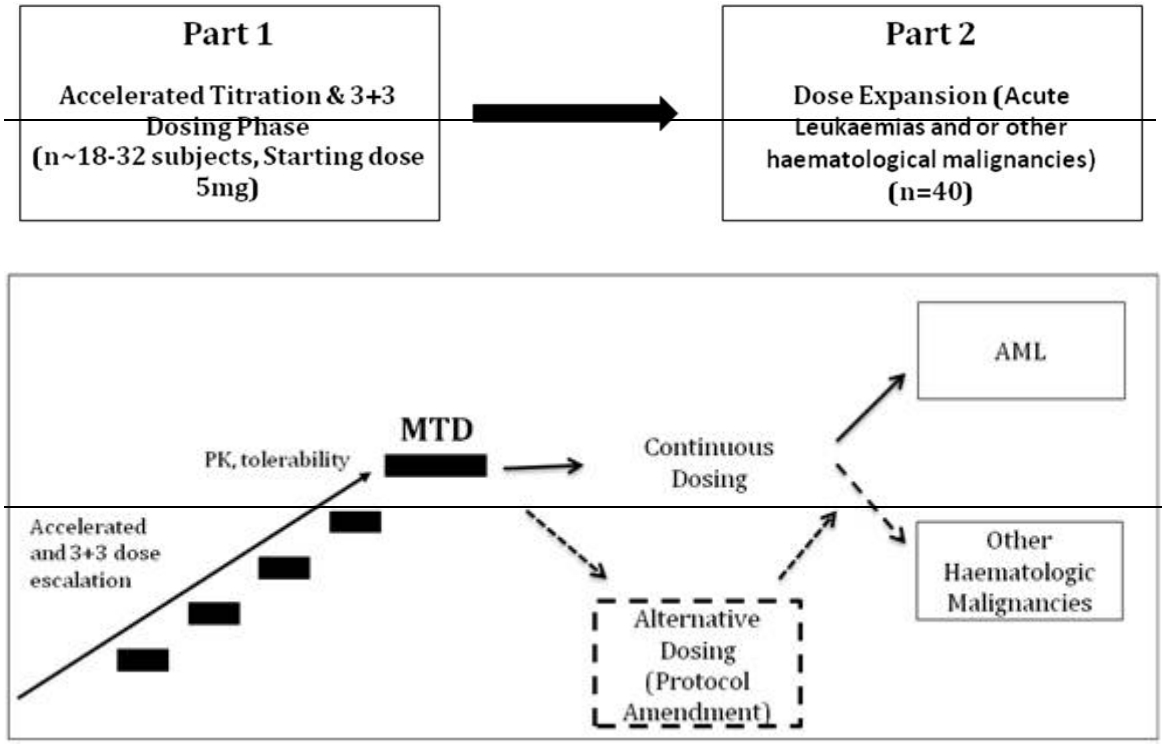
Paragraph 2

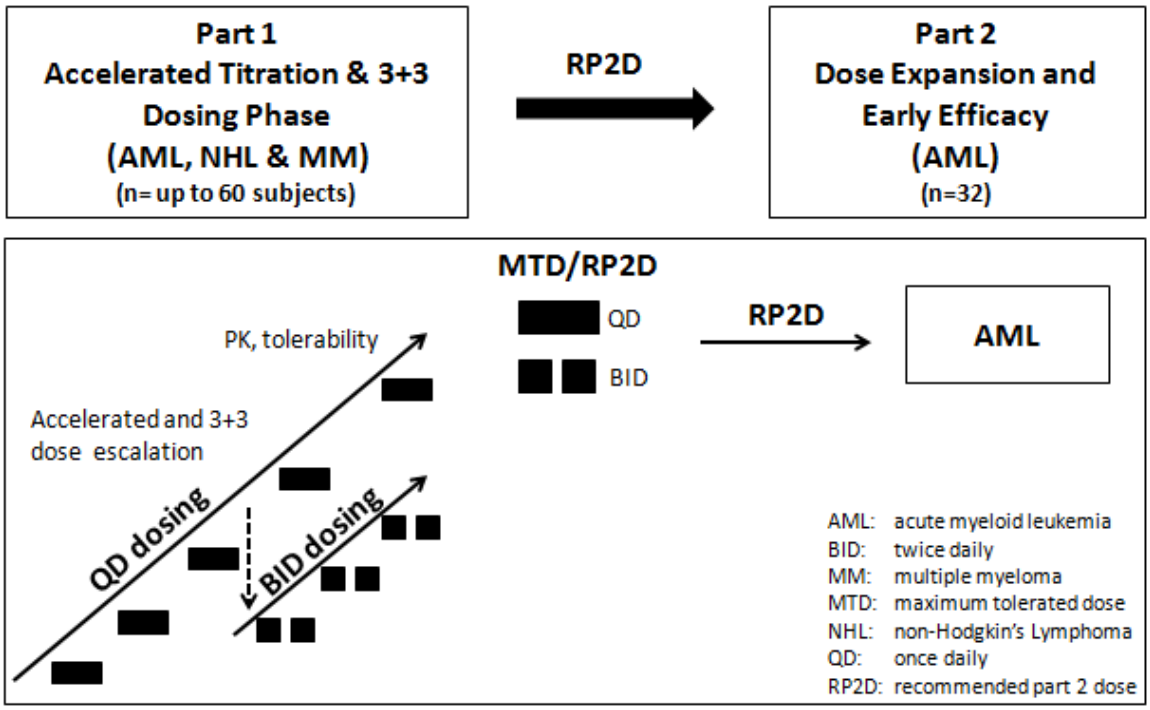
This is an open-label repeat dose, multicenter, 2-part study to determine the MTD in subjects with acute leukemia and multiple myeloma/non-Hodgkin's Lymphoma, and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily (QD) orally and twice daily (BID) orally. Part 1 will be conducted in adult subjects with relapsed and/or refractory hematological malignancies. An expansion cohort (Part 2) is planned to further explore clinical activity of GSK525762 in subjects with specific subtypes of acute leukemias based on emerging data (Figure 3).

Figure 3. Study Schema

Rationale for Change: The figure was updated to reflect the addition of a separate BID dosing cohort.

Superseded and Revised Figure:





Section 3.2.1. Part 1 Dose Escalation

Rationale for Change: Addition of BID dosing cohort and clarification of dose escalation design taking into account different indications.

Revised Text:

Thereafter, subjects will be enrolled in a standard 3+3 design. Separate dose escalation cohorts will be opened for QD and BID dosing.

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 ~~N-CRM~~Neuenschwander continual 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 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 ~~100~~200 mg per day is reached. After the MTD has been determined in Part1, then Part 2 dose expansion cohorts will be opened.

Due to the potentially different MTD in subjects with acute leukemia compared to myeloma/lymphoma (Section 1.3.3), MTD will initially be established in subjects with AML and subjects with MM/NHL may be enrolled at dose levels cleared in subjects with AML.

Section 3.2.1.1. Dose Escalation and Schedule

Rationale for Change: Clarification of the duration of telemetry.

Revised Text:

Table 1. Three Week DLT monitoring: Dosing Schedule and Cardiac Monitoring

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	Dose ECG, Holter 48h Telemetry*	Dose ECG, ~~Telemetry~~ →	Dose	Dose	Dose ECG, Holter	**off** ECG	**off**

* 48h Telemetry: start predose d1, remove on d3

Please refer to Time and Events Section 5 for more details

Section 3.2.1.2. Accelerated Dose Escalation in Part 1

Rationale for Change: Simplification by document cross referencing and clarification of prerequisite for accelerated dose escalation.

Revised Text:

One subject per dose level in the accelerated dose escalation schema will be treated to minimize suboptimal drug exposures, starting with Dose Level 1 and continuing until one subject experiences ≥ Grade 2 drug related non-hematological toxicity, or DLT (except for pre-specified Grade 3 non-serious non-hematological drug related adverse event, see Section 3.2.2 ~~(based on National Cancer Institute- Common Terminology Criteria for Adverse Events Version 4.0 [NCI-CTCAE v4.0] [NCI, 2009]) that would allow continuation of accelerated dose escalation~~; (Table 2). 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, see Section 3.2.1.3).

Table 2 Accelerated Dose Escalation Procedures in Part 1

Row 3

Dose Level	Change in Dose
Subsequent dose levels	Increase by ≤2-fold after a subject clears the previous dose cohort (No subjects with ≥ Grade 2 drug related toxicity AND no subjects with any DLTs in first 3 weeks of treatment)

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

Section 3.2.1.3. 3 + 3 Dose Escalation in Part 1

Rationale for Change: The process of dose escalation with respect to the different indications was clarified and the figure was updated to include the BID dosing cohort

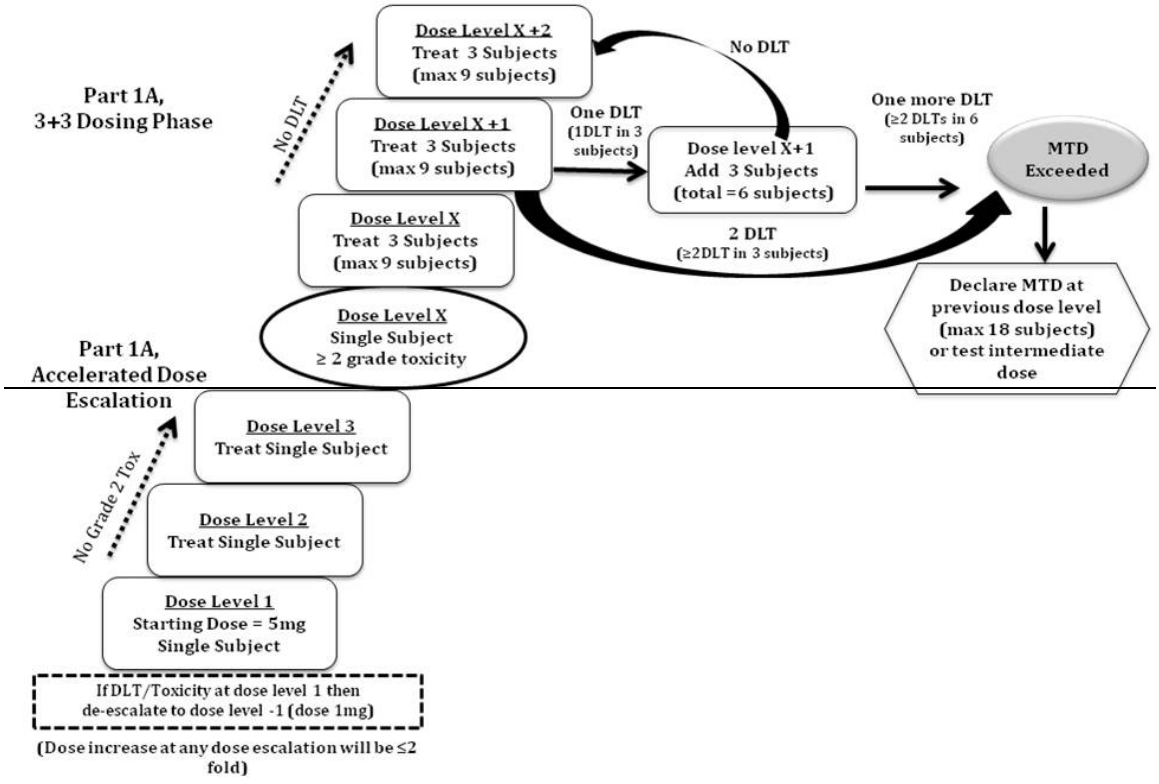
Revised Text:

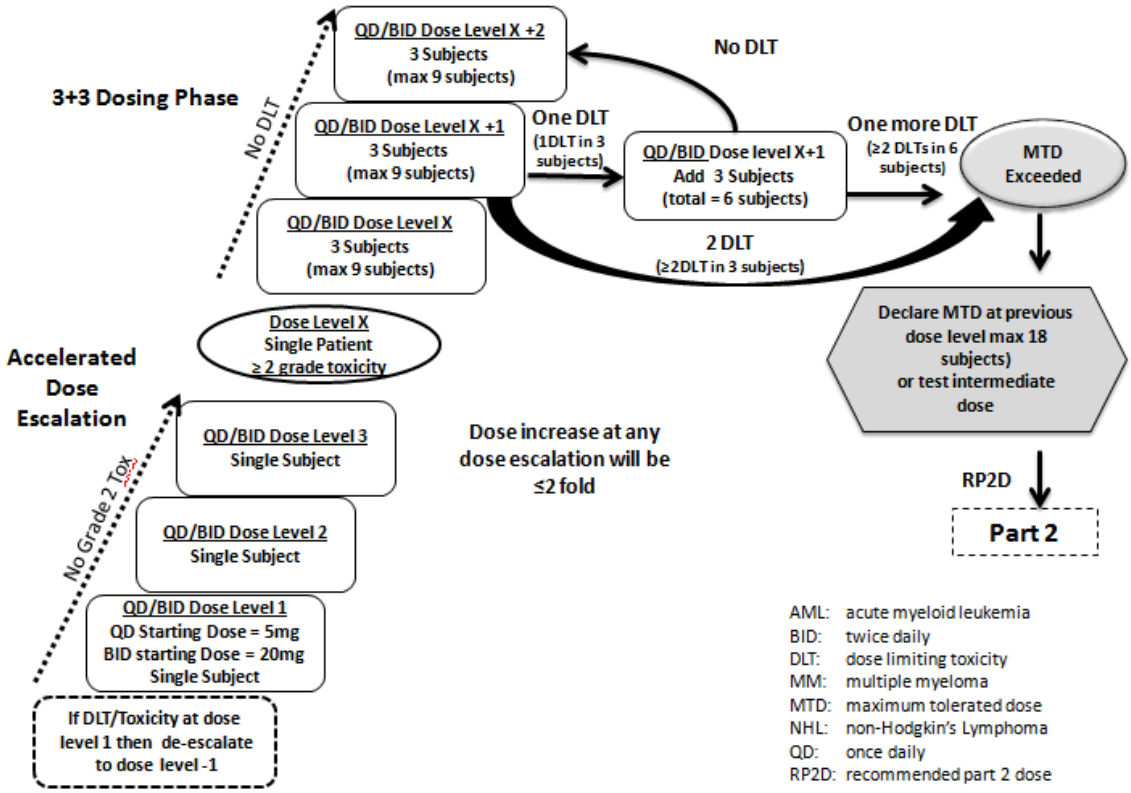
Paragraph 3

Once the MTD is reached and RP2D is determined, up to 12 additional subjects may be enrolled at the MTD to evaluate safety, additional PK, and obtain tumor tissue for PD biomarkers. Additional subjects may be enrolled at the MTD, and at least 1 dose level below MTD, to confirm if the MTD is appropriate for AML ~~subjects. Should AML patients have lower tolerability to GSK525762, then a lower MTD/RP2D could be selected for AML subjects.~~and NHL/MM subjects. Up to an additional 6 subjects may be enrolled at any dose level below the MTD in order to obtain additional tumour tissue for PD biomarkers to better understand the dose/exposure/PD relationship. Additional cohorts (with daily exposure not exceeding MTD exposure) may also be initiated to explore alternative dosing schedules to optimize the PK, safety and tolerability profile. The enrolment of additional subjects as described could be in parallel with Part 2 enrolment. Although DLT will not be based on the additional subjects enrolled into the study to further evaluate safety, PK, to obtain tumor tissue for biomarkers, data from these additional subjects will be considered in defining final MTD and RP2D (Figure 4).

Superseded and updated Figure

Figure 4. Dose Escalation Schema (Part 1)





Section 3.2.1.5. BID dosing

Rationale for Change: Updated to reflect addition of BID dosing cohort to protocol and information how BID dosing will be implemented.

Revised Text:

~~Schedules that use a shorter recovery period, e.g., twice~~Twice daily (BID) dosing, ~~may~~will also be explored initially in subjects with AML as described in Section 1.3.2~~. This approach will be considered if the safety, PK, and emerging PD data suggest that a sufficient therapeutic exposure cannot be achieved using the initial schedule. If a shorter recovery period is used, the~~ . The initial dose level for BID will be ~~≤50%~~a maximum of ~~the highest completed~~20 mg (ie 2x 20mg 12 hours apart, total daily dose of 40mg) or a dose level ~~(at or below MTD) with the initial schedule~~lower than 20 mg depending on emerging safety, PK and PD data and dosing will be separated by approximately 12 hours. Escalation can then proceed as described using the 3 + 3 dose escalation. ~~Alternative schedules with intense supportive care~~Subjects may need to undergo dose modification(s) to manage toxicities. A dose adjustment (e.g., QD at the same dose level or lower BID dose level) may ~~also~~be made after consultation with GSK medical monitor. The investigator should use clinical judgment to determine whether the dosing scheduling may be ~~explored~~contributing to any potential toxicity necessitating dose adjustment, and make the appropriate change after consultation with the GSK Medical Monitor.

Section 3.2.1.6. Intra-Subject Dose Escalation

Rationale for Change: Requirement for additional PK samples for intra-subject dose escalation added.

Revised Text:

Paragraph 2

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 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.

Section 3.2.2. Dose Limiting Toxicity (DLT)

Rationale for Change: DLT criteria for myelosuppression were differentiated by indication and refined to account for the differences due to the underlying disease.

Revised Text:

An event will be considered a DLT if it occurs within the first 3 weeks of treatment and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment.

- Prolonged myelosuppression, as ~~defined by the National Cancer Institute (NCI) criteria specific for leukemia, i.e., marrow cellularity <5% on day 42 or later (6 weeks) from start of therapy without evidence of leukemia which can occur outside of the 3 week DLT window.~~follows:

- For leukemia:
  - At 6 weeks, bone marrow biopsy that demonstrates no evidence of residual leukemia AND EITHER:
    - Marrow aplasia, defined as <5% cellularity by trephine biopsy, OR
    - Peripheral cytopenias, defined as ANC ≤500/uL and/or platelets ≤25,000/uL (if baseline ANC and/or platelets were > 500/uL and/or 25,000/uL, respectively)
- For myeloma or lymphoma:
  - Grade 4 neutropenia persisting for ≥7 days or febrile neutropenia ~~in patients with myeloma or lymphoma.~~not responding to treatment within 24h
  - Grade 4 thrombocytopenia ~~in patients with myeloma or lymphoma.~~lasting more than 7 day and do not respond to transfusions or Grade 3 associated with bleeding (>10mL)

Section 3.2.4. Part 2 AML Expansion Cohort

Rationale for Change: Section was updated to reflect that analysis of Part 2 data will include analysis of Part 1 data; hence fewer subjects are required for Part 2. Decision steps for interim and final analysis were updated based on the updated number of subjects required for analysis.

Revised Text:

Up to ~~40~~32 subjects with specific relapsed and/or refractory acute myeloid leukemias (and/or other subsets), determined based on emerging data (preclinical and clinical data from Part 1), may be enrolled in an expansion cohort at the RP2D. This will be conducted 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.

The ~~Phase~~Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored with the constraint of both Type I and Type II error rates. Clinical response will be defined as CR, CRp, PR, or morphologic leukemia-free state.

The interim analysis will be conducted after efficacy data at a dose level based on RP2D are available on a minimum of 10 patients. ~~An initial total of 20 subjects will be recruited at a dose level based on RP2D.~~ The number of subjects will be increased up to a total of ~~40~~ 32 depending on the results observed. The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility are indicated in Table 4. The methodology is based on the predictive probability of success if enrolment continues to ~~40~~32 subjects [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

For the interim analysis at N=17, if observe one or no response in the first evaluable 17 subjects, the enrollment will be stopped due to futility. Otherwise, the enrolment will continue. For the final analysis at N=32, if observe at least 7 responses in 32 evaluable subjects, sufficient statistical evidence has been provided in favor of declaring response rate >30%.

Table 4 Part 2 Decision Making Criteria at Interim Analysis and Final Analysis

Number of Evaluable Subjects Enrolled	≤ This Number Of Objective Responses To Stop Early For Futility/Not Reject Null Hypothesis At The End Of Study	≥ This Number of Objective Responses to Continue Enrolment/Reject Null Hypothesis at the End of Study
~~20~~10	~~1~~0	~~2~~1
17	1	2
20	1	2
22	2	3
26	3	4
29	4	5
31	5	6
~~40~~32	~~4~~6	~~5~~7

Section 4.1. Number of Subjects

Rationale for Change: Section was updated to reflect that analysis of Part 2 data will include analysis of Part 1 data; hence fewer subjects are required for Part 2.

Revised Text:

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 20 to 30 evaluable subjects will be enrolled. Part 2 will enroll up to ~~40~~32 subjects with specific relapsed and/or refractory acute myeloid leukemias. See Section 11.1 for sample size assumptions.

Section 4.2. Eligibility Criteria

Section 4.2.1 Inclusion Criteria

The changes that were implemented in Section 4.2.1 of the protocol are documented in the change section of the protocol synopsis under 'Inclusion Criteria'

Changes in Section 4.2.1 that are not documented in the change section of the synopsis are documented below.

Revised Text:

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.

Section 4.2. Exclusion Criteria

The changes that were implemented in Section 4.2.2 of the protocol are documented in the change section of the protocol synopsis under 'Exclusion Criteria'

Section 4.2.3.1. Permanent Discontinuation from Study Treatment

Rationale for Change: Implemented based on MHRA feedback on a similar protocol

Revised Text:

Paragraph 2

In addition study treatment ~~may~~will be permanently discontinued for any of the following reasons:

- Substantial deviation(s) from the protocol

Section 4.2.3.2. Subject Completion

Rationale for Change: Clarification of definition of completion for Part 1 and Part 2 separately.

Revised Text:

~~A subject will be considered to have~~For Part 1 (dose-escalation phase) subjects who are not treated with the RP2D, a completed subject is one who has 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.

For Part 1 AML subjects who are treated at RP2D and for Part 2 (expansion cohorts) subjects, a completed subject is one who has discontinued study treatment and was followed to death or has died while receiving study treatment.

Section 5. TIME AND EVENTS TABLES

Table 6. Time and Events: Part 1

Rationale for Change: The table was simplified by moving text into the table reference section and providing cross references instead. W6 D1 was added to allow for increased frequency of hematological assessments. Sampling for PK and PD were revised based on ongoing research.

Revised Text:

A column for W6 D1 Visit has been added

In the heading row 'Study Drug', text added 'QD or BID details' and referred to Table 9 and Table 10

For Pregnancy test/ testosterone row, the following text has been deleted and superscript 'a' was added instead: ~~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.)~~

For Vital Signs row, the following text has been deleted and superscript 'b' added: ~~(SBP, DBP, heart rate, respiratory rate, temp.)~~ [b]

For Pulmonary function test, the following text has been deleted and superscript 'c' added: ~~(As appropriate [subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation])~~ [c]

For Adverse events row, following text was revised: AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.5.)

In the heading row 'Laboratory assessments', text revised: For details please see Table 7 ~~following tables~~

For Laboratory assessments tests: W5, D1 and W6, D1 visit added

For 12-lead ECGs row, the following text has been deleted and superscript 'd' added: ~~(Screening ECGs within 14 days of first dose. Triplicate ECGs prior to dosing. For timing of ECGs on "O" days, see and .~~ [d] ~~Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs performed daily through W2.)~~

In Telemetry the following text edit were made: 'Telemetry (Starting predose d1 ~~and~~ for ~~at least~~min 48 h, remove on d3)'.

For PK Blood samples for GSK525762 following visit were added: W1-D3 (with referring to Superscript "f").

For PK blood samples for metabolite evaluation (only at MTD or RP2D in 6 subjects) following visit were added: W3 D1

Specific parameter mentioned in PD Blood samples for biomarkers assessment as "mRNA".

PD Tumor Sample (with referring to Superscript "f"]) to be drawn: this was applicable for entire study duration (part 1) was replaced with applicability to limiting to Screening visit [with referring to Superscript "g"] and W1 D3 visit. Following text was deleted: ~~Tissue and Timing to be based on tumor type and emerging data. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM~~

Translational Research heading was referred to superscript "h"

The following text has been updated in the investigation: Blood samples for Translational Medicine study~~circulating exploratory biomarkers (cfDNA etc.)~~

Footnote text was revised as:

a. 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.

b. Vital signs include SBP, DBP, heart rate, respiratory rate and temperature

c. Pulmonary tests as appropriate: subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation

~~a~~d. 12-lead ECGs : Screening ECGs within 14 days of first dose. Triplicate ECGs prior to dosing. For timing of ECGs on "O" days, see Table 9 for QD and Table 10 for

BID. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs performed daily through W2.)

~~b~~e. For subjects on study longer than 12 weeks, collect a pre-dose PK sample q6W.

~~e~~f. During 3+3 dose escalation, PD tumor ~~samples~~sample collection will be mandatory unless infeasible to collect, and approval is obtained by the GSK medical monitor. Subjects with MM or AML will have bone marrow aspirates collected ~~when feasible (~~on W1 D3 approximately 2-4 hours after the dose. Subjects with NHL will have a lymph node biopsy collected on W1D3 approximately 3-5 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM see Table 8 disease specific assessments for details).

~~d~~g. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.

~~e~~h. Refer to Section 6.6 for details on Translational Research and Appendix 5 for details on PGx Research.

Table 7. Time and Events: Part 1 Laboratory Assessments

Rationale for Change: W6 D1 was added to allow for increased frequency of hematological assessments. Sampling for hematology was increased for enhanced patient monitoring.

Revised Text:

Sub headings “Assessment and Notes” added.

For Hematology parameter following note added: Increase frequency as medically indicated and following Visits are added: W2 D1, W2 D6, W5 D1, W6 D1.

BNP-9 was replaced by NT pro-BNP and was amended as N-ternimal prohormone, throughout the table.

Following abbreviations was expanded in footnote: NT-pro BNP=N-ternimal prohormone B-type Natriuretic Peptide;

Table 8. Time and Events: Disease Specific Assessments: Part 1 (Multiple Myeloma [MM] Assessments)

Rationale for Change: Sampling time points for disease assessments and time point for efficacy assessments were specified in alignment with standard of care and after discussion with internal and external experts.

Revised Text:

For BM aspirate for disease assessment and Bone marrow biopsy for disease assessment the following information was deleted: ~~1 or 2 sample collections between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of aspirate).~~

For Efficacy assessment: The following information "~~Efficacy assessments for MM are described in Appendix 6 : Response Criteria for Multiple Myeloma~~" was replaced with "Every 6 weeks after wk4; Response criteria in Appendix 6". Additionally, the following Visit assessments are added: W4 D1 and q6W D1.

Footnote was deleted: ~~a. An extra specimen will be collected for PD assessments from consenting subjects when feasible.~~

Table 8. Time and Events: Disease Specific Assessments: Part 1 (Lymphoma Assessments)

Rationale for Change: Sampling time points for disease assessments, requirement for flow cytometry, time points for CT scans and time point for efficacy assessments were revised in alignment with standard of care and after discussion with internal and external experts.

Revised Text:

Flow cytometry assessments removed.

For Bone marrow/tissue biopsy for disease assessment the following information was deleted: : ~~1 or 2 biopsies between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of biopsy~~. e); instead assessment was added between W4 and q3W.

For CT Scan assessments: information added to Q6W D1 – Q12W D1: Wk 16, wk 24 , then q12wks

For Efficacy assessment: The following information "~~Efficacy assessments for lymphoma are described in Appendix 7: Response Criteria for Lymphoma~~" was removed and Footnote point "f" is referred. Following Visit was added: W7 D1, information added to Q6W D1 – Q12W D1: Wk 16, wk 24 , then q12wks.

Footnote referred for PET Scan assessments: "d" and "e"

Following text in footnote is revised:

a. Including date of first diagnosis ~~of MDS, sAML/MDS or de novo AML~~ disease stage, and complete history of diagnostic results and therapies.
b. Prognostic markers include: ALC, FLIPI-1, FLIPI-2 (includes ß2-microglobulin), FcR gamma 3A.
~~c. Immunohistochemistry or flow cytometry for immunophenotyping~~.
c. A sample will be required only if clinically appropriate for the lymphoma subtype at screening unless an appropriate previous sample is available. A follow-up bone marrow biopsy will be performed no later than 8 weeks following CR (as judged by investigator) in accordance with the response guidelines (Appendix 7) if a subjects had involvement of the BM ~~sample were positive~~ at the start of the study.
~~e. An extra specimen will be collected for PD assessments from consenting subjects when feasible.~~
d. Baseline/Screening CT and PET scans may be obtained within 35 days of first dose~~, similar to the requirement for obtaining ECHO.~~ Follow-up CT scans at week 7 wk 16, wk 24 and then every 12 weeks.

e. PET or PET/CT scan only if clinically indicated (e.g., confirmation of CR for Diffuse large B-cell lymphoma).
f. Efficacy assessments for lymphoma at week 7 , wk 16, wk 24 and then every 12 weeks.. Assessments are described in Appendix 7 : Response Criteria for Lymphoma

Table 8. Time and Events: Disease Specific Assessments: Part 1 (Leukaemia Assessments)

Rationale for Change: Sampling time points for disease assessments and time point for efficacy assessments were specified in alignment with standard of care and after discussion with internal and external experts.

Revised Text:

For BM biopsy and or aspirate the following information was deleted:: ~~1 or 2 sample collections between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of bone marrow sample collection~~.

For Efficacy assessment: The following information "~~Efficacy assessments for leukemia are described in Appendix 8 Response Criteria for Leukaemias~~" was deleted. Week 4 Day 1 and q3W Day 1 visits are added.

Following text in footnote is revised:

b. This bone marrow sample is required for disease assessment, but a peripheral blood sample can be taken if the bone marrow sample could not be collected. See the study procedures manual (SPM) for sample handling. ~~An extra specimen will be collected for PD assessments from consenting subjects when feasible.~~

g. Efficacy assessments for leukemia at wk 4 and every 3 weeks thereafter. Assesments are described in Appendix 8: Response Criteria for Leukaemias.

Table 9: Time and Events: Part 1 (QD cohorts) Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling

Rationale for Change: Two tables were combined and timing of dose was added as 0h for simplification and to ensure better compliance. Sampling time points for PK, mRNA and cytokines were revised based on ongoing research.

Revised Text:

Table title deleted: ~~Table 9. Time and Events: Part 1 Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling, Week 1. And Table 10. Time and Events: Part 1 Serial Electrocardiograms and Pharmacokinetics, Week 2 and Week 7.~~

Table renamed: Time and Events: Part 1 (QD cohorts) Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling.

Procedure / time after dose	W1D1 – ~~W1D2~~									W1D2		W1D5		
	pre dose	0 h	15 min ± 5m	30 min ±5 m	1h ±10m	2h ±15m	4h ±15m	8h ±1 h	12h ±~~12~~ h	24 h ±1 h	0h	0 h	30 min ±10 m	3h ±30 m
Dose		X									X	X		
12-lead ECG[a]	X		X	X	X	X	X	X	X	X			X	X
PK sample for GSK525762[~~a~~b]	X		X	X	X	X	X	X	X	X[~~a~~b]			X	X
PK sample for metabolite [b,c]	X		X	X	X	X	X	X	X	X[~~a~~b]				
Blood sample for biomarkers (~~PD~~mRNA)	~~X~~[b] X[d]					X	X	X	X	X				
Plasma cytokine sample	~~X~~[b] X[d]					X	X	X	X	X				
Urine PK sampling [c]	X	0-2 h				2-~~24 12~~ 24h								

Procedure / time after dose	W2 D4	W2 D6	W2D7~~ + 2 days~~									W3D 1		W7D1 ±4 days [e] ~~(if dose was escalated, +4 to +7 days)~~			
	pre dose	pre dose	pre dose	0 h	15 min ± 5m	30 min ±5 m	1h ±10m	2h ±15m	4h ±15m	8 h ± 1 h	12 h ± 1 h	24 h ± 1 h	0 h	pre dose	0 h	0.5-2 h	4-8 h
Dose				X									X		X		
12-lead ECG [a]	X	X	X		X	X	X	X	X	X	X	X		X		X	X
PK sample for GSK525762	X	X	X		X	X	X	X	X	X	X	X		X		X	X
PK sample for metabolite [c]			X		X	X	X	X	X	X	X	X					
Blood sample biomarkers (mRNA)			X						X								
Plasma cytokines samples			X					X	X	X	X	X					
Urine PK sampling [c]				0-2h				2-~~24h12~~24h									

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

a. In triplicate, 5 minutes apart and within 10 min prior to PK draw; **For time points with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.**
b. Sample to be obtained before dosing on Week 1, Day 2.
c. only at MTD or RP2D in 6 subjects
d. May be collected within 14 days prior to first dose.
e. if dose was escalated, +4 to +7 days

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Table 10 added: Time and Events: Part 1 (BID Cohorts) Serial Electrocardiograms, Pharmacokinetics and Biomarker Sampling

Rationale for Change: Addition of BID dosing cohort to study.

	W1D1																W1D2		W1 D3	W1 D4	W1D5			
Timepoint; Hours after AM dose (hours after PM dose)	Pre-Dose	0h	15 min ± 5m	30 min ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h	12h±1h	12h (0h)	15 min ± 5m	30 min ±5m	13h (1h) ±10m	14h (2h) ±15m	16h (4h) ±15m	20h (8h) ±1h	24h (12h)±1h	AM & PM	AM & PM	AM & PM	AM	30 min ±5m	3h ±15m	PM
Dose		X								X								X X	XX	XX	X			X
12-lead ECG [a]	X		X	X	X	X	X	X	X			X	X	X	X	X	X					X	X	
PK GSK525762	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X					X	X	
Biomarker sample (mRNA) [c]	X [d]					X	X	X	X					X	X	X	X							
Cytokine/APP	X [d]					X	X	X	X					X	X	X	X							
Urine PK [b]	X	0-2				2-24																		

	W2D 4		W2D 6		W2D7															W3D1		W7D1±4 days [e]				
Time point; Hours after AM dose (hours after PM dose)	pre AM dose	AM & PM	pre AM dose	AM & PM	Pre dose	0h	15 min ± 5m	30 min ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h	12h±1h	12h (0h)	15 min ± 5m	30 min ±5m	13h (1h) ±5m	14h (2h) ±15m	16h (4h) ±15m	20h (8h) ±1h	24h (12h)±1h	AM & PM	pre dose	0h	0.5-2h	4 - 8h	12h
Dose		X X		X X		X								X								XX		X			X
12-lead ECG [a]	X		X		X		X	X	X	X	X	X	X		♦	♦	♦	♦	♦	♦	X		X		X	X	
PK GSK525762	X		X		X		X	X	X	X	X	X	X		♦	♦	♦	♦	♦	♦	X		X		X	X	
Biomarker sample (mRNA) [c]					X						X								♦		X						
Cytokine/APP					X					X	X	X									X						
Urine PK [b]						0-2				2-12 (♦ 2-24)																	

a. in triplicate, 5 minutes apart and within 10 minutes prior to PK draw; **For timpoint with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.**

b. only at MTD or RP2D in 6 subjects,

c. Blood sample for PD biomarker

d. May be collected within 14 days prior to first dose

e. if dose was escalated, +4 to +7 days

APP=acute phase protein; ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose;

♦=optional assessment, for subjects staying overnight only

Table 11. Time and Events: Part 2

Rationale for Change: Clarification of study drug dispensing and AE reporting in line with existing text in protocol body. W1D3 was added to allow for more frequent hematology testing. Telemetry was added in alignment with Part 1. Additional time point for PK/PD was added based on ongoing research and in alignment with Part 1.

Revised Text:

Column for W1D3 was added

For dispensing study drug row, the following information was updated between Cycle 1, W1 D1 to Cycle 4 W10 D1 continuous daily dosing (unless safety, PK or PD data necessitate a different dosing schedule), see Section 3.2.4

For Adverse events row, the following text was revised: AEs & SAEs continuous from first dose; SAEs (If study related) ~~continuous~~ from signing of informed consent (see Section 6.7.5.)

Assessment added: Telemetry (Starting predose d1, for min 48 h, remove on d3) see Section 6.3.7.

For PD Tumor sample (biopsy), the following information was deleted: ~~1 biopsy between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of tumor sample collection~~); instead visit added on W1D3. For screening visit footnote "d" added, for W1D3 footnote "e" added.

For PK Blood samples W1D3 visit was added.

Assessment updated in Translational Research: Blood samples for ~~circulating biomarkers (cfDNA etc.)~~ Translational Medicine study.

Footnote point "b" was added: Vital signs include SBP, DBP, heart rate, respiratory rate and temperature

Table 12. Time and Events: Part 2 Laboratory Assessments

Rationale for Change: To allow more frequent hematology assessments for patient monitoring.

Revised Text:

Point "a" of footnote added and are referred for Hematology parameters from Cycle 1, W1D1 – Cycle 3, W7D1: Assess platelet count as clinically appropriate but at minimum twice weekly for weeks 1 and 2; weekly for weeks 3 to 8.

Table 13. Disease Specific Assessments: Part 2

Rationale for Change: Sampling time points for BM sample and time point for efficacy assessments were specified in alignment with standard of care and after discussion with internal and external experts.

Revised Text:

For BM biopsy and or aspirate the following information was deleted: ~~for disease characteristics and/or PD assessment~~. ~~1 or 2 sample collections between W1D2 and W4D1, timing to be optimized based on emerging data. PK sample to be obtained within 1 hr of bone marrow sample collection.~~

For Efficacy assessment: The following information was deleted "~~Efficacy assessments for leukemia are described in Appendix 8 : Response Criteria for Leukaemias.~~". Instead visits W4D1, W7D1, W10 D1, q3WD1 were added

Following text added in footnote:

b. This bone marrow sample is required, but a peripheral blood sample can be taken if the bone marrow sample could not be collected. W1D3 sample will be collected approximately 2-4 hours after dose. PK sample to be obtained within 1 hour of aspirate See SPM for sample handling.

g. Efficacy assessments for leukemia are described in Appendix 8: Response Criteria for Leukaemias.

Section 6.2. Baseline Assessment

Rationale for Change: Key baseline assessments were omitted from the body text in prior versions and were added for completeness.

Revised Text:

Subjects diagnosed with refractory hematological malignancy for MM, lymphoma and/or leukemias, will be ~~treated and~~ assessed at baseline for ~~appropriate~~ general disease characteristics as noted in Section 6.2.1 and tumor type specific measures as noted in ~~Appendix 6~~ Section 6.2.2, ~~Appendix 7~~ Section 6.2.3 and ~~Appendix 8~~ Section 6.2.4, respectively.

Baseline is defined as the assessment closest to first dose, ie W1D1assessment or screening if SCR sample collected within 72h of first dose.

6.2.1 Baseline assessment for all Subjects

- Primary tumor type (immunophenotyping and histology if applicable)
- History of other tumor types/medical history
- Date of initial diagnosis of primary tumor type
- Date of relapse/progression
- Details of any metastatic disease

6.2.2 Baseline assessment for Subjects with leukemia

AML:

- WHO classification
- FAB classification
- Source of AML
- Cytogenetics

CLL

- Modified Rai staging at initial diagnosis and screening
- Binet stage at initial diagnosis and screening
- Indication of active disease: evidence of bone marrow failure, splenomegaly, lymphadenopathy, lymphocytosis, B-symptoms
- Cytogenetics

6.2.3 Baseline assessment for Subjects with lymphoma

- Ann Arbor staging at initial diagnosis and screening
- Number of sites with extranodal involvement at initial diagnosis
- Follicular Lymphoma International Prognostic Index (FLIPI) 1 and 2
- FCgR3a genotype and other cytogenetics/molecular analysis applicable such as antigen gene receptor rearrangements, BCL2 rearrangements and translocations.

6.2.4 Baseline assessment for Subjects with myeloma

- International staging system (ISS) stage at initial diagnosis and screening
- Type (active or smoldering)
- Presence of plasmacytoma
- Cytogenetics
- Presence of extramedullary disease
- Laboratory assessment: Total protein, paraprotein, CRP and β2-microglobulin; for secretory MM: SPEP, UPEP, IgG, IgA, IgM, FLC assay

Section 6.3.5. Electrocardiograms

Rationale for Change: Text was moved for better visibility. Clarification of definition of baseline was added.

Revised Text:

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) discontinue study medications and notify the GSK Medical Monitor. Subject may restart if QTcF <480 after discussion with medical monitor	
Baseline QTcF value	**Discontinuation QTcF**
<450 msec	>480 msec or ≥60 msec over baseline ~~a~~

~~May restart if QTcF <480 after discussion with medical monitor, see~~* Baseline results are defined by the nearest time point 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.

Section 6.3.7. 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**.**

Revised Text:

Paragraph 2 and 3 added

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.

Section 6.4.1. Disease Assessment

Rationale for Change: Overall survival was added as secondary endpoint, therefore longer follow up is required.

Revised Text:

Paragraph 2

Subjects enrolled in Part 1 at RP2D and Part 2 are to be followed until death for assessment of overall survival (OS).

Section 6.5.3. Urine Collection

Rationale for Change: Flexibility added for shorter interval depending on if subject is hospitalized for treatment or not. Sample time point added based on ongoing research.

Revised Text:

Urine samples for quantitative analysis of GSK525762 will be collected over a dosing interval (12 or 24 hours) in two samples (first sample collected 0-2hr and second sample collected 2-24hr) immediately following dosing on Week 1 Day 1 and Week 2 Day 7. Urine samples will be collected from at least 6 subjects in Part 1 at the MTD. Additional sampling may be instituted based on emerging data.

Section 6.7.6. Method of Detecting AEs and SAEs

Rationale for Change: Language not required for study in adults

Revised Text:

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

"How are you feeling?" ~~or for pediatric studies, "How does your child seem to feel?"~~

"Have you had any (other) medical problems since your last visit/contact?" ~~or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"~~

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" ~~or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"~~

Section 7.3. Meals and Dietary Restrictions

Rationale for Change: Language added for consistency and in alignment with existing language in T&E

Revised Text:

Subjects will fast for at least one hour prior to each dose of study drug. No food or antacid should be taken for 2 hours after dosing. Subjects should not eat a heavy meal in the morning prior to the 1 hour washout before dosing to minimize potential risk for food interaction. On serial PK sampling 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 7.7.1. Dose and Safety Management Guidelines

Rationale for Change: Additional guidance for investigators on dose adjustment for thrombocytopenia. Clarification of definition of baseline.

Revised Text:

Table 18 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (<50,000, ≥25,000)	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 Temporarily interrupt study medication and monitor CBC every 2-3 days. If platelet counts recover to Grade 2 discuss with medical monitor resuming treatment at the same or adjusted dose based on sound medical judgement. Platelet transfusion is allowed based on institutional guidelines. In case of platelet transfusion, hold drug for at least 7 days from day of transfusion, and if platelet counts recover to Grade 2 consider initiating treatment at a lower dose using sound clinical judgement and after consulting with the GSK medical monitor. Discontinue treatment if drug has to be held for >14 days or greater than 2 dose reductions required.
	Grade 4 (<25,000)	

Table footnote:

Note added in the Table footnote for QTcF parameters"

*Baseline results are defined by the nearest time point prior to first dose. If W1D1 results are available, these are considered the baseline results. If screening occurred within 72h of fit dose, W1D1 samples are not needed and screening data are considered as baseline.

Section 7.7.2. Dose Adjustments for Toxicity

Rationale for Change: Correction

Revised Text:

Heading of the table replaced "GSK525762" by "Action"

Section 8. 8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Rationale for Change: Correction in alignment with T&E

Revised Text:

Subjects will be instructed to inform the investigator prior to starting any new medications from ~~the time of first dose of study treatment~~ signing informed consent until the end of the study (Final Study Visit).

Section 8.2.1. Cautionary Medications

Rationale for Change: Original data source not valid anymore and therefore updated.

Footnote Text for Table 20 revised:

Data Source: ~~[www.QTdrugs.org, 2008]~~CredibleMeds, 2014.

Section 8.2.2. Drugs Potentially Affecting GSK525762 Pharmacokinetics

Rationale for Change: Text was removed as no data is currently available to support claim

Revised Text:

The precise *in vivo* metabolic liability for GSK525762 has yet to be assessed. *In vitro* data suggests that GSK525762 has a ~~negligible turnover and~~ low potential to inhibit the major human CYP isoforms (IC50's $\geq$ 33 μM) with no evidence for time dependent inhibition of CYP2D6 or CYP3A4.

Section 8.3. Prohibited Medications

Rationale for Change: Original data source not valid anymore and therefore updated

Footnote Text for Table 22 revised:

1. Data Source: ~~[www.QTdrugs.org, 2008]~~[CredibleMeds, 2014]
The above table is not exhaustive and prohibited drugs are defined by the online version at the time of screening of the subject.

Section 11.1.1. Part I, Dose Escalation

Rationale for Change: Higher number due to the addition of BIC cohort

Revised Text:

The sample size in Part 1 is not driven by statistical considerations. The total number of subjects will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately ~~30~~60.

Section 11.1.2. Part 2, Expansion Cohort

Rationale for Change: The response rates for the hypothesis were raised to reflect standard of care after discussion with internal and external experts in this indication. Calculation were updated also taking into account the revised sample size with AML subjects from Part 1 being included in the analysis of part 2.

Revised Text:

The primary goal of Part 2 is to detect a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, PR or a morphologic leukemia-free state) of ~~20~~30% in AML relative to a ~~5~~10% response rate suggesting no activity.

Symbolically, the null hypothesis is:

H_0: RR≤~~5~~10%

The alternative hypothesis is:

H_A:RR≥~~20~~30%

Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥~~20% and ≥5~~30% at interim and final analysis using a weak/non-informative prior.

~~To determine a maximal sample size for Part 2, a traditional, 2-stage Green-Dahlberg design [, 1992] was evaluated. To test the hypotheses (RR=20% versus RR=5%) by Green-Dahlberg design, 40 subjects would be needed to minimize the Type I (< 5%) and Type II error rate (i.e., Power > 85%).~~

~~Using this sample size, a Bayesian design was evaluated.~~ A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior 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 and the likelihood (i.e., the data). A very weak prior Beta (0.~~02~~03, 0.~~08~~07) with a mean response rate of ~~20~~30% 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 and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.,

p ~ Beta (0.~~02~~03 + x, 0.~~08~~07 + n-x) with the posterior mean (0.~~02~~03+ x)/(0. 1 + n).

Starting with a cohort of ~~20~~10 subjects and allowing for a maximum sample size of 32 subjects at the RP2D with stopping guidelines as described in Section 4.2.3.2~~40~~, this ~~Bayesian~~ design will have a ~~t~~Type I ~~error rate~~Error (α) of ~~5%~~0.04 and ~~89~~87% power. ~~For the interim analysis at N=20, if the predictive probability that the response rate ≥20% (H1) is small (i.e., less than 2% chance) or equivalent to observe one or no response in the first evaluable 20 subjects, the enrollment will be stopped due to futility.~~ Futility analysis will be based on subjects who have at least one post-baseline disease assessment. ~~Otherwise, the enrolment will continue to the target~~ The trial will be stopped early for futility if the predictive probability of success (that the response rate ≥30%) is less than 1%. If the true response rate is 10%, the average sample size ~~of 40. For the final analysis, if the posterior probability that the response rate of >5% (H0) is large (i.e., greater than~~

~~95% chance), or equivalent to observe at least 5 responses in 40 subjects, sufficient statistical evidence has been provided in favor of declaring response rate >20%.~~

~~The design property, by utilizing the decision rule specified in Section ,~~ is 20 and ~~sample size of 40 subjects are shown (). The probability of early termination of the trial is calculated by applying method of Lee et al [, 2008]. The~~ the probability of early termination (PET) for futility is ~~74% under~~93%. If the ~~null hypothesized~~true response rate~~,~~ is 30%, the average sample size is 31 subjects and the ~~risk to incorrectly stop the trial early if the drug is effective is approximately 1%.~~PET is 9%.

~~Table 23 Bayesian Design Performance~~

~~If True Response Rate to GSK525762 is: (%)~~	~~Probability of Early Termination~~	~~Probability of Rejecting the Null Hypothesis~~
~~5%~~	~~0.74~~	~~0.041 (Type I error)~~
~~20%~~	~~0.069~~	~~0.89 (Power)~~

Section 11.1.3. Sensitivity Analysis

Rationale for Change: No sample size sensitivity analysis was performed

Revised Text:

~~The Bayesian design property, with a varying underlying true response rate between 5% and 20% and a maximum sample size of 40. When the true response rate is close to 20% (P_1), the probability of stopping the trial for futility is low. As the true response rate decreases, the probability of stopping the trial for futility increases.~~

~~Table 24 Bayesian Design Performance by Response Rates~~

~~If True Response Rate to GSK525762 is: (%)~~	~~Probability of Early Termination~~	~~Probability of Rejecting the Null Hypothesis~~
~~10%~~	~~0.39~~	~~0.33~~
~~15%~~	~~0.18~~	~~0.68~~

No analysis of sample size sensitivity was performed.

Section 11.4. Interim Analysis

Rationale for Change: Language amended in alignment with amended decision making criteria (Section 3.2)

Revised Text:

Paragraph 2, 3 and 4

~~One interim analysis~~ For Part 2, after the initial 10 subjects have enrolled at the selected dose regimen for the Expansion Cohort, data will be ~~performed for Part 2 of the study. The primary analysis of this includes boundaries~~reviewed for ~~early decision~~clinical benefit on ~~futility. This procedure controls the Type I~~an ongoing basis and ~~II error rates at the nominal level. One formal interim analysis~~the number of subjects with observed clinical benefit will be ~~conducted for the study.~~

~~At~~compared with the ~~interim analysis, the predictive probability given by Bayesian statistics will be used for decision making. Based on the available data at each interim and a non-informative Beta (0.02, 0.08) prior, the posterior distribution of the response rate follows a beta distribution, i.e., p ~ Beta(0.02+x, 0.08+n-x) where p denotes the response rate for GSK525762, x represents the numbers of responses observed~~ stopping guidelines provided in ~~the current n patients.~~

~~For the interim analysis, if the predictive probability that the trial is declared successful (prob(response rate ≥20%)) is small (decision rule, less than~~ Section 3.2.4~~%), the trial will be terminated due to futility. It is calculated that at least 2 responses in 20 patients are needed to further progress the study~~.5.

Section 11.5. Final Analysis

Rationale for Change: In alignment with OS added as secondary endpoint

Revised Text:

Paragraph 2

Final OS analysis will occur when at least 70% of subjects are dead, have withdrawn consent, or are lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up, whichever is earlier.

Section 11.6.1. Primary Analysis

Rationale for Change: The response rates for the hypothesis testing were raised to reflect standard of care after discussion with internal and external experts in this indication. M3 AML will be assessed separately as this subtype of AML has a different course of disease.

Revised Text:

Paragraph 2 and 3

The primary aim of Part 2 is to detect a clinically meaningful response rate of ~~20~~30% relative to a ~~5~~10% response rate suggesting no activity.

Response rate is defined as the percentage of subjects who achieved CR, CRp, PR and a morphologic leukemia-free state among subjects who received at least one dose of treatment in the target population. Response rate and the associated 2-sided 95% exact confidence limits will be provided. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided. Response rates of subjects with AML M3 will be summarised separately.

Section 11.6.2. Secondary Analysis (new section added)

Rationale for Change: Overall survival as added as a clinically meaningful secondary endpoint. M3 subtype, if enrolled, will be excluded because the course of the disease differs and could confound interpretation.

Revised Text:

OS along with 95% confidence intervals for MM, lymphoma and/or leukemias subjects treated at RP2D, will be estimated using the Kaplan Meier method. OS analysis for AML will exclude subjects with AML subtype M3. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis.

Section 11.8. Pharmacokinetic Analysis

Rationale for Change: Addition to account for the implementation of a BID as well as QD dosing regimen.

Revised Text:

Paragraph 3 and 4

Plasma concentration-time data will be listed by dose, dosing regimen, and summarized using descriptive statistics (n, mean, standard deviation [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) PK 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 day, dose and dose regimen cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered. and dosing regimen. If more than 2 dose cohorts are evaluated, dose proportionality of AUC and Cmax for GSK525762 will be assessed using the power model (details will be provided in the RAP).

Section 14. REFERENCES

Rationale for Change: Original data source for QT drugs was not valid anymore and therefore reference was updated. Investigator brochure reference was updated with the most recent version. Cross references were updated accordingly.

Revised Text:

CredibleMeds. List of drugs with a risk of Torsades de Pointes. Available at: http://www.crediblemeds.org Accessed 18-Aug-2014

~~www.QTdrugs.org. At: http://www.azcert.org (revised 25-Mar-2008).~~

GlaxoSmithKline Document Number 2011N113741_03 Study ID Version 3. GSK 525762 Investigator's Brochure. Report Date 27-Mar-2014.

~~GlaxoSmithKline Document Number 2011N113741_02 Study ID Version 2. GSK 525762 Investigator's Brochure. Report Date 16-Apr-2013.~~

Section 15.4 Appendix 4: Dose Adjustment/Stopping Criteria/Supportive Care

Rationale for Change: Correction

Revised Text:

Diarrhea, For Grade 3 to 4 diarrhea or complicated Grade 1 to 2 diarrhea

Point 2: Discontinue ~~GSK1120212~~GSK525762 treatment and hold until symptoms resolve to ≤Grade 1 or baseline. Consider re-starting therapy at a reduced dose.

Section 15.7 Appendix 7: Response Criteria for Lymphoma

Rationale for Change: Updated to be in alignment with lymphoma guidelines

Revised Text:

Point 4: If the bone marrow was involved by lymphoma prior to treatment, the biopsy must be cleared. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in subject outcome.

Section 15.8.1 Acute Leukemias, MDS, Chronic Myelogenous Leukemia in Blast Phase (CML-BP), Chronic MyeloMonocytic Leukaemia (CMML)

Rationale for Change: Clarifications and alignment with respective leukemia guidelines

Revised Text:

Partial remission: Count recovery as per CR, with 6 to 25% abnormal cells in the marrow or 50% decrease in bone marrow blasts. (AML only: If all other criteria for CR are met, then a value of <5% blasts with Auer rods present or abnormal morphology is considered partial remission).

CRp: ~~As~~Marrow response as per CR but platelet count <100 x 10^9/L.

Section 15.8.2. CLL

Rationale for Change: Alignment with respective CLL guidelines

Revised Text:

Complete Response:

Peripheral blood: Absolute lymphocyte count (ALC) <4 x 10^9/L with Hb >11 g/dL, ANC ≥1.5 x 10^9/L and platelet count >100 x 10^9/L (without need for growths factors or transfusions).

Tumor: disappearance of all palpable lymph nodes, spleen, and liver without the appearance of new lesions. Absence of constitutional symptoms.

Bone Marrow: <30% lymphocytes in normocellular marrow; if lymphoid nodules are seen, response is deemed as nodular ~~CR.~~(nPR). If all CR criteria are fulfilled but subject has drug-related cytopenia, consider CR with incomplete bone marrow recovery (CRi).

Progressive Disease or Relapse of Disease

Peripheral blood: A ≥50% increase in ALC over baseline in first course, or lowest prior thereafter, with a sustained level >~~10~~5 x 10^9/L.

Tumor: An increase in the product of two perpendicular diameters of a measured lesion by ≥50% over the size present at entry on study or for subjects who respond, the size at the time of maximum regression and/or the appearance of new areas of malignant disease. Transformation to a more aggressive histology (e.g., Richter's syndrome). Deterioration in performance status or increasing symptoms do not constitute progression; however, their appearance should initiate a new evaluation for extent of disease.

Section 15.10 Appendix 13: Updated PK data from protocols BET115521and BET116183 (new section added)

Rationale for Change: New data available

Added Text:

As of 11-August-2014, the pharmacokinetics of GSK525762 has been evaluated in 19 subjects in study BET115521 following single and repeated once daily administration of 2 mg to 60 mg of GSK525762 and in 2 subjects in study BET116183 following single and repeated once daily administration of 5 and 10 mg of GSK525762. The summary statistics of the preliminary PK parameters are summarized in Table 24 and Table 25 after single and repeat once 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 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 24. Summary Statistics of GSK525762 Preliminary PK Parameters Following a Single Oral Administration of GSK525762 in Study BET115521 and BET116183

Parameters	2 mg N=3	4 mg N=4	5 mg N=1	8 mg N=1	10 mg N=1	16 mg N=3	30 mg N=4	60 mg N=4
Cmax, ng/mL	51.0 (41%)	70.4 (29%)	90.6	120	117	176 (37%)	604 (30%)	940 (31%)
Tmax, h	0.5 (0.5 - 0.6)	1.2 (0.5 - 2.0)	0.62	1.1	2.0	2.0	2.0 (0.97 - 2.0)	1.0 (0.5 - 2.0)
AUC, ng.h/mL	172 (42%)	361 (35%)	467	434	1092	884 (40%)	4420 (63%)	3670 (54%)
$t_{1/2z}$, h	3.3 (103%)	5.1 (36%)	4.01	2.95	5.74	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. All data are from BET115521 study except for the 5 mg and 10 mg doses that were evaluated in BET116183 study.

Table 25. Summary Statistics of GSK525762 Preliminary PK Parameters Following Repeat Daily Oral Administration of GSK525762 in Study BET115521 and BET116183

Parameters	2 mg N= 1	4 mg N=2	5 mg N= 1	8 mg N= 1	10 mg N= 1	16 mg N=3	30 mg N=4	60 mg N=3
Cmax, ng/mL	52	47.6 ; 59.9	103	103	133	138 (25%)	603 (17%)	807 (36%)
Tmax, h	1.0	1.0 ; 4.0	0.5	0.5	0.5	1.5	0.9 (0.32 - 4.0)	1.0 (0.50 - 1.0)
AUCτ, ng.h/mL	160	225 ; 497	511	330	911	674 (21%)	3150 (55%)	2910 (56%)
$t_{1/2z}$, h	4.27	3.69 ; 4.46	3.54	4.92	5.26	3.6 (7.8%)	5.2 (26%)	3.13 (40%)
Cmax Week 3 / Cmax Week 1	1.42	0.968 ; 0.609	1.14	0.857	1.14	0.780 (12%)	0.998 (24%)	1.12 (10%)
AUCτ Week 3 / AUC Week 1	1.38	0.900 ; 1.64	1.10	0.759	0.834	0.774 (20%)	0.724 (12%)	0.779 (13%)
AUCτ week 3 / AUCt Week 1	1.39	0.904 ; 1.67	1.11	0.763	0.890	0.792 (20%)	0.799 (11%)	0.807 (10%)

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. All data are from BET115521 study except for the 5 and 10 mg dose that were evaluated in BET116183 study.

15.17. Appendix 17: Protocol Changes for Amendment 4 (06-APR-2015) from the Protocol Amendment 3 (12-NOV-2014)

Where the Amendment Applies

Amendment 4 applies to all study centres.

General Protocol Changes

Amendment 4: An update to the QTc management guidelines and enhanced guidance for management and dose modifications for thrombocytopenia, specifically for subjects with AML, has been added. Separation of cohorts in Part 1 was included to determine MTD/RP2D separately in AML, MM, NHL cohorts. Eligibility criteria were refined to account for new platelet management guidelines. Eligibility regarding prior allogeneic stem cell transplant and CNS disease were simplified. Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2. PD assessments have been removed from Part 2 and tumor biopsies were added in Part 2 for translational research. The 100 mg dose strength was removed due to a change in manufacturing. Minor clarifications, reformatting of tables and typographical errors were also addressed in this amendment.

Changes are noted below with ~~strikethrough~~ to identify deleted text and underlining to identify new or replacement text.

15.14.1 List of Changes

Title Page, Authors

Rationale for change: Additional authors contributed to the amendment.

Revised Text (~~strikethrough~~=deleted text; underline=new text):

Added Authors:

PPD	Oncology Stats and Programming, USA
PPD	Global Clinical Operational Sciences, USA
PPD	RD PCPS Qsci Clinical Statistics, USA

PROTOCOL SYNOPSIS

Revised Text:

Added EudraCT No.:

- **EudraCT NO:** 2013-000445-39

STUDY DESIGN AND DURATION

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data.

Revised 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 Part 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with relapsed refractory hematological malignancies will be enrolled in once daily (QD) and twice daily (BID) dosing cohorts until a maximum tolerated dose (MTD) is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Part 2 will explore clinical activity at the MTD or RP2D; separate expansion cohorts will be planned for acute myeloid leukemia (AML), non-Hodgkin's Lymphoma (NHL, including an exploratory sub-cohort of subjects with myc and BCL2 and/or BCL6 rearrangements/overexpression [double- and triple-hit lymphoma]),), and multiple myeloma (MM). ~~An expansion cohort is planned in subjects with acute myeloid leukemias to further explore clinical activity at the MTD or RP2D (Part 2).~~

OBJECTIVES AND ENDPOINTS:

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data.

Revised Text:

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) and/or twice daily (BID) dosing schedules, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with ~~relapsed and/or refractory~~ acute leukemia (AML), ~~and other hematologic malignancies~~ multiple myeloma (MM), or non-Hodgkin's lymphoma (NHL).	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD and/or BID dosing schedules.	• Pharmacogenomic (PGx) study using ~~blood or buccal~~ clinical samples.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	To evaluate clinical efficacy after treatment with GSK525762 ~~in relapsed or refractory~~ acute myeloid leukemia (~~r/r~~ AML).	• For AML: Objective response rate (% of subjects achieving Complete Response (CR), Partial Response (PR), CRp (as per CR but platelet count <100 x 10^9/L) or morphologic leukemia-free state) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in multiple myeloma (MM)	• For MM: Objective response rate (defined as the percentage of subjects that have achieved a CR, VGPR, or PR) per response criteria
	• To evaluate clinical efficacy after treatment with GSK525762 in non-Hodgkin's Lymphoma (NHL)	• For NHL: Objective response rate (defined as the percentage of subjects that have achieved a CR, or PR) per response criteria
Secondary	To characterize the PK of GSK525762 in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	16 To evaluate the exposure response (i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	• PK/PD relationship between GSK525762 exposure markers and safety and efficacy parameters.
	17 To evaluate the safety and tolerability of RP2D of GSK525762 in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	18 To evaluate the relationship between GSK525762 exposure and PD response in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	• Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	• To determine the clinical activity of GSK525762 in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	• Overall survival (OS), the time from the treatment start date until death from any cause)
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762	• Pharmacogenomic (PGx) study using ~~or buccal~~ clinical ~~blood~~ samples

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • Acute leukemia: A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with acute leukemia. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.30, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • Multiple myeloma: A response rate of 20% relative to a 5% response rate suggesting no activity in subjects with multiple myeloma.. This will be conducted by testing the null hypothesis that P0≤0.05 versus the alternative that P1≥0.20, assuming the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20. • Non-Hodgkin's lymphoma (non double hit (DH) lymphoma): A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with non-Hodgkin's lymphoma. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.30, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. Subjects with DHL will be evaluated separately for efficacy, but no hypothesis testing will be conducted on the DHL cohort.

Subject Sample:

Rationale for Change: The approximate number of subjects planned for enrollment has been increased to account for the additional expansion cohorts for MM and NHL in Part 2.

Revised Text:

Up to ~~100~~180 subjects worldwide

INCLUSION/EXCLUSION CRITERIA:

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data. Eligibility criteria were refined with to account for new platelet management guidelines. Eligibility regarding prior allogeneic stem cell transplant and CNS disease were simplified.

Revised Text:

Inclusion Criteria

3 In Part 1, subjects must have relapsed and/or refractory hematologic malignancies (leukemias, myeloproliferative neoplasms, lymphomas, and myelomas) for which no standard therapies are available or anticipated to result in remission.

In Part 2, subjects must have Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).

Subjects with AML (Part 1 and Part 2), are eligible if they

- have relapsed and/or refractory disease, *OR*

- are ≥65 years of age and not candidates for or have refused standard chemotherapy.

- In Part 2, the NHL cohort will separately enrol subjects with double- and triple hit lymphoma, so that a minimum of 10 subjects with this subset of disease will be enrolled. To be eligible for this sub-cohort, tumor sample from the subject must demonstrate rearrangement and/or overexpression of MYC and either BCL2 and/or BCL6 genes. Evaluation of double- or triple-hit status may be performed via appropriate local testing, and the determination of double- or triple-hit diagnosis will be at the discretion of the investigator and GSK Medical Monitor.

4 Subjects ~~who have previously received an autologous~~ with a prior history of stem cell transplant are allowed if

- At least ~~a minimum of~~ 3 months ~~has~~ have elapsed from the time of transplant, ~~(T0)~~ *and*
- the subject has recovered from transplant-associated toxicities prior to the first dose of GSK525762*, and*~~.~~
- For subjects with a prior history of allogeneic transplant,
  2. the subject has been off systemic immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids) for at least 1 month prior to the first dose of GSK525762. Topical steroids are permitted
  3. there are no signs or symptoms of graft versus host disease, other than Grade 1 skin involvement

Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Platelets (for subjects with lymphoma)	≥ 75,000 (transfusion independent)
Platelets (for subjects with MM)	≥ 50,000 (transfusion independent)
Platelets (for subjects with acute leukemia)	≥10,000 (transfusions permitted to bring platelet count to >10,000)~~No restrictions~~

1. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2
2. Refer Cockcroft Gault formula
3. For MM subjects, adequate renal function is defined as serum creatinine ≤2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ~~calculated creatinine clearance criteria is <2.5mg/dL or 24-hour urine creatinine clearance of~~ ≥ 30 mL/min
4. If TSH is abnormal but free T3 and or Free T4 are normal, then the subject can be enrolled.

Exclusion Criteria

3 Currently receiving cancer therapy (chemotherapy, radiation therapy, immuno-therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization).

Note: the following are allowed:

Hydroxyurea for proliferative disease

Corticosteroids ~~for leukemia~~

Use of hematopoetic growth factors is permitted at the discretion of the investigator according to published guidelines (e.g., National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), etc.).

4 Evidence of severe of uncontrolled infection.~~Subjects with prior allogeneic stem cell transplant are excluded unless~~

- ~~transplant was >60 days prior to study enrolment.~~
- ~~subject has not taken immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) for at least 1 month~~
- ~~no signs or symptoms of graft versus host disease other than Grade 1 skin involvement~~
- ~~no active infection~~

8 Symptomatic or untreated CNS disease, ~~leptomeningeal or brain metastases or spinal cord compression, other compressive mass, uncontrolled painful lesion, bone fracture, etc (e.g., change in mental status, focal weakness).~~

- Subjects with a history of CNS disease (leukemia, lymphoma or myeloma) are permitted to enrol if they ~~were~~ have previously received appropriate therapy and CNS remission has been documented.~~treated for CNS leukemia or brain metastases and have had stable central nervous system (CNS) disease (verified with consecutive imaging studies) for >2 months, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 1 month prior to study Day 1.~~
- Subject with primary CNS lymphoma (defined as isolated CNS lymphoma without systemic involvement) are excluded from study.

12 Evidence of ~~pulmonary~~ hemoptysis within the last 7 days.

Statistical Analysis

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data and hypothesis testing was added or modified for AML, MM, and NHL (non-DHL) cohorts.

Revised Text:

- **STATISICAL 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. Part 2 of the study is designed to evaluate preliminary efficacy. Futility assessment will be conducted on an ongoing basis, starting with a minimum of 10 treated subjects assessed for response. The assessments are based on the predictive~~predicted~~ probability of success (response rate > historical response rate) with a maximum of 32 subjects treated per cohort (for AML and non DH NHL cohorts) or 37 subjects treated (MM cohort) and assessed for response. Additionally at least 10 DHL

subjects will be treated. No hypothesis testing will be conducted for the DHL cohort. For additional details, please refer to the reporting and analysis plan (RAP).

Section 1.2 Study Population Rationale

Rationale for Change: The correction is a minor clarifying point.

Revised Text:

First paragraph fourth sentence:

- This down regulation results in significant anti-tumour activity both *in vitro* and in animal models of ~~advanced~~ disease [Delmore, 2011; Mertz, 2011].

Section 1.3.1.2. Predicted therapeutic dose range

Rationale for Change: The correction is a minor clarifying point.

Revised Text:

- *Third sentence:*
- The potential therapeutic dose for GSK525762 in humans was derived using available preclinical PK, data from *in vitro* cell lines of hematological origin, and efficacy data from OPM-2 multiple myeloma tumour xenograft studies.

Section 1.3.3. Dose escalation steps (QD and BID)

Rationale for Change: The MTD of GSK525762 may be different for AML, NHL, and MM and revisions were made to reflect these potential differences.

Revised Text:

Second paragraph:

The MTD of GSK525762 may be different for AML, NHL, and MM. To fully evaluate this, each dose escalation step will be evaluated separately for the three disease types. Parallel cohorts will commence upon termination of accelerated dose titration (Section 3.2.1.2) and follow the 3 + 3 design described in Section 3.2.1.3. ~~The MTD in subjects with leukemia may differ from the MTD in subjects with multiple myeloma and lymphoma therefore once the 40 mg dose cohort is cleared in AML, the MTD determination of MM and NHL subjects will begin at the 40 mg dose level.ML subjects will be enrolled initially to determine the MTD for AML. Once the 40 mg dose cohort is cleared in AML, the MTD determination of MM and NHL subjects will begin at the 40 mg dose level.~~

Section 1.4. Rationale for Study and Endpoints

Rationale for Change: The MTD of GSK525762 may be different for AML, NHL, and MM and revisions were made to reflect these potential differences.

Revised Text:

Second paragraph:

The BET116183 study has 2 parts. Part 1 is a dose finding study, which will include subjects with ~~relapsed refractory~~ hematologic malignancies to determine an MTD. Part 2 is a cohort expansion, which will study the RP2D of GSK525762 to determine preliminary efficacy, safety and tolerability in three separate cohorts of subjects with acute myeloid leukemias, multiple myeloma and non-Hodgkin's lymphoma.

Section 1.5.2. Benefit Assessment

Rationale for Change: The correction is a minor clarifying point.

Revised Text:

- Study BET116183 is an open-label, dose escalation study and the first study of this agent to be conducted in subjects with ~~relapsed and/or refractory~~ hematological malignancies for which no standard therapies are anticipated to result in a durable remission.

Section 2. Objectives, Endpoints, Hypotheses

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data.

Revised Text:

Part 1

	Part 1 Objectives	Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) and/or twice daily (BID) dosing schedules, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with ~~relapsed and/or refractory~~ acute leukemia (AML) ~~and other hematologic malignancies~~ multiple myeloma (MM), or non-Hodgkin's lymphoma (NHL).	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Exploratory	○ To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD and/or BID dosing schedules.	○ Pharmacogenomic (PGx) study using ~~blood or buccal~~ clinical samples

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 ~~in relapsed or refractory~~ acute myeloid leukemia (~~r/r~~ AML).	• For AML: Objective response rate (% of subjects achieving Complete Response (CR), Partial Response (PR), CRp (as per CR but platelet count <100 x 10^9/L) or morphologic leukemia-free state) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in multiple myeloma (MM)	• For MM: Objective response rate (defined as the percentage of subjects that have achieved a CR, VGPR, or PR) per response criteria
	• To evaluate clinical efficacy after treatment with GSK525762 in non-Hodgkin's Lymphoma (NHL)	• For NHL: Objective response rate (defined as the percentage of subjects that have achieved a CR, or PR) per response criteria
Secondary	• To characterize the PK of GSK525762 in 3 disease-specific cohorts subjects with ~~r/r~~ AML, MM or NHL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the exposure response (i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	○ PK/PD relationship between GSK525762 exposure markers and safety and efficacy parameters.
	• To evaluate the safety and tolerability of RP2D of GSK525762 in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	• To evaluate the relationship between GSK525762 exposure and PD response in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	○ Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	• To determine the clinical activity of GSK525762 in 3 disease-specific cohorts of subjects with ~~r/r~~ AML, MM or NHL.	○ Overall survival (OS , the time from the treatment start date until death from any cause)
Exploratory	○ To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762	• Pharmacogenomic (PGx) study using ~~or buccal~~ clinical ~~blood~~ samples

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • Acute leukemia: A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with acute leukemia. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.30, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • Multiple myeloma: A response rate of 20% relative to a 5% response rate suggesting no activity in subjects with multiple myeloma.. This will be conducted by testing the null hypothesis that P0≤0.05 versus the alternative that P1≥0.20, assuming the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20. • Non-Hodgkin's lymphoma (non DHL): A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with non-Hodgkin's lymphoma. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.30, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. No hypothesis testing will be conducted on the DHL cohort.

Section 3.1. Study Design/Schematic

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data.

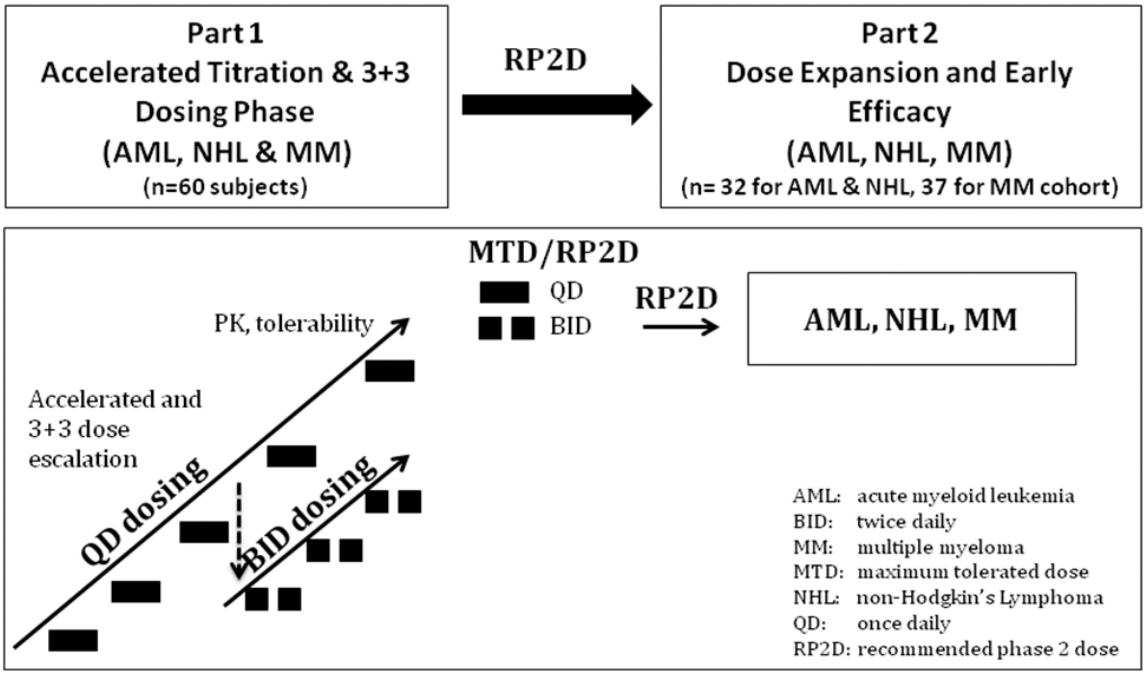
Revised Text:

This is an open-label repeat dose, multicenter, 2-part study to determine the MTD in subjects with acute leukemia and multiple myeloma/non-Hodgkin's Lymphoma, and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily (QD) orally and twice daily (BID) orally. Part 1 will be conducted in adult subjects with relapsed and/or refractory hematological malignancies. ~~An e~~Expansion cohorts ~~cohort~~ (Part 2) are ~~is~~ planned to further explore clinical activity of GSK525762 in subjects with ~~specific subtypes of~~ acute myeloid leukemias, multiple myeloma, and non-Hodgkin's lymphomas ~~based on emerging data~~ (Figure 3).

Figure 3 Study Schema

In the figure below the heading Part 2: (n=32 for AML & NHL~~MM~~, 37 for MM~~NHL~~ cohort)

Revised figure



Section 3.2.1. Part 1: Dose Escalation

Rationale for Change: The MTD of GSK525762 may be different for AML, NHL, and MM and revisions were made to reflect these potential differences.

Revised Text:

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 non-hematological toxicity, (except for a pre-specified Grade 3 non-serious non-hematological drug related adverse event that would allow continuation of accelerated dose escalation; Section 3.2.1.7). During accelerated dose titration, there will be a single cohort comprised of all eligible subjects; parallel cohorts will not be evaluated during this stage.

Thereafter, subjects will be enrolled in a standard 3+3 design. Separate dose escalation cohorts will be opened for subjects with AML, NHL, MM, as well as for QD and BID dosing.

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 Neuenschwander continual 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 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 200 mg per day is reached. After the MTD has been determined in Part1, then Part 2 dose expansion cohorts will be opened.

- Due to the potentially different MTD in subjects with AML, NHL, and MM ~~acute leukemia compared to myeloma/lymphoma~~ (Section 1.3.3), each dose escalation step will be evaluated separately for the three disease types. ~~MTD will initially be established in subjects with AML and subjects with MM/NHL may be enrolled at dose levels cleared in subjects with AML.~~

Section 3.2.1.1. Dose Escalation and Schedule

Rationale for Change: The MTD of GSK525762 may be different for AML, NHL, and MM and revisions were made to reflect these potential differences.

Revised Text:

Table 1 Three Week DLT monitoring: Dosing Schedule and Cardiac Monitoring (QD and BID)

Section 3.2.1.2. Accelerated Dose Escalation in Part 1

- *Last sentence of first paragraph:*
- Once this occurs, the accelerated dose escalation will terminate, and subjects will be enrolled in one of three disease-specific cohorts (AML, MM, or NHL) under a standard 3+3 design (~~i.e., 3 subject cohorts, see~~ Section 3.2.1.3).

Section 3.2.1.3. 3 + 3 Dose Escalation in Part 1

Rationale for Change: The MTD of GSK525762 may be different for AML, NHL, and MM and revisions were made to reflect these potential differences.

Revised Text:

- Due to the potentially different MTDs in acute leukemia, MM, and NHL, dose escalation will be evaluated in three separate cohorts divided by disease subtype. These cohorts will be evaluated in parallel with each other, and DLT/MTD determination will be made separately for each cohort.
- Upon termination of accelerated dose titration, two additional subjects with the final disease type will be enrolled, for a total of three subjects with that disease type at that dose level. Three additional subjects with each of the two other disease subtypes will also be enrolled at that dose level, for a total of nine subjects at each dose level.
- ~~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.~~ For each cohort, ~~I~~if no DLTs are observed in any of the 3 subjects, then dosing will

proceed to the next higher dose level (≤2 fold increase in dose). Subjects within each cohort will be entered in a staggered approach with at least 3 days between each subject to minimize the risk of inadvertently exceeding the MTD in multiple subjects. Each disease cohort may initiate dosing independent of the other two (i.e., subjects with different diseases may start therapy <3 days apart, but subjects with the same disease must be separated by at least three days). Escalation to the next dose level will not increase greater than 2 fold from the previous dose level. If 2 or more DLTs in 6 subjects are observed at any dose level, the MTD will have been exceeded (Table 3).

- Once the MTD is reached and RP2D is determined, up to 12 additional subjects within each cohort may be enrolled at the MTD to evaluate safety, additional PK, and obtain ~~tumor tissue~~ clinical samples for PD biomarkers. Additional subjects may be enrolled at the MTD, and at least 1 dose level below MTD, to confirm if the MTD is appropriate for AML, MM and NHL~~/MM~~ subjects. Up to an additional 6 subjects may be enrolled at any dose level below the MTD in order to obtain additional ~~tumour tissue~~ clinical specimens for PD biomarkers to better understand the dose/exposure/PD relationship. Additional cohorts (with daily exposure not exceeding MTD exposure) may also be initiated to explore alternative dosing schedules to optimize the PK, safety and tolerability profile. The enrolment of additional subjects as described could be in parallel with Part 2 enrolment. Although DLT will not be based on the additional subjects enrolled into the study to further evaluate safety, PK, to obtain tumor tissue for biomarkers, data from these additional subjects will be considered in defining final MTD and RP2D (Figure 4).

Section 3.2.1.5. BID dosing

Rationale for Change: These corrections are minor clarifying points.

Revised Text:

- *First sentence in the first paragraph:*
- Twice daily (BID) dosing, ~~will~~ may also be explored, initially in subjects with ~~AML~~acute leukemia, as described in Section 1.3.2.

Section 3.2.2. Dose Limiting Toxicity (DLT)

Rationale for Change: These corrections are to correct typographical errors.

Revised Text:

- *Point number 6:*

- ALT ≥~~>~~3xULN + bilirubin ≥2xULN (>35% direct) or ALT between 3-5xULN with bilirubin < 2xULN but with hepatitis symptoms or rash or ALT ≥~~>~~5xULN.

Section 3.2.4. Part 2: Disease Specific Expansion Cohorts

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data and hypothesis testing was added or modified for AML, MM, and NHL (non-DHL) cohorts.

Revised Text:

3.2.4. Part 2: ~~AML~~ Disease Specific Expansion Cohorts

Up to 32 subjects (per cohort) with ~~specific relapsed and/or refractory~~ acute myeloid leukemia or ~~leukemias (and/or other subsets), determined based on emerging data (preclinical and clinical data from Part 1),~~ non-Hodgkin's lymphoma (non-DHL), and up to 37 subjects with multiple myeloma may be enrolled in an expansion cohort at the RP2D. ~~This~~These will be conducted 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.

At least 10 subjects with tumor that is positive for rearrangements or overexpression of MYC plus BCL-2 and/or BCL-6 genes (double- and triple-hit lymphoma) will be enrolled. These subjects will be evaluated separately for efficacy, but hypotheses will not be tested. See Section 11.1 for description of the plan for analysis of the NHL cohorts.

Plasma samples for PK evaluation will be collected in all subjects. Plasma samples and ~~tumor biopsies~~ other clinical samples (e.g. lymph node or bone marrow biopsies) will be collected pre- and post- study drug treatment as defined in the Time and Events Table in Section 5 for the PD evaluation.

The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored with the constraint of both Type I and Type II error rates. Clinical response will be defined ~~as CR, CRp, PR, or morphologic leukemia-free state~~ per standard evaluation criteria (see Appendix 6, Appendix 7 and Appendix 8).

~~The~~ For each cohort, an interim analysis will be conducted after efficacy data at a dose level based on RP2D are available on a minimum of 10 ~~patients~~ subjects in the AML and NHL (non-DHL) cohorts and a minimum of 13 subjects in the MM cohort. The number of subjects ~~will~~ may be increased up to a total of 32 for the AML and NHL(non-DHL) cohorts and up to a total of 37 for the MM cohort depending on the results observed; a separate decision will be made for each disease cohort. The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility, are indicated in Figure 5 and Figure 6~~Table 4~~. The methodology is based on the predictive probability of success (response rate > historical response rate) if enrolment continues to 32 subjects for AML and NHL (non-DHL) and 37 subjects for MM [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

For AML and NHL (non-DHL) cohorts: Ten subjects will be enrolled in each cohort at the RP2D to examine safety and efficacy. If zero responses are observed in either cohort, then that cohort will be terminated and no further subjects will be enrolled due to futility.

A single response in a cohort will be adequate to pursue further enrolment. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 5. A maximum of 32 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrolment decisions.

Figure 5 Diagram of Stopping Rules for AML and NHL (non-DHL) Cohort Expansion

	Number of Responders						
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	■	■	■				
26	■	■	■	■			
27	■	■	■	■			
28	■	■	■	■			
29	■	■	■	■	■		
30	■	■	■	■	■		
31	■	■	■	■	■	■	
32	■	■	■	■	■	■	■

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 may be stopped.

For the MM cohort: Thirteen subjects will be enrolled in each cohort at the RP2D to examine safety and efficacy. If zero responses are observed in either cohort, then that cohort will be terminated and no further subjects will be enrolled due to futility. A single response in a cohort will be adequate to pursue further enrolment. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 6. A maximum of 37 subjects will be enrolled at the RP2D. All available data will be considered in making enrolment decisions.

Figure 6 Diagram of Stopping Rules for MM Cohort Expansion

Number of Subjects	0	1	2	3	4
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					

The shaded regions are the specific regions for stopping the study for futility. For instance, if there is no response in 13 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and the study may be stopped.

~~For the interim analysis at N=17, if one or no response is observed in the first evaluable 17 subjects, the enrollment will be stopped due to futility. Otherwise, the enrolment will continue. For the final analysis at N=32, if observe at least 7 responses in 32 evaluable subjects, sufficient statistical evidence has been provided in favor of declaring response rate >30%.~~

~~Table 4 Part 2 Decision Making Criteria at Interim Analysis and Final Analysis~~

~~Number of Evaluable Subjects Enrolled~~	~~≤ This Number Of Objective Responses To Stop Early For Futility/Not Reject Null Hypothesis At The End Of Study~~	~~≥ This Number of Objective Responses to Continue Enrolment/Reject Null Hypothesis at the End of Study~~
~~10~~	~~0~~	~~1~~
~~17~~	~~1~~	~~2~~
~~20~~	~~1~~	~~2~~
~~22~~	~~2~~	~~3~~
~~26~~	~~3~~	~~4~~
~~29~~	~~4~~	~~5~~
~~31~~	~~5~~	~~6~~
~~32~~	~~6~~	~~7~~

Section 4.1. Number of Subjects

Rationale for Change: The number of subjects were modified based on the clarification of BID dose expansion, separate dose cohorts for AML, MM, and NHL, and the addition of MM and NHL cohorts in Part 2.

Revised Text:

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 ~~20 to 30~~ 60 to 70 evaluable subjects will be enrolled. Part 2 will enroll up to ~~32~~111 subjects (three disease-specific cohorts of 32 to 37 subjects each, depending on disease subtype, and one disease-specific cohort of 10 subjects) ~~with specific relapsed and/or refractory acute myeloid leukemias~~. See Section 11.1 for sample size assumptions.

Section 4.2.1. Inclusion Criteria

Rationale for Change: Inclusion of dose expansion cohorts for MM and NHL has been added in Part 2 based upon emerging pre-clinical data. Eligibility criteria were refined with to account for new platelet management guidelines. Eligibility regarding prior allogeneic stem cell transplant were simplified.

Revised Text:

Inclusion criteria 3: In Part 1, subjects must have relapsed and/or refractory hematologic malignancies (leukemias, myeloproliferative neoplasms, lymphomas, and myelomas) for which no standard therapies are available or anticipated to result in remission.

In Part 2, subjects must have Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).

Subjects with AML (Part 1 and Part 2), are eligible if they

- have relapsed and/or refractory disease, *OR*
- are ≥65 years of age and not candidates for or have refused standard chemotherapy.

- In Part 2, the NHL cohort will separately enrol subjects with double- and triple hit lymphoma, so that a minimum of 10 subjects with this subset of disease will be enrolled. To be eligible for this sub-cohort, tumor sample from the subject must demonstrate rearrangement and/or overexpression of MYC and either BCL2 and/or BCL6 genes. Evaluation of double- or triple-hit status may be performed via appropriate local testing, and the determination of double- or triple-hit diagnosis will be at the discretion of the investigator and GSK Medical Monitor.

Inclusion criteria 4: Subjects with a prior history of ~~who have previously received an autologous~~ stem cell transplant (autologous and/or allogeneic) are allowed if

- At least 3 ~~a minimum of~~ months has elapsed from the time of transplant ~~(T0)~~ *and*
- the subject has recovered from transplant-associated toxicities prior to the first dose of GSK525762, *and*
- For subjects with a prior history of allogeneic transplant,

4. the subject has been off systemic immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, mycophenolate mofetil, or corticosteroids) for at least 1 month prior to the first dose of GSK525762. Topical steroids are permitted
5. there are no signs or symptoms of graft versus host disease, other than Grade 1 skin involvement.

Inclusion criteria 10: Adequate organ system functions (at both screening and where applicable pre first dose) as defined in Table 4 ~~Table 5~~.

Table ~~4~~5 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Platelets (for subjects with lymphoma) Platelets (for subjects with MM) Platelets (for subjects with acute leukemia)	≥ 75,000 (transfusion independent) ≥ 50,000 (transfusion independent) ≥10,000 (transfusions permitted to bring platelet count to >10,000) ~~No restrictions~~

a. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2
b. See Appendix 1 for Cockcroft Gault formula
c. For MM subjects, adequate renal function is defined as serum creatinine ≤2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ~~calculated creatinine clearance criteria is <2.5mg/dL or 24-hour urine creatinine clearance of~~ ≥ 30 mL/min
d. If TSH is abnormal but free T3 and or Free T4 are normal, then the subject can be enrolled.

Section 4.2.2. Exclusion Criteria

Rationale for Change: Eligibility criteria regarding CNS disease and subject completion were simplified.

Revised Text:

Exclusion criteria 3: Currently receiving cancer therapy (chemotherapy, radiation therapy, immuno- therapy, biologic therapy, hormonal therapy, surgery, and/or tumour embolization).

Note: the following are allowed:

Hydroxyurea for proliferative disease

Corticosteroids ~~*for leukemia*~~

Use of hematopoetic growth factors is permitted at the discretion of the investigator according to published guidelines (e.g., National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), etc.).

Exclusion criteria 4: Evidence of severe of uncontrolled infection.~~Subjects with prior allogeneic stem cell transplant are excluded, unless.~~

- ~~transplant was >60 days prior to study enrolment.~~
- ~~subject has not taken immunosuppressive medications (including but not limited to: cyclosporine, tacrolimus, methotrexate, or mycophenolate mofetil) for at least 1 month~~
- ~~no signs or symptoms of graft versus host disease other than Grade 1 skin involvement~~
- ~~no active infection~~

Exclusion criteria 8: Symptomatic or untreated CNS disease ~~leptomeningeal or brain metastases or spinal cord compression, other compressive mass, uncontrolled painful lesion, bone fracture, etc (e.g., change in mental status, focal weakness)~~,

- Subjects with a history of CNS disease (leukemia, lymphoma or myeloma) are permitted to enrol if they ~~were~~ have previously received appropriate therapy and CNS remission has been documented.~~treated for CNS leukemia or brain metastases and have had stable central nervous system (CNS) disease (verified with consecutive imaging studies) for >2 months, are asymptomatic and off corticosteroids, or are on stable dose of corticosteroids for at least 1 month prior to study Day 1.~~
- Subject with primary CNS lymphoma (defined as isolated CNS lymphoma without systemic involvement) are excluded from study.
-

Exclusion criteria 12: Evidence of ~~pulmonary~~ hemoptysis within the last 7 days.

4.2.3.2. Subject Completion

- *Second paragraph:*
- For subjects treated at the RP2D (subset of Part 1 and all of Part 2) ~~Part 1 AML subjects who are treated at RP2D and for Part 2 (expansion cohorts) subjects~~, a completed subject is one who has discontinued study treatment and was followed to death or has died while receiving study treatment.

Section 5. TIME AND EVENTS TABLES

Rationale for Change: The changes were made to clarify or correct disease assessments and revised tissue collection schedule for translational research. The specific details of assessments during BID administration were added.

Revised Text:

Table 5~~6~~ Time and Events: Part 1

PK blood samples for metabolite evaluation: Week 2 D6 deleted

Blood samples for plasma cytokines: W3D1 added

PK Urine samples: SCR and Week 2 D6 deleted

Pharmacogenomics (PGx) ~~blood~~ sample : Screening deleted and W1D1 added

Translational Research: Archival tumor tissue deleted

In footnote second sentence:

Disease assessment will be collected for subjects who discontinue study medication due to any reason other than progression or death (as described in Table 7).

In foot note:

Point number f: During 3+3 dose escalation, PD tumor sample collection will be mandatory unless infeasible to collect, and approval is obtained by the GSK medical monitor. Subjects with MM or AML will have bone marrow aspirates collected on W1

D3 approximately 2-4 hours after the dose. Subjects with NHL will have a lymph node biopsy collected on W1D3 approximately 3-5 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as the hours post-dose for collection remain as described. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM see Table 8 disease specific assessments for details).

Table 6~~7~~ Time and Events: Part 1 Laboratory Assessments

Revised Text:

Troponin, NT pro-BNP Assessment Notes

W1D1, W1D2: troponin local lab sample 3X/24h; central troponin lab sample 1X/24h. Unscheduled troponin collect 2 samples: 1 for local, 1 for central lab~~; NT pro-BNP should be obtained on same day as electrocardiogram is performed~~.

Revised Text:

Table 7~~8~~ Disease Specific Assessments: Part 1 and 2

Multiple Myeloma (MM) Assessments														
		SCR	**Week 1**			**Week 2**		**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Procedure	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease Characteristics	Including cytogenetics as appropriate	X												
Total Protein, CRP, β2 microglobulin		X							X	X	X	X		
SPEP, ~~UPEP~~ FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM~~; UPEP performed if protein present in urine~~.	X							X	X	X		X	
~~Calculated Quantitative paraprotein~~UPEP	Only required if paraprotein is present in urine	X							X		X		X	
~~CRP, β2 microglobulin~~		~~X~~							~~X~~		~~X~~	~~X~~		
~~FLC assay~~	~~Not required for subjects with non-secretory MM~~	~~X~~							~~X~~		~~X~~	~~X~~		
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X							X		X	X		
BM aspirate and biopsy ~~for disease assessment~~	Required for non-secretory MM, or as appropriate for other ~~MM~~subjects	X									X			
~~Bone marrow biopsy for disease assessment~~		~~X~~												
~~Efficacy~~ Response assessment	Every 6 weeks after wk4; Response criteria in Appendix 6								X		X		X	

Lymphoma Assessments															
		SCR	**Week 1**			**Week 2**		**W4**		**W7**	**W10**	**q3W**	**q6W**	**q12W**	**EOT**
Procedure	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history[a] immunophenotypes, cytogenetics and ~~History~~ [a]prognostic markers[b]		X													
~~Lymphoma prognostic markers~~ [b]		~~X~~													
β2-microglobulin		X						X							
B Symptoms		X						X		X	X	X			
Lymph node and organ exam		X						X		X	X	X			
Bone marrow/tissue biopsy ~~for disease assessment~~ [c]		X						X							
CT Scan [d]		X								X			Wk 16, wk 24, then q12wks ~~X~~		
PET Scan [d, e]		X								X					
~~Efficacy~~ Response evaluation [f]										X			Wk 16, wk 24, then q12wks		

a. Including date of first diagnosis, disease stage, and complete history of diagnostic results and therapies.
b. Examples of prognostic markers may include: ALC, FLIPI-1, FLIPI-2 (includes ß2-microglobulin), FcR gamma 3A.
c. A sample will be required ~~only if clinically appropriate for the lymphoma subtype~~ at screening only if clinically appropriate for the lymphoma subtype AND~~unless~~ an appropriate previous sample is available. A follow-up bone marrow biopsy will be performed no later than 8 weeks following CR (as judged by investigator) in accordance with the response guidelines (Appendix 7)- if a subject~~s~~ had involvement of the BM at the start of the study.
d. Baseline/Screening CT and PET scans may be obtained within 35 days of first dose Follow-up CT scans at week 7 wk 16, wk 24 and then every 12 weeks.
e. PET or PET/CT scan ~~only~~ if clinically indicated (e.g., confirmation of CR for- Diffuse large B-cell lymphoma).
f. ~~Efficacy assessments~~Evaluation of response for lymphoma at week 7 ~~,~~ ~~wk~~ week 16, ~~wk~~ week 24 and then every 12 weeks.~~.~~ Assessments are described in Appendix 7 : Response Criteria for Lymphoma

Leukaemia Assessments															
		SCR	**Week 1**			**Week 2**		**W3**	**Wk 4**	**W5**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Procedure	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history, immuno-~~phenotypes~~ phenotype, cytogenetics and molecular studies as appropriate and History [a]		X													
Lymph node and spleen assessment	Only as appropriate	X							X		X	X	X		X
BM biopsy and aspirate	FISH, cytogenetics, FLT3, IgVH, Zap-70 as appropriate	X[b]							X[c]			X[c]			X
~~BM biopsy and or aspirate~~	~~FISH, cytogenetics, FLT3, IgVH, Zap-70 as appropriate~~	~~X~~ [b]							~~X~~ [c]						~~X~~
Transfusion History [d]		X				X		X	X	X	X	X	X		
Bleeding History		X				X		X	X	X	X	X	X		
Hematology [e, f]		X				X		X	X	X	X	X	X		
~~Efficacy~~ Response assessment [g]									X			X	~~X~~	X	

a. Including date of ~~first~~ diagnosis ~~of MDS, sAML/MDS or de novo AML~~ and complete history of diagnostic results and therapies.

b. This bone marrow sample is required for baseline disease assessment , but a peripheral blood sample can be taken if the bone marrow sample could not be collected. See the study procedures manual (SPM) for sample handling.

c. Bone marrow biopsy and aspirate obtained for the assessment of response~~. The assessment of response should occur between 1 – 4 weeks of count recovery (ANC > 1000/µl and platelets > 100,000/µl),~~ Subjects should be off cytokine support (GCSF or GMCSF) for a minimum of 7 days before obtaining bone marrow to document remission.

d. Platelet and blood transfusions to be assessed at designated visits and summarized per unit on a weekly cumulative basis.

e. Hematology includes complete blood count (CBC) with white blood cell count differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes) and platelets; hemoglobin, hematocrit, red blood cell count. A CBC with differential and platelets, hemoglobin and hematocrit may be performed daily during in-patient care; once subject is discharged, assessments to continue weekly until disease response assessment. This is collected at baseline/screening; daily during chemotherapy treatment, then weekly. Platelet count achievement of 20,000/mL for 3 days is entered into the eCRF and the date of platelet count achievement of

100,000/mL is entered into the eCRF.

f. A blood cell smear to measure peripheral blood blasts.

g. ~~Efficacy~~ Response assessments for leukemia at wk 4, wk 10 and every ~~3~~6 weeks thereafter. Assessments are described in Appendix 8: Response Criteria for Leukaemias.

Revised Text:

Table 8~~9~~ Time and Events: Part 1 (QD cohorts) Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling

Procedure / time after dose	W1D1									W1D2		W1D5		
	pre dose	0 h	15 min ± 5m	30 min ±5 m	1h ±10m	2h ±15m	4h ±15m	8h ±1 h	12h ~~±1h~~ 2h	24 h ±1 h	0h	0 h	30 min ±10 m	3h ±30 m
Dose		X									X	X		
12-lead ECG [a]	X		X	X	X	X	X	X	X	X			X	X
PK sample for GSK525762 [b]	X		X	X	X	X	X	X	X	X [b]			X	X
PK sample for metabolite [b,c]	X		X	X	X	X	X	X	X	X [b]				
Blood sample for biomarkers (mRNA)	X[d]					X	X	X	X	X				
Plasma cytokine sample	X[d]					X	X	X	X	X				
Urine PK sampling [c]	X	0-2 h				2-24h								
Urine metabolite sampling[c]	X	0-2 h				2-24h								

Procedure / time after dose	W2 D4	W2 D6	W2D7									W3D 1		W7D1 ±4 days [e]			
	pre dose	pre dose	pre dose	0 h	15 min ± 5m	30 min ±5 m	1h ±10m	2h ±15m	4h ±15m	8h ± 1 h	12 h ± 1 h	24 h ± 1 h	0 h	pre dose	0 h	0.5-2 h	4-8 h
Dose				X									X		X		
12-lead ECG [a]	X	X	X		X	X	X	X	X	X	X	X		X		X	X
PK sample for GSK525762	X	X	X		X	X	X	X	X	X	X	X		X		X	X
PK sample for metabolite [c]			X		X	X	X	X	X	X	X	X					
Blood sample biomarkers (mRNA)			X						X								
Plasma cytokines samples			X					X	X	X	X	X					
Urine PK sampling [c]				0-2h				2-24h									
Urine metabolite sampling[c]				0-2h				2-24h									

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

a. The ECGs are taken i~~.~~n triplicate, 5 minutes apart and within 10 min prior to PK draw~~;~~. **For timepoint with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of**

the window.

b. Sample to be obtained before dosing on Week 1, Day 2.
c. Urine PK sample is collected only at MTD or RP2D in 6 subjects
d. May be collected within 14 days prior to first dose.
e. If dose was escalated, the W4D1 visit may be performed +4 to +7 days.

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Revised Text:

Table 9~~10~~ Time and Events: Part 1 (BID Cohorts) Serial Electrocardiograms, Pharmacokinetics and Biomarker Sampling

	W1D1																W1D2		W1 D3	W1 D4	W1D5			
Timepoint; Hours after AM dose (hours after PM dose)	Pre-Dose	0h	15 min ± 5m	30 min ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h Predose	12h+1h-15min	12h (0h)	12 h 15 min ± 5m	12h 30 min ±5m	13h (1h) ±10m	14h (2h) ±15m	16h (4h) ±15m	20h (8h) ±1h	24h (12h)±1h prior to dosing	AM & PM	AM & PM	AM & PM	AM	30 min ±5m	3h ±15m	PM
Dose		X								X								X X	XX	XX	X			X
12-lead ECG [a]	X		X	X	X	X	X	X	X			X	X	X	♦ X	♦ X	X					X	X	
PK GSK525762 [b]	X		X	X	X	X	X	X	X		X	X	X	X	♦ X	♦ X	X					X	X	
Biomarker sample (mRNA) [c]	X [d]					X	X	X	X					♦ X	♦ X	♦ X	X							
Cytokine/APP	X [d]					X	X	X	X					♦ X	♦ X	♦ X	X							
Urine PK [bf]	X	0-2				2-12				2-24														

	W2D 4		W2D 6		W2D7															W3D1		W7D1 ±4 days [e]				
Time point; Hours after AM dose (hours after PM dose)	pre AM dose	AM & PM	pre AM dose	AM & PM	Pre dose	0h	15 min ± 5m	30 min ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h Predose	12h+1h-5min	12h (0h)	12 h 15 min	12h 30 min ±5m	13h (1h) ±10m	14h (2h) ±15m	16h (4h) ±15m	20h (8h) ±1h	24h (12h)±1h Prior to dosing	AM & PM	pre dose	0h	0.5-2h	4 - 8h	12h
Dose		X X		X X		X								X								XX		X		X
12-lead ECG [a]	X		X		X		X	X	X	X	X	X	X		♦	♦	♦	♦	♦	♦	X		X		X	X	
PK GSK525762	X		X		X		X	X	X	X	X	X	X		♦	♦	♦	♦	♦	♦	X		X		X	X	
Biomarker sample (mRNA) [c]					X						X								♦		X						
Cytokine/APP					X					X	X	X									X						
Urine PK [bf]						0-2				2-12			2-12 (♦ 2-24)														

a. The ECGs are taken in triplicate, 5 minutes apart and within 10 minutes prior to PK draw;. **For time points with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow**

scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.

b. ~~only at MTD or RP2D in 6 subjects,~~ PK blood sample collected overnight may be kept refrigerated at 4°C in the event the laboratory is closed.
c. Blood sample for PD biomarker~~.~~
d. May be collected within 14 days prior to first dose
e. ~~I~~if dose was escalated, the W4D1 visit may be performed +4 to +7 days.
f. Urine PK sample is collected only at MTD or RP2D in 6 subjects.

APP=acute phase protein; ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose;
♦=optional assessment where feasible (e.g., for subjects staying overnight only).

Revised Text:

Table 10~~11~~ Time and Events: Part 2 Expansion Cohort

Part 2 Procedure (Notes)		SCR	Cycle 1				Cycle 2	Cycle 3	Cycle 4	Further Cycles		EOT
			W1 D1	W1 D3	W2 D1	W3 D1	W4 D1	W7 D1	W10 D1	q3W D1	q6W D1	
~~**Tumor PD Assessment**~~												
~~PD Tumor sample (biopsy)~~		~~X~~ [d]		~~X~~ [e]								
PK and Blood PD												
PK Blood 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 to 2 h postdose, single draw between 4-8h postdose W7 and Q6W only predose		X	X [e]			X	X			X	
~~PD Blood sample for biomarker (mRNA)~~			~~X~~					~~X~~				~~X~~
~~Blood samples for plasma cytokines~~			~~X~~					~~X~~				
Translational Research												
PGx ~~blood~~ sample			X									
Tumor sample (biopsy)		X [d]		X [e]								X [f]
Blood samples for Translational Medicine study		X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression									
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 (as described in Table 7). 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.												

1. 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.
2. Vital signs include SBP, DBP, heart rate, respiratory rate and temperature
3. Screening ECGs within 35 days of first dose. ECGs prior to dosing. If QTcF increase >30msec, ECGs performed

daily through W2.

4. Pretreatment biopsy for ~~PD~~ tumor sample must be performed within 14 days of first dose.
5. Subjects with MM or AML will have bone marrow aspirates collected on W1 D3 approximately 2-4 hours after the dose. Subjects with NHL will have a lymph node biopsy collected on W1D3 approximately 3-5 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as **the hours post-dose for collection remain as described**. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM see Table 8 disease specific assessments for details).
6. The collection of tumor samples for translational research are requested at end of treatment for subjects with progressive disease.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; PD=Pharmacodynamics; PK=Pharmacokinetics; PGx=Pharmacogenetics; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; Wk=week

Revised Text:

Deleted below table:

Table 13 Disease Specific Assessments: Part 2

Section 6.1.2. Visit Windows

Rationale for Change: The changes were minor corrections made for clarity.

Revised Text:

Second paragraph onwards:

~~**Part 1 only -**~~ **Visits during Week 1:** Based on subject and clinic schedule, Week 1 Day 5 assessments can be ± 1 day.

~~**Part 1 only -**~~ **Visits between Week 2 through ~~to~~ Week 34:** Based on subject and clinic schedule, assessments can be +3 days.

~~**Part 1 and Part 2 -**~~ **Visits between Week 4 through ~~to~~ Week 9:** Clinic visits can be scheduled ±3 days.

~~**Part 1 and Part 2 - Monthly v**~~**Visits after Week 10 ~~9 until Week 52:~~** ~~After the first disease assessment has been completed then the month clinic visits can be scheduled ± 5 days.~~

~~**Part 1 and Part 2 - Monthly visits after Week 52:** clinic visits can~~ may be scheduled ± 7 days.

Section 6.2. Baseline Assessment

Rationale for Change: The changes were minor corrections made for clarity.

Revised Text:

Subjects diagnosed with refractory hematological malignancy ~~for~~ (MM, lymphoma and/or acute leukemias), will be assessed at baseline for general disease characteristics as noted in Section 6.2.1 and tumor type specific measures as noted in Section 6.2.2, Section 6.2.3 and Section 6.2.4, respectively.

Baseline is defined as the assessment closest to first dose, (i.e., Week[W]1Day[D]~~W1D~~1 assessment) or screening if SCR sample collected within 72h of first dose.

Section 6.2.3. Baseline assessment for Subjects with lymphoma

Rationale for Change: The additions include description for diagnosis of double- and triple-hit lymphoma.

Revised Text:

Below point added:

- FISH, cytogenetics/molecular analysis, and/or IHC for MYC, BCL2, and/or BCL6 (only required to enrol in double- and triple-hit lymphoma sub-cohort).

Section 6.3.5. Electrocardiograms

Rationale for Change: The changes include updated QTc management guidelines.

Revised Text:

Fourth paragraph:

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 Section 7.7 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.

~~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.~~

~~*RR=Time interval from the onset of one QRS complex to the onset of the next QRS complex.~~

~~Table 14 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) discontinue study medications and notify the GSK Medical Monitor. Subject may restart if QTcF <480 after discussion with medical monitor~~	
~~Baseline QTcF value~~	**~~Discontinuation QTcF~~**
~~<450 msec~~	~~>480 msec or ≥60 msec over baseline~~

~~* Baseline results are defined by the nearest time point 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.~~

Section 6.3.6. Holter Monitoring

Rationale for Change: Minor reference and clarification added.

Revised Text:

Second paragraph last sentence:

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.

Section 6.3.7. Telemetry

Rationale for Change: Correction was added to clarify that Holter review was not required for dosing.

Revised Text:

First paragraph last sentence:

~~Day 3 dosing should proceed only after review of Holter data by an appropriate physician.~~

Section 6.3.8. Clinical Laboratory Assessments

Rationale for Change: Clarification added to further define AEs.

Revised Text:

Fourth paragraph:

Abnormal laboratory results that are considered by the investigator to be clinically significant should be recorded on the eCRF as AEs. Laboratory results or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay, must be recorded as an associated AE or SAE. In addition, these clinically significant abnormal laboratory results should be followed until the abnormality resolves or is determined to be stable.

Section 6.4.1. Disease Assessment

Rationale for Change: Minor reference and clarification added.

Revised Text:

Response will be assessed as outlined in the Section 5 Time and Events Table 7~~8~~ by the investigator using the appropriate criteria for MM, lymphoma and/or leukemias, as noted in Appendix 6, Appendix 7 and Appendix 8, respectively. ~~See the SPM for additional instructions.~~

Section 6.5.3. Urine Collection

Rationale for Change: Clarification added for sample collection during BID.

Revised Text:

For QD cohorts, ~~U~~urine samples for quantitative analysis of GSK525762 will be collected over a dosing interval (12 or 24 hours) in two samples (first sample collected 0-2hr and second sample collected 2-24hr) immediately following dosing on Week 1 Day 1 and Week 2 Day 7. For the BID cohort, the first sample will be collected over 0-2h and the second over 2-12h, also immediately following dosing on Week 1 Day 1 and Week 2

Day 7. Urine samples will be collected from at least 6 subjects in Part 1 at the MTD. Additional sampling may be instituted based on emerging data.

Section 6.6. Translational Research

Rationale for Change: The rationale and overall schedule for collection of biological samples was added as a reference.

Revised Text:

Blood and or tumor tissue specimens will be collected at various times throughout the study in order to support research aimed at understanding the biological effect of GSK525762 and BET inhibition as well as identifying indicators of sensitivity or resistance to GSK525762.

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. 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.

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.

Section 6.6.1. Tumor Specific Tissue Collection

Rationale for Change: The schedule for the collection of biological samples was clarified or changed for each disease type due to emerging pre-clinical data.

Revised Text:

6.6.1. Tumor Specific Tissue ~~and Blood~~ Collection ~~from All Subjects~~

The tissue collection and PD tests for Part 1 are disease specific and outlined below:

- For subjects with leukemias, changes in specific protein markers and/or mRNA expression signatures will be assessed in bone marrow and/or tumor cell-enriched PBMCs isolated from whole blood.
- For subjects with lymphomas, lymph node biopsies (or bone marrow, if appropriate) will be required before and after treatment to evaluate changes in tumor-specific protein markers and/or gene expression signatures.
- For subjects with MM, bone marrow will be evaluated for changes in tumor-specific protein markers and/or gene expression signatures (for example, c-Myc).

The tissue collection to support translational and mechanistic research for Part 2 is also disease specific and is similar to that described above.

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.

~~All subjects in Part 1 and 2 will be asked to submit the following:~~

- ~~An archival (most recent) tumor specimen in order to conduct retrospective tests for the identification of potential markers of sensitivity or resistance. This exploratory work may include protein measurements, mRNA measurements as well as DNA (mutation, DNA copy number, translocation) and epigenetic (DNA methylation, microRNA) measurements. Results of previous cytogenetic work performed on the subject will also be collected.~~
- ~~A biopsy at progression or end of treatment, when feasible to collect.~~
- ~~Blood samples collected at various times:~~
- ~~At screening, disease assessment and disease progression for plasma isolation and studying circulating biomarkers (eg, cfDNA).~~
- ~~At pre and post dose for treatment related changes in RNA.~~
- ~~At pre and post dose for treatment related changes in plasma cytokines.~~

~~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.~~

Section 6.6.2. Blood Sample Collection for Surrogate PD Biomarkers

Rationale for Change: The rationale for the collection of biological samples was added for clarity.

Revised Text:

6.6.2. ~~Tumor Tissue~~Blood Sample Collection for Surrogate PD ~~Cohort~~Biomarkers

Blood samples collected at time points described below and in the Time and Events tables for PK and PD testing will be required for all subjects.

- Part 1 &2: At screening, disease assessment and disease progression for plasma isolation and studying circulating biomarkers (eg, cfDNA).
- Part 1 Only: At pre and post dose for treatment related changes in RNA.
- Part 1 Only: At pre and post dose for treatment related changes in plasma cytokines.

6.6.2.1. Plasma for Changes in 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-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.

6.6.2.2. Whole Blood for Changes in 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, may also be performed using whole blood mRNA from selected patients.~~Subjects who consent to tumor PD assessments will also be required to provide pre- and post-treatment tumor specimens as appropriate in order to assess tumor PD response. The PD tests and tissue required are disease specific as outlined below.~~

- ~~For subjects with leukemias, changes in specific protein markers and/or mRNA expression signatures will be assessed in bone marrow and/or tumor cell-enriched PBMCs isolated from whole blood.~~
- ~~For subjects with lymphomas, lymph node biopsies (or bone marrow, if appropriate) will be required before and after treatment to evaluate changes in tumor-specific protein markers and/or gene expression signatures.~~
- ~~For subjects with MM, bone marrow will be evaluated for changes in tumor-specific protein markers and/or gene expression signatures (for example, c-Myc).~~

Section 6.9. Pharmacogenetics

Rationale for Change: An additional assessment was added to evaluate potential excretion mechanisms.

Revised Text:

Second paragraph:

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in selected candidate genes in DNA from ~~blood~~ saliva will be analysed to determine their relationship with response (safety, tolerability, PK, and efficacy) to treatment with GSK525762.

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Rationale for Change: The deletion of the 100 mg dose strength reflects a change in manufacturing.

Revised Text:

Table 14~~17~~ Investigational Product Dosage/ Administration

Investigational Product				
Product name:	GSK525762 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			~~white to off-white, capsule shaped, biconvex tablets with no markings~~

Section 7.7.1. Dose and Safety Management Guidelines

Rationale for Change: The change in thrombocytopenia management guidelines were introduced to ensure consistent management of thrombocytopenia in a disease-specific manner. The QTc management guidelines were updated to ensure consistency with new QTc management guidelines.

Revised Text:

Table 15~~18~~ Dose Adjustment/Stopping Safety Criteria

Toxicity	**Dose Adjustment/ Stopping Criteria**	**Management Guidelines**
Thrombocytopenia	Grade 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	After discussion with medical monitor and using sound clinical judgement, continue at same dose or dose reduce to previously cleared dose level. ~~adjust dose (e.g. consider reduced daily dosing or dosing on alternate days)~~. Monitor CBC at least twice a week, or more frequently if necessary clinically indicated.
	Grade 4 (platelets <25,000/mm^3) and/or any grade accompanied by severe bleeding related to thrombocytopenia	For Lymphoma and Multiple Myeloma: ~~Temporarily i~~Interrupt study medication and monitor CBC every 2-3 days. 1. If platelet counts recover to Grade 2 and are steady for at least 2 CBC measurements at least 3 days apart, or rising, discuss with the medical monitor. Based on clinical judgement, resume ~~resuming~~ treatment at the same or ~~adjusted~~ previously cleared lower dose ~~based on sound medical judgement~~. 2. Platelet transfusion is allowed based on institutional guidelines. ~~In case of~~ If platelet transfusions are required, hold drug ~~for at least 7 days from day of transfusion, and if~~ until platelet counts recover to Grade 2, and are steady for at least 2 CBC measurements at least 3 days apart, or rising. Using clinical judgement and after consultation with the medical monitor, consider ~~initiating~~ resuming treatment at ~~a~~ same or the previously cleared lower dose ~~using sound clinical judgement and after consulting with the GSK medical monitor~~. 3. Discontinue treatment if drug has to be held for >14 days ~~or greater than 2 dose reductions required~~. For Acute Myeloid Leukemia - if platelet count <25,000 but ≥10,000mm^3: Use clinical judgement to institute more frequent monitoring as necessary. For Acute Myeloid Leukemia - if platelet count <10,000/mm^3: 1. Continue treatment and start platelet transfusion as per institutional guidelines. After platelet transfusion, assess platelet level within a couple of hours of transfusion. Institute more frequent monitoring as clinically indicated. 2. If repeat platelet transfusions are not able to rescue platelet count to ≥10,000/mm^3(or to ≥20,000/mm^{3}in case of accompanying fever, sepsis, or minor bleeding) in 2 days, then interrupt treatment. If subsequent transfusions are able to increase the platelet count within 14 days of interruption, consider restarting therapy at the same or previously cleared dose after discussing with the medical monitor and approval by GSK medical governance. If transfusions

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		are unable to increase the platelet count within 14 days of interruption, therapy will be discontinued. 3. Use of adjunctive therapies is permitted. 4. Use of hydroxyurea is permitted in the setting of increased blast counts in conjunction with decreased platelet counts.
QTcF	If >30msec and < 60 msec change from baseline AND manual QTcF <500 (average of three ECGs over at least 15 minutes)	• Continue current dose of GSK525762 • 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.
	If ≥ 60 msec change from baseline occurs OR QTcF ≥500 (average of three ECGs over at least 15 minutes)	• Discontinue GSK525762 and notify the GSK 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 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 <480 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 GSK Medical 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.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		• If approval for re-challenge is granted, the subject must be re-consented (with a separate informed consent specific to 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 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
~~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 > 4 mmol/L (2) Maintain serum magnesium levels 0.85 mmol/L • Consider 24 hour or longer telemetry monitoring if clinically indicated.~~
~~QTcF~~	~~If a >60msec change from baseline* and QTcF<480 msec (Averaged manual overread of three ECGs over at least 15 minutes).~~	~~Grade 1 or 2 Temporarily interrupt study medication 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 > 4 mmol/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.~~

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
~~QTcF~~	~~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)~~	~~Permanently discontinue study medications and notify the GSK Medical Monitor.~~ ~~• If the subject QTcF 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 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 institutional normal range,~~ ~~• (3) a favorable risk/benefit profile,~~ ~~• (4) approval by the internal GSK Medical Monitor,~~ ~~• (5) IRB/ EC 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:~~ ~~• (1) Evaluation by cardiologist.~~ ~~• (2) 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. Consider also doing telemetry if needed.~~

Section 8.2.1. Cautionary Medications

Rationale for Change: The data source was updated for the table in this section.

Revised Text:

Table 17~~20~~ Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Generic Name	Brand Name
Astemizole	Hismanal
Amiodarone	Cordarone, Pacerone, Nexterone
Citalopram	Celexa, Cipramil
Chlorpromazine	Thorazine
Clarithromycin	Biaxin
Escitalopram	Lexapro
Haloperidol	Haldol
Moxifloxacin	Avelox, Avalox, Avelon, Moxeza, and Vigamox

1. NOTE: 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.
2. Data Source: CredibleMeds, 2014~~5~~ (www.crediblemeds.org)

After starting cautionary medications such as in ~~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) those listed in~~ Table 17~~20~~ it is recommended that ECGs are implemented daily until the steady state is reached. If there are abnormalities, implement additional cardiotoxicity monitoring.

Section 8.3. Prohibited Medications

Rationale for Change: The data source was updated in this section.

Revised Text:

Table 19~~22~~ Drugs with a Risk of Torsades de Pointes that are Prohibited

In footnote:

Data Source: CredibleMeds, 2014~~5~~ (www.crediblemeds.org)

Fourth paragraph:

If a subject requires medication for hyperemesis, due to the potential of serotonin 5-HT3 receptor antagonists to increase QTcF, palonosetron (up to a maximum dose of 0.25 mg daily) and ondansetron (up to~~at~~ a maximum dose of 8 mg TID) are the only allowed drugs in this class.

Section 10. DATA MANAGEMENT

Rationale for Change: The data management guidelines for screen failures were clarified in this section.

Revised Text:

Fifth Paragraph:

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently enrolled. Data for screen failures will be collected in source documentation at the site but will not be transmitted to GSK.

Section 11.1.1. Part I, Dose Escalation

Rationale for Change: The statistical design for Part 1 was clarified in this section.

Revised Text:

The sample size in Part 1 is not driven by statistical considerations. The total number of subjects will depend on the number of dose escalations needed. However, the maximum anticipated number of subjects will be approximately 60-70.

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.

Section 11.1.2. Part 2, Expansion Cohort

Rationale for Change: MM and NHL cohorts were added to Part 2 and the statistical design for Part 2 was clarified in this section.

Revised Text:

The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with AML, MM, and NHL.

- For AML, efficacy is defined as ~~detect~~ a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, PR or a morphologic leukemia-free state) of 30% ~~in AML~~ relative to a 10% response rate suggesting no activity.
- For MM, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, VGPR, or PR) of 20% relative to a 5% response rate suggesting no activity.
- For NHL, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, or PR) of 30% relative to a 10% response rate suggesting no activity. For this cohort, double/triple-hit lymphoma subjects will be excluded from initial efficacy analysis and will be evaluated separately.

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 (e.g. Beta (0.03, 0.07)) 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.

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

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 3.2.4.

For the AML and NHL disease cohorts.~~>Symbolically, the null hypothesis is:~~

~~H_0: RR≤10%~~

~~The alternative hypothesis is:~~

~~H_A:RR≥30%~~

~~Bayesian statistics will be employed to calculate the predictive probability that the response rate ≥30% at interim and final analysis using a weak/non-informative prior. A Bayesian analysis expresses uncertainty about a parameter in terms of probability. A prior 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 and the likelihood (i.e., the data). A very weak prior Beta (0.03, 0.07) with a mean response rate of 30% 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 and the likelihood of the observed data x, the posterior distribution of the response rate follows a beta distribution, i.e.,~~

~~p ~ Beta (0.03 + x, 0.07 + n-x) with the posterior mean (0.03+ x)/(0. 1 + n).~~

~~S~~starting with a cohort of 10 subjects and allowing for a maximum sample size of 32 subjects at the RP2D with stopping guidelines as described in Section ~~4.2.3.2~~3.2.4, this design will have a Type I Error (α) of 0.034~~04~~ and 87% power. Futility analysis will be based on subjects who have at least one post-baseline disease assessment. The trial will

be stopped early for futility if the predictive probability of success (that the response rate ~~≥≥30%~~ historical response rate) is less than 1%. If the true response rate is 10%, the average sample size is 20 and the probability of early termination (PET) for futility is 93%. If the true response rate is 30%, the average sample size is 31 subjects and the PET is 9%.

For the MM disease cohort, starting with a cohort of 13 subjects and allowing for a maximum sample size of 37 subjects at the RP2D with stopping guidelines as described in Section 3.2.4, this design will have a Type I Error (α) of 0.032 and 85% power. Futility analysis will be based on subjects who have at least one post-baseline disease assessment. The trial will be stopped early for futility if the predictive probability of success (that the response rate ≥historical response rate) is less than 1%. If the true response rate is 5%, the average sample size is 22 and the probability of early termination (PET) for futility is 91%. If the true response rate is 20%, the average sample size is 36 subjects and the PET is 10%.

Section 11.4. Interim Analysis

Rationale for Change: MM and NHL cohorts were added to Part 2 and the statistical design for Part 2 was clarified in this section.

Revised Text:

Second and third paragraphs:

For each disease type in Part 2, after the initial 10 subjects in the AML and NHL cohorts and initial 13 subjects in the MM cohort have enrolled at the selected dose regimen for the Expansion Cohort, data will be reviewed for clinical benefit on an ongoing basis and the number of subjects with observed clinical benefit will be compared with the stopping guidelines provided in Section 3.2.4.

The study will not only stop due to lack of efficacy. The trial will may continue to enrol the maximum planned sample size to provide a better an estimate on the distribution of the response rate in the target patient populations.

Section 11.6.1. Primary Analysis

Rationale for Change: MM and NHL cohorts were added to Part 2 and the statistical design for Part 2 was clarified in this section.

Revised Text:

Second paragraph onwards:

The primary aim of Part 2 is to detect demonstrate a possibly ~~a~~ clinically meaningful response rate ~~of 30% relative to a 10% response rate suggesting no activity~~ in each of the disease cohorts separately. Each disease subtype (AML, MM, and NHL) will be evaluated separately.

Overall Response rate is defined as

- AML: T~~t~~he percentage of subjects who achieved CR, CRp, PR and a morphologic leukemia-free state. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided. Response rates of subjects with AML M3 will be summarised separately.
- MM: The percentage of subjects who achieved CR, VGPR, or PR.
- NHL: The percentage of subjects who achieved CR or PR. Response rates of subjects with double/triple-hit lymphoma will be summarised separately.

~~among~~ All subjects who received at least one dose of treatment ~~in the target population~~ will be included in the evaluation for response. Response rates and the associated 2-sided 95% exact confidence limits will be provided. ~~A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided. Response rates of subjects with AML M3 will be summarised separately.~~

Section 11.6.2. Secondary Analysis

Rationale for Change: The statistical design for the secondary endpoints in Part 2 was clarified in this section.

Revised Text:

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 for NHL, CR, CRp, PR or morphologically leukemia free for AML, and CR, VGPR, or PR for MM as the time from the first documented evidence response 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 response as the time from first dose to the first documented evidence of response.

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 response will be included. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP.

OS along with 95% confidence intervals for MM, lymphoma and~~/or~~ leukemia~~s~~ subjects treated ~~at RP2D~~in Part 1 and Part 2, will be estimated using the Kaplan Meier method. OS analysis for AML will exclude subjects with AML subtype M3. NHL will be separately reported based on double/triple hit status. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis.

Section 11.7.3. Clinical Laboratory Evaluations

Rationale for Change: Minor correction was made.

Revised Text:

Second sentence:

Laboratory test results outside the reference ranges that do not have ~~an~~ associated NCI-CTCAE criteria will be summarized using proportions.

Section 12.6. Study and Site Closure

Rationale for Change: The terms for site closure were clarified.

Revised Text:

Third paragraph:

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). GSK may also close sites which fail to recruit. When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

Fifth paragraph:

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

Section 14. REFERENCES

Rationale for Change: The data source was updated.

Revised Text:

Seventh reference:

CredibleMeds. List of drugs with a risk of Torsades de Pointes. Available at: http://www.crediblemeds.org Accessed ~~18 Aug 2014~~ 02 March 2015

Section 15.3. Appendix 3: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Rationale for Change: Minor corrections were made due to changes in figures.

Revised Text:

Liver Chemistry Follow-up Procedures

First sentence:

Refer to the diagram in Figure 7 ~~Figure 5~~ for a visual presentation of the procedures listed below.

Liver Chemistry Monitoring Criteria

Second paragraph:

Refer to Figure 7 ~~Figure 5~~ for the algorithm of liver chemistry monitoring, stopping and follow up criteria.

Liver Safety Drug Restart Guidelines

Drug Restart/Rechallenge Process (also see Figure 8 ~~Figure 6~~)

Second paragraph:

GSK Medical Monitor & Clinical Safety Physician to review the subject's restart/rechallenge risk factors & complete checklist (Table 20~~23~~)

Section 15.4. Appendix 4: Dose Adjustment/Stopping Criteria/Supportive Care

Rationale for Change: Minor correction.

Revised Text:

Fever

First paragraph:

Safety monitoring cytokine blood samples may be collected (based on Section 7.7.1 of the protocol). These samples include (but not limited to) assessments for TNF-alpha, IL-1, IL-6, and IL-10 ~~as outlined in the SPM~~.

Section 15.5. Appendix 5: Pharmacogenetic Research

Rationale for Change: An additional assessment and clarifications were added based on emerging data.

Revised Text:

PGx Associations with Safety Events

Third paragraph:

Collection of whole ~~blood~~saliva samples, 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.

Study Assessments and Procedures

~~In addition to any blood samples taken for the clinical study, a whole blood~~A saliva sample ~~(~10mL)~~ will be collected for the PGx research using an Oragene DNA self collection tube ~~containing ethylenediaminetetraacetic acid (EDTA)~~. It is recommended that the ~~blood~~ saliva sample be taken at ~~the first opportunity after a subject has been randomized and provided informed consent for PGx research~~day 1, but may be taken at any time while the subject is participating in the clinical study after the subjects provided informed consent for the PGx research.

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~~ saliva 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~~ saliva 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.

Following subsection deleted:

~~**Screen and Baseline Failures**~~

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

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~~ sample being taken for PGx research.

15.18. Appendix 18: Protocol Changes for Amendment 5 (08-JUL-2015) from the Protocol Amendment 4 (06-APR-2015)

Where the Amendment Applies

Amendment 5 applies to all study centres.

General Protocol Changes

Amendment 5: Updated inclusion criteria and guidance on contraception use based on emerging data from preclinical studies of embryo-fetal development. Minor clarifications were made regarding the Echo and Holter monitoring requirements and the list of medications with risk for Torsades de Pointes and prohibited medications were updated. The AML response criteria were updated with modified Cheson 2003 guidelines. Futhermore, the dosing schedule was updated to a continuous daily dosing schedule. Finally, after an internal QTc analysis and evaluation of cardiac safety data collected from all subjects in the BET115521 study up to and including the 100mg QD cohort available by 15 May 2015, the 48-hour telemetry requirement has been removed for all parts of the study and the frequency of Holter Monitoring was decreased in Part 1. Minor clarifications, reformatting of tables and typographical errors were also addressed in this amendment.

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

18.14.1 List of Changes

Sponsor/medical monitor Information Page

Medical Monitor and Sponsor Contact Information:

Rationale for Change: Updated to include back up medical monitor's cell phone number.

Revised Text:

After-hours Phone/Cell/Pager Number PPD for secondary medical monitor has been added.

ABBREVIATIONS

Rationale for Change: Abbreviations deleted as part of the protocol amendment

Deleted Text:

~~HI~~	~~Hematologic Improvement~~
~~IVCD~~	~~Intraventricular conduction delays~~
~~RBC~~	~~Red blood cell~~

PROTOCOL SYNOPSIS

- **STUDY DESIGN AND DURATION:**

Rationale for Change: Minor correction

Revised Text:

Second sentence:

Eligible subjects with relapsed refractory hematological malignancies will be enrolled in once daily (OD) and/or twice daily (BID) dosing cohorts until a maximum tolerated dose (MTD) is established.

- **OBJECTIVES AND ENDPOINTS:**

Rationale for Change: Minor correction

Revised Text:

	Part 1 Objectives	Part 1 Endpoints
Secondary	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration following QD and/or BID dosing schedules.	• GSK525762 PK parameters following single- ~~(Day 1)~~ and repeat-dose ~~(Day 15)~~ administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.

- **INCLUSION/EXCLUSION CRITERIA:**

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 8: A female subject is eligible to participate if she is of:

- *Second bullet point:* 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 ~~4 weeks~~ 7 months after the last dose of study medication.

Inclusion criteria 9: 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.

- **DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**:

Rationale for Change: The original dosing schedule (1,3,5,7) was designed to include a dosing break over the course of the first week to monitor for any potential immediate toxicities before moving into continuous daily dosing in the second 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:

- Starting dose will be 5 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. BID dosing will be explored in a parallel cohort. Alternate dosing schedules e.g. intermittent dosing~~)~~ may be required to manage toxicities and may be considered based on investigator assessment and after consultation with GSK~~; and may be implemented if the safety, pharmacokinetic (PK), and pharmacodynamic (PD) data suggest that a sufficient therapeutic exposure cannot be achieved using the protocol schedule and after~~ without requiring a protocol amendment.

- **SAFETY MEASUREMENTS**:

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:

- Routine physical examinations, vital sign measurements, echocardiograms, and monitoring of adverse events will be performed. ~~Stringent~~ Cardiac 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, Week 1, and Week 4, 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). Laboratory testing includes, in addition to standard hematology, clinical chemistry, pancreatic, coagulation, and liver chemistry panels, testing for troponin, N-terminal prohormone B-type Natriuretic Peptide (NT pro-BNP), c-peptide, 1,5-Anhydroglucitol (1, 5 AG), Hemoglobin A1c (HbA1c), and thyroid monitoring. Additional safety assessments may be necessary based on emerging data.

Section 1.3.1.1.2. Human Pharmacokinetics and Equivalent Exposure for NOEL for QTc prolongation

Rationale for Change: Minor correction

Revised Text:

Last Paragraph:

Updated PK information obtained after first subject first dose is presented in Section 15.10. ~~Appendix 13 (Section 15.13)~~

Section 1.3.2.2. Clinical Rationale for BID

Rationale for Change: Minor correction

Revised Text:

First paragraph:

Pharmacokinetics of GSK525762 has been evaluated in subjects in studies BET115521 and BET116183 following single and repeated daily administration of GSK525762 ~~(Section 15.13)~~ Section 15.10.

Section 1.5.1. Risk Assessment

Rationale for Change: Minor correction

Revised Text:

First paragraph, second sentence:

Toxicology studies performed in dogs, rats and mice suggest that the primary toxicities of GSK525762 are gastrointestinal, cardiovascular, pancreatic, hematologic and reproductive (see the GSK525762 IB [GlaxoSmithKline Document Number 2011N113741_03~~], Section 4.4).~~]).

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:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** (up to 20%; 41 msec in dog) Can occur or persists after drug is cleared from plasma; general trend to increase on repeat dosing; no potentiation beyond day13 in 28 day toxicology study in dogs. Reversible on cessation of dosing; not potentiated on subsequent dosing following a 7 day dosing holiday. No significant arrhythmias were detected in preclinical studies. No clear link to human	ICF includes the risk of (fatal) arrhythmias Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK] and creatine kinase-MB [CK-MB]), cardiac monitoring (electrocardiograms [ECGs], Holter monitoring and cardiac

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	ether à go-go-related gene (hERG) binding or trafficking. No evidence of heart accumulation of GSK525762. Mechanism & risk for Torsades de Pointe is unclear. **Blood pressure (BP**) Variable changes in blood pressure following a single dose (no effects were observed in the 28 day toxicology studies); increase in mean BP up to 11 mmHg; decrease in mean BP up to 13 mmHg. **QA interval** (indirect measure of cardiac contractility). Increased QA interval at single non-tolerated doses; up to 10msec. No effects were observed in the 28 day toxicology studies).	ejection fraction) during the study, and dose stopping/modifications criteria for the management cardiac events. Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 8.3). ~~All subjects will receive their first doses of study medication (Week 1 Day 1 and Week 1 Day 2) in the hospital with telemetry monitoring for the first 48 hours of dosing.~~ 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. 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 and including 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 5. 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

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		normal range.
Reproductive	GSK525762 has shown adverse and potentially irreversible effects on testes in rats, rabbits and dogs, with no ~~no~~ observed adverse effect level (NOAEL) in rabbits. An effect on spermatogenesis is anticipated. In definitive four-week oral toxicology studies, sperm retention and degenerative effects occurred in male dogs and rats. Degenerative changes were also observed in rabbits dosed dermally for 14 days. ~~In a dose range rat embryofetal development study, GSK525762 has been shown to impact fetal development at doses ≥1 mg/kg/day, including embryo-fetal toxicity, leading to a complete loss of litters at 30 mg/kg/day and developmental toxicity including fetal malformations at doses ≥1 mg/kg/day. These adverse reproductive effects occur in rats at systemic exposures approximately 3-fold below the exposure observed in patients given 2 mg/day on the ongoing dose escalation Phase 1 clinical trial BET115521. The findings from the dose-range reproductive toxicity study in rats with GSK525762 are consistent with literature reports that BRD2, BRD3, BRD4 and BRDT have crucial roles in reproductive function and embryofetal development (see the GSK 525762 IB [GlaxoSmithKline Document Number 2011N113741_03] for references). Based on the findings in this reproductive toxicity study in rats with GSK525762, there is a substantiated risk for adverse effects on embryofetal development. There is a theoretical risk that GSK525762 may also impact female reproductive organs (ovaries). A rat female fertility study is ongoing to evaluate this risk.~~ 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	ICF includes the risk of damage to reproductive organs such as testes or ovaries. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and complete) for male subjects. ICF includes the potential risk of reproductive effects. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	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.	

Section 3.2.1.1. Dose Escalation and Schedule

Rationale for Change: The original dosing schedule was designed to include a dosing break during the first week to monitor for any potential immediate toxicities before moving into continuous daily dosing in the second 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 staggered dosing schedule will be implemented to monitor for safety including any delayed toxicity. This approach allows repeat dosing in a step-wise fashion to detect changes in safety, such as cardiotoxicity. Based on a low risk of drug accumulation and the aggressive nature of relapsed and/or refractory hematologic malignancies, a three week period will be used for DLT monitoring and dose escalation decision making. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data and ~~after~~ without requiring a protocol amendment.

In Part 1, subjects will follow the dose schedule outlined ~~below~~ in Table 1. Alternative dosings regimens and/or schedule may be implemented based on emerging PK and safety data. ~~Specifically, in Week 1 subjects will receive study drug on Day 1 through Day 5, and rest Day 6 and Day 7. From Week 2 the subject will start daily dosing which will continue until study completion (Section 4.2.3).~~

Extensive monitoring for cardiac safety signals will be performed including ~~in subject telemetry during the first 48 hours after initial study treatment as well as~~ triplicate 12-lead ECG and 24-hour Holter monitoring on the days indicated in Table 1.

Table 1 Three Week DLT monitoring: Dosing Schedule and Cardiac Monitoring (QD and BID)

Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	Dose ECG, ~~Holter 48h Telemetry*~~	Dose ECG, →	Dose	Dose	Dose ECG, Holter	~~off~~Dose ECG	~~off~~Dose
Week 2	Dose ECG	Dose	Dose	Dose ECG	Dose	Dose ECG	Dose ECG, ~~Holter~~
Week 3	Dose ECG	Dose	Dose	Dose ECG	Dose	Dose	Dose

~~* 48h Telemetry: start predose d1, remove on d3~~

Please refer to Time and Events Tables Section 5 for more details

Section 3.2.1.4. 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:

Added text at the end of second paragraph:

If alternative dosing schedules are explored, PK sampling times and other safety assessments may be modified to reflect the new dosing schedule.

Section 3.2.1.5. BID dosing

Rationale for Change: Minor correction

Revised Text:

First paragraph:

~~Twice daily (BID) dosing, may also be explored, initially in subjects with acute leukemia, as described in Section 1.3.2.~~ The initial dose level for BID will be a maximum of 20 mg (ie 2x 20mg 12 hours apart, total daily dose of 40mg) or a dose level lower than 20 mg depending on emerging safety, PK and PD data and dosing will be separated by approximately 12 hours. Escalation can then proceed as described using the 3 + 3 dose escalation.

3.2.4. Part 2: Disease Specific Expansion Cohorts

Rationale for Change: 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.

Revised Text:

Footnotes of 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 1% or less (the futility criterion) and ~~the study~~ further enrollment in these cohorts may 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 8: A female subject is eligible to participate if she is of:

- *Second bullet point:* 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 ~~4 weeks~~ 7 months after the last dose of study medication.

Inclusion criteria 9: 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: Updates were made to this section to further clarify the follow up phase requirements

Revised Text:

Last Paragraph:

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post study treatment follow-up as specified in the Section 5 Time and Events Tables.

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

- 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 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. Upon discontinuation, any samples previously collected for PD and/or translational research will be retained and tested as defined in the protocol, unless consent is specifically withdrawn.

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.

Revised Text:

Table 5 Time and Events: Part 1

																													q3w and q6w Initiated from Wk 10		
Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**						
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**							
TREATMENT PHASE																																
Study Drug: For QD or BID details see Table 8 and Table 9																																
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																
Safety																																
Height and weight (Height at SCR only)	X	X				X			X							X		X		X		X	X	X		X					
Cardiac Monitoring																																
Holter monitoring (At least 24 h, on dosing days start predose)	X	~~X~~				X									~~X~~			X					~~X~~									
~~Telemetry (Starting predose d1 for min 48 h, remove on d3)~~		~~X →~~																														

Table 6 Time and Events: Part 1 Laboratory Assessments

Table column heading text q3w and q6w Initiated from Wk 10 has been added above the columns of q3WD1 and q6WD1.

Troponin, NT pro-BNP Assessment Notes:

Troponin: W1D1 &~~,~~ W1D2: ~~troponin~~ local lab sample collect 3X/~~24h~~per day; central troponin lab sample 1X/~~24h~~per day. All other timepoints and u~~U~~nscheduled troponin, collect 2 samples: 1 for local, 1 for central lab.

Table 7 Disease Specific Assessments: Part 1 and 2

Table column heading text q3w and q6w Initiated from Wk 10 has been added above the columns of q3WD1 and q6WD1 under Multiple Myeloma (MM) and Leukaemia Assessments.

Table column heading text q3w and q6w Initiated from Wk 10 has been added above the columns of q6WD1 and q12WD1 under Lymphoma Assessments.

Table 9 Time and Events: Part 1 (BID Cohorts) Serial Electrocardiograms, Pharmacokinetics and Biomarker Sampling

12-lead ECG measurement added at 12 hours and 15 minutes time point at W1D1

The event name ~~cytokine/APP~~ changed to plasma cytokines samples

Table 10 Time and Events: Part 2 Expansion Cohort

Revised table column heading text "Further Cycles (q3w and q6w Initiated from Wk 10)" above the columns of q3WD1 and q6WD1.

Deleted a Part 2 Procedure "~~Telemetry (Starting predose d1, for min 48 h, remove on d3) see Section 6.3.7~~" from the table.

Table 11 Time and Events: Part 2 Laboratory Assessments

Revised table column heading text "Further Cycles (q3w and q6w Initiated from Wk 10)" above the columns of q3WD1 and q6WD1.

The event name ~~Cytokines~~ changed to Safety Cytokines and the timing changed as follows: as clinically appropriate following fever

Section 6.3.4. 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 Left ventricular ejection fraction (LVEF) compared to baseline concurrent with LVEF < LLN will be required by GSK for review.~~

All ECHO data ~~may~~ will be transferred and reviewed by an independent cardiologist.

Section 6.3.6. 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:

Third paragraph onwards:

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 <u>data</u> ~~ECGs~~ were 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 described in the Section 5 Time and Events. 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 6.3.7. 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:

Whole section deleted:

~~6.3.7. Telemetry~~

~~To complement real-time ECG assessments, monitoring for potential adverse arrhythmias will be conducted utilizing continuous telemetry for at least 48 hours from the start of~~

~~dosing. 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.~~

Section 6.5.2. Plasma Sample Analysis

Rationale for Change: A statement was added to further clarify planned analysis for plasma samples from subjects.

Revised Text:

First Paragraph:

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 6.5.3. Urine Collection

Second Paragraph:

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 6.6. Translational Research

Rationale for Change: A statement was added in this section to further clarify analysis of samples from the leukemia population.

Revised Text:

End of second paragraph:

In certain settings such as leukemia specimens, samples may be used to evaluate changes in leukemic stem cell populations or to generate PDX models.

Section 6.8.1. 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:

Reporting of any pregnancies~~All pregnancies~~ in female subjects and/or female partners of male subjects will be collected after the start of dosing and until ~~16 weeks~~ 7 months after the last dose of study drug.

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 17 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Generic Name	Brand Name
~~Clarithromycin~~	~~Biaxin~~
~~Haloperidol~~	~~Haldol~~

Section 8.2.2. Drugs Potentially Affecting GSK525762 Pharmacokinetics

Rationale for Change: This section was updated with emerging metabolite data from the ongoing clinical studies with GSK525762.

Revised Text:

~~The precise in vivo metabolic liability for GSK525762 has yet to be assessed. In vitro data suggests that GSK525762 has a low potential to inhibit the major human CYP isoforms (IC50's ≥ 33 μM) 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 as they may increase or decrease exposure to GSK525762. Table 18 provides a list of possible~~

~~medication including but not limited to those drug substances that may alter GSK525762 exposure.~~

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. Potential interactions with other Cytochrome P450 metabolized drugs have not been assessed.

Table 18 Drugs Potentially Affecting GSK525762 Pharmacokinetics Resulting in Increased or Decreased GSK525762 Exposure

Drug Class	Agent
Drugs that may increase exposure to GSK525762 (CYP3A4 ~~or CYP2D6~~ Inhibitors)	
Antifungals	Fluconazole (>150 mg daily), itraconazole, ketoconazole, terbinafine, posaconazole, voriconazole
Antidepressants	~~Bupropion, duloxetine, fluoxetine,~~ fluvoxamine, nefazodone ~~paroxetine,~~
	~~Cinacalcet, diphenydramine, perhexiline~~

Section 8.3. Prohibited Medications

Rationale for Change:

Revised Text: 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

Table 19 Drugs with a Risk of Torsades de Pointes that are Prohibited

Generic Name	Brand Name
Clarithromycin	Biaxin, Prevpac

Section 9.1.1. 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 method 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:

Fourth Paragraph:

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

Third bullet point:

- ~~Double barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository).~~

Section 9.1.2. 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 GSK525762 being transferred to a developing embryo or fetus via the semen.

Revised Text:

At the end the following text added:

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. Primary Analysis

Rationale for Change: This section was updated to be in line with the Response Criteria for Leukaemias referenced in Section 15.8

Revised Text:

Third paragraph: Overall Response rate is defined as

First bullet point:

- AML: The percentage of subjects who achieved CR, CRp, CRi, and PR ~~and a morphologic leukemia-free state~~. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided. Response rates of subjects with AML M3 will be summarised separately.

Section 11.6.2. Secondary Analysis

Rationale for Change: Minor correction

Revised Text:

Second paragraph: The duration of response is defined for the subject or subjects with a confirmed CR or PR for NHL, CR, CRp, CRi, or PR ~~or morphologically leukemia free~~ for AML, and CR, VGPR, or PR for MM as the time from the first documented evidence response 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.

Section 14. REFERENCES

Rationale for Change: This section was updated to be in line with the Response Criteria for Leukaemias referenced in Section 15.8

Revised Text:

Following references were deleted:

~~Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood*. 2000; 96: 3671-4.~~

~~Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003. 21:4642-9. Erratum in: *J Clin Oncol*. 2004; 22:576.~~

~~Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. 2006; 108: 419-25.~~

Following reference was added:

Cheson BD, Bennett JM, Kopecky KJ, et al.. International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003 Dec 15;21(24):4642-9.

Section 15.5. Appendix 5: Pharmacogenetic Research

Rationale for Change: Minor Correction

Revised Text:

PGx Associations with Safety Events

Collection of ~~whole~~ saliva samples, 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.

Section 15.8.1. Acute Leukemias, MDS, Chronic Myelogenous Leukemia in Blast Phase (CML-BP), Chronic MyeloMonocytic Leukaemia (CMML)

Rationale for Change: This section was updated to reflect the Cheson 2003 response criteria.

Revised Text:

[~~Cheson, 2000; Cheson, 2004; Cheson, 2006~~ Modified Cheson 2003]

Complete remission (CR): The subject must achieve a morphologic leukemia-free state (≤5% blasts) and have no evidence of extramedullary disease. The subject must be free of all symptoms related to leukemia, ~~and~~ have an absolute neutrophil count ≥1 x 10^9/L and platelet count ≥100 x 10^9/L, and ~~normal marrow differential (≤5% blasts)~~ be transfusion independent.

CRp: Marrow response as per CR but platelet count <100 x 10^9/L.

CRi: Marrow response as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L.

Partial remission (PR): ~~Count recovery as per CR, with 6 to 25% abnormal cells in the marrow or 50% decrease in bone marrow blasts. (AML only: If all other criteria for CR are met, then a value of <5% blasts with Auer rods present or abnormal morphology is considered partial remission)~~ A decrease from baseline of at least 50% in the number of bone marrow blasts, to between 5% and 25% of the bone marrow aspirate.

No response: Subject does not meet criteria for CR, CRp, CRi, or PR.

Recurrence: Morphologic relapse, defined as the reappearance of peripheral blasts or increase in bone marrow blasts ≥ 5% not attributable to any other cause (e.g., infection, growth factor support, bone marrow regeneration)

~~**Morphologic leukemia-free state:** Normal marrow differential (<5% blasts); neutrophil and platelet counts are not considered. (AML only)~~

Marrow CR: Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pre-treatment (MDS only)

~~Hematologic Improvement (HI):~~ ~~Hematologic improvement should be described by the number of individual, positively affected cell lines (e.g., HI-E; HI-E + HI-N; HI-E+ HI-P + HI-N).~~

~~Erythroid response (HI-E)~~

~~Major response: For subjects with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for red blood cell (RBC) transfusion-dependent subjects, transfusion independence.~~

~~Minor response: For subjects with pretreatment hemoglobin less than 11g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent subjects, 50% decrease in transfusion requirements.~~

~~Platelet response (HI-P)~~

~~Major response: For subjects with a pretreatment platelet count less than 100×10^9/L, an absolute increase of 30×10^9/L or more; for platelet transfusion-dependent subjects, stabilization of platelet transfusion independence.~~

~~Minor response: For subjects with a pre-treatment platelet count less than 100×10^9/L a 50% or more increase in platelet count with a net increase greater than 10×10^9/L but less than 30×10^9/L.~~

~~Neutrophil response (HI-N)~~

~~Major response: For absolute neutrophil count (ANC) less than 1.5×10^9/L before therapy, at least a 100% increase, or an absolute increase of more than 0.5×10^9/L, whichever is greater.~~

~~Minor response: For ANC less than 1.5×10^9/L before therapy, ANC increase of at least 100%, but absolute increase less than 0.5×10^9/L.~~

~~Progression/relapse after HI:~~ ~~One or more of the following: a 50% or greater decrement from maximum response levels in granulocytes or platelets, a reduction in hemoglobin concentration by at least 2 g/dL, or transfusion.~~

15.19. Appendix 19: Protocol Changes for Amendment 6 (15-MAR-2016) from the Protocol Amendment 5 (08-JUL-2015)

Where the Amendment Applies

Amendment 6 applies to all study centres.

General Protocol Changes

Amendment 6: Updated Section 6.1.2. Visit Windows to provide additional clarification on clinical visits. Updated Section 7.1. GSK525762 Investigational Product Dosage/Administration to include both amorphous free base and crystalline besylate formulations of GSK525762 in the study. Updated Section 7.3. Meals and Dietary Restrictions to include the meals and dietary requirements for the new besylate formulation included in the study.Minor clarifications, reformatting of tables and typographical errors were also addressed in this amendment.

Changes are noted below with ~~strikethrough~~ to identify deleted text and underlining to identify new or replacement text.

List of Changes

Sponsor/medical monitor Information Page

Medical Monitor and Sponsor Contact Information:

Rationale for Change: Change in primary and secondary medical monitors.

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 ~~MD, PhD~~	PPD	PPD		GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD
Secondary Medical Monitor	PPD MD, Ph PPD ~~MD, PhD~~	PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road, UP4410 Collegeville, PA 19426, USA PPD

Section 5 TIME AND EVENTS TABLES

Rationale for Change: Minor change was made to ensure consistency with the body text.

Revised Text:

Table 10 Time and Events: Part 2 Expansion Cohort

Part 2 Procedure (Notes):

TREATMENT PHASE					
Study Drug					
Dispense study drug (Administer about same time of day. ~~No food or antacids 1h before and 2h after.)~~		Continuous daily dosing (unless safety, PK or PD data necessitate a different dosing schedule), see Section 3.2.4	X		

Section 6.1.2. Visit Windows

Rationale for Change: This section was revised to provide additional clarification on clinical visits.

Revised Text:

Fifth paragraph onwards:

Every 3-week and 6-week visits Week 10 through Week 48 Clinic visits can be scheduled ± 7 days.

After Week 48: Every 3-week visits are no longer required, based on clinical judgment. Every 6-week clinic visits must include safety assessments from the "q3w" column in the Time and Events Table and can be scheduled ± 7 days. Response assessments may be scheduled ± 7 days.

~~**Visits after Week 10** may be scheduled ± 7 days.~~

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Rationale for Change: This section was revised to include both amorphous free base and crystalline besylate formulations of GSK525762 in the study.

Revised Text:

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 (Table 14) and a crystalline, besylate formulation (Table 15) will be utilized.

In the BET115521 study, a sub-study was conducted to evaluate the PK characteristics of the new besylate formulation. This sub-study was an open-label, randomized, single dose, four period, cross over sub-study performed 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.

The sub-study results showed that 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.

Either amorphous or besylate tablets may be used in Part 1, based on the bioequivalence described above. During the DLT observation period, subjects will only receive one or the other formulation; any individual cohort will only enrol subjects receiving a single formulation type. Upon completion of the DLT observation window, subjects may be changed from amorphous to besylate tablets at the equivalent dose.

The besylate tablet will be utilized in Part 2.

When used under the conditions of handling and administration described in Section 7.2, 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 14 GSK525762 Amorphous Free Base Investigational Product Dosage/ Administration

Investigational Product			
Product name:	GSK525762 Amorphous Free Base Tablets		
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		
Route/ Administration/ Duration:	Oral; see the Section 5 Time and Events Tables for schedule and administration timings		
Dosing instructions:	Dose with 240 mL water and should be taken within a similar time frame each morning. 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 15 GSK525762 Besylate Investigational Product Dosage/Administration

Investigational Product			
Product name:	GSK525762 Besylate Tablets		
Unit dose strength(s)/Dosage level(s):	5mg	25mg	50mg
Dosage form	Tablet	Tablet	Tablet
Manufacturer	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
Route/ Administration/ Duration:	**Oral;** see Time and Event Tables for schedule and administration timings		
Dosing instructions for Part 1:	Dose with 240 mL water and should be taken at the same time each day, preferably in the morning**. 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.)		
Dosing Instructions for Part 2	Dose with 240mL water and should be taken at the same time each day, preferably in the morning. (If a subject vomits after taking study drug, the subject should be instructed not to retake the dose and should take the next scheduled dose.)		

Section 7.3. Meals and Dietary Restrictions

Rationale for Change: This section was revised to include the meals and dietary requirements for the new besylate formulation included in the study.

Revised Text:

Subjects enrolled under Part 1 will fast for at least one hour prior to each dose of study drug (amorphous free or besylate). No food or antacid should be taken for 2 hours after dosing. Subjects should not eat a heavy meal in the morning prior to the 1 hour washout before dosing to minimize potential risk for food interaction. On serial PK sampling 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.

If a subject vomits after taking study medication, 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 PK, PD and safety data. Any change in fasting requirements will be communicated to each investigator and site staff in a future protocol amendment. Should a twice daily regimen be required, additional consideration will be paid to this requirement once the escalation period is past.

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

Based on the results of the BET115521 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 for subjects in Part 2 only except on Serial PK sampling days (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.

15.20. Appendix 20: Protocol Changes for Amendment 7 (23-JUN-2016) from the Protocol Amendment 6 (15-MAR-2016)

Where the Amendment Applies

Amendment 7 applies to all study centres.

General Protocol Changes

Amendment 7: Study design was amended to include collection of additional safety data of GSK525762 BID dosing (exploratory cohort) after determination of maximum tolerated dose with QD dose and to evaluate the preliminary efficacy of GSK525762 BID dosing. The secondary objectives of Part 1 were updated to include evaluation of clinical efficacy of GSK525762 (overall response rate). The endpoints for secondary objective of Part 2 (determination of clinical activity of GSK525762) was updated to include TTP, DOR, PFS for MM and NHL. Eligibility criteria were clarified specifying hematologic malignancies (AML, MM, NHL) for both Part 1 and 2. Risk associated with drug interaction was updated. Permanent discontinuation from study treatment section was updated. Time and events tables were also updated in line with study design modifications. Whole section of urine collection was removed. Tables of cautionary medications, prohibited medications and drugs affecting PK of GSK525762 were updated. Interim analysis was included for part 1. Minor clarifications, formatting and typographical errors were also addressed in this amendment.

Changes are noted below with ~~strikethrough~~ to identify deleted text and <u>underlining</u> to identify new or replacement text.

15.17.1 List of Changes

Title Page, Authors

Rationale for change: The sponsor information were updated based on internal GSK team personnel changes.

Revised Text:

PPD	~~Oncology Stats and Programming, USA~~
PPD	Precision Medicine and Diagnostics, USA
PPD	Biology, Epigenetics Management, USA
PPD	Global Clinical Operational Sciences, USA
PPD	~~Global Clinical Safety & Pharmacovigilance, USA~~
PPD	RD PCPS Qsci Clinical Statistics, USA
PPD	~~Global Formulation Development, PTS, USA~~
PPD	Biotransformation and Drug Disposition, PTS, UK
PPD	~~Molecular Medicine Unit, USA~~
PPD	Cancer Research Epigenetics Management, USA
PPD	Clinical Pharmacology Modeling & Simulation, USA
PPD	~~Global Clinical Operational Sciences, USA~~
PPD	Global Clinical Operational Sciences, USA
PPD	<u>Precision Medicine and Diagnostics, USA</u>
PPD	Clinical Oncology, USA

PPD ~~Global Clinical Operational Sciences, UK~~
PPD Precision Medicine and Diagnostics, USA
PPD SA Pathology, PTS, UK
PPD
PPD EpiNova DPU, UK
PPD Global Clinical Safety & Pharmacovigilance, USA
PPD Biology, Epigenetics Management, USA
PPD Statistics, Oncology TA Group, USA

LIST OF ABBREVIATIONS

Rationale for Change: Abbreviation deleted and added as part of the protocol amendment

Deleted/Added Text:

~~CV~~	~~Coefficient of variance~~
CTCL	Cutaneous T cell lymphoma
DHL	Double hit lymphoma
DLBCL	Diffuse large B cell lymphoma
DOR	Duration of Response
EOT	End of treatment
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
ISS	International Staging System
ORR	Overall Response rate
PFS	Progression Free Survival
TTP	Time to Progression

PROTOCOL SYNOPSIS

- **STUDY DESIGN AND DURATION:**

Rationale for Change: Twice daily dosing will no longer be completed prior to determining the Maximum Tolerated Dose (MTD) if a twice daily dosing is explored this will occur after the MTD/R2PD has been determined.

Revised Text:

- Eligible subjects with select relapsed refractory hematological malignancies(acute myeloid leukemia [AML], non-Hodgkin's Lymphoma [NHL]and multiple myeloma [MM]), will be enrolled in once daily (QO~~D~~D) ~~and/or twice daily (BID) dosing~~ cohorts until a maximum tolerated dose (MTD) is established. Subjects

may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. Upon determination of the MTD, twice daily (BID) dosing cohorts may be opened to collect additional safety data and evaluate the preliminary efficacy of GSK525762 administered BID.

- **STUDY RATIONALE**

Rationale for Change: This section was updated to further clarify the disease subtypes.

Revised Test:

Current data from GSK525762 preclinical development indicate a potential to inhibit the BET family of bromodomain (BRD) proteins and that this inhibition may have clinical utility in the treatment of various tumors, including hematological malignancies. Relapsed and/or refractory hematological malignancies such as Acute Myeloid Leukemia (AML), ~~Adult Acute Lymphoblastic Leukemia (ALL),~~ non-Hodgkin's Lymphoma (NHL), and Multiple Myeloma (MM) ~~and high-risk Myelodysplastic Syndromes (MDS)~~ have an overall poor outlook. This is the first study of this agent to be conducted in subjects with these relapsed and/or refractory hematological malignancies ~~for which no standard therapies are anticipated to result in a durable remission~~ with few or no conventional treatment options that could be expected to provide any lasting benefit.

- **OBJECTIVES AND ENDPOINTS:**

Rationale for Change: This section was updated to remove twice daily dosing from the primary objectives, Overall response rate and safety and tolerability were added as secondary endpoints and metabolite and urine excretion endpoints have been removed from exploratory research.

Revised Text:

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) administration~~and/or twice daily (BID) dosing schedules~~, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with acute myeloid leukemia (AML), multiple myeloma (MM), or non-Hodgkin's lymphoma (NHL).	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).

Part 1 Objectives		Part 1 Endpoints
Secondary	• To evaluate clinical efficacy following QD administration in subjects with AML, MM, and NHL.	• Overall response rate (ORR), as measured by standard response criteria
	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration following QD and/or twice daily (BID) dosing schedules.	• GSK525762 PK parameters following single- and repeat-dose administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters following QD and/or BID dosing schedules.	• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC), following single and repeat-dose oral administration of GSK525762)
	• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic (PD) response following QD and/or BID dosing schedules.	• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	• Assess overall response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.
	• To evaluate safety, tolerability, and efficacy following BID administration of GSK525762 in subjects with AML, MM, and NHL	• AEs, SAEs, DLTs, dose reductions or delays, withdrawals due to toxicities, changes in safety assessments, and ORR (as measured by standard response criteria)
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD and/or BID dosing	• Pharmacogenomic (PGx) study using clinical samples.

Part 1 Objectives		Part 1 Endpoints
	schedules.	
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response.
	~~• To generate samples (data reported separately) with which to characterize the metabolic profile of GSK525762 after single and repeat-dosing (In the PK/PD expansion cohort only).~~	~~• Samples to characterize the metabolites in plasma and/or urine.~~
	~~• To determine the amount of GSK525762 excreted in urine after oral single and repeat-dosing.~~	~~• Concentration of GSK525762 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time.~~

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in acute myeloid leukemia (AML).	• For AML: Objective response rate (% of subjects achieving Complete Response [~~(~~CR]~~)~~, ~~Partial Response (PR),~~ CRp [~~(~~as per CR but platelet count <100 x 10^9/L]~~)~~, CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR],~~morphologic leukemia-free state~~) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in multiple myeloma (MM)	• For MM: Objective response rate (defined as the percentage of subjects that have achieved a stringent CR [sCR], CR, very good partial response [VGPR], or PR) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in non-Hodgkin's Lymphoma (NHL)	• For NHL: Objective response rate (defined as the percentage of subjects that have achieved a CR, or PR) per response criteria.
Secondary	• To characterize the PK of GSK525762 in 3 disease-specific cohorts of subjects with AML, MM or NHL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the exposure response	• PK/PD relationship between

Part 2 Objectives		Part 2 Endpoints
	(i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with AML, MM or NHL.	GSK525762 exposure markers and safety and efficacy parameters.
	• To evaluate the safety and tolerability of RP2D of GSK525762 in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	• To evaluate the relationship between GSK525762 dose~~exposure~~ and PD response in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	• To determine the clinical activity of GSK525762 in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• TTP (Time to Progression) , DOR (Duration of Response), PFS (Progression Free Survival) for MM and NHL • Overall survival (OS, the time from the treatment start date until death from any cause) for AML, MM and NHL.
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical samples.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response; Leukemic Stem Cell studies; PDX model studies and other translational medicine studies.

- **INCLUSION/EXCLUSION CRITERIA:**

Inclusion Criteria

Rationale for Change: This section was updated to clarify and standardize NHL and MM eligibility.

Revised Text:

Inclusion criteria 2: Males and females 18 years old or older*Inclusion criteria 3 and 4:* In Part 1 and~~, subjects must have relapsed and/or refractory hematologic malignancies (e.g.,~~

~~leukemias, myeloproliferative neoplasms, lymphomas, and myelomas) for which no standard therapies are available or anticipated to result in remission.~~

~~In~~ Part 2, subjects must have Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).

- Subjects with AML ~~(Part 1 and Part 2)~~, are eligible if they
  - have relapsed and/or refractory disease, *OR*
  - are ≥65 years of age and not candidates for or have refused standard chemotherapy.
- Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination.
- Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20).
  - In Part 2, the NHL cohort will separately enrol subjects with double- and triple hit lymphoma, so that a minimum of 10 subjects with this subset of disease will be enrolled. To be eligible for this sub-cohort, tumor sample from the subject must demonstrate rearrangement and/or overexpression of MYC and either BCL2 and/or BCL6 genes. Evaluation of double- or triple-hit status may be performed via appropriate local testing, and the determination of double- or triple-hit diagnosis will be at the discretion of the investigator and GSK Medical Monitor.

Inclusion criteria 9: 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 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.

Definitions for Adequate Organ Function

System	Laboratory Values
Renal	
Creatinine[3] OR Calculated creatinine clearance [calculated by Cockcroft Gault formula[2, 3]] OR 24-hour urine creatinine clearance[3]	≤1.5 X ULN ~~(≤2 X ULN for MM)~~ ≥ 50 mL/min ≥ 50 mL/min

1. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2
2. Refer to Appendix 1 for Cockcroft Gault formula
3. For MM subjects, adequate renal function is defined as serum creatinine ≤2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ≥ 30 mL/min
4. If TSH is abnormal but free T3 and or Free T4 are normal, then the subject can be enrolled.

Exclusion Criteria

Rationale for Change: This section was updated to clarify the allowable timeframe.

Revised Text:

Exclusion criteria 3, second Note, first sentence:

Note: the following are NOT allowed:

Investigational anti-cancer drug within 2 weeks ~~(or 5 half-lives of the drug, whichever is longer)~~ prior to the first dose of GSK525762.

- **DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN:**

Rationale for Change: This section was updated to remove exploring twice daily dosing in the determination of the MTD.

Revised Text:

Third sentence

BID dosing will be explored ~~in a parallel cohort~~once MTD has been identified in once daily dosing; the total daily dose administered BID will not exceed the QD MTD.

- **EFFICACY MEASUREMENTS:**

Rationale for Change: This section was updated to add Overall response rate and Overall survival as efficacy measures

Revised Text:

- ~~Type~~ ORR and OS in AML, MM, and NHL; time to progression and duration of response in ~~AML,~~ MM and NHL.

- **STASTICAL ANALYSIS:**

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 the end of Part 2

Revised Text:

Second sentence

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; details will be included in the Reporting Analysis Plan (RAP).

Last sentence

For additional details, please refer to the ~~reporting and analysis plan (~~RAP~~).~~

Section 1.2. Study Population Rationale

Rationale for Change: This section was updated to clarify the indications.

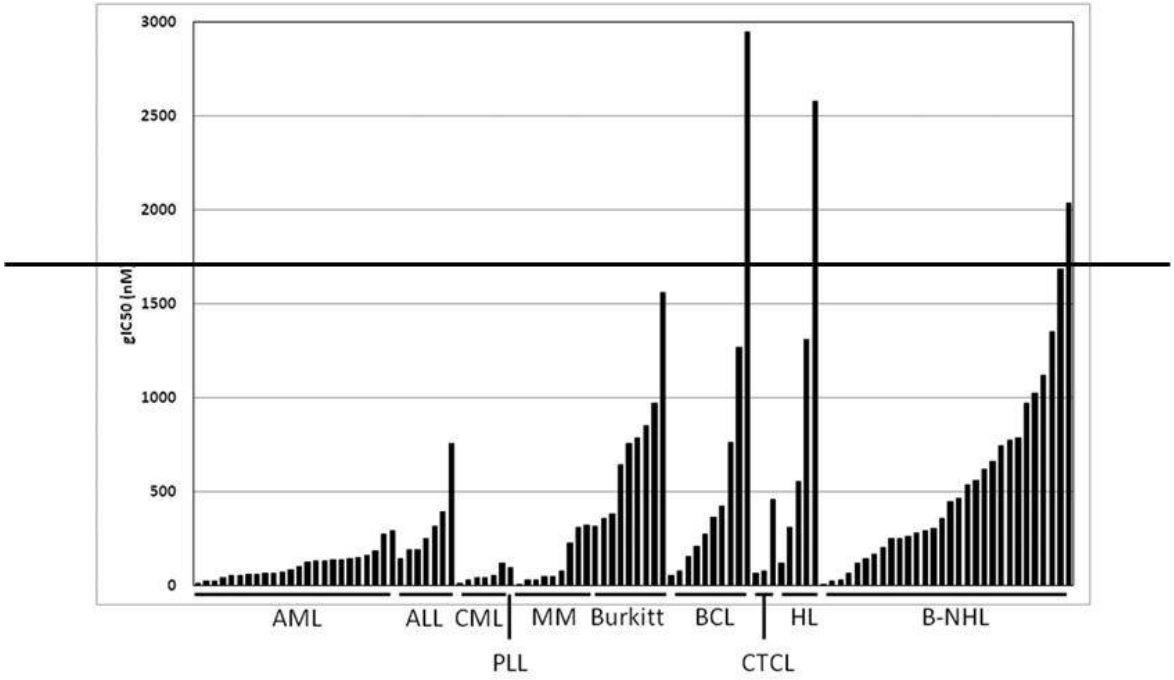
Revised Text:

First paragraph, first sentence

Relapsed and/or refractory hematological malignancies such as AML, ~~ALL,~~ NHL, and MM ~~and high-risk Myelodysplastic Syndromes (MDS)~~ have an overall poor outlook.

Figure 1

Hematological cancer cell line sensitivity to GSK525762, ~~6~~3-day growth-death assay



Cell Line / Tumor Type	% Sensitive Lines[a]	Total Lines	Median gIC_{50}
ALL	100	4	0.29
AML	96	25	0.10
Burkitt	50	8	1.2
CML	100	4	0.32
CTCL	100	3	0.22
DLBCL	90	29	0.17
Erythroleukemia	100	2	0.38

Cell Line / Tumor Type	% Sensitive Lines[a]	Total Lines	Median gIC$_{50}$
FL	100	4	0.06
MCL	80	5	0.80
MM	100	12	0.06

a. Cell lines defined as sensitive to GSK525762 if the gIC50 <1.0 M.

Abbreviations: ALL = Acute lymphoblastic leukemia; AML = Acute myeloid leukemia; CML = Chronic myeloid leukemia; CTCL = Cutaneous T cell lymphoma; DLBCL = Diffuse large B cell lymphoma; FL = Follicular lymphoma; gIC$_{50}$ = Growth IC$_{50}$, 6-day assay; MCL = Mantle cell lymphoma; MM = Multiple myeloma.

Third paragraph, first two sentences

Ninety-one percent of hematological cancer cell lines tested (~~94/104~~87/96) are ~~highly~~ sensitive to GSK525762, exhibiting growth IC50 (gIC50) values below 1.0μM. Some of the most sensitive hematological cancer cell types include ~~CML~~ FL (median gIC50= ~~40~~60 nM), MM (median gIC50= ~~49~~60 nM), ~~CTCL (median gIC50= 77 nM), and~~ AML (median gIC50= ~~94~~ 100 nM), and DLBCL (median gIC50= 170 nM).

Section 1.3.1.1.2. Human Pharmacokinetics and Equivalent Exposure for NOEL for QTc prolongation

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:

Last sentence

~~Updated~~ PK information obtained up to January 2016 is available in the Investigator's Brochure Section 5.2~~after first subject first dose is presented in Section 15.10~~.

Section 1.3.2.2. Clinical Rationale for BID

Rationale for Change: This section was updated to include reference to the latest Investigator Brochure, and provide brief summary of data analysed to date.

Revised Text:

~~Pharmacokinetics of GSK525762 has been evaluated in subjects in studies BET115521 and BET116183 following single and repeated daily administration of GSK525762 Section 15.10.~~

As described in the GSK525762 IB, Section 5.2, GSK525762 pharmacokinetics following once and twice daily administration is characterized by a rapid absorption with maximum concentration occurring mostly within two hours ~~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~~.

Based on the pharmacokinetics of GSK525762 observed to date, and evidence of a short half-life of about 5 hours, trough concentrations at 100 mg QD are predicted to be below the average in vitro IC50 (0.08 uM to 1.3 uM) for the tumor types selected for this study. ~~Furthermore, based on the pharmacokinetics to date, it is predicted that even 100 mg QD doses would result in the trough concentrations below the average in vitro IC50.~~ Dividing the daily dose into two doses administered about 12 hours apart would allow the trough concentration to be above the lower *in vitro* IC50 for doses around 30 mg BID.

Section 1.3.2.3. Starting Dose for BID

Rationale for Change: This section was updated to include reference to the latest Investigator Brochure, and provide brief summary of data analysed to date.

Revised Text:

As detailed in the GSK525762 IB, Section 5.2.2 and Section 5.3.1, doses of 20 mg and 30 mg BID have been administered to subjects with solid tumors. The PK and safety/tolerability profile for the 30 mg BID dose is comparable to subjects treated with an equivalent total daily dose (i.e., 60 mg once daily). In this study, once the QD MTD of GSK525762 has been identified for each disease subtype (AML, MM, and NHL), an exploratory cohort will be opened for each disease type to evaluate safety, tolerability, and preliminary efficacy of BID dosing.

For each disease subtype, the total daily dose selected for BID evaluation will be no higher than the once-daily MTD, divided approximately equally between two doses administered approximately 12 hours apart.

~~The maximum starting dose for BID will be 20 mg provided the 40 mg QD dose cohort has been cleared.~~ A lower BID ~~starting~~ dose ~~will~~ may be considered depending on emerging safety, PK, and PD data.

Section 1.3.3. Dose escalation steps (QD Only)

Rationale for Change: Removed BID as this will no longer be a part of dose escalation

Revised Text:

1.3.3. Dose escalation steps (QD only)~~(QD and BID)~~

Section 1.5.1. Risk Assessment

Rationale for Change: This section was updated based on emerging metabolite data.

Revised Text:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Drug Interactions	~~There is low potential for GSK525762 to induce or inhibit cytochrome P450 (CYP) enzymes or to inhibit P-glycoprotein (Pgp) or Breast Cancer Resistance Protein (BCRP).~~ ~~The precise *in vivo* metabolic liability for GSK525762 has yet to be assessed. *In vitro* data suggests that GSK525762 has a negligible turnover and low potential to inhibit the major human CYP isoforms (IC50s ≥ 33 µM) with no evidence for time dependent inhibition of CYP2D6 or CYP3A4.~~ GSK525762 is a substrate for CYP3A4 enzymes, and for P-gp and BCRP transporters. GSK525762 clearance is virtually solely via CYP3A4. There is evidence of potential auto-induction after repeat dosing in clinical studies since reduction in parent exposures (~25% at lower doses to ≥60% at doses ≥60mg, mainly in BET115521 study) have been observed. There is low potential for GSK525762 to induce or inhibit cytochrome P450 (CYP) enzymes or to inhibit P-glycoprotein (Pgp) or Breast Cancer Resistance Protein (BCRP) based on in vitro data. GSK525762 was shown to be an inhibitor of OATP1B1 and OAT3 in vitro.	~~The potential for drug-drug interactions will be monitored in clinical trials.~~ Use of concomitant medications, herbal medicines and fruit juices that are strong or moderate CYP3A4 inhibitors or inducers should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. Use of concomitant medications that are sensitive substrates of OATP1B1 and OAT3 should be done with caution.

Section 1.5.2. Benefit Assessment

Rationale for Change: This section was updated to clarify eligibility.

Revised Text:

First sentence

Study BET116183 is an open-label, dose escalation study and the first study of this agent

to be conducted in subjects with hematological malignancies ~~for which no standard therapies are anticipated to result in a durable remission~~ that have not responded to or have relapsed following standard therapy.

Section 2. OBJECTIVE, ENDPOINTS, HYPOTHESIS

Rationale for Change: This section was updated to remove twice daily dosing from the primary objectives. Overall response rate and safety and tolerability were added as secondary endpoints and metabolite and urine excretion endpoints have been removed from exploratory research.

Revised Text:

Part 1

Part 1 Objectives		Part 1 Endpoints
Primary	• To determine the safety, tolerability and maximum tolerated dose (MTD) following once daily (QD) administration~~and/or twice daily (BID) dosing schedules~~, establishing the recommended Phase 2 dose (RP2D) of GSK525762 in adult subjects with acute myeloid leukemia (AML), multiple myeloma (MM), or non-Hodgkin's lymphoma (NHL).	• Adverse Events (AEs), Serious Adverse Events (SAEs), Dose Limiting Toxicity (DLT), dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters).
Secondary	• To evaluate clinical efficacy following QD administration in subjects with AML, MM, and NHL.	• Overall response rate (ORR), as measured by standard response criteria
	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration following QD and/or twice daily (BID) dosing schedules.	• GSK525762 PK parameters following single- and repeat-dose administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters following QD and/or BID dosing schedules.	• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC), following

Part 1 Objectives		Part 1 Endpoints
		single and repeat-dose oral administration of GSK525762~~)~~
	• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic (PD) response following QD and/or BID dosing schedules.	• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	• Assess overall response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.
	• To evaluate safety, tolerability, and efficacy following BID administration of GSK525762 in subjects with AML, MM, and NHL	• AEs, SAEs, DLTs, dose reductions or delays, withdrawals due to toxicities, changes in safety assessments, and ORR (as measured by standard response criteria)
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD and/or BID dosing schedules.	• Pharmacogenomic (PGx) study using clinical samples.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response.
	~~• To generate samples (data reported separately) with which to characterize the metabolic profile of GSK525762 after single and repeat-dosing (In the PK/PD expansion cohort only).~~	~~• Samples to characterize the metabolites in plasma and/or urine.~~
	~~• To determine the amount of GSK525762 excreted in urine after oral single and repeat-dosing.~~	~~• Concentration of GSK525762 in urine measured with an investigational bio-analytical method and extrapolated to total amount excreted in urine over time.~~

Hypothesis	• No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in acute myeloid leukemia (AML).	• For AML: Objective response rate (% of subjects achieving Complete Response [(CR]), ~~Partial Response (PR),~~ CRp [(as per CR but platelet count <100 x 10^9/L]), CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR],~~morphologic leukemia-free state~~) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in multiple myeloma (MM)	• For MM: Objective response rate (defined as the percentage of subjects that have achieved a stringent CR [sCR], CR, very good partial response [VGPR], or PR) per response criteria.
	• To evaluate clinical efficacy after treatment with GSK525762 in non-Hodgkin's Lymphoma (NHL)	• For NHL: Objective response rate (defined as the percentage of subjects that have achieved a CR, or PR) per response criteria.
Secondary	• To characterize the PK of GSK525762 in 3 disease-specific cohorts of subjects with AML, MM or NHL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the exposure response (i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• PK/PD relationship between GSK525762 exposure markers and safety and efficacy parameters.
	• To evaluate the safety and tolerability of RP2D of GSK525762 in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	• To evaluate the relationship between GSK525762 dose~~exposure~~ and PD response in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.

Part 2 Objectives		Part 2 Endpoints
	• To determine the clinical activity of GSK525762 in 3 disease-specific cohorts of subjects with AML, MM or NHL.	• TTP (Time to Progression) , DOR (Duration of Response), PFS (Progression Free Survival) for MM and NHL • Overall survival (OS, the time from the treatment start date until death from any cause) for AML, MM and NHL.
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical samples.
	• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK525762.	• Transcriptomics and protein studies of blood and tumor cells; correlation of tumor baseline genetic and genomic profiles with response; Leukemic Stem Cell studies; PDX model studies and other translational medicine studies.

Section 3.1. Study Design/Schematic

Rationale for Change: This section was updated to remove twice daily dosing from the escalation phase.

Revised Text:

Second paragraph

This is an open-label repeat dose, multicenter, 2-part study to determine the MTD in subjects with acute myeloid leukemia, ~~and~~ multiple myeloma, and ~~/~~non-Hodgkin's Lymphoma, and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily (QD) orally ~~and twice daily (BID) orally~~. Safety, tolerability, PK, and efficacy will also be explored in a limited number of subjects treated twice daily (BID). Both Parts~~Part 1~~ will be conducted in adult subjects with relapsed and/or refractory ~~hematological malignancies. Expansion cohorts (Part 2) are planned to further explore clinical activity of GSK525762 in subjects with~~ acute myeloid leukemia~~s~~, multiple myeloma, and non-Hodgkin's lymphomas (Figure 3).

Revised Figure 3

Figure was modified to remove assessment of BID dosing in parallel with QD. Number of subjects were also modified.

Section 3.2.1. Part 1: Dose Escalation

Rationale for Change: This section was updated to remove twice daily dosing from the escalation phase.

Revised Text:

Second paragraph

Thereafter, subjects will be enrolled in a standard 3+3 design. Separate dose escalation cohorts will be opened for subjects with AML, NHL, and MM~~, as well as for QD and BID dosing~~.

Fourth paragraph

Dose escalation will continue until an MTD is determined or until a dose of 200 mg per day is reached. After the MTD has been determined for a disease type in Part1, then BID cohort(s) (Section 3.2.1.5) and the Part 2 dose expansion cohorts will be opened for that disease type.

Section 3.2.1.2. Accelerated Dose Escalation in Part 1

Rationale for Change: This section was updated to remove twice daily dosing from the escalation phase.

Revised Text:

Table 2, footnote

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

Section 3.2.1.3. 3 + 3 Dose Escalation in Part 1

Rationale for Change: This section was updated to clearly define the percentage of doses a subject must receive to be evaluable.

Revised Text:

Third paragraph

Subjects unable to receive at least 75% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

Revised Figure 4

Figure was modified to clarify assessment of BID dosing after MTD is declared with QD dosing.

Section 3.2.1.4. Alteration Schedule

Rationale for Change: This section was updated to add specifics altering decisions based on toxicities. Additionally added specific language as to the PK sampling that is required when a dose reduction/escalation occurs.

Revised Text:

Third and fourth paragraph

Subjects may need to undergo dose modification(s) to manage toxicities. A dose adjustment may be made after consultation with the 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.

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 3.2.1.5. BID Dosing

Rationale for Change: This section was updated to clarify that BID dosing will occur after MTD is determined per disease subtype.

Revised Text:

Once the MTD of QD administration has been identified for a disease subtype, a cohort may be opened to explore the safety, tolerability, PK, and efficacy of GSK525762 when administered BID. Initially, only one cohort per disease type is planned, though lower doses may be explored based on toxicity observed after the initial few subjects. The selected total daily dose (administered in two approximately equal doses) for BID administration will not exceed the QD MTD. A lower starting dose may be selected~~The initial dose level for BID will be a maximum of 20 mg (ie 2x 20mg 12 hours apart, total daily dose of 40mg) or a dose level lower than 20 mg~~ depending on emerging safety, PK and PD data. ~~and d~~Dosing will be separated by approximately 12 hours. ~~Escalation can then proceed as described using the 3 + 3 dose escalation.~~ The total number of evaluable subjects per disease type treated BID will not exceed 10 subjects.

~~Subjects may need to undergo dose modification(s) to manage toxicities. A dose adjustment (e.g., QD at the same dose level or lower BID dose level) may be made after consultation with the 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 3.2.1.6. Intra-Subject Dose Escalation

Rationale for Change: Minor updates were made to this section to further clarify when an intra-subject dose escalation may occur.

Revised Text:

First and second sentence of first paragraph

Intra-subject dose escalations may be considered on a case-by-case basis, provided that a higher dose level cohort (accelerated phase or 3+3 phase) has been cleared ~~without a DLT~~, and after review of all safety data and approval by a GSK Medical Monitor and discussion with the investigator. The subject on a lower dose level may be increased up to the highest dose level ~~tested~~cleared.

Section 3.2.2. Dose Limiting Toxicity (DLT)

Rationale for Change: This section was updated to clearly define the percentage of doses a subject must receive to be evaluable and to further clarify Dose limiting toxicities.

Revised Text:

First paragraph

An event will be considered a DLT if it occurs within the first 3 weeks of treatment and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment. As described in Section 3.2.1.3, subjects unable to receive at least 75% of scheduled doses for reasons other than toxicity (e.g., acute illness, disease progression) will not be evaluable for DLT purposes and will be replaced in the cohort.

Third paragraph

- Grade 4 thrombocytopenia lasting more than 7 day and ~~do~~ not respond<u>ing</u> to transfusions, or Grade 3 <u>thrombocytopenia</u> associated with bleeding (>10mL)

Third bullet of third paragraph

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, <u>and/or</u> 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 criterion 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).

Section 3.2.3. Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

Rationale for Change: Minor update was made to further clarify that a separate RP2D will be determined per disease type.

Revised Text:

Second sentence

The RP2D will be determined based on the MTD or biologically active dose (example: clinical response), the safety profile, and available PD data generated from all subjects in Part 1 for that disease type.

Section 4.1 Number of Subjects

Rationale for Change: Added reference for evaluable subjects.

Revised Text:

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 60 to 70 evaluable (as described in Section 11) subjects will be enrolled. Part 2 will enroll up to 111 subjects (three disease-specific cohorts of 32 to 37 subjects each, depending on disease subtype, and one disease-specific cohort of 10 subjects)

Section 4.2.1. Inclusion Criteria

Rationale for Change: This section was updated to clarify and standardize NHL and MM eligibility.

Revised Text:

Inclusion criteria 3: In Part 1 and~~, subjects must have relapsed and/or refractory hematologic malignancies (e.g., leukemias, myeloproliferative neoplasms, lymphomas, and myelomas) for which no standard therapies are available or anticipated to result in remission.~~

~~In~~ Part 2, subjects must have Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).

- Subjects with AML ~~(Part 1 and Part 2)~~, are eligible if they
    - have relapsed and/or refractory disease, *OR*
    - are ≥65 years of age and not candidates for or have refused standard chemotherapy.
- Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination.
- Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20).

- In Part 2, the NHL cohort will separately enrol subjects with double- and triple hit lymphoma, so that a minimum of 10 subjects with this subset of disease will be enrolled. To be eligible for this sub-cohort, tumor sample from the subject must demonstrate rearrangement and/or overexpression of MYC and either BCL2 and/or BCL6 genes. Evaluation of double- or triple-hit status may be performed via appropriate local testing, and the determination of double- or triple-hit diagnosis will be at the discretion of the investigator and GSK Medical Monitor.

Inclusion criteria 9: 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 16 weeks after the last dose of study medication. In addition, male subjects whose partners are or become pregnant ~~on study medication~~ must continue to use condoms for 7 days after stopping study medications.

Table 4 Definitions for Adequate Organ Function

System	Laboratory Values
Renal[3]	
Creatinine[3] OR Calculated creatinine clearance [calculated by Cockcroft Gault formula[2, 3]] OR 24-hour urine creatinine clearance [3]	≤1.5 X ULN ~~(≤2 X ULN for MM)~~ ≥ 50 mL/min ≥ 50 mL/min

5. If bleeding risk discharged in Part 1, coagulation criteria may be adjusted for Part 2
6. Refer to Appendix 1 for Cockcroft Gault formula
7. For MM subjects, adequate renal function is defined as serum creatinine ≤ 2.5 mg/dL OR creatinine clearance (either calculated or obtained via 24 hr urine collection) ≥ 30 mL/min
8. If TSH is abnormal but free T3 and or Free T4 are normal, then the subject can be enrolled.

Exclusion Criteria

Rationale for Change: This section was updated to clarify the allowable timeframe.

Revised Text:

Exclusion criteria 3, second Note, first sentence:

Note: the following are NOT allowed:

Investigational anti-cancer drug within 2 weeks ~~(or 5 half-lives of the drug, whichever is longer)~~ prior to the first dose of GSK525762.

Section 4.2.3.1. Permanent Discontinuation from Study Treatment

Rationale for Change: This section was updated to provide clear guidance as to requirements if a subject dies.

Revised Text:

Third paragraph

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and electronic case report form (eCRF). If a subject dies while on study, the cause of death should be recorded in the eCRF.

Section 4.2.3.2. Subject Completion

Rationale for Change: This section was modified to clearly define in Part 1 and Part 2 a subject who has completed the study.

Revised Text:

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

- they complete screening assessments, the 21-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. 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. 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 in 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.~~For Part 1 (dose-escalation phase) subjects who are not treated with the RP2D, a completed subject is one who has 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.~~

~~For subjects treated at the RP2D (subset of Part 1 and all of Part 2), a completed subject is one who has discontinued study treatment and was followed to death or has died while receiving study treatment.~~

~~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.~~

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.

Revised Text:

Table 5 Time and Events Table: Part 1

																										Starting from W10~~k 10~~		
Procedure (Notes)		**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
			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[a]		X																										
Disease characteristics		X																										
Cardiology eval~~uation~~		X																										
Prior therapy		X																										
Register subject		X																										
TREATMENT PHASE																												
Study Drug: For QD or BID details see Table 8 and Table 9																												
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																					

																									Starting from W10~~k 10~~				
Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**		**EOT**		
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**					
Review subject diary (Not required when dosed in clinic.)									X							X		X		X		X	X	X				
Safety																													
Pregnancy test/ testosterone [ab]	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		
Vital Signs [bc]	X	X				X			X							X		X		X		X	X	X		X		
Height and weight (Height at Scr only)	X	X				X			X							X		X		X		X	X	X		X		
Chest x-ray	X																												
Pulmonary function test [cd]	X																												
Adverse events	AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.5)																												
Concomitant medications	continuous from signing of informed consent																												
Laboratory assessments: For details please see Table 6																													
Tests	X	X	X			X			X					X		X		X		X	X	X	X	X	X		X		
Cardiac Monitoring																													
ECHO (Within 35 days of first dose)	X													X						X			X		X	X		
12-lead ECGs [de]	X	O	O			O	~~X~~		X			X		X	O	X	X	X	~~X~~	X		O	X	X		X		
Holter monitoring (At least 24 h, on dosing days start predose)	X					X												X											
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see Table 8 and Table 9																													
PK Blood samples for GSK525762		X	X	X [ghf]		X						X		X	X	X						X		X[ef]				
~~PK blood samples for metabolite evaluation (only at MTD or RP2D in 6 subjects)~~		~~X~~	~~X~~												~~X~~	~~X~~														
PD Blood samples for biomarkers (mRNA)		X	X												X													X	
Blood samples for plasma cytokines		X	X												X	X													
~~PK Urine samples~~		~~X~~	~~X~~												~~X~~	~~X~~													

Procedure (Notes)	SCR	Week 1 D1	Week 1 D2	Week 1 D3	Week 1 D4	Week 1 D5	Week 1 D6	Week 1 D7	Week 2 D1	Week 2 D2	Week 2 D3	Week 2 D4	Week 2 D5	Week 2 D6	Week 2 D7	W3 D1	W3 D4	W4 D1	W4 D4	W5 D1	W6 D1	W7 D1	W10 D1	Starting from W10 ~~k 10~~ q3W D1	Starting from W10 ~~k 10~~ q6W D1	EOT
~~(only at MTD or RP2D in 6 subjects)~~																										
PD Tumor Sample	X[g]			X[~~f~~ h]																						
Translational Research [~~h~~ i]																										
Pharmacogenomics (PGx) sample		X																								
Blood samples for Translational Medicine study	X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression																								
Tumor biopsy at progression																										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 (as described in Table 7). 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.																										

a. Medical, surgical, alcohol, tobacco and treatment history, including date (month and year) of first diagnosis, histology, and current sites of disease, will be taken as part of the medical history and disease status.
b. 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.
c. Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate and temperature
d. Pulmonary tests as appropriate: subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation
e. 12-lead ECGs : Screening ECGs within 14 days of first dose. Triplicate ECGs prior to dosing. For timing of ECGs on "O" days, see Table 8 for QD and Table 9 for BID. Otherwise, triplicate ECGs at approximately same time of day, and prior to dose on dosing days. If QTcF increase >30msec, ECGs performed daily through W2.)
f. For subjects on study longer than 12 weeks, collect a pre-dose PK sample q6W. Reduce to q12w after 12 months on study.
g. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.
h. During 3+3 dose escalation, PD tumor sample collection will be mandatory unless infeasible to collect, and approval is obtained by the GSK medical monitor. Subjects with MM ~~or AML~~ will have bone marrow aspirates collected on W1 D3 ~~approximately~~ within ~~2-4~~3-6 hours after the dose. Subjects with AML will have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on W1 D3 within 3-6 hours after the dose. Subjects with NHL will have a ~~lymph node~~tissue biopsy (lymph node or other affected organ/region) collected on W1D3 ~~approximately~~ within 3-~~5~~ 6 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as the hours post-dose for collection remain as described. A PK sample will need to be obtained within 1 hour of the tissue sampling. Details described in the SPM see Table 7 disease specific assessments for details).
~~i. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.~~

																										Starting from W10~~k 10~~		
Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**		**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	

i. Refer to Section 6.6 for details on Translational Research and Appendix 5 for details on PGx Research.

Abbreviations: ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PGx=Pharmacogenetics; COPD=Chronic obstructive pulmonary disease; SPM=Study Procedures Manual; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 6 Time and Events: Part 1 Laboratory Assessments

														q3w and q6w Initiated from Wk 10		
NB: On dosing days, collect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within ~~72h~~ 24h of first dose.		**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Assessment	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
HBsAg, HepC antibody	If hepatitis C antibody positive, perform third generation immunoassay (if test is available) on same sample to confirm results, or alternatively, use HCV RNA test (either quantitative or qualitative).	X														

Table 7 Disease Specific Assessments: Part 1 and 2

Multiple Myeloma (MM) Assessments														
												q3w and q6w Initiated from Wk 10		
Procedure	**Notes**	**SCR**	**Week 1**			**Week 2**		**W 3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
			D 1	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease Characteristics	Including cytogenetics as appropriate	X												
Total Protein, CRP, β2 microglobulin		X							X	X	X	X		
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM;	X							X	X	X		X	
UPEP	Only required if paraprotein is present in urine	X							X		X		X	
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X							X		X	X		
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X									X			
Response assessment	Every 6 weeks after wk4; Response criteria in Appendix 6								X		X		X	

Lymphoma Assessments															
												q3w and q6w Initiated from Wk 10			
	Notes	**SCR**	**Week 1**			**Week 2**		**W4**		**W7**	**W10**	**q3W**	**q6W**	**q12W**	**EOT**
Procedure			**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history[a] immunophenotypes, cytogenetics and prognostic markers [b]		X													
β2-microglobulin		X						X							
B Symptoms		X						X		X	X	X			
Lymph node and organ exam		X						X		X	X	X			
Bone marrow/tissue biopsy [c]		X								X					
~~Bone marrow/tissue biopsy [c]~~		~~X~~						~~X~~							
CT Scan [d]		X								X			Wk 16, wk 24, then q12wks		
PET Scan [d, e]		X								X					
Response evaluation [f]										X			Wk 16, wk 24, then q12wks		

a. Including date of first diagnosis, disease stage, and complete history of diagnostic results and therapies.
b. Examples of prognostic markers may include: ALC, FLIPI-1, FLIPI-2 (includes ß2-microglobulin), FcR gamma 3A.
c. A sample will be required at screening only if clinically appropriate for the lymphoma subtype AND an appropriate previous sample is available. A follow-up bone marrow biopsy will be performed no later than 8 weeks following CR (as judged by investigator) in accordance with the response guidelines (Appendix 7) if a subject had involvement of the BM at the start of the study.
d. Baseline/Screening Computerized Tomography (CT) and PET scans may be obtained within 35 days of first dose Follow-up CT scans at week 7 wk 16, wk 24 and then every 12 weeks.
e. PET or PET/CT scan if clinically indicated (e.g., confirmation of CR for Diffuse large B-cell lymphoma).
f. Evaluation of response for lymphoma at week 7, week 16, week 24 and then every 12 weeks. Assessments are described in Appendix 7 : Response Criteria for Lymphoma.

Leukaemia Assessments															
												q3w and q6w Initiated from Wk 10			
Procedure	**Notes**	**SCR**	**Week 1**			**Week 2**		**W3**	**Wk4**	**W5**	**W 7**	**W10**	**q3W**	**q6W**	**EO T**
			D1	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history, immuno-phenotype, cytogenetics and molecular studies as appropriate and History [a]		X													
Lymph node and spleen assessment	Only as appropriate	X							X		X	X	X		X
Response Assessment[b]		X							X			X		X	X
~~BM biopsy and aspirate~~	~~FISH, cytogenetics, FLT3, IgVH, Zap-70 as appropriate~~	~~X[b]~~							~~X[c]~~			~~X[c]~~			~~X~~
Transfusion History [c,d]		X				X		X	X	X	X	X	X		
Bleeding History		X				X		X	X	X	X	X	X		
Hematology [e,f] [d,e]		X				X		X	X	X	X	X	X		
~~Response assessment~~ [g]									~~X~~			~~X~~		~~X~~	

a. Including date of diagnosis and complete history of diagnostic results and therapies.
b. Bone marrow biopsy/aspirate should be obtained for response assessment at the timepoints indicated. Subjects without marrow involvement may be assessed by other means (e.g., medical photography for leukemia cutis) after discussion with the medical monitor, provided that the same method is used for all assessments of that subject. Response criteria are described in Appendix 8. ~~This bone marrow sample is required for baseline disease assessment, but a~~A peripheral blood sample can be taken at baseline if ~~the~~ a bone marrow sample ~~could~~ can not be collected. ~~See the study procedures manual (SPM) for sample handling.~~ Subjects should be off cytokine support (granulocyte colony-stimulating factor [GCSF] or granulocyte-macrophage colony-stimulating factor [GMCSF]) for a minimum of 7 days before obtaining bone marrow to document remission.~~Bone marrow biopsy and aspirate obtained for the assessment of response. Subjects should be off cytokine support (granulocyte colony-stimulating factor [GCSF] or granulocyte-macrophage colony-stimulating factor [GMCSF]) for a minimum of 7 days before obtaining bone marrow to document remission.~~
c. Platelet and blood transfusions to be assessed at designated visits and summarized per unit on a weekly cumulative basis.
d. Hematology includes complete blood count (CBC) with white blood cell count differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes) and platelets; hemoglobin, hematocrit, red blood cell count. A CBC with differential and platelets, hemoglobin and hematocrit may be performed daily during in-patient care; once subject is discharged, assessments to continue weekly until disease response assessment. This is collected at baseline/screening; daily during chemotherapy treatment, then weekly. Platelet count achievement of 20,000/mL for 3 days is entered into the eCRF and the date of platelet count achievement of 100,000/mL is entered into the eCRF.
e. A blood cell smear to measure peripheral blood blasts.

~~Response assessments for leukemia at wk 4, wk 10 and every 6 weeks thereafter. Assessments are described in Appendix 8: Response Criteria for Leukaemias.~~

Table 8 Time and Events: Part 1 (QD cohorts) Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling

	W1D1									**W1D2**		**W1D5**		
Procedure / time after dose	**pre dose**	**0h**	**15 min ± 5m**	**30 min ±5 m**	**1h ±10m**	**2h ±15 m**	**4h ±15 m**	**8h ±1h**	**12h ±2h**	**24h ±1 h**	**0h**	**0 h**	**30 min ±10m**	**3h ±30 m**
Dose		X									X	X		
12-lead ECG [a]	X		X	X	X	X	X	X	X	X			X	X
PK sample for GSK525762 [b]	X		X	X	X	X	X	X	X	X [b]			X	X
~~PK sample for metabolite [b,e]~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X [b]~~				
Blood sample for biomarkers (mRNA)	X[cd]					X	X	X	X	X				
Plasma cytokine sample	X[cd]					X	X	X	X	X				
~~Urine PK sampling [e]~~	~~X~~	~~0-2 h~~				~~2-24h~~								
~~Urine metabolite sampling[e]~~	~~X~~	~~0-2 h~~				~~2-24h~~								

	W2D4	**W2D6**	**W2D7** (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed)									**W3D1**		**W7D1 ±4 days [de]**			
Procedure / time after dose	**pre dose**	**pre dose**	**pre dose**	**0 h**	**15 min ± 5 m**	**30 min ±5m**	**1h ±10 m**	**2h ±15 m**	**4h ±15 m**	**8 h ± 1 h**	**12 h ±2 h**	**24 h ±1 h**	**0 h**	**pre dose**	**0 h**	**0.5 -2h**	**4 - 8 h**
Dose				X									X		X		
12-lead ECG [a]	X	X	X		X	X	X	X	X	X	X	X		X		X	X
PK sample for GSK525762	X	X	X		X	X	X	X	X	X	X	X		X		X	X
~~PK sample for metab~~			~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~					

~~olite~~ [c]																	
Blood sample biomarkers (mRNA)			X						X								
Plasma cytokines samples			X					X	X	X	X	X					
~~Urine PK sampling~~ [c]				~~0-2h~~				~~2-24h~~									
~~Urine metabolite sampling~~ [c]				~~0-2h~~				~~2-24h~~									

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

a. The ECGs are taken in triplicate, 5 minutes apart and within 10 min prior to PK draw. **For timepoint with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.**
b. Sample to be obtained before dosing on Week 1, Day 2.
~~Urine PK sample is collected only at MTD or RP2D in 6 subjects~~
c. May be collected within 14 days prior to first dose.
d. If dose was escalated, the W4D1 visit may be performed +4 to +7 days.

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Table 9 Time and Events: Part 1 (BID Cohorts) Serial Electrocardiograms, Pharmacokinetics and Biomarker Sampling

	W1D1																	**~~W1D2~~**		**~~W1 D3~~**	**~~W1 D4~~**	**W1D5**			
Timepoint; Hours after AM dose ~~(hours after PM dose)~~	Pre-Dose	0h	~~15 min ± 5m~~	30 min ±5m	1h ±10m	~~2h ±15m~~	4h ±15m	8h ±1h	~~Predose 12h-15 min~~	12h (0h)	~~12 h 15 min±5m~~	~~12h 30 min ±5m~~	~~13h (1h) ±10m~~	~~14h (2h) ±15m~~	~~16h (4h) ±15m~~	~~20h (8h) ±1h~~		~~24h (12h)±1h prior to dosing~~	~~AM & PM~~	~~AM & PM~~	~~AM & PM~~	AM	30 min ±5m	3h ±15m	PM
Dose		X								X									~~X~~ X	~~XX~~	~~XX~~	X			X
12-lead ECG [a]	X		~~X~~	X	X	~~X~~	X	X	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	✦	✦		~~X~~					X	X	
PK GSK525762 [b]	X		~~X~~	X	X	~~X~~	X	X	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~	✦	✦		~~X~~					X	X	
Biomarker sample (mRNA) [c]	X[d]					~~X~~	X	X	~~X~~					✦	✦	✦		~~X~~							
Plasma cytokines samples	X[d]					~~X~~	X	X	~~X~~					✦	✦	✦		~~X~~							
~~Urine PK~~ [f]	~~X~~	~~0 2~~				~~2 12~~																			

	W2D4		W2D6		W2D7															W3D1		W7D1 ±4 days [e]				
Time point; Hours after AM dose (hours after PM dose)	pre AM dose	AM & PM	~~pre AM dose~~	AM & PM	Pre dose	0h	~~15 min ± 5m~~	30 min ±5m	1h ±10m	~~2h ±15m~~	4h ±15m	~~8h ±1h~~	~~Predose~~ 12h -15min	12h (0h)	~~12h15 min ±5m~~	~~12h 30 min ±5m~~	~~13h (1h) ±10m~~	~~14h (2h) ±15m~~	~~16h (4h) ±15m~~	~~20h (8h) ±1h~~	~~24h (12h)±1h~~ Prior to dosing	~~AM & PM~~	pre dose	0h	0.5-2h	4 - 8h	12h
Dose		X X		X X		X								X								~~XX~~		X			X
12-lead ECG [a]	X		~~X~~		X		~~X~~	X	X	~~X~~	X	~~X~~	~~X~~		~~♦~~	~~♦~~	♦	♦	~~♦~~	~~♦~~	~~X~~		X		X	X	
PK GSK525762	X		~~X~~		X		~~X~~	X	X	~~X~~	X	~~X~~	~~X~~		~~♦~~	~~♦~~	♦	♦	~~♦~~	~~♦~~	~~X~~		X		X	X	
Biomarker sample (mRNA) [c]					X						X								~~♦~~		~~X~~						
Plasma cytokines samples					X					~~X~~	X	~~X~~									~~X~~						
~~Urine PK [f]~~						~~0-2~~				~~2-12~~																	

a. The ECGs are taken in triplicate, 5 minutes apart and within 10 minutes prior to PK draw. **For time points with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.**

b. PK blood sample collected overnight may be kept refrigerated at 4°C in the event the laboratory is closed.

c. Blood sample for PD biomarker.

d. May be collected within 14 days prior to first dose

e. If dose was escalated, the W4D1 visit may be performed +4 to +7 days.

~~f. Urine PK sample is collected only at MTD or RP2D in 6 subjects.~~

APP=acute phase protein; ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose;

~~♦=optional assessment where feasible (e.g., for subjects staying overnight only).~~

Table 10 Time and Events: Part 2 Expansion Cohort

Part 2 Procedure (Notes)		**SCR**	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
			W1	~~**W1**~~	**W 2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
			D1	~~**D3**~~	**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[a]		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.)			Continuous daily dosing (unless safety, PK or PD data necessitate a different dosing schedule), see Section 3.2.4							X		
Review compliance (Not required when dosed in clinic.)					X	X	X	<u>X</u>	X	<u>X</u>	X	<u>X</u>
~~**Safety**~~												
Pregnancy test/testosterone [ab]		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

Part 2 Procedure (Notes)	**SCR**	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
		W1	~~**W1**~~	**W 2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
		D1	~~**D3**~~	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Vital Signs [bc]/Pain Assessment	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	AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.5)										
Concomitant medications	continuous from signing of informed consent										
Laboratory assessments: For details please see Table 11											
Tests	X	X		X	X	X	X	X	X	X	X
Cardiac Monitoring											
ECHO (Within 35 days of first dose).	X	~~X~~				X	X	X		X	X
12-lead ECGs [cd]	X	X		X	X	X	X	X	X		X
Holter monitoring (Min 24h, on dosing days start predose)	X					X					

Part 2 Procedure (Notes)		SCR	Cycle 1				Cycle 2	Cycle 3	Cycle 4	Further Cycles (q3w and q6w Initiated from Wk 10)		EOT
			W1	~~W1~~	W2	W3	W4	W7	W10	q3W	q6W	
			D1	~~D3~~	D1	D1	D1	D1	D1	D1	D1	
PK and Blood PD												
PK Blood samples	Three samples to be collected each sampling day~~for each type of analysis~~: During the first 3 weeks collect a ~~P~~predose (within 60 minutes prior to dose), a single draw between 0.5 to 2 h postdose,and a single draw between 4-8h		X	~~X~~[e]		X[f]	~~X~~	X			X	

Part 2 Procedure (Notes)		SCR	Cycle 1				Cycle 2	Cycle 3	Cycle 4	Further Cycles (q3w and q6w Initiated from Wk 10)		EOT
			W1	~~W1~~	W2	W3	W4	W7	W10	q3W	q6W	
			D1	~~D3~~	D1	D1	D1	D1	D1	D1	D1	
	postdose (fasting requirements apply). Thereafter W7 and Q6W only a predose and 0.5 hour post dose sample are collected ~~W7 and Q6W only predose~~											
Translational Research												
PGx sample			X									
Tumor sample (e.g., bone marrow biopsy, lymph node biopsy, or peripheral blood collection [only for		X~~de~~		~~X e~~		X[f]						X~~gf~~

Part 2 Procedure (Notes)	**SCR**	**Cycle 1**				**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
		W1	~~**W1**~~	**W 2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
		D1	~~**D3**~~	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
subjects with circulating disease])~~(biopsy)~~											
Blood samples for ~~Translational Medicine study~~ exploratory translational research	X				X[f]	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression or when patient is discontinued from study/end of treatment					
~~Blood samples for Translational Medicine study~~	~~X~~	~~Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression~~									
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 (as described in Table 7). 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 2 Procedure (Notes)		Cycle 1				Cycle 2	Cycle 3	Cycle 4	Further Cycles (q3w and q6w Initiated from Wk 10)		
	SC	W1	~~W1~~	W 2	W3	W4	W7	W10	q3W	q6W	
	R	D1	~~D3~~	D1	D1	D1	D1	D1	D1	D1	EOT

a. Medical, surgical, alcohol, tobacco and treatment history, including date (month and year) of first diagnosis, histology, and current sites of disease, will be taken as part of the medical history and disease status

b. 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.

c. Vital signs include SBP, DBP, heart rate, respiratory rate and temperature

d. Screening ECGs within 35 days of first dose. ECGs prior to dosing. If QTcF increase >30msec, ECGs should be repeated every 2-3 days until the QTcF is within 30 msec of baseline~~performed daily through W2~~.

e. Pretreatment biopsy for tumor sample must be performed within 14 days of first dose.

f. Subjects with MM or ~~AML will~~should have bone marrow aspirates collected on ~~W1 D3~~ W3D1 within ~~approximately 2-4~~ 3-6 hours after the dose. Subjects with AML should have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on W3 D1 within 3-6 hours after the dose. Subjects with NHL will have a lymph node biopsy collected on ~~W1 D3~~ W3D1 within ~~approximately~~ 3-~~5~~ 6 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as **the hours post-dose for collection remain as described**. **A PK sample will need to be obtained within 1 hour of the tissue sampling**. Details described in the SPM see Table 7 disease specific assessments for details).

g. ~~The collection of~~ T~~t~~umor samples for translational research are requested at end of treatment for subjects with progressive disease.

Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; PD=Pharmacodynamics; PK=Pharmacokinetics; PGx=Pharmacogenetics; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; Wk=week

Table 11 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~~ 24h of first dose. (Notes)**		Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles q3w and q6w Initiated from Wk 10		
		W1	W2	W3	W4	W7	W10	q3W	q6W	
	SCR	D1	D1	D1	D1	D1	D1	D1	D1	EOT

a. Assess platelet count as clinically appropriate but at minimum twice weekly for weeks 1 and 2; weekly for weeks 3 to 8.

Abbreviations: NT-proBNP=N-terminal pro–B-type Natriuretic Peptide; 1,5 AG=1,5-Anhydroglucitol; Hb=Hemoglobin; TSH=Thyroid Stimulating Hormone; HBsAg = Hepatitis B surface Antigen HepC=Hepatitis C; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; q12W=every 12 weeks; SCR=Screening Visit; W=week

Section 6.1.2. Visit Windows

Rationale for Change: The visit windows were updated to clarify timing of the visits.

Revised Text:

Screening (baseline to pre-dose): All assessments should be completed within 14 days prior to screening unless otherwise noted in the Section 5 Time and Events Tables. Note for females, pregnancy testing should be performed within 7 days prior to first dose. Also, clinical labs performed during screening within ~~72~~ 24 hours of first dose do not need to be repeated on Day 1.

Visits during Week 1: Based on subject and clinic schedule, Week 1 Day 5 assessments can be ± 1 day.

Visits between Week 2 through Week 3 (inclusive): Based on subject and clinic schedule, assessments can be +3 days.

Visits between Week 4 through Week 9 (inclusive): Clinic visits can be scheduled ±3 days.

Every 3-week and 6-week visits from Week 10 through Week 48 Clinic visits can be scheduled ± 7 days.

After Week 48: Every 3-week visits are no longer required, based on clinical judgment. Every 6-week clinic visits must include safety assessments from the "q3w" column in the Time and Events Table and can be scheduled ± 7 days. Response assessments may be scheduled ± 7 days.

Discontinuation visit: should be within 14 ~~to 28~~ days from last dose of study drugs. 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.

Section 6.2. Baseline Assessment

Rationale for Change: This section was updated to provide consistency throughout protocol.

Revised Text:

Subjects diagnosed with refractory hematological malignancy (MM, lymphoma and/or acute myeloid leukemias~~)~~, will be assessed at baseline for general disease characteristics as noted in Section 6.2.1 and tumor type specific measures as noted in Section 6.2.2, Section 6.2.3 and Section 6.2.4, respectively.

Baseline is defined as the assessment closest to first dose, (i.e., Week[W]1Day[D]1 assessment) or screening if SCR sample collected within 24h of first dose.

Section 6.2.1. Baseline assessment for all subjects

- Primary tumor type (immunophenotyping and histology if applicable)
- History of other tumor types/medical history
- Date of initial diagnosis of primary tumor type
- Date of relapse/progression
- ~~Details of any metastatic disease~~

Section 6.2.2. Baseline assessment for subjects with AML

6.2.2 Baseline assessment for Subjects with ~~leukemia~~AML

~~**AML:**~~

- WHO classification
- FAB classification
- ~~Source of AML~~
- Cytogenetics

~~**CLL**~~

- ~~Modified Rai staging at initial diagnosis and screening~~
- ~~Binet stage at initial diagnosis and screening~~
- ~~Indication of active disease: evidence of bone marrow failure, splenomegaly, lymphadenopathy, lymphocytosis, B-symptoms~~
- ~~Cytogenetics~~

Section 6.3.1. Physical Examination

Rationale for Change: The section was updated to clarify the Investigator responsibility and the possible need to consult a cardiologist.

Revised Text:

Last sentence

Cardiovascular medical history/risk factors will also be assessed at baseline by the Investigator. Additional assessment by a cardiologist may be required at the discretion of the Investigator and/or Medical Monitor [prior to enrolment/first dose] if any cardiovascular risk factors or ECG/laboratory abnormalities are identified.~~a cardiologist.~~

Section 6.3.6. Holter Monitoring

Revised Text:

Second and third sentence

~~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, 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~~ may 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 were collected. The final intervals and morphology analyses entered into the database will be those generated by the central ECG laboratory.

Section 6.4.1. Disease Assessment

Rationale for Change: This section was updated to reflect the disease types and provide consistency throughout the protocol.

Revised Text:

First sentence

Response will be assessed as outlined in the Section 5 Time and Events Table 7 by the investigator using the appropriate criteria for MM, lymphoma and/or ~~leukemias~~AML, as noted in Appendix 6, Appendix 7 and Appendix 8, respectively.

Section 6.5.3. Urine Collection

Rationale for Change: This section was removed as metabolite collection and analysis will no longer be required as enough data was collected during the BET115521 study.

Revised Text:

Whole section deleted

~~**6.5.3. Urine Collection**~~

~~For QD cohorts, urine samples for quantitative analysis of GSK525762 will be collected over a dosing interval (12 or 24 hours) in two samples (first sample collected 0-2hr and second sample collected 2-24hr) immediately following dosing on Week 1 Day 1 and Week 2 Day 7. For the BID cohort, the first sample will be collected over 0-2h and the second over 2-12h, also immediately following dosing on Week 1 Day 1 and Week 2 Day 7. Urine samples will be collected from at least 6 subjects in Part 1 at the MTD. Additional sampling may be instituted based on emerging data.~~

~~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.~~

Section 6.6.1. Tumor Specific Tissue Collection

Rationale for Change: This section was updated to provide consistency throughout the protocol.

Revised Text:

- *Second and third sentence*
- For subjects with ~~leukemias~~ AML, changes in specific protein markers and/or mRNA expression signatures will be assessed in bone marrow and/or tumor cell-enriched PBMCs isolated from whole blood.
- For subjects with lymphomas, ~~lymph node~~ tissue biopsies ~~(or bone marrow, if appropriate)~~ will be required before and after treatment to evaluate changes in tumor-specific protein markers and/or gene expression signatures.

Section 6.6.2. Blood sample collection for Exploratory Translational Research

Rationale for Change: This section was updated to clarify the translational research which will be performed.

Revised Text:

- *Section heading and first bullet*

6.6.2. Blood sample collection for ~~Surrogate PD Biomarkers~~ Exploratory Translational Research

- Part 1 &2: At screening, date of bone marrow biopsy (Part 2 only), disease assessment and disease progression for isolating plasma for circulating biomarkers (eg, cfDNA), ~~isolation~~ PBMCs and neutrophils ~~and studying~~

Section 6.9. Pharmacogenetics

Rationale for Change: Minor correction made for consistency.

Revised Text:

- *Second paragraph, first sentence*
- Subjects who provide consent will have a ~~blood~~ saliva sample taken for analysis.

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:

- *Storage, last two sentences*

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 7.7.1. Dose and Safety Management Guidelines

Rationale for Change: The 10% coefficient of variability was removed as this is not standardized.

Revised Text:

- *Table 16*

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
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. • 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 based on discussion with GSK Medical Monitor.
Pneumonitis	• Grade 1	• (For <u>all</u> 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 (wnl). Continue investigational drug(s) at current dose(s).
	• Grade 2	• Consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, Diffusing Capacity of the Lung for Carbon Monoxide (DLCO), and 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 infectious 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	• <u>Permanently discontinue investigational drug</u> • Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		2, 5 mins apart). Repeat evaluations at least every 8 weeks until return to normal. Bronchoscopy with biopsy and/or BAL is recommended. • Consider corticosteroids if infectious origin is ruled out. Taper as medically indicated. • ~~(Grade 3) Discontinue investigational drug(s) (Grade 4) Discontinue investigational drug(s)~~
	• Grade 3-4	• Temporary discontinuation of study medication and monitor for change in severity • Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. • Collect "Cytokine blood samples" (which include blood sample for TNF-alpha, IL-1,IL-6, IL-10). Collect blood culture and investigate viral infections as applicable. • May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.

a. These guidelines are for suspected drug associated fever; please perform any additional tests as clinically appropriate for other causes of fever such as infection.

*Baseline results are defined by the nearest time point prior to first dose. If W1D1 results are available, these are considered the baseline results. If screening occurred within 72h of fit dose, W1D1 samples are not needed and screening data are considered as baseline.

Abbreviations: GSK=GlaxoSmithKline; QTcF= QT duration corrected for heart rate by Fridericia's formula; ECG=Electrocardiogram; IRB=Institutional review board; EC=Ethics committee; ULN=Upper limit of normal; LLN=Lower limit of normal; ~~CV= Coefficient of variance;~~ LVEF= Left ventricular ejection fraction; ALT=Alanine Transferase; BAL=Bronchoalveolar lavage; DLCO=Diffusing Capacity of the Lung for Carbon Monoxide; IL=Interleukin

Section 8.2.1. Cautionary Medications

Rationale for Change: This section was updated to reflect the most recent listing of medications per CredibleMeds, 15 May 2016.

Revised Text:

- *Table 18 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution*

~~**Generic Name**~~	~~**Brand Name**~~
~~Astemizole~~	~~Hismanal~~
~~Amiodarone~~	~~Cordarone, Pacerone, Nexterone~~
~~Citalopram~~	~~Celexa, Cipramil~~
~~Chlorpromazine~~	~~Thorazine~~
~~Escitalopram~~	~~Lexapro~~
~~Moxifloxacin~~	~~Avelox, Avalox, Avelon, Moxeza, and Vigamox~~
Alfuzosin	Lithium
Apomorphine	Mifepristone
Aripiprazole	Mirabegron
Artenimol + piperaquine	Mirtazapine
Asenapine	Moexipril/HCTZ
Atomoxetine	Nicardipine
Bedaquiline	Norfloxacin
Buprenorphine	Nortriptyline
Clomipramine	Ofloxacin
Clozapine	Olanzapine
Cyamemazine	Oxytocin
Degarelix	Paliperidone
Delamanid	Pasireotide
Desipramine	Perflutren lipid microspheres
Dexmedetomidine	Pipamperone
Dolasetron	Promethazine
Ezogabine	Rilpivirine
Famotidine	Risperidone
Felbamate	Roxithromycin
Fingolimod	Saquinavir
Fluconazole	Sertindole
Foscarnet	Telavancin
Gemifloxacin	Telithromycin
Granisetron	Tetrabenazine
Hydrocodone – ER	Tizanidine
Iloperidone	Tolterodine
Imipramine	Trimipramine
Isradipine	Tropisetron
Leuprolide	Vardenafil
Levofloxacin	Venlafaxine

~~NOTE: 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: CredibleMeds, 15 May 2016~~5~~ (www.crediblemeds.org).

Section 8.2.2. Drugs Potentially Affecting GSK525762 Pharmacokinetics

Rationale for Change: This DDI section was updated based on emerging metabolite data.

Revised Text:

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. Potential interactions with other Cytochrome P450 metabolized drugs have not been assessed.

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).

~~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. Potential interactions with other Cytochrome P450 metabolized drugs have not been assessed.~~

- *Table 19 Drugs Potentially Affecting GSK525762 Pharmacokinetics Resulting in Increased or Decreased GSK525762 Exposure*

Drug Class	Agent
Drugs that may decrease exposure to GSK525762 (CYP and/or Pgp Inducers)	
Antibiotics	Nafcillin, all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)
Anticonvulsants	Phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)
Antiretrovirals	Efavirenz, etravirine, nevirapine, tipranivir,
Glucocorticoids (oral)	Cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)
Other	Bosentan, St. John's Wort, modafinil
Drugs that may increase exposure to GSK525762 (CYP3A4 Inhibitors)	
Antibiotics	Clarithromycin, ~~flucloxacillin,~~ telithromycin, troleandomycin~~,~~
Antifungals	Fluconazole (>150 mg daily), itraconazole, ketoconazole, ~~terbinafine,~~ posaconazole,voriconazole
Anti~~retro~~virals~~, Protease Inhibitors~~	Amprenavir, atazanavir, boceprevir, delaviridine, fosamprenavir, indinavir, lopinivir,nelfinavir, ritonavir, saquinavir, telaprevir
Calcium channel blockers	Diltiazem, verapamil
Antidepressants, anxiolytics	~~, fluvoxamine,~~ nefazodone, tofisopam
GI Agents	Cimetidine
Other	Seville oranges, grapefruit or grapefruit juice and/or kumquats, pomegranate or pomegranate juice, pomelos, exotic citrus fruit (i.e., star fruit, bitter melon), grapefruit hybrids or fruit juices, or other foods and juices known to inhibit CYP3A4

NOTE: Topical or inhaled steroids are permitted.

Section 8.3. Prohibited Medications

Rationale for Change: This section was updated to reflect the most recent listing of prohibited medications per CredibleMeds, 15 May 2016.

- **Revised Text:**
- *Second paragraph, first sentence*
- 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, or 14 days, whichever is longer, 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.

- *Table 20 Drugs with a Risk of Torsades de Pointes that are Prohibited*

~~Generic Name~~	~~Brand Name~~
~~Arsenic trioxide~~	~~Trisenox~~
~~Bepridil~~	~~Vascor~~
~~Chloroquine~~	~~Aralen~~
~~Cisapride~~	~~Propulsid~~
~~Clarithromycin~~	~~Biaxin, Prevpac~~
~~Disopyramide~~	~~Norpace~~
~~Dofetilide~~	~~Tikosyn~~
~~Domperidone~~	~~Motilium~~
~~Droperidol~~	~~Inapsine~~
~~Erythromycin~~	~~Erythrocin, E.E.S.~~
~~Haloperidol~~	~~Haldol~~
~~Halofantrine~~	~~Halfan~~
~~Ibutilide~~	~~Corvert~~
~~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~~
Amiodarone	Grepafloxacin
Anagrelide	Halofantrine
Azithromycin	Haloperidol
Chloroquine	Ibutilide
Chlorpromazine	Levomepromazine
Cilostazol	Methadone
Ciprofloxacin	Moxifloxacin
Citalopram	Papaverine
Clarithromycin	Pentamidine (IV)
Cocaine	Pimozide
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone	Quinidine
Donepezil	Sevoflurane
Dronedarone	Sotalol
Droperidol	Sulpiride
Escitalopram	Thioridazine
Flecainide	

NOTE: 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: CredibleMeds, 15 May 2016~~5~~ (www.crediblemeds.org).

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

- *Third paragraph*
- 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 5 half-lives of the drug or 14 days whichever is longer,** prior to the administration of the first dose of study drug in order for the subject to meet study eligibility.

Section 8.4. Non-Drug Therapies

Rationale for Change: This section was updated to clarify the requirements in Part 1 of the study.

- **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. Subjects enrolled in Part 1 of the study should abstain from coffee and tea from 24 hours prior to an extensive PK collection day (i.e. W1D1 and W2D7) until the end of PK collection on that day

Section 9.1.1. Female Subjects

Rationale for Change: This section was updated to further clarify hormonal forms of birth control.

- **Revised Text:**
- *Last sentence*

~~H~~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.

Section 9.1.2. Male Subjects

Rationale for Change: This section was updated to further clarify the contraception requirements for male subjects with a female partner of child bearing potential.

- **Revised Text:**

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**, or**

- Condom use **PLUS** partner use of highly effective contraceptive ~~such as occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/film/cream/suppository), or intrauterine device.~~ (<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, **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

Male subjects whose partners are or become pregnant must use condoms while on study and for 7 days after stopping study medication(s).

Male subjects should be advised not to donate sperm while on study and for 16 weeks after the last dose of study drug(s).

~~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 9.2. Caffeine, Alcohol, and Tobacco

Rationale for Change: This section was updated to clarify that subjects must abstain during Part 1.

- **Revised Text:**

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 PK and or PD sample during each extensive PK session in Part 1.

Section 11.1.1. Part I, Dose Escalation

Rationale for Change: This section was included to allow for subjects from Part 1 to be included in the efficacy analysis.

- **Revised Text:**
- *Last sentence*

Subjects in Part 1 treated at the RP2D may be included in the efficacy analysis as described in Section 11.6.1.

Section 11.1.1. Part 2, Expansion Cohort

Rationale for Change: This section was included to allow for subjects from Part 1 to be included in the efficacy analysis

- **Revised Text:**
- *First paragraph, first and second bullet*

- For AML, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, CRp, CRi, or PR ~~or a morphologic leukemia-free state~~) of 30% relative to a 10% response rate suggesting no activity.
- For MM, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a sCR, CR, VGPR, or PR) of 20% relative to a 5% response rate suggesting no activity.

- *Fourth paragraph*

Futility analysis for each disease cohort will begin when response data is available for at least 10 subjects treated at the RP2D in Part 1 and Part 2. 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 3.2.4.

Section 11.2. Analysis Population

Rationale for Change: The analyses sections were updated throughout the protocol to allow for flexibility to conduct an interim analysis during the study, prior to the 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 sentence

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

Section 11.4. Interim Analysis

Rationale for Change: The analyses sections were updated throughout the protocol to allow for flexibility to conduct an interim analysis during the study, prior to the end of Part 2.

- **Revised Text:**

~~No formal interim analysis will be performed for Part 1 of the study. Safety, PK, and PD marker data will be examined ongoing while the study is being conducted.~~

Interim analysis on Part 1 may be conducted when

- Part1 is completed or
- All subjects enrolled in any or all of AML, MM, and NHL cohorts in Part 1 have had at least one post-baseline disease assessment or progressed or died or withdrawn from the study

For each disease type in Part 2, after the initial 10 evaluable subjects in the AML and NHL cohorts and initial 13 evaluable subjects in the MM cohort have enrolled at the selected dose regimen for the Expansion Cohort, data will be reviewed for clinical benefit on an ongoing basis and the number of subjects with observed clinical benefit will be compared with the stopping guidelines provided in Section 3.2.4. Subjects in Part 1 treated at the RP2D may be included in this analysis of efficacy.

The study will not ~~only~~ stop due to ~~lack of~~ efficacy. The trial ~~will~~ may continue to enrol the maximum planned sample size to provide a better an estimate on the distribution of the response rate in the target patient populations.

Section 11.5. Final Analysis

Rationale for Change: The analyses sections were updated throughout the protocol to allow for flexibility to conduct an interim analysis during the study, prior to the end of Part 2.

- **Revised Text:**

Final primary analysis will occur when at least 70% of subjects are dead, have withdrawn consent, or are lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up, whichever is earlier.

The data will be listed and summarized mostly by doses. Separate analyses will be provided for Part 1 and in Part 2 where applicable. In some instances, analysis may also be generated based on the dose of GSK525762. Data from Part 1 and Part 2 may be combined for some analyses at the end of the trial, as appropriate. More detail on the data displays will be provided in the RAP.

~~Final OS analysis will occur when at least 70% of subjects are dead, have withdrawn consent, or are lost to follow-up, or all subjects still in follow-up have had at least 5 years follow-up, whichever is earlier.~~ Final OS analysis may be conducted when all subjects have completed the study.

Section 11.6.1. Primary Analysis

Rationale for Change: The analyses sections were updated throughout the protocol to allow for flexibility to conduct an interim analysis during the study, prior to the end of Part 2. This section was included to allow for subjects from Part 1 to be included in the efficacy analysis.

- **Revised Text:**

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and response criteria described in the Section 5 Time and Events Table 7 for MM, lymphoma and/or leukemias, as noted in Appendix 6, Appendix 7 and Appendix 8, respectively. If the data warrant, the response data will be summarized by dose level. In addition, any subject in Part 1 treated at the RP2D may be included in the analysis of efficacy described below.

The primary aim of Part 2 is to detect demonstrate a possibly clinically meaningful response rate in each of the disease cohorts separately. Each disease subtype (AML, MM, and NHL) will be evaluated separately.

Overall Response rate is defined as

- AML: The percentage of subjects who achieved CR, CRp, CRi, and PR. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided. Response rates of subjects with AML M3 will be summarised separately.
- MM: The percentage of subjects who achieved sCR, CR, VGPR, or PR.
- NHL: The percentage of subjects who achieved CR or PR. Response rates of subjects with double/triple-hit lymphoma will be summarised separately.

All subjects who received at least one dose of treatment will be included in the evaluation for response. Response rates and the associated 2-sided 95% exact confidence limits will be provided.

Section 11.6.2. Secondary Analysis

Rationale for Change: This section was updated to align with the primary and secondary endpoints.

- **Revised Text:**

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~~Not Evaluable) 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 if data warrant.

The duration of response is defined for the subject or subjects with a ~~confirmed~~ CR or PR for NHL, ~~CR, CRp, CRi, or PR for AML,~~ and sCR, CR, VGPR, or PR for MM as the time from the first documented evidence response 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~~ Progression is calculated from the start of treatment ~~defined,~~ 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.

~~for subjects with a confirmed response as the time from first dose to the first documented evidence of response.~~

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

OS along with 95% confidence intervals for MM, lymphoma and leukemia subjects treated in Part 1 and Part 2, will be estimated using the Kaplan Meier method if data warrant. OS analysis for AML will exclude subjects with AML subtype M3. NHL will be separately reported based on double/triple hit status. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis.

Section 11.8. Pharmacokinetic Analysis

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 GSK CPMS. Plasma GSK525762 and relevant metabolite(s), 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 pharmacology 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 from the ratio of AUC(0-τ) in Week 2 Day 7 / AUC(0-τ) in Week 1 Day 1. The ratio of AUC(0-τ) on Week 2 Day 7 / Week 1 Day 1 AUC(0-∞) 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.~~

Plasma concentration-time data will be listed by dose, dosing regimen, and summarized using descriptive statistics (n, mean, standard deviation [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) PK 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 day, dose and dose regimen cohort will be reported.

Cmax and AUC (AUC(0-∞), single dose, and AUC(0-τ), steady state) will be plotted as a function of the dose administered and dosing regimen. If more than 2 dose cohorts are evaluated, dose proportionality of AUC and Cmax for GSK525762 will be assessed using the power model (details will be provided in the RAP).

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

Section 11.9. Pharmacokinetic/Pharmacodynamic Analysis

Rationale for Change: Minor update

- **Revised Text:**

Last paragraph

Overall efficacy data and overall tumor burden may be described using ~~ordered~~ categorical<u>/</u>~~ model and~~ continuous models with summary exposure parameters (e.g., Cmax, Cτ, and Cav) as covariates derived from the population PK analysis. Further model details will be provided in the RAP.

Section 12.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Rationale for Change: Removed the reference of subjects less than 18 years of age as a subject must be 18 or older to be eligible.

Last paragraph

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.

Section 15.8.1. Acute Leukemias, MDS, Chronic Myelogenous Leukemia in Blast Phase (CML-BP), Chronic MyeloMonocytic Leukaemia (CMML)

Rationale for Change: This section was updated to align the leukemia population as was done throughout the protocol as all leukemia subjects enrolled to date have been acute myeloid leukemia.

- **Revised Text:**

Section 15.8.1. Acute Myeloid Leukemia~~s, MDS, Chronic Myelogenous Leukemia in Blast Phase (CML-BP), Chronic MyeloMonocytic Leukaemia (CMML)~~

Last sentence

~~**Marrow CR**: Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pre-treatment (MDS only)~~

Section 15.8.2. CLL

Rationale for Change: This section was removed as the leukemia population was updated to only include acute myeloid leukemia.

- **Revised Text:**

Section 15.8.2. CLL

~~[Hallek, 2008]~~

~~**Complete Response:**~~

~~Peripheral blood: Absolute lymphocyte count (ALC) <4 x 10^9/L with Hb >11 g/dL, ANC ≥1.5 x 10^9/L and platelet count >100 x 10^9/L (without need for growths factors or transfusions).~~

~~Tumor: disappearance of all palpable lymph nodes, spleen, and liver without the appearance of new lesions. Absence of constitutional symptoms.~~

~~Bone Marrow: <30% lymphocytes in normocellular marrow; if lymphoid nodules are seen, response is deemed as nodular (nPR). If all CR criteria are fulfilled but subject~~

has drug-related cytopenia, consider CR with incomplete bone marrow recovery (CRi).

Partial Response:

Peripheral blood: ALC reduced by ≥50% from pre-treatment baseline value, Hb >11 g/dL or 50% improvement over baseline without transfusions, ANC ≥1.5 x 10^9/L or 50% improvement over baseline, and platelet count >100 x 10^9/L or 50% improvement over baseline.

Tumor: When compared with pre-treatment measurements, a reduction ≥50% in measurable lesions without the appearance of new lesions.

Progressive Disease or Relapse of Disease

Peripheral blood: A ≥50% increase in ALC over baseline in first course, or lowest prior thereafter, with a sustained level >5 x 10^9/L.

Tumor: An increase in the product of two perpendicular diameters of a measured lesion by ≥50% over the size present at entry on study or for subjects who respond, the size at the time of maximum regression and/or the appearance of new areas of malignant disease. Transformation to a more aggressive histology (e.g., Richter's syndrome). Deterioration in performance status or increasing symptoms do not constitute progression; however, their appearance should initiate a new evaluation for extent of disease.

Section 15.8.3. Agnogenic Myeloid Metaplasia (AMM)

Rationale for Change: This section was removed as the leukemia population was updated to only include acute myeloid leukemia.

- **Revised Text:**

Section 15.8.3. Agnogenic Myeloid Metaplasia (AMM)

[Tefferi, 2001]

Complete Response: Absence of signs or symptoms of the disease. White blood cells (WBC) between 1 to 10 x 10^9/L with no peripheral blasts, promyelocytes, or myelocytes and with normalization of bone marrow (<5% blasts in normocellular or hypercellular marrow).

Resolution of pretreatment cytopenias:

ANC ≥1.0 x 10^9/L without G-CSF or GM-CSF.

Hgb ≥12.0 gm/dL (11.0 gm/dL for females) without erythropoietin or transfusion support.

PLT ≥100 x 10^9/L without growth factor or transfusion support.

~~**Resolution of pretreatment leukocytosis and/or thrombocytosis:**~~

~~WBC ≤10 x 10^9/L without peripheral blasts, promyelocytes, or myelocytes.~~

~~PLT ≥100 x 10^9/L but less than 450 x 10^9/L.~~

~~**Partial Response:**~~

~~Improvement of two or more of the following:~~

~~ANC: Increase by 100% and to above 10^9/L for neutropenia.~~

~~WBC: between 1 - 10 x 10^9/L with persistence of immature cells (blasts, myelocytes, metamyelocytes) for pretreatment leukocytosis.~~

~~Hemoglobin: Increase by 2 gm/dL if it was below 10 gm/dL or decrease in transfusion requirements by at least 50% (decrease in frequency and/or volume).~~

~~Platelet Count: below that level prior to therapy or persistent thrombocytosis >450 x 10^9/L but < 50% of pre-treatment.~~

~~Marrow Blasts: Reduction of marrow blasts to 5% or less if it was above 10% in normocellular or hypercellular marrow.~~

~~Organomegaly: Reduction in splenomegaly and/or hepatomegaly by 50% of pre-treatment dimensions (measured as length below the left costal margin on palpation) confirmed by imaging in difficult cases.~~

Section 14. Reference

Rationale for Change: Reference updated as per latest version available.

- **Revised Text:**

CredibleMeds. List of drugs with a risk of Torsades de Pointes. Available at: http://www.crediblemeds.org Accessed 02 March 201~~5~~6

~~Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008; 11: 5446-56~~

~~Tefferi A. Chronic myeloid disorders: Classification and treatment overview. *Semin Hematol*. 2001; 38(1 Suppl 2): 1-4~~

15.21. Appendix 21: Protocol Changes for Amendment 8 (14-FEB-2017) from the Protocol Amendment 7 (23-JUN-2016)

Where the Amendment Applies

Amendment 8 applies to all study centres.

General Protocol Changes

Amendment 8:

The study population for the AML cohort in Part 2 was amended from a population of subjects with AML to a population of subjects with relapsed or refractory myelodysplastic syndrome (MDS) or hypoproliferative AML that has arisen from an antecedent MDS. The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new population. The safety assessments were updated to be in line with the Investigator Brochure. The dose limiting toxicity criteria were modified to remove the specific criteria for leukemia. The time and events tables were updated to reduce the cardiac monitoring (ecg, holter and troponin), remove mRNA and cytokine collection, add a Pain Assessment, addition of an exploratory translational research blood draw and to add Factor VII assay collection. The disease related events/outcomes section was removed and the pregnancy reporting timeframe was reduced to 24 hours. Fever was removed from the dose adjusting/stopping safety criteria. Aspirin and non-steroidal-anti-inflammatory drugs (NSAIDs) were added to the Cautionary medications. Response Criteria for MDS was added as an Appendix.

GlaxoSmithKline Document Number 2011N113741_03 Version 3 changed to GlaxoSmithKline Document Number 2011N113741_05 Version 5 throughout the document.

Table numbers are updated (Figure no.1 becomes Table no. 1 Three Week DLT monitoring: Dosing Schedule and Cardiac Monitoring (QD and BID) and Table No.1 Accelerated Dose Escalation Procedures in Part 1is deleted, all other Table numbers are same). Figure numbers are updated throughout the document (Figure no. 2 now becomes Figure no. 1, Figure no. 3 becomes Figure no. 2 and so on). Minor clarifications, formatting and typographical errors were also addressed in this amendment.

Changes are noted below with strikethrough to identify deleted text and <u>underlining</u> to identify new or replacement text.

PROTOCOL SYNOPSIS

- **STUDY DESIGN AND DURATION:**

Rationale for Change: After an evaluation of data from the Part 1 AML cohort, the following observations prompted changes to the Part 2 cohort: clinical responses were observed at doses of 60 mg and above, these responses occurred in subjects whose disease harbored complex karyotype and recurrent mutations in TP53 and in proteins that regulate gene expression, suggesting that these subjects had an antecedent MDS that transformed to AML. Furthermore, most subjects with AML discontinued GSK525762

early in the course of their treatment as a consequence of their underlying AML or disease complications. Responses tended to be delayed (at the four week mark or later, with many requiring more than 10 weeks to manifest). Thus, most subjects were not remaining on study for long enough to achieve benefit. In order to maximize time on-study, Part 2 was updated to enroll subjects with a more slowly-progressing disease that maintained many of the clinical characteristics of the AML responses that were observed in Part 1.

Revised Text:

Part 2 will explore clinical activity at the MTD or RP2D; separate expansion cohorts will be planned for myeloid malignancies (high-risk myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML] that has evolved from an antecedent MDS, hereafter referred as the "myeloid cohort"), non-Hodgkin's Lymphoma (NHL, including an exploratory sub-cohort of subjects with myc and B-Cell Leukemia (BCL)2 and/or BCL6 rearrangements/overexpression [double- and triple-hit lymphoma]), and multiple myeloma (MM).

STUDY RATIONALE:

Rationale for Change: This section was updated to include the MDS Population.

Revised Text:

Relapsed and/or refractory hematological malignancies such as MDS, ~~Acute Myeloid Leukemia~~ ~~(~~AML~~)~~, ~~non-Hodgkin's Lymphoma(~~NHL~~)~~, and ~~Multiple Myeloma~~ ~~(~~MM~~)~~ have an overall poor outlook. This is the first study of this agent to be conducted in subjects with these relapsed and/or refractory hematological malignancies with few or no conventional treatment options that could be expected to provide any lasting benefit.

- **OBJECTIVES AND ENDPOINTS:**

Rationale for Change: This section was updated to include the MDS population and remove the BID administration objective to remove obligation of this cohort and make it optional.

Revised Text:

Part 1

Part 1 Objectives		Part 1 Endpoints
Secondary	• To evaluate clinical efficacy following QD administration in subjects with AML, MM, and NHL.	• Objective ~~Overall~~ response rate (ORR), as measured by standard response criteria
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	• Assess objective ~~overall~~ response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's

Part 1 Objectives		Part 1 Endpoints
		lymphoma, as a function of dose and exposure markers.
	~~• To evaluate safety, tolerability, and efficacy following BID administration of GSK525762 in subjects with AML, MM, and NHL~~	~~• AEs, SAEs, DLTs, dose reductions or delays, withdrawals due to toxicities, changes in safety assessments, and ORR (as measured by standard response criteria)~~
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD ~~and/or BID~~ dosing schedules.	• Pharmacogenomic (PGx) study using clinical samples.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort").	• For ~~AML~~MDS cohort: Objective response rate (% of subjects achieving Complete Response [CR], marrow CR, CRp [as per CR but platelet count <100 x 10^9/L], CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR],) per response criteria.
Secondary	• To characterize the PK of GSK525762 in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the exposure response (i.e., PK~~)~~/PD) relationship between GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL.	• PK/PD relationship between GSK525762 exposure markers and safety and efficacy parameters.
	• To evaluate the safety and tolerability of RP2D of GSK525762 in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	~~• To evaluate the relationship between GSK525762 dose and PD response in 3 disease-specific cohorts of subjects with AML, MM or NHL.~~	~~• Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.~~

Part 2 Objectives		Part 2 Endpoints
	• To determine the clinical activity of GSK525762 in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL.	• TTP (Time to Progression) , DOR (Duration of Response), PFS (Progression Free Survival) for MDS/AML, MM and NHL • Overall survival (OS, the time from the treatment start date until death from any cause) for ~~AML~~MDS/AML, MM and NHL.

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • ~~Acute myeloid leukemia~~Myelodysplastic syndrome and transformed MDS: A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with ~~acute leukemia~~MDS/AML.

- **INCLUSION/EXCLUSION CRITERIA:**

Rationale for Change: This section was updated to include criteria specific for the MDS population and also update contraception language based on GSK guidances.

Revised Text:

Inclusion Criteria

9. Males subjects with a female partner of childbearing potential or who is pregnant must agree to use one of the methods of contraception specified in Section 9.1. 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, male subjects whose partners are or become pregnant must use/continue to use condoms until 16 weeks after last dose of study medication.

3. ~~In Part 1 and Part 2~~ sSubjects must have a diagnosis of relapsed or refractory Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).

- (Part 1 only): Subjects with AML~~,~~ are eligible if they
  - have relapsed and/or refractory disease, *OR*

- (Part 2 only): Subjects with MDS/AML (myeloid cohort) are eligible if they:
  - Have high-risk (defined as intermediate [INT]-2 or higher by International Prognostic Scoring System [IPSS] criteria [Greenberg], or high/very high by IPSS-Revised [IPSS-R] criteria [Greenberg]) MDS that has relapsed after or been refractory to prior therapy with hypomethylating agent, *OR*
  - Have AML that has arisen from an antecedent MDS (irrespective of IPSS/IPSS-R score)

- Subjects must have progressed despite, or failed to respond to, prior therapy with hypomethylating agent, *AND*
- At least one bone marrow biopsy obtained within 28 days of first dose of GSK525762 must demonstrate a marrow blast percentage of no more than 30%
- Note: If marrow blasts exceed 30% on any biopsy within 28 days of first dose of GSK525762, enrolment will only be permitted after discussion with the medical monitor

- (Part 1 and Part 2): Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent,
- (Part 1 and Part 2): Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy,

Definitions for Adequate Organ Function

Rationale for Change: Inclusion criteria were made more restrictive in order to reduce the risk of bleeding events.

Revised Text:

System	Laboratory Values
Hematologic	
Coagulation assays (prothrombin time/ international normalized ratio [PT/INR] and activated partial thromboplastin time [aPTT] [1]	≤1.~~5~~2 X upper limit of normal (ULN)

Exclusion Criteria

Rationale for Change: Minor correction

Revised Text:

4. Evidence of severe ~~of~~ or uncontrolled infection.

- **DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN**:

Rationale for Change: Minor correction

Revised Text:

BID dosing ~~will~~ may be explored once MTD has been identified in once daily dosing; the total daily dose administered BID may not exceed the QD MTD.

PHARMACOKINETIC/PHARMACODYNAMIC MEASUREMENTS:

Rationale for Change: This section was updated to clarify that blood sampling for PD measurements will not be completed for all subjects.

Revised Text:

There will be serial blood sampling for PK and PD (in some subjects) measurements in Part 1 of this study and more limited PK sampling in Part 2 of this study.

EFFICACY MEASUREMENTS:

Rationale for Change: Addition of PFS and the MDS patient population to align with the newly revised objectives and endpoints.

Revised Text:

ORR, PFS and OS in AML, MDS, MM, and NHL; time to progression and duration of response in MM and NHL

SAFETY MEASUREMENTS:

Rationale for Change: After an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 120 mg QD cohort available by 10Jun2016, 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:

Cardiac safety monitoring will be required, consisting of ~~24 hours of Holter monitoring at Screening, Week 1, and Week 4, 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).

STATISICAL ANALYSIS:

Rationale for Change: This section was updated for Part 2 of the study to include population change from AML to MDS.

Revised Text:

The assessments are based on the predictive probability of success (response rate > historical response rate) with a maximum of 32 subjects treated per cohort (for ~~AML~~MDS and non- double hit NHL cohorts) or 37 subjects treated (MM cohort) and assessed for response.

Section 1.2. Study Population Rationale

Rationale for Change: After an evaluation of data from the Part 1 AML cohort, the following observations prompted changes to the Part 2 cohort: clinical responses were observed at doses of 60 mg and above,- these responses occurred in subjects whose disease harbored complex karyotype and recurrent mutations in TP53 and in proteins that regulate gene expression, suggesting that these subjects had an antecedent MDS that transformed to AML. Furthermore, most subjects with AML discontinued GSK525762 early in the course of their treatment as a consequence of their underlying AML or disease complications. Responses tended to be delayed (at the four week mark or later,

with many requiring more than 10 weeks to manifest). Thus, most subjects were not remaining on study for long enough to achieve benefit. In order to maximize time on-study, Part 2 was updated to enroll subjects with a more slowly-progressing disease that maintained many of the clinical characteristics of the AML responses that were observed in Part 1.

Revised Text:

MDS and AML are related neoplasms of myeloid cells characterized by an excess of immature myeloblasts in the bone marrow, as well as ineffective hematopoiesis leading to peripheral cytopenias. MDS and AML exist along a spectrum defined by the percentage of marrow blasts, with > 20% delineating the boundary between the two diseases. While AML may arise *de novo,* it may also evolve from an antecedent myelodysplasia or myeloproliferative syndrome. Both AML and MDS are increasingly defined by genetic characteristics, with cytogenetic abnormalities and mutations in genes involved in RNA splicing and epigenetic regulation frequently observed in MDS as well as AML that transformed from MDS. The only approved therapies for MDS are the hypomethylating agents 5-azacitidine and decitabine; these agents are frequently used in patients with AML who are not suitable candidates for aggressive induction chemotherapy (e.g., as a consequence of advanced age or other comorbidity). To date, there are no second-line agents for subjects who did not respond to or who have progressed despite hypomethylating agent therapy, and overall survival for patients who have failed prior therapy is typically measured in months (Prebet, 2011; Sekeres, 2013; Jabbour, 2010).

Non-Hodkin's lymphomas are a family of more than sixty malignancies arising from abnormal lymphoid, histiocytoid, or dendritic cell development (Swerdlow, 2016). They constitute a spectrum of diseases that may be focal or systemic, indolent or aggressive, based on the underlying cell of origin and other biological factors. Therapy is customized for each patient based on the disease subtype and location and typically involves radiation, systemic therapy, or both. Recently, targeted systemic therapies have emerged and have been approved based on promising response data. However, NHL is an incurable disease for most patients and thus new approaches are necessary in the face of inexorable progression and relapse.

Multiple myeloma is a neoplastic proliferation of plasma cells. In almost all cases, myeloma is incurable; though novel therapies have emerged in the past decade and a half, most patients with multiple myeloma will die from their disease. Thus, new therapies are necessary.

Relapsed and/or refractory hematological malignancies such as AML, MDS, NHL, and MM have an overall poor outlook.

Section 1.3.2.3 Starting Dose for BID

Rationale for Change: This section was updated to add flexibility to the BID dosing regimen.

Revised Text:

First paragraph third sentence:

In this study, once the QD MTD of GSK525762 has been identified for each disease subtype (AML/MDS, MM, and NHL), an exploratory cohort ~~will~~ may be opened in one or more of the ~~for each some?~~ disease types to evaluate safety, tolerability, and preliminary efficacy of BID dosing.

Section 1.3.3 Dose escalation steps (QD only)

Rationale for Change: This section was updated to include the MDS population.

Revised Text:

Second paragraph first sentence:

The MTD of GSK525762 may be different for AML/MDS, NHL, and MM.

Section 1.4 Rationale for Study and Endpoints

Rationale for Change: After an evaluation of data from the Part 1 AML cohort, the following observations prompted changes to the Part 2 cohort: clinical responses were observed at doses of 60 mg and above,- these responses occurred in subjects whose disease harbored complex karyotype and recurrent mutations in TP53 and in proteins that regulate gene expression, suggesting that these subjects had an antecedent MDS that transformed to AML. Furthermore, most subjects with AML discontinued GSK525762 early in the course of their treatment as a consequence of their underlying AML or disease complications. Responses tended to be delayed (at the four week mark or later, with many requiring more than 10 weeks to manifest). Thus, most subjects were not remaining on study for long enough to achieve benefit. In order to maximize time on-study, Part 2 was updated to enroll subjects with a more slowly-progressing disease that maintained many of the clinical characteristics of the AML responses that were observed in Part 1.

Revised Text:

Second paragraph third sentence onwards:

Part 2 is a cohort expansion, which will study the RP2D of GSK525762 to determine preliminary efficacy, safety and tolerability in three separate cohorts of subjects with ~~acute myeloid leukemias~~myeloid neoplasms (myelodysplastic syndrome [MDS] or MDS that has transformed to AML), multiple myeloma and non-Hodgkin's lymphoma.

Originally, Part 2 of the study was designed to evaluate preliminary clinical efficacy in relapsed or refractory AML, MM, and NHL. However, after an evaluation of data from the Part 1 AML cohort, the following observations prompted changes to the Part 2 cohort; clinical responses were observed at doses of 60 mg and above,these responses occurred in subjects whose disease harbored complex karyotype and recurrent mutations

in TP53 and in proteins that regulate gene expression, suggesting that these subjects had an antecedent MDS that transformed to AML. Furthermore, most subjects with AML discontinued GSK525762 early in the course of their treatment as a consequence of their underlying AML or disease complications. Responses tended to be delayed (at the four week mark or later, with many requiring more than 10 weeks to manifest). Thus, most subjects were not remaining on study for long enough to achieve benefit. In order to maximize time on-study, Part 2 was updated to enroll subjects with a more slowly-progressing disease that maintained many of the clinical characteristics of the AML responses that were observed in Part 1 (i.e., MDS and MDS that has transformed to AML with a low burden of disease).

Section 1.5.1. Risk Assessment

Rationale for Change: This section was updated to reflect the results of ongoing toxicology studies.

Revised Text:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Lymphoid / Hematologic	Lymphoid / hematologic toxicity was observed in rats and dogs and the effects contributed to the definition of severely toxic repeat dose in rats (30 mg/kg). The effects manifested as hypocellularity in bone marrow, thymus, spleen and lymph nodes; decreased spleen and thymic weight; mild hemolysis; ~~decreased white cell /lymphocyte count and~~ variable and inconsistent changes in white cell /lymphocyte count, multiple red blood cells parameters and reticulocyte counts. Minimal bone marrow hypocellularity was still evident in male rats previously given 30/20 mg/kg/day for 13 weeks following a 17 week off dose period. Changes relating to coagulation were evident in both rats (considered non-adverse) and dogs (considered adverse at 3 mg/kg/day). These included a reduction in platelet counts (54%) and an increase in activated partial thromboplastin time (aPTT; 1.38X). Full recovery of aPTT and a compensatory increase in platelet counts in dogs (1.27X) was evident following the 3 week off-dose period.	ICF includes the risk of lymphoid / hematologic toxicity. Protocol includes laboratory assessments (complete blood count [CBC] and coagulation factors [international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT)], exclusion criteria if there is evidence of clinically significant bleeding episodes, monitoring for bruising/infection and dose stopping/modifications criteria. 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 the subject's PT/PTT meet entry criteria.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** (up to 20%; 41 msec in dog) Can occur or persists after drug is cleared from plasma; general trend to increase on repeat dosing; no potentiation beyond day13 in 28 day toxicology study in dogs. Reversible on cessation of dosing; not potentiated on subsequent dosing following a 7 day dosing holiday. No significant arrhythmias were detected in preclinical studies. No clear link to human ether à go-go-related gene (hERG) binding or trafficking. No evidence of heart accumulation of GSK525762. Mechanism & risk for Torsades de Pointe is unclear. **Blood pressure (BP**) Variable changes in blood pressure following a single dose (≥1 mg/kg in dogs and 60 mg/kg in rats); no effects were observed in the 728 day ~~toxicology~~ repeat dose dog CV study~~ies~~; increase in mean BP up to 11 mmHg; decrease in mean BP up to 13 mmHg. **QA interval** (indirect measure of cardiac contractility). ~~Increased~~ Decreased QA interval at single non-tolerated doses in dog (no effect seen in rats); up to 10 msec. No effects were observed in the 7 day repeat dose dog CV ~~28 day~~ study; No echocardiography changes in the 28 day dog toxicology study~~ies~~.	ICF includes the risk of (fatal) arrhythmias Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK] and creatine kinase-MB [CK-MB]), cardiac monitoring (electrocardiograms [ECGs], ~~Holter monitoring~~ and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for the management cardiac events. Drugs with a risk of Torsades de Pointes are prohibited, (refer to Section 8.3). 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. 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 and including 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 5 and removed in Protocol Amendment 8 following additional analysis of all available data by the cut off of

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
		10-Jun-2016. 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
Cardiovascular - Troponin	Elevations in cardiac biomarkers relative to 4 week Good Laboratory Practice (GLP) toxicology study control group in: • Cardiac troponin I (up to 15X in rat and 4.7X in dog) • Cardiac troponin T (up to 8.9X in rat) • Myosin light chain III (up to 4.8X in rat) • NT-proANP (up to 1.54X in rat) Changes were reversible and there was no evidence of compound related myocardial histopathological changes in either species after ~~28~~ up to 3 months ~~days~~ of dosing.	ICF includes the risk of myocardial infarction. Protocol includes troponin monitoring (local laboratory monitoring for troponin I or T based on availability and troponin T at central laboratory) and dose stopping/modifications criteria for the management of cardiac toxicity. .
Reproductive	GSK525762 has shown adverse degenerative ~~and potentially irreversible~~ effects on testes in rats, rabbits and dogs, with no observed adverse effect level (NOAEL) in rabbits. 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. ~~An effect on spermatogenesis is anticipated. In definitive four-week oral toxicology studies,~~	ICF includes the risk of damage to reproductive organs such as testes or ovaries. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female subjects and collecting testosterone (free and complete) for male subjects. ICF includes the potential risk of reproductive effects. Protocol includes specific contraceptive guidelines and precautions for males and females and pregnancy testing for female

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	~~sperm retention and degenerative effects occurred in male dogs and rats. Degenerative changes were also observed in rabbits dosed dermally for 14 days~~. ~~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.~~ GSK525762 has shown effects on female fertility (disrupted estrous cyclicity, delays to mating and/or reduced fertility index), embryo-fetal toxicity and embryofetal developmental (decreased fetal body weight, fetal malformations or variations and / or pre- and post-implantation loss). A NOAEL has yet to be determined. There is a substantiated risk	subjects.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	for adverse effects on embryofetal development and impacts on female fertility.	
Pancreatic	A male rat-specific pancreatic change (islet cell fibrosis / fibroplasias and peri-islet haemorrhage, pigmented macrophages and inflammation) was observed at a dose of 30 mg/kg/day in the 4 week study only. No effects were observed in the 3 month toxicology studies. Following the 3 week off-dose period, these changes were decreased in incidence and/or severity. An unrelated pancreatic lesion (acinar cell apoptosis, vacuolation and/or degranulation) was present in female dogs given 3 mg/kg/day.	ICF includes the risk of pancreatic effects. Protocol includes laboratory assessments (glucose -serum and urine, insulin and 1,5-Anhydroglucitol (1,5-AG), c-petide, Hemoglobin A1c (HbA1c), amylase, lipase) as appropriate and monitoring for signs of gastric distress, abdominal pain, and clinical signs of malabsorption. Protocol also includes dose stopping/modifications criteria for the management of hypo/hyperglycemia.
Liver/Gallbladder	Non-adverse liver changes were observed in preclinical toxicology studies including increases in bilirubin levels and transient increases in AST in rats. Hepatocellular necrosis was observed in a single rat at a non-tolerated dose (30 mg/kg/day). 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. ~~Non-adverse changes observed in the 28 day toxicology studies include:~~ ~~Dog: increased gall bladder vacuolation and decreased cytoplasmic rarefaction in the liver was evident in dogs dosed at ≥1 mg/kg/day for 28 days.~~ ~~Rat – Necrosis (single decedent rat killed on Day 20) and ground glass cytoplasm and/or centrilobular hypertrophy was observed in rats dosed at 30 mg/kg/day; decreased inflammatory cell infiltrate at ≥3 mg/kg/day~~	ICF includes the risk of hepatic/gallbladder effects. Protocol includes hepatic eligibility criteria, laboratory assessments during the study, dose stopping/modifications criteria for the management hepatic events.
Lung effects	Aggregates of foamy macrophages in peribronchiolar 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 finding is	ICF includes the risk of lung effects. Protocol includes pulmonary function assessments as

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	unlikely to affect pulmonary function ~~however the effect of dosing beyond 4 weeks is unknown.~~ No effects were observed in the 3 month toxicology studies. For more information, see the GSK 525762 IB [GlaxoSmithKline Document Number 2011N113741_03].	appropriate (subjects with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage, chest radiation) chest x-ray at baseline and dose stopping/modifications criteria for pneumonitis.
Kidney	Eosinophilic inclusions and/or tubular basophilia were observed in the kidneys of rats in preclinical toxicology studies up to 3 months dosing. ~~Eosinophilic inclusions were observed in the kidneys of female rats dosed with 30 mg/kg/day for 28 days.~~ These changes were considered non-adverse ~~in this study~~.	Protocol includes renal monitoring including urinalysis (assessment for protein) and creatinine.
Effect on Teeth	Effects (disruption of dentin formation) on incisors (teeth that continually grow in rodents) were evident in male rats given ≥10 mg/kg/day GSK525762 and both male and female rats at 30 mg/kg/day in the 13 week study, which resulted in pale and broken teeth during the in-life phase of the study from Week 8. These microscopic effects were lower in severity and incidence after a minimum of 3 week off dose period. No effects were observed in molar teeth (non-growing).	Unlikely to affect adults.
~~**Cytokines**~~	~~*In vitro* incubation of human whole blood with GSK525762 for 24 hours resulted in a time and concentration-dependent induction of Interleukin (IL)-1β. This effect was not observed in whole blood from other species (rat and dog) or in preparations of human peripheral blood mononuclear cells (PBMCs) or neutrophils.~~	~~Protocol includes close monitoring for fever, obtaining cytokine levels (e.g., Tumor Necrosis Factor (TNF)-alpha,IL-1,IL-6, IL-10) in the case of grade 2-4 fever, and dose stopping/modifications criteria for fever.~~.

Section 2. OBJECTIVE, ENDPOINTS, HYPOTHESIS

Rationale for Change: This section was updated to include the MDS population.

Revised Text:

Part 1

Part 1 Objectives		Part 1 Endpoints
Secondary	• To evaluate clinical efficacy following QD administration in subjects with AML, MM, and NHL.	• Objective ~~Overall~~ response rate (ORR), as measured by standard response criteria
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	• Assess objective ~~overall~~ response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.
	~~• To evaluate safety, tolerability, and efficacy following BID administration of GSK525762 in subjects with AML, MM, and NHL~~	~~• AEs, SAEs, DLTs, dose reductions or delays, withdrawals due to toxicities, changes in safety assessments, and ORR (as measured by standard response criteria)~~
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 following QD ~~and/or BID~~ dosing schedules.	• Pharmacogenomic (PGx) study using clinical samples.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in ~~acute myeloid~~ high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort") ~~leukemia (AML)~~.	• For ~~AML~~MDS cohort: Objective response rate (% of subjects achieving Complete Response [CR], Marrow CR, CRp [as per CR but platelet count <100 x 10^9/L], CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR],) per response criteria.
Secondary	• To characterize the PK of GSK525762 in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• To evaluate the exposure response (i.e., PK/PD) relationship between	• PK/PD relationship between GSK525762 exposure markers and safety and efficacy

Part 2 Objectives		Part 2 Endpoints
	GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL.	parameters.
	• To evaluate the safety and tolerability of RP2D of GSK525762 in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	~~• To evaluate the relationship between GSK525762 dose and PD response in 3 disease-specific cohorts of subjects with AML, MM or NHL.~~	~~• Dose related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.~~
	• To determine the clinical activity of GSK525762 in 3 disease-specific cohorts of subjects with ~~AML~~MDS/AML, MM or NHL.	• TTP (Time to Progression) , DOR (Duration of Response), PFS (Progression Free Survival) for MDS/AML, MM and NHL • Overall survival (OS, the time from the treatment start date until death from any cause) for ~~AML~~MDS/AML, MM and NHL.

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • ~~Acute myeloid leukemia~~Myelodysplastic syndrome and transformed MDS: A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with ~~acute leukemia~~ MDS/AML.

Section 3.1. Study Design/Schematic

Rationale for Change: This section was updated to include the AML and MDS populations. Additionally the collection of blood samples intended for the analysis of mRNA and cytokines for BET116183 study has ceased. These samples were being collected as part of a collaboration with Epinova for biomarker studies to assess target engagement after BET inhibitor treatment. Similar analysis was being done in the BET115521 study (solid tumor). We were informed that sufficient data from the BET115521 study had been generated to make future decisions to support clinical expansion with this drug. Therefore, no additional samples from the BET116183 study would need to be collected and/or analyzed.

Revised Text:

Second Paragraph onwards

This is an open-label repeat dose, multicenter, 2-part study to determine the MTD in subjects with ~~acute myeloid leukemia~~ myeloid malignancies, multiple myeloma, and non-Hodgkin's Lymphoma, and the recommended Phase 2 dose (RP2D) for GSK525762 given once-daily (QD) orally. Safety, tolerability, PK, and efficacy ~~will~~ may also be

explored in a limited number of subjects treated twice daily (BID). Both parts will be conducted in adult subjects with relapsed and/or refractory ~~acute myeloid leukemia~~ myeloid malignancies, multiple myeloma, and non-Hodgkin's lymphomas.

In both Parts 1 and 2, all subjects will be evaluated for systemic BET inhibitory effects in blood (whole blood transcriptional). A subset of subjects in Part 1 will also be evaluated for plasma cytokine profiling~~. and plasma cytokine profiling~~). In addition, pre-treatment and post-treatment bone marrow, whole blood for PBMC isolation or lymph node samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Section 3.2.1. Part 1: Dose Escalation

Rationale for Change: This section was updated to include the AML and MDS populations.

Revised Text:

Fifth Paragraph first sentence

Due to the potentially different MTD in subjects with ~~AML~~ myeloid neoplasms, NHL, and MM (Section 1.3.3), each dose escalation step will be evaluated separately for the three disease types.

Section 3.2.1.1 Dose Escalation and Schedule

Rationale for Change: The cardiac safety monitoring was removed to avoid duplication as all cardiac assessments can be found in the T&E table.

Revised Text:

Second Paragraph Onwards

~~In Part 1, subjects will follow the dose schedule outlined in Table 5. Alternative dosing regimens and/or schedule may be implemented based on emerging PK and safety data.~~

Extensive monitoring for cardiac safety signals will be performed including triplicate 12-lead ECG and ~~24-hour Holter monitoring~~ on the days indicated in the Time and Events Table .~~Table 5~~

~~Table 24 Three Week DLT monitoring: Dosing Schedule and Cardiac Monitoring (QD and BID)~~

~~Dose~~	~~Day 1~~	~~Day 2~~	~~Day 3~~	~~Day 4~~	~~Day 5~~	~~Day 6~~	~~Day 7~~
~~Week 1~~	~~Dose ECG,~~	~~Dose ECG,~~	~~Dose~~	~~Dose~~	~~Dose ECG, Holter~~	~~Dose ECG~~	~~Dose~~
~~Week 2~~	~~Dose ECG~~	~~Dose~~	~~Dose~~	~~Dose ECG~~	~~Dose~~	~~Dose ECG~~	~~Dose ECG,~~
~~Week 3~~	~~Dose ECG~~	~~Dose~~	~~Dose~~	~~Dose ECG~~	~~Dose~~	~~Dose~~	~~Dose~~
~~Please refer to Time and Events Tables Section 5 for more details~~							

Section 3.2.1.3. 3 + 3 Dose Escalation in Part 1

Rationale for Change: This section was updated to include the AML and MDS populations.

Revised Text:

First Paragraph first sentence

Due to the potentially different MTDs in ~~acute leukemia~~ myeloid neoplasms, MM, and NHL, dose escalation will be evaluated in three separate cohorts divided by disease subtype

Section 3.2.1.5. BID dosing

Rationale for Change: This section was updated to allow a BID cohort to open simultaneously regardless of disease type.

Revised Text:

First paragraph second sentence

~~Initially, only one cohort per disease type is planned, though lower doses may be explored based on toxicity observed after the initial few subjects~~.

Section 3.2.1.6. Intra-Subject Dose Escalation

Rationale for Change: Minor clarification.

Revised Text:

Second paragraph first sentence

Subjects approved for intra-subject dose escalation ~~will~~ may 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

Section 3.2.2. Dose Limiting Toxicity (DLT)

Rationale for Change: This section was updated as the DLT window for this study is 3 weeks, so a 6-week myelosuppression criterion is outside the window for DLT observation.

Revised Text:

Events under Prolonged myelosupression for leukemia

- ~~For leukemia:~~
- ~~At 6 weeks, bone marrow biopsy that demonstrates no evidence of residual leukemia AND EITHER:~~
- ~~Marrow aplasia, defined as <5% cellularity by trephine biopsy, OR~~
- ~~Peripheral cytopenias, defined as absolute neutrophil count (ANC) ≤500/uL and/or platelets ≤25,000/uL (if baseline ANC and/or platelets were >500/uL and/or 25,000/uL, respectively)~~

Section 3.2.4. Part 2: Disease Specific Expansion Cohorts

Rationale for Change: This section was updated to include the MDS population.

Revised Text:

Up to 32 subjects (per cohort) with ~~acute myeloid leukemia~~ myelodysplastic syndrome or non-Hodgkin's lymphoma (non-DHL), and up to 37 subjects with multiple myeloma, may be enrolled in an expansion cohort at the RP2D. These will be conducted 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~~,~~ or 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.

At least 10 subjects with tumor that is positive for rearrangement or overexpression of MYC plus BCL-2 and/or BCL-6 genes (double- and triple-hit lymphoma) will be enrolled. These subjects will be evaluated separately for efficacy, but hypotheses will not be tested. See Section 11.1 for description of the plan for analysis of the NHL cohorts.

Plasma samples for PK evaluation will be collected in all subjects. ~~Plasma samples and other clinical samples (e.g. lymph node or bone marrow biopsies) will be collected pre- and post- study drug treatment as defined in the Time and Events Table in Section 5 for the PD evaluation.~~

The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored with the constraint of both Type I and Type II error rates. Clinical response

will be defined per standard evaluation criteria (see Appendix 6, Appendix 7 and Appendix 8).

For each cohort, an interim analysis will be conducted after efficacy data at a dose level based on RP2D are available on a minimum of 10 subjects in the ~~AML~~MDS and NHL (non-DHL) cohorts and a minimum of 13 subjects in the MM cohort. The number of subjects may be increased up to a total of 32 for the ~~AML~~MDS and NHL (non-DHL) cohorts and up to a total of 37 for the MM cohort depending on the results observed; a separate decision will be made for each disease cohort. The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility, are indicated in Figure 4 and Figure 5. The methodology is based on the predictive probability of success (response rate > historical response rate) if enrolment continues to 32 subjects for ~~AML~~MDS and NHL (non-DHL) and 37 subjects for MM [Lee, 2008]. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

For ~~AML~~MDS and NHL (non-DHL) cohorts: Ten subjects will be enrolled in each cohort at the RP2D to examine safety and efficacy. If zero responses are observed in either cohort, then that cohort will be terminated and no further subjects will be enrolled due to futility. A single response in a cohort will be adequate to pursue further enrolment. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4. A maximum of 32 subjects per cohort will be enrolled at the RP2D. All available data will be considered in making enrolment decisions.

Figure 4 Diagram of Stopping Rules for ~~AML~~MDS and NHL (non-DHL) Cohort Expansion

Section 4.2.1. Inclusion Criteria

Rationale for Change: This section was updated to include criteria specific for the MDS population

Revised Text:

3~~. In Part 1 and Part 2, s~~Subjects must have a diagnosis of relapsed or refractory Acute Myeloid Leukemia (AML), Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).

- (Part 1 only) Subjects with AML, are eligible if they
  - have relapsed and/or refractory disease, *OR*
  - are ≥65 years of age and not candidates for or have refused standard chemotherapy.
- (Part 2 only): Subjects with MDS/AML are eligible if they:
  - Have high-risk (defined as intermediate [INT]-2 or higher by International Prognostic Scoring System [IPSS] criteria [Greenberg], or high/very high by IPSS-Revised [IPSS-R] criteria [Greenberg]) MDS that has relapsed after or been refractory to prior therapy with hypomethylating agent, *OR*

- Have AML that has arisen ~~progressed~~ from an antecedent MDS (irrespective of IPSS/IPSS-R score)
  - Subjects must have progressed despite, or failed to respond to, prior therapy with hypomethylating agent, *AND*
  - At least one bone marrow biopsy obtained within 28 days of first dose of GSK525762 must demonstrate a marrow blast percentage of no more than 30%

    Note: If marrow blasts exceed 30% on any biopsy within 28 days of first dose, enrolment will only be permitted after discussion with the medical monitor

- (Part 1 and Part 2): Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination
- (Part 1 and Part 2): Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20)

9. Males subjects with a female partner of childbearing potential or who is pregnant must agree to use one of the methods of contraception specified in Section 9.1. 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, male subjects whose partners are or become pregnant must use/continue to use condoms until 16 weeks after last dose of study medication.

Table 4 Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Hemoglobin (only for myeloma and lymphoma)	≥8.0 g/dL
Coagulation assays (prothrombin time/ international normalized ratio [PT/INR] and activated partial thromboplastin time [aPTT][1]	≤1.2~~5~~ X upper limit of normal (ULN)

Section 4.2.2. Exclusion Criteria

Rationale for Change: Minor correction

Revised Text

4. Evidence of severe or~~f~~ uncontrolled infection.

Section 5 Time and Events Table

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 holter monitoring, revised ECG schedule, and removal of blood sample collections for cytokines and mRNA.

Revised Text

Table 5 Time and Events: Part 1

																											Starting from W10		
Procedure (Notes)		**SCR**	**Week 1**							**Week 2**							**W3**		**W4**	**W5**	**W6**	**W7**	**W10**	**q3w**	**q6w**	**EOT**			
			D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**~~D4~~**	**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[a]		X																											
Disease characteristics		X																											
Cardiology eval.		X																											
Prior therapy		X																											
Register subject		X																											
TREATMENT PHASE																													
Study Drug: For QD or BID details see Table 8 and Table 9																													
Administer study drug (Administer about same time of day. No food or antacids 1h before and 2h after.)			Daily																										
Review subject diary (Not required when dosed in clinic.)										X							X		X	X		X	X	X				
Safety																													
Pregnancy test/ testosterone [b]		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			
Vital Signs [c]/Pain Assessment		X	X				X			X							X		X	X		X	X	X		X		
Height and weight (Height at Scr only)		X	X				X			X							X		X	X		X	X	X		X		
Chest x-ray		X																											
Pulmonary function test [d]		X																											
Adverse events		AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.4)																											
Concomitant medications		continuous from signing of informed consent																											

																								Starting from W10		
Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**	**W5**	**W6**	**W7**	**W10**	**q3w**	**q6w**	**EOT**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**~~D4~~**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Laboratory assessments: For details please see Table 6																										
Tests	X	X	X			X			X					X		X		X	X	X	X	X	X	X	X
Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**	**W5**	**W6**	**W7**	**W10**	**q3W**	**q6w**	**EOT**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D4**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Cardiac Monitoring																										
ECHO (Within 35 days of first dose)	X													X					X			X		X	X
12-lead ECGs [e]	X	O	~~O~~			O			X			~~X~~		~~X~~	O	~~X~~	~~X~~	X	X		O	X	X		X
~~Holter monitoring (At least 24 h, on dosing days start predose)~~	~~X~~					~~X~~												~~X~~							
Pharmacokinetics (PK) and Pharmacodynamics (PD): For details please see Table 8 and Table 9																										
PK Blood samples for GSK525762		X	X [k]	X [h]		X						~~X~~		X	X	X [k]					X			X[f]	
~~PD Blood samples for biomarkers (mRNA)~~		~~X~~	~~X~~												~~X~~											~~X~~
~~Blood samples for plasma cytokines~~		~~X~~	~~X~~												~~X~~	~~X~~										
PD Tumor Sample	X [g]			X [h]																						
Translational Research [i]																										
Pharmacogenomics (PGx) sample		X																								
~~Blood samples for Translational Medicine study~~ Blood sample for exploratory translational research	X	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression or when patient is discontinued from study/end of treatment[j] ~~Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression~~																								
Tumor biopsy at progression																										X
FOLLOW-UP PHASE																										

																										Starting from W10		
Procedure (Notes)	**SCR**	**Week 1**							**Week 2**							**W3**		**W4**	**W5**	**W6**	**W7**	**W10**	**q3w**	**q6w**	**EOT**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D1**	~~**D4**~~	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
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 (as described in Table 7). 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.																												

a. Medical, surgical, alcohol, tobacco and treatment history, including date (month and year) of first diagnosis, histology, and current sites of disease, will be taken as part of the medical history and disease status.

a. 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. Pregnancy testing not required for females of non-childbearing potential as defined in Section 4.2.1.

b. Vital signs include systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate and temperature

c. Pulmonary tests as appropriate: subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation

d. 12-lead ECGs : Screening ECGs within 14 days of first dose. Triplicate ECGs prior to dosing. For timing of ECGs on "O" days, see Table 8 for QD and Table 9 for BID. Otherwise, triplicate ECGs at approximately same time of day, and prior to ~~dose on dosing days~~dosing. If QTcF increase >30msec, ECGs performed daily through W2.

e. For subjects on study longer than 12 weeks, collect a pre-dose PK sample q6W. Reduce to q12w after 12 months on study.

f. Pretreatment biopsy for PD tumor sample must be performed within 14 days of first dose.

g. During 3+3 dose escalation, PD tumor sample collection will be mandatory unless infeasible to collect, and approval is obtained by the GSK medical monitor. Subjects with MM will have bone marrow aspirates collected on W1 D3 within 3-6 hours after the dose. Subjects with AML will have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on W1 D3 within 3-6 hours after the dose. Subjects with NHL will have a tissue biopsy (lymph node or other affected organ/region) collected on W1D3 within 3-6 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as the hours post-dose for collection remain as described. A PK sample will need to be obtained within 1 hour of the tissue sampling. ~~Details described in the SPM~~ S~~s~~ee Table 7 disease specific assessments for details).

h. Refer to Section 6.6 for details on Translational Research and Appendix 5 for details on PGx Research.

i. Refer to Table 7 Disease Specific Assessments for timepoints.

j. Assessment only completed for Part 1 QD subjects

Abbreviations: ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PGx=Pharmacogenetics; COPD=Chronic obstructive pulmonary disease; SPM=Study Procedures Manual; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 6 Time and Events: Part 1 Laboratory Assessments

														q3w and q6w Initiated from Wk 10		
NB: ~~On dosing days,~~ Ccollect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 24h of first dose.		**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Assessment	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Troponin, NT pro-BNP	~~Troponin: W1D1 &W1D2: local lab sample collect 3X/per day; central troponin lab sample 1X/per day~~. Troponin: ~~All other timepoints and unscheduled troponin, c~~Collect 2 samples: ~~1 for local, 1 for central lab~~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		X	X
Hematology	Increase frequency as medically indicated	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
Creatine phosphor-kinase~~, CK-MB~~	~~CK-MB at predose and 12-18 h post dose take on W1D1, and as clinically appropriate.~~	X	X	X	X	X	X	X	X				X		X	X
CK-MB	CK-MB at predose and 12-18 h post dose take on W1D1, and as clinically appropriate.	X	X	X	X	X	X	X	X				X		X	X
Liver chemistry		X	X	X	X	X	X	X	X			X	X	X		X
LDH		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; performed at baseline and repeated if necessary during the study.	X														
HbA1c	Performed at baseline and repeated if necessary during the study.	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
Pregnancy test,	Serum pregnancy test within 7 days of first dose; urine or	X	X						X				X	X		X

														q3w and q6w Initiated from Wk 10		
NB: ~~On dosing days,~~ Ccollect blood samples prior to dosing. W1D1 samples not needed if SCR sample collected within 24h of first dose.		**SCR**	**W1**			**W2**		**W3**	**W4**	**W5**	**W6**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Assessment	**Notes**		**D1**	**D2**	**D5**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
females	serum test thereafter															
Testosterone, males	Complete and free testosterone at SCR; free testosterone thereafter	X	X						X				X	X		X
~~Safety Cytokines~~		~~X~~	*~~as clinically appropriate following fever~~*													
HBsAg, HepC antibody	If hepatitis C antibody positive, perform third generation immunoassay (if test is available) on same sample to confirm results, or alternatively, use HCV RNA test (either quantitative or qualitative).	X														

Abbreviations: 1,5 AG=1,5-Anhydroglucitol, NT-pro BNP=N-ternimal prohormone B-type Natriuretic Peptide; C=cycle; CK-MB=Creatine Kinase – MB (isoform); LDH=Lactate dehydrogenase; TSH=Thyroid stimulating hormone; HBsAg = Hepatitis B surface Antigen; HepC=Hepatitis C; HCV Hepatitis C Virus; RNA=Ribonucleic acid; D=day; EOT=End of Treatment Visit; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; W=week

Table 7 Disease Specific Assessments: Part 1 and 2

Multiple Myeloma (MM) Assessments														
												q3w and q6w Initiated from Wk 10		
		SCR	**~~Week 1~~**			**~~Week 2~~**		**~~W3~~**	**W4**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
Procedure	**Notes**		**~~D1~~**	**~~D2~~**	**~~D5~~**	**~~D1~~**	**~~D6~~**	**~~D1~~**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease Characteristics	Including cytogenetics as appropriate	X												
Total Protein, CRP, β2 microglobulin		X							X	X	X	X		
SPEP, FLC assay, quantitative immunoglobulins (IgG, IgA, IgM)	Not required for subjects with non-secretory MM;	X							X	X	X		X	
UPEP	Only required if paraprotein is present in urine	X							X		X		X	
Extramedullary Disease Assessment	Only required for MM with extramedullary disease	X							X		X	X		
Blood sample for exploratory translational research	A blood sample for exploratory translational research should be collected at EOT and/or date of progression and at timepoints as indicated	X							X		X			X
BM aspirate and biopsy	Required for non-secretory MM, or as appropriate for other subjects	X									X			
Response assessment	Every 6 weeks after wk4; Response criteria in Appendix 6								X		X		X	X

Lymphoma Assessments															
													q3w and q6w Initiated from Wk 10		
		SCR	**~~Week 1~~**			**~~Week 2~~**		**W4**		**W7**	**W10**	**q3W**	**q6W**	**q12W**	**EOT**
Procedure	**Notes**		**~~D1~~**	**~~D2~~**	**~~D5~~**	**~~D1~~**	**~~D6~~**	**~~D1~~**	**~~D4~~**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history[a] immunophenotypes, cytogenetics and prognostic markers [b]		X													
β2-microglobulin		X						X							
B Symptoms		X						X		X	X	X			
Lymph node and organ exam		X						X		X	X	X			
Bone marrow/tissue biopsy [c]		X								X					
Blood sample for exploratory translational research		X								X			Wk 16, wk 24, then q12wks		X[g]
CT Scan [d]		X								X			Wk 16, wk 24, then q12wks		X
PET Scan [d, e]		X								X					
Response evaluation [f]										X			Wk 16, wk 24, then q12wks		X

a. Including date of first diagnosis, disease stage, and complete history of diagnostic results and therapies.
b. Examples of prognostic markers may include: ALC, FLIPI-1, FLIPI-2 (includes ß2-microglobulin), FcR gamma 3A.
c. A sample will be required at screening only if clinically appropriate for the lymphoma subtype AND an appropriate previous sample is available. A follow-up bone marrow biopsy will be performed no later than 8 weeks following CR (as judged by investigator) in accordance with the response guidelines (Appendix 7) if a subject had involvement of the BM at the start of the study.
d. Baseline/Screening Computerized Tomography (CT) and PET scans may be obtained within 35 days of first dose Follow-up CT scans at week 7 wk 16, wk 24 and then every 12 weeks.
e. PET or PET/CT scan if clinically indicated (e.g., confirmation of CR for Diffuse large B-cell lymphoma).
f. Evaluation of response for lymphoma at week 7, week 16, week 24 and then every 12 weeks. Assessments are described in Appendix 7 : Response Criteria for Lymphoma.
g. A blood sample for exploratory translational research should be collected at EOT and/or date of progression

MDS and Leukaemia Assessments															
													q3w and q6w Initiated from Wk 10		
Procedure	**Notes**	**SCR**	**~~Week 1~~**			**Week 2**		**W3**	**Wk4**	**W5**	**W7**	**W10**	**q3W**	**q6W**	**EOT**
			~~D1~~	**~~D2~~**	**~~D5~~**	**D1**	**D6**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Disease characteristics, including history, immuno-phenotype, cytogenetics and molecular studies as appropriate and History [a]		X													
Lymph node and spleen assessment	Only as appropriate	X							X		X	X	X		X
Response Assessment[b]		X							X			X		X	X
Blood sample for exploratory translational research		X							X			X		X	X[f]
Transfusion History [c]		X				X		X	X	X	X	X	X		
Bleeding History		X				X		X	X	X	X	X	X		
Hematology [d, e]		X				X		X	X	X	X	X	X		

A. Including date of diagnosis and complete history of diagnostic results and therapies.

B. Bone marrow biopsy/aspirate should be obtained for response assessment at the timepoints indicated. Subjects without marrow involvement may be assessed by other means (e.g., medical photography for leukemia cutis) after discussion with the medical monitor, provided that the same method is used for all assessments of that subject. Response criteria for AML are described in Appendix 8; response criteria for MDS are described in Appendix 9. For subjects with AML, ~~A~~a peripheral blood sample can be taken at baseline if a bone marrow sample cannot be collected. Subjects should be off cytokine support (granulocyte colony-stimulating factor [GCSF] or granulocyte-macrophage colony-stimulating factor [GMCSF]) for a minimum of 7 days before obtaining bone marrow to document remission.

a. Platelet and blood transfusions to be assessed at designated visits and summarized per unit on a weekly cumulative basis.

b. Hematology includes complete blood count (CBC) with white blood cell count differential (including neutrophils, eosinophils, basophils, lymphocytes and monocytes) and platelets; hemoglobin, hematocrit, red blood cell count. A CBC with differential and platelets, hemoglobin and hematocrit may be performed daily during in-patient care; once subject is discharged, assessments to continue weekly until disease response assessment. This is collected at baseline/screening;, ~~daily during chemotherapy treatment~~ then weekly. Platelet count achievement of 20,000/mL for 3 days is entered into the eCRF and the date of platelet count achievement of 100,000/mL is entered into the eCRF.

c. A blood cell smear to measure peripheral blood blasts.

d. A blood sample for exploratory translational research should be collected at EOT and/or date of progression

Table 8 Time and Events: Part 1 (QD cohorts) Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling

Procedure / time after dose	W1D1									W1D2		W1D5		
	pre dose	0h	15 min ± 5m	30 min ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h	12h ±2h	24h ±1h	0h	0h	~~30 min ±0~~ 2h ±15m	~~3h ±30m~~ 4h ±15m
Dose		X									X	X		
12-lead ECG [a]	X		~~X~~	~~X~~	~~X~~	X	X						X	X
PK sample for GSK525762 [b]	X		X	X	X	X	X	X	X	X [b]			X	X
~~Blood sample for biomarkers (mRNA)~~	~~X~~[c]					~~X~~	~~X~~	~~X~~	~~X~~	~~X~~				
~~Plasma cytokine sample~~	~~X~~[c]					~~X~~	~~X~~	~~X~~	~~X~~	~~X~~				

Procedure / time after dose	W2D4	W2D6	W2D7 (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed)									W3D1		W7D1 ±4 days [c ~~d~~]			
	pre dose	pre dose	pre dose	0h	15 min ± 5m	30 min ±5m	1h ±10m	2h ±15m	4h ±15m	8h ±1h	12h ±2h	24h ±1h	0h	pre dose	0h	0.5-2h	4 - 8h
Dose				X									X		X		
12-lead ECG [a]	~~X~~	~~X~~	X		~~X~~	~~X~~	~~X~~	X	X	~~X~~	~~X~~	~~X~~		X		X	X
PK sample for GSK525762	X	X	X		X	X	X	X	X	X	X	X		X		X	X
~~Blood sample for biomarkers (mRNA)~~			~~X~~														
~~Plasma cytokine sample~~			~~X~~					~~X~~	~~X~~	~~X~~	~~X~~	~~X~~					

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

~~a.~~ The ECGs are taken in triplicate, 5 minutes apart and within 10 min prior to PK draw. ~~For timepoint with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.~~

b. Sample to be obtained before dosing on Week 1, Day 2.

~~c. May be collected within 14 days prior to first dose~~

~~d~~ c. If dose was escalated, the W4D1 visit may be performed +4 to +7 days.

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

Table 9 Time and Events: Part 1 (BID Cohorts) Serial Electrocardiograms, Pharmacokinetics and Biomarker Sampling

	W1D1							W1D5				W2D4		W2D6		W2D7						W7D1 ±4 days [e]				
Timepoint; Hours after AM dose	Pre-Dose	0h	30 min ±5m	2h ~~±15m~~ ~~1h~~ ~~±10m~~	4h ±15m	8h ±1h	12h (0h)	AM	~~30 min ±5m~~ 2h ±15m	4h ±15m ~~3h~~ ±15m	PM	pre AM dose	AM & PM	pre AM dose	AM & PM	Pre-Dose	0h	~~30 min ±5m~~	~~1h ±10m~~ 2h ±15m	4h ±15m	12h (0h)	pre dose	0h	0.5-2h	4 - 8h	12h
Dose		X					X	X			X		XX		XX		X					X		X			X
12-lead ECG [a]	X		~~X~~	X	X	~~X~~			X	X		~~X~~		~~X~~		X		~~X~~	X	X		X		X	X	
PK GSK525762[b]	X		X	X	X	X			X	X		X		X		X		X	X	X		X		X	X	
~~Blood sample for biomarkers (mRNA)~~	~~X~~[d]				~~X~~	~~X~~										~~X~~				~~X~~						
~~Plasma cytokine sample~~	~~X~~[d]				~~X~~	~~X~~										~~X~~				~~X~~						

~~a.~~ The ECGs are taken in triplicate, 5 minutes apart and within 10 minutes prior to PK draw. ~~For time points with a ±5 minute it is acceptable for the first ECG to be out of the minus 5-min window to allow scheduling in this short time frame, as long as PK sample is collected after the last ECG and at least within +5 minutes of the window.~~

b. PK blood sample collected overnight may be kept refrigerated at 4°C in the event the laboratory is closed.

~~c. Blood sample for PD biomarker.~~

~~d. May be collected within 14 days prior to first dose~~

~~e~~c. If dose was escalated, the W4D1 visit may be performed +4 to +7 days.

APP=acute phase protein; ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose;

Table 10 Time and Events: Part 2 Expansion Cohort

Part 2 Procedure (Notes)		**SCR**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
			W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
			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[a]		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.)			Continuous daily dosing (unless safety, PK or PD data necessitate a different dosing schedule), see Section 3.2.4						X		
Review compliance (Not required when dosed in clinic.)				X	X	X	X	X	X	X	X
Pregnancy test/testosterone[b]		X	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
Vital Signs [c]/Pain Assessment		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			AEs & SAEs continuous from first dose; SAEs (If study related) from signing of informed consent (see Section 6.7.4~~6.7.5~~)								
Concomitant medications			continuous from signing of informed consent								
Laboratory assessments: For details please see Table 11											
Tests		X	X	X	X	X	X	X	X	X	X
Cardiac Monitoring											
ECHO (Within 35 days of first dose).		X				X	X	X		X	X
12-lead ECGs [d]		X	X	X	X	X	X	X	X		X
~~Holter monitoring (Min 24h, on dosing days start predose)~~		~~X~~				~~X~~					

Part 2 Procedure (Notes)		**SCR**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
			W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
			D1	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
PK and Blood PD											
PK Blood samples	Three samples to be collected each sampling day: During the first 3 weeks collect a predose (within 60 minutes prior to dose), a single draw between 0.5 to 2 h postdose, and a single draw between 4-8h postdose (fasting requirements apply). Thereafter W7 and Q6W only a predose and 0.5 hour post dose sample are collected		X		X[f]		X			X	
Translational Research											
PGx sample			X								
Tumor sample (e.g., bone marrow biopsy, lymph node biopsy, or peripheral blood collection [only for subjects with circulating disease])		X[e]			X[f]						X[g]
Blood samples for exploratory translational research		X			X[f]	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression or when patient is discontinued from study/end of treatment					

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 (as described in Table7). 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.

a. Medical, surgical, alcohol, tobacco and treatment history, including date (month and year) of first diagnosis, histology, and current sites of disease, will be taken as part of the medical history and disease status
b. 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. Pregnancy testing not required for females of non-childbearing potential as defined in Section 4.2.1.
c. Vital signs include SBP, DBP, heart rate, respiratory rate and temperature
d. Screening ECGs within 35 days of first dose. ECGs prior to dosing. If QTcF increase >30msec, ECGs should be repeated every 2-3 days until the QTcF is within 30 msec of baseline.
e. Pretreatment biopsy for tumor sample must be performed within 14 days of first dose.
f. Subjects with MM or should have bone marrow aspirates collected on W3D1 within3-6 hours after the dose. Subjects with AML should have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on W3 D1 within 3-6 hours after the dose. Subjects with NHL will have a

Part 2 Procedure (Notes)	**SCR**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
		W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
		D1	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
lymph node biopsy collected on W3D1 within 3-6 hours after the dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as **the hours post-dose for collection remain as described**. **A PK sample will need to be obtained within 1 hour of the tissue sampling**. ~~Details described in the SPM~~ See See Table 7 disease specific assessments for details). g. Tumor samples for translational research are requested at end of treatment for subjects with progressive disease. Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; ECHO=echocardiogram; ECG=electrocardiogram; QTcF=QT duration corrected for heart rate by Fridericia's formula; PD=Pharmacodynamics; PK=Pharmacokinetics; PGx=Pharmacogenetics; D=day; EOT=End-of-Treatment; q3W=every 3 weeks; q6W=every 6 weeks; SCR=Screening; Wk=week										

Table 11 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 24h of first dose. (Notes)**	**SCR**	**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles q3w and q6w Initiated from Wk 10**		**EOT**
		W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
		D1	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
~~Safety Cytokines~~	~~X~~	~~as clinically appropriate *following fever*~~								

a. Assess platelet count as clinically appropriate but at minimum twice weekly for weeks 1 and 2; weekly for weeks 3 to 8.
Abbreviations: NT-proBNP=N-terminal pro–B-type Natriuretic Peptide; 1,5 AG=1,5-Anhydroglucitol; Hb=Hemoglobin; TSH=Thyroid Stimulating Hormone; HBsAg = Hepatitis B surface Antigen HepC=Hepatitis C; D=day; EOT=End of Treatment Visit; q4W=Every 4 weeks; q8W=every 8 weeks; q12W=every 12 weeks; SCR=Screening Visit; W=week

Section 6.1.2 Visit Windows

Rationale for Change: This section was updated to be consistent with the T&E table

Revised Text

Visits between Week 4 through Week 9 (inclusive): Clinic visits can be scheduled ~~±3~~ 4 days.

Section 6.2 Baseline Assessment

Rationale for Change: This section was updated to include the MDS population

Revised Text

Subjects diagnosed with refractory hematological malignancy (MM, lymphoma, MDS and/or ~~acute myeloid leukemia~~ AML), will be assessed at baseline for general disease characteristics

Section 6.2.2 Baseline assessment for Subjects with MDS/AML

Rationale for Change: This section was updated to include the MDS population

Revised Text

- WHO classification
- FAB classification (AML only)
- Cytogenetics
- IPSS/IPSS-R classification (MDS only)

Section 6.3.5 Electrocardiograms

Rationale for Change: After an internal QTc analysis and evaluation of cardiac safety data collected from all subjects up to the 120 mg QD cohort available by 10Jun2016, 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

~~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.~~

~~**Section 6.3.6 Holter Monitoring**~~

~~Digital Holter ECG data will be obtained from a 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 Section 5 Time and Events Tables and should be obtained prior to phlebotomy and vital sign time points.~~

~~Analysis of intervals and morphology from the continuous digital ECG data may 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 were collected. The final intervals and morphology analyses entered into the database will be those generated by the central ECG laboratory.~~

Section 6.3.6 Clinical Laboratory Assessments

Rationale for Change: This section was updated as the processing and handling of all samples is found in the central lab manual.

Revised Text

All protocol required safety laboratory assessments, as defined in Section 5, are performed at the institution's local laboratory. All non-safety assessments (e.g., PK samples, biopsy, translational samples) will be assessed by a central laboratory. ~~Please refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.~~

Table 12 Clinical Laboratory Tests

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, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)
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)
HBsAg, HepC antibody
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)
24-hour urine creatinine clearance (if needed)
~~Cytokine Samples~~

Section 6.4.1 Disease Assessment

Rationale for Change: This section was updated to include the MDS population

Revised Text

Response will be assessed as outlined in the Section 5 Time and Events Table 7 Table by the investigator using the appropriate criteria for MM, lymphoma ~~and~~ AML, and MDS, as noted in Appendix 6, Appendix 7 ~~and~~ Appendix 8, and Appendix ~~XXX~~9, respectively.

Section 6.5.1 Blood Sample Collection

Rationale for Change: This section was updated as the processing and handling of all samples is found in the central lab manual.

Revised Text

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

Section 6.6 Translational Research

Rationale for Change: This section was updated to include all myeloid malignancies

Revised Text

Toward that end the successful collection of quality tumor specimens will be critical to furthering our understanding of BET biology and ~~in~~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. In certain settings such as myeloid malignancies ~~leukemia specimens~~, samples may be used to evaluate changes in leukemic stem cell populations or to generate PDX models.

Section 6.6.2. Blood Sample Collection for Exploratory Translational Research

Rationale for Change: The collection of blood samples intended for the analysis of mRNA and cytokines for BET116183 study has ceased. These samples were being collected as part of a collaboration with Epinova for biomarker studies to assess target engagement after BET inhibitor treatment. Similar analysis was being done in the BET115521 study (solid tumor). We were informed that sufficient data from the BET115521 study had been generated to make future decisions to support clinical expansion with this drug. Therefore, no additional samples from the BET116183 study would need to be collected and/or analyzed.

Revised Text

Blood samples collected at time points described below and in the Time and Events tables for PK and PD testing may ~~will~~ be required for all subjects.

- Part 1 &2: At screening, date of bone marrow biopsy (Part 2 only), disease assessment (Table 7) and disease progression for isolating plasma for circulating biomarkers (eg, cfDNA) , PBMCs and neutrophils.
- ~~Part 1 Only: At pre and post dose for treatment related changes in RNA.~~
- ~~Part 1 Only: At pre and post dose for treatment related changes in plasma cytokines.~~

Section 6.6.2.1 deleted

Rationale for Change: This section was deleted as the collection of blood samples intended for the analysis of mRNA and cytokines for BET116183 study has ceased. These samples were being collected as part of a collaboration with Epinova for biomarker studies to assess target engagement after BET inhibitor treatment. Similar analysis was being done in the BET115521 study (solid tumor). We were informed that sufficient data

from the BET115521 study had been generated to make future decisions to support clinical expansion with this drug. Therefore, no additional samples from the BET116183 study would need to be collected and/or analyzed.

~~**Section 6.6.2.1 Plasma for Changes in 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-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 6.6.2.2 deleted

Rationale for Change: This section was deleted as the collection of blood samples intended for the analysis of mRNA and cytokines for BET116183 study has ceased. These samples were being collected as part of a collaboration with Epinova for biomarker studies to assess target engagement after BET inhibitor treatment. Similar analysis was being done in the BET115521 study (solid tumor). We were informed that sufficient data from the BET115521 study had been generated to make future decisions to support clinical expansion with this drug. Therefore, no additional samples from the BET116183 study would need to be collected and/or analyzed

~~**Section 6.6.2.2 Whole Blood for Changes in 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, may also be performed using whole blood mRNA from selected patients.~~

Section 6.7.4 deleted

~~**Section 6.7.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**~~

~~An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded on the Death eCRF form. However, if the underlying disease (i.e., progression) is greater than that which would~~

~~normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.~~

New Section 6.7.4. Time Period and Frequency of Detecting AEs and SAEs

Rationale for Change: Updated to be consistent with current guidelines.

Revised Text:

Third paragraph Last Line

All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.7.6 ~~6.7.7~~.

Table 13 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~~2 Weeks~~	Pregnancy Notification Form	~~2 Weeks~~24 hours	Pregnancy Follow up Form

6.8.1. Time period for collecting pregnancy information

Information from Section 6.8.2 included as part of Section 6.8.1 itself.

Rationale for Change: Updated to be consistent with current guidelines.

Revised Text

Section 6.8.2—Action to be taken if pregnancy occurs

The investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a subject's pregnancy.

~~. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks 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.

Fourth 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 6.7.6 ~~6.7.7.~~

Section 6.8.3 Action to be taken if pregnancy occurs in a female partner of a male study subject

Rationale for Change: Updated to be consistent with current guidelines

Revised Text

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours~~weeks~~ 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.

Section 7.6.1 Dose and Safety Management Guidelines

Rationale for Change: This section was updated to remove fever as originally the fever guidelines were included due to the possibility of a cytokine storm. To date there have been no occurrences pre-clinically or clinically to warrant a need for guidelines.

Revised Text

Table 16 Dose Adjustment/Stopping Safety Criteria

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
Thrombocytopenia	Grade 1 & 2	Continue dosing at same dose level with weekly or more frequent monitoring as necessary
	Grade 3 (platelets <50,000, ≥25,000/mm^3)	After discussion with medical monitor and using sound clinical judgement, continue at same dose or dose reduce to previously cleared dose level. Monitor CBC at least twice a week, or more frequently if clinically indicated.
	Grade 4 (platelets <25,000/mm^3) and/or any grade	For Lymphoma and Multiple Myeloma: Interrupt study medication and monitor CBC every 2-3 days.

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
	accompanied by severe bleeding related to thrombocytopenia	**1.** If platelet counts recover to Grade 2 and are steady for at least 2 CBC measurements at least 3 days apart, or rising, discuss with the medical monitor. Based on clinical judgement, resume treatment at the same or previously cleared lower dose. **2.** Platelet transfusion is allowed based on institutional guidelines. If platelet transfusions are required, hold drug until platelet counts recover to Grade 2, and are steady for at least 2 CBC measurements at least 3 days apart, or rising. Using clinical judgement and after consultation with the medical monitor, consider resuming treatment at same or the previously cleared lower dose. **3.** Discontinue treatment if drug has to be held for >14 days. For Acute Myeloid Leukemia and Myelodysplastic Syndrome - if platelet count <25,000/mm^3 but ≥10,000/mm^3: Use clinical judgement to institute more frequent monitoring as necessary. For Acute Myeloid Leukemia and Myelodysplastic Syndrome - if platelet count <10,000/mm^3 : **1.** Continue treatment and start platelet transfusion as per institutional guidelines. After platelet transfusion, assess platelet level within a couple of hours of transfusion. Institute more frequent monitoring as clinically indicated. **2.** If repeat platelet transfusions are not able to rescue platelet count to ≥10,000/mm^3 (or to ≥20,000/mm^{3}in case of accompanying fever, sepsis, or minor bleeding) in 2 days, then interrupt treatment. If subsequent transfusions are able to increase the platelet count within 14 days of interruption, consider

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		restarting therapy at the same or previously cleared dose after discussing with the medical monitor and approval by GSK medical governance. If transfusions are unable to increase the platelet count within 14 days of interruption, therapy will be discontinued. **3.** Use of adjunctive therapies is permitted. **4.** Use of hydroxyurea is permitted in the setting of increased blast counts in conjunction with decreased platelet counts.
~~Fever [a]~~	~~• Grade 1~~	~~• Continue current dose(s) of study treatment(s) and monitor for change in severity.~~
	~~• Grade 2~~	~~• Consider temporary discontinuation of study medication and monitor for change in severity.~~ ~~• Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea. Assess vital signs.~~ ~~• Collect "Cytokine blood samples" (which include blood sample for TNF-alpha, IL-1,IL-6, IL-10). Collect blood culture and investigate viral infections as applicable.~~ ~~• May consider restarting study treatment at a reduced dose or dose level pre-event based on discussion with GSK Medical monitor~~
	~~• Grade 3-4~~	~~• Temporary discontinuation of study medication and monitor for change in severity~~ ~~• Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea.~~ ~~• Collect "Cytokine blood samples" (which include blood sample for TNF-alpha, IL-1,IL-6, IL-10). Collect blood culture and investigate viral infections as applicable.~~ ~~• May consider restarting study treatment at a~~

Toxicity	Dose Adjustment/ Stopping Criteria	Management Guidelines
		~~reduced dose or dose level pre-event based on discussion with GSK Medical Monitor.~~

~~*Baseline results are defined by the nearest time point prior to first dose. If W1D1 results are available, these are considered the baseline results. If screening occurred within 72h of fit dose, W1D1 samples are not needed and screening data are considered as baseline.~~

Section 8.2 Cautionary Medications

Rationale for Change: This section was updated to include additional criteria for cautionary medications and to clarifyspecific Part 1 requirement.

Revised Text:

Third and fourth paragraph

Aspirin may not be administered at doses that exceed 81 mg per day. Non-steroidal anti-inflammatory agents should avoided except where they provide benefit over other analgesics; if administered, they should be used with caution and consideration should be given to co-administration with proton pump inhibitors.

During Part 1, Antacids should not be consumed for at least 1h before and 2h after administration of GSK525762.

Section 8.2.2 Drugs Potentially Affecting GSK525762 Pharmacokinetics or affected by GSK525762 ~~Pharmacokinetics~~

Rationale for Change: This section updated in response to new pharmacokinetic data.

Revised Text:

In vitro data suggests that GSK525762 is only metabolized by CYP3A4 and thus coadministration of potent inducers and moderate or potent 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 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 is an 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.

~~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. Potential interactions with other Cytochrome P450 metabolized drugs have not been assessed.~~

~~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).~~

Footnote of Table 19

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

Section 8.4 Non-Drug Therapies

Rationale for Change: Minor clarification

Revised Text:

Third paragraph

Herbal products include, but are not limited to:

- St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, ginseng, and marijuana~~.~~

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

Section 9.1.2 Males Subjects

Rationale for Change: This section updated to align with the Inclusion criteria

Revised Text:

- Vasectomy (documentation of azoospermia)

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. Male

subjects whose partners are or become pregnant must use condoms while on study and for 16 weeks after stopping study medication(s).

Section 11.1.2 Part 2, Expansion Cohort

Rationale for Change: After an evaluation of data from the Part 1 AML cohort, the following observations prompted changes to the Part 2 cohort: clinical responses were observed at doses of 60 mg and above,- these responses occurred in subjects whose disease harbored complex karyotype and recurrent mutations in TP53 and in proteins that regulate gene expression, suggesting that these subjects had an antecedent MDS that transformed to AML. Furthermore, most subjects with AML discontinued GSK525762 early in the course of their treatment as a consequence of their underlying AML or disease complications. Responses tended to be delayed (at the four week mark or later, with many requiring more than 10 weeks to manifest). Thus, most subjects were not remaining on study for long enough to achieve benefit. In order to maximize time on-study, Part 2 was updated to enroll subjects with a more slowly-progressing disease that maintained many of the clinical characteristics of the AML responses that were observed in Part 1.

Revised Text:

Primary goals and 5th paragraph

The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with ~~AML~~MDS, MM, and NHL.

- For ~~AML~~MDS, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, ~~CRp, CR~~marrow CR, or PR) of 30% relative to a 10% response rate suggesting no activity. Historically, hypomethylating agent failure has conferred a poor prognosis, with a response rate to second-line therapy of 10% or less (Prebet, 2011). Investigational agents have demonstrated a response rate of approximately 30%, though no effects on overall survival have been reported (Seetharam, 2010). Because of the high unmet medical need of relapsed/refractory MDS, and because no agent to date has exceeded the 30% response rate published above, 30% was chosen as a realistic goal for subjects with MDS.
- For MM, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a sCR, CR, VGPR, or PR) of 20% relative to a 5% response rate suggesting no activity. These values were identified in a recent meta-analysis that suggested that a response rate of 20% or greater in the relapsed/refractory population was highly predictive of clinical success, whereas older agents with limited clinical activity had a negligible response rate (Kortuem, Zidich, Schuster, et al, Clinical Lymphoma, Myeloma and Leukemia 2014).
- For NHL, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, or PR) of 30% relative to a 10% response rate suggesting no activity. These response rates were consistent with

multiple ongoing studies of single agent, targeted therapy in Phase I clinical trials for subjects with relapsed/refractory NHL. For this cohort, double/triple-hit lymphoma subjects will be excluded from initial efficacy analysis and will be evaluated separately.

5th paragraph

For the ~~AML~~MDS and NHL disease cohorts, starting with a cohort of 10 subjects and allowing for a maximum sample size of 32 subjects at the RP2D with stopping guidelines as described in Section 3.2.4, this design will have a Type I Error (α) of 0.034 and 87% power.

Section 11.4 Interim Analysis

Rationale for Change: This section was updated to include the MDS population

Revised Text:

2nd Paragraph

For each disease type in Part 2, after the initial 10 evaluable subjects in the ~~AML~~MDS or ~~and~~ NHL cohorts and initial 13 evaluable subjects in the MM cohort have enrolled at the selected dose regimen for the Expansion Cohort, data will be reviewed for clinical benefit on an ongoing basis and the number of subjects with observed clinical benefit will be compared with the stopping guidelines provided in Section 3.2.4.

Section 11.6.1 Primary Analysis

Rationale for Change: This section was updated to include the MDS population

Revised Text:

Second paragraph

The primary aim of Part 2 is to detect demonstrate a possibly clinically meaningful response rate in each of the disease cohorts separately. Each disease subtype (~~AML~~MDS, MM, and NHL) will be evaluated separately.

Overall response rate definition

Overall Response rate is defined as

- ~~AML~~MDS: The percentage of subjects who achieved CR, ~~CRp, CR~~marrow CR, and PR. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided~~. Response rates of subjects with AML M3 will be summarized separately.~~
- MM: The percentage of subjects who achieved sCR, CR, VGPR, or PR.
- NHL: The percentage of subjects who achieved CR or PR. Response rates of subjects with double/triple-hit lymphoma will be summarised separately.

Section 11.6.2 Secondary Analysis

Rationale for Change: This section was updated to include the MDS population

Revised Text:

Last paragraph

OS along with 95% confidence intervals for leukemia subjects in Part 1, MDS subjects in Part 2, and MM and ~~,~~lymphoma ~~and leukemia~~ subjects treated in Part 1 and Part 2, will be estimated using the Kaplan Meier method if data warrant. OS analysis for AML will exclude subjects with AML subtype M3. NHL will be separately reported based on double/triple hit status. All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis.

Section 13 COUNTRY SPECIFIC

Modifications include an updated protocol synopsis as outlined in Section 15.12~~15.11~~. The protocol amendment 1 may also apply to other countries if specifically requested.

Section 14 References

Rationale for Change: References were added based on updates made throughout the protocol amendment.

Revised Text:

One reference was updated and 8 new references are added

Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006; 8:419-426.

GlaxoSmithKline Document Number 2011N113741_~~03~~05 Version ~~3~~5. GSK525762 Investigator's Brochure. Report Date ~~27~~28-Mar-~~2014~~2016.

Greenberg P, C Cox, MM LeBeau, P Fenaux, P Morel, et al. *Blood* 1997*;*89*(6):*2079-2088

Greenberg PL, H Tuechler, J Schanz, G Sanz, G Garcia-Manero, et al. Blood 2012 120:2454-2465

Jabbour, Garcia-Manero, Batty, Shan, et al. Outcome of Patients with Myelodysplastic Syndrome after Failure of Decitabine Therapy. *Cancer*, 2010; 116(16): 3830-4

Kantarjian H, Garcia-Manero G, O'Brien S, et al. Phase I clinical and pharmacokinetic study of oral sapacitabine in patients with acute leukemia and myelodysplastic syndrome. *J Clin Oncol*. 2010 Jan 10;28(2):285-91. Epub 2009 Nov 23.

Kortuem KM, Zidich K, Schuster SR, Khan ML, Jimenez-Zepeda VH, Mikhael JR, etal. Activity of 129 single-agent drugs in 228 phase I and II clinical trials in multiple myeloma. *Clinical lymphoma, myeloma & leukemia.* 2014;14:284-90 e5.

Prebet T, Gore SD, Esterni B, Gardin C, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Aug 20;29(24):3322–7

Seetharam M, Fan A, Tran M, Xu L, et al. Treatment of Higher Risk Myelodsplastic Syndrome Patients Unresponsive to Hypomethylating Agents with ON 01910.NA *Leukemia Research.* 2012; Jan; 36(1): 98–103.

Sekeres MA and Cutler C. How We Treat Higher-Risk Myelodysplastic Syndromes *Blood*. 2014; Feb 6;123(6):829-36.

Swerdlow, Campo, Pileri, et al. The 2016 revision of the World Health Organization Classification of Lymphoid Neoplasms. *Blood* 2016; 127(20):2375-2390.

Section 15.4 Appendix 4: Dose Adjustment/Stopping Criteria/Supportive Care

Rationale for Change: This section was updated to remove fever as originally the fever guidelines were included due to the possibility of a cytokine storm. To date there have been no occurrences pre-clinically or clinically to warrant a need for guidelines. Additionally in the hematologic malignancy population, fever is routinely associated with infection and treated with antimicrobials and supportive care.

Revised Text:

Fever was deleted

~~**Fever**~~

~~Safety monitoring cytokine blood samples may be collected (based on Section 7.6.1 of the protocol). These samples include (but not limited to) assessments for TNF-alpha, IL-1, IL-6, and IL-10.~~

~~Assess or inquire if the subject is experiencing in combination with fever: swelling, redness, extreme fatigue or nausea.~~

Section 15.8 Appendix 8: Response Criteria for Acute Myeloid Leukaemia

Rationale for Change: Clarified in title that response criteria is specific to the AML population

Revised Text:

Title was updated and title (as subsection) was deleted

Section 15.9 Appendix 9: Response Criteria for Myelodysplastic Syndrome

Rationale for Change: Response Criteria added for Part 2 MDS study population.

Revised Text:

Appendix 9 on response criteria for Myelodysplastic Syndrome newly added

[Cheson, 2006]

Complete remission (CR): Bone marrow ≤5% myeloblasts with normal maturation of all cell lines. Persistent dysplasia may be noted. The subject must have a haemoglobin concentration of ≥11 g/dL, an absolute neutrophil count ≥1 x 10^9/L, a platelet count ≥100 x 10^9/L, and have 0% blasts in the peripheral blood.

Marrow CR: Bone marrow ≤5% myeloblasts and decrease by ≥50% over pretreatment

Partial remission (PR): Bone marrow blasts decreased by ≥50% over pretreatment but still >5%. Cellularity and morphology not relevant

Stable disease: Failure to achieve at least PR, but no evidence of progression for > 8 weeks

Disease progression: For patients with:

- Less than 5% blasts: ≥50% increase in blasts to > 5% blasts
- 5% - 10% blasts: ≥50% increase to >10% blasts
- 10% - 20% blasts: ≥50% increase to >20% blasts
- 20% - 30% blasts: ≥50% increase to >30% blasts

AND

Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets, reduction in haemoglobin by ≥2 g/dL, transfusion dependence

Relapse after CR or PR: At least one of the following: return to pretreatment bone marrow blast percentage, decrement of ≥50% from maximum remission/response levels in granulocytes or platelets, reduction in haemoglobin concentration by ≥1.5 g/dL or transfusion dependence

15.22. Appendix 22: Protocol Changes for Amendment 9 (15-Mar-2018) from the Protocol Amendment 8 (14-FEB-2017)

Where the Amendment Applies

Amendment 9 applies to all study centres.

Summary of the changes with rationale

Amendment 9:

The study population for the NHL cohort in Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL). The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2. Eligibility criteria for all populations were updated (ECOG, cardiac safety). The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile, and BID dosing was removed. Medications affecting QT prolongation were re-categorized from prohibited to cautionary. Liver chemistry monitoring, interruption stopping and follow-up criteria were updated as per latest criteria. Response Criteria for CTCL was added as an Appendix, and a QOL questionnaire (SKINDEX-29) was added. Minor clarifications, formatting and typographical errors were also addressed in this amendment.

Changes are noted below with strikethrough to identify deleted text and underlining to identify new or replacement text.

Overall change: IB has been updated with latest version 2017 throughout the document.

List of specific changes

Title Page

Rationale for Change: change to study staff

Revised Text:

Author (s):

PPD ~~Precision Medicine and Diagnostics, USA~~

PPD (Biology, Epigenetics Management, USA)

PPD ~~Global Clinical Operational Sciences, USA~~

PPD Statistics, Oncology TA Group, USA)

PPD (Biotransformation and Drug Disposition, PTS, UK)

PPD (Cancer Research Epigenetics Management, USA)

PPD (Clinical Pharmacology Modeling & Simulation, USA)

PPD Global Clinical Safety & Pharmacovigilance, USA)

PPD (Global Clinical Operational Sciences, USA)

PPD Precision Medicine and Diagnostics, USA)

PPD Clinical Oncology, USA)

PPD (Pathology, PTS, UK)

PPD ~~EpiNova DPU, UK~~

PPD ~~Global Clinical Safety & Pharmacovigilance, USA~~

PPD (Global Clinical Safety & Pharmacovigilance, USA)

PPD (Global Clinical Operational Sciences, USA)

PPD (Biology, Epigenetics Management, USA)

PPD ~~Statistics, Oncology TA Group, USA~~

PROTOCOL SYNOPSIS

STUDY DESIGN AND DURATION:

Rationale for Change: Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL) given the observed response rate in CTCL.

Revised Text:

This study is divided into 2 parts: Part 1 of the study is a dose escalation phase to select the recommended Part 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after oral administration of GSK525762. Eligible subjects with select relapsed refractory hematological malignancies (acute myeloid leukemia [AML], non-Hodgkin's Lymphoma [NHL] and multiple myeloma [MM]), will be enrolled in once daily (QD) cohorts until a maximum tolerated dose (MTD) is established. Subjects may continue treatment in the study until disease progression, unacceptable toxicity, or withdrawal of consent. ~~Upon determination of the MTD, twice daily (BID) dosing cohorts may be opened to collect additional safety data and evaluate the preliminary efficacy of GSK525762 administered BID.~~ Part 2 will explore clinical activity at the MTD or RP2D; separate expansion cohorts will be planned for myeloid malignancies (high-risk myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML] that has evolved from an antecedent MDS, hereafter referred as the "myeloid cohort"), ~~non-Hodgkin's Lymphoma (NHL, including an exploratory sub-cohort of subjects with myc and B-Cell Leukemia (BCL)2 and/or BCL6 rearrangements/overexpression [double- and triple-hit lymphoma])~~and cutaneous T-cell lymphomas (mycosis fungoides [MF], Sézary syndrome [SS], primary cutaneous anaplastic large cell lymphoma [pcALCL], and large cell transformation of underlying

MF/SS; hereafter referred as the "cutaneous T cell lymphoma [CTCL] cohort").~~., and multiple myeloma (MM).~~

STUDY RATIONALE:

Rationale for Change: Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL) given the observed response rate in CTCL.

Revised Text:

Addition at the end of the paragraph:

Dose escalation initially focused on AML, NHL (without consideration to histologic subtype), and MM, based on preclinical data. Emerging clinical data demonstrated delayed response in AML subjects, many of whom had evidence of antecedent MDS. In the NHL cohort, more robust clinical efficacy was observed in subjects with CTCL compared to other NHL subtypes. As a result of these observations, dose expansion (Part 2) was modified to evaluate MDS and CTCL instead of AML and unselected NHL, respectively.

OBJECTIVES AND ENDPOINTS:

Rationale for Change: The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2. BID dosing was also removed.

Revised Text:

Part 1:

Part 1 Objectives		Part 1 Endpoints
Secondary	• To characterize the Pharmacokinetic (PK) of GSK525762, and relevant metabolites, as applicable, after single- and repeat-dose administration ~~following QD and/or twice daily (BID) dosing schedules~~.	• PK parameters for GSK525762 and relevant metabolites, as applicable, ~~PK parameters~~ following single- and repeat-dose administration of GSK525762, including Area under concentration-time curve (AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2, eff}$), time invariance and accumulation ratio.

Part 1 Objectives		Part 1 Endpoints
	~~• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters following QD and/or BID dosing schedules.~~	~~• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC, following single and repeat-dose oral administration of GSK525762)~~
	~~• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic (PD) response following QD and/or BID dosing schedules.~~	~~• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.~~
	~~• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762~~	~~• Assess objective response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.~~
Exploratory	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters.	• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC, following single and repeat-dose oral administration of GSK525762)
	• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic response.	• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by BRD proteins) in tumor tissue and/or peripheral blood samples.
	• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762	• Assess objective response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.
	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 ~~following QD dosing schedules~~.	• Pharmacogenomic (PGx) study using clinical samples.

Part 2:

Part 2 Objectives	Part 2 Endpoints

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort").	• For MDS cohort: ~~Objective response rate (~~ORR (defined as the percentage~~%~~ of subjects achieving Complete Response [CR], marrow CR, CRp [as per CR but platelet count <100 x 10^9/L], CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR],) per response criteria.
	• ~~To evaluate clinical efficacy after treatment with GSK525762 in multiple myeloma (MM)~~	• ~~For MM: Objective response rate (defined as the percentage of subjects that have achieved a stringent CR [sCR], CR, very good partial response [VGPR], or PR) per response criteria.~~
	• To evaluate clinical efficacy after treatment with GSK525762 in ~~non-Hodgkin's Lymphoma (NHL)~~CTCL	• For ~~NHL~~CTCL: ~~Objective response rate (~~ORR4~~);~~ defined as the percentage ~~%~~ of subjects that have achieved a CR~~,~~ or PR, per global response criteria and the modified severity weighted assessment tool (mSWAT), lasting more than 4 months ~~according to the modified severity weighted assessment tool (mSWAT) defined as the percentage of subjects that have achieved a CR, or PR) per global response criteria, based on the modified severity weighted assessment tool (mSWAT).~~
Secondary	• To evaluate the effect of GSK525762 on disease-related symptoms, as reported by subjects (CTCL cohort only)	• For CTCL: measure the effects of skin disease based on quality of life questionaire~~utilizing~~ Skindex-29 ~~Patient reported outcomes (DEFINE HERE)~~
	• To characterize the PK of GSK525762, and relevant metabolites, as applicable, in ~~3~~ 2 disease-specific cohorts of subjects with MDS/AML, ~~MM or NHL~~or -CTCL after repeat-dose administration.	• Population PK parameters for GSK525762 , and relevant metabolites, as applicable, such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• ~~To evaluate the exposure response (i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in 3 disease-specific cohorts of subjects with MDS/AML, MM or .NHL.~~	• ~~PK/PD rRelationship between GSK525762 exposure markers and safety and efficacy parameters.~~
	• To evaluate the safety and tolerability of RP2D of GSK525762 in ~~3~~ 2 disease-specific cohorts of subjects with MDS/AML, ~~MM~~ or CTCL.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.

Part 2 Objectives		Part 2 Endpoints
	• To determine the clinical activity of GSK525762 in ~~3~~ 2 disease-specific cohorts of subjects with MDS/AML, ~~MM~~ or ~~NHL~~CTCL.	• ~~TTP (Time to Progression) , DOR~~ Duration of response (~~Duration of Response~~DOR, time from onset of response to earlier date of disease progression or death due to any cause) for MDS/AML and CTCL~~,~~ • ~~PFS~~ Progression free survival (~~Progression Free Survival~~PFS, time from the treatment start date to earlier date of disease progression or death due to any cause) for MDS/AML~~, MM~~ and ~~NHL~~ CTCL. • ~~Rate of objective global response with a duration of 4 months or more (ORR4) in CTCL~~ • Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML~~, MM~~, and CTCL~~.~~
	• ~~To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.~~	• ~~Pharmacogenomic (PGx) study using clinical samples.~~
Exploratory	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762.	• Pharmacogenomic (PGx) study using clinical samples.
	• To evaluate the exposure response relationship between GSK525762 and safety/efficacy parameters in 2 disease-specific cohorts of subjects with MDS/AML, or CTCL.	• Relationship between GSK525762 exposure markers and safety and efficacy parameters.

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • Myelodysplastic syndrome and transformed MDS: A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with MDS/AML. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.30, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • ~~Multiple myeloma: A response rate of 20% relative to a 5% response rate suggesting no activity in subjects with multiple myeloma. This will be conducted by testing the null hypothesis that P0≤0.05 versus the alternative that P1≥0.20, assuming the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20.~~ • ~~Non-Hodgkin's lymphoma (non-double hit lymphoma [DHL]):~~CTCL: A response rate, lasting more than 4 months, of 4~~3~~0% relative to a 2~~1~~0% response rate suggesting no activity in subjects with ~~non-Hodgkin's lymphoma~~CTCL. This will be conducted by testing the null hypothesis that P0≤0.2~~1~~0 versus the alternative that P1≥0.4~~3~~0, assuming the maximum response rate for an ineffective drug is 0.2~~1~~0 and the minimum response rate for an effective drug is 0.4~~3~~0. ~~Subjects with DHL will be evaluated separately for efficacy, but no hypothesis testing will be conducted on the DHL cohort.~~

SUBJECT SAMPLE:

Rationale for Change: Total number of subjects updated to reflect changes in study population

Revised Text:

Up to ~~180~~ 138 subjects worldwide

INCLUSION/EXCLUSION CRITERIA:

Rationale for Change: Eligibility criteria for all populations were updated (ECOG, cardiac safety). The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile, and BID dosing was removed. Medications affecting QT prolongation were re-categorized from prohibited to cautionary.

Revised Text:

Inclusion Criteria

Inclusion criterion 3

Subjects must have a diagnosis of one of the following hematologic malignancies, which has relapsed or been refractory to treatment as follows-:~~Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).~~

Inclusion criterion 3 Bullet 3 onwards

- (Part 1~~ and Part 2~~): Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination
- (Part 1 ~~and Part 2~~only): Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20)
- (Part 2 only): Subjects will be eligible for enrolment into the CTCL cohort if they:
    - Have histologically- or cytology-proven diagnosis of CTCL (MF, SS, pcALCL, or large cell transformation of underlying MF/SS) that has failed to respond to, or progressed despite, at least one prior systemic therapy
- ~~In Part 2, the NHL cohort will separately enrol subjects with double- and triple hit lymphoma, so that a minimum of 10 subjects with this subset of disease will be enrolled. To be eligible for this sub-cohort, tumor sample from the subject must demonstrate rearrangement and/or overexpression of~~

~~MYC and either BCL2 and/or BCL6 genes. Evaluation of double- or triple-hit status may be performed via appropriate local testing, and the determination of double- or triple-hit diagnosis will be at the discretion of the investigator and GSK Medical Monitor~~.

Inclusion criterion 5

Eastern Cooperative Oncology Group (ECOG) performance status of:

- ≤1 for all Part 1 Cohorts (AML, MM, and NHL)
- ~~.~~ ≤2 for ~~the~~all Part 2 cohorts (MDS/AML and CTCL)

Definitions for Adequate Organ Function

Renal	
Creatinine[3] OR Calculated creatinine clearance [calculated by Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method ~~Cockcroft-Gault formula~~[2, 3]] OR 24-hour urine creatinine clearance [3]	≤1.5 X ULN ≥50 mL/min ≥50 mL/min

Footnote 2 deleted

~~Refer to Appendix 1 for Cockcroft-Gault formula~~

Exclusion Criteria

Exclusion criterion 1

Haematological malignancy associated with human immunodeficiency virus (HIV) infection or solid organ transplant or ~~history of known~~positive Hepatitis B Antigen or positive Hepatitis C antibody at screening or within 3 months prior to first dose (subjects with positive Hepatitis C antibody may be enrolled, provided that the confirmatory test [e.g., ~~confirmed by Recombinant ImmunoBlot Assay [RIBA], if available or alternately confirmed by~~ Hepatitis C Virus [HCV] Ribonucleic acid [RNA] polymerase chain reaction [PCR]] is negative).

Exclusion criterion 3 Note 2

Corticosteroids (topical and/or systemic)

Exclusion criterion 5

Use of anticoagulants (e.g., warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of GSK525762. Low dose (prophylactic) anticoagulants (e.g., low molecular weight heparin (LMWH) or oral anticoagulants) is permitted. In addition, INR must be monitored in accordance with local institutional practices, as appropriate.

Exclusion criterion 6

Current use of a prohibited medication or ~~requires any of these medications~~planned use of a prohibited medication during treatment with ~~the investigational drugs~~GSK525762. ~~This includes excluding current medications known or suspected to be associated with QT prolongation. In addition, any subject who is expected to require a QT prolonging medication while on trial should not be enrolled.~~

Exclusion criterion 9

Cardiac abnormalities as evidenced by any of the following:

- History or current clinically significant conduction abnormalities, uncontrolled arrhythmias or hypertension.
- ~~Clinically significant conduction abnormalities or arrhythmias, 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).
- Recent h~~H~~istory (within the past 3 months) of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting. ~~within the past 3 months.~~

Exclusion criterion 10 Bullet point 1

- Baseline QTcF interval ≥~~450~~ 480 msec.

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN:

Rationale for Change: BID dosing removed from asset development strategy in heme

Revised Text:

Sentence 3 deleted:

~~BID dosing may be explored once MTD has been identified in once daily dosing; the total daily dose administered BID will not exceed the QD MTD.~~

EFFICACY MEASUREMENTS:

Rationale for Change: new ORR4 criteria added for CTCL cohort

Revised Text:

ORR, PFS and OS in AML, MDS, MM, and ~~NHL~~CTCL; time to progression (TTP) and duration of response in MM and CTCL. Rate of objective response lasting at least 4 months (ORR4) in CTCL

SAFETY MEASUREMENTS

Rationale for Change: Reduction in the cardiac monitoring based on updated risk/benefit profile.

Revised Text:

Sentence 3

Cardiac safety monitoring will be required, consisting of ~~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).

STATISICAL ANALYSIS:

Rationale for Change: revision of statistics plan to align with revision of subject cohorts

Revised Text:

Sentence 6 onwards:

The assessments are based on the predictive probability of success ~~(response rate > historical response rate), with a~~if the enrolment continues to the maximum of 32 subjects in the MDS cohort and 37 subjects in the CTCL cohort respectively~~, or 37 subjects treated (MM cohort) and assessed for response~~. Subjects ~~treated~~enrolled in Part 1, at the Part 2 dose, for diseases under study in Part 2, will~~may~~ be included in Part 2 ~~efficacy~~ analysis.~~Additionally at least 10 DHL subjects will be treated. No hypothesis testing will be conducted for the DHL cohort. For additional details, please refer to the RAP.~~

Section 1.2. Study Population Rationale

Rationale for Change: Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL) given the observed response rate in CTCL.

Revised Text:

Paragraph 3:

Cutaneous T-cell lymphomas are a family of NHLs characterized by skin infiltration by CD4-positive T-cells. These diseases are characterized by erythroderma and/or tumor-phase growths on the skin, as well as intense pruritis as a consequence of upregulation of multiple pro-inflammatory cytokines (Ahern, 2012). Targeted systemic therapies remain the cornerstone of treatment for many patients, including those with limited-stage disease, both to control the disease itself as well as to reduce the overall symptomatic burden (Whittaker, 2016). Recently, a role for BRD4 in the expression of lymphoma-associated genes has been demonstrated (Kohnken, Blood 2017), making BET inhibition a rational approach for treatment of CTCL.

Section 1.3.2 BID Dose Cohort

Rationale for Change: BID removed from asset development strategy in heme

Revised Text:

~~1.3.2. BID Dose Cohort~~

~~1.3.2.1. Preclinical Rationale for BID~~

~~Recent clinical and pre-clinical pharmacokinetic and pharmacodynamic data suggests a potential benefit of a twice daily (BID) dosing regimen compared to QD dosing [GSK525762 IB, GlaxoSmithKline Document Number 2011N113741_05]. 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 cell line 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.~~

~~QD and BID dosing have been further explored in a number of in vivo xenograft efficacy studies. 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 a 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 observe equivalent or improved efficacy with BID dosing in all xenograft models tested.~~

~~1.3.2.2. Clinical Rationale for BID~~

~~As described in the GSK525762 IB, Section 5.2, GSK525762 pharmacokinetics following once and twice daily administration is characterized by a rapid absorption with maximum concentration occurring mostly within two hours after dosing. GSK525762 is eliminated rapidly with an average terminal phase half-life of 3 to 7 hours.~~

~~Based on the pharmacokinetics of GSK525762 observed to date, and evidence of a short half-life of about 5 hours, trough concentrations at 100 mg QD are predicted to be 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 allow the trough concentration to be above the lower in vitro IC50 for doses around 30 mg BID.~~

~~1.3.2.3. Starting Dose for BID~~

~~As detailed in the GSK525762 IB, Section 5.2.2 and Section 5.3.1, doses of 20 mg and 30 mg BID have been administered to subjects with solid tumors. The PK and safety/tolerability profile for the 30 mg BID dose is comparable to subjects treated with an equivalent total daily dose (i.e., 60 mg once daily). In this study, once the QD MTD of GSK525762 has been identified for each disease subtype (AML/MDS, MM, and NHL), an exploratory cohort may be opened in one or more of the disease types to evaluate safety, tolerability, and preliminary efficacy of BID dosing.~~

~~For each disease subtype, the total daily dose selected for BID evaluation will be no higher than the once-daily MTD, divided approximately equally between two doses administered approximately 12 hours apart. A lower BID dose may be considered depending on emerging safety, PK, and PD data.~~

Section 1.4. Rationale for Study and Endpoints

Rationale for Change: Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL) given the observed response rate in CTCL.

Revised Text:

Paragraph 2 sentence 3

Part 2 is a cohort expansion, which will study the RP2D of GSK525762 to determine preliminary efficacy, safety and tolerability in three separate cohorts of subjects with myeloid neoplasms (myelodysplastic syndrome [MDS] or MDS that has transformed to AML), ~~multiple myeloma~~ and ~~non-Hodgkin's lymphoma~~ CTCL.

Paragraph 4

The original study design included a dose expansion in non-Hodgkin's lymphoma, enrolling subjects regardless of histological subtype. Furthermore, this cohort enrolled subjects with double- and triple-hit lymphoma (i.e., B-cell lymphomas with rearrangement and/or overexpression of myc and BCL2 and/or BCL6) in an exploratory sub-cohort. However, interim analysis of the Part 1 data demonstrated limited activity in both B-cell lymphomas in general as well as double/triple hit lymphomas. Responses, including very deep, durable responses, were achieved in subjects with CTCL and other T-cell lymphomas of the skin. Therefore, Part 2 of the study was amended to restrict enrollment to these diseases, for which emerging clinical data suggested a reasonable rate of benefit.

Section 1.5.1. Risk Assessment

Rationale for Change: Risk assessment tables revised in accordance with changes to benefit/risk profile of the asset.

Revised Text:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Cardiovascular – QT prolongation	**QTc prolongation** (up to 20%; 41 msec in dog) Can occur or persists after drug is cleared from plasma; general trend to increase on repeat dosing; no potentiation beyond day13 in 28 day toxicology study in dogs. Reversible on cessation of dosing; not potentiated on subsequent dosing following a 7 day dosing holiday. No significant arrhythmias were detected in preclinical studies. No clear link to human ether à go-go-related gene (hERG) binding or trafficking. No evidence of heart accumulation	~~ICF includes the risk of (fatal) arrhythmias~~ Protocol includes cardiovascular eligibility criteria, laboratory assessments (potassium and magnesium, N-terminal pro–B-Type natriuretic peptide [NT-proBNP], creatine kinase [CK] and creatine kinase-MB [CK-MB]), cardiac monitoring (electrocardiograms [ECGs], and cardiac ejection fraction) during the study, and dose stopping/modifications criteria for

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	of GSK525762. Mechanism & risk for Torsades de Pointe is unclear. A review of all available data as of November 2017 (representing 271 subjects dosed up to 100 mg in the BET115521 solid tumor study and up to 120 mg in the BET116183 heme malignancy study) demonstrated a clinically negligible effect on QT in humans. **Blood pressure (BP**) Variable changes in blood pressure following a single dose (≥1 mg/kg in dogs and 60 mg/kg in rats); no effects were observed in the 7 day repeat dose dog CV study; increase in mean BP up to 11 mmHg; decrease in mean BP up to 13 mmHg. **QA interval** (indirect measure of cardiac contractility). Decreased QA interval at single non-tolerated doses in dog (no effect seen in rats); up to 10 msec. No effects were observed in the 7 day repeat dose dog CV study; No echocardiography changes in the 28 day dog toxicology study.	the management cardiac events. Drugs with a risk of ~~Torsades de Pointes~~QT prolongation must ~~are prohibited~~be used with caution, (refer to Section 8.3). 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, 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 and including 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 5 and removed in Protocol Amendment 8 following additional analysis of all available data by the cut off of 10-Jun-2016. 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
Cardiovascular -	Elevations in cardiac biomarkers relative to 4	~~ICF includes the risk of myocardial~~

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
Troponin	week Good Laboratory Practice (GLP) toxicology study control group in: • Cardiac troponin I (up to 15X in rat and 4.7X in dog) • Cardiac troponin T (up to 8.9X in rat) • Myosin light chain III (up to 4.8X in rat) • NT-proANP (up to 1.54X in rat) Changes were reversible and there was no evidence of compound related myocardial histopathological changes in either species after up to 3 months of dosing.	~~infarction.~~ Protocol includes troponin monitoring (local laboratory monitoring for troponin I or T based on availability and troponin T at central laboratory) and dose stopping/modifications criteria for the management of cardiac toxicity. .
Lung effects	Aggregates of foamy macrophages in peribronchiolar 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 finding is unlikely to affect pulmonary function. No effects were observed in the 3 month toxicology studies. For more information, see the GSK 525762 IB [GlaxoSmithKline Document Number ~~2011N113741_05~~2011N113741_06].	ICF includes the risk of lung effects. ~~Protocol includes pulmonary function assessments as appropriate (subjects with severe Chronic Obstructive Pulmonary Disease [COPD], history of pneumonitis, alveolar haemorrhage, chest radiation) chest x-ray at baseline and dose stopping/modifications criteria for pneumonitis.~~
Drug Interactions	GSK525762 is a substrate for CYP3A4 enzymes, and for P-gp and breast cancer resistance protein (BCRP) transporters. GSK525762 clearance is virtually solely via CYP3A4. There is evidence of potential auto-induction after repeat dosing in clinical studies since reduction in parent exposures (~25% at lower doses to ≥60% at doses ≥60mg, mainly in BET115521 study) have been observed. There is low potential for GSK525762 to inhibit cytochrome P450 (CYP) enzymes or to inhibit P-gp or BCRP based on in vitro data. GSK525762 was shown to be an inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1) and organic anion transporter 3 (OAT3) in vitro. GSK525762 was shown to be a moderate inducer of CYP3A4 in a human hepatocyte induction study~~There is low potential for~~	Use of concomitant medications, herbal medicines and fruit juices that are strong or moderate CYP3A4 inhibitors or inducers should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. Potent inhibitors of BCRP and P-glycoprotein transporters, such as cyclosporine, tacrolimus, or ketoconazole, should be avoided. Use of concomitant medications that are sensitive substrates of OATP1B1 and OAT3 should be done with caution. Medications that have a narrow

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy
	~~GSK525762 to induce or inhibit cytochrome P450 (CYP) enzymes or to inhibit P-glycoprotein (Pgp) or Breast Cancer Resistance Protein (BCRP) based on in vitro data. GSK525762 was shown to be an inhibitor of OATP1B1 and OAT3 in vitro~~.	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.

Section 2. OBJECTIVES, ENDPOINTS, HYPOTHESES

Rationale for Change: The study population for the NHL cohort in Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL). The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2, and BID dosing was removed. Medications affecting QT prolongation were re-categorized from prohibited to cautionary. Response Criteria for CTCL was added as an Appendix, and a QOL questionnaire (SKINDEX-29) was added

Revised Text:

Part 1

Part 1 Objectives		Part 1 Endpoints
Secondary	• To characterize the Pharmacokinetic (PK) of GSK525762 after single- and repeat-dose administration ~~following QD and/or twice daily (BID) dosing schedules~~.	• GSK525762 PK parameters following single- (Day 1) and repeat-dose (Day 15) administration of GSK525762, including Area under concentration-time curve(AUC), Minimum observed concentration (Cmin), Pre-dose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax), Apparent terminal half-life ($t_{1/2}$) (or $t_{1/2}$, eff), time invariance and accumulation ratio.
	~~• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters following QD and/or BID dosing schedules.~~	~~• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC), following single and repeat-dose oral administration of GSK525762~~
	~~• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic (PD) response following QD and/or BID dosing schedules.~~	~~• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by Bromodomain [BRD] proteins) in tumor tissue and/or peripheral blood samples.~~
	~~• To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762~~	~~• Assess objective response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.~~
Exploratory	• To evaluate the relationship between GSK525762 exposure and cardiac and other safety parameters~~.~~	• Changes in cardiac QT duration corrected for heart rate by Fridericia's formula (QTcF) and other safety parameters in relation to GSK525762 exposure markers (dose, concentration, Cmax, AUC), following single and repeat-dose oral administration of GSK525762
	• To evaluate the relationship between GSK525762 dose/exposure and pharmacodynamic response~~.~~	• Dose/exposure markers related change in molecular markers (e.g., gene transcription and/or expression of proteins regulated by Bromodomain [BRD] proteins) in tumor tissue and/or peripheral blood samples.

Part 1 Objectives		Part 1 Endpoints
	• <u>To evaluate the relationship between GSK525762 dose and exposure with clinical activity of GSK525762</u>	• <u>Assess objective response rate (ORR) according to disease specific assessments for leukemia, multiple myeloma, and non-Hodgkin's lymphoma, as a function of dose and exposure markers.</u>
	• To investigate the relationship between genetic variants in candidate genes and the pharmacokinetics (PK) and safety profile of GSK525762 ~~following QD dosing schedules~~.	• Pharmacogenomic (PGx) study using clinical l samples.

Part 2

Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort").	• For MDS Cohort: ~~Objective response rate~~ORR (defined as the percentage~~%~~ of subjects achieving Complete Response (CR), Marrow CR, CRp [as per CR but platelet count <100 x 10^9/L], CRi [as per CR but platelet count <100 x 10^9/L or neutrophil count <1 x 10^9/L], or Partial Response [PR] per response criteria.
	• ~~To evaluate clinical efficacy after treatment with GSK525762 in multiple myeloma (MM).~~	• ~~For MM: Objective response rate (defined as the percentage of subjects that have achieved a stringent CR [sCR], CR, VGPR, or PR) per response criteria.~~
	• To evaluate clinical efficacy after treatment with GSK525762 in CTCL~~non-Hodgkin's Lymphoma (NHL)~~.	• For CTCL: ORR4; defined as the percentage of subjects that have achieved a CR or PR, per global response criteria and the modified severity weighted assessment tool (mSWAT), lasting more than 4 months ~~For NHL: Objective response rate (defined as the percentage of subjects that have achieved a CR, or PR) per response criteria.~~
Secondary	• To evaluate the effect of GSK525762 on disease-related symptoms, as reported by subjects (CTCL cohort only)~~PRO~~	• For CTCL: measure the effects of skin disease based on quality of life ~~utilizing~~questionaire Skindex-29
	• To characterize the PK of GSK525762 in 3 disease specific cohorts of subjects with MDS/AML, ~~MM,~~ or CTCL~~NHL~~ after repeat-dose administration.	• Population PK parameters for GSK525762 such as apparent clearance following oral administration (CL/F) and volume of distribution (V/F), and relevant covariates which may influence exposure (e.g., age, weight, or disease associated covariates).
	• ~~To evaluate the exposure response (i.e., PK/PD) relationship between GSK525762 and safety/efficacy parameters in 3 2 disease-specific cohorts of subjects with MDS/AML, MM, or or CTCLNHL.~~	• ~~PK/PD relationship between GSK525762 exposure markers and safety and efficacy parameters.~~
	• To evaluate the safety and tolerability of RP2D of GSK525762 in ~~3~~ 2 disease-specific cohorts of subjects with MDS/AML, ~~MM, or~~ or CTCL~~NHL~~.	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, and cardiac parameters) at RP2D.
	• To determine the clinical activity of	• ~~TTP (Time to Progression) , DOR~~

Part 2 Objectives		Part 2 Endpoints
	GSK525762 in ~~3~~2 disease-specific cohorts of subjects with MDS/AML, ~~MM, or~~ or CTCL~~NHL~~.	~~(Duration of Response), PFS~~ Progression free survival (~~Progression Free Survival~~PFS, time from treatment start date to disease progression or death due to any cause, whichever is earlier) for MDS/AML, ~~MM~~ and ~~NH~~CTCL.~~L~~ Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML, ~~MM~~ and CTCL.~~NHL~~ • Duration of response (DOR, time from onset of response to disease progression or death due to any cause, whichever is earlier in responders) for MDS/AML, and CTCL • ~~Rate of objective global response with a duration of 4 months or more (ORR4) in CTCL~~ • Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML, and CTCL
Exploratory	• To evaluate the exposure response relationship between GSK525762 and safety/efficacy parameters in 2 disease-specific cohorts of subjects with MDS/AML, or CTCL.	• Relationship between GSK525762 exposure markers and safety and efficacy parameters.

Hypothesis	The primary goal of Part 2 is to detect a clinically meaningful response rate, defined as follows: • Myelodysplastic syndrome and transformed MDS (myeloid cohort): A response rate of 30% relative to a 10% response rate suggesting no activity in subjects with MDS/AML. This will be conducted by testing the null hypothesis that P0≤0.10 versus the alternative that P1≥0.300, assuming the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • ~~Multiple myeloma: A response rate of 20% relative to a 5% response rate suggesting no activity in subjects with multiple myeloma. This will be conducted by testing the null hypothesis that P0≤0.05 versus the alternative that P1≥0.20, assuming the maximum response rate for an ineffective drug is 0.05 and the minimum response rate for an effective drug is 0.20.~~ • CTCL: ~~Non-Hodgkin's lymphoma (non-double hit lymphoma [DHL]):~~ A response rate, lasting more than 4 months, of 4~~3~~0% relative to a 2~~1~~0% response rate suggesting no activity in subjects with ~~non-Hodgkin's lymphoma~~CTCL. This will be conducted by testing the null hypothesis that P0≤0.2~~1~~0 versus the alternative that P1≥0.4~~3~~0, assuming the maximum response rate for an ineffective drug is 0.2~~1~~0 and the minimum response rate for an effective drug is 0.4~~3~~0. ~~Subjects with DHL will be evaluated separately for efficacy, but no hypothesis testing will be conducted on the DHL cohort.~~

Section 3.1. Study Design/Schematic

Rationale for Change: The study population for the NHL cohort in Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL). The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2.

Revised Text:

Paragraph 2 sentence 2 onwards

~~Safety, tolerability, PK, and efficacy may also be explored in a limited number of subjects treated twice daily (BID).~~ Part 1 will ~~Both parts will~~ be conducted in adult subjects with relapsed and/or refractory myeloid malignancies, multiple myeloma, and non-Hodgkin's lymphomas. Part 2 will be conducted in adult subjects with relapsed and/or refractory myeloid malignancies and cutaneous T-cell lymphoma (Figure 2).

Figure 2 Study Schema

In Part 2 text box

(MDS/AML, CTCL ~~NHL, MM~~)

(n=32 for MDS/AML ~~& MM~~, 36~~7~~ for CTCL ~~NHL~~)

In MTD/RP2D text box

~~BID~~

MDS/AML, ~~NHL, MM~~CTCL

Paragraph 3

In both Parts 1 and 2, ~~all~~ subjects ~~will~~ may be evaluated for systemic BET inhibitory effects in blood (whole blood transcriptional). A subset of subjects in Part 1 ~~will~~ may also be evaluated for plasma cytokine profiling. In addition, pre-treatment and post-treatment bone marrow, skin, whole blood for PBMC isolation or lymph node samples will be collected from selected subjects to be evaluated for target engagement and effects of GSK525762 on tumor biology.

Section 3.2.1. Part 1: Dose Escalation

Rationale for Change: removed of BID dosing from DE plan

Revised Text:

Paragraph 4

Dose escalation will continue until an MTD is determined or until a dose of 200 mg per day is reached. After the MTD has been determined ~~for a disease type~~ in Part1 for each disease type, ~~then BID cohort(s) (Section 1.1.1.13.2.1.5) and the~~ then the Part 2 dose expansion cohorts will be opened for that disease type.

Section 3.2.1.1. Dose Escalation and Schedule

Rationale for Change: revision of cardiac monitoring criteria due to changes in benefit/risk profile

Revised Text:

Paragraph 2

Extensive monitoring for cardiac safety signals will be performed including ~~triplicate~~ 12-lead ECG on the days indicated in the Time and Events Table.

Section 3.2.1.3. 3 + 3 Dose Escalation in Part 1

Rationale for Change: BID dosing removed per changes in asset development strategy for heme

Revised Text:

Figure 3 Dose Escalation Schema (Part 1)

BID text box removed

~~BID (QD MTD, divided approximately equally)~~

Following abbreviations removed

~~AML: acute myeloid leukemia~~

~~BID: twice daily~~

~~MM: multiple myeloma~~

~~NHL: non-Hodgkin's Lymphoma~~

Table 3 3 + 3 Dose Escalation Design

For 0 out of 3 subjects, "≥" symbol was added before Grade 2 toxicity for the action "Escalate to next dose level with an increase of ≤50% if, in the first 3 weeks of any cohort".

Section 3.2.1.4. Alteration of Schedule

Rationale for Change: modification to PK sampling timepoints for subjects undergoing dose escalation/de-escalation

Revised Text:

Paragraph 4

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~~ at least 7 days at the adjusted dose level.

Section 3.2.1.5. BID dosing

Rationale for Change: BID dosing removed per changes in asset development strategy for heme

Revised Text:

~~**3.2.1.5. BID dosing**~~

~~Once the MTD of QD administration has been identified for a disease subtype, a cohort may be opened to explore the safety, tolerability, PK, and efficacy of GSK525762 when administered BID. . The selected total daily dose (administered in two approximately equal doses) for BID administration will not exceed the QD MTD. A lower starting dose may be selected depending on emerging safety, PK and PD data. Dosing will be separated by approximately 12 hours. The total number of evaluable subjects per disease type treated BID will not exceed 10 subjects.~~

Section 3.2.1.5. Intra-Subject Dose Escalation

Rationale for Change: modification to PK sampling timepoints for subjects undergoing dose escalation/de-escalation

Revised Text:

Paragraph 2 sentence 1:

Subjects approved for intra-subject dose escalation may require additional limited PK sampling (pre-dose, 0.5, 3 and 6-8 hours) at the higher dose, as determined by GSK Clinical Pharmacology, after at least 7 days at the adjusted dose level.

Section 3.2.4. Part 2: Disease Specific Expansion Cohorts

Rationale for Change: The study population for the NHL cohort in Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL). The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2.

Revised Text:

Up to 32 subjects ~~(per cohort)~~ with myelodysplastic syndrome ~~or non-Hodgkin's lymphoma (non-DHL)~~, and up to 37 subjects~~ with multiple myeloma~~, CTCL (as defined in Section 4.2.1) may be enrolled in an expansion cohort at the RP2D. These will be conducted 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 or PK 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.

~~At least 10 subjects with tumor that is positive for rearrangement or overexpression of MYC plus BCL-2 and/or BCL-6 genes (double- and triple-hit lymphoma) will be~~

~~enrolled. These subjects will be evaluated separately for efficacy, but hypotheses will not be tested. See Section 11.1 for description of the plan for analysis of the NHL cohorts.~~

Plasma samples for PK evaluation will be collected in all subjects. The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored with the constraint of both Type I and Type II error rates. Clinical response will be defined per standard evaluation criteria (see Appendix 6, Appendix 7 and Appendix 8). Patient-reported outcome questionaire, Skindex 29 (Appendix 11) will be used to gauge the effects of treatment with GSK525762 on the quality of life and other subjective measures in subjects with CTCL.

For each cohort, the first~~an~~ interim analysis will be conducted after ~~efficacy data at a dose level based on RP2D are available on a minimum of~~at least 10 subjects become evaluable (have had at least one-post baseline disease assessment, have progressed or died, or have discontinued from study treatment) in the MDS and CTCL ~~NHL (non-DHL)~~ cohorts respectively. ~~and a minimum of 13 subjects in the MM cohort.~~ The number of subjects may be increased up to a total of 32 for the MDS cohort and up to a total of 37 for the CTCL cohort, ~~NHL (non-DHL) cohorts and up to a total of 37 for the MM cohort~~ depending on the results observed; a separate decision will be made for each disease cohort. The decision rules, specifying the number of subjects with a clinical response needed for continuing enrolment or, stopping for futility, are indicated in Figure 4 and Figure 5. The methodology is based on the predictive probability of success ~~(response rate > historical response rate)~~ if enrolment continues to maximum number of~~32~~ subjects for MDS and CTCL ~~NHL (non-DHL) and 37 subjects for MM [Lee, 2008]~~. Subjects enrolled in Part 1 with the same type of disease as Part 2, and treated at the RP2D, will be included in the Part 2 analysis. These rules are intended as a guideline. Actual decisions will depend on the totality of the data.

For MDS and CTCL ~~NHL (non-DHL)~~ cohorts: ~~Ten subjects will be enrolled in each cohort at the RP2D to examine safety and efficacy. If zero responses are observed in either cohort, then that cohort will be terminated and no further subjects will be enrolled due to futility.~~when 10 subjects are included in the first interim analysis, a~~A~~ single responder~~se~~ in a cohort will be adequate to pursue further enrolment. The number of observed confirmed responses will guide further enrolment according to the rules summarized in Figure 4 and Figure 5. A maximum of 32 subjects ~~per cohort~~with MDS and 37 subjects with CTCL will be enrolled at the RP2D. All available data will be considered in making enrolment decisions.

Paragraph 6

~~For the MM cohort: Thirteen subjects will be enrolled at the RP2D to examine safety and efficacy. If zero responses are observed in this cohort, then no further MM subjects will be enrolled due to futility. A single response will be adequate to pursue further enrolment. 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 6 Diagram of Stopping Rules for ~~MM~~ CTCL Cohort Expansion

Number of Subjects	0	1	2	3	4	5	6	7	8	9	10	11
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	■	■	■	■	■	■	■	■	■	■	■	■

The shaded regions are the specific regions for stopping enrollment for futility. For instance, if there is no response in ~~13~~ 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and further enrollment in this cohort may be stopped.

Section 4.1. Number of Subjects

Rationale for Change: total number of subjects updated to reflect changes in study population

Revised Text:

Part 2 will enroll up to ~~111~~ 69 subjects (~~three~~ two disease-specific cohorts of 32 and 37 subjects, for the MDS and CTCL cohorts, respectively ~~to 37 subjects each, depending on disease subtype, and one disease-specific cohort of 10 subjects).~~)

Section 4.2.1. Inclusion Criteria

Rationale for Change: The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2. Eligibility criteria for all populations were updated (ECOG, cardiac safety).

Revised Text:

Inclusion criterion 3

Subjects must have a diagnosis of one of the following hematologic malignancies, which has relapsed or been refractory to treatment as follows-:~~Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), Multiple Myeloma (MM), or non-Hodgkin's Lymphoma (NHL).~~

Inclusion criterion 3 Bullet 3 onwards

- (Part 1 ~~and Part 2~~): Subjects with multiple myeloma are eligible if they have progressed despite therapy with an alkylating agent, proteasome inhibitor, and immunomodulatory agent, either as individual regimens or in combination
- (Part 1 ~~and Part 2~~only): Subjects with NHL are eligible if they have received at least two prior lines of systemic therapy, including at least one line of immunochemotherapy with an anti-CD20 antibody (if their tumor expresses CD20)
- (Part 2 only): Subjects will be eligible for enrolment into the CTCL cohort if they:
    - Have histologically- or cytology-proven diagnosis of CTCL (mycosis fungoides [MF], Sézary syndrome [SS], primary cutaneous anaplastic large cell lymphoma [pcALCL], or large cell transformation of underlying MF/SS) that has failed to respond to, or progressed despite, at least one prior systemic therapy
- ~~In Part 2, the NHL cohort will separately enrol subjects with double- and triple hit lymphoma, so that a minimum of 10 subjects with this subset of disease will be enrolled. To be eligible for this sub-cohort, tumor sample from the subject must demonstrate rearrangement and/or overexpression of MYC and either BCL2 and/or BCL6 genes. Evaluation of double- or triple-~~

~~hit status may be performed via appropriate local testing, and the determination of double- or triple-hit diagnosis will be at the discretion of the investigator and GSK Medical Monitor~~.

Inclusion criterion 5

Eastern Cooperative Oncology Group (ECOG) performance status of:

- ≤1 for all Part 1 Cohorts (AML, MM, and NHL)
- ≤2 for ~~the~~all Part 2 cohorts (MDS/AML and CTCL)

Definitions for Adequate Organ Function

Renal	
Creatinine[3] OR Calculated creatinine clearance [calculated by Chronic Kidney Disease Epidemiology Collaborative (CKD-Epi) method ~~Cockcroft Gault formula~~[2, 3]] OR 24-hour urine creatinine clearance [3]	≤1.5 X ULN ≥50 mL/min ≥50 mL/min

Footnote 2

Refer to Appendix 1 for ~~Cockcroft Gault~~CKD-Epi formula

Section 4.2.2. Exclusion Criteria

Rationale for Change: The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2. Eligibility criteria for all populations were updated (ECOG, cardiac safety).

Revised Text:

Exclusion criterion 1

Haematological malignancy associated with human immunodeficiency virus (HIV) infection or solid organ transplant or ~~history of known~~positive Hepatitis B Antigen or positive Hepatitis C antibody at screening (subjects with positive Hepatitis C antibody may be enrolled, provided that the confirmatory test [e.g. Heptatitis C Virus ~~confirmed by Recombinant ImmunoBlot Assay [RIBA], if available or alternately confirmed by~~ Hepatitis C Virus [HCV] Ribonucleic acid [RNA] polymerase chain reaction [PCR] is negative).

Exclusion criterion 3 Note 2

Corticosteroids (topical and/or systemic)

Exclusion criterion 5

Use of anticoagulants (e.g., warfarin, heparin) at therapeutic levels within 7 days prior to the first dose of GSK525762. Low dose (prophylactic) anticoagulants (e.g., low molecular weight heparin (LMWH) or oral anticoagulants) is permitted. In addition, INR must be monitored in accordance with local institutional practices, as appropriate.

Exclusion criterion 6

Current use of a prohibited medication or ~~requires any of these medications~~planned use of a forbidden medication during treatment with ~~the investigational drugs~~GSK525762. ~~This includes excluding current medications known or suspected to be associated with QT prolongation. In addition, any subject who is expected to require a QT prolonging medication while on trial should not be enrolled.~~

Exclusion criterion 9

Cardiac abnormalities as evidenced by any of the following:

- History or current clinically significant conduction abnormalities, uncontrolled arrhythmias or hypertension.
- ~~Clinically significant conduction abnormalities or arrhythmias, 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) [Appendix 2].
- Recent h~~H~~istory (within the past 3 months) of acute coronary syndromes (including unstable angina and myocardial infarction), coronary angioplasty, or stenting. ~~within the past 3 months.~~

Exclusion criterion 10 Bullet point 1

Baseline QTcF interval ≥~~450~~ 480 msec.

Section 4.2.3.1. Permanent Discontinuation from Study Treatment

Rationale for Change: language added for CTCL specific population

Revised Text:

Paragraph 1 sentence 3

For subjects with CTCL, in cases where the definition of progressive disease (PD) or relapse is met but the clinical impression is questionable, documentation for a period of at least 4 weeks is also recommended to avoid a subject being removed prematurely from the study.

Section 4.2.3.2. Subject Completion

Rationale for Change: clarification/simplification of wording

Revised Text:

Paragraph 2

In Part 2, a subject will be considered to have completed the study if the subject is followed until death or the end of study.~~:~~

- ~~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.~~

Section 5. TIME AND EVENTS TABLES

Rationale for Change: The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile, and BID dosing was removed. Medications affecting QT prolongation were re-categorized from prohibited to cautionary. Response Criteria for CTCL was added as an Appendix, and a QOL questionnaire (SKINDEX-29) was added.

Revised Text:

Table 5 Time and Events: Part 1

Heading text within table:

Study Drug: For ~~QD or BID~~ details see Table 8 and Table 9

Safety

~~Pulmonary function test d~~ removed

Cardiac Monitoring

ECHO or MUGA (Within 35 days of first dose)

Footnote d:

~~Pulmonary tests as appropriate: subjects with severe COPD, history of pneumonitis, alveolar hemorrhage, chest radiation~~

Footnote e:

12-lead ECGs: Screening ECGs within 14 days of first dose. ~~Triplicate ECGs prior to dosing~~. For timing of ECGs on "O" days, see Table 8 for QD~~ and Table 9 for BID~~. Otherwise, ~~triplicate~~ ECGs at approximately same time of day, and prior to dosing. ~~If QTcF increase >30msec, ECGs performed daily through W2.~~

Table 6 Time and Events: Part 1 Laboratory Assessments

CK-MB assessment has been removed for W1 D2, W1 D5, W2 D1, W2 D6, W3 D1, W4 D1, W10 D1, q6W, and EOT timepoints.

HBsAg, HepC antibody Notes:

If hepatitis C antibody positive, a confirmatory study (e.g., HCV RNA PCR) should be performed as per local standard~~perform third generation immunoassay (if test is available) on same sample to confirm results, or alternatively, use HCV RNA test (either quantitative or qualitative).~~

Footnotes:

PCR=polymerase chain reaction added

Table 7 Disease Specific Assessments~~: Part 1 and 2~~

Heading text within table:

Multiple Myeloma (MM) Assessments (Part 1)

Blood sample for exploratory translational research on q6W D1 added

Heading text within table:

~~Lymphoma~~ NHL Assessments (Part 1)

CTCL Assessments (Part 2)							
Procedure	SCR	W3 D1	W7 D1	W10 D1	~~q3W D1~~	W16 and beyond	EOT
Disease characteristics, including history[a] and current staging	X						
Skin assessment (e.g., medical photography)	X		X			Wk 16, wk 24, then q12wks	X
Cross-sectional imaging[b]	X		X			Wk 16, wk 24, then q12wks	X
Quantitative evaluation of disease in blood (e.g., flow cytometry)	X		X			Wk 16, wk 24, then q12wks	X
Gobal response scoring[c]	X		X			Wk 16, wk 24, then q12wks	X
Skindex 29 (Quality of life/symptom assessment)	X	X	X	~~x~~X		Wk 16, wk 24, then q12wks	X
Tissue biopsy[d]	X	X					X
Blood sample for exploratory translational research[e]	X	X	X			Wk 16, wk 24, then q12wks	X

a. Including date of first diagnosis, disease stage, and history of prior therapies
b. CT, PET/CT, or MRI may be used, as per standard practice
c. Global response score (refer to Appendix 10 for full description) takes into account status of disease as measured by assessment of skin, lymph nodes, viscera, and blood. Any response or PR should be confirmed by repeat assessment no sooner than 4 weeks after the assessment demonstrating response.
d. Punch biopsy of affected skin lesion should be performed at times indicated for translational research. Pre- and post-dose biopsies should be collected from the same lesion. The W3D1 biopsy should be collected within 3-6 hours after the dose
e. Blood samples should be collected within 3-6 hours after the dose~~.~~

MDS and Leukaemia Assessments (Part 1 and Part 2)

Response Assessment at Screening removed.

Table 8 Time and Events: Part 1 ~~(QD cohorts)~~ Serial Electrocardiograms, Pharmacokinetics, and Biomarker Sampling

Procedure / time after dose	W2 D4	W2 D6	W2D7 (if dose has been altered (including held and resumed) serial PK sampling should occur 4 to 7 days after dosing resumed)									W3D 1		W7D1 ±4 days [c]			
	pre dose	pre dose	pre dose	0 h	15 min ± 5m	30 min ±5 m	1h ±10m	2h ±15m	4h ±15m	8 h ± 1 h	12 h ± 2 h	24 h ± 1 h	0 h	pre dose	0 h	0.5-2 h	4 - 8h
Dose				X									X		X		
12-lead ECG ~~a~~			X					X	X					X		X	X
PK sample for GSK525762	~~X~~	X	X		X	X	X	X	X	X	X	X [b]		X		X	X

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

a. ~~The ECGs are taken in triplicate, 5 minutes apart and~~A single ECG should be collected at each timepoint, within 10 min prior to PK draw. .

b. Sample to be obtained before dosing on Week 1, Day 2 or Week 3 Day 1~~.~~

c. If dose was escalated, the W7D1 visit may be performed +4 to +7 days.

Abbreviations: ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose.

~~**Table 9 Time and Events: Part 1 (BID Cohorts) Serial Electrocardiograms, Pharmacokinetics and Biomarker Sampling**~~

~~Timepoint: Hours after AM dose~~	~~W1D1~~							~~W1D5~~				~~W2D4~~		~~W2D6~~		~~W2D7~~					~~W7D1 ±4 days [c]~~				
	~~Pre-Dose~~	~~0h~~	~~30 min ±5m~~	~~2h ±15m~~	~~4h ±15m~~	~~8h ±1h~~	~~12h (0h)~~	~~AM~~	~~2h ±15m~~	~~4h ±15m~~	~~PM~~	~~pre AM dose~~	~~AM & PM~~	~~pre AM dose~~	~~AM & PM~~	~~Pre-Dose~~	~~0h~~	~~2h ±15m~~	~~4h ±15m~~	~~12h (0h)~~	~~pre dose~~	~~0h~~	~~0.5-2h~~	~~4 – 8h~~	~~12h~~
~~Dose~~		~~X~~					~~X~~	~~X~~			~~X~~		~~X X~~		~~X X~~		~~X~~			~~X~~		~~X~~			~~X~~
~~12-lead ECG [a]~~	~~X~~			~~X~~	~~X~~				~~X~~	~~X~~						~~X~~		~~X~~	~~X~~		~~X~~		~~X~~	~~X~~	
~~PK GSK525762 [b]~~	~~X~~		~~X~~	~~X~~	~~X~~	~~X~~			~~X~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~		~~X~~		~~X~~	~~X~~	

~~a. The ECGs are taken in triplicate, 5 minutes apart and within 10 minutes prior to PK draw.~~

~~b. PK blood sample collected overnight may be kept refrigerated at 4°C in the event the laboratory is closed.~~

~~c. If dose was escalated, the W7D1 visit may be performed +4 to +7 days.~~

~~APP=acute phase protein; ECG=electrocardiogram; PK=Pharmacokinetics; MTD Maximum Tolerated Dose;~~

Table 10 Time and Events: Part 2 Expansion Cohort

Pulmonary function test at Screening has been removed

Cardiac Monitoring

ECHO or MUGA (Within 35 days of first dose).

PK and Blood pharmacodynamics notes:

Three samples to be collected each sampling day: During the first 3 weeks collect a predose (within 60 minutes prior to dose), a single draw between 0.5 to 2 h postdose, and a single draw between 4-8h postdose (fasting requirements apply). Thereafter W7 and Q6W only a predose and 0.5 hour post dose sample are collected. PK sampling may be discontinued after 6 months on study

Part 2 Procedure (Notes)		**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles (q3w and q6w Initiated from Wk 10)**		**EOT**
		W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
	SCR	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	
Translational Research										
PGx sample		X								
Tumor sample (e.g., bone marrow biopsy, ~~lymph node~~skin punch biopsy, or peripheral blood collection [only for subjects with circulating disease])	X [e]			X [f] (CTCL only)~~f~~	X [f] (MDS/AML only)					X [g]
Blood samples for exploratory translational research	X			X [f] (CTCL only)	X [f] (MDS/AML only)	Additional samples will be collected on the date of disease assessment/bone marrow biopsy and date of progression or when patient is discontinued from study/end of treatment				

Footnote f:

~~Subjects with MM or should have bone marrow aspirates collected on W3D1 within3-6 hours after the dose.~~ Subjects with MDS/AML should have bone marrow aspirates or peripheral blood collection (provided that there are sufficient leukemic cells in the peripheral circulation) collected on ~~W3~~ W4 D1 within 3-6 hours after the dose. Subjects with ~~NHL~~CTCL will have a ~~lymph node~~punch biopsy of the skin and blood sample collected on W3D1 within 3-6 hours after the dose. Any additional blood samples should be collected within 3-6 hours post-dose. Timing of tissue collection will be based on tumor type and may be modified based on emerging data. For operational reasons sampling can be delayed by up to 2 days as long as **the hours post-dose for collection remain as described**. **A PK sample will need to be obtained within 1 hour of the**

tissue sampling. For CTCL subjects the 4-8 hour PK sample required to be drawn can be utilized as the sample that is required after tissue sampling. See Table 7 disease specific assessments for details).

Table 11 Time and Events: Part 2 Laboratory Assessments

***NB*: Collect blood samples prior to dosing. W1D1 samples not needed if SCR sample is within 24h of first dose. (Notes)**		**Cycle 1**			**Cycle 2**	**Cycle 3**	**Cycle 4**	**Further Cycles q3w and q6w Initiated from Wk 10**		
		W1	**W2**	**W3**	**W4**	**W7**	**W10**	**q3W**	**q6W**	
	SCR	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**EOT**
HBsAg, HepC antibody (If hepatitis C antibody positive, a confirmatory study [e.g., HCV RNA PCR] should be performed as per local standard~~perform third generation immunoassay on same sample to confirm results~~)	X									

Section 6.1.2. Visit Windows

Rationale for Change: clarification needed for study visit window

Revised Text:

At the end following added:

Discontinuation Survival Follow Up Visit: can be scheduled ± 7 days

Section 6.2 Baseline Assessment

Rationale for Change: wording revised to reflect changes in cohorts

Revised Text:

Subjects diagnosed with refractory hematological malignancy (MM, ~~lymphoma~~NHL (excepting CTCL), CTCL, MDS and/or AML), will be assessed at baseline for general disease characteristics as noted in Section 6.2.1 and tumor type specific measures as noted in Section 6.2.2, Section 6.2.3 ~~and~~ Section 6.2.4, and Section 6.2.5, respectively.

Section 6.2.3. Baseline assessment for Subjects with ~~lymphoma~~ NHL (excepting CTCL)

Rationale for Change: clarification of name of cohort/population

Revised Text:

Section heading changed as mentioned above

Section 6.2.4 Baseline assessment for Subjects with CTCL

Rationale for Change: new required baseline assessments for CTCL specific cohort

Revised Text:

6.2.4 Baseline assessment for Subjects with CTCL

- Modified International Society for Cutaneous Lymphomas (ISCL)/ European Organization of Research and Treatment of Cancer (EORTC) stage at initial diagnosis and screening (Appendix 10, Table 22)
- Quality of life assessment (Skindex-29 [refer to Appendix 11])

Section 6.3.4. ~~Echocardiogram (ECHO)~~ 6.3.4. Left ventricular ejection fraction (LVEF) Evaluation

Rationale for Change: updating study procedures to permit additional imaging modalities

Revised Text:

For all subjects, ~~ECHOs~~ evaluation of cardiac output will be performed at screening and at assessment times as outlined in Section 5. While ECHO is the preferred modality of imaging, MUGA scans may be accepted as an alternative. Subjects should have the same assessment modality performed at each time point listed in Section 5. When possible, ECHOs/MUGAs should be evaluated and compared to baseline by the same reader. All ECHO/MUGA data may be transferred and reviewed by an independent cardiologist.

Section 6.3.5. Electrocardiograms

Rationale for Change: The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile

Revised Text:

Paragraph 1 bullet point 2 and 3:

- ~~During Part 1, triplicate 12-lead ECG should be performed at all time points indicated in the Section 5 Time and Events Tables.~~
- ~~During Part 2, single 12-lead ECGs should be performed at the time points indicated in the Section 5 Time and Events Tables.~~

Paragraph 3 bullet point 1:

- QTc interval ≥~~500~~ 530 msec OR interval increase from baseline ≥60 msec: Investigational product (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 Section 7.6 for rechallenge guidelines).

Paragraph 6:

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.~~

Section 6.3.6. Clinical Laboratory Assessments

Rationale for Change: fasting requirements reduced to increase subject compliance

Revised Text:

Paragraph 2:

Subjects should be instructed to fast (no food and only water allowed) for ~~10~~ 8 hours prior to any fasting laboratory assessments (example: fasting glucose, fasting lipid panel, etc.).

Section 6.4.1. Disease Assessment

Rationale for Change: wording changed to reflect A9 cohort changes

Revised Text:

Response will be assessed as outlined in the Section 5 Time and Events Table 7 Table by the investigator using the appropriate criteria for MM, lymphoma, CTCL, AML, and MDS, as noted in Appendix 6, Appendix 7 Appendix 8, ~~and~~ Appendix 9, and Appendix 10, respectively.

Section 6.5.1. Blood Sample Collection

Rationale for Change: additional analyses to be performed based on emerging data

Revised Text:

Paragraph 1 sentence 1:

Blood samples to enable quantification of GSK525762, and relevant metabolites, as applicable, in plasma will be collected at the time points indicated in the Section 5 Time and Events Tables.

Section 6.6.2. Blood Sample Collection for Exploratory Translational Research

Rationale for Change: clarification to required procedures for MDS specific population

Revised Text:

Paragraph 1 bullet point 1:

- Part 1 &2: At screening, date of bone marrow biopsy (Part 2 MDS cohort only), disease assessment (Table 7) and disease progression for isolating plasma for circulating biomarkers (eg, cfDNA) , PBMCs and neutrophils.

Section 6.10. Quality of Life/Patient-Reported Outcomes

Rationale for Change: Skindex-29 as part of addition of CTCL cohort

Revised Text:

6.10. Quality of Life/Patient-Reported Outcomes

Patient-reported outcome, Skindex 29 (refer to Appendix 11) will be used to gauge the effects of treatment with GSK525762 on the quality of life and other subjective measures in subjects with CTCL.

Section 7.1. GSK525762 Investigational Product Dosage/Administration

Rationale for Change: modification/clarification to IP handling requirements

Revised Text:

~~When used under the conditions of handling and administration described in Section 7.2, investigational product is not expected to pose significant safety risks to site staff.~~ Precaution will be taken to avoid direct contact with the study treatment.~~-~~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 15 GSK525762 Besylate Investigational Product Dosage/Administration

	Investigational Product			
Product name:		GSK525762 Besylate Tablets		
Unit dose strength(s)/Dosage level(s):	5mg	20mg	25mg	50mg
Dosage form	Tablet	Tablet	Tablet	Tablet
Manufacturer	GSK	GSK	GSK	GSK
Physical description:	White to slightly colored, round, biconvex tablet.	Yellowish pink, round, biconvex tablet	White to slightly colored, round, biconvex tablet	White to slightly colored, oval shaped tablet

Section 7.2. Handling and Storage of Study Treatment

Rationale for Change: modification/clarification to IP handling requirements

Revised Text:

Handling

Precaution will be taken to avoid direct contact with the study treatment.

~~Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff.~~ An 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

Section 7.3. Meals and Dietary Restrictions

Rationale for Change: clarification to meals/dietary requirements

Revised Text:

Paragraph 4 sentence 1:

Based on the results of the BET115521 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 for subjects in Part 2 only except on Serial PK sampling days (Week 1 and Week 43) or days in which required for fasting blood draws.

Section 7.7.1. Dose and Safety Management Guidelines

Rationale for Change: The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile, and BID dosing was removed. Medications affecting QT prolongation were re-categorized from prohibited to cautionary.

Revised Text:

Table 16 Dose Adjustment/Stopping Safety Criteria

Stopping criteria: QTcF <~~500~~ 530

Management guidelines: QTcF

(1) QTcF event reduced to <48~~5~~0 msec,

(5) Institutional IRB (or equivalent) approval (if required), and

Section 7.7.2. Dose Adjustments for Toxicity

Rationale for Change: correction of study number

Revised Text:

Paragraph 2 sentence 1:

Dose escalation decisions will take into account all available data, including PK data and the safety profile of prior cohorts, relevant data from Study BET116183~~5221~~, and will occur following review of these data by the investigator(s), GSK medical monitor, pharmacokineticist, and statistician.

Section 8.2. Cautionary/Prohibited Medications

Rationale for Change: modifications to criteria based on updated risk/benefit profile

Revised Text:

Paragraph 2:

Subjects must not receive other anti-cancer therapy (including chemotherapy, immunotherapy, biologic therapy, or hormonal therapy, whether approved or investigational) while on treatment in this study. Short courses of steroids may be co-administered with permission from the GSK medical monitor.

Paragraph 4 onwards:

Aspirin may not be administered at doses that exceed ~~81~~ 100 mg per day. Non-steroidal anti-inflammatory agents should be avoided except where they provide benefit over other analgesics; if administered, they should be used with caution and consideration should be given to co-administration with proton pump inhibitors.

Co-administration of medications that are associated with prolonged QT interval (please refer to crediblemeds.org for a complete list of these medications) is permitted as follows:

- If a subject is taking a QT-prolonging medication prior to first dose of GSK525762, then the subject may continue to take this medication without additional monitoring, so long as the baseline QTcF meets criteria as described in Section 4.2.2
- If a subject must initiate a QT-prolonging medication while receiving GSK525762, then additional ECG monitoring should be implemented, per local standard, until the QT-prolonging medication achieves therapeutic concentrations. Refer to Table 16 for QT management guidelines.

Section 8.2.1. Cautionary Medications

Rationale for Change: Eligibility criteria for all populations were updated (ECOG, cardiac safety). The time and events tables were updated to reduce the cardiac monitoring based on updated risk/benefit profile, and medications affecting QT prolongation were re-categorized from prohibited to cautionary.

Revised Text:

~~**8.2.1. Cautionary 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) those listed in Table 18.~~

Table 18 Drugs with a Risk of Torsades de Pointes which are permitted for co-administration with Extreme Caution

Alfuzosin	Lithium
Apomorphine	Mifepristone
Aripiprazole	Mirabegron
Artenimol + piperaquine	Mirtazapine
Asenapine	Moexipril/HCTZ
Atomoxetine	Nicardipine
Bedaquiline	Norfloxacin
Buprenorphine	Nortriptyline
Clomipramine	Ofloxacin
Clozapine	Olanzapine
Cyamemazine	Oxytocin
Degarelix	Paliperidone
Delamanid	Pasireotide
Desipramine	Perflutren lipid microspheres
Dexmedetomidine	Pipamperone
Dolasetron	Promethazine
Ezogabine	Rilpivirine
Famotidine	Risperidone
Felbamate	Roxithromycin
Fingolimod	Saquinavir
Fluconazole	Sertindole
Foscarnet	Telavancin
Gemifloxacin	Telithromycin
Granisetron	Tetrabenazine
Hydrocodone – ER	Tizanidine
Iloperidone	Tolterodine
Imipramine	Trimipramine
Isradipine	Tropisetron
Leuprolide	Vardenafil
Levofloxacin	Venlafaxine

Data Source: CredibleMeds, 15 May 2016 (www.crediblemeds.org).

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

After starting cautionary medications such as in Table 18 it is recommended that ECGs are implemented daily until the steady state is reached. If there are abnormalities, implement additional cardiotoxicity monitoring.

Section 8.2.1. Drugs Potentially Affecting GSK525762 Pharmacokinetics or affected by GSK525762

Rationale for Change: simplification/clarification to wording

Revised Text:

Paragraph 1:

In vitro data suggests that GSK525762 is only metabolized by CYP3A4 and thus coadministration of potent inducers and moderate or potent inhibitors of CYP3A4 should be avoided during the course of the study where possible as they may respectively decrease or increase exposure to GSK525762. Note: any medication (including antibacterials, antifungals, or antivirals) which are necessary for the health, well-being, and standard clinical care of patients with hematologic malignancies are exempt from the restrictions below.

~~**Table 19 Drugs Potentially Affecting GSK525762 Pharmacokinetics Resulting in Increased or Decreased GSK525762 Exposure**~~

~~Drug Class~~	~~Agent~~
~~**Drugs that may decrease exposure to GSK525762 (CYP and/or Pgp Inducers)**~~	
~~Antibiotics~~	~~Nafcillin, all rifamycin class agents (e.g., rifampicin, rifabutin, rifapentine)~~
~~Anticonvulsants~~	~~Phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)~~
~~Antiretrovirals~~	~~Efavirenz, etravirine, nevirapine, tipranivir,~~
~~Glucocorticoids (oral)~~	~~Cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)~~
~~Other~~	~~Bosentan, St. John's Wort, modafinil~~
~~**Drugs that may increase exposure to GSK525762 (CYP3A4 Inhibitors)**~~	
~~Antibiotics~~	~~Clarithromycin, telithromycin, troleandomycin~~
~~Antifungals~~	~~Fluconazole (>150 mg daily), itraconazole, ketoconazole, , posaconazole,voriconazole~~
~~Antivirals~~	~~Amprenavir, atazanavir, boceprevir, delaviridine, fosamprenavir, indinavir, lopinivir,nelfinavir, ritonavir, saquinavir, telaprevir~~
~~Calcium channel blockers~~	~~Diltiazem, verapamil~~
~~Antidepressants, anxiolytics~~	~~nefazodone, tofisopam~~
~~GI Agents~~	~~Cimetidine~~
~~Other~~	~~Seville oranges, grapefruit or grapefruit juice and/or kumquats, pomegranate or pomegranate juice, pomelos, exotic citrus fruit (i.e., star fruit, bitter melon), grapefruit hybrids or fruit juices, or other foods and juices known to inhibit CYP3A4~~

~~NOTE: Topical or inhaled steroids are permitted.~~

Section 8.3. Prohibited Medications

Rationale for Change: modifications to criteria based on updated risk/benefit profile

Revised Text:

~~**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, or 14 days, whichever is longer, 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) those listed in Table 20.~~

~~**Table 20 Drugs with a Risk of Torsades de Pointes that are Prohibited**~~

~~Amiodarone~~	~~Grepafloxacin~~
~~Anagrelide~~	~~Halofantrine~~
~~Azithromycin~~	~~Haloperidol~~
~~Chloroquine~~	~~Ibutilide~~
~~Chlorpromazine~~	~~Levomepromazine~~
~~Cilostazol~~	~~Methadone~~
~~Ciprofloxacin~~	~~Moxifloxacin~~
~~Citalopram~~	~~Papaverine~~
~~Clarithromycin~~	~~Pentamidine (IV)~~
~~Cocaine~~	~~Pimozide~~
~~Disopyramide~~	~~Procainamide~~
~~Dofetilide~~	~~Propofol~~
~~Domperidone~~	~~Quinidine~~
~~Donepezil~~	~~Sevoflurane~~
~~Dronedarone~~	~~Sotalol~~
~~Droperidol~~	~~Sulpiride~~
~~Escitalopram~~	~~Thioridazine~~
~~Flecainide~~	

~~NOTE: 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: CredibleMeds, 15 May 2016 (www.crediblemeds.org).~~

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

~~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 5 half-lives of the drug or 14 days whichever is longer,** 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 (up to a maximum dose of 0.25 mg daily) and ondansetron (up to a maximum dose of 8 mg TID) are the only allowed drugs in this class.~~

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

Section 8.3. Non-Drug Therapies

Rationale for Change: clarification of permitted procedures

Revised Text:

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, except as follows:~~.~~

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. Irradiated/resected lesions should not subsequently be utilized as the sole lesion(s) for response assessment determination. ~~Subjects may receive palliative radiation treatment during this study.~~

Section 8.5. Treatment of Study Treatment Overdose

Rationale for Change: urine sample not needed

Revised Text:

Paragraph 1 bullet point 3 sub point 1:

- This plasma ~~or urine~~ sample should be collected as soon as possible from the date of the last dose of on-study dosing.

Section 9.1.1. Female Subjects

Rationale for Change: criteria updated following conversation with GSK reproductive panel

Revised Text:

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-

ovulation methods) and withdrawal are NOT acceptable methods of contraception.
Contraceptive Methods with a Failure Rate of ≤ 1%

- Intrauterine device (IUD) or intrauterine system (IUS) that meets the < 1% failure rate as stated in the product label
    - Note: Hormonal IUDs may only be used if the following criteria are met:
        - Male condoms are required AND
        - Subjects are informed of the potential for reduced systemic hormone levels from the IUD when taking GSK525762

Section 9.1.2. Male Subjects

Rationale for Change: criteria updated following conversation with GSK reproductive panel

Revised Text:

Paragraph 3:

Male subjects whose partners are pregnant, or whose partners~~or~~ become pregnant during participation in the study, must use condoms ~~while on study~~from the first dose of study medication and for 16 weeks after stopping study medication(s).

Section 11.1.2. Part 2, Expansion Cohort

Rationale for Change: The study population for the NHL cohort in Part 2 was amended from a population of subjects with NHL to a population of subjects with cutaneous T-cell lymphoma (CTCL). The Part 2 primary and secondary objectives along with the eligibility criteria were updated to include this new CTCL population, and removal of expansion into multiple myeloma in Part 2.

Revised Text:

Paragraph 1:

The primary goal of Part 2 is to evaluate disease-specific efficacy in subjects with MDS, ~~MM,~~ and CTCL ~~NHL~~.

Bullet point 2 onwards:

- ~~For MM, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a sCR, CR, VGPR, or PR) of 20% relative to a 5% response rate suggesting no activity. These values were identified in a recent meta-analysis that suggested that a response rate of 20% or greater in the relapsed/refractory population was highly predictive of clinical success, whereas older agents with limited clinical activity had a negligible response rate (Kortuem, 2014).~~
- For ~~cutaneous lymphoma~~NHL~~~~CTCL, efficacy is defined as a clinically meaningful response rate (defined as the percentage of subjects that have achieved a CR, or PR lasting more than 4 months) of ~~4~~3~~~~0% relative to a ~~2~~1~~~~0% response rate suggesting no

activity. Multiple clinical studies with active and approved agents have demonstrated a response rate of 30-40% in a comparable patient population (Duvic, 2007; Piekarz, 2007; Whittaker, 2010). Therefore, a target response rate of 40% was chosen to represent the response rate of an active agent. Conversely, an agent with a response rate of 20% is unlikely to be developed further; this is approximately the response rate of placebo described in the denileukin difitox package insert (ONTAK package insert). Therefore, 20% was chosen to represent the activity of a futile agent. ~~These response rates were consistent with multiple ongoing studies of single agent, targeted therapy in Phase I clinical trials for subjects with relapsed/refractory NHL. For this cohort, double/triple-hit lymphoma subjects will be excluded from initial efficacy analysis and will be evaluated separately.~~

Paragraph 6 onwards:

For the MDS ~~and cutaneous lymphomaNHLCTCL disease~~ cohort~~s~~, starting with a cohort of 10 subjects and allowing for a maximum sample size of 32 subjects at the RP2D with stopping guidelines as described in Section 3.2.4, this design will have a Type I Error (α) of 0.034 and 87% power. Futility analysis will be based on subjects who have at least one post-baseline disease assessment, have progressed or died, or have permanently discontinued from study treatment. The trial will be stopped early for futility if the predictive probability of success (that the response rate ≥ historical response rate) is less than 1%. If the true response rate is 10%, the average sample size is 20 and the probability of early termination ~~(PET)~~ for futility is 93%. If the true response rate is 30%, the average sample size is 31 subjects and the probability of early termination ~~PET~~ is 9%.

For the ~~MM disease~~CTCL cohort, starting with a cohort of ~~13~~10 subjects and allowing for a maximum sample size of 37 subjects at the RP2D with stopping guidelines as described in Section 3.2.4, this design will have a Type I Error (α) of 0.~~032~~049 and 85.2% power. Futility analysis will be based on subjects who have at least one post-baseline disease assessment, have progressed or died, or have permanently discontinued from study treatment. The trial will be stopped early for futility if the predictive probability of success (that the response rate ≥ historical response rate) is less than 1%. If the true response rate is ~~5~~20%, the average sample size is ~~22~~23 and the probability of early termination ~~(PET)~~ for futility is ~~91~~92%. If the true response rate is ~~20~~40%, the average sample size is 36 subjects and the probability of early termination ~~PET~~ is ~~10%~~11%.

Section 11.4. Interim Analysis

Rationale for Change: Stats plan revised to align with A9 changes

Revised Text:

Paragraph 2:

For each disease type in Part 2, after ~~the initial 10 evaluable~~at least 10 subjects in the MDS or cutaneous lymphoma ~~NHL~~ cohorts ~~and initial 13 evaluable subjects in the MM cohort have enrolled~~become evaluable (have had at least one post baseline disease assessment, have progressed or died, or have permanently discontinued from study treatment) at the selected dose regimen for the Expansion Cohort, data will be reviewed

for clinical benefit on an ongoing basis and the number of subjects with observed clinical benefit will be compared with the stopping guidelines provided in Section 3.2.4. For the CTCL cohort, ~~S~~subjects with CTCL in Part 1 treated at the RP2D ~~may~~ will be included in this analysis of efficacy.

Section 11.6.1. Primary Analysis

Rationale for Change: Stats plan revised to align with A9 changes

Revised Text:

Paragraph 2 onwards:

The primary aim of Part 2 is to detect ~~demonstrate~~ a possibly clinically meaningful response rate in each of the disease cohorts separately. Each disease ~~sub~~type (MDS~~, MM,~~ and CTCL~~NHL~~) will be evaluated separately.

Overall Response rate is defined as

- MDS: The percentage of subjects who achieved CR, marrow CR, ~~and~~ or PR, as defined in Appendix 9. A waterfall plot of percent change from baseline in bone marrow blasts and peripheral blasts will be provided.
- ~~MM: The percentage of subjects who achieved sCR, CR, VGPR, or PR.~~
- ~~Cutaneous lymphoma~~NHL~~L~~CTCL: ORR4 is defined as percentage of subjects who achieved a CR or PR lasting at least 4 months. Responses will be defined as per consensus guidelines (Olsen 2011) using mSWAT criteria (Appendix 11). All subjects treated at RP2D with CTCL will be counted as the denominator. The estimate for ORR4 along with 95% exact confidence interval will be provided. ~~The percentage of subjects who achieved CR or PR. Response rates of subjects with double/triple-hit lymphoma will be summarised separately.~~

For subjects in the CTCL cohort, scans, photographs and raw flow cytometry used for response assessments may be requested for independent review. Further details regarding collection, storage, and transmission of these will be provided in the SRM

Section 11.6.2. Secondary Analysis

Rationale for Change: Stats plan revised to align with A9 changes

Revised Text:

Paragraph 3 onwards:

The duration of response is defined for ~~the subject or subjects~~ responders (subjects with CR, marrow CR, or PR for MDS cohort, or subjects with a CR or PR for ~~cutaneous lymphoma~~NHL~~L~~CTCL cohort), ~~and sCR, CR, VGPR, or PR for MM~~ as the time from the first documented evidence of response 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 Progression is calculated from the start of treatment 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.~~

If sample size permits, duration of response ~~and time to progression~~ will be summarized descriptively using Kaplan-Meier medians and quartiles. Censoring rules for duration of response will follow the rules for PFS outlined in detail in the RAP

OS along with 95% confidence intervals for leukemia subjects in Part 1, MDS subjects in Part 2, and MM ~~and lymphoma~~ subjects treated in Part 1 and cutaneous lymphoma subjects treated in Part 2, will be estimated using the Kaplan Meier method if data warrant. OS analysis for AML will exclude subjects with AML subtype M3. ~~NHL will be separately reported based on double/triple hit status.~~ All cause mortality will be used and censoring will be performed using the date of last known contact for those who are alive or lost to follow-up at the time of analysis.

Section 11.9. Pharmacokinetic/Pharmacodynamic Analyses

Rationale for Change: Stats plan revised to align with A9 changes

Revised Text:

Added sentence at the end:

This analysis may be reported separately.

Section 11.12. Quality of Life Analyses

Rationale for Change: Skindex-29 added as part of A9 CTCL cohort

Revised Text:

11.12. Quality of Life Analyses

Skindex-29 inquires about how often during the previous four weeks the patient experienced the effect described in each item. It includes three domains: Emotional, Symptoms, and Functioning as well as an additional item about Treatment that is not scored. Details about the score derivation and analysis will be provided in the RAP. See Appendix 11 for more details.

Section 14. REFERENCES

Rationale for Change: additional references added for CTCL cohort

Revised Text:

Following references have been added/updated:

Ahern K, Gilmore ES, Poligone B. Pruritus in cutaneous T-cell lymphoma: a review. *J Am Acad Dermatol*. 2012;67(4):760-768.

Duvic M, Talpur R, Ni X, Zhang C, Hazarika P, Kelly C, et al. Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). *Blood*. 2007 Jan 1;109(1):31-39.

GlaxoSmithKline Document Number 2011N113741_06~~2011N113741_05~~ Version 6~~5~~. GSK525762 Investigator's Brochure. Report Date 06-Apr-2017~~28 Mar 2016~~.

Kohnken R, Wen J, Mundy-Bosse B, McConnell K, Keiter A, Grinshpun L, et al. Diminished microRNA-29b level is associated with BRD4-mediated activation of oncogenes in cutaneous T-cell lymphoma. *Blood*. 2017;131(7):771-781.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI,, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, et al. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneousT-cell lymphoma. *J Clin Oncol*. 2007;25: 3109-3115.

Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. *J Clin Oncol*. 2011;29(18):2598-607.

ONTAK (denileukin diftitox) Product Information. October, 2008.

Piekarz RL, Frye R, Turner M, Wright JJ, Allen SL, Kirschbaum MH, et al. Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma. *J Clin Oncol*. 2009;27(32):5410-5417.

Whittaker S, Hoppe R, Prince HM. How I treat mycosis fungoides and Sézary syndrome. *Blood*. 2016;127(25):3142-3153.

Whittaker SJ, Demierre MF, Kim EJ, Rook AH, Lerner A, Duvic M, et al. Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2010;28(29):4485-4491.

Section 15.1. Appendix 1: ~~Cockcroft-Gault~~CKD-Epi Formula

Rationale for Change: change in alignment with GSK nephrology panel

Revised Text:

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

Females, serum creatinine >62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-1.209} \times 0.993^{\text{age}}$

Females, serum creatinine ≤62 µmol/L: $144 \times (\text{serum creatinine} \times 0.0113/0.7)^{-0.329} \times 0.993^{age}$

Males, serum creatinine >80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-1.209} \times 0.993^{age}$

Males, serum creatinine ≤80 µmol/L: $141 \times (\text{serum creatinine} \times 0.0113/0.9)^{-0.411} \times 0.993^{age}$

[Levey, 2009]

~~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.*~~

Section 15.3 Appendix 3: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Rationale for Change: updated as per latest criteria

Revised Text:

Phase I/II liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

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	
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is granted** • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant 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 participants 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 participants weekly until liver chemistries resolve, stabilize or return to within baseline

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant 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 participants 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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) 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 participant'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 SRM.

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.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

~~Liver chemistry stopping criteria~~

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

liver chemistry stopping criteria is/are met. ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured)

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

- ALT ≥5xULN.
- ALT ≥3xULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
- 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. See following section for details on weekly follow-up procedures for these subjects.

Liver Chemistry Follow-up Procedures

Refer to the diagram in Figure 7 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined above**:**

- Immediately and permanently withdraw the subject from study treatment
- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event eCRFs. If the event also meets the criteria of an SAE (see Section 6.7.2 of the protocol), the SAE data collection tool will be completed separately with the relevant details
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s).

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:

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

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

- **This event is considered an SAE** (see Section 6.7.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, ALP, bilirubin) resolve, stabilize or return to within baseline values.

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

- Viral hepatitis serology including:
  - 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.
- 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 eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥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 eCRF.
- Record use of concomitant medications such as acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the Concomitant Medications eCRF page.
- Record alcohol use on the Liver Event CRF page.

~~The following assessments are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN but are optional for other abnormal liver chemistries:~~

- ~~Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.~~
- ~~Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.~~
- ~~Liver Imaging and/or Liver Biopsy CRF pages are also to be completed if these tests are performed. 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. **NOTE**: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1153793.~~

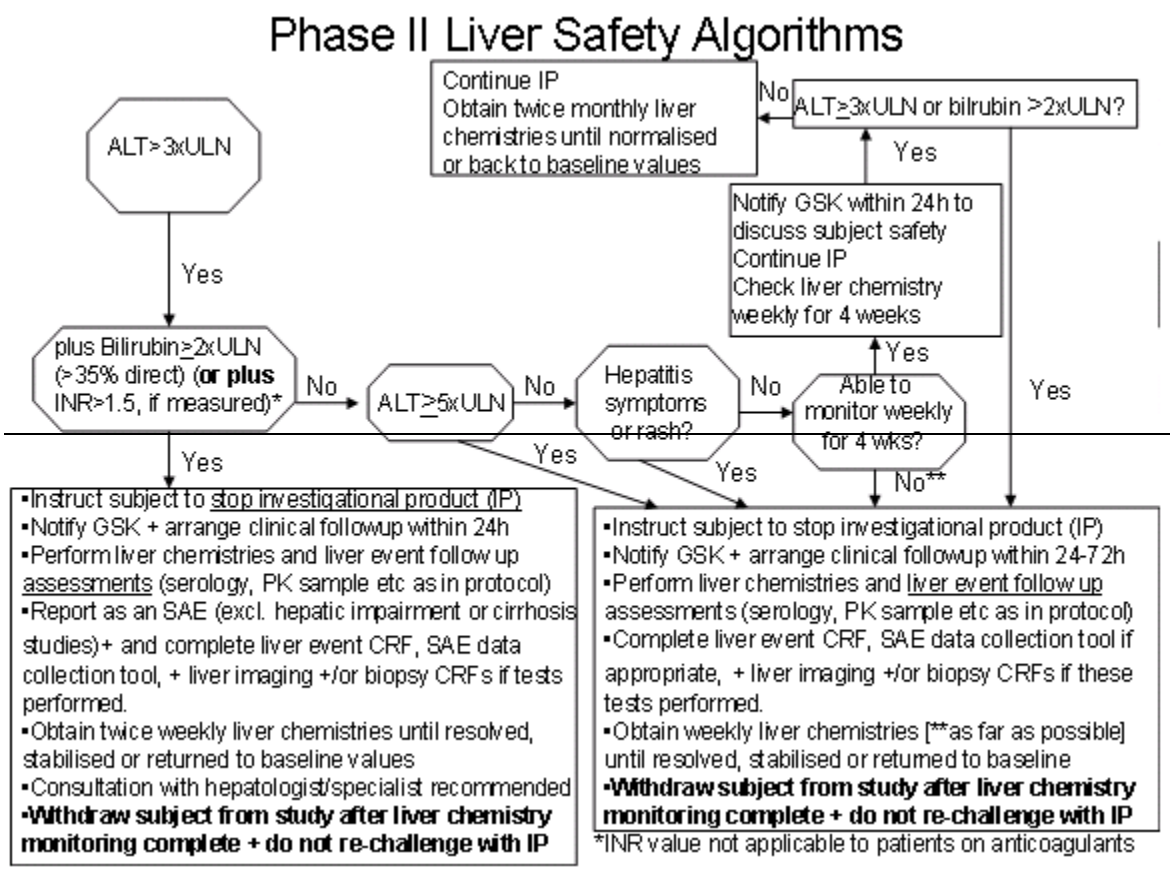
~~Liver Chemistry Monitoring Criteria~~

~~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, ALP, 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 6 for the algorithm of liver chemistry monitoring, stopping and follow up criteria.~~

~~Figure 6 Liver Safety Algorithms~~



Liver Safety Drug Restart Guidelines

If participant meets liver chemistry stopping criteria do not restart/rechallenge participant 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 participant

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

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 (Andrade, 2009) with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- participant 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; Hunt, 2010)
- 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 participant 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 participant 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 participant 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 participant 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.
- Participants 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, participant 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 participant's outcome following study treatment rechallenge.

- GSK to be notified of any adverse events, as per Section 6.7.

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

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).
- Possible study treatment-induced liver injury has been excluded by the investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia). Where a study treatment has an identified genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate), the presence of the marker should be excluded. If study treatment-related liver injury cannot be excluded, the guidance on rechallenge in Section 7.7 will apply.
- There is no evidence of alcoholic hepatitis.
- 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 participant 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 participant 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.
- Participants 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, participant 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 participant's outcome following study treatment restart.

- GSK to be notified of any adverse events, as per Section 6.7.

References:

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

~~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~~** ~~[Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered in one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality. Risk factors for a fatal drug restart/rechallenge outcome include: hypersensitivity1 with initial liver injury (e.g., fever, rash, eosinophilia), jaundice or bilirubin>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 Figure 7)~~

~~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 (Table 17).~~

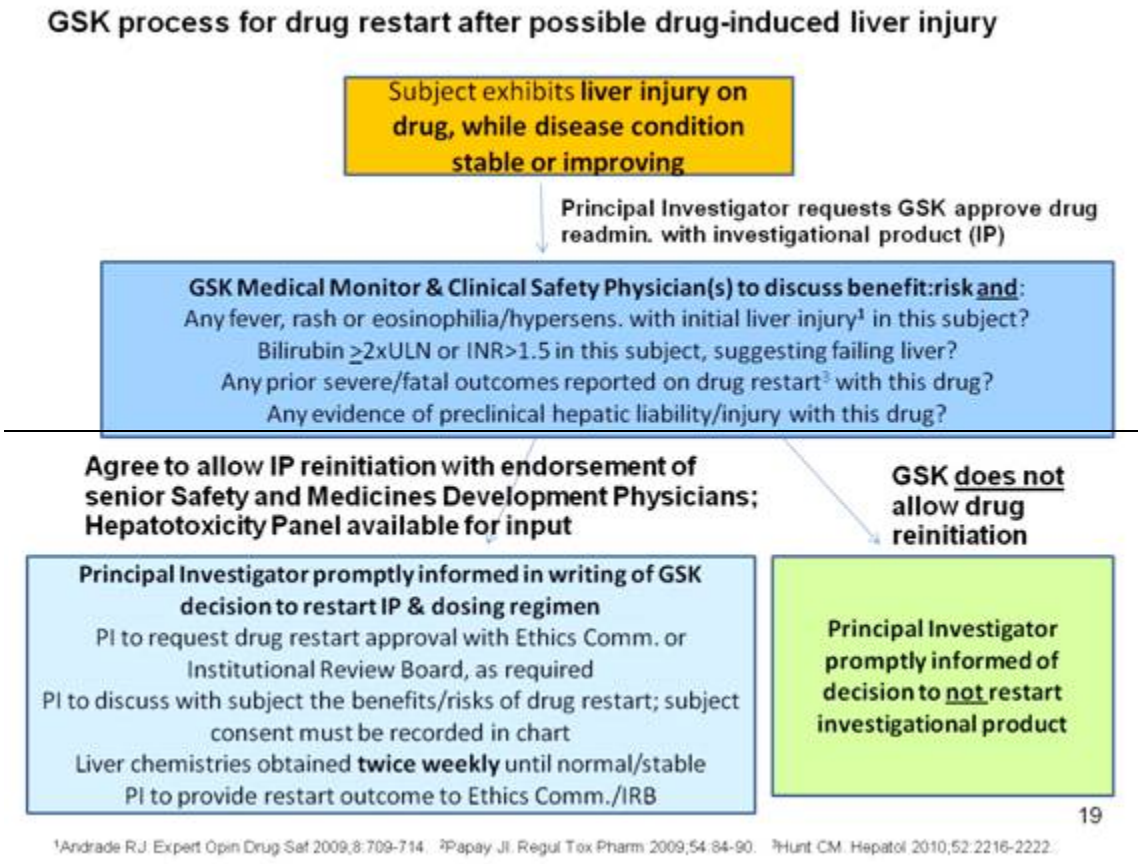
Table 17 Checklist for drug restart/rechallenge for critical medicine

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:		
1. fever, rash, eosinophilia, or hypersensitivity		
2. 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 PI must ensure the following:

- The PI is to obtain IRB/ EC 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 IRB/ EC is to be informed of the subject's outcome, as required.
- GSK is to be notified of any adverse events, as per Section 6.7 of the protocol.

~~**Figure 7 Process for Drug Restart After Possible Drug-induced Liver Injury**~~



Section 15.7. Appendix 7: Response Criteria for Non-Hodgkin's Lymphoma (Part 1)

Rationale for Change: addition of CTCL specific criteria

Revised Text:

The section heading changed as mentioned above

Section 15.10. Appendix 10: Staging and Response Criteria for CTCL (mSWAT method)

Rationale for Change: addition of staging and response criteria for CTCL

Revised Text:

15.10. Appendix 10: Staging and Response Criteria for CTCL (mSWAT method)

[Olsen, 2011]

15.10.1. Staging of Subjects with CTCL

Table 17. Modified ISCL/EORTC Revisions to the tumor-node-metastasis-blood (TNMB) Classification of MF/SS

TNMB Stages	**Description of TNMB**
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or National Cancer Institute (NCI) LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement

TNMB Stages	**Description of TNMB**
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/µL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; NCI, National Cancer Institute.

*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

†Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.

‡The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Table 18. Modified ISCL/EORTC Revisions to the Staging of MF/SS

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

15.10.2. Response Assessment of Subjects with CTCL

Refer to Table 20, Table 21, Table 23, Table 24, and Table 25 for definitions of response in each category. All subjects achieving CR or PR should be confirmed by repeat assessment no sooner than 4 weeks after the prior assessment demonstrating response.

Table 19 Global Response Score

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		

Global Score*	Definition	Skin	Nodes	Blood	Viscera
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.

Refer to Table 22 for definition of mSWAT

Table 20 Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

NOTE. Based on modified Severity Weighted Assessment Tool score.

*A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there

is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome (see histologic criteria for early mycosis fungoides7), the response should be considered a partial response only.

†Whichever criterion occurs first.

Table 21 Modified Severity Weighted Assessment Tool (mSWAT)

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor				

NOTE. mSWAT score equals summation of each column line.

Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool.

*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

‡Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

Table 22 Response in Lymph Nodes

Response	Definition
CR	All lymph nodes are now ≤1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

*Peripheral and central lymph nodes.

†Whichever criterion occurs first.

Table 23 Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or New organ involvement or Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.

*Whichever criterion occurs first.

Table 24 Response in Blood

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/µL or

Response	**Definition**
	Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/µL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

*As determined by absolute numbers of neoplastic cells/µL.

†If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.

‡There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.

§Whichever occurs first.

Section 15.11 Appendix 11: Patient Reported Outcomes Assessments for CTCL (Skindex-29)

15.11.1 US English Skindex-29

Note: please refer to the SPM for additional translations of Skindex-29

Skindex29
©MMChrm,1996

DERMATOLOGY SURVEY

This survey concerns the skin condition which has bothered you the most during the past four weeks.

Skindex29 - United States/English -Mapi.
Skindex29_AUS.0_eng-USton.doc

Skindex29
©MMChren,1996

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

Please turn to next page

Skindex29 - United States/English -Mapi.

Skindex29
©MMChren,1996

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

Skindex29 - United States/English -Mapi.