CONFIDENTIAL

The GlaxoSmithKline group of companies BET116183

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

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
Effective Date	:	Refer to Document Date

Description :

The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol BET116183.

This RAP is intended to describe the safety, efficacy and pharmacokinetic analyses required for the study.

This RAP will be provided to the study team members to convey the content of the Part 1 Interim Analysis and Part 2 Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

PPD Principal Statistician (Clinical Statistics)	28-JUN-2019
PPD Statistics Leader (Clinical Statistics)	10-MAR-2020

RAP Team Reviews (Confirmation Method: Email):

Reviewer	Date
PPD Clinical Investigational Lead	22-APR-2020
PPD Pharmacokineticist	22-APR-2020

Clinical Statistics and Clinical Programming Line Approvals (Method: Pharma TMF eSignature):

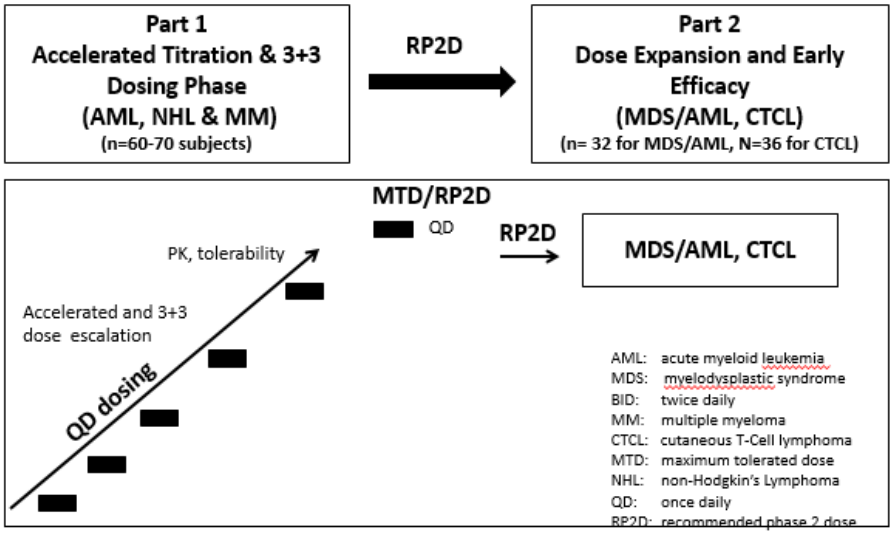
Approver
PPD Senior Director (Clinical Statistics)
PPD Director (Clinical Programming)

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Study Report for Protocol BET116183. This RAP is intended to describe the safety and efficacy analyses required for the study. This document will be provided to the study team members to convey the content of interim analysis and the Statistical Analysis Complete (SAC) deliverables.
Protocol	This RAP is based on the protocol amendment 9 [(Dated: 15/MAR/2018) of study BET116183(GSK Document No.: 2013N159121_10)] and eCRF Version 4.0
Primary Objectives	Part 1: 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). Part 2: 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"). To evaluate clinical efficacy after treatment with GSK525762 in cutaneous T-cell lymphoma (CTCL).
Primary Endpoints	Part 1: 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 2: 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. 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.
Study Design	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

Overview	Key Elements of the RAP
	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 CTCL (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 "CTCL cohort").  **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**
Planned Analyses	Part 1: Interim analysis on Part 1 may be conducted when • Part 1 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 Part 2: For each disease type, after at least 10 subjects in the MDS or CTCL cohorts become evaluable (have had at least one post baseline disease assessment, have progressed, 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 3.1.2 (Figure 1 & Figure 2). The study will not stop due to efficacy. The trial may continue to enrol the maximum planned sample size to provide a better estimate of the distribution of the response

Overview	Key Elements of the RAP
	rate in the target patient populations. Final analyses will be carried-out when 70% of subjects enrolled in Part 2 have progressed or died.
Analysis Populations	All Treated 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 Population: This will consist of those participants in All Treated Subjects Population for whom a PK sample is obtained and analyzed. The Pharmacodynamic Population: This will consist of those subjects in All Subjects Population who contribute pharmacodynamic/biomarker samples.
Hypothesis	No formal statistical hypotheses will be tested in Part 1. Analysis will be descriptive and exploratory. The primary goal of Part 2 is to demonstrate a clinically meaningful response, defined as follows: MDS cohort: A response rate (ORR) of 30% relative to a 10% response rate suggesting no activity. The null hypothesis that $P0 \leq 0.10$ will be tested versus the alternative that $P1 \geq 0.30$, assuming that the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. CTCL cohort: A response rate (ORR4) of 40% relative to a 20% response rate suggesting no activity. The null hypothesis that $P0 \leq 0.20$ will be tested versus the alternative that $P1 \geq 0.40$, assuming that the maximum response rate for an ineffective drug is 0.20 and the minimum response rate for an effective drug is 0.40.
Primary Analyses	Part 1: Summary of AEs, SAEs, DLTs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments. Part 2: a) Each disease subtype (MDS and CTCL) will be evaluated separately to detect a possibly clinically meaningful response rate. Objective Response rate is defined as: • MDS cohort: ORR is the percentage of subjects who achieved Complete Response (CR), Marrow CR, or Partial Response [PR] per response criteria. • CTCL cohort: ORR4 is the percentage of subjects who CR or PR lasting at least 4 months per consensus guidelines using mSWAT criteria. b) Analysis of Skindex-29 questionnaire results for the CTCL cohort.
Secondary	Part 1: Anti-tumor activities will be evaluated based on clinical evidence and

Overview	Key Elements of the RAP
Analyses	response criteria described for MM, lymphoma and/or leukemias (per Protocol Appendix 6, Appendix 7, Appendix 8, Appendix 9, Appendix 10). Part 2: Analysis of PFS (Progression Free Survival), OS (overall survival, the time from the treatment start date until death from any cause) and DOR (duration of objective response).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Effective June 19, 2019, GSK made the decision to close enrolment to the Part 2 MDS cohort; although GSK525762 showed some activity, in most patients this response does not translate into hematologic improvement and with the increasing amount of clinical data available on BET inhibitors, the opportunity for GSK525762 to show a differentiated profile with significant additional clinical benefit has decreased. This decision did not impact the Part 2 CTCL cohort, which remained open to enrolment.

Effective November 27, 2019, GSK made the decision to close the study; although GSK525762 showed some activity in hematologic malignancies the magnitude of clinical benefit and durability of response remain limited. Moreover, with recent approvals of other agents for relapsed/refractory CTCL, the opportunity for GSK525762 to show a differentiated profile with significant additional clinical benefit has decreased.

The follow-up Overall Survival analysis will therefore not be performed.

2.2. Study Objective(s) and Endpoint(s)

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), Predose (trough) concentration at the end of a dosing interval ($C\tau$), Maximum observed concentration (Cmax), Time of maximum concentration (tmax),

Part 1 Objectives		Part 1 Endpoints
		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 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

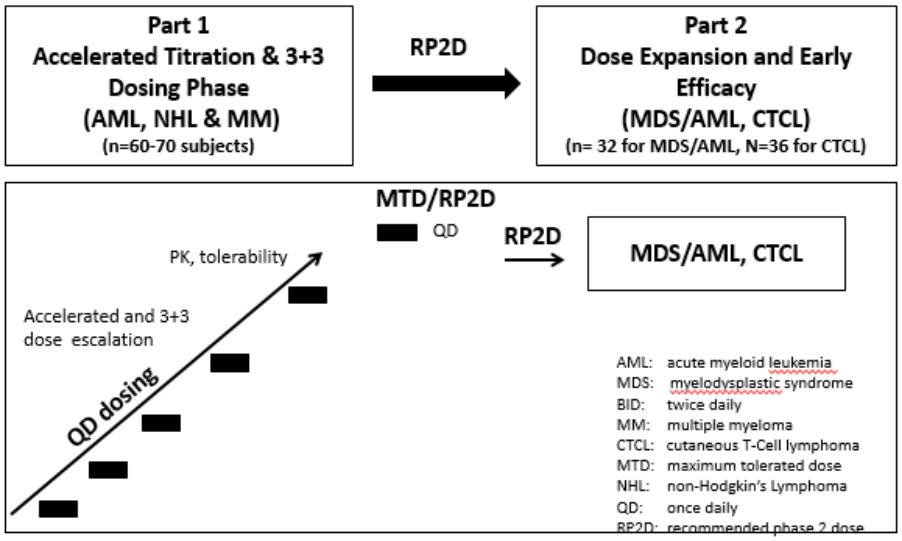
Part 2 Objectives		Part 2 Endpoints
Primary	• To evaluate clinical efficacy after treatment with GSK525762 in high-risk myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) that has evolved from an antecedent MDS ("myeloid cohort").	• For MDS cohort: ORR (defined as the percentage of subjects 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 questionnaire 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 MDS/AML, 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.
	• 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/AML and CTCL. • Overall survival (OS, the time from the treatment start date until death from any cause) for MDS/AML, and CTCL

Part 2 Objectives		Part 2 Endpoints
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: • MDS cohort: A response rate (ORR) of 30% relative to a 10% response rate suggesting no activity. The null hypothesis that P0≤0.10 will be tested versus the alternative that P1≥0.30, assuming that the maximum response rate for an ineffective drug is 0.10 and the minimum response rate for an effective drug is 0.30. • CTCL cohort: A response rate (ORR4) of 40% relative to a 20% response rate suggesting no activity in subjects with CTCL. The null hypothesis that P0≤0.20 will be tested versus the alternative that P1≥0.40, assuming that the maximum response rate for an ineffective drug is 0.20 and the minimum response rate for an effective drug is 0.40.

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	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.

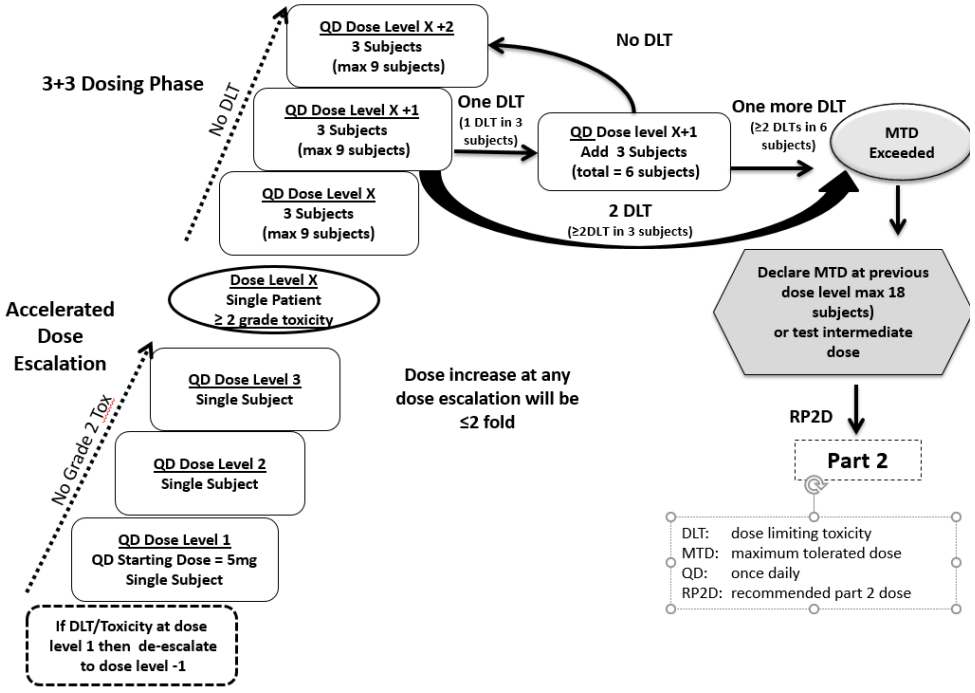


Objective: To evaluate and define safety and tolerability in heme tumors with continuous (and intermittent dosing) Starting dose of 5 mg
Dose escalation window 3 weeks
Evaluate preliminary efficacy in AML or select AML subtypes

Part 1 – Dose escalation: 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). 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]. 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 Part 1, the

Overview of Study Design and Key Features	
	Part 2 dose expansion cohorts will be opened for that disease type. **Part 2 - Disease Specific Expansion:** Up to 32 subjects with MDS and up to 37 subjects with CTCL, 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 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. The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored continuously for clinical response, with the constraint of both Type I and Type II error rates.
Dosing	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. Dose Escalation Schema (Part 1) 
Interim Analysis	Interim analysis on Part 1 may be conducted when • Part 1 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

Overview of Study Design and Key Features	
	For Part 2, 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, 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 study will not stop due to efficacy.

2.4. Statistical Hypotheses

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

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

- For MDS, a clinically meaningful response rate (the percentage of subjects that have achieved a CR, marrow CR, or PR) is defined as 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, a clinically meaningful response rate (the percentage of subjects that have achieved a CR, or PR lasting more than 4 months) is defined as 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.

3. PLANNED ANALYSES

3.1. Interim Analyses

Interim analysis of the key parameters may be carried-out before the conclusion of the study.

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

Dose escalation and stopping rules are guidelines for decision-making and the totality of the data will be considered by the team when making a decision. Clinical trial data used in these decisions will be in-stream data only; that is, the data will not necessarily be cleaned in advance of the formal interim analyses.

3.1.1. Part 1: Dose Escalation Phase

The interim analysis on Part 1 may be conducted when

- Part 1 is completed
- 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

3.1.1.1. Description of the New Continual Reassessment Method

The N-CRM is a type of Bayesian adaptive dose-escalation scheme that estimates the parameters of a statistical model relating dose and toxicity and is expected to locate the MTD efficiently while minimizing the number of subjects exposed to pharmacologically inactive or unsafe dose levels. The method is fully adaptive and makes use of all the toxicity information available at the time of each dose assignment. N-CRM estimates may be provided at dose escalation meetings as supportive material to the primary 3+3 dose escalation design.

The N-CRM estimates, for each potential dose, the (Bayesian) posterior probabilities that the DLT rate lies in each of four predefined toxicity ranges:

A dose falls in the **Under-dosing** range if the rate of a DLT at the dose is in the interval [0%, 16%).

A dose falls in the **Target** toxicity range if the rate of a DLT at the dose is in the interval [16%, 33%).

A dose falls in the **Excessive** toxicity range if the rate of a DLT at the dose is in the interval [33%, 60%).

A dose falls in the **Unacceptable** toxicity range if the rate of a DLT at the dose is in the interval [60%, 100%].

Additionally, the following over-dose constraints for the recommended dose will be maintained:

The posterior probability of the DLT rate lying in the Excessive Toxicity or Unacceptable Toxicity range is 0.25 or less.

The recommended dose is no more than 2 times that of the previous dose.

Note that a de-escalation recommendation is possible using this method. At the time of each dose-escalation decision, the dose with the highest posterior probability of lying in the Target Toxicity range (subject to the given constraints) will be the model-recommended dose for the next cohort.

3.1.1.2. Prior Probability Distribution

Elicited prior probabilities of a DLT at each dose were used to determine the prior distribution of the parameters of an explicit logistic dose-toxicity model, namely

$$ln\left(p_d/(1-p_d)\right) = \alpha + \beta * ln\left(d/d_m\right),$$

where p_d is the probability of a DLT at dose d, and d_m is a reference dose.

The prior distribution of (α, ln(β)) will be assumed to be bivariate normal with means (standard deviations): E[α]=−1.4346 (1.829), E[ln(β)]=-0.0394 (0.4282), with correlation between α and ln(β) set to ρ=−0.25 and d_m=50mg.

3.1.1.3. Displays To Be Created For Dose Escalation Review

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). 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.

Evaluation of at least three subjects who have completed one dosing level is required prior to determining the dose for the next cohort.

Review of preliminary data will be performed after completion of each dosing cohort in Part 1. Preliminary safety and study population data may include a demographic summary, adverse event (AE) summary, AE summary by maximum toxicity category, SAE listing, listing of AEs that are reported to be DLT's, and listing of AEs leading to dose modification. Spreadsheets containing relevant study data may also be supplied by the study data manager.

Further, after the first instance of a DLT and for each subsequent cohort, the recommended dose from the N-CRM method and updated posterior estimates of the probabilities of being in each dose-toxicity range may be provided. The Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 2.4 or higher) software from Tessella will be used to make N-CRM calculations.

Prior to determining a dose for the next cohort, exploratory analyses will be conducted to assess the relationship of dose levels with safety, PK, and pharmacodynamic parameters using all data from available cohorts.

The GSK study team, in collaboration with study investigators, will review all relevant data to support:

- whether the current dose had acceptable toxicity, and
- the decision regarding the next dose level based on the totality of the data

3.1.2. Part 2: Disease Specific Expansion Cohorts

For each disease type in Part 2, after the initial 10 evaluable subjects in the MDS and CTCL cohorts 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.

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

3.1.2.1. Stopping Rules for Futility

The Part 2 portion of the study will employ a Bayesian design that allows the trial to be monitored continuously for clinical response, with the constraint of both Type I and Type II error rates. Clinical response will be defined per standard evaluation criteria (see protocol Appendix 9 and Appendix 10).

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, 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 1 and Figure 2. The methodology is based on the predictive probability of success if enrolment continues to maximum number of subjects for MDS and CTCL. 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 1 and Figure 2. 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 1 Diagram of Stopping Rules for MDS Cohort Expansion (Part 2)

	Number of Responders						
Number of Evaluable 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 enrolment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and further enrolment in this cohort may be stopped.

Figure 2 Diagram of Stopping Rules for CTCL Cohort Expansion (Part 2)

	Number of Responders											
Number of Evaluable 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 enrolment for futility. For instance, if there is no response in 10 subjects, then the predictive probability for success will be 1% or less (the futility criterion) and further enrolment in this cohort may be stopped.

3.1.2.2. Operating Characteristics of the Stopping Rules for Futility

The stopping rules in Figure 1 and Figure 2 are based on the methodology of Lee & Liu [Lee, 2008].

Futility analysis for each disease cohort will begin when response data is available for at least 10 subjects treated at the RP2D in 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 3.1.2.1.

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 3.1.2.1, 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, 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 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 3.1.2.1, 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, 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%.

3.1.2.3. Displays To Be Created For Disease Specific Expansion Cohort Review

Evaluable Subjects

Since subjects treated at RP2D enrol at different times, not all subjects will have been on the study long enough to have single or multiple post-baseline disease assessments. Since disease assessments are to be completed every 4 weeks, subjects who have at least one post-baseline radiological disease assessment and have been on study for at least 28 days or have progressed, died or have withdrawn from the study due to any reason will be included in the futility analysis.

If the disease specific response requires a confirmation, then subjects who have at least two post-baseline radiological disease assessments and have been on the study for at least 28 days or have progressed, died or have withdrawn from the study due to any reason will be included in the futility analysis. To be assigned a status of confirmed PR or confirmed CR, a confirmatory disease assessment should be performed no less than four weeks (28 days) after the criteria for response are first met. The definition of ongoing

with stable disease is for subjects with Stable Disease as the best overall response and still on treatment at the time of futility analysis.

A listing of subject status and best overall response will be provided using the All Treated Population (see Section 4 for definition). This listing will be sorted by date of first dose and will show whether or not each subject is ongoing study treatment, whether the subject has had at least two post-baseline radiological disease assessments, whether the subject is evaluable for the futility analysis, and best confirmed and unconfirmed response.

Displays

Summaries of confirmed best response will be provided so that the study team can compare the study data to the stopping rules for futility and to the success rules. These will include all Evaluable Subjects. Summaries of unconfirmed best response will also be provided.

The total number of subjects with confirmed or unconfirmed responses or who are ongoing with stable disease should be compared to the futility boundary to prevent stopping the trial for futility before confirmed responses are fully realized. If this count is within the futility region, the study may be stopped based on the totality of the data. The purpose of including ongoing subjects with stable disease in this count is to avoid incorrectly stopping the study early when responses of ongoing subjects have not been fully realized.

As always, these rules are guidelines for decision-making and the totality of the data will be considered by the team when making a decision to stop the study.

Table 1 Examples of Documentation of Recommendation from Futility Analysis During Part 2 (Disease Specific Expansion Cohort)

Example 1:

Number of MDS Subjects (All Treated Subjects):	20
Number of MDS Evaluable Subjects:	18
Futility Region:	1 or less
Number With Confirmed Response:	2
Number With Unconfirmed Response:	0
Number Ongoing with Stable Disease:	1
Recommendation:	**Continue**

Note: Repeat table for MM and NHL. Compare (Number with Confirmed Response + Number Ongoing with Unconfirmed Response & SD) to Futility Region.

Example 2:

Number of MDS Subjects (All Treated Subjects):	20
Number of MDS Evaluable Subjects:	18
Futility Region:	1 or less
Number With Confirmed Response:	0
Number With Unconfirmed Response:	0
Number Ongoing with Stable Disease:	1
Recommendation:	**Stop**

Note: Repeat table for MM and NHL. Compare (Number with Confirmed Response + Number Ongoing with Unconfirmed Response & SD) to Futility Region.

3.2. Final Analyses

Final analysis will occur when 70% of subjects enrolled in Part 2 have progressed or died.

Summaries will be split by part, disease cohort and dose.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Treated	• This population will consist of all subjects that received at least one dose of study treatment.	• Clinical Activity • Safety
Pharmacokinetic (PK)	• All subjects in the All Treated Population for whom a PK sample is obtained and analyzed	• PK
Pharmacodynamic (PD)	• All subjects in the All Treated Population who contribute pharmacodynamic/biomarker samples	• PD

NOTES:

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion of data from the analysis are captured in the protocol deviations dataset.

- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA DNALYSES AND DATA HANDLING CONVENTIONS

Table 2 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 2 Overview of Appendices

Section	Component
13.4	Appendix 4: Data Display Standards & Handling Conventions
13.5	Appendix 5: Derived and Transformed Data
13.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
13.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the All Treated population, unless otherwise specified.

Full details of data displays are presented in Appendix 11: List of Data Displays.

6.1.1. Disposition of Subjects

A summary of subject disposition will be provided. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who are ongoing or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date and reasons for study treatment discontinuation as well as study part of discontinuation.

6.1.2. Protocol Deviations

All protocol deviations will be summarized and listed and will include inclusion and exclusion deviations.

6.1.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g. age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed. In addition, age will also be categorized and summarized by <18, 18-64, 65-74, and >74. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

Prior anti-cancer therapy, including radiotherapy, will be summarised. In addition, summaries coded using GSK Drug coding dictionary, summarized by type of therapy will be presented. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, Ingredient, and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior cancer-related surgeries will be summarized.

Subjects diagnosed with refractory hematological malignancy (MM, lymphoma and/or acute myeloid leukemia), will be summarised at baseline for general disease characteristics and tumor type specifics. Separate summaries of disease characteristics at initial diagnosis and screening will be provided. Medical conditions will be summarized by past and current categories.

Table 3 Baseline disease characteristics for general and tumor type specific

Disease Specific Cohorts	Baseline disease characteristics
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
Subjects with AML	• WHO classification • FAB classification • Cytogenetics
Subjects with MDS	• WHO classification • IPSS/IPSS-R classification • Cytogenetics
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)
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 (Protocol Appendix 10, Table 22) • Quality of life assessment (Skindex-29, see RAP Section 8 and Protocol Appendix 11)
Subjects with myeloma	• International staging system (ISS) stage at initial diagnosis and screening • Type (active or smoldering)

Disease Specific Cohorts	Baseline disease characteristics
	• 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

6.1.4. Treatment Compliance

A listing of planned and actual treatments will be produced.

In addition, summaries of study treatment exposure and dose modifications (e.g. number of dose reductions, number of dose interruptions) will further characterize compliance.

6.1.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. ATC classification Level 1 (Body System) information will be included in the dataset created but will not appear on the summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient “Amoxycillin”. In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE.

Blood products or blood supportive care products will be summarized separately. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided.

Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

7. EFFICACY ANALYSES

7.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the All Treated population, unless otherwise specified, and all summaries and data listings will use treatment labels as specified in Section 13.4.1.

Full details of data displays are presented in Appendix 11: List of Data Displays.

7.2. Primary Efficacy Analyses

For Part 1, anti-tumor activities will be evaluated based on clinical evidence and investigator assessment using disease cohort-specific response criteria as described in the protocol.

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

Objective Response rate is defined as

Disease Cohort	Objective Response Rate	Reference
MM	The percentage of subjects who achieved sCR, CR, VGPR, or PR.	Rajkumar, 2011 for the Uniform Reporting of Clinical Trials: Report of the International Myeloma Working Group (IMWG) Consensus Panel
NHL	The percentage of subjects who achieved CR or PR. Response rates of subjects with double/triple-hit lymphoma will be summarised separately.	International Workshop to standardize response criteria for Non-Hodgkin's Lymphomas [Cheson, 2007]
AML	The percentage of subjects who achieved CR, CRp, CRi, and PR.	Modified Cheson, 2003
MDS	The percentage of subjects achieving Complete Response [CR], marrow CR, CRp [as per CR but platelet count <100 x 109/L], Cri [as per CR but platelet count <100 x 109/L or neutrophil count <1 x 109/L], or Partial Response [PR],) per response criteria.	Cheson, 2006
CTCL	The percentage of subjects achieving CR or PR for at least 4 months	Olsen, 2011

The ORR will be calculated from the investigator's assessment of response recorded as below:

Disease Cohort	Response Assessment Time	Response Criteria **Protocol**
MM	week 4 and every 6 weeks after	Appendix 6
NHL	at week 7, week 16, week 24 and then every 12 weeks	Appendix 7
AML	week 4 and every 6 weeks after	Appendix 8
MDS	week 4 and every 6 weeks after	Appendix 9
CTCL	SCR, week 7, week 16, week 24 and then every 12 weeks	Appendix 10

All subjects who received at least one dose of treatment will be included in the evaluation for response. Subjects with unknown or missing response will be treated as non-responders; i.e. they will be included in the denominator when calculating the percentages. Response rates and the associated 2-sided 95% exact confidence limits will be provided.

Bayesian statistics will be employed to calculate the predictive probability that the response rate at end of study is greater than the historic response rate given interim analyses results, using a weak/non-informative prior. The methodology is described in Lee & Liu [Lee, 2008]. Here, a prior Beta distribution with a mean response rate equal to the target response rate is assumed (e.g. Beta (0.03, 0.07)).

Futility analysis for each disease cohort will begin when response data is available for at least 10 subjects treated at the RP2D in 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%.

Disease Specific Cohort	**Statistical Analyses**
MDS	Starting with a cohort of 10 subjects and allowing for a maximum sample size of 32 subjects at the RP2D the stopping guidelines are described in Figure 1, Section 3.1.2.1.
CTCL	Starting with a cohort of 10 subjects and allowing for a maximum sample size of 37 subjects at the RP2D the stopping guidelines are described in Figure 2, Section 3.1.2.1.

7.3. Secondary Efficacy Analyses

The secondary efficacy analyses will be based on the All Treated Subjects population, unless otherwise specified.

Secondary Efficacy Parameters	
Duration of Response (DOR)	• DOR is defined for the subjects with a CR or PR lasting 4 months for CTCL, and CR, marrow CR, CRp, Cri or PR for MDS as the time from the first documented evidence response until the first documented disease progression or death due to any cause.
Progression-Free Survival (PFS)	• PFS is defined as the interval of time (in months) between the date of first dose and the earlier of the date of disease progression and the date of death due to any cause.
Overall Survival (OS)	• OS is defined as the interval of time (in months) between the date of first dose and the date of death due to any cause.

For the analysis of 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.

PFS, OS and DOR will be summarized using the Kaplan-Meier method if the data warrant.

OS 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.

Censoring Rules

The date of documented disease progression will be defined as the first date of disease progression according to clinical or radiological assessment.

If there is no adequate baseline assessment, the subjects will be censored at their date of first dose day. Subjects without any adequate post-baseline disease assessments will be censored at the date of first dose day.

Subjects who progressed or died after two or more missed consecutive assessments will be censored at their date of last adequate assessment prior to progression or death. An adequate assessment is defined as an assessment where the visit level response is **not** Not Evaluable, Unknown, or Not Applicable

Censoring rules are defined in the table below.

Subjects should not start subsequent anti-cancer therapy while on study. For subjects who receive subsequent anti-cancer therapy the following rules will apply:

- If the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month), the imputation rules described in Section 13.6.2.1 will be applied. No imputation will be made for completely missing dates.
- If anti-cancer therapy is started prior to documented disease progression, PFS will be censored at the date of the last adequate assessment prior to documented disease progression
- Otherwise, PFS will be censored at the date of the last adequate assessment prior to the date of initiation of anti-cancer therapy. If an assessment occurs on the same day as the start of new anti-cancer therapy, the assessment will be used, as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy.

If a subject has neither progressed nor died nor started new anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment. The date of response will be used as the censoring date.

A summary of the assignments for progression and censoring dates for PFS are specified in the table below.

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
No (or inadequate) baseline or post-baseline disease assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First Dose Date	Censored

Censoring Rules		
Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome: Event (Progression/Death) or Censoring**
Progression documented between scheduled visits	Date of assessment of progression	Event
No progression *(or death)*	Date of last 'adequate' assessment of response	Censored
New anticancer treatment started *(prior to documented disease progression)*[1]	Date of last 'adequate' assessment of response *(on or prior to starting anti-cancer therapy)*	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after two or more missed visits	Date of last 'adequate' assessment of response[2] prior to progression or death	Censored

NOTES :

[1] If PD and New anti-cancer therapy occur on the same day, assume the progression was documented first (e.g. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of baseline visit.

8. QUALITY OF LIFE ANALYSES

8.1. Overview of Planned Analyses

The quality of life analyses will be based on the All Treated population, unless otherwise specified.

8.2. Skindex-29 Questionnaire

For the CTCL cohort, the effects of treatment on disease-related symptoms/quality of life will be assessed using the Skindex-29 Questionnaire (Protocol Appendix 11). Skindex-29 inquires about how often (*Never, Rarely, Sometimes, Often, All the time)* 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 (item 18) that is not scored.

Domain	Number of Items	Item Number* (corresponding to questionnaire)
Symptoms	7	CCI [redacted]
Emotions	10	CCI [redacted]
Functioning	12	CCI [redacted]

*Note: Item 18 is not included in the scoring

All responses are transformed to a linear scale of 100, varying from CCI [redacted] (CCI [redacted] to CCI [redacted] (CCI [redacted]), so that a higher score implies higher impact of skin disease.

CCI [redacted]

Skindex scores are reported as three scale scores, corresponding to the three domains; a scale score is the mean of a patient's responses to items in a given domain. The change from baseline in Skindex scores will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

8.3. Missing Data

If responses to more than 25% of items are missing overall, the questionnaire is eliminated. If any scale has more than 25% of the responses missing, the scale is missing. Scale scores are the average of non-missing items in a given scale. An item with multiple answers is considered missing.

9. SAFETY ANALYSES

9.1. Overview of Planned Analyses

The safety analyses will be based on the All Treated Subjects population, unless otherwise specified.

Details of data displays are presented in Appendix 11: List of Data Displays.

9.2. Extent of Exposure

Exposure to study treatment in weeks will be summarised.

Dose will be summarized using mean, median, standard deviation, minimum, and maximum.

Dose delays, reductions, and interruptions will also be summarised. The summaries of dose modifications will be provided only if the data warrant.

9.3. Adverse Events

An overview summary of AEs, including but not limited to counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, Grade 3-5 AEs, Grade 3-5 AEs related to study treatment, AEs leading to dose reductions, AEs leading to dose delays OR interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced. A summary of non-serious AEs that occurred in strictly 5% of the subjects or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. events with 4.9% incidence rate should not be included in this table). The summary will be displayed by Medical Dictionary for Regulatory Affairs (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. AEs will be coded to the PT level using the MedDRA dictionary.

A summary of number and percentage of subjects with any AEs by maximum grade will be produced. AEs will be sorted by PT in descending order of total incidence. The summary will use the following algorithms for counting the subject:

Preferred term row: Subjects experiencing the same AE PT several times with different grades will only be counted once with the maximum grade.

Any event row: Each subject with at least one AE will be counted only once at the maximum grade no matter how many events they have.

The number and percentage of AEs (all grades) will be summarized in descending order of total incidence by SOC and PT, and by PT only. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as “Yes”. A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as ‘Yes’ or missing. The summary table will be displayed in descending order of total incidence by PT only. All AEs will be listed.

A listing of adverse events recorded as dose-limiting toxicities will be provided. Additionally, a summary of the number of patients experiencing DLT’s in each cohort will be provided.

9.3.1. Adverse Events of Special Interest

For each category of adverse event of special interest (AESI) listed below, a comprehensive list of MedDRA preferred terms, based on clinical review, will be used. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional AESI, therefore the list of AESI categories as well as specific preferred terms to be used for each AESI event category will be based on the safety review team agreement in place at the time of reporting.

The AESI include but are not limited to the following categories:

- Haematopoietic thrombocytopenia Standardized MedDRA Query (SMQ)
- Haemorrhages [excluding laboratory terms] [NARROW] SMQ
- Anaemias non-haemolytic and marrow depression, High Level Group Term (HLGT)
- Torsade de pointes/QT prolongation [NARROW] SMQ
- Drug related hepatic disorders - comprehensive search [NARROW] SMQ
- Renal MedDRA Preferred Terms

The number and percentage of subjects with these events will be summarized by the AESI category. Additionally, the preferred terms included for each category and maximum toxicity grade will be provided in one table. The summary of event characteristics for each category of AESI will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The worst-case approach will be applied at subject level for the event outcome and maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject. For action taken to an event, subject will be counted once under each action, e.g. if a subject has an event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions. For each category of AESI, the summary of onset and duration will also be provided. Time to onset (days) and duration of first occurrence (days) will be summarized. In addition to descriptive statistics (mean, median, min, max), time to onset will be summarized in categories of 1-14 days, 15-28 days and >28 days, and duration of first occurrence will be summarized in categories of 1-5 days, 6-10 days, >10 days.

In addition, AESI will be listed separately.

9.3.2. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death relative

to the last dose of medication (>28 days or ≤28 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The summary table will be displayed in descending order of total incidence by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst-case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all AEs. Separate supportive listings with subject-level details will be generated for Fatal SAEs and Non-Fatal SAEs.

9.3.3. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

AEs Leading to Discontinuation of Study Treatment or Withdrawal from the Study AEs Leading to Dose Interruptions AEs Leadings to Dose Reductionsding to Dose Delays An AE leading to dose modification is an AE for which the action with respect to dosing f dose. AEs that lead to both a dose modification and a discontinuation of study treatment will only appear in the AEs leading to discontinuation of study treatment summary.

9.4. Pregnancies

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects or subjects' partner become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

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.

9.5. Clinical Laboratory Evaluations

The following laboratory tests will be collected:

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 Lactate dehydrogenase	Calcium Ionized calcium	Total protein	

Hematology		
Platelet count	Automated White Blood Cell Differential:	
Red blood cell count	Neutrophils (absolute)	
White blood cell count (absolute)	Lymphocytes (absolute) Monocytes (absolute)	
Blast count	Eosinophils (absolute)	
Hemoglobin	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)

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v4.0).

Summary of change from baseline lab values by scheduled visits using mean, median, standard deviation, minimum, and maximum will be provided.

Summaries of worst-case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. The summary will include grade increase from baseline by scheduled visits and the worst case post-baseline grade. For laboratory tests that are graded for both low and high values, categories will be summarised separately and labeled by direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.0, summaries of worst-case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized at each scheduled visit as well as for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the same time interval, then the subject is counted in both the “Decrease to Low” categories and the “Increase to High” categories.

Separate summaries for hematology and chemistry laboratory tests will be produced.

A supporting listing of laboratory data for subjects with abnormalities of potential clinical concern will be provided. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in Section 13.4.2.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

9.5.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided. Liver function tests will be listed for all subjects with Grade 3 or greater toxicities in any liver function test. A separate listing will be provided for all subjects with possible Hy's law event, possible Hy's law cases are defined as any elevated (ALT≥3×ULN **and** total bilirubin≥2×ULN (with direct bilirubin ≥35% of total bilirubin, if direct bilirubin is measured)) **OR** (ALT ≥3×ULN **and** INR >1.5, if INR is measured).

9.6. Other Safety Measures

Unless otherwise specified, the denominator in the percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

9.6.1. Vital Signs

Change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

Summaries of values of potential clinical concern with respect to the categories defined in Section 13.7.3 will be performed. These summaries will display the number and percentage of subjects with any Potential Clinical Importance (PCI) at each scheduled assessment time and for the worst-case post-baseline.

9.6.2. Pain Assessment

Pain will be assessed using a visual analog scale (Protocol Appendix 12) using Wong-Baker Faces Pain Rating Scale. The change from baseline in pain score (values of (0 to 10)) will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

9.6.3. Performance Status

ECOG performance status will be listed.

9.6.4. ECG

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. A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings with respect to the

categories defined in Section 13.7.2 will be displayed by scheduled visits as well as for the worst-case post-baseline.

Change from baseline in ECG values will be summarized at each scheduled assessment time and for the worst-case post-baseline. Only the post-baseline assessments that used the same source (i.e. local or central cardiologist read) as the baseline assessments will be used to derive the change from baseline, data from the two sources will not be combined.

QTcF prolongation will be monitored throughout the study. The QTc data analysis will use the collected values based on Fridericia formula. The QTc values based on Fridericia formula will be rounded to the integer and the values will be categorized into the following CTCAE grade and ranges: Grade 0 (<450 msec), Grade 1 (450-480 msec), Grade 2 (481-500 msec), and Grade 3 (≥501 msec). Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 for the worst-case post-baseline only. Missing baseline grade will be assumed as grade 0. Listings of abnormal ECG findings and a listing of ECG values will be provided.

9.6.5. LVEF

Change from baseline in LVEF will be summarized at each scheduled assessment time and for the worst-case post-baseline. Only the post-baseline assessments that used the same method (i.e. Echocardiogram ECHO or Multiple Grated Acquisition MUGA) or source (i.e. local or central read) as the baseline assessments will be used to derive the change from baseline, data from different methods and sources should not be combined.

Summaries of values of potential clinical concern with respect to the categories defined in Section 13.7.4 will be performed. These summaries will display the number and percentage of subjects with any PCI at each scheduled assessment time and for the worst-case post-baseline.

LVEF results will also be listed with subject level details including absolute change from baseline.

9.6.6. Liver Events

For any liver events that occur during the study, the liver event information for RUCUM score will be summarized, including whether the subject was age 55 or over, whether the subject became pregnant, liver imaging normal or not, a biopsy was taken or not, whether there was fasting or significant dietary change, whether the subject took any unconventional medications, timing when the event occurs (while on treatment or after stopping treatment) and summary statistics for time from first dose to start of liver event and time from last dose to start of liver event. If the number of events does not support a summary, then only listings will be produced.

For subjects with multiple events, the first event will be used for the summary tables. All events with subject level details will be displayed in a supporting listing.

10. PHARMACOKINETIC ANALYSES

10.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the PK population, unless otherwise specified.

The planned analyses are presented in Appendix 11: List of Data Displays.

10.2. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Process & Standards).

Two major metabolites of GSK525762, GSK3529246 and GSK3536835, have been observed in humans. GSK3536835 was found to be unstable under bioanalytical conditions. Therefore, the two major active metabolites were measured together following full conversion of GSK3536835 to GSK3529246 prior to analysis and the active metabolites (GSK3529246 + GSK3536835) are reported as one entity, GSK3529246.

Concentration of GSK525762, active metabolites (GSK3529246) and GSK525762 total active moiety (i.e. GSK525762 + GSK3529246 after conversion to nM concentrations) will be listed for each subject.

Individual plots of concentration over time will be provided for each analyte using actual elapsed time for GSK525762, active metabolites (GSK3529246) and total active moiety.

Summaries of plasma concentration will be produced separately for GSK525762 in both ng/mL and nM, active metabolites (GSK3529246) in both ng/mL and nM and the total active moiety of GSK525762 (GSK525762 + GSK3529246 after conversion to nM concentrations) in nM. Plasma concentration-time data will be summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) by planned relative assessment time.

Mean and/or median values will be plotted over time using nominal visit. GSK525762, GSK3529246, and the total active moiety concentration-time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations.

10.3. Pharmacokinetic Parameters

10.3.1. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed below will be determined from the concentration-time data for GSK525762, active metabolites (GSK3529246), the total active moiety (i.e. GSK525762 + GSK3529246 after conversion to nM concentrations),

as data permits. The molecular weight of GSK525762 is 424 g/mol and the molecular weight of GSK3529246 is 396 g/mol.

The total active moiety concentration in nmol/L will be computed as (GSK525762 concentration in ng/mL / molecular weight of 424 * 1000) + (GSK3529246 concentration in ng/mL / molecular weight of 396 * 1000).

Pharmacokinetic parameters described in Table 4 will be determined from the plasma concentration-time data, as data permits.

Table 4 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z** This will be calculated for Week 1/Day 1 only
AUC(0-τ)	Area under the concentration-time curve from time zero to the predose of the next dose. For BID administration, AUC(0-24) will also be computed, as data permits.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data. For BID administration, Cmax will be obtained after each administration, i.e. morning and evening administration, as data permits.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **$t_{½} = \ln 2 / \lambda z$**
λz	Apparent terminal phase elimination rate constant
Cτ	Trough concentration
CL/F	Apparent Clearance
V/F	Apparent Volume
C_{min}	Minimum plasma concentration, determined directly from the concentration-time data

NOTES:

- Additional parameters may be included as required.

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.

10.3.2. Analysis of Pharmacokinetic Parameters

Descriptive summaries and listings for plasma pharmacokinetic parameters (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, CV% and 95% confidence interval of log-transformed parameters (if applicable)) will be reported.

10.4. Population Pharmacokinetic (PopPK) Analyses

Molibresib and active metabolites (GSK3529246) plasma concentration-time data from Part 2 subjects will be analyzed by population pharmacokinetic (PopPK) methods using a non-linear mixed-effects modelling approach.

The key objective of this analysis is:

- Compute molibresib and active metabolites (GSK3529246) individual PK parameters using the PopPK model developed for molibresib and active metabolites (GSK3529246) for the study BET115521

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D.

The details for this PopPK analysis are provided in Appendix 12.

11. PHARMACODYNAMIC ANALYSES

11.1. Overview of Planned Pharmacodynamic Analyses

The pharmacodynamic analyses will be detailed in a Pharmacodynamic RAP supplement and will not be discussed as part of this RAP.

12. REFERENCES

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

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.

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.

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.

GlaxoSmithKline Document Number 2011N113741_03 Version 3. GSK525762 Investigator's Brochure. Report Date 27-Mar-2014.

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

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.

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

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.

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.

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, 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 drugrechallenge. *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.

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 Tcell lymphoma. *J Clin Oncol*. 2010;28(29):4485-4491.

13. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 13.1	Appendix 1: Time and Events
Section 13.2	Appendix 2: Assessment Windows
Section 13.3	Appendix 3: Treatment States & Phases
Section 13.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 13.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 13.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 13.7	Appendix 7: Values of Potential Clinical Importance
Section 13.8	Appendix 8: Multicentre Studies • Laboratory Values • ECG • Vital Signs
Section 13.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 13.10	Appendix 10: Abbreviations & Trade Marks
Section 13.11	Appendix 11: List of Data Displays
Section 13.12	Appendix 12: Population Pharmacokinetic Analysis

13.1. Appendix 1: Time & Events

13.1.1. Protocol Defined Time & Events

See Protocol Section 5.

13.2. Appendix 2: Assessment Windows

13.2.1. Assessment Windows

No assessment windows will be applied. Time and event table's supplemental footnotes describe assessment windows.

13.3. Appendix 3: Treatment States and Phases

13.3.1. Treatment Phases

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, echocardiogram (ECHO), Eastern Cooperative Oncology Group (ECOG) result, and other safety domains will be assigned to the treatment phases defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 13.6.2.1). Flag variables (time in relation to study treatment) indicating the study time periods will be added to these datasets.

Assessments and events will be classified according to the time of occurrence relative to Study Treatment Start Date.

Treatment Phase	Definition
Pre-Therapy	Date ≤ Study Treatment Start Date
On-Therapy	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 28 days
Post-Therapy	Date > Study Treatment Stop Date + 28 days

Some datasets include the first dose day as On-therapy and some exclude the first dose day as On-Therapy. The first dose day (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, lab tests, cardiac scan, and other safety domains. The first dose day (Day 1) is considered to be On-therapy for adverse events and concomitant medications.

13.3.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

13.3.2.1. Treatment States for Disease Response Data

Treatment State	Definition
Duration of Response	Date of Progression – Date of First Partial or Complete Response of a Confirmed Partial or Complete Response + 1

13.3.2.2. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before 28 days after treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ 28 days]
Post-Treatment	If AE onset date is after the treatment stop date +_28 days. AE Start Date > Study Treatment Stop Date + 28 days
Onset Time Since 1st Dose (Days)	• If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date • If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date

Treatment State	Definition
	+1 • Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
Treatment	**Data Display**	**Description**	**Order [1]**
Part 1	GSK525762 5mg QD (AML)	GSK525762 5mg once daily AML	1
	GSK525762 20mg QD (AML)	GSK525762 20mg once daily AML	2
	GSK525762 60mg QD (AML)	GSK525762 60mg once daily AML	3
	GSK525762 75mg QD (AML)	GSK525762 75mg once daily AML	4
	GSK525762 80mg QD (AML)	GSK525762 80mg once daily AML	5
	GSK525762 100mg QD (AML)	GSK525762 100mg once daily AML	6
	GSK525762 120mg QD (AML)	GSK525762 120mg once daily AML	7
	GSK525762 10mg QD (NHL)	GSK525762 10mg once daily NHL	8
	GSK525762 40mg QD (NHL)	GSK525762 40mg once daily NHL	9
	GSK525762 60mg QD (NHL)	GSK525762 60mg once daily NHL	10
	GSK525762 80mg QD (NHL)	GSK525762 80mg once daily NHL	11
	GSK525762 30mg QD (MM)	GSK525762 30mg once daily MM	12
	GSK525762 40mg QD (MM)	GSK525762 40mg once daily MM	13
	GSK525762 60mg QD (MM)	GSK525762 60mg once daily MM	14
Part 2	GSK525762 75mg QD (MDS)	GSK525762 75mg once daily MDS	1
	GSK525762 60mg QD (CTCL)	GSK525762 60mg once daily CTCL	2
Total	Total	All subjects combined	

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Disease Specific Expansion Cohort Descriptions		
Group Description	**Data Display**	**Order [1]**
Acute Myeloid Leukemia	AML	1
Non-Hodgkin's Lymphoma	NHL	2
Multiple Myeloma	MM	3
High-Risk Myelodysplastic Syndromes	MDS	4
Cutaneous Cell lymphoma	CTCL	5
Combined Cohorts	All Subjects	6

Study Part Descriptions		
Group Description	**Data Display**	**Order [1]**
Part 1: Dose Escalation Phase	Part 1	1
Part 2: Expansion Phase	Part 2	2
Combined Study Parts	All Study Parts	3

13.4.2. Baseline Definition & Derivations

13.4.2.1. Baseline Definitions

For all endpoints unless otherwise specified baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date. If time is collected, then the most recent pre-dose value is used. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

For ECG analyses, subject level baseline is defined as the mean of triplicate baseline assessments.

13.4.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

13.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The current supported versions of SAS software be used.	
Reporting Area	
HARP Server	US1SALX00259
HARP Area	Compound: GSK525762, Study: BET116183
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	

Reporting Process
• RTF files will be generated for SAC and IA upon request.

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to SOP_00000314000: Non-compartmental Analysis of Clinical Pharmacokinetic Data. Note: Concentration values will be imputed as per GUI_51487
ADPC data file	To create ADPC the SDTM PC domain dataset will be merged with the Subject-Level Analysis Dataset (to get demographic

	information) and with SDTM EX domain (to get reference timepoint date). Reference timepoint date will be populated for both study drug and active metabolite based on study treatment information from SDTM EX domain. To populate analysis values in ADPC (AVAL(C)) adjustments to the PCSTRESN will be done based on imputation rules from "Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global" document. Total Moiety parameter will be added, along with concentrations of study drug and active metabolite, and derived as the sum of study drug and active metabolite concentrations converted to nM units.
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only. Assign zero to NQ values (Refer to GUI_51487 for further details)
Pharmacokinetic Parameter Derivation	
PK Parameters to be Derived by PK Programmer	PK parameters will be derived by the PK Programmer
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = sqrt(exp(SD^2) - 1) * 100 (SD = SD of log transformed data) [2] CV_w (%) = sqrt(exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Being Log Transformed	Tmax
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.5. Appendix 5: Derived and Transformed Data

13.5.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a visit the value closest to the target day for that visit will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from study treatment start date:
  • Assessment Date = Missing, then Study Day = Missing
  • Assessment Date < Study Treatment Start Date, then Study Day = Ref Date – Study Treatment Start Date
  • Assessment Data ≥ Study Treatment Start Date, then Study Day = Ref Date – (Study Treatment Start Date) + 1

13.5.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / Height (m)^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

13.5.3. Safety

Adverse Events
AE'S OF Special Interest

The list below shows the AE categories of special interest. For preferred terms within each category, refer to MedDRA.

- Haematopoietic thrombocytopenia Standardized MedDRA Query (SMQ)
- Haemorrhages [excluding laboratory terms] [NARROW] SMQ
- Anaemias non-haemolytic and marrow depression, High Level Group Term (HLGT)
- Torsade de pointes/QT prolongation [NARROW] SMQ
- Drug related hepatic disorders - comprehensive search [NARROW] SMQ
- Renal MedDRA Preferred Terms

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

13.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail

General	• In Part 1, a subject will be considered to have completed the study if
	  ○ they complete screening assessments, the 28-day DLT observation period, and the end-of-treatment follow-up visit,
	  ○ they progress or die while receiving study treatment, or
	  ○ are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.
	• In Part 2, a subject will be considered to have completed the study if:
	  ○ they progressed or die while receiving study treatment, or
	  ○ are receiving ongoing study treatment at the time of the Sponsor's decision to close the study.
	• Withdrawn subjects may be replaced in the study.
	• All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.6.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.6.2.1. Handling of Missing and Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g. duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in the overall survival analysis dataset.

With the exception of new anti-cancer start date on the Oncology time to event analysis dataset and exposure end date on the Exposure analysis dataset, imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Details on imputing partial dates for specific datasets are outlined below.

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.
Anti-Cancer Therapy and Radiotherapy	• Completely missing start or end dates will remain missing, with no imputation applied. • If partial start date contains a year only set to January 1st. • If partial start date contains a month and year set to the 1st of the month. • No imputation for partial end dates will be performed.
Surgical Procedures	• No Imputation for completely missing dates • If partial date contains a year only set to January 1st. • If partial date contains a month and year set to the 1st of the month
Concomitant Medication and Blood Supportive Products	• No Imputation for completely missing start or end dates • If study treatment start date is missing, a '01' will be used for the day and 'January' will be used for the month. • If study treatment stop date is missing, then a '28/29/30/31' will be used for the day (dependent on the month and year) and 'December' will be used for the month.
Time to Event for	• Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define

Element	Reporting Detail
Anti-Cancer Therapy Where applicable: Radiotherapy, Surgical Procedures	event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed dates will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures datasets. • No Imputation for completely missing start dates • No imputation for missing start day and month (note: the eCRF should only allow for missing day) • If partial start date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial start date falls in the same month as the subject's last assessment and the subject's last assessment is progressive disease (PD), then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month. • No imputation for partial end dates will be performed
Exposure End Dates for Subjects Who Are Still on Study at the Time of Analysis	• If exposure end date is missing, then assign exposure end date as the earliest of: the date of the data cutoff, the date of withdrawal from the study, or the death date. • The imputed exposure end date will be used to calculate cumulative dose and exposure duration. • The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. • Imputed exposure end dates will also be stored on the study treatment end date variable. • For subjects who have missing end dates in their last exposure record because they are still on study treatment, the on-therapy indicator variables (time in relation to study treatment) are assigned to on-therapy for all records where the 'dataset'. 'date' is after or on the study treatment start date.

13.6.3. Handling of Missing Data for Skindex-29 Questionnaire

Element	Reporting Detail
Missing Items in Questionnaire	• If responses to more than 25% of items are missing overall, the questionnaire is eliminated. • If any scale has more than 25% of the responses missing, the scale is missing. • Scale scores are the average of non-missing items in a given scale. • An item with multiple answers is considered missing.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. Laboratory Values

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data that are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

13.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec	≥ 450	< 481
		≥ 481	< 501
		≥ 501	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 30	≤ 60
	msec	> 60	

13.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	>120	<140 (Grade 1)
	mmHg	≥140	<160 (Grade 2)
	mmHg		≥160 (Grade 3)
Diastolic Blood Pressure	mmHg	> 80	< 90 (Grade 1)
	mmHg	≥ 90	< 100 (Grade 2)
	mmHg		≥ 100 (Grade 3)
Heart Rate	bpm	< 60	> 100
Temperature	Degrees C	≤ 35	≥ 38

13.7.4. Left Ventricular Ejection Fraction

LVEF	Units	Clinical Concern Range
Absolute Change from Baseline	%	0 < Decrease < 10
	%	10 ≤ Decrease < 20
	%	Decrease ≥ 20
	%	Decrease ≥ 0 and ≥ LLN
	%	Decrease ≥ 10 and < LLN
	%	Decrease ≥ 20 and ≥ LLN
	%	Decrease ≥ 20 and < LLN
Relative Percent Change from Baseline	%	Decrease ≥ 20 and ≥ LLN
	%	Decrease ≥ 20 and < LLN

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

13.8. Appendix 8: Multi-center Studies

13.8.1. Methods for Handling Centres

Data from all participating centers will be pooled prior to analysis.

It is anticipated that subject accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative and will not, therefore, be provided.

13.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

13.9.1. Model Checking and Diagnostics for Statistical Analyses

Not applicable for this study.

13.10. Appendix 10 – Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
GSK	GlaxoSmithKline

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
FACTs
SAS
WinNonlin

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.23	
Efficacy	2.1 to 2.5	
Quality of Life	2.6	
Safety	3.1 to 3.39	
Pharmacokinetic	4.1 to 4.6	4.7 to 4.11
Section	**Listings**	
ICH Listings	1 to 46	

13.11.2. Deliverable [Priority]

Delivery	Description
IA	Interim Analyses
SAC	Final Statistical Analysis Complete

13.11.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Treated	ES1	Summary of Subject Status and Reason for Study Withdrawal		SAC
1.2.	All Treated	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.4.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID		SAC
Protocol Deviation					
1.5.	All Treated	DV1	Summary of Important Protocol Deviations		SAC
Population Analysed					
1.6.	Screened	SP1	Summary of Study Population		SAC
1.7.	Screened	SP2	Summary of Exclusions from Study Population		SAC
Demographic and Baseline Characteristics					
1.8.	All Treated	DM1 / DM3	Summary of Demographic Characteristics	Include Performance Status	SAC
1.9.	All Treated	DM11	Summary of Age Ranges		SAC
1.10.	All Treated	DM5	Summary of Race and Racial Combinations		SAC
1.11.	All Treated	DC1	Summary of Disease Characteristics at Initial Diagnosis		SAC
1.12.	All Treated	DC2	Summary of Disease Characteristics at Screening		SAC
1.13.	All Treated	LA11	Summary of Disease Burden at Baseline		SAC
Prior and Concomitant Medications					
1.14.	All Treated	AC1	Summary of Prior Anti-Cancer Therapy		SAC
1.15.	All Treated	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens		SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.16.	All Treated	CM1	Summary of Prior Dictionary Coded Anti-Cancer Therapy		SAC
1.17.	All Treated	AC1	Summary of Prior Cancer Related Surgical Procedures		SAC
1.18.	All Treated	AC4	Summary of Best Response to the Most Recent Prior Anti-Cancer Therapy		SAC
1.19.	All Treated	MH1	Summary of Past Medical Conditions		SAC
1.20.	All Treated	CM1	Summary of Concomitant Medications		SAC
1.21.	All Treated	BP1A	Summary of Blood Products		SAC
1.22.	All Treated	BP1C	Summary of Blood Supportive Care Products		SAC
1.23.	All Treated	MH1	Summary of Current Medical Conditions		SAC

13.11.4. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Objective Response					
2.1.	All Treated	RE1a	Summary of Investigator-Assessed Best Response (With Confirmation)		SAC
2.2.	All Treated	RE1a	Summary of Investigator-Assessed Best Response (Without Confirmation)		SAC
2.3.	All Treated	TTE1a	Summary of Duration of Response		SAC
Progression Free Survival					
2.4.	All Treated	TTE1	Summary of Progression-Free Survival		SAC
Overall Survival					
2.5.	All Treated	TTE1	Summary of Overall Survival		SAC

13.11.5. Quality of Life Tables

Quality of Life: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Skindex-29 Score					
2.6.	All Treated	VS1	Summary of Change from Baseline in Skindex-29 Score	Include the questionnaire's three scales	SAC

13.11.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	All Treated	OEX1	Summary of Exposure to GSK525762		SAC
3.2.	All Treated	ODMOD1	Summary of Dose Reductions of GSK525762		SAC
3.3.	All Treated	ODMOD2	Summary of Dose Interruptions of GSK525762		SAC
3.4.	All Treated	ODMOD3	Summary of Dose Delays of GSK525762		SAC
Adverse Events					
3.5.	All Treated	AE13	Adverse Event Overview		SAC
3.6.	All Treated	AE1	Summary of Adverse Events by System Organ Class and Preferred Term		SAC
3.7.	All Treated	AE1/AE3	Summary of Adverse Events by Preferred Term	By PT only	SAC
3.8.	All Treated	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency		SAC
3.9.	All Treated	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment	By PT	SAC
3.10.	All Treated	AE3	Summary of Adverse Events Leading to Dose Reduction	By PT	SAC
3.11.	All Treated	AE3	Summary of Adverse Events Leading to Dose Interruption	By PT	SAC
3.12.	All Treated	AE3	Summary of Adverse Events Leading to Dose Delay	By PT	SAC
3.13.	All Treated	OAE01	Summary of Adverse Events by Maximum Grade	By PT only	SAC
3.14.	All Treated	AE19	Summary of Dose Limiting Toxicities (DLT) During the Determinative Period		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.15.	All Treated	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA	SAC
3.16.	All Treated	AE1/AE3	Summary of Drug-Related Adverse Events by Preferred Term	By PT only	SAC
3.17.	All Treated	AE3	Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency		SAC
3.18.	All Treated	AE16	Summary of Serious Adverse Events by Preferred Term (Number of Participants and Occurrences)	FDAAA, by PT only	SAC
3.19.	All Treated	AE3	Summary of Serious Drug-Related Adverse Events by Preferred Term		SAC
3.20.	All Treated	AE1	Summary of Adverse Events of Special Interest by Category and Preferred Term	Categories as in Section 13.5.3.	SAC
3.21.	All Treated	ESI1	Summary of Adverse Events of Special Interest Characteristics		SAC
3.22.	All Treated	ESI2b	Summary of Onset and Duration of the First Occurrence of Adverse Events of Special Interest		SAC
3.23.	All Treated	DTH1a	Summary of Deaths		SAC
Laboratory					
3.24.	All Treated	OLB9	Summary of Chemistry Grade Changes from Baseline Grade	Include Troponin, NT-proBNP, Factor VII Activity, Prothrombin International Normalized Ratio where applicable Include footnote for baseline definition	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.25.	All Treated	OLB11	Summary of Chemistry Changes from Baseline with Respect to the Normal Range	For laboratory tests which cannot be graded (include Troponin, NT-proBNP, Factor VII Activity, Prothrombin International Normalized Ratio where applicable) Include footnote for baseline definition	SAC
3.26.	All Treated	OLB9	Summary of Hematology Grade Changes from Baseline Grade	Include Platelets Include footnote for baseline definition	SAC
3.27.	All Treated	OLB11	Summary of Hematology Changes from Baseline with Respect to the Normal Range	For laboratory tests which cannot be graded Include footnote for baseline definition	SAC
3.28.	All Treated	LB1	Summary of Urine Concentration Changes from Baseline	Include footnote for baseline definition	SAC
3.29.	All Treated	OUR1B	Summary of Worst-case Urinalysis Result Increases from Baseline	Include footnote for baseline definition	SAC
3.30.	All Treated	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting		SAC
3.31.	All Treated	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
3.32.	All Treated	EG1	Summary of ECG Findings		SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.33.	All Treated	EG2	Summary of Change from Baseline in ECG Values	Include footnote for baseline definition By local/central read, specify in title which	SAC
3.34.	All Treated	OECG1B/EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline F	Include QTcF > 500 msec Include footnote for baseline definition By local/central read, specify in title which	SAC
3.35.	All Treated	OECG2B/EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline	Include change in QTcF > 60 msec Include footnote for baseline definition By local/central read, specify in title which	SAC
LVEF					
3.36.	All Treated	OLVEF1A/OLVEF1B	Summary of Left Ventricular Ejection Fraction Change from Baseline	Include footnote for baseline definition	SAC
Vital Signs					
3.37.	All Treated	VS1	Summary of Change from Baseline in Vital Signs	Include footnote for baseline definition	SAC
3.38.	All Treated	VS3	Summary of Worst Case Vital Sign Results Relative to Normal Range Post-Baseline Relative to Baseline	Include footnote for baseline definition	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pain					
3.39.	All Treated	VS1	Summary of Change from Baseline in Pain	Include footnote for baseline definition	SAC

13.11.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Drug Concentration Measure					
4.1.	PK	PK01	Summary of GSK525762 Pharmacokinetic Concentration-Time Data by Dose Level and Cohort	Summarise in both ng/mL and nM	SAC
4.2.	PK	PK01	Summary of GSK3529246 -Active Metabolites Pharmacokinetic Concentration-Time Data by Dose Level and Cohort	Summarise in both ng/mL and nM	SAC
4.3.	PK	PK01	Summary of Total Active Moiety Pharmacokinetic Concentration-Time Data by Dose Level and Cohort	Summarise in nM only	SAC
Pharmacokinetic Parameters					
4.4.	PK	PK06	Summary of Derived GSK525762 Pharmacokinetic Parameters	PK parameters: AUC, Cmax, Tmax, Ct, Cmin, t1/2, time invariance, accumulation Ratio, determined from the concentration-time data in ng/ml and in nM after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.5.	PK	PK06	Summary of Derived GSK3529246 -Active Metabolites Pharmacokinetic Parameters	PK parameters: AUC, Cmax, Tmax, Ct, Cmin, t1/2, time invariance, accumulation Ratio, determined from the concentration-time data in ng/ml and in nM after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	SAC
4.6.	PK	PK06	Summary of Derived Total Active Moiety Pharmacokinetic Parameters	PK parameters: AUC, Cmax, Tmax, Ct, Cmin, t1/2, time invariance, accumulation Ratio, determined from the concentration-time data in ng/ml to nM after conversion from ng/mL to nM; descriptive summaries: mean, SD, median, min, max, geometric mean & SD, CV%, and 95%CI of log-transformed parameters, if applicable	SAC

13.11.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.7.	PK	PK16	Individual GSK525762 Concentration-Time Plots (Linear and Semi-Log)	ng/mL	SAC
4.8.	PK	PK16	Individual GSK3529246 Active Metabolites Concentration-Time Plots (Linear and Semi-Log)	ng/mL	SAC
4.9.	PK	PK16	Individual Total Active Moiety Concentration-Time Plots (Linear and Semi-Log)	nM	SAC
4.10.	PK	PK17	Mean Concentration-Time Plots (Linear and Semi-Log)	GSK525762, GSK3529246, and the total active moiety concentration-time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations	SAC
4.11.	PK	PK18	Median Concentration-Time Plots (Linear and Semi-Log)	GSK525762, GSK3529246, and the total active moiety concentration-time profiles will be overlaid on the same plot once concentrations have been converted to nM concentrations	SAC

13.11.9. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.	All Treated	ES2	Listing of Reasons for Study Withdrawal		SAC
2.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
3.	All Treated	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
4.	All Treated	SP3	Listing of Subjects Excluded from Any Population		SAC
5.	All Treated	DV2	Listing of Important Protocol Deviations		SAC
6.	All Treated	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
7.	All Treated	DM2	Listing of Demographic Characteristics		SAC
8.	All Treated	DM9	Listing of Race		SAC
9.	All Treated	TA1	Listing of Planned and Actual Treatments		SAC
10.	All Treated	AC6	Listing of Prior Anti-Cancer Therapy		SAC
11.	All Treated	RE5	Listing of Investigator-Assessed Tumour Responses	Include subject status	SAC
12.	All Treated	OEX3a	Listing of Exposure Data		SAC
13.	All Treated	BP4	Listing of Blood Products or Blood Supportive Care Products		SAC
14.	All Treated	OAE03	Listing of Subject Numbers for Individual Adverse Events		SAC
15.	All Treated	OAE04	Listing of All Adverse Events		SAC
16.	All Treated	OAE04	Listing of Fatal Serious Adverse Events		SAC
17.	All Treated	OAE04	Listing of Non-Fatal Serious Adverse Events		SAC
18.	All Treated	AE8	Listing of Adverse Events of Special Interest		SAC
19.	All Treated	OAE04	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
20.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Interruptions		SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
21.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Reductions		SAC
22.	All Treated	OAE04	Listing of Adverse Events Leading to Dose Delays		SAC
23.	All Treated	AE2	Relationship of Adverse Event SOCs, HLGTs/HLTs/PTs, and Verbatim Text		SAC
24.	All Treated	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
25.	All Treated	DL3	Listing of Dose-Limiting Toxicities during the Determinative Period		SAC
26.	All Treated	DTH3	Listing of Deaths		SAC
27.	All Treated	EG3	Listing of All ECG Values for Subjects with Abnormal Values		SAC
28.	All Treated	EG5	Listing of ECG Findings		SAC
29.	All Treated	OECG5A	Listing of QTcF Values of Potential Clinical Importance		SAC
30.	All Treated	OLB7	Listing of All Laboratory Data for Subjects with Any Value Outside Normal Range		SAC
31.	All Treated	LB14	Listing of Laboratory Data with Character Results		SAC
32.	All Treated	UR2A	Listing of Urinalysis Data for Subjects with Abnormalities of Potential Clinical Concern		SAC
33.	All Treated	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events		SAC
34.	All Treated	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		SAC
35.	All Treated	VS4	Listing of Vital Signs for Subjects with Abnormal Values		SAC
36.	All Treated	PS5A	Listing of ECOG Performance Status		SAC
37.	All Treated	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
38.	All Treated	OLVEF2B	Listing of Left Ventricular Ejection Fraction Results		SAC
39.	All Treated	LB5	Listing of Factor VII Activity (%)		SAC
40.	All Treated	LB5	Listing of Prothrombin International Normalized Ratio		SAC
41.	PK	PK07	Listing of GSK525762 Pharmacokinetic Concentration-Time Data		SAC
42.	PK	PK07	Listing of GSK525762-Active Metabolite Pharmacokinetic Concentration-Time Data		SAC
43.	PK	PK07	Listing of Total Active Moiety Pharmacokinetic Concentration-Time Data		SAC
44.	PK	PK13	Listing of Derived GSK525762 Pharmacokinetic Parameters		SAC
45.	PK	PK13	Listing of Derived GSK525762-Active Metabolite Pharmacokinetic Parameters		SAC
46.	PK	PK13	Listing of Total Active Moiety Pharmacokinetic Parameters		SAC

13.12. Appendix 12: Population Pharmacokinetic Analysis

Molibresib and active metabolites (GSK3529246) plasma concentration-time data will be analyzed by Pop PK methods using a non-linear mixed-effects modelling approach.

The key objective of this analysis is:

- Compute molibresib and active metabolites (GSK3529246) individual PK parameters using the PopPK model developed for molibresib and active metabolites (GSK3529246) for the study BET115521

13.12.1. Systems

The quantitative analysis will be performed using NONMEM (ICON Solutions) and PsN (Perl Speaks NONMEM) or another software platform deemed appropriate. Graphical displays and, if needed, modifications of the dataset will be produced using R (The R Foundation for Statistical Computing). The analysis will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline using the currently supported versions of all software packages.

13.12.2. Data Assembly

Subject data will be collected in the electronic CRF and will be transmitted into a validated database by GSK data management. Derived/processed variables will be provided by or under the guidance of Clinical Programming. Plasma samples will be analyzed under supervision of Department of Bioanalysis, Immunogenicity and Biomarker, IVIVT, GSK, using approved analytical methodology. Data will be transferred electronically to data managers to be processed and stored in the GSK database. GSK or a designated third party will generate the NONMEM input dataset.

13.12.3. Model Development

A population pharmacokinetic model for oral molibresib and active metabolites (GSK3529246) in subjects with solid tumors in study BET115521 has been developed (2020N436237_00) and will be applied to the BET116183 Part 2 dataset.

Initially, empirical Bayes estimates will be derived applying the BET115521 study PopPK model to the dataset with the MAXEVAL=0 option. If the corresponding model diagnostics indicate that the BET115521 study PopPK model is appropriate to represent the molibresib and active metabolites (GSK3529246) PK data in part 2 of study BET116183, then individual estimates will be based on the study BET115521 PopPK parameters.

If the parameter set of the BET115521 PopPK model applied to the BET116183 data set results in substantial bias, the parameters of the BET115521 PopPK model will be re-estimated for the BET116183 PK data alone before generating the individual PK parameter estimates. Certain parameter values may be fixed to the value in the BET115521 PopPK model, if they cannot be estimated with sufficient precision within the BET116183 PK population. Covariates not available for the BET116183 PK population but present in the BET115521 PopPK model may be removed from the BET116183 PopPK model. Lastly, a model refinement step, if performed, will include, but may not be limited to, a qualification and possible modification of the models random effect structure.

13.12.3.1. Model Qualification

Any model development will be supported and the final model will be qualified using the following criteria where appropriate:

- Scientific plausibility of parameter estimates
- Goodness of fit plots
- Relative standard errors (RSE) of the parameter estimates
- Objective function value
- Distribution and shrinkage of random effects;
- Successful minimization and execution of covariance step
- Condition number (ratio of the largest and smallest eigenvalue of the covariance matrix
- Visual predictive check
- Bootstrap (if deemed necessary/feasible)

Signature Page for 116183 TMF-1758938 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 07-May-2020 13:04:36 GMT+0000

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 07-May-2020 13:28:28 GMT+0000

Signature Page for TMF-1758938 v1.0