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

Title	:	Reporting and Analysis Plan for a phase I open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of GSK2879552 given orally in subjects with relapsed/refractory acute myeloid leukemia
Compound Number	:	GSK2879552
Effective Date	:	26-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2013N163643_05.
- 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 Statistical Analysis Complete (SAC) deliverable. Due to early termination of the study, Part 2 was not initiated. This document will only include the reporting plan for subjects enrolled in the study.

RAP Author(s):

Authors:	Date	Approval Method
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RAP Team Approvals:

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

GlaxoSmithKline Document Number	Date	Version
2013N163643_00	2014-MAY-02	Original
2013N163643_01	2014-OCT-01	Amendment No. 01
DLT criteria are revised according to the regulatory agency request. PD sampling requirements and subject populations are also clarified.		
2013N163643_02	2015-MAY-27	Amendment No. 02
Additional eligibility criteria and safety monitoring measures are put in place to address recent safety findings.		
2013N163643_03	2016-MAY-09	Amendment No.03
A combination arm with ATRA is added. One of the Dose Limiting Toxicities criteria has been revised according to the NCI criteria. Pharmacodynamic/exploratory sample collection and processing have been changed. Pharmacogenetic sample has been added. The criteria for Progressive Disease and Stable Disease have been added in the response criteria. Concomitant medications have been updated. sion		
2013N163643_04	2017-MAY-02	Amendment No. 4
Add language to include a stopping rule that halts enrollment upon the occurrence of any encephalopathy, unless clearly attributable to central nervous system disease involvement or intercurrent illness.		
2013N163643_05	2017-OCT-06	Amendment No. 5
Modify renal entrance criteria to align with regulatory agencies. Add additional dose adjustment language for hematologic toxicities. Optimize DLT criteria and safety management for retinoic acid syndrome. Add de-escalation language for both GSK2879552 and ATRA. Move PD secondary objective and endpoint to exploratory. Clarified definition of objective response rate (ORR). Included duration of response (DoR), time to response (TTR) and progression-free survival (PFS) as the secondary objectives in the expansion cohort. Updated statistical section to clarify data from Part 1 and Part 2 may be combined for analyses if appropriate. Deleted “dose limiting toxicity” as the safety endpoint of expansion cohort. Update and clarify inconsistencies within protocol: update dose escalation committee language to align with new standard language, define the “baseline” MOCA, baseline assessment of vitamin B12, TSH, free T3 or free T4 added at screening visit, define time window for informed consent, clarify urine metabolite and PK sample collections, add morphology to analysis of bone marrow		

aspirates, clarify use of azoles permitted on study and other administrative updates.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Due to the early termination of the study 200200, this RAP is developed for an abbreviated CPSR. Since Part 2 cohort expansion was not initiated prior to study closure, no statistical analysis will be performed for Part 2.

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• Interim Analysis and CSR for Part 2	• No Statistical Analysis for Part 2	• Part 2 was not implemented
• Full CSR	• Abbreviated CSR	• Study terminated
• Pharmacokinetic Analysis of ATRA for Part 1	• Pharmacokinetic Analysis of ATRA for Part 1 will not be performed	• ATRA samples not provided to the analytical lab with adequate protection to light resulting in a very limited number of analysable samples which concentration are listed.

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

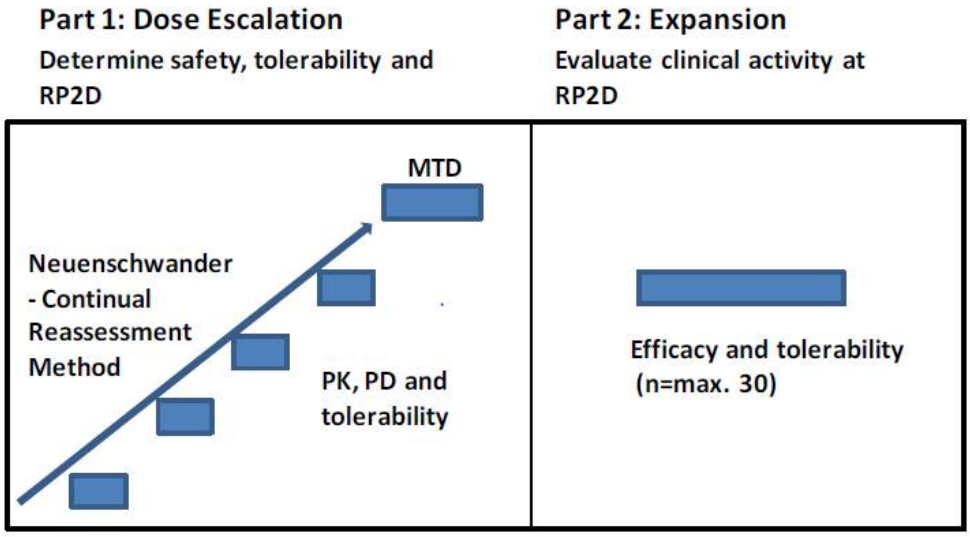
Part 1 Objectives	**Part 1 Endpoints**
Primary Objectives	**Primary Endpoints**
• To determine the safety, tolerability, MTD and/or RP2D and regimen of GSK2879552, alone or in combination with ATRA, given orally in adult subjects with AML.	• AEs, SAEs, dose limiting toxicities, dose reductions or delays, withdrawals due to toxicities and changes in safety parameters (e.g., laboratory values, vital signs, electrocardiograms [ECGs], physical examinations).
Secondary Objectives	**Secondary Endpoints**
• To characterize the PK of GSK2879552, alone or in combination with ATRA, after single and repeat-dose oral administration.	• GSK2879552 PK parameters following single-(Day 1) and repeat-dose (Day 15) administration of GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase and/or effective half-life), accumulation ratio, and time invariance
• To evaluate clinical response after treatment with GSK2879552, alone or in combination with ATRA.	• Objective response rate defined as the percentage of subjects achieving complete remission (CR), partial remission (PR), CRp (as per CR but platelet

Part 1 Objectives	Part 1 Endpoints
	Count <100 x 109/L) and morphologic leukemia free state per response criteria (Cheson, 2003).
• To characterize the PK of ATRA in combination with GSK2879552 after single and repeat-dose oral administration.	• ATRA PK parameters following single and repeat-dose administration of ATRA and GSK2879552, including AUC, Cmax, tmax, t½ (terminal phase) .
Exploratory Objectives	**Exploratory Endpoints**
• To explore markers of differentiation (including morphology) in response to GSK2879552, alone or in combination with ATRA.	• Change from baseline expression in cell surface markers in AML cells derived from bone marrow and/or peripheral blood.
• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552, alone or in combination with ATRA.	• Analysis of morphology, DNA, RNA and/or protein markers in blasts cells in bone marrow aspirates and/or peripheral blood.
• To evaluate the relationship between GSK2879552 exposure, alone or in combination with ATRA and safety/efficacy/PD parameters.	• Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax, Cmin or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b
• To characterize the metabolite profile of GSK2879552 after oral single and repeat-dosing in some subjects	• GSK2879552 metabolites in plasma and/or urine
• To determine the amount of GSK2879552 excreted in urine after oral single and repeat dosing in some subjects treated with GSK2879552	• Concentration of GSK2879552 in urine measured with an investigational bioanalytical method and extrapolated to total amount excreted in urine over time.
• To investigate the relationship between genetic variants in candidate genes, PK and safety profile of GSK2879552, alone or in combination with ATRA.	• Pharmacogenomic (PGx) study using buccal samples.

Part 2 Objectives	Part 2 Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate clinical activity of GSK2879552, alone or in combination with ATRA at the respective RP2D given orally in adult subjects with AML.	• Objective response rate defined as the percentage of subjects achieving complete remission (CR), partial remission (PR), CRp (as per CR but platelet Count <100 x 109/L) and morphologic leukemia free state per response criteria (Cheson, 2003).
Secondary Objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of respective RP2D of GSK2879552, alone or in	• AEs, SAEs, dose reductions or delays, withdrawals due to toxicities and changes in safety assessments (e.g., laboratory parameters, vital signs, ECGs, physical

Part 2 Objectives	Part 2 Endpoints
combination with ATRA.	examinations).
• To characterize the population PK of GSK2879552, alone or in combination with ATRA.	• Population PK parameters for GSK2879552 such as clearance (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 clinical activity in terms of duration of response, time to response (TTR) and progression free survival (PFS)	• Duration of response (DoR), defined as the time from first documented evidence of PR or better until disease progression (PD) or death, among responders, i.e. confirmed PR or better. • Time to Response is defined as the time from first dose to the first documented evidence of response (PR or better). • Progression-free survival (PFS), defined as the time from first dose until the earliest date of disease progression (PD), or death due to any cause.
Exploratory Objectives	**Exploratory Endpoints**
• To investigate the mechanism of action and indicators of sensitivity and resistance to GSK2879552, alone or in combination with ATRA.	• Analysis of morphology, DNA, RNA and/or protein markers in blast cells from bone marrow aspirate and/or peripheral blood sample.
• To evaluate the exposure response (PK/PD) relationship between GSK2879552, alone or in combination with ATRA and safety/efficacy/PD parameters.	• Relationship between GSK2879552 exposure markers (e.g. dose, concentration, Cmax or AUC (0-tau)) and safety/efficacy/PD parameters. PD parameters assessed by change from baseline in select biomarkers, e.g. CD86 and CD11b
• To investigate the relationship between genetic variants in candidate genes, PK and safety profile of GSK2879552, alone or in combination with ATRA.	• Pharmacogenomic (PGx) study using buccal samples

2.3. Study Design

Overview of Study Design and Key Features	
 • PK/PD expansion: Any dose level could be expanded up to 12 subjects during dose escalation. • Alternative dosing schedule may be explored.	
Design Features	Part 1: Dose Escalation Phase GSK2879552 Monotherapy • In Cohort 1, a single subject will receive a dose of GSK2879552 1 mg once daily. The subject in Cohort 1will be evaluated for dose limiting toxicities (DLTs) during the first 4 weeks of treatment (DLT observation window), and the safety and PK data will be reviewed prior to a dose escalation decision and starting Cohort 2. If the first subject becomes unevaluable for reasons other than toxicity, another subject will be recruited. The dose-escalation decision and rationale will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK). • Starting with Cohort 2, the dose escalation will continue using the Neuenschwander - continuous reassessment method (N-CRM) [Neuenschwander, 2008]. A sufficient number of subjects will be enrolled in each cohort to ensure that data from at least one subject that has completed the DLT observation window is available prior to defining a new dose and starting the next cohort. In addition, subjects who fail to take at least 75% of their scheduled doses in the 4 weeks for reasons other than toxicity will be replaced. GSK2879552 and ATRA combination • In Cohort 1, three subjects will receive GSK2879552 2 mg once daily. After all three subjects complete the first 4 weeks of treatment, the safety data will be reviewed for DLT. Available PK and PD data will be also reviewed prior to a dose escalation decision and starting Cohort 2. Each cohort will enroll 3 or more subjects to obtain sufficient data. If any subject becomes unevaluable for reasons other than toxicity, a replacement subject will be enrolled. In addition, subjects who fail to take at least 75%

Overview of Study Design and Key Features	
	of their scheduled doses of each drug in the first 4 weeks for reasons other than toxicity will be replaced. • Starting with Cohort1, the dose escalation will use the N-CRM with prior DLT information of GSK2879552 and ATRA monotherapies and follow the same rule with regards to the number of subjects, maximum dose increment, and the completion of dose escalation as in Monotherapy. PK/PD Expansion Cohort • Any dose level(s) in Part 1 may be expanded up to 12 subjects in order to collect adequate data on safety, PK or PD. However, PD sample (peripheral blood and bone marrow aspirate) collection may be stopped early at the sponsor's discretion. Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional data. These subjects may have the dose escalated to a higher completed dose level (not exceeding the maximum tolerated dose [MTD]) once the necessary PK/PD procedures have been completed. Part 2: Expansion Cohort • Once the respective RP2D have been determined, an expansion cohort of up to 30 subjects each, GSK2879552 mono-therapy or in combination with ATRA, will be enrolled in order to better characterize the clinical activity and safety profile of the RP2D. • Additional expansion cohorts may be initiated to test the efficacy of i) GSK2879552 at RP2D in ≥60 years old treatment naïve subjects, and ii) GSK2879552 in combination with other agents (demonstrated synergy in pre-clinical studies) in relapsed/refractory or ≥60 years old treatment naïve subjects. • The statistical design and number of subjects to be enrolled in the dose expansion cohort is based on the predictive probability of success if enrollment continues until all planned subjects are recruited [Lee, 2008]. The predictive probability design allows for evaluation of stopping rules after each subject once a minimum number of subjects are evaluable. In this particular study, we will stop only for futility. • Futility analysis for each dose expansion cohort will begin when response data is available for at least 10 evaluable subjects. The dose expansion cohort may be stopped early for futility if the predictive probability of success (response rate ≥ historical response rate) is less than 5%.
Dosing	• In Part 1, in Cohort 1, a single subject will receive a dose of GSK2879552 1 mg once daily. The subject in Cohort 1 must complete a full 28 days of dosing, and the safety and PK data will be reviewed prior to starting Cohort 2. • Starting with Cohort 2 the dose escalation will continue using the Neuenschwander - continuous reassessment method (N-CRM). • Upon review of the safety, tolerability, clinical activity, PK, PD data, the RP2D or doses will be selected. • Subjects may be enrolled at previously completed dose levels for the purpose of obtaining additional PK or PD data. • In Part 2, once the RP2D has been determined, subjects will be enrolled at the RP2D and will be evaluated for safety and efficacy while monitoring the futility stopping rules.
Time & Events	• Refer to Protocol Amendment 5 Section 7.1 Time and Event Table(s)

Overview of Study Design and Key Features	
Treatment Assignment	Subjects will be identified by a unique subject number that will remain consistent for the duration of the study, except for subjects who are allowed intra-subject dose escalation and start the treatment from Day 1 with the new subject numbers allocated to them.
Interim Analysis	• In Part 1, interim analyses to inform dose escalation will be performed following the completion of each monotherapy and combination dose cohort in part 1. The primary driver for dose escalation decisions in Part 1 will be governed by an N-CRM model for the mono-therapy dose cohorts and a Bayesian copula regression for the combination dose cohorts. They will be used to predict the probability of DLT at the dose levels yet to be tested to further guide these decisions. • After the initial 10 evaluable subjects, have enrolled at the RP2D dose, response data will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided in Section 13.4.2 of Protocol Amendment 5.

NOTES:

- Due to the business decision of study termination, Part 2 was not implemented. As a result, the remainder of this document contains no content related to Part 2 and will only provide information related to Part 1.

2.4. Statistical Hypotheses / Statistical Analyses

No formal statistical hypotheses are being tested. Analysis of the data obtained from this study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data obtained from this study.

3. PLANNED ANALYSES

3.1. Interim Analyses

In Part 1, interim analyses to inform dose escalation will be performed following the completion of each monotherapy and combination dose cohort in part 1. The primary driver for dose escalation decisions in Part 1 will be governed by a N-CRM model for the mono-therapy dose cohorts and a Bayesian copula regression for the combination dose cohorts. They will be used to predict the probability of DLT at the dose levels yet to be tested to further guide these decisions.

Interim analysis on Part 1 may also be conducted when all subjects enrolled in Part 1 have had at least one post-baseline disease assessments or progressed or died or withdrawn from the study.

Additionally, safety, PK, PD/biomarker data may be examined during Part 1. Prior to determining GSK2879552 dose for the next monotherapy cohort, exploratory analysis maybe conducted to assess the relationship of GSK2879552 dose levels with safety, PK and PD parameters using all data from available cohorts.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
2. All criteria for unblinding the randomization codes have been met.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All subjects who were screened for eligibility	• Screen Failure
Enrolled	• All participants who passed screening and entered the study.	• Number of participants by Country and Siteid • Age Ranges
All Treated Subjects	• All randomized participants who received at least one dose of study treatment.	• Study Pop, Safety, Efficacy
Pharmacokinetic	• All treated subjects for whom a PK sample is obtained and analysed.	• PK
Pharmacodynamic	• All treated subjects who contribute to PD/Biomarker samples.	• PD

Refer to Appendix 10 List of Data Displays which details the population used for each display.

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 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 from the analysis are captured and categorised on the protocol deviations dataset.

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

A separate listing of all inclusion/exclusion criteria deviations will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

		Data Displays for Reporting	
Code	**Description**	**Description**	**Order in TLF**
A	GSK2879552	1mg QD	1
		2mg QD	2
		4mg QD	3
		8mg QD	4
		12mg QD	5
		20mg QD	6
		2mg QD/ATRA 45mg/m2/day	7
		20mg QD PK/PD EXPANSION	8

5.2. Baseline Definitions

- Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.5	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Disposition of Subjects

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 listing of reasons for treatment discontinuation will also be provided. A listing of reasons for screen failure will also be provided.

6.3. Protocol Deviations

Important protocol deviations will be listed and will include inclusion and exclusion deviations as well as other deviations.

Participants excluded from any population will be listed.

6.4. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, >=65-84, and >=85. The count and percentage will be computed for sex and ethnicity. A separate summary of age ranges will be produced for study disclosure requirements.

Race and racial combinations will be summarized. A listing of race will also be provided.

Current and past medical conditions will be summarized and listed.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary. A listing of prior anti-cancer therapy will show ATC Level 1, Ingredient, and verbatim text. Prior anti-cancer therapy and prior cancer related surgeries will be listed.

Disease Characteristics at Screening will be listed.

A listing of substance use will also be provided.

6.5. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary and summarized. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Concomitant Medications will be listed.

6.6. Extent of Exposure

Extent of exposure of GSK2879552, alone or in combination with ATRA will depend on tolerability of the subjects to the doses administered and the course of their disease. The number of subjects exposed to GSK2879552, alone or in combination with ATRA will be summarized for each dose level administered according to the duration of therapy. The duration of exposure to study treatment in weeks (from first day to last day of treatment plus) will also be summarised.

All the dose reductions, dose escalations and dose interruptions will be summarised and listed separately.

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7. SAFETY ANALYSES

The safety analyses will be based on the All Treated Subjects population, unless otherwise specified. All summaries will be presented by dose level.

Study population analyses will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), serious AEs (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

AEs will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the PT level using the MedDRA dictionary. The relationship of AE system organ, preferred term, and verbatim text will be listed. The subject numbers for individual AEs will be listed.

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by System Organ Class (SOC) and Preferred term (PT) in descending order of total incidence.

The relationship between MedDRA SOC, PT, and Verbatim Text will be listed.

A listing of All AEs will be provided.

Serious adverse events by system organ class and preferred term (number of participants and occurrences) will be summarized. All serious adverse events (SAEs) will be tabulated based on the number and percentage of subjects who experienced the event. The summary tables will be displayed in descending order of total incidence.

Separate listings will be generated for all fatal SAEs and non-fatal SAEs.

7.2. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each of the AESI.

The events of special interest include:

- Encepalopathy
- Thrombocytopenia
- Hemorrhages
- Diarrhea

- Nausea & Vomiting
- Constipation
- Infections
- Neutropenia
- Fatigue
- Anemia

One summary giving number and percentage of subjects for each of these AESI will be provided. Separate listing for each of the AESI will also be provided.

7.3. Clinical Laboratory Analyses

Laboratory evaluations will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 10: List of Data Displays.

The assessment of laboratory toxicities will examine the following laboratory tests as specified in Table 2 below.

Table 2 Laboratory Tests

Hematology
Platelet count
White blood cell (WBC) Count (absolute)
Hemoglobin
Automated WBC Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Red blood cell (RBC) Indices (at screening and if Hemoglobin decrease ≥2 g/dL compared to baseline):
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin(MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Reticulocytes
RBC

Clinical Chemistry			
Blood urea nitrogen	Potassium	Aspartate aminotransferase (AST)	Total and Direct bilirubin[1]
Creatinine	Chloride	Alanine aminotransferase (ALT)	
Glucose, random	Total CO2	Albumin	
Sodium	Calcium[2]	Alkaline phosphatase (ALP)	
Magnesium	Phosphorus	Lactate dehydrogenase (LDH)	
Fasting Lipid panel including fractionated serum cholesterol, triglycerides, total cholesterol, HDL and LDL			
Estimated glomerular filtration (Modification of Diet in Renal Disease) or 24 hr urine creatinine clearance[3]			
Beta-hCG pregnancy test for appropriate females (serum or urine)			
Coagulation			
Prothrombin time/International normalized ratio (PT/INR)			
Partial prothrombin time (PTT)			
Urinalysis			
Specific gravity			
pH – dipstick			
Glucose – dipstick			
Protein – dipstick			
Blood – dipstick			
Ketones – dipstick			
Microscopic examination required (if blood or protein by dipstick ≥1+)			
Urine total protein to creatinine ratio (UPC ratio) – (if protein by dipstick ≥2+)			

1. Bilirubin fractionation is required if total bilirubin >2x ULN
2. For screening ionized calcium is acceptable
3. The Modification of Diet in Renal Disease Equation will be used to determine an estimated glomerular filtration rate.

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

For hematology, RBC is not gradable by CTCAE v4.0.

For clinical chemistry, BUN, LDH and estimated creatinine clearance are not gradable by CTCAE v4.0.

For coagulation tests, INR and partial thromboplastin time are gradable by CTCAE v4.0 but prothrombin time is not.

For all laboratory results, displays for hematology, clinical chemistry, and liver function tests will be separately produced.

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. For laboratory tests that are graded for both

low and high values, summaries will be done 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 for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the post-baseline time period, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

A supporting listing of all chemistry and haematology laboratory data will be provided.

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.

7.3.1. Liver Function Analyses

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

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 times ULN **and** INR >1.5, if INR is measured).

7.4. Other Safety Analyses

The analyses of non-laboratory safety assessment results will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

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.

ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline. The summaries for the QTc will use the collected value based on QTcB and QTcF.

The QTcB and QTcF values will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480), Grade 2 (481-500), and Grade 3 (≥501). Summaries of grades will display the number and percentage of subjects by grade in the worst case post-baseline. Similarly, grade changes relative to baseline grade will also be generated.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

Vital Signs

Changes in heart rate from baseline, Increase in Blood Pressure from baseline and changes in Temperature from baseline will be summarised.

A separate listing of vital signs will also be produced.

Left Ventricular Ejection Fraction

A listing of the left ventricular ejection fraction results will be generated.

ECOG Performance Status

A summary of change from baseline in ECOG performance status by scheduled visits will be performed. Summaries will use frequency and percentage of subjects at each planned assessment time, best and worst-case post baseline.

A supporting listing will also be provided.

Montreal Cognitive Assessment (MOCA)

A listing of the Montreal Cognitive Assessment will be generated.

8. EFFICACY ANALYSES

All efficacy analyses will be based on the All Treated Subjects population unless otherwise specified. All analyses will be presented by dose of study treatment. Details of the planned displays are provided in Appendix 10: List of Data Displays.

Response rate (RR) is defined as the percentage of subjects who achieved CR, CRp, PR or morphologic leukemia-free state (MLFS) among subjects who received at least one dose of treatment.

The investigator-assessed best response along with response rate (Without confirmation) will be summarized by dose of study treatment. A listing of investigator assessed responses (Without Confirmation) will be provided.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK.

The results of the pharmacokinetic analysis may be provided in a report separate from the main CSR.

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

The GSK2879552 concentration-time data will be summarized by planned time point and dose cohort. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum). The ATRA concentration-time data will be listed.

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 11.5 Reporting Process & Standards).

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic analysis of GSK2879552 will be conducted by noncompartmental methods using WinNonlin (Version 6.3 or higher). However pharmacokinetic analysis of ATRA will not be conducted due to the sample size limitations. The following pharmacokinetic parameters will be determined for if data permit:

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-τ)	Area under the concentration-time curve during a dosing interval of duration "tau".
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 Day 1 only
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / λz**
λz	Apparent terminal phase elimination rate constant
Cτ	Trough concentration

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 Day 15/ AUC(0-τ) in Day 1. The ratio of AUC(0-τ) on Day 15/ Day 1 AUC(0-∞) will be calculated to assess time invariance.

9.1.2. Population of Interest

The primary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Plasma concentration-time data for GSK2879552 and ATRA will be listed by dose and Plasma concentration-time data for GSK2879552 will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) by planned relative assessment time. Mean and/ or median values will be plotted over time. Individual plasma and urinary (if available) PK parameters values as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric mean, and the standard deviation, Coefficient of variance [CV]% and 95% confidence interval of log-transformed parameters, if applicable) by dose cohort will be reported.
The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available.

9.1.3.1. Dose proportionality

If data permits, dose proportionality will be assessed using power model for:

- AUC(0-∞) and Cmax on Day 1
- AUC(0-τ) and Cmax on Day 15

Dose proportionality of GSK2879552 AUC(0-∞) and Cmax following single dose administration and AUC(0-τ) and Cmax following repeat dose administration will be evaluated using the power model as described below:

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

where a is the intercept and b is the slope.

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

9.1.3.2. Accumulation

If data permits, accumulation using ANOVA will be performed for AUC(0-τ) on Day 15 vs AUC(0-τ) on Day 1 by dose cohort.

To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) based on AUC data will be determined as follows:

$$Ro = AUC(0\text{-}\tau)_{D15} / AUC(0\text{-}\tau)_{D1}$$

Assuming both linear and time-invariant pharmacokinetics, the Ro at steady-state should be unity.

An ANOVA with a random effect term for subject and fixed effect terms for day will be performed by dose on the $\log_e$-transformed PK parameters AUC(0-τ). Day will be treated as a class variable in the model. The accumulation ratio of GSK2879552 will be estimated by calculating the ratio of the geometric least squares (GLS) means of the PK parameter between Day 15 and Day 1 for all dose levels and the corresponding 90% CI for each ratio.

The accumulation ratio will be summarized by dose.

9.1.3.3. Time Invariance

To evaluate whether the pharmacokinetics remains unaltered after repeat dosing a similar analysis to that described above will be carried out after $\log_e$-transformation of AUC(0-∞) for D1 and AUC(0-τ) for D15, the difference of which provides the steady-state ratio (Rs).

A mixed effect model will be fitted with day as a fixed effect and subject as a random effect for each treatment (dose) separately. AUC(0-τ) on D15 will be compared to AUC(0-∞) on D1 in order to assess time invariance for each dose. The Kenward & Roger (KR) degrees of freedom approach will be used. The ratio and 90% confidence interval will be calculated by back-transforming the difference between the least square means for the two days and associated 90% confidence interval, for each dose. Assuming both linear and time-invariant pharmacokinetics, the Rs at steady-state should be one.

The time invariance ratio will be summarized by dose.

10. REFERENCES

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

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SOP_54838 (6.0): Development, Review and Approval of Reporting and Analysis Plans

11. APPENDICES

11.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

11.1.1. Exclusions from Per Protocol Population

There will be no Per Protocol population used for any displays or statistical analysis.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

Refer to Protocol Amendment 5 Section 7.1.

11.3. Appendix 3: Assessment Windows

No assessment windows will be applied.

11.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

11.4.1. Study Phases

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

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

11.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: Compound: GSK2879552, Study:200200
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards	
Generation of RTF Files	
• RTF files will be generated for tables and figures.	

11.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• 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, unless otherwise stated. • 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.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and figures.

• All unscheduled visits will be included in listings
Descriptive Summary Statistics
Continuous Data: Refer to IDSL Statistical Principle 6.06.1
Categorical Data: N, n, frequency, %
Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

11.5.3. Reporting Standards for Pharmacokinetic

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 [Insert document name]. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. 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.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to GUI_51487

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis 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 time window the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit 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 First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

11.6.2. Study Population

Demography
Age
• Age will be calculated based on the Screening visit date • 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 '30JUN'.
Body Mass Index
• 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** • Participants 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. • Note: GSK2879552 exposure data will only be used for the above calculation.

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A subject will be considered to have completed the study if they complete screening assessments, at least 28 days of study treatment(s) and the post-treatment follow-up visit. • If subjects which prematurely discontinue, additional subjects may be enrolled as replacement subjects at the discretion of the Sponsor in consultation with the investigator. • Subjects who fail to take at least 75% of their scheduled doses in the first 28 days for reasons other than toxicity (e.g., dose limiting toxicities) will be replaced • All available data from participants 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. • Withdrawal visits will be summarised as withdrawal visits.

11.7.2. 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: o 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. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. 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.

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. In addition, partial dates may be imputed for 'slotting' data to study time periods or for specific analysis purposes as outlined below.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month, and year	• No Imputation for completely missing dates
		day,	• If study treatment start date is missing (i.e. subject did

Dataset	Date	Missing Element	Rule
		month	not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. • Else set start date = study treatment start date. o Else set start date = January 1.
		Day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. • Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date		• No imputation for partial end dates will be performed

Concomitant Medication and Blood and Blood Supportive Care Products:

Start and end dates may be imputed for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but should not be permanently stored in the analysis datasets.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. ▪ Else set start date = study treatment start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. ▪ Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact.

11.7.3. Imputation of Missing Exposure End Dates

For subjects who have missing end dates in their last exposure record potentially due to being lost to follow-up, the last contact date will be imputed as the last exposure date (i.e. date of last dose). This imputation will only be used when needed.

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. 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.

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.

11.9. Appendix 9: Abbreviations & Trade Marks

11.9.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Events of Special Interest
ATRA	All Trans-Retinoic Acid
A&R	Analysis and Reporting
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRF	Case Report Form
CS	Clinical Statistics
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Register
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DLT	Dose Limiting Toxicity
DP	Decimal Places
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IP	Investigational Product
MOCA	Montreal Cognitive Assessment
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PD	Pharmacodynamic
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
RP2D	Recommended Phase 2 Dose
SAC	Statistical Analysis Complete
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

11.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

11.10. Appendix 10: List of Data Displays

11.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.15	N. A
Efficacy	2.1	N. A
Safety	3.1 to 3.20	N. A
Pharmacokinetic	4.1 to 4.6	N. A
Section	**Listings**	
ICH Listings	1 to 34	
Other Listings	35 to 48	

11.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.10.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	All Treated Subjects	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Treated Subjects	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment		SAC
1.3.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Demographic and Baseline Characteristics					
1.4.	All Treated Subjects	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.5.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.6.	All Treated Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
Medical History and Concomitant Medications					
1.7.	All Treated Subjects	MH1	Summary of Current/Past Medical Conditions		SAC
1.8.	All Treated Subjects	CM8	Summary of Concomitant Medications	Include both prior and concomitant medications	SAC
Exposure and Treatment Compliance					
1.9.	All Treated Subjects	POP_T1	Summary of Exposure to GSK2879552	Include 2mg QD/ATRA 45mg/m2/day	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.10.	All Treated Subjects	ODMOD1	Summary of Dose Reductions to GSK2879552		SAC
1.11.	All Treated Subjects	ODMOD8	Summary of Dose Escalations to GSK2879552		SAC
1.12.	All Treated Subjects	ODMOD2	Summary of Dose Interruptions to GSK2879552		SAC
Prior Anti-Cancer Therapy and Surgical Procedures					
1.13.	All Treated Subjects	AC1	Summary of Prior Anti-Cancer Therapy		SAC
1.14.	All Treated Subjects	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens		SAC
1.15.	All Treated Subjects	OSP1	Summary of Cancer Related Surgical Procedures		SAC

11.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Clinical Response					
2.1.	All Treated Subjects	Re1a	Summary of Investigator-Assessed Best Response (Without Confirmation)	1. Investigator Assessed Responses would be reported. No confirmation on responses are required. 2. Include the response categories collected in eCRF. i.e. 1. Complete remission (CR) 2. As per CR but PLT < 100 x10^9/L (CRp) 3. Morphologic leukaemia-free state(MLFS) 4. Partial remission (PR) 5. Stable disease 6. Progressive Disease or Relapse of Disease 7. Not evaluable 3. Include just the first two segments of the template. i.e. Best Response and Response rate. 4. Response rate = CR+CRp+MLFS+PR 5. P-value for response rate would not be reported.	SAC

11.10.6. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	All Treated Subjects	OAE7	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term		SAC
3.2.	All Treated Subjects	AE3	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC
3.3.	All Treated Subjects	AE13	Overview of Adverse Events		SAC
3.4.	All Treated Subjects	IDSL AE's of Special Interest – EXAMPLE METABOLIC 14.1	Summary of All Adverse Events of Special Interest		SAC
3.5.	All Treated Subjects	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT	SAC
Serious and Other Significant Adverse Events					
3.6.	All Treated Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PleaseLaboratory: Chemistry					
3.7.	All Treated Subjects	OLB9C	Summary of Clinical Chemistry Toxicity Grade Change from Baseline Grade	For gradable Clinical chemistry tests. By dose, and overall. Include Worst-case.	SAC
3.8.	All Treated Subjects	OLB11C	Summary of Clinical Chemistry Laboratory Changes from Baseline with Respect to the Normal Range	For non-gradable lab tests. By dose, and overall.	SAC
Laboratory: Hematology					
3.9.	All Treated Subjects	OLB9C	Summary of Haematology Toxicity Grade Change from Baseline Grade	For gradable Haematology tests. By dose, and overall. Include Worst-case.	SAC
3.10.	All Treated Subjects	OLB11C	Summary of Clinical Hematology Laboratory Changes from Baseline with Respect to the Normal Range	For non-gradable lab tests. By dose, and overall.	SAC
Laboratory: Hepatobiliary (Liver)					
3.11.	All Treated Subjects	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities		SAC
ECG					
3.12.	All Treated Subjects	EG1	Summary of ECG Findings		SAC
3.13.	All Treated Subjects	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.14.	All Treated Subjects	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category		SAC
3.15.	All Treated Subjects	SAF_T1	Summary of Maximum QTc Grades Post-Baseline Relative to Baseline		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.16.	All Treated Subjects	SAF_T1	Summary of Maximum Increase in QTc Grades Post-Baseline Relative to Baseline		SAC
Vital Signs					
3.17.	All Treated Subjects	OVT1B	Summary of Changes in Heart Rate from Baseline		SAC
3.18.	All Treated Subjects	OVT2B	Summary of Increases in Blood Pressure from Baseline		SAC
3.19.	All Treated Subjects	OVT1B	Summary of Changes in Temperature from Baseline	The following categories need to be included: Decrease to <=35 Change to normal or no change Increase to >=38	SAC
ECOG					
3.20.	All Treated Subjects	PS4A	Summary of Change in ECOG 'Performance Status' from Baseline		SAC

11.10.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
PK Concentration					
4.1.	Pharmacokinetic	PK01	Summary of GSK2879552 Plasma Pharmacokinetic Concentration-Time Data		SAC
PK Parameters					
4.2.	Pharmacokinetic	PK06	Summary of Derived GSK2879552 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed)		SAC
4.3.	Pharmacokinetic	PK_T1	Summary of Statistical Analysis to Assess the Dose Proportionality for AUC (0-∞) and Cmax Using Power Model – Day 1		SAC
4.4.	Pharmacokinetic	PK_T1	Summary of Statistical Analysis to Assess the Dose Proportionality for AUC (0-τ) and Cmax Using Power Model – Day 15		SAC
4.5.	Pharmacokinetic	PK_T2	Summary of Statistical Analysis to Assess the Accumulation for AUC (0-τ) on Day 15 vs AUC(0-τ) on Day 1 by Dose		SAC
4.6.	Pharmacokinetic	PK_T2	Summary of Statistical Analysis to Assess the Time Invariance based on AUC(0-∞) on Day 1 and AUC(0-τ) on Day 15 by Dose		SAC

11.10.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	All Treated Subjects	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	All Treated Subjects	SD2	Listing of Reasons for Study Treatment Discontinuation	Remove “Number of cycles” column. Add investigational product as one of the column	SAC
Protocol Deviations					
4.	All Treated Subjects	DV2	Listing of Important Protocol Deviations		SAC
5.	Screened	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
6.	Enrolled	SP3	Listing of Participants Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
7.	All Treated Subjects	DM2	Listing of Demographic Characteristics		SAC
8.	All Treated Subjects	DM9	Listing of Race		SAC
Medical History and Concomitant Medications					
9.	All Treated Subjects	MH2	Listing of Past/Current Medical Conditions	Oncology specific template to be used	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
10.	All Treated Subjects	OCM1A	Listing of Concomitant Medications	Include both prior and concomitant medications	SAC
Exposure and Treatment Compliance					
11.	All Treated Subjects	EX3	Listing of Exposure Data	Include a flag variable to indicate imputed date.	SAC
12.	All Treated Subjects	ODMOD10A	Listing of Dose Reductions		SAC
13.	All Treated Subjects	ODMOD11A	Listing of Dose Interruptions		SAC
14.	All Treated Subjects	ODMOD15A	Listing of Dose Escalations		SAC
Adverse Events					
15.	All Treated Subjects	OAE04	Listing of All Adverse Events		SAC
16.	All Treated Subjects	OAE03	Listing of Subject Numbers for Individual Adverse Events		SAC
17.	All Treated Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC
18.	All Treated Subjects	OAE04	Listing of Encephalopathy: Adverse Event of Special Interest		SAC
19.	All Treated Subjects	OAE04	Listing of Thrombocytopenia: Adverse Event of Special Interest		SAC
20.	All Treated Subjects	OAE04	Listing of Hemorrhages: Adverse Event of Special Interest		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
21.	All Treated Subjects	OAE04	Listing of Diarrhoea: Adverse Event of Special Interest		SAC
22.	All Treated Subjects	OAE04	Listing of Nausea and Vomiting: Adverse Event of Special Interest		SAC
23.	All Treated Subjects	OAE04	Listing of Constipation: Adverse Event of Special Interest		SAC
24.	All Treated Subjects	OAE04	Listing of Infections: Adverse Event of Special Interest		SAC
25.	All Treated Subjects	OAE04	Listing of Neutropenia: Adverse Event of Special Interest		SAC
26.	All Treated Subjects	OAE04	Listing of Fatigue: Adverse Event of Special Interest		SAC
27.	All Treated Subjects	OAE04	Listing of Anaemia: Adverse Event of Special Interest		SAC
Serious and Other Significant Adverse Events					
28.	All Treated Subjects	OAE4	Listing of Fatal Serious Adverse Events		SAC
29.	All Treated Subjects	OAE4	Listing of Non-Fatal Serious Adverse Events		SAC
All Laboratory					
30.	All Treated Subjects	OLB7	Listing of Clinical Chemistry Laboratory Data		SAC
31.	All Treated Subjects	OLB7	Listing of Haematology Laboratory Data		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ECG					
32.	All Treated Subjects	EG3	Listing of ECG Values		SAC
33.	All Treated Subjects	EG5	Listing of Abnormal ECG Findings		SAC
Vital Signs					
34.	All Treated Subjects	VS4	Listing of Vital Signs		SAC

11.10.9. Non-ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Substance Use					
35.	All Treated Subjects	SU2	Listing of Substance Use		SAC
Prior Anti-Cancer Therapy and Surgical Procedure					
36.	All Treated Subjects	AC6	Listing of Prior Anti-Cancer Therapy Regimens		SAC
37.	All Treated Subjects	OSP3	Listing of Cancer Related Surgical Procedures		SAC
Blood Products					
38.	All Treated Subjects	BP4	Listing of Blood Products		SAC
Disease Characteristics					
39.	All Treated Subjects	POP_L1	Listing of Disease Characteristics at Screening		SAC
Efficacy					
40.	All Treated Subjects	EFF_L1	Listing of Investigator-Assessed Responses (Without Confirmation)		SAC
Safety					
41.	All Treated Subjects	OLVEF2A	Listing of Left Ventricular Ejection Fraction Results		SAC
42.	All Treated Subjects	PS5A	Listing of ECOG Performance Status		SAC
43.	All Treated Subjects	SAF_L1	Listing of Montreal Cognitive Assessment (MOCA)		SAC
44.	All Treated Subjects	DTH3	Listing of Death		SAC
45.	All Treated Subjects	LIVER6	Listing of Liver Stopping Event Information for RUCAM Score		SAC

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
PK					
46.	Pharmacokinetic	PK07	Listing of GSK2879552 Plasma PK Concentration-Time Data		SAC
47.	Pharmacokinetic	PK07	Listing of ATRA Plasma PK Concentration-Time Data		SAC
48.	Pharmacokinetic	PK13	Listing of GSK2879552 Plasma PK Parameters Data		SAC

11.11. Appendix 11: Example Mock Shells for Data Displays

Example: POP_T1 Page 1 of n
Protocol: 200200
Population: All Treated Subjects

Table X
Summary of Exposure to GSK2879552

		1mg QD	2mg QD	4mg QD	8mg QD	12mg QD	20mg QD
Duration of Exposure(weeks) [1]	n	X	X	X	X	X	X
	Mean	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
	SD	X.XXXX	X.XXXX	X.XXXX	X.XXXX	X.XXXX	X.XXXX
	Median	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
	Min.	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Max.	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
Average Daily Dose(mg) [2]	n	X	X	X	X	X	X
	Mean	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
	SD	X.XXXX	X.XXXX	X.XXXX	X.XXXX	X.XXXX	X.XXXX

	Median	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
	Min.	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Max.	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX

Note : [1] Duration of exposure = end date of GSK2879552 - start date of GSK2879552 + 1.
[2] Average daily dose = Cumulative dose divided by duration of exposure.

Example: POP_L1
Protocol: 200200
Population: All Treated Subjects

Listing X

Listing of Disease Characteristics at Screening

Treatment: 1mg QD

Centre Id/ Subj.	Visceral or non-visceral disease	Date of Last Recurrence/Time since recurrence(days)	Date of Last Progression/Time since progression(days)	WHO classification of AML/WHO classification of AML subtype	FAB classification of AML	Lines of therapy completed Screen	History of CNS lesions
PPD	Non-visceral	25AUG2014/ 64	25AUG2014/ 64	AML, not otherwise categorized/AML with maturation	M2	4 lines	N

Example: EFF_L1
Protocol: 200200
Population: All Treated Subjects

Listing X
Listing of Investigator-Assessed Responses (Without Confirmation)

Treatment: 1mg QD

Centre Id/ Subj.	Age(y)/ Sex/ Race	Visit	Date	Resp. Day	Response Assessment
PPD	68/ M/ White - White/Caucasian/European Heritage	Day 15	PPD	16	Stable disease

Example: SAF_T1
Protocol: 200200
Population: All Treated Subjects

Table X

Summary of Maximum QTc Grades Post-Baseline Relative to Baseline

Treatment	N	Corrected QT (Bazett's correction) interval (MSEC)	Corrected QT (Friedericia's correction) interval (MSEC)				
			Grade 0	Grade 1	Grade 2	Grade 3	Missing
1mg QD	1	Grade 0	1 (100%)	0	0	0	0
		Grade 1	0	0	0	0	0
		Grade 2	0	0	0	0	0
		Grade 3	0	0	0	0	0
		Missing	0	0	0	0	0
2mg QD	2	Grade 0	1 (50%)	0	0	0	0
		Grade 1	1 (50%)	0	0	0	0
		Grade 2	0	0	0	0	0
		Grade 3	0	0	0	0	0
		Missing	0	0	0	0	0
4mg QD	7	Grade 0	7 (100%)	0	0	0	0
		Grade 1	0	0	0	0	0
		Grade 2	0	0	0	0	0
		Grade 3	0	0	0	0	0
		Missing	0	0	0	0	0
8mg QD	5	Grade 0	1 (33%)	0	0	0	0
		Grade 1	1 (33%)	0	0	0	0
		Grade 2	0	0	0	0	0
		Grade 3	0	0	0	0	0
		Missing	1 (33%)	0	0	0	0

Example: SAF_L1
Protocol: 200200
Population: All Treated Subjects

Listing X
Listing of Montreal Cognitive Assessment (MOCA)

Treatment	Centre ID/ Subj.	Age(y)/ Sex/ Race	Visit	Date of Assessment/Time of Assessment Study day	MOCA Education	MOCA Total Score
8.0mg QD	PPD	68/ M/ White - White/Caucasian/European Heritage	SCREENING	PPD 10:30 -4	<= 12 years education	26

Example: PK_T1
Protocol: 200200
Population: Pharmacokinetic

Table X
Summary of Statistical Analysis to Assess the Dose Proportionality for AUC(0-∞) and Cmax Using Power Model – Day 1

Parameter	Number of subjects	Estimated Mean Slope	90% Confidence Interval	
			90% CI Low	90% CI High
AUC(0-inf)	XX	X.XXX	X.XXX	X.XXX
Cmax	XX	X.XXX	X.XXX	X.XXX

Note: Repeat the same for Table No. 4.5: Summary of Statistical Analysis to Assess the Dose Proportionality for AUC(0-τ) and Cmax Using Power Model – Day 15

Example: PK_T2
Protocol: 200200
Population: Pharmacokinetic

Table X

Summary of Statistical Analysis to Assess the Accumulation for AUC (0-τ) on Day 15 vs AUC(0-τ) on Day 1 by Dose

		Geometric LSMean		Comparison		90% Confidence
Treatment	n	Test	Ref.	Test/Ref.	Ratio	Interval
1mg QD	X	XX.XX	XX.XX	Day 15 vs Day 1	X.XXX	(X.XXX, X.XXX)
2mg QD	X	XX.XX	XX.XX	Day 15 vs Day 1	X.XXX	(X.XXX, X.XXX)

Note: Repeat the same for Table No. 4.7: Summary of Statistical Analysis to Assess the Time Invariance based on AUC(0-∞) on D1 and AUC(0-τ) on Day 15 by Dose