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Title:	Reporting and Analysis Plan for a phase I, first time in human, open-label, dose escalation study to investigate the safety, pharmacokinetics, and pharmacodynamics of anti-HER3 monoclonal antibody GSK2849330 in subjects with advanced HER3-positive solid tumors

Compound Number: GSK2849330

Effective Date: 15-AUG-2016

Description: The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol RM2007/00642/02. This RAP is intended to describe the safety, pharmacokinetics, pharmacodynamics and biomarker analyses required for the study. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Subject: First Time in Human, Oncology, GSK2849330, HER3 inhibitor, solid tumors

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Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BLDPROD	Blood and Supportive Care Products Dataset
CI	Confidence Interval
CONMED	Concomitant Medication Dataset
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Anti-cancer Therapy Dataset
DISCHA1	Disease Characteristics Dataset
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
HR	Hazard Ratio
IDMC	Independent Data Review Committee
IDSL	Integrated Data Standards Library
ITT	Intent to Treat
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Medical Affairs
NCI	National Cancer Institutes
ONCTTE	Oncology Time to Event Dataset
ONCSURV	Oncology Survival Dataset
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PGx	Pharmacogenetics
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RAMOS	Registration and Medication Ordering System
RADIO	Radiotherapy Dataset
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RESP2	Best Response Dataset
SAE	Serious Adverse Event
SD	Stable Disease

SOC	System Organ Class
SRT	Safety Review Team
ULN	Upper Limit of Normal

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analysis to for the Clinical Study Reports (CSRs) for HER117158 (Protocol GlaxoSmithKline Document Number 2012N152466_02).

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze of the study data. Interim analyses are detailed within Section 4.1, where applicable.

Revision Chronology:		
Original Document Number 2012N152466_00	2013-AUG-06	Original
Amendment 1 2012N152466_01	2014-SEP-10	• Four molecularly-defined, tumour histology groups were added to Part 2. • Additional inclusion criteria were added. • Number of subjects in Part 1 was changed from 10 to 13. • An additional cohort of subjects was added to Part 1. • Permitted and prohibited medications were classified. • A rational for adding weekly dosing was added/ PK sampling times were revised for the amendment. The predicted half-life and dose frequency were changed. Preliminary nocompartmental and population PK parameters were added. • An Efficacy Population was defined. • Definitions for subject and study completion, timing of disease assessment, and serum samples at the end of the study were clarified. • Recommendations for management of diarrhea were expanded. • The requirements for selected cytokines samples i subjects experiencing infusion-related reactions. • Vials containing 5 mL of investigational

Revision Chronology:		
		product was introduced. • Clarification regarding ECHO as the preferred method of LVEF was clarified. • Criteria for withholding of study treatment for QTc prolongation was clarified.
Amendment 2 2012N152466_02	2015-JAN-09	• Inclusion criteria for Part 2, DLT definition. tumour biopsy, total blood volume of PK sampling were modified. • Inconsistencies in the Time and Events table were corrected.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Part 1: Dose Escalation and PK-PD Cohorts

Objective	Endpoint
Primary	
• To determine the safety and tolerability of GSK2849330 in subjects with advanced HER3-positive solid tumors.	• AEs, serious adverse events (SAEs), DLTs, and changes in laboratory values, electrocardiograms (ECGs), and vital signs.
Secondary	
• To characterize the PK of GSK2849330 following IV administration.	• PK parameter values for GSK2849330.
• To evaluate preliminary evidence of target engagement and PD effects of GSK2849330.	• Total and phospho-HER3 from tumor tissue.
• To determine the recommended dose regimen(s) of GSK2849330 for further exploration in Part 2.	• Safety, tolerability, PK, and available PD data.
• To evaluate the immunogenicity of GSK2849330 following IV administration.	• Antibodies to GSK2849330 assessed in serum.
Exploratory	
• To further evaluate preliminary	• Pre- and post- treatment biomarkers (cells,

Objective	Endpoint
evidence of target engagement and PD effects of GSK2849330. • To explore relationships between GSK2849330 PK, markers of target engagement, and /or PD markers. • To explore preliminary clinical tumor outcomes after treatment with GSK2849330.	proteins, ribonucleic acid [RNA] and/or deoxyribonucleic acid [DNA]) from circulation, skin, and/or tumor tissue. • GSK2849330 concentration-time profile and PK parameters, target engagement and PD markers in circulation, skin, and/or tumor. • Preliminary evidence of clinical benefit as assessed by overall response rate (ORR), tumor markers, and other measures of clinical benefit.
Pharmacogenetic (PGx) Exploratory	
• To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.	• Genetic variations in selected candidate genes, such as the FCγreceptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.

2.2. Part 2: Expansion Cohorts

Objective	Endpoint
Primary	
• To evaluate the safety of GSK2849330 in a larger cohort at the dose regimen(s) recommended for further exploration in Part 1.	• AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs.
Secondary	
• To evaluate preliminary evidence of clinical benefit.	• ORR, tumor markers, and other measures of clinical benefit.
• To further characterize target engagement and PD effects of GSK2849330.	• Total and phospho-HER3 from tumor tissue.
• To further characterize the PK of GSK2849330.	• PK parameter values for GSK2849330.
• To characterize relationship between GSK2849330 PK, markers of target engagement, and/or PD markers.	• Antibodies to GSK2849330 in serum.
• To evaluate the immunogenicity of GSK2849330 following IV administration.	
Exploratory	
• To explore additional measures of clinical benefit.	• Progression free survival (PFS), ORR according to immune-related response criteria (irRc) and modified Response Evaluation Criteria in Solid Tumors mRECIST where applicable, and other tumor markers and measures of clinical benefit.
• To further characterize target engagement and PD effects of GSK2849330.	• Pre- and post- treatment biomarkers (cells, proteins, RNA and/or DNA) from circulation, skin, and/or tumor tissue.
• To explore relationship between pre-treatment HER3 expression level and clinical outcome.	• Pre-treatment HER3 expression levels, efficacy outcome parameters.
• To identify molecular features potentially predictive of response to GSK2849330.	• Prediction analysis of biomarkers (cells, DNA, RNA or protein) in tumor, skin, and/or circulation with efficacy endpoints.

Objective	Endpoint
Pharmacogenetic (PGx) Exploratory	
• To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.	• Genetic variations in selected candidate genes, such as the FCγreceptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.

3. STUDY DESIGN

This is a Phase I, FTIH, open-label, multi-center, dose-escalation study of the anti-HER3 antibody, GSK2849330, in subjects with advanced solid tumors expressing HER3 (2+ or 3+). The study will be conducted in two parts as depicted below.

Part 1
Dose Escalation Cohorts
To determine the safety, tolerability, PK and preliminary PD of GSK2849330, in support of selection of the recommended dose(s) and regimen(s) for further exploration in subjects with advanced solid tumors with HER3 expression

PK/PD Cohorts

Subjects that agree to give pre- and on- treatment tumor biopsies will be enrolled in the PK/PD cohorts to support selection of the recommended dose(s) and regimen(s) for Part 2. Up to 3 subjects with evaluable pre- and on-treatment tumor biopsies will be enrolled at each dose level after that dose is determined tolerable.

↓

Part 2
Expansion Cohort
To determine safety and preliminary evidence of clinical benefit of GSK2849330, and to further evaluate the PK and PD of GSK2849330 at the recommended Part 2 dose(s) and regimen(s) in subjects with selected HER3 or HER 3 and NRG1 expressing tumor types.

Dose Escalation Cohorts will identify the MTD on the fixed-dose dosing schedule using an accelerated titration scheme followed by Neuenschwader-Continuous Reassessment Method (N-CRM).

The proposed starting dose and schedule of GSK2849330 is 1.4 mg/kg weekly given for 28 days. The single subject in Cohort 1 only must complete a full 28 days of dosing, and the safety and PK data will be reviewed.

The planned dose and schedule for Cohort 2, 3 and 4 are corresponding 3 mg/kg every 2 weeks, 10 mg/kg every 2 weeks and 30 mg/kg every 2 weeks given for 28 days. Starting with Cohort 2, the dose escalation will continue using N-CRM method with 3 subjects in each cohort. In cohort 2 through 4, the first subjects in each cohort will begin dosing and

be observed for at least 24 hours prior to dosing the rest of the that cohort at same dose level.

Additional subjects may also be enrolled at any specified dose level to further characterize the safety. Additional doses and schedules and loading doses may be explored based on emerging safety, PK and PD data.

PK-PD Cohorts Once a given dose escalation cohort is filled, additional subjects may be enrolled into a PK/PD cohort (at any dose level determined to be tolerable) to allow for the collection of data on the PD effects of GSK2849330 as well as additional PK data. All subjects in cohorts 5 through 7, as depicted in Table 1, must be enrolled in the PK/PD cohorts. Subjects enrolled in the PK/PD cohorts must meet all of the relevant inclusion and exclusion criteria, have disease that is amenable to biopsy, and also agree to have pre- and on-treatment biopsies in addition to the other study procedures. Subjects will be enrolled in PK/PD cohorts in order to obtain up to 3 evaluable pre- and on-treatment biopsy pairs per dose level (see SPM for additional details). Subjects who do not agree to, or who are unable to provide pre- and on-treatment biopsies in the PD expansion may enroll in dose escalation cohorts in Part 1 as they become available.

Table 1 Subject Cohorts and Planned Doses for Part 1

Dose Level	**Dose**	**N Dose Escalation Cohorts**	**N[a] PK-PD Cohorts**
1	1.4 mg/kg weekly	1 (minimum)	up to 3
2	3 mg/kg every 2 weeks	3 (minimum)	up to 3
3	10 mg/kg every 2 weeks	3 (minimum)	up to 3
4	30 mg/kg every 2 weeks	3 (minimum)	up to 3
5 (Optional)	Lower dose and/or extended interval	NA	up to 3
6 (Optional)	Lower dose and/or extended interval	NA	up to 3
7 (Optional)	Lower dose and/or extended interval	NA	up to 3

a) A sufficient number of subjects will be enrolled in the PK/PD cohorts to obtain up to 3 evaluable pre- and on-treatment biopsy pairs per dose level (see the SPM for additional details).

Expansion Cohorts Subjects will be enrolled in up to 4 expansion cohorts to explore further the safety and tolerability of GSK2849330 in targeted populations. The planned tumor types are documented in Protocol Amendment 2. If possible, all expansion cohorts may be opened in parallel, and will initially enroll 12 subjects with the option of

expanding to a maximum of 30 subjects if futility criteria are not met using the well established methodology of [Lee, 2008] Predictive Probability of success (See Protocol Section 13.2.2 and Section 13.6.2 for additional details).

4. PLANNED ANALYSES

4.1. Interim Analyses

No formal interim analyses are planned. However, dose escalation decision during Part 1 will be based on N-CRM design and reviews of all available data, including pharmacokinetic data and the safety profile of prior cohorts. For these reviews, the GSK Pharmacokineticist will derive the standard PK parameters using nominal PK sample time for each subject and summarize these data by dose. AE, demographic, vital, and laboratory parameters will be listed and summarized by Oncology Clinical Statistician and Programmer. Oncology Clinical Statistician also will provide the posterior toxicity interval probabilities for each planned dose, the fitted toxicity curve and recommended dose for next cohort by N-CRM to the team for review.

4.2. Final Analyses

The final planned analyses will be performed after all subjects have completed the study and after database freeze. See Section 19 for all final planned analyses for this study.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Part 1: Dose-Escalation Phase

The total number of subjects in the Part 1 dose escalation will depend on the number of dose escalations needed, but the minimum number of subjects anticipated to complete dose escalation is 13 if there are no DLT observed; if there are any DLTs observed, more than 13 subjects will be enrolled in dose escalation. Up to an additional 21 subjects with evaluable pre- and on-treatment paired biopsies might be enrolled for the purpose of the PK/PD cohorts in Part 1. Therefore, up to approximately 34 subjects may be enrolled into Part 1. The selection of sample size 34 is based on the goal of fully exploring available dose ranges for purposes of selecting an appropriate regimen(s) for Part 2. This will include a number of cohorts to establish an initial understanding of the dose-response relationship as well as to evaluate a range of PD biomarkers that may reveal the biological activity of GSK2849330. The initial cohort (1.4 mg/kg) will have 1 subject and Cohorts 2 through 5 will have 3 subjects in the dose escalation phase and up to an additional 3 subjects with evaluable pre- and on-treatment paired biopsies in each of these cohorts for the PK/PD cohorts. The actual number of cohorts and subjects will depend in part on the observed toxicity and the PK and PD observed during the dose escalation.

Simulations were conducted to determine the average sample size and percentage of time each dose was selected under 3 different scenarios: almost no toxicity scenario, little toxicity scenario and moderate toxicity scenario. For each scenario, 5000 clinical trials were simulated using the planned doses. Details are provided in Table 2.

The specified prior probabilities discussed in the Protocol Section 3.3 were used to determine an explicit equation for the prior distribution using the FACTS software. The parameters (s.d.) of the explicit distribution are α=-5.334(1.9913), ln(β)=-0.0579 (0.1018), and ρ=-0.9977 where α and ln(β) are distributed as bivariate normal with correlation ρ.

Table 2 Simulation Results for Various Scenarios

Dose (mg/kg)	Scenario 1: Almost No Toxicity		Scenario 2: Little Toxicity		Scenario 3: Moderate Toxicity	
	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)
1.4	0.00005	0	0.0005	0.8	0.05	5.2
3	0.0005	0	0.1	10	0.1	14.2
10	0.005	0.2	0.2	33	0.2	37.4
30	0.055	99.8	0.25	56.2	0.3	43.2

The average sample size over the 5000 clinical trials simulated under Scenarios 1-3 was 15.2, 15.5, and 15.1 respectively.

5.2. Part 2: Molecularly-Defined Tumor Histology Groups

Once the recommended dose(s) and schedule(s) is/are confirmed from Part 1, at least 12 and up to 30 subjects per group will be enrolled at that dose(s) in Part 2, guided by decision rules defined in the Protocol in Section 13.6.2. These guidelines are based on the predictive probabilities of success if enrollment were to continue to 30 subjects using the methodology of [Lee, 2008].

The null hypothesis is:

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

The alternative hypothesis is:

$$H_A: p \geq 30\%$$

Starting with a group of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 94% power. Group enrollment will be stopped early for futility if the predictive probability of success is less than 6%. The trial would not stop early for success. The Bayesian Prior was Beta (0.2, 0.8), a weak prior with a mean response rate of 20%. The group outcome will be considered successful if the posterior probability of (P >0.10 | observed data) is ≥80%. The futility boundary described in the Protocol Section 13.6.2 was calculated based on the optimizing criterion of maximizing the power under the alternative hypothesis.

Under the null hypothesis, the expected sample size is 20 subjects and the probability of early termination is 77%. Under the alternative hypothesis, the expected sample size is 29 subjects and the probability of early termination is 5%.

5.3. Sample Size Sensitivity

No analysis of sample size sensitivity was performed.

5.3.1. Sample Size Re-estimation

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

6. ANALYSIS POPULATIONS

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2849330. Safety will be evaluated based on this analysis population.

The **PK Concentration Population** will consist of all subjects from the All Treated Population for whom at least one post-dose PK sample is obtained and analyzed. This population will be used for the concentration tables, listings, and figures.

The **PK Parameter Population** will consist of all subjects from the PK Concentration Population for whom valid and valuable pharmacokinetic parameters were derived. This population will be used in the assessment and characterization of PK parameters.

The **PD Population** will consist of all subjects from the All Treated Population and for whom at least one evaluable paired pre-treatment PD sample and on-treatment PD sample were obtained and analyzed. This population will be used in all PD tables, listings, and figures.

The **PGx Population** will consists of All treated Population subjects who have not received an allergenic bone marrow transplant, and voluntary agree to participate in the PGx analysis of the study, and refusal to participate will not indicate withdrawal from the clinical study. This population will be used in listing of PGx sampling accountability.

6.1. Analysis Datasets

Analysis datasets are “analysis-ready” datasets, i.e., analysis datasets that have a structure and content that allows statistical analysis to be performed with minimal programming. An analysis-ready dataset is ready to be used directly by statistical analysis software with only minimal additional processing, as sorting of the observations or the selection of the appropriate records from the analysis dataset. No complex data manipulations such as transformations or transpositions are required to perform the supported analysis.

7. TREATMENT COMPARISONS

With respect to primary objectives and endpoints, no formal treatment comparisons are being tested. The primary focus will be on determining the RP2D based on the safety,

efficacy, PD and PK of pharmacokinetics of GSK2849330 in subjects with advanced cancer. Most of the analysis will be descriptive or exploratory.

7.1. Data Display Treatment and Other Subgroup Descriptors

Treatment groups with the same dose and the same administration frequency will be combined in final analyses as displayed in the table below. All data will be summarized or listed by the treatment group except PK concentration data, which will be listed by part and dose cohort.

Treatment Code	Treatment Description	Treatment Label / Column Header
1	Part 1 DE Cohort: 1.4 mg/kg weekly	Part 1 Cohort: 1.4 mg/kg weekly
2	Part 1 DE Cohort: 3 mg/kg every 2 weeks	Part 1 Cohort: 3 mg/kg every 2 weeks
3	Part 1 DE & PK/PD Cohort: 10 mg/kg every 2 weeks	Part 1 Cohort: 10 mg/kg every 2 weeks
4	Part 1 DE & PK/PD Cohort: 30 mg/kg every 2 weeks	Part 1 Cohort: 30 mg/kg every 2 weeks
5	Part 1 DE & PK/PD Cohort: 30 mg/kg weekly	Part 1 Cohort: 30 mg/kg weekly
6	Part 1 PK/PD Cohort: 3 mg/kg weekly	Part 1 Cohort: 3 mg/kg weekly
7	Part 2 Expansion Cohort: 30 mg/kg	Part 2 Cohort: 30 mg/kg

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis datasets will be created according to IDSL standards, and data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

8.1. Reporting Conventions

- All data are reported according to the dose/regimen initially received by the subject.
- Data will be listed by treatment group, centre ID, and subject.
- Planned times relative to investigational product dosing will be used in all summary tables and figures.
- Unscheduled visits will be included in the listing using actual time and may be used in deriving the maximum or minimum value over time (e.g. worst-case value post dose). However, unscheduled visits will not be included in summaries by planned time.

- Only pre-specified planned times will be used in the summaries, statistical analyses and calculations of any derived parameters (except for PK parameters). Unscheduled readings (lab, EGC, etc) will only be listed.
- Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots. Planned times will be used in the descriptive summaries and in mean and median plots. Listings of PK concentration-time data will be done by actual sampling times relative to dosing time.
- No formal assessment windows will be defined for the purpose of classifying measurements obtained outside scheduled assessment times.
- Programmers should refer to GSK IDSL standards (when applicable) for decimal place conventions and expand if necessary. Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), median, minimum and maximum for continuous variables and n and percent for categorical variables. Display minimum and maximum in the same precision as data was collected, mean and median using 1 additional decimal place, and SD using 2 additional decimal places.
- This is a multicenter study. Data from all study sites will be integrated and no controlling for centre-effect will be considered in the statistical analyses.
- Analyses are to be performed using the SAS System, Version 9.3 or higher. Programs will be imported into HARP and the final output will be produced by running drivers in HARP. Some graphics may be produced using the TSCG (Tibco Spotfire Clinical Graphics) - comprising of S-Plus (R) 7.0.6 or higher.
- Deviations from the analyses in the RAP will be identified in the final CSR.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study or investigational drug will be documented with the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations defined in Section 6.

In the event that the study is prematurely discontinued, all available data will be listed and a review will be carried out by the study team to assess which statistical analyses are still considered appropriate.

Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument. Those data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Because the length of treatment for each subject will depend on the efficacy and toxicity of the treatment, the duration of treatment will vary across subjects. Similarly the duration of follow up will also vary. All available safety, and efficacy data will be analyzed using suitable statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing data. For endpoints which determine the percentage of responders, subjects with unknown/not evaluable or missing best overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

Subjects with the designation of treatment relationship for adverse events (AE)s and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes". There will be no other imputation for missing data other than what's described in Section 9.2 for partial dates and for missing exposure end dates.

9.2. Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of core standard algorithms and standard Oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

9.2.1. Reference dates

The following reference dates will be used:

- Data of Screening: for Age. Because age is an eligibility requirement.
- Treatment Start Date: for safety. Will be used to calculate study day for safety measures.
- Treatment Start Date: for efficacy. Will be used to calculate study day for efficacy measures and baseline characteristics (such as time since initial diagnosis), as well as efficacy durations.

9.2.2. Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

9.2.3. Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date then efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest

occurs prior to the efficacy reference date then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0.

9.2.4. Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.
- If the reference date is before the event date then the elapsed time is the reference date minus the event date.

For converting all other durations (e.g., duration of adverse events, duration of exposure, age) to weeks, months or years use the following:

- To report the duration in weeks divide the number of days by 7.
- To report the duration in months use:

  (YEAR(stopdate + 1) - YEAR(startdate)) * 12 + (MONTH(stopdate + 1) - month(startdate) - 1) + (DAY(stopdate + 1) > = DAY(startdate))
- To report the duration in years use:

  intck('year', startdate, stopdate + 1) - (month(stopdate + 1) < month(startdate) or (month(stopdate + 1) = month(startdate) and day(stopdate + 1) < day(startdate)))

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

9.2.5. Imputation of 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 (see Section 9.3) or for specific analysis purposes as outlined below.

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

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

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

Adverse Events (AE):

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	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.

Dataset	Date	Missing Element	Rule
		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

9.2.6. Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date. For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. If there are no central labs collected for a subject and lab test prior to or on the first dose of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first dose of study treatment will be defined as the baseline value.

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

Parameter	Baseline Days Collected		Baseline To Be Used in Analysis / Summaries
	Screening	Day 1 Pre-dose	
Laboratory	X	X	Day 1 Pre-dose
Vital Signs	X	X	Day 1 Pre-dose
ECG	X	X	Day 1 Pre-dose

9.2.7. Change from baseline

Change from baseline will be presented for safety data as described in Section 19.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

9.2.8. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst- case post-baseline. For summaries that collapse data across multiple planned time intervals, mean data will be selected at each collapsed interval.

If multiple assessments on different days are reported for the same scheduled assessment, then the latest assessment for that scheduled assessment will be analyzed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the mean of multiple measurements reported for the same date will be analyzed, with the exception of laboratory data reported from both central and local laboratories. If laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analyzed to provide consistency with measurements from other subjects. For example, for ECG data where 3 assessments are collected for each scheduled planned time, the first 3 measures will be used to compute the mean values for ECG intervals at each scheduled planned time.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

9.2.9. Actual Treatment

The subjects' actual treatment will be derived from exposure data provided by Clinical Operations. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

9.2.10. Cardiac Scan Modalities (ECHO/MUGA)

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a subject throughout the study. The absolute change from baseline values will not be calculated for any subjects where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

9.2.11. Derived and Transformed Variables

See Section 11 for details on analyses for overall response, overall response rate, duration of response.

Deriving and Summarizing Pharmacokinetic Parameters

See Section 13 for derivation of PK parameters.

ECG Correct QT Intervals

The following parameters will be derived if applicable. They are derived to the same number of decimal places as the raw data.

Variable	Description	Algorithm
RR	RR interval	• If QTcB is machine read and QTcF is not provided, then: RR = [(QT/QTcB)^(2)]*1000 • If QTcF is machine read and QTcB is not provided, then: RR = [(QT/QTcF)^(3)]*1000 • If ECGs are manually read, the RR value preceding the measured QT interval should be a collected value --- Do Not Derive.
QTcB	QTc interval, using Bazett's correction	• If not provided in dataset, derive: QTcB = QT / ((RR/1000)^1/2), where RR is in msec
QTcF	QTc interval, using Fredericia's correction	• If not provided in dataset, derive: QTcF = QT / ((RR/1000)^1/3), where RR is in msec

9.3. Study Time Periods

9.3.1. Time in Relation to Treatment

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, ECHO/MUGA, and questionnaire data (ECOG), will be assigned to the study time periods defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 9.2). Flag variables (time in relation to study treatment) indicating the study time periods will be added to these datasets.

Pre-therapy is defined as the time prior to the subject's first dose of study treatment.

On-therapy is defined as the time from first dose of study treatment to the last dose date of study treatment + 28 days.

Post-therapy is defined as any time at least 45 days or 5 half lives (whichever comes later) after the last dose of study treatment.

Some datasets include the first dose day as On-therapy and some exclude the first dose date as On-Therapy. The first dose day and time (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, and lab tests, if the time is before first dose. The

first dose day (Day 1) is considered to be On-therapy for adverse events and concomitant medications.

9.3.2. Study Time Periods for Concomitant Medications

Concomitant Medication start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medications dataset.

- **Start relative to treatment:** Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment, or start date is missing and end date is before study treatment start date. Else assign to 'DURING' if the start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.
- **End relative to treatment:** Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-therapy period or if subject is ongoing (not all study treatment discontinuation records completed). Else assign to 'AFTER' if start date is after the on-therapy period or (end date is missing and start relative to treatment='AFTER').

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').
- Summary of Concomitant Medications with On-Therapy Onset: This summary will contain medications with start date after study treatment start date. In addition, any medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include concomitant medication records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER').

9.4. Values of Potential Clinical Importance

9.4.1. Laboratory Parameters

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

9.4.2. ECG Parameters:

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify QTc (Bazett's or Fridericia's) values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Note that there is a slight inconsistency between CTCAE v4 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF [QTcB] interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	Msec
Increase from baseline QTcF [QTcB]	Increase of ≥31 to ≤60 Increase of >60	Msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
PR interval	<110 (L) and >220 (H)	Msec
QRS interval	<75 (L) and >110 (H)	Msec

9.4.3. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline temperature	Increase to ≥38	Degrees C
Decrease from baseline Diastolic Blood Pressure	Decrease to ≤35	Degrees C

9.4.4. Left Ventricular Ejection Fraction

The following criteria will be used to flag left ventricular ejection fraction (LVEF) values that are values of potential clinical importance:

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'.

LVEF Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute change from baseline LVEF	• No change or any increase • Any decrease o >0-<10 decrease o 10-19 decrease o ≥20 decrease o ≥10 decrease and ≥ LLN o ≥10 decrease and below LLN o ≥20 decrease and ≥ LLN o ≥20 decrease and below LLN	%
Relative to change from baseline LVEF	• ≥20 decrease and ≥ LLN • ≥20 decrease and below LLN	

10. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on All Treated Subjects population, and all summaries and data listings will use treatment labels as specified in Section 7.

The lists of displays for Study Population, including population to use for each display, are shown in Section 19 of the RAP.

10.1. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 6 will be provided by treatment and overall.

The end of study record will be summarized. This display will show the number and percentage of subjects who completed or withdrew from the study, including primary reason for study withdrawal by cohort and for all subjects.

The list of end of study record will be provided for all subjects. The listing will include study day when subjects discontinue study as well as the reason of subject prematurely withdraw from the study.

10.2. Protocol Deviations

Protocol deviations will be reviewed by study team. Only protocol deviations classified as not “Excluded from protocol deviation analysis reporting” will be summarized and listed.

An additional listing of inclusion/exclusion deviations will also be provided.

10.3. Demographic and Baseline Characteristics

The demographic characteristics e.g., age, race, ethnicity, sex, baseline height, and baseline body weight will be summarized and listed. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, country will be included in demographic summary. And age will also be categorized and summarized by <18, 18-64, 65-74, and >74 for Development of Safety Update Report (DSUR). The count and percentage will be computed for sex and ethnicity. A summary of country and age category of 18-64, 65-84, and ≥85 will be provided for EU Clinical Trials Register.

Race will be summarized and listed.

Disease history and characteristics, time since initial diagnosis in months, stage at initial diagnosis, date of initial diagnosis will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided.

Substance use, including smoking history, and alcohol use and caffeine use, will be listed.

Prior anti-cancer therapies will be summarized and listed. Prior cancer related surgeries will be summarized and listed. Medical conditions present at screening will be listed.

Summary of baseline ECOG performance status and HER3 and NRG1 status will be provided.

10.4. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. 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. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

Concomitant medications will be summarized separately for medications with onset date within the on-therapy period and for medications with onset date within the pre-therapy period. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

11. ANTI-CANCER ACTIVITY ANALYSES

An abbreviated efficacy analyses will be performed because of the early stopping of study. All analyses will be based on the All Treated population as defined in Section 6 unless otherwise specified.

The primary efficacy endpoint of overall response rate (ORR) determined by investigator according to standard RECIST v1.1 (E.A. Eisenhauer, 2009). Summary of Investigator

assessed best response by dose group and for all subjects will be provided. The duration of response is defined as time from first documented evidence of CR or PR until first documented disease progression or death due to any cause, which will be calculated for subjects with confirmed CR or PR per RECIST v1.1 and listed in the listing of investigator assessed response. The measurement of target lesion and non-target lesion will be listed, separately.

Listings of tumour markers and other measures of clinical benefit will be provided.

12. SAFETY ANALYSES

Unless otherwise specified, all the safety analyses will be based on the All Treated population as defined in Section 6 and summaries will include all events or assessments collected during the study.

The lists of displays for safety analyses, including population to use for each display, are shown in Section 19 of the RAP.

12.1. Extent of Exposure

Extent of exposure to GSK2849330 will be captured in the listing of study treatments. The listing will be sorted by part, treatment group, centre, and subject ID. It will include start and stop dates, times of treatment administration (infusion start and stop times), number of days on study, dose, number of days on study treatment, and dose deviation.

Exposure to GSK2849330 and duration on treatment will be summarized for all subjects by treatment dose. Cumulative dose, number of weeks on study treatment and duration on treatment will be included in the summary of exposure to IP. Duration on treatment is defined as days from the first dose to the last dose, regardless of dose interruption. In addition to mean, median, min and max, duration on treatment will also be summarized in the following categories: < 4 weeks, 4-8 weeks, 8-12 weeks, and ≥ 12 weeks.

All the dose reductions, dose escalations, missed doses and dose delays will be listed separately.

It is expected that deviations from planned therapies may occur and therefore a listing of planned and actual treatments will be produced.

A horizontal bar graph of duration of treatment will be produced that displays duration of treatment in weeks by primary tumour type and initial dose for each subject.

12.2. Adverse Events

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

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

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

The following two types of summaries for AEs and drug related AEs will be provided:

- Summary of all AEs by frequency, which is a summary of the number and percentage of subjects with all treatment emergent AEs. Adverse events will be grouped by preferred term and sorted in descending order based on total incidence in all treatment groups.
- Summary of all AEs by maximum toxicity grade, which is a summary of the number and percentage of subjects with all treatment emergent adverse events by intensity or grade. Relevant treatment emergent adverse events will be grouped by the preferred term, and sorted in descending order based on total incidence in all treatment groups.

Treatment emergent AE is defined as adverse events which occur or worsen on or after date and time of first dose of investigational product.

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. Additionally, a listing of subject IDs for each individual AE will be produced.

A listing of adverse events recorded as dose-limiting toxicities will be provided.

Listing of adverse events for subjects with grade 3 or higher AEs will be provided. In addition, a summary table of non-serious adverse events by system organ class and preferred term with occurrences >=5% will be generated.

12.3. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events. 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 adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

The events of special interest include:

- AEs related to infusion reactions, which include new onset fever, myalgia, chills, rigors, nausea, vomiting, malaise occurring during the infusion to 1 hour after the infusion
- AEs related to allergic reaction include dyspnea, edema etc.
- Diarrhea of any grade

Summaries of the number and percentage of subjects with these events will be provided for each type of events separately, if data permit.

Characteristics (e.g. number of occurrences, action taken, grade, etc) of the three type AEs of special interest will be listed.

Listing of cardiovascular adverse events will be provided including the following AEs and SAEs.

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

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12.4. Deaths and Serious Adverse Events

A listing by subject of all deaths will be produced. Primary cause of death, subreason of death, date of death and time from last dose will be listed for each subject who died.

All SAEs will be tabulated based on the number and percentage of subjects by frequency and maximum grade. SAEs are included in the listing of all adverse events. A supportive listing with all SAEs will be generated including fatal SAEs.

In addition, summary table of serious adverse events for all subjects by system organ class and preferred term including drug-related status and fatal status will be generated.

12.5. 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 listed separately with subject level details:

- AEs Leading to Discontinuation of Study Treatment or Withdrawal from the Study
- AEs leading to Dose Interruptions or Dose Delay or Dose Reductions

12.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects and 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.

12.7. Clinical Laboratory Evaluations

The assessment of laboratory toxicities will examine the following laboratory tests:

Hematology			
Platelet Count		*RBC Indices*:	*Automated WBC Differential:*
Red blood cell (RBC) Count		Mean corpuscular volume (MCV)	Neutrophils
White blood cell (WBC) Count (absolute)		Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte Count		Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Clinical Chemistry			
Blood urea nitrogen (BUN) or urea	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Glucose, fasting	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other tests			
PT, INR, PTT			
Testosterone (male subjects only)			
Luteinizing Hormone (LH) (male subjects only)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

Summaries of change from baseline for clinical chemistry and haematology data by maximum toxicity grade will be provided by scheduled visits for all the lab tests that are gradable by CTCAE v4.0. Number and percentage of subjects with any post-baseline

grade increase or any maximum increase to grade 3 or grade 4 will be displayed in the table. Data collected in unscheduled visits will be included in the summary of worst case on therapy category. Data with missing baseline grade will be excluded from the summary.

Another set of tables of summary of change from baseline for lab data 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. In addition, the summary will include worst case changes from baseline with respect to normal range including non-scheduled visits.

Laboratory data of clinical chemistry, haematology, urinalysis, coagulation and other data will be listed for all subjects, respectively.

A supporting listing of subjects with Grade 3 or higher toxicities will be provided separately for each of above lab categories. All laboratory data will be reported under standard units.

12.7.1. Analyses of Liver Function Tests

Hepatobiliary laboratory abnormalities will be summarized. 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, which is defined as ALT ≥3ULN and bilirubin ≥ 2ULN.

12.8. Other Safety Measures

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.

Values of vital signs as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition vital sign values will be categorized as follows:

- Systolic BP (mmHg): Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159) and Grade 3 (≥160), and Decrease to <90.
- Diastolic BP (mmHg): Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), and Grade 3 (≥100), and Decrease to <=35.
- Heart rate (beats/min): <60, 60-100, and >100
- Temperature (°C): <35, 36-37, ≥38

Summaries of increase in vital signs and decreases in systolic BP from the baseline with respect to the categories defined above, and details in Section 9.4.3, will be performed.

Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

ECG

As per the protocol, all ECGs will be single assessments unless clinically significant abnormality is observed, in which case repeat ECG twice more, for a total of 3 ECGs within approximately 5-15 minutes. Manual calculation for all 3 ECGs should be done using Fridericia's formula (QTcF=QT/RR1/3) in view of the complex relationship between QT and RR.

Any clinical decisions should be based on the average of all three ECGs.

The following parameters will be derived if applicable, where they are derived to the same number of decimal places as the raw data.

Variable	Description	Algorithm
RR	RR interval	• If QTcB is machine read and QTcF is not provided, then: RR = [(QT/QTcB)^(2)]*1000 • If QTcF is machine read and QTcB is not provided, then: RR = [(QT/QTcF)^(3)]*1000 • If ECGs are manually read, the RR value preceding the measured QT interval should be a collected value --- Do Not Derive.
QTcB	QTc interval, using Bazett's correction	• If not provided in dataset, derive: QTcB = QT / ((RR/1000)^1/2), where RR is in msec
QTcF	QTc interval, using Fredericia's correction	• If not provided in dataset, derive: QTcF = QT / ((RR/1000)^1/3), where RR is in msec

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 part, dose group, and scheduled visits as well as for the worst case post-baseline. See Section 9.4.2 for details.

In addition, ECG interval values will be also be summarized.

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

A figure plotting the baseline QTc and the worst-case post-baseline values will be produced. The figure will have reference lines at 450 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45 degree line), at equality plus 30 msec, and at equality plus 60 msec.

LVEF

Absolute change from baseline in LVEF will be summarized at each scheduled assessment time and in the worst case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- Any increase
- No change
- Any decrease:
- >0-<10 decrease
- 10-19 decrease
- >=20 decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

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

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.

13. PHARMACOKINETIC ANALYSES

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Data Sciences - Oncology, GlaxoSmithKline.

The merge of PK concentration data and CRF data to generate a dataset with actual blood sampling times, actual time relative to dosing, and PK concentrations will be performed after DBF by, or under the direct auspices of Clinical Statistics, Oncology Quantitative Sciences (Programmer), GlaxoSmithKline.

Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Pharmacology Modeling and Simulation (CPMS), GlaxoSmithKline.

Statistical analysis of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Statistics Oncology Quantitative Sciences (Statistician), GlaxoSmithKline.

Unless otherwise stated, all tables, figures and listings in this section will be based on the Pharmacokinetic, or PK Parameter population, and all summaries, figures will use treatment labels as specified in Section 7 and PK concentration listing will be presented by part and dose level.

The lists of displays for PK, including population to use for each display, are shown in Section 19 of the RAP.

13.1. Drug Concentration Measures

Concentrations of GSK2849330 in the collected PK plasma samples will be determined using the currently validated and approved analytical ELISA assay. The generated concentration data will be reported in SMS2000. Raw data will be stored in the GLP Archives, GSK. The analysis and reporting of the PK drug concentrations of GSK2849330 will be performed under the management of Bioanalysis, Immunogenicity and Biomarkers (BIB), In Vitro/In Vivo Translation, GSK.

All PK concentration listing displays will be based on PK Concentration Population, and PK concentration summary displays (tables/figures) will be based on PK parameter population.

Concentrations of GSK2849330 in plasma will be listed by part, original dose group and nominal time and summarised by dose group and nominal time. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance document GUI_51487, “Non-Compartmental Analysis of Pharmacokinetic Data”, for more information regarding the handling of plasma concentrations below the assay’s lower limit of quantification (NQ).

Individual GSK2849330 concentration-time profiles and median/mean profiles by treatment dose group will be plotted using actual elapsed time for individual plots and

nominal time for median/mean profiles for each study part. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot). See Section 19 Pharmacokinetic Source Figures and Tables for details.

Any concentration data excluded from the derivation of PK parameters by CPMS should be omitted from any figures and summaries, and flagged with an asterisk in the relevant data listings, with a footnote to indicate that these values have been omitted from subsequent analyses.

13.2. Deriving and Summarizing Pharmacokinetic Parameters

All PK parameter displays will be based on PK parameter population.

As data permit, the following pharmacokinetic parameters will be determined from the plasma concentration-time data for GSK2849330. The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin Professional Version 6.3 or higher. All calculations of non-compartmental parameters will be based on actual sampling times.

1. The first occurrence of the maximum observed plasma concentration determined directly from the raw concentration-time data (Cmax).
2. The time at which Cmax is observed will be determined directly from the raw concentration-time data (tmax).
3. The apparent terminal elimination half-life ($t_{1/2}$) obtained as the ratio of $\ln 2/\lambda z$, where λz is the terminal phase rate constant estimated by linear regression analysis of the log transformed concentration-time data
4. The time to reach the last quantifiable concentration (tlast)
5. The area under the plasma concentration-time curve to the last quantifiable concentration (AUC(0-t)) determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.
6. The AUC to a fixed nominal time (AUC(0-168)) will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.
7. The AUC over the dosing interval (AUC(0-τ)), where τ is the dosing interval, will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.
8. The AUC extrapolated to infinity (AUC(0-∞)) will be calculated, where data permit, as the sum of AUC(0-t) and $C_t/\lambda z$, where Ct is the observed [insert matrix] concentration of the last quantifiable time-point and λz is the terminal phase rate constant obtained from the log-linear regression analysis.
9. The percentage of AUC(0-∞) obtained by extrapolation (%AUC∞ex) will be calculated as the ratio of [AUC(0-∞) minus AUC(0-t)] to AUC(0-∞) X 100.

10. Cτ: pre-dose (trough) concentration at the end of the dosing interval on the specified days (Only for Days 8, 15 and 22 where available).
11. Clearance (CL) after single dose for iv administration (CLiv) CL = Dose/AUC(0-∞)

13.3. Statistical Analyses of Pharmacokinetic Data

Statistical analyses of pharmacokinetic parameters will be responsibility of Oncology, Clinical Statistics, GSK. Statistical analysis of the exploratory compartmental PK parameters data will be the responsibility of CPMS, Quantitative Sciences, GSK.

PK data will be presented in graphical and/or tabular form and will be summarized descriptively.

For all statistical analyses, AUC(0-∞), AUC(0-t), AUC(0-τ)), AUC(0-168), t1/2, and Cmax will be separately analysed after $\log_e$-transformation.

Individual plasma PK parameters values as well as descriptive summary (mean, SD, median, minimum, maximum, geometric mean, and the standard deviation, 95% confidence interval (CI) of log-transformed parameters (if applicable) by dose group will be reported.

Pre-dose trough concentration ($C\tau$) samples obtained immediately before the morning dose on Days 8, 15, and 29 will be presented in a listing and will be summarized descriptively by dose.

Box plot figures will be generated based on dose normalized data for Cmax and AUC(0-∞), AUC(0-168), and AUC(0-τ)) as a function of the dose administered.

Individual and Box Plot of Plasma GSK2636771 Pre-Dose Concentration Data on Day 8, 15 and 29 by Dose Cohort in Part 1 will be provided.

Statistical analysis of Cmax and AUC may be performed as appropriate dose proportionality.

13.4. Population Pharmacokinetic Analyses

Data permitting, population PK analysis will be performed by, or under the direct auspices of CPMS, GlaxoSmithKline.

Plasma concentration-time data from the groups in Part 2 may be combined with data from dose escalation and further analyzed using a population approach. A nonlinear mixed effect model may be used to determine population PK parameters and important covariates (biomarker, or disease related covariates).

PK data will be presented in graphical and/or tabular form and will be summarized descriptively.

14. PHARMACODYNAMIC AND BIOMARKERS ANALYSES

14.1. Pharmacodynamic Analyses

Pre-treatment and on-treatment biopsy tissues (tumor and normal skin) will be analyzed for markers of the HER3 pathway such as HER3 and including biomarkers indicative of pathway activation and proliferation (pHER3, Ki67) using IHC as the method to determine protein expression levels. Markers related to the other mechanisms of action attributed GSK2849330 such as ADCC and CDC may be analyzed.

Serum HER3 (also known as 'soluble HER3') pre and on-treatment analyses will be performed. Descriptive summary (mean, SD, median, minimum, maximum) of absolute test value will be reported by dose group. The summary of change from baseline serum HER3 will also be provided. The baseline of HER3 data is defined as the test value measured at Day 1 Pre-dose. The individual serum HER3 concentration over time data for will be plotted. Box plot figures will be generated as a function of the dose administered. Listing of the serum HER3 data will be provided.

Data permitting, exploratory population PD analyses of other peripheral blood markers will be provided.

14.2. Biomarker Analyses

The results of these biomarker investigations which include analysis of biomarker associated with anti-cancer activity parameters may be reported separately from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Descriptive summary (mean, SD, median, minimum, maximum) for CD marker data will be reported by dose group. A listing of CD marker data will be provided.

Additional exploratory analyses may be performed to further characterize novel biomarkers.

15. IMMUNOGENICITY ANALYSIS

Serum samples for determination of anti-GSK2849330 antibodies will be taken from all subjects in this study at the time-points specified in the Time and Events Tables in Section 7.1 in the protocol. Samples will be analyzed for the presence of anti-GSK2849330 antibodies using a validated immunoelectrochemiluminescent (ECL) assay. The assay involves screening, confirmation and titration steps (tiered-testing approach). If serum samples contain anti-GSK2849330 antibodies, they will be further analyzed for the specificity of antibodies by a confirmation assay. Confirmed positive samples will be titrated to obtain the titers of antibodies.
Immunogenicity results will be summarized and the results for antibody positive subjects will be presented in a listing. The immunogenicity results of anti-GSK2949330 positive incidence and titer will be reported at the end of the study.

16. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

If data permit, exploratory PK/PD analyses may be performed by, or under the direct auspices of, CPMS, GlaxoSmithKline to examine the potential relationships between GSK2949330 PK and PD endpoints such as total and phosphor-HER3 from tumor tissue, pre- and post-treatment biomarkers (cells, proteins, ribonucleic acid [RNA] and/or deoxyribonucleic acid [DNA]) from circulation, skin, and/or tumor tissue. In addition, analyses may be may be performed to examine the potential relationship between GSK2949330 concentration/PK and clinical activity endpoints such as ORR and/or safety measurements such as QTc or AEs. The data from this study may be combined with data from other studies for a population PK/PD analysis, which will be reported separately. Further details of population PK/PD analyses will be described in a separate RAP.

17. PHARMACOGENETIC DATA ANALYSES

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

The candidate genes that may be investigated in this study include the following: the GSK Absorption, Distribution, Metabolism and Excretion genes. These play a central role in drug PK and PD. In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to GSK2849330. The genes that may code for these proteins may also be studied.

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

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

18. REFERENCES

Bernstein L, Anderson J, Pike M. Estimation of the proportional hazard in two-treatment-group clinical trials. Biometrics, 1981; 37:513-519.

Berry G, Kitchen R, Mock P. A Comparison of two simple hazard ratio estimators based on the Logrank Test. Statistics in Medicine, 1991; 10:749-755.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982; 38:29-41.

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E.A. Eisenhauer, P. Therasse, J. Bogaerts et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009 (45): 228-247.

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Hollander M, Wolfe DA. *Nonparametric Statistical Methods.* 2nd ed. New York: John Wiley & Sons; 1999.

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika, 1983; 70(3):659-663.

Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. Journal of Pharmacokinetics and Biopharmaceutics, 1987; 15(6):657-80.

SOP_130050: Managing Protocol Deviations

SOP_54838: Development, Review and Approval of Reporting and Analysis Plans

SOP_54839: Development of Summary Document Analysis Plans

19. ATTACHMENTS

19.1. Table of Contents for Data Display Specifications

For the Clinical Study Report the following section numbering will apply:

Section 9: Study Population

Section 10: Efficacy

Section 11: Safety presented

Section 12: Pharmacokinetic

Section 13: Pharmacodynamic / Biomarker

Section 14: Immunogenicity

Listed below are the planned figures, tables and listings to be produced for inclusion in the GSK2849330 clinical study report:

- The 'IDSL No. / Example Shell' column refers to the relevant example in the Integrated Data Standards Library (IDSL) database
- Unless otherwise indicated, these refer to the core IDSL data standards located under:
    - 'Data Standards' → 'By Component' in the IDSL database
- 'CP' refers to the Clinical Pharmacology (CP) modified core IDSL standards located under:
    - 'Supporting Documentation' →'TST Use of IDSL Core Choices' → 'Clin Pharm' in the IDSL database
- 'PD' refers to the Clinical Pharmacology data standards located under 'Data Standards' → 'By Therapeutic Component' → 'Clin Pharm' in the IDSL database.

19.1.1. Study Population

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Deliverable
9.1	All Treated	ES6	Summary of Study Eligibility in Screening	Including screening failure and reason of failure	SAC
9.2	All Treated	POP1	Summary of Analysis Populations	Footnote subject ID and excluded population	SAC
9.3	All Treated	DV1A	Summary of Protocol Deviation	Add a column for Total	SAC
9.4	All treated	ES1	Summary of Subject Disposition		SAC
9.5	All treated	DM1	Summary of Demographic Characteristics	Include height, weight and BMI at screening or baseline, and country; add age by categories.	SAC
9.6	All treated	DM5	Summary of Race		SAC
9.7	All treated	LA1	Summary of Disease Characteristics at Baseline		SAC
9.8	All Treated	CM8	Summary of Concomitant Medication by Ingredient for Medication Started prior Study Treatment	only for medications start prior to study and continue during study	SAC
9.9	All Treated	CM8	Summary of Concomitant Medication by Ingredient	Including medications start on or after date of first dose; excluding ones taken post therapy period.	SAC
9.10	All Treated	AC3	Summary of Prior Anti-Cancer Therapies	/arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ac3.sas	SAC
9.11	All Treated		Summary of Baseline ECOG Performance Status	/arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ecog.sas	SAC
9.12	All Treated	PS4A/ Shell	Summary of Change from Baseline in ECOG Performance Status		SAC

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Deliverable
9.1	All Treated	ES6	Summary of Study Eligibility in Screening	Including screening failure and reason of failure	SAC
9.13	All Treated		Summary of Country and Age Group	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_dm_agecat.sas	
9.14	All Treated		Summary of Baseline HER3 and NRG1 Status		

19.1.2. Efficacy Figures and Tables

Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable
10.1	All Treated	RE1a	Summary of Investigator Assessed Best Response (RECIST 1.1 Criteria)	Best Resp. only	SAC
10.2	All Treated	RE5	Listing of Investigator-Assessed Tumor Responses (RECIST1.1 Criteria)		SAC
10.3	All Treated	LA2	Listing of Target Lesion (RECIST v1.1)		SAC
10.4	All Treated	LA3	Listing of Non-target Lesion (RECIST v1.1)		SAC

19.1.3. Safety Figures & Tables

Figures

No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable
11.1	All Treated	OEX12	Plot of Duration of Treatment (Weeks) by Primary Tumour Type and Initial Dose	/arenv/arprod/gsk2636771/p3b115717/sac/drivers/f_durtrt.sas	SAC
11.2	All Treated	OECG4	QTcF Shifts from Baseline to Worst-case Post Baseline		SAC

Tables

No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable
11.1	All Treated	OEX1	Summary of Exposure to GSK2849330	Including Ave. Dose, Cum. Dose, Time on study treatment (weeks)	SAC
11.2	All Treated	OEX3a	Listing of Exposure to GSK2849330		SAC
11.3	All Treated	IP2	Listing of Investigational Product Compliance	If IPCOMP data is available	SAC
11.4	All Treated		Summary of Dose Reduction	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_dosredgsk.sas	SAC
11.5	All Treated		Summary of Dose Interruption	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_dosintgsk.sas	SAC
11.6	All Treated	AE3	Summary of All Adverse Events by Frequency		SAC
11.7	All Treated	OAE07	Summary of All Adverse Events by Maximum Grade		SAC
11.8	All Treated	AE3	Summary of Drug-Related Adverse Events		SAC

No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable
11.9	All Treated	OAE07	Summary of Drug-Related Adverse by Maximum Grade		SAC
11.10	All treated	AE3	Summary of Serious adverse events by Frequency		SAC
11.11	All treated	OAE07	Summary of Serious adverse events by Maximum Grade		SAC
11.12	All treated		Adverse Events Overview	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ae_overview.sas	SAC
11.13		AE8	Listing of Fatal Serious Adverse Events		SAC
11.14	All treated	DL3	Listing of Dose-Limiting Toxicities	For DE cohorts only	SAC
11.15	All treated	AE8	Listing of subjects with Grade 3 or Higher Adverse Events		SAC
11.16	All treated	AE3	Summary of Adverse Events of Special Interest	See Section 12.3	SAC
11.17	All treated	AE8	Listing of Cardiovascular Adverse Events	See RAP Section 12.4	SAC
11.18	All treated	AE8	Listing of AEs leading to dose delay or reduction or interruption		SAC
11.19	All treated	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study		SAC
11.20	All treated	DTH3	Listing of deaths	including time from last dose	SAC
11.21	All treated		Summary of Non-serious Adverse Events by Preferred Team with Occurrences >=5%	/arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ae_non_ser.sas	SAC
11.22	All treated		Summary of Serious Adverse Events by Preferred Term Including Drug-related Status and Fatal Status	/arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ae_ser_2.sas	SAC
11.23	All treated	OLB6	Summary of Clinical Chemistry Toxicity Grade Change from Baseline	.	SAC

No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable
11.24	All treated	OLB6	Summary of Haematologic Toxicity Grade Change from Baseline		SAC
11.25	All treated	OLB6	Summary of Urinalysis Toxicity Grade Change from Baseline		SAC
11.26	All treated	OLB11B	Summary of Clinical Chemistry Data Changes from Baseline with Respect to the Normal Range		SAC
11.27	All treated	OLB11B	Summary of Haematologic Data Changes from Baseline with Respect to the Normal Range		SAC
11.28	All treated	OLB11B	Summary of Urinalysis Data Changes from Baseline with Respect to the Normal Range		SAC
11.29	All treated	UR3	Summary of Urinalysis Dipstick Results		SAC
11.30	All treated	OLIVER1	Summary of Hepatobiliary Laboratory Abnormalities		SAC
11.31	All treated	OLB7	Listing of Liver Function Tests for Subjects Meeting Potential Hy's Law	put 'No data to report', if no subject meets the Law,	SAC
11.32	All treated	OVT1A	Summary of Heart Rate and Temperature Worst-Case Change from Baseline		SAC
11.33	All treated		Summary of Blood Pressure Worst-Case Change from Baseline	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_vit_chgbl_bp.sas	SAC
11.34	All treated		Summary of Worst-Case Increases in QTcF	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_qtcf4.sas	SAC
11.35	All treated		Summary of Worst-Case QTcF Increases from Baseline	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_qtcf3.sas	SAC
11.36	All treated	EG3	Listing of Subjects with QTcF >=501 msec		SAC
11.37	All treated	EG2	Summary of ECG Values		SAC

No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable
11.38	All treated	EG1	Summary of ECG Findings	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ecgfind.sas	SAC
11.39	All treated	OLVEF1B	Summary of Left Ventricular Ejection Fraction Change from Baseline		SAC
11.40	All treated		Summary of Worst-Case ECOG Performance Status Shifts from Baseline	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ecog_shift.sas	SAC

19.1.4. Pharmacodynamic/Biomarkers Figures and Tables

Figures

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
12.1	PD	PKONE, PKCF1	Individual Serum HER3 Concentration-Time plots (Linear and Semi-log)		SAC
12.2	PD		Box plot of Serum HER3 data by Dose Cohort	arenv/arprod/gsk263677 1/p3b115717/sac/drivers /f_pkp_box_single.sas	SAC

Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
12.1	PD	PD1/Shell	Summary of Serum HER3 Data by Dose Cohort		SAC
12.2	PD	PD1/Shell	Summary of Change from Baseline of Serum HER3 Data by Dose Cohort		
12.3	PD	PD1/Shell	Summary of CD marker Data (%) by Dose Cohort		SAC
12.4	PD	PD1/Shell	Summary of CD marker Data (cells/cumm) by Dose Cohort		SAC
12.5	PD	Non-standard	Listing of Biomarker Data	by subjid, visit, bicat, bimeth, biorres in BIOMARK dataset	SAC
12.6	PD	PD10/Shell	Listing of Serum HER3 Data		SAC
12.7	PD	PD10/Shell	Listing of CD Marker Data		SAC

19.1.5. Pharmacokinetic Figures and Tables

Figures

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
13.1	PK parameter	PK16a, pkcf1p	Individual Plasma GSK2849330 Concentration-Time Plots by Dose Cohort in Part 1 (Linear and Semi-log)		SAC
13.2	PK parameter	PK17, PKCF2	Mean (± SD) GSK2849330 Plasma Concentration-Time Plots by Dose Cohort in Part 1 (Linear and Semi-log)		SAC
13.3	PK parameter	PK18, pkcf3	Median GSK2849330 Plasma Concentration-Time Plots by Dose in Part 1 (Linear and Semi-log)		SAC
13.4	PK parameter		Individual and Box Plot of Dose-Normalized Plasma GSK2636771 PK Parameters by Dose Cohort in Part 1	For Cmax, AUC(0-∞), AUC(0-168), and AUC(0-τ) arenv/arprod/gsk2636771/p3b115717/sac/drivers/f_pkp_box_single.sas	SAC
13.5	PK parameter		Individual and Box Plot of Plasma GSK2636771 Pre-Dose Concentration Data on Day 8, 15 and 29 by Dose Cohort in Part 1	arenv/arprod/gsk2636771/p3b115717/sac/drivers/f_pkc_box_pre.sas	SAC

Tables

No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
13.1	PK parameter	PK01, pkct1	Summary of GSK2849330 Plasma Concentration-Time data by Dose		SAC
13.2	PK parameter	PKPT2	Summary of Derived Plasma GSK2849330 Pharmacokinetic Parameters by Dose		SAC
13.3	PK Conc.	PKCl1P	Listing of Plasma GSK2849330 PK Concentration-Time Data	By part and original dose cohort	SAC
13.4	PK Parameter	PKPL1P	Listing of Plasma GSK2849330 PK Parameters Data		SAC

19.1.6. Immunogenicity

Tables

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
14.1	All Treated	Shell	Summary of Immunogenicity of Anti-GSK2849330 Antibody Results	Only output data when IGSCATCD=2 (confirmed results)	SAC
14.2	All Treated	Shell	Listing of Anti-GSK2849330 Antibody Results	Output records for subjects with IGSCATCD=2 and IGSORRSCD=1; See details in shell	SAC
14.3	All Treated	Non-standard	Listing of Immunogenicity Sample Accountabilities	All information	SAC

19.1.7. ICH Listings

Table No	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Deliverable Priority
Study Population					
1	All Treated	TA1	Listing of Planned and Actual Treatments		SAC
2	All Treated	ES2	Listing of End of Study Records	Including all subjects; add a column of 'Complete study' with values of 'Yes' or 'No'; change column title of 'Date of Withdrawal' to 'Date of Disposition';	SAC
3	All Treated	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
4	All Treated	DV2	Listing of Protocol Deviations		SAC
5	All Treated	DM2	Listing of Demographic characteristics		SAC
6	All Treated	DM9	Listing of Race		SAC
7	All Treated	DC2	Listings of Disease Characteristics at Initial Diagnosis		SAC
8	All Treated	MH2	Listing of Medical Conditions for All Subjects		SAC
9	All Treated	AC6	Listing of Prior Anti-Cancer Chemotherapy, Hormanal, Immunotherapy, Small Molecule Targeted Therapy, and Biologic Therapy		SAC
10	All Treated	AC7	Listing of Prior Anti-Cancer Radiation Therapy		SAC
11	All Treated		Listing of Prior Cancer Related Surgical Procedures	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_surgery.sas	SAC
12	All Treated	CP_CM3	Listing of Concomitant Medications by Generic Term		SAC
Safety					
13	All Treated	OEX3a	Listing of Exposure to GSK2849330		SAC

Table No	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Deliverable Priority
14	All Treated		Listing of Exposure to Investigational Product	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_exp.sas	SAC
15	All Treated		Listing of Dose Reduction	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_exp_reductn.sas	SAC
16	All Treated		Listing of Dose Delay/Interruption	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_exp_intrup.sas	SAC
17	All Treated		Listing of Dose Escalation	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_exp_escal.sas	SAC
18	All treated	AE2	Relationship between System Organ Class and Verbatim Text		SAC
19	All Treated	OAE03	Listing of Subject Numbers for Individual Adverse Events		SAC
20	All Treated	AE8	Listing of All Adverse Events		SAC
21	All Treated	AE8	Listing of All Drug-Related Adverse Events		SAC
22	All Treated	AE8	Listing of All Serious Adverse Events		SAC
23	All treated	AE8	Listing of Adverse Events of Special Interest	See RAP Section 12.3	SAC
24	All treated		Listing of Liver Event Information for RUCAM Score	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_rucam.sas	SAC
25	All Treated	OLB7	Listing of Chemistry Laboratory Data		
26	All Treated	OLB7	Listing of Haematology Laboratory Data		SAC
27	All Treated	OLB7	Listing of Urine Laboratory Data		SAC
28	All Treated	OLB7	Listing of Coagulation and Other Laboratory Data		SAC
29	All treated	OLB7	Listing of Subjects with Grade 3 or Higher Toxicity in Clinical Chemistry Data		SAC
30	All treated	OLB7	Listing of Subjects with Grade 3 or Higher Toxicity in Haemetology Data		SAC

Table No	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Deliverable Priority
31	All treated	OLB7	Listing of Subjects with Grade 3 or Higher Toxicity in Urinalysis Data		SAC
32	All treated		Listing of Subjects with Grade 3 or Higher Toxicity in Liver Function Test	arenv/arprod/gsk2256098/fak114746/sac/drivers/l_lft8.sas	SAC

19.1.8. Other Listings

No.	Population	IDSL / TST ID / Example Shell	Title	Programming Notes	Deliverable [Priority]
1	All Treated	Non-standard	Listing of Randomisation	All information in RANDALL	SAC
2	All Treated	Non-standard	Listing of Substance Use	Including last date, type, history, average unit etc. in SUBUSE	SAC
3	All treated		Listing of Liver Event Information for RUCAM Score	arenv/arprod/gsk2636771/p3b115717/sac/drivers/l_rucam.sas	SAC
4	All treated	LB13	Listing of Reference Ranges for Clinical Laboratory Tests		SAC
5	All Treated	EG3	Listing of ECG Interval Data		SAC
6	All Treated	CP_EG5	Listing of Subjects with Clinical Significant Abnormal ECG findings		SAC
7	All Treated	OECG5A	Listing of Fridericia's QTc Values greater than 501		SAC
8	All Treated	OVT7A	Listing of All Vital Signs		SAC
9	All Treated	OLVEF2A	Listing of Echocardiogram Results		SAC
10	All Treated	PS5A	Listing of ECOG Performance Status		SAC
11	All Treated	Non-standard	Listing of Biomarkers in Screening	Including test methods, tests, results in BIOMARK	SAC
12	PGx	Non-standard	Listing of Pharmacogenetic sample accountability	All information in GENPRO	

19.2. Data Display Specifications (Example Shells)

Protocol : HER117158
Population : All Treated

Table x.x Summary of number of subjects with positive immunogenicity results by visit (Safety population)

Sampling Time Point	Cohort 1 (N=X)	Cohort 2 (N=X)	Cohort 3 (N=X)	Cohort X (N=X)
Week 0 (Baseline)	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)
Week X	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)
Any visit post-baseline	x/x (xx%)	x/x (xx%)	x/x (xx%)	x/x (xx%)

Note: This listing includes all subjects tested positive for anti-GSK2849330 antibody in confirmatory testing at any time during the study.

Percentages are calculated specific for each treatment arm and each sampling time point.

The denominator is the total number of subjects tested for anti-GSK2849330 antibody, and the numerator is the number of subjects tested positive for anti-GSK2849330 antibody in confirmatory testing.

Protocol : HER117158
Population : All Treated

Listing x.x Listing of Immunogenicity Results For Anti-GSK2849330 Positive Subjects

				Anti-GSK2849330 Antibody		
Inv./ Subj.	GSK2849330 Dose/Dose Interval	Sampling Time Point	Date of Sampling	Screening Result	Confirming Result	Titer
xxxxx/ xxxxxx	xx/xx	xxxxxxxxxx	DDMMMYYYY	Neg		
		xxxxxxxxxx	DDMMMYYYY	Pos	Pos	xx
		xxxxxxxxxx	DDMMMYYYY	Pos	Pos	xx

Note:

1. Move column 'GSK2849330 Dose/Dose Interval' to first column and change it to Treatment, i.e. "Part 1 Cohort: 3 mg/kg weekly".
2. Add "GSK2849330 Conc. (µg/mL)"as last column with value of pre-dose PK Conc. merged by VISIT for this listing.
3. Add 'Study Day' in column of 'Date of Sampling'.

Example PD1
Protocol: HER117158
Population: PD Population

Table 2
Summary of CD Marker Data (%) by Dose Cohort

CD Markers	Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
CD 45									
	Part 1 Cohort: 1.4 mg/kg weekly	24	Pre-dose	24	NQ		NQ	NQ	xxxx
			30m	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
			1h	23	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
			2h	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
	Part 1 Cohort: 3 mg/kg every 2 weeks	24	Pre-dose	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
			30m	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
			1h	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
			2h	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx

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Example PD1
Protocol: HER117158
Population: PD Population

Table 1
Summary of Serum HER3 Data by Dose Cohort

Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Part 1 Cohort: 1.4 mg/kg weekly	24	Pre-dose	24	NQ		NQ	NQ	xxxx
		30m	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		1h	23	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		2h	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
Part 1 Cohort: 3 mg/kg every 2 weeks	24	Pre-dose	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		30m	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		1h	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		2h	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx

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Example PD1
Protocol: HER117158
Population: PD Population

Table 1
Summary of Change from Baseline value of Serum HER3 Data by Dose Cohort

Treatment	N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Part 1 Cohort: 1.4 mg/kg weekly	24	30m	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		1h	23	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		2h	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
Part 1 Cohort: 3 mg/kg every 2 weeks	24	30m	24	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		1h	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx
		2h	21	xxxx.xx	xx.xx	xxxx.x	xxxx	xxxx

Example PD10
Protocol: HER117158
Population: PD Population

Table 2
Listing of Serum HER3 Concentration-Time Data

Treatment	Inv./ Subj.	VISIT	Date	Actual Time	Planned Relative Time	Concentration (unit)	PK Concentration (unit)
Part 1 Cohort: 1.4 mg/kg weekly	PPD	Day 1	01JAN2003	08:55	Pre-dose	NQ (<0.23)	
			01JAN2003	10:05	1h	xxxx	
			01JAN2003	11:00	2h	xxxx	
			07JAN2003	08:55	Pre-dose	xxxx	
			07JAN2003	10:00	1h	xxxx	
			07JAN2003	10:59	2h	xxxx	
Part 1 Cohort: 3 mg/kg every 2 weeks			01JAN2003	08:55	Pre-dose	xxxx	
			01JAN2003	10:05	1h	xxxx	
			01JAN2003	11:00	2h	NR	

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